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Canadian Headache Society Guideline Acute Drug Therapy for Migraine Headache

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Canadian Headache Society Guideline: Acute Drug Therapy for Migraine Headache

Irene Worthington¹, Tamara Pringsheim³, Marek J. Gawel^{1,8,9},
Jonathan Gladstone^{1,2}, Paul Cooper⁴, Esma Dilli⁵, Michel Aube⁶,
Elizabeth Leroux⁷, Werner J. Becker³ on behalf of the Canadian Headache
Society Acute Migraine Treatment Guideline Development Group

ABSTRACT: Objectives: The primary objective of this guideline is to assist the practitioner in choosing an appropriate acute medication for an individual with migraine, based on current evidence in the medical literature and expert consensus. It is focused on patients with episodic migraine (headache on ≤ 14 days a month). **Methods:** A detailed search strategy was used to find relevant meta-analyses, systematic reviews and randomized double-blind controlled trials. Recommendations were graded with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, using a consensus group. In addition, a general literature review and expert consensus were used for aspects of acute therapy for which randomized controlled trials are not available. **Results:** Twelve acute medications received a strong recommendation for use in acute migraine therapy (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ASA, ibuprofen, naproxen sodium, diclofenac potassium, and acetaminophen). Four received a weak recommendation for use (dihydroergotamine, ergotamine, codeine-containing combination analgesics, and tramadol-containing combination analgesics). Three of these were NOT recommended for routine use (ergotamine, and codeine- and tramadol-containing medications). Strong recommendations were made to avoid use of butorphanol and butalbital-containing medications. Metoclopramide and domperidone were strongly recommended for use where necessary. Our analysis also resulted in the formulation of eight general acute migraine treatment strategies. These were grouped into: 1) two mild-moderate attack strategies, 2) two moderate-severe attack or NSAID failure strategies, 3) three refractory migraine strategies, and 4) a vasoconstrictor unresponsive-contraindicated strategy. Additional strategies were developed for menstrual migraine, migraine during pregnancy, and migraine during lactation. **Conclusion:** This guideline provides evidence-based advice on acute pharmacological migraine therapy, and should be helpful to both health professionals and patients. The available medications have been organized into a series of strategies based on patient clinical features. These strategies may help practitioners make appropriate acute medication choices for patients with migraine.

RÉSUMÉ: Lignes directrices de la Canadian Headache Society : médicaments pour traiter la crise aiguë de migraine. Objectifs : L'objectif principal de ces lignes directrices est d'aider le médecin à choisir une médication appropriée pour un individu qui présente des crises aiguës de migraine. Ces lignes directrices sont basées sur les données actuelles de la littérature médicale et sur un consensus expert. Elles sont ciblées sur les patients qui souffrent de migraine épisodique (céphalée présente ≤ 14 jours par mois). **Méthode :** Une stratégie de recherche détaillée a été utilisée pour identifier les méta-analyses pertinentes, les revues systématiques et les essais contrôlés randomisés, à double insu. Les recommandations ont été classées selon le Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group au moyen d'un groupe de consensus. De plus, une revue générale de la littérature et un consensus expert ont été utilisés pour traiter des aspects du traitement de la crise aiguë pour lesquels des essais contrôlés randomisés ne sont pas disponibles. **Résultats :** Douze médicaments pour le traitement de la crise aiguë ont reçu une forte recommandation pour leur utilisation comme traitement de la crise aiguë de migraine (l'almotriptan, l'électriptan, le frovatriptan, le naratriptan, le rizatriptan, le sumatriptan, le zolmitriptan, l'ASA, l'ibuprofène, le naproxène sodique, le diclofénac potassique et l'acétaminophène). Quatre ont reçu une faible recommandation pour leur utilisation (la dihydroergotamine, l'ergotamine, les analgésiques contenant de la codéine et les analgésiques contenant du tramadol). Trois n'étaient pas recommandés pour utilisation de routine (l'ergotamine et les médicaments contenant de la codéine et ceux contenant du tramadol). Une forte recommandation a été émise contre l'utilisation du butorphanol et des médicaments contenant du butalbital. La métoclopramide et le dompéridone ont été fortement recommandés pour utilisation au besoin. Notre analyse a également mené à l'élaboration de huit stratégies générales de traitement. Elles ont été regroupées ainsi : 1) deux stratégies pour traiter les crises légères ou modérées ; 2) deux stratégies pour traiter les crises modérées ou sévères ou lors d'un échec du traitement par les AINS ; 3) trois stratégies pour le traitement de la migraine réfractaire et 4) une stratégie pour traiter un patient qui ne répond pas à un vasoconstricteur ou chez qui une telle médication est contre-indiquée. Des stratégies additionnelles ont été développées pour la migraine menstruelle, la migraine pendant la grossesse et la migraine pendant la lactation. **Conclusion :** Ces lignes directrices fournissent des conseils fondés sur des preuves sur le traitement pharmacologique de la crise aiguë de migraine et devraient être utiles tant aux professionnels de la santé qu'aux patients. Les médicaments disponibles ont été organisés en une série de stratégies selon le tableau clinique que présente le patient. Ces stratégies peuvent aider les médecins à choisir une médication appropriée pour traiter les crises aiguës chez les patients atteints de migraine.

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Werner J Becker was the primary author of Sections 3, 4, and 5, and of Appendices 1 and 2. He contributed to Sections 1 and 2 and the final preparation of the manuscript, and participated in all consensus groups.

Tamara Pringsheim assisted in the literature review, provided valuable advice for the data analysis, and provided extensive feedback on the manuscript.

Marek J Gawel provided extensive feedback on the manuscript and participated in consensus groups.

Jonathan Gladstone provided extensive feedback on the manuscript and participated in consensus groups.

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Irene Worthington has served on Advisory Boards and/or received speaker's honoraria or educational travel grants from Merck, Glaxo Smith Kline, Tribute Pharmaceuticals, Pfizer, and Astra Zeneca.

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Guideline Structure

This guideline is divided into five sections and two appendices. The targeted review in Section 2 is the core of the guideline, but Sections 1 and 3 address many other issues important for acute migraine treatment for which randomized controlled trial information is not available.

A guideline summary for primary care physicians and a summary for patients are also provided. Appendix 1 provides a detailed summary of how the guideline was developed. Appendix 2 provides a patient information sheet on acute migraine treatment. Appendix 3 provides a headache diary with instructions. A headache diary can also be downloaded from headachenetwork.ca. The sections and appendices are listed below. Each contains its own references in order to allow it to be used on its own, and to allow for easier updating:

Section 1: Introduction to the Guideline, and General Principles of Acute Migraine Management

Section 2: Targeted Review: Medications for Acute Migraine Treatment

Section 3: Pharmacological Acute Migraine Treatment Strategies: Choosing the Right Drug for a Specific Patient

Section 4: Acute Drug Therapy for Migraine Headache: Guideline Summary for Primary Care Physicians

Section 5: Acute Drug Therapy for Migraine Headache: Guideline Summary for Patients and Their Families

Appendix 1: Guideline Development Summary

Appendix 2: Acute Migraine Treatment: Information for Patients

Appendix 3: Headache Diary

Disclaimer: This guideline is designed to offer evidence-based strategies for the acute treatment of migraine. It is not, however, intended to replace clinical judgment or establish a treatment protocol for all individuals with migraine. Although every attempt has been made to provide current information, it is the responsibility of the practitioner to ensure that drugs and dosages are used correctly.

Introduction to the Guideline, and General Principles of Acute Migraine Management

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Jonathan Gladstone^{1,2}, Paul Cooper⁴, Esma Dilli⁵, Michel Aube⁶,
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Society Acute Migraine Treatment Guideline Development Group

ABSTRACT: Objectives: To provide an overview of the objectives and target population of the guideline, and to review the general principles of acute pharmacological migraine therapy. **Methods:** A general literature review and several consensus groups were used to formulate an expert consensus for the general use of acute migraine medications. **Results:** The objective of the guideline is to assist the physician in choosing an appropriate acute migraine medication for an individual with migraine, and thereby to reduce migraine-related disability. The target population includes adults with episodic migraine (patients with migraine headache < 15 days/month). This guideline is intended primarily for physicians who treat patients with migraine. Other health professionals may also find this guideline helpful. Acute migraine therapy should be considered for the great majority of patients with migraine. A specific acute medication is chosen based on evidence for efficacy, tolerability, migraine attack severity, patient preference, and on the presence of co-existing disorders. General principles of acute migraine therapy include that the response of a patient to any given medication cannot be predicted with certainty, and that treatment early in the attack is generally more effective than treatment later once the migraine attack is fully developed. A suitable treatment approach (stratified or stepped approaches) and drug formulation (injection, tablet, wafer, powdered formulation, or nasal spray) should be chosen based on patient clinical features. Excessively frequent use of acute medications (medication overuse) should be avoided. Two or more acute medications can be combined if necessary. **Conclusions:** This guideline provides evidence-based advice on the use of acute medications for migraine, and should provide useful guidance for acute migraine therapy to both health professionals and patients.

RÉSUMÉ: Introduction aux lignes directrices et aux principes généraux du traitement de la crise aiguë de migraine. Objectifs : Le but de cet article est de fournir un aperçu des objectifs et de la population ciblée par les lignes directrices et de revoir les principes généraux du traitement pharmacologique de la crise aiguë de migraine. **Méthode :** Nous avons effectué une revue de littérature et utilisé plusieurs groupes de consensus pour formuler un consensus expert concernant l'utilisation générale des médicaments pour traiter la crise aiguë de migraine. **Résultats :** L'objectif des lignes directrices est d'aider le médecin à choisir un médicament approprié pour traiter la crise aiguë de migraine chez un individu présentant de la migraine et ainsi diminuer l'invalidité due à la migraine. La population cible est constituée d'adultes présentant de la migraine épisodique (des patients qui présentent une céphalée migraineuse < 15 jours par mois). Ces lignes directrices sont destinées essentiellement aux médecins qui traitent des patients migraineux. Les autres professionnels de la santé peuvent également en tirer profit. Le choix du traitement de la crise aiguë de migraine est basé sur des preuves de son efficacité et de sa tolérabilité, sur la sévérité des crises de migraine, sur les préférences du patient et sur la présence de comorbidités. Parmi les principes généraux du traitement de la crise aiguë de migraine, il est important de noter que la réponse d'un patient à un médicament particulier ne peut être prédite avec certitude et que le traitement administré tôt au cours de la crise est généralement plus efficace que le traitement administré lorsque la crise de migraine est bien installée. Une méthode de traitement convenable (méthode stratifiée ou par étapes) et la formulation du médicament (injection, comprimé, capsule, poudre ou vaporisation nasale) devraient être choisies en fonction des manifestations cliniques que présente le patient. Une fréquence excessive d'utilisation de la médication de phase aiguë (surconsommation de médicaments) est à éviter. Deux médicaments ou plus pour traiter une crise aiguë peuvent être combinés si nécessaire. **Conclusions :** Ces lignes directrices fournissent des conseils fondés sur des preuves pour l'utilisation de la médication pour traiter la crise aiguë de migraine et fournissent des conseils utiles sur son traitement, tant pour les professionnels de la santé que pour les patients.

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Migraine is a common neurological disorder, which can produce significant disability, and reduce health-related quality of life.^{1,2} Canadian studies have shown migraine prevalence rates of 23 to 26% in women, and 7.8 to 10% in men.²⁻⁴

Over 4,000,000 Canadians suffer from migraine⁵, and as a result migraine is associated with a substantial social and economic impact. A study done in 1990 calculated that 7,000,000

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workdays were lost annually in Canada due to migraine.⁴ Disability related to migraine has been recognized by the World Health Organization, which ranked migraine as 19th among all causes of disability in terms of years lived with disability.⁶

The International Headache Society (IHS) has classified two major subtypes: migraine without aura, and migraine with aura. Migraine without aura is the most common migraine subtype, and is characterized by headache attacks lasting 4 to 72 hours. Headache attacks are usually accompanied by other symptoms including photophobia, phonophobia, nausea, and sometimes vomiting (for diagnostic criteria see Tables 1 and 2). Individuals with migraine with aura experience in addition reversible focal neurological symptoms, which usually precede the headache and last up to 60 minutes, or occasionally longer (Table 2).^{7,8}

Acute (symptomatic) pharmacological migraine therapy refers to the use of medication to treat individual migraine attacks. The great majority of adults with migraine in Canada (90%) use acute medications for their migraine attacks.² Acute medications are, however, only one component of migraine treatment. Based on headache frequency in population studies, it would appear that up to 25% of migraine sufferers might also benefit from the use of daily preventive medications to reduce migraine frequency.⁹ Pharmacological prophylaxis should be considered in patients with frequent and/or refractory migraine attacks. All migraine sufferers should also consider careful management of lifestyle factors and specific migraine triggers, which can potentially increase migraine frequency (see Headache Network Canada website: <http://www.headache-network.ca> (in English and French), Migraine Quebec website: www.migrainequebec.com (in French; to be translated into English), and American Headache Society website: <http://www.americanheadachesociety.org/professionalresources/TriggerAvoidanceInformation.asp>). In addition, behavioural interventions including the mastery of relaxation techniques, stress management, pacing, cognitive behavioural therapy, and biofeedback have the potential to benefit many migraine sufferers.¹⁰⁻¹²

Table 1: International Headache Society criteria for migraine without aura⁸

-
- A. At least 5 attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
- unilateral location
 - pulsating quality
 - moderate or severe pain intensity
 - aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During headache, at least one of the following is present:
- nausea and / or vomiting
 - photophobia and phonophobia
- E. Not attributed to another disorder
-

Acute pharmacological migraine therapy includes both “migraine-specific” medications (e.g., triptans, dihydroergotamine), and “non-specific” medications (e.g., ASA, acetaminophen, NSAIDs). It also includes adjunctive drugs such as anti-emetics (e.g., domperidone, metoclopramide, prochlorperazine) in oral or rectal formulations. The introduction of sumatriptan subcutaneous injection in 1991 represented a significant advance in the management of migraine. When the first Canadian migraine guidelines were published in 1997, the only triptan available was sumatriptan.⁷ Since that time, six more triptans have become available to Canadians. Although triptans are generally considered to be the most effective of the acute migraine medications overall, as recently as 2005, only 8% of Canadians listed a triptan as their main migraine medication.² Under-utilization of effective acute therapies has the potential to negatively impact quality of life for migraine sufferers. Population-based data in 2005 indicated that at least 200,000 Canadian women with migraine were very unsatisfied with the effectiveness of their acute migraine medications.^{2,13}

These guidelines have been developed to assist both health professionals and patients to develop more effective acute migraine treatment strategies.

Table 2: International Headache Society criteria for typical migraine with aura*⁸

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- A. At least 2 attacks fulfilling criteria B-D
- B. Aura consisting of at least one of the following, but no motor weakness:
1. fully reversible visual symptoms including positive features (e.g., flickering lights, spots or lines) and/or negative features (i.e., loss of vision)
 2. fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
1. homonymous visual symptoms and/or unilateral sensory symptoms
 2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 3. each symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache fulfilling criteria B-D for Migraine without aura begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder
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* Other less common types of migraine with aura include typical aura with non-migraine headache, typical aura without headache, familial hemiplegic migraine, and others.

Guideline Objectives and Target Population

Objectives

The primary objective of this guideline is to assist the physician in choosing an appropriate acute medication for an individual with migraine, based on current evidence in the medical literature. An additional objective is to assist the practitioner in using the chosen medication in the most effective manner.

The main clinical question that this guideline aims to help answer for the medical practitioner is, “Which acute medication should be prescribed for an individual patient in a specific clinical situation?”

The ultimate purpose or goal of this guideline is to reduce the headache-related disability suffered by individuals with migraine.

Target population

This guideline provides evidence-based recommendations for the outpatient acute management of adults (18 years-of-age or older) with episodic migraine (patients who experience migraine headache attacks on less than 15 days/month). It does not include recommendations for pediatric patients and for the emergency room management of acute migraine.

Although it is likely that physicians will extrapolate from the evidence presented here and use it for the care of patients with chronic migraine (headache on 15 days a month or more, with diagnostic criteria for migraine met on at least eight days a month), many of the clinical trials reviewed for this guideline did not include patients with headache frequencies of this magnitude.

Who should use this guideline?

This guideline is intended primarily for physicians who treat patients with migraine, including both family physicians, and specialists. Other health professionals who treat patients with migraine may also find this guideline helpful. As migraine is a chronic disorder, and it is important that patients with migraine partner with their health care professionals in order to achieve the best management success possible, individuals with migraine and their families may also find this guideline useful.

Expert consensus and recommendations

The core of this guideline is Section 2 “Targeted Review: Medications for Acute Migraine Treatment”. The recommendations in this section are based on a targeted review as described in that section. Evidence from randomized controlled trials is not available, however, to guide clinicians with regard to all the clinical decisions that must be made. To recognize this, treatment suggestions made in other sections of this guideline are labeled as “expert consensus”, as they are based on a general literature review and on the expert opinion of clinicians experienced in migraine treatment. These expert opinions were developed through expert consensus groups (See Appendix 1).

Goals of Acute Migraine Therapy

The goals of acute (or symptomatic) migraine therapy are to relieve pain and the associated symptoms of migraine (e.g., nausea, vomiting, photophobia, phonophobia) rapidly and consistently, with minimal or no adverse events, and to relieve migraine-related disability so that the patient can return quickly to normal function.⁷ Although some patients may be able to achieve the goal of becoming pain-free within two hours of taking an acute medication, those who only achieve partial headache relief (pain reduction) should try at least several acute medications (including several triptans if not contraindicated) over time for different migraine attacks, to determine if it is possible for them to reach this goal.

General Principles of Acute Migraine Therapy

1. The response of the individual with migraine to a specific acute drug cannot be predicted with certainty

Response to acute medications is individual and idiosyncratic.⁷ If the response to the first medication is not excellent, several medications may need to be tried (in succession) over time for different attacks to determine the most suitable medication in terms of efficacy and tolerability. Access to two different medications may be necessary if a patient suffers from attacks of varying severities. The choice of a particular symptomatic medication should take into account the efficacy of past treatments, and the presence of any concomitant disorders that may preclude use of certain medications. For patients with severe attacks, a rescue medication may be needed if their usual medication fails.

EXPERT CONSENSUS

- i. Several acute medication trials may be necessary before an appropriate acute medication is found for a specific patient. Some patients with attacks of varying severity may need access to more than one medication for successful migraine management.
- ii. A rescue plan should be discussed with patients with severe migraine attacks whose usual acute medication does not provide adequate headache relief consistently for every attack.

2. Early intervention: Most patients should be encouraged to take their acute medication early in the attack

To experience maximum effectiveness, patients should use acute medications as early as possible after headache onset, and while the pain is still mild. For the triptans, several prospective studies have shown improved efficacy with early treatment (see Table 6 in Section 2). Triptans may be more effective when taken early in the attack, because they can prevent but not reverse central sensitization. Central sensitization, as manifested by cutaneous allodynia, may occur in up to 75% of patients within 20 to 60 minutes of migraine onset.¹⁴

When discussing early treatment, patients should be educated with regard to the effects of medication overuse, and the need to differentiate migraine attacks from tension-type headache. For patients with frequent migraine attacks, early treatment may need to be used very cautiously. More effective acute treatment may result in less symptomatic medication use; however,

indiscriminate use of early treatment has the potential to lead to acute medication overuse in some patients.¹⁵ Patients may find taking acute medication during the migraine aura useful to manage their headaches, but for triptans there is evidence that they are best taken at the onset of head pain rather than during the aura. This is particularly true for subcutaneous sumatriptan (see Section 3).

EXPERT CONSENSUS

- i. *Patients should be advised to take acute medications as early as possible during their migraine attacks while pain is still mild, unless at risk for medication overuse headache.*

3. An appropriate treatment approach should be chosen

Three basic treatment strategies have been documented as options for acute migraine treatment.¹⁶ In Section 3 of this guideline, we use the term “strategy” for acute treatment paradigms for specific patient groups, based on patient clinical features. To avoid confusion, we will therefore use the term “approach” rather than “strategy” for the more broad or generalized concepts of stratified and step care approaches to care, while recognizing that these were termed “strategies” in the original publications that described them:

- “Stratified care”:** The medication chosen for a patient is based on attack severity and/or degree of migraine-related disability.^{17,18}
- “Step care within an attack”:** A simple analgesic or NSAID is used initially for a migraine attack. If the first medication is not successful, another medication (e.g., a triptan), is used a few hours later.
- “Step care across attacks”:** The practitioner prescribes an initial medication (e.g., NSAID), and the patient tries this for several attacks. If this medication is not sufficiently effective, the practitioner would prescribe another medication (e.g., a triptan) for subsequent attacks.

In practice, many patients have tried several non-prescription medications prior to consulting a physician for their headaches; therefore, a “step care across attacks” approach is already in place when the physician prescribes a more effective medication.

“Stratified care” is likely to be the most effective acute treatment approach, and has been shown to be cost effective.¹⁹ It has been promoted by several guidelines (The U.S. Headache Consortium²⁰, and the European Federation of Neurological Societies^{21,22}). Stratified care is the model of care recommended here for patients with the most severe migraine attacks, while a modified or “hybrid” model of care, which incorporates features of both stratified care and the “step care across attacks” model, is recommended for most patients with migraine in this guideline (see Section 3). “Step care within an attack” has been promoted by some guidelines, but it has the disadvantage that if the first medication fails, the second presumably more effective medication may fail as well, because it is taken later in the attack (at a time when it may no longer be as effective as it could have been if taken earlier). The “step care across attacks” approach has the potential disadvantage that if the initial medication provided by the physician is ineffective, patients may become discouraged and not pursue additional medical care for their

migraine (become a “lapsed consulter”). If this approach is chosen, patients should be informed early of the remaining treatment options, so that they realize other therapies are available for their migraine should that prove necessary.

It needs to be recognized that many patients with migraine have more than one attack severity. If they are able to identify early in the attack whether they are going to experience a severe attack or one of lesser intensity, they may be able to choose an appropriate medication for their attack based on the stratified care model. If patients are unable to identify the ultimate severity of their migraine attack early in its course, a “step care within an attack” approach may be appropriate if the majority of their attacks are relatively mild and respond to an NSAID or other medication, and if their more severe attacks still respond to their second medication even when taken later in the attack.

EXPERT CONSENSUS

- When recommending an acute migraine medication, consideration should be given to attack severity (“stratified care” approach) and past response to medications.*
- If a “step care across attacks” approach is chosen, patients should be educated with regard to remaining available treatment options, to reduce the risk of patients becoming discouraged and no longer consulting for their headaches.*
- Although a “step care within an attack” approach may be suitable for some patients, patients should be advised that most acute medications are more effective if taken early in the migraine attack.*

4. A suitable medication formulation should be chosen

Patient preference needs to be considered when recommending a particular medication formulation.^{23,24} However, some formulations have advantages over others in specific clinical situations. For some patients, it may be advantageous to use one formulation for some attacks, and another formulation for others.

- For migraine attacks that build up very rapidly and/or are characterized by early vomiting, and for attacks that present full-blown upon awakening, an injectable formulation (e.g., subcutaneous sumatriptan) has the potential to be most effective.²⁵⁻²⁷
- Patients with nausea and those who vomit only later in the attack may find nasal spray formulations to be more helpful than oral formulations, as medications delivered by nasal spray are partially absorbed through the nasal mucosa.^{23,24,28,29}
- Patients with lesser degrees of nausea or nausea that is exacerbated by taking water, and those who wish to treat their attacks early in situations where water may not be readily available, may find the orally disintegrating tablets more useful than regular tablets which are swallowed. Orally disintegrating tablets do not have a faster onset of action, as they are not absorbed through the buccal mucosa, but rather are swallowed with saliva, and absorbed in gastrointestinal tract.^{23,24,30}
- For patients without significant nausea, regular oral

tablets, orally disintegrating tablets, nasal sprays and injections are all appropriate options. The injection formulation has the greatest efficacy, but higher cost and more discomfort.^{26,27} Because of partial nasal absorption, nasal spray formulations may have a slightly faster onset of action than tablets.^{28,29} The evidence for significant absorption through the nasal mucosa is strongest for zolmitriptan nasal spray.^{31,32}

- e. Some oral formulations are designed for faster drug delivery and onset of action, as compared to regular oral tablets. Examples are diclofenac powder for oral solution, sumatriptan DF (fast dissolving) tablet, and others (e.g., effervescent ASA, liquid-containing NSAID preparations). Patients should be made aware of these options where appropriate, so that those with migraine attacks that increase rapidly in intensity can take advantage of these special formulations if they wish to.

EXPERT CONSENSUS

- i. *When choosing an acute migraine medication for a specific patient, consideration should be given to the clinical features of the attack including rate of increase of headache intensity and the presence of nausea and / or vomiting early in the attack, and an appropriate medication formulation should be chosen. Some patients may require more than one formulation.*

5. Medication overuse needs to be avoided because of the risk of medication overuse headache

All the commonly used acute medications have the potential to cause medication overuse headache (MOH) in patients with migraine when used too frequently over a period of several months or more.³³⁻³⁵ To avoid MOH, commonly accepted recommendations are to:

- Limit use of acetaminophen, ASA, and NSAIDs to a maximum of 14 days a month.^{36,37}
- Limit use of triptans, ergotamine, opioids and combination analgesics to a maximum of 9 days a month.^{36,37}

For patients taking medications from both classes, the important principle is for the patient to be free of acute medications at least 20 days a month.^{36,37} The International Headache Society (IHS) Diagnostic Criteria indicate that patients taking both triptans and NSAIDs should limit their use of these to a total of 9 days a month to avoid risk of MOH (http://ihs-classification.org/en/01_einleitung/03_anleitung/).

For patients with frequent attacks who are at risk of MOH, behavioural approaches to migraine management and prophylactic medications should be considered in addition to acute medications.

EXPERT CONSENSUS

- i. *When initiating treatment with acute migraine medications, the patient should be educated with regard to medication overuse headache. Patients should avoid use of ASA, NSAIDs and acetaminophen on more than 14 days per month, and use of triptans, ergots, opioids, or combination analgesics on more than 9 days a month. Patients taking different acute medications on different*

days should limit their total use of acute medications to 9 days a month if one of their medications is a triptan, a combination analgesic, an ergotamine, or an opioid.

- Patients should be advised to monitor their acute medication use if their attacks are frequent, preferably with a headache diary, in order to reduce the risk of medication overuse headache.*
- Pharmacological prophylaxis should be considered for patients with frequent migraine attacks who may be at risk of medication overuse.*

6. Two or more acute medications can be combined if necessary

Some patients may obtain better migraine attack relief if they take two or more acute medications simultaneously for their migraine attacks. For many patients, triptans satisfactorily treat migraine related nausea as well as the headache. Others, however, may benefit from taking an anti-nauseant (e.g., metoclopramide 10 mg) with their triptan. Some patients with attacks that do not respond satisfactorily to a triptan alone may have better relief if they take an NSAID (e.g., naproxen sodium 550 mg) with their triptan. These acute treatment options are discussed in more detail in Section 3 of the guideline.

EXPERT CONSENSUS

- i. *Although a single acute medication may relieve migraine attacks satisfactorily for many patients, others may benefit from taking more than one medication simultaneously (e.g., an NSAID with an anti-nauseant; an anti-nauseant with a triptan, or a triptan with an NSAID).*

Choosing an Acute Migraine Medication

There is no ideal acute migraine medication. Practitioners should find the principles of acute migraine therapy outlined above helpful in choosing an acute medication for a specific patient. Medication cost has not been directly considered in the recommendations in this guideline, although it is considered to some extent in the “combined acute medication treatment approach” in Section 3. In this approach, unless the patient has severe attacks and fits into the “stratified care” approach, less expensive NSAIDs are tried before a triptan is chosen (if necessary) as the patient’s primary acute medication.

In addition, other considerations in choosing an acute medication for a specific patient include:

1. Efficacy: How strong is the evidence that the drug is effective in acute migraine therapy and how effective is it compared to other treatment options?
2. Drug side effect profile: How safe is the drug, and how well tolerated?
3. Co-existing medical and/or psychiatric disorders: Does the patient have another disorder that is a contraindication for some of the acute migraine medications (e.g., a history of peptic ulcer, or cardiovascular disease)?
4. Patient preference: Section 2 provides information on the evidence for efficacy and side effects of the various acute migraine medications. Further guidance in choosing an acute medication for a specific patient is given in Section 3. A patient survey has indicated that an overwhelming

majority of patients consider complete relief of head pain, no recurrence, and rapid onset of action as important or very important attributes of acute migraine therapy.³⁸ Fortunately, many clinical trials use endpoints relevant to these preferences, and these are used in this guideline where possible.

REFERENCES

1. Becker WJ, Gladstone JP, Aube M. Migraine prevalence, diagnosis, and disability. *Can J Neurol Sci.* 2007;34:S3-9.
2. Cooke LJ, Becker WJ. Migraine prevalence, treatment and impact: the Canadian women and migraine study. *Can J Neurol Sci.* 2010;37:580-7.
3. O'Brien B, Goeree R, Streiner D. Prevalence of migraine headache in Canada: a population-based survey. *Int J Epidemiol.* 1994;23:1020-6.
4. Pryse-Phillips W, Findlay H, Tugwell P, Edmeads J, Murray TJ, Nelson RF. A Canadian population survey on the clinical, epidemiologic and societal impact of migraine and tension-type headache. *Can J Neurol Sci.* 1992;19:333-9.
5. Becker WJ, Christie SN, Mackie G, Cooper P, Canadian Headache Society Migraine Strategy Task Force. Consensus statement: the development of a national Canadian Migraine Strategy. *Can J Neurol Sci.* 2010;37:449-56.
6. Leonardi M, Steiner TJ, Scher AT, Lipton RB. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *J Headache Pain.* 2005;6:429-40.
7. Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. [see comment] [erratum appears in CMAJ 1997 Nov 15;157(10):1354]. [Review] [160 refs]. *CMAJ.* 1997;156:1273-87.
8. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24:9-160.
9. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache.* 2001;41:646-57.
10. Sauro KM, Becker WJ. Multidisciplinary treatment for headache in the Canadian healthcare setting. *Can J Neurol Sci.* 2008;35:46-56.
11. Rains JC, Penzien DB, McCrory DC, Gray RN. Behavioral headache treatment: history, review of the empirical literature, and methodological critique. *Headache.* 2005;45:S92-109.
12. Pringsheim T, Davenport WJ, MacKie G, et al. Introduction to the guideline, and general principles of migraine prophylaxis - Section i. *Can J Neurol Sci.* 2012;39:S3-7.
13. Becker WJ, Gawel M, Mackie G, South V, Christie SN. Migraine treatment. *Can J Neurol Sci.* 2007;34:S10-9.
14. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain.* 2000;123:1703-9.
15. Moschiano F, D'Amico D, Allais G, et al. Early triptan intervention in migraine: an overview. [Review] [20 refs]. *Neurol Sci.* 2005;26:s108-10.
16. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP, Disability in Strategies of Care Studygroup. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. [see comment]. *JAMA.* 2000;284:2599-605.
17. Lipton RB, Bigal ME, Amatriek JC, Stewart WF. Tools for diagnosing migraine and measuring its severity. *Headache* 2004;44:387-98.
18. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the Migraine Disability Assessment (MIDAS) questionnaire. *Headache.* 2001;41:854-61.
19. Williams P, Dowson AJ, Rapoport AM, Sawyer J. The cost effectiveness of stratified care in the management of migraine. *Pharmacoeconomics.* 2001;19:819-29.
20. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;55:754-62.
21. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol* 2006;13:560-72.
22. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. *Eur J Neurol.* 2009;16:968-81.
23. Gladstone JP, Gawel M. Newer formulations of the triptans: advances in migraine management. [Review] [116 refs]. *Drugs.* 2003;63:2285-305.
24. Rapoport AM, Tepper SJ, Bigal ME, Sheftell FD. The triptan formulations : how to match patients and products. [Review] [75 refs]. *CNS Drugs.* 2003;17:431-47.
25. Anonymous. Treatment of migraine attacks with sumatriptan. The Subcutaneous Sumatriptan International Study Group. *N Engl J Med.* 1991;325:316-21.
26. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs.* 2000;60:1259-87.
27. Gawel MJ, Worthington I, Maggisano A. A systematic review of the use of triptans in acute migraine.[see comment]. [Review] [74 refs]. *Can J Neurol Sci.* 2001;28:30-41.
28. Gawel M, Worthington I. Intranasal zolmitriptan. *Expert Opin Pharmacother.* 2005;6:1019-24.
29. Rapoport A, Winner P. Nasal delivery of antimigraine drugs: clinical rationale and evidence base. *Headache.* 2006;46:S192-201.
30. Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs.* 2010;70:1505-18.
31. Yates R, Sörensen J, Bergström M, et al. Distribution of intranasal C-zolmitriptan assessed by positron emission tomography. *Cephalalgia.* 2005 Dec;25(12):1103-9.
32. Kagedal M, Zingmark P-, Hedlund C, Yates R. True nasopharyngeal absorption of zolmitriptan after administration via nasal spray in healthy male volunteers. *American Journal of Drug Delivery.* 2005;3:133-40.
33. Dodick D, Freitag F. Evidence-based understanding of medication-overuse headache: clinical implications. *Headache.* 2006;46:S202-11.
34. Tepper SJ, Tepper DE. Breaking the cycle of medication overuse headache. *Cleve Clin J Med.* 2010;77:236-42.
35. Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. *Lancet Neurology.* 2010;9:391-401.
36. Silberstein SD, Olesen J, Bousser MG, et al International Headache Society. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia.* 2005;25:460-5.
37. Headache Classification Committee. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia.* 2006;26:742-6.
38. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? *Headache.* 2002;42:3-9.

Targeted Review: Medications for Acute Migraine Treatment

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ABSTRACT: Objective: To assess the evidence base for drugs used for acute treatment of episodic migraine (headache on ≤ 14 days a month) in Canada. **Methods:** A detailed search strategy was employed to find relevant published clinical trials of drugs used in Canada for the acute treatment of migraine in adults. Primarily meta-analyses and systematic reviews were included. Where these were not available for a drug or were out of date, individual clinical trial reports were utilized. Only double-blind randomized clinical trials with placebo or active drug controls were included in the analysis. Recommendations and levels of evidence were graded according to the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, using a consensus group. **Results:** Eighteen acute migraine medications and two adjunctive medications were evaluated. Twelve acute medications received a strong recommendation with supporting high quality evidence for use in acute migraine therapy (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ASA, ibuprofen, naproxen sodium, diclofenac potassium, and acetaminophen). Four acute medications received a weak recommendation for use with low or moderate quality evidence (dihydroergotamine, ergotamine, codeine-containing combination analgesics, and tramadol-containing combination analgesics). Three of these medications were NOT recommended for routine use (ergotamine, and codeine- and tramadol-containing medications), and strong recommendations were made to avoid use of butorphanol and butalbital-containing medications. Both metoclopramide and domperidone received a strong recommendation for use with acute migraine attack medications where necessary. **Conclusion:** Our targeted review formulated recommendations for the available acute medications for migraine treatment according to the GRADE method. This should be helpful for practitioners who prescribe medications for acute migraine treatment.

RÉSUMÉ: Revue ciblée : les médicaments pour traiter la crise aiguë de migraine. Objectif : Le but de l'étude était d'évaluer les données sur lesquelles est fondée l'utilisation des médicaments pour le traitement de la crise aiguë de migraine épisodique (céphalée présente ≤ 14 jours par mois) au Canada. **Méthode :** Nous avons utilisé une stratégie de recherche détaillée pour identifier les essais cliniques publiés qui étaient pertinents et qui portaient sur les médicaments utilisés au Canada pour le traitement de la crise aiguë de migraine chez l'adulte. Ce sont principalement des méta-analyses et des revues systématiques qui ont été utilisées. Seuls les essais cliniques randomisés à double insu, contrôlés par placebo ou médicament actif, ont été inclus dans l'analyse. Les recommandations et les niveaux de preuve ont été classés selon les principes du Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, par un groupe de consensus. **Résultats :** Dix-huit médicaments pour traiter la crise aiguë de migraine et deux médicaments d'appoint ont été évalués. Douze médicaments ont reçu une forte recommandation fondée sur des données de haute qualité pour leur utilisation dans le traitement de la crise aiguë de migraine (l'almotriptan, l'électriptan, le frovatriptan, le naratriptan, le rizatriptan, le sumatriptan, le zolmitriptan, l'ASA, l'ibuprofène, le naproxène sodique, le diclofénac potassique et l'acétaminophène). Quatre médicaments pour traiter la crise aiguë de migraine ont reçu une recommandation faible fondée sur des données de qualité faible ou modérée (la dihydroergotamine, l'ergotamine, les analgésiques contenant de la codéine et les analgésiques contenant du tramadol). Trois de ces médicaments n'étaient pas recommandés pour utilisation de routine (l'ergotamine et les médicaments contenant de la codéine et les médicaments contenant du tramadol) et des recommandations fortes ont été émises contre l'utilisation de médicaments contenant du butorphanol et du batalbital. Le métoclopramide et le dompéridone ont reçu une forte recommandation pour leur utilisation en association avec les médicaments pour traiter les crises aiguës de migraine si nécessaire. **Conclusion :** Notre revue ciblée nous a mené à formuler des recommandations selon la méthode GRADE concernant les médicaments disponibles pour traiter la crise aiguë de migraine. Ceci devrait aider les médecins qui prescrivent des médicaments pour traiter la crise aiguë de migraine.

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Canadian guidelines for the pharmacological treatment of migraine were first published in 1997.¹ At that time, the only migraine specific medications available were the ergot derivatives (ergotamine and dihydroergotamine), and the 5-HT_{1B/1D} receptor agonist (triptan), sumatriptan. Since publication of these guidelines, another six triptans have become available in Canada. Non-specific acute medications (e.g., ASA, NSAIDs, and acetaminophen) also have a role in migraine

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management. The objective of this section of the guideline is to assess the evidence base for drugs used for acute treatment of episodic migraine (headache on ≤ 14 days a month) in Canada.

METHODOLOGY

A targeted review of the literature as outlined below was completed to assess available evidence for acute migraine medications in adults. Only drugs available in Canada are included in the guideline. Appendix 1 provides more information on the development of this guideline. For further details on the general principles of acute medication use, please see Section 1 of this guideline. Section 3 provides treatment strategies for choosing a specific acute medication for an individual patient.

Literature Search Strategy

A MEDLINE search of the English language for migraine disorders and use of triptans, ergotamine, dihydroergotamine, analgesics, NSAIDs, and antiemetics was performed. Only randomized, controlled trials (RCTs) and meta-analyses/systematic reviews of acute migraine medications in adults (18 years-of-age and older) and available in Canada were included. The initial search was limited to the years 1996 - May 2006 (first Canadian migraine guidelines were published in 1997). The search was updated in May 2010, and again in May 2012.

The following terms were used:

- exp. migraine disorders, and
- sumatriptan or almotriptan or eletriptan or naratriptan or rizatriptan or zolmitriptan or frovatriptan or “triptan”, or
- exp. anti-inflammatory agents, non-steroidal, or
- exp. aspirin, or acetaminophen, or exp. analgesics, or
- ergotamine or dihydroergotamine, or
- exp. barbiturates or butalbital, or
- metoclopramide or domperidone or dimenhydrinate or exp. antiemetics
- limits: human, adults (18 years-of-age and older), English, randomized controlled trial (RCT) or meta-analysis

The Cochrane Collaboration® and EMBASE were also searched for systematic reviews/meta-analyses. Clinical trials of acute medications used in the emergency room (e.g., parenteral antiemetics) were excluded.

Evaluating Efficacy of Acute Therapies (endpoints)

Various endpoints to assess efficacy of acute therapies have been used in clinical trials. Primary endpoints include “headache response” and “pain-free”. “Headache response” (also called “pain relief” or “headache relief”) is defined as a decrease in headache intensity from moderate or severe to mild or none, evaluated at pre-specified time intervals (e.g., 1, 2 or 4 hours). This endpoint has been used in most clinical trials. A “pain-free” outcome (moderate or severe to none) can also be measured at pre-specified time intervals. This is a desirable endpoint, which is endorsed by the International Headache Society (IHS); however, many older trials did not use this endpoint. “Sustained pain-free” refers to the number (%) of patients who are pain-free at two hours, and remain pain-free over the next 22 hours (without additional acute medication). Headache recurrence

refers to the re-emergence of a moderate or severe headache (generally within 24 hours) after an initial headache response.

Consistency of response refers to reproducible pain relief over several attacks. Other secondary outcomes include the ability to reduce associated symptoms of nausea, vomiting, photophobia and phonophobia. Reduction in clinical disability refers to the medication’s ability to reduce functional impairment due to pain and associated migraine symptoms. These outcomes may be measured within a single attack or across multiple attacks. The most important outcomes desired by patients are pain-free outcomes (two hour pain-free) and sustained pain-free over 24 hours.²

Comparison of acute migraine therapies is complicated by use of different outcome measures in different clinical trials. Debate continues about the best outcome measure in assessing a drug’s efficacy in acute migraine therapy. It should be noted that newer drugs (e.g., triptans) tend to have more RCTs and better trial methodology than older drugs (e.g., ergot derivatives); this may result in newer drugs being favoured over older ones.

Criteria for Considering Studies for this Guideline

Only RCTs and meta-analyses/systematic reviews of acute migraine medications in adults (English language) were included in this guideline. Due to the large number of placebo-controlled trials of individual triptans, meta-analyses/systematic reviews, if available, rather than individual RCTs were included. However, if no meta-analyses/systematic reviews were found for a particular drug, then RCTs were included. Clinical trials of acute medications in the emergency room setting or in pediatric patients were excluded.

Methods of the Review

Titles and abstracts of studies and meta-analyses identified by the literature search were screened for eligibility by two independent reviewers for the initial search (IW and MJG), for the second search (up to May 2010; IW and TP), and for the third search (2010 – May 2012; IW and WJB). Papers that could not be excluded with certainty on the basis of the information contained in the title or abstract were reviewed in full. Papers passing the initial screening process were retrieved and the full text was reviewed.

Grading of Recommendations and Assessment of Overall Quality of Evidence

The recommendations were graded based on the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. Using the GRADE system, the strength of a recommendation reflects the extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects.³ The strength of a recommendation in the GRADE system is based on several factors including⁴:

1. The balance between the desirable and undesirable consequences of a therapy, for example, the balance between the benefits and the side effects of a drug.
2. The quality of the evidence on which judgements of the magnitude of the benefit and the potential harm of an intervention are based.

Table 1: Levels of evidence: GRADE system³

Level of Evidence	Definition
High quality	We are confident that the true effect lies close to the estimate given by the evidence available.
Moderate quality	We are moderately confident in the effect estimate, but there is a possibility it is substantially different.
Low quality	Our confidence in the effect estimate is limited. The true effect may be substantially different.
Very low quality	We have little confidence in the effect estimate.

We graded the strength of the recommendations in this section of the guideline based on the above, using expert consensus groups (see Appendix 1). Uncertainty about or variability in patient values and preferences, also part of the GRADE process, were considered. We did not specifically consider treatment cost. The quality of evidence for or against the use of a drug was placed into one of four categories: high, moderate, low, and very low.⁵ Importantly, these categories were used to classify the body of evidence related to a medication rather than individual research studies or clinical trials. Definitions for the categories used for evidence quality are given in Table 1.

The GRADE system was chosen to classify the recommendations in this guideline because it appeared to allow for the best characterization of a recommendation, given that drug efficacy, drug side effects, and the degree of evidence available in the literature were all considered in grading a recommendation. There is some evidence that it is among the best recommendation grading system in terms of influencing the decisions of clinicians.⁶

GRADE recommendations are made in two categories. A strong recommendation means that the intervention could be used for most patients, and that the benefits of therapy outweigh the potential risks. A weak recommendation indicates that the intervention could still be applied to a majority of patients, but it would not be appropriate for many. With a weak recommendation, the balance between risks and benefits is closer or more uncertain. In other words, whether the intervention is suitable for a patient depends a great deal on the clinical situation and the nature of the patient. For this reason, weak recommendations are sometimes called “conditional” recommendations, as whether they are appropriate depends (or is conditional) on the details of the clinical situation much more so than for a strong recommendation.⁷ The quality of evidence supporting the recommendation indicates how much confidence we have in that recommendation. The meaning of the various recommendation categories and their clinical implications are given in Table 2.^{4,5,7} As shown in Table 2, it is important to recognize that the recommendations as formulated in GRADE are somewhat dichotomous. If the benefits clearly outweigh the risks and burdens, a medication gets a strong recommendation, even though the evidence that the drug is effective may not be strong. Thus, for a drug with very few side effects, it is possible to have a strong recommendation coupled with low quality evidence (i.e., “Strong – low quality evidence”).

ACUTE THERAPIES: EVIDENCE FOR EFFICACY

Migraine-Specific and Non-Specific Agents

In 2002, a quantitative systematic review/meta-analysis (54 trials) of pharmacological treatments (triptans, dihydroergotamine, ASA plus metoclopramide) for acute migraine concluded that most interventions are effective. However, this review did not include NSAIDs or acetaminophen. Numbers-needed-to treat (NNTs) were calculated. For headache relief at 2 hours (h), NNTs ranged from 2.0 for subcutaneous

Table 2: Recommendation grades: meaning and clinical implications*

Recommendation Grade	Benefit versus Risks	Clinical Implications
Strong – high quality evidence	Benefits clearly outweigh risks and burden for most patients	Can apply to most patients in most circumstances
Strong – moderate quality evidence	Benefits clearly outweigh risks and burden for most patients	Can apply to most patients, but there is a chance the recommendations may change with more research
Strong – low quality evidence	Benefits clearly outweigh risks and burden for most patients	Can apply to most patients, but there is a good chance the recommendations could change with more research
Weak – high quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances
Weak – moderate quality evidence	Benefits are more closely balanced with risks and burdens for many patients	Whether a medication is used will depend upon patient circumstances, but there is less certainty about when it should be used
Weak – low quality evidence	Benefits are more closely balanced with risks and burdens	There is considerable uncertainty about when to use this medication

*Only categories used in this guideline are shown

sumatriptan 6 mg (most effective) to 5.4 for naratriptan 2.5 mg (least effective). For pain-free endpoint at 2 h, NNTs ranged from 2.0 for subcutaneous sumatriptan 6 mg (most effective) to 8.6 for ASA 900 mg plus metoclopramide 10 mg (least effective). For sustained relief endpoint over 24 hours (headache response at 2 h and no recurrence within 24 h), NNTs ranged from 2.8 for eletriptan 80 mg (most effective; not an approved dose in Canada) to 8.3 for rizatriptan 5 mg (least effective).⁸

1. MIGRAINE-SPECIFIC AGENTS

Triptans (selective serotonin 5-HT_{1B/1D} receptor agonists)

Overview

The triptans are serotonin (5HT) agonists that are relatively specific for the 5HT_{1B} and 5HT_{1D} receptors. Because of this specificity, they offer relatively good migraine relief for many patients, with fewer side effects than the older ergot derivatives. There are currently seven triptans available in Canada: almotriptan (oral tablet), eletriptan (oral tablet), frovatriptan (oral tablet), naratriptan (oral tablet), rizatriptan (oral tablet, orally disintegrating tablet), sumatriptan (subcutaneous injection, oral tablet, fast-disintegrating oral tablet, nasal spray), and zolmitriptan (oral tablet, orally disintegrating tablet, nasal spray). Triptans are vasoconstrictors and therefore, are contraindicated in patients with coronary and cerebrovascular disease, but have proven remarkably safe in patients without vascular disease.⁹⁻¹¹ There has also been concern about serotonin syndrome, particularly when the triptans are used in association with other drugs that enhance serotonergic activity, but clinical experience indicates that serotonin syndrome must be extremely rare with triptan use, even in the presence of concomitant selective serotonin reuptake inhibitor (SSRI) use.^{12,13} Section 3 of the guideline discusses all these issues in more detail. A disadvantage of triptans is their relatively high cost compared to other acute therapies; however, generic versions of triptans are now available at a slightly lower cost.

There is no single, randomized, controlled trial comparing all of the triptans with each other. Most trials compare a triptan to placebo, and head-to-head trials usually compare sumatriptan with one other triptan. Therefore, meta-analyses and comprehensive reviews (e.g., Cochrane Database) must be used to compare efficacy among triptans.⁹

Meta-analyses/systematic reviews of triptans

A meta-analysis of 53 randomized, double-blind, controlled (placebo or active comparator) trials in adults published in 2002 concluded that all oral triptans are effective and well tolerated.¹⁴ This meta-analysis included published studies, as well as “raw patient data” provided by pharmaceutical companies. Rizatriptan 10 mg, eletriptan 80 mg (not an approved dose in Canada), and almotriptan 12.5 mg provided the highest likelihood of consistent success over multiple attacks (inpatient consistency; headache response and pain-free at 2h); however, sumatriptan featured the longest clinical experience and widest range of formulations. Rizatriptan 10 mg was superior to sumatriptan 100 mg in terms of efficacy (sustained pain freedom at 24 h) and consistency. Eletriptan 80 mg was superior to sumatriptan 100 mg in terms of efficacy (pain relief at 2 h and sustained pain freedom at 24 h) but was associated

with lower tolerability. Almotriptan 12.5 mg showed better sustained pain freedom compared to sumatriptan 100 mg, combined with good tolerability.^{14,15}

A systematic review of double-blind, randomized, clinical trials of oral triptans reporting data after a single migraine attack was published in 2007; this analysis did not include raw data submitted by pharmaceutical companies, only published trials.¹⁶ The main objective was to compare the efficacy and tolerability of seven currently marketed oral, non-re-encapsulated triptan formulations (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) versus placebo for the treatment of moderate-to-severe migraine attacks. Out of 221 publications reviewed, 38 studies were included in the analysis. All of the triptans provided significant relief (i.e., headache response) and/or absence of pain at 2 h (i.e., pain-free), as well as relief of pain (i.e., headache response) at 1 h, when compared with placebo. After 30 minutes, rizatriptan 10 mg (regular and orally disintegrating tablets), sumatriptan 50 and 100 mg (fast dissolving tablets), and sumatriptan 50 mg (regular tablets) showed significant headache response compared to placebo; fast-dissolving sumatriptan 100 mg was the only oral triptan that was superior to placebo for the pain-free endpoint at 30 minutes. Eletriptan 40 mg and fast-dissolving sumatriptan 50 mg and 100 mg showed a lower rate of recurrence than placebo at 24 hours, whereas rizatriptan 10 mg tablets showed a greater rate of recurrence than placebo.

Another systematic review was undertaken to consolidate evidence concerning safety and efficacy of triptans available in Canada at the time of publication in 2001 (sumatriptan, rizatriptan, naratriptan, zolmitriptan), and to provide guidelines for selection of a triptan.¹⁷ Data from published, randomized, placebo-controlled trials were pooled. A combined number need to treat (NNT) and number needed to harm (NNH) was generated for each triptan. The lowest NNT (highest efficacy) for headache response/pain-free at 2 h was observed with subcutaneous sumatriptan. Among the oral triptans, the lowest NNT was observed with rizatriptan (highest efficacy), and the highest NNT with naratriptan (lowest efficacy). The lowest NNH (i.e., most harm) was seen with subcutaneous sumatriptan. Rizatriptan appeared to provide earlier and better relief of migraine-associated nausea than the other oral triptans (i.e., naratriptan, sumatriptan, zolmitriptan). The authors concluded that all of the currently available triptans are effective symptomatic medications for acute migraine attacks. Sumatriptan had the most extensive data supporting its efficacy, tolerability, and safety; however, the newer triptans have some advantages over sumatriptan. Although there are differences among the triptans, they appear to be relatively small.¹⁷

Individual triptan meta-analyses (see Table 3)

Individual meta-analyses have been published for the following triptans: sumatriptan (oral, subcutaneous, intranasal), naratriptan, frovatriptan, almotriptan, and zolmitriptan.

Triptans versus triptans (see Table 4)

There are relatively few randomized, controlled, head-to-head trials comparing triptans to each other. Most head-to-head trials compare oral sumatriptan to one of the other triptans, and have utilized the 2-h headache response as a primary efficacy

measure (2 h pain-free response is a preferred endpoint in clinical trials).⁹

Although all seven triptans available in Canada show significant efficacy and good tolerability, and the differences between them are relatively small, head-to-head trials do support the presence of some differences. Unfortunately, comparison trials do not exist for all the triptans, and there are concerns that the results of some of them may have been affected by encapsulation. Based on available trials, it is possible to draw some conclusions, recognizing that the response of the individual patient to a specific triptan cannot be predicted, and as has often been said, the differences among patients appear greater than the differences among the triptans themselves. Rizatriptan (10 mg) does tend to provide faster headache relief compared to a number of other oral triptans, and better relief of nausea than sumatriptan. Eletriptan (40 mg) may show a greater sustained 24 hour response rate than sumatriptan, due at least in part to a relatively low headache recurrence rate. Almotriptan (12.5 mg) tends to show a lower adverse event rate than some other triptans (zolmitriptan and sumatriptan). Naratriptan and frovatriptan tend to have a slower onset of action and, therefore, a lower response rate at early time points after treatment, although in the direct comparison trials (see Table 4), frovatriptan (2.5 mg) appears to show similar efficacy at 2 h compared to several other triptans. These studies were relatively small with limited power to detect differences, however, and should therefore be interpreted with caution.

Triptans versus ASA and NSAIDs (see Table 5)

Overall, results of comparative trials have indicated that NSAIDs are generally as effective as triptans (see Acetylsalicylic acid and NSAIDs sections). However, experience in clinical practice suggests that oral triptans are superior to non-specific acute treatments in many patients (see “Triptans versus non-triptans: summary”).

Triptans versus ergot derivatives

Triptans have shown superior efficacy over ergotamine/caffeine in acute migraine (see Ergotamine section).

Triptans versus non-triptans – summary

There are relatively few randomized, controlled trials comparing triptans to other classes of acute migraine medications. Most of the trials compared sumatriptan to other drugs. In many of the trials, differences between triptans and other acute migraine medications on primary endpoints were not dramatic. In a review of published trials comparing oral triptans with non-triptans in 2004, Lipton et al found that data suggested a significantly greater benefit with triptans than ergotamine, but no significant difference between triptans and NSAIDs or other analgesics.¹⁸

However, experience in clinical practice suggests that oral triptans are superior to non-specific acute treatments in many patients. Thus, there appears to be a discrepancy between clinical trial results and clinical experience. Several explanations have been proposed for this discrepancy: statistically significant differences may not have been noted due to lack of adequate statistical power in clinical trials; patient selection, whereby

patients treated with triptans in clinical practice may be relatively more responsive to triptans and less responsive to other agents than patients participating in clinical trials; headache response at 2 h, an endpoint in many clinical trials, may not fully capture the benefits of triptans relative to other agents, as assessed in clinical practice; waiting until pain is moderate or severe, as required in most clinical trials, may disadvantage triptans relative to comparators, whereas early treatment during mild pain may increase the benefit of triptans versus other classes of drugs.¹⁸

Triptans combined with NSAIDs

Since multiple peripheral and central neural mechanisms may be involved in migraine pathophysiology, drug combinations may potentially achieve better response rates than single drugs. A few studies have evaluated the efficacy of triptans combined with NSAIDs.

A multicentre, randomized, double-blind, double-dummy, placebo-controlled, four-arm study (n=972) evaluated the efficacy and tolerability of the combination of oral sumatriptan 50 mg (encapsulated) and naproxen sodium 500 mg (as two separate tablets).¹⁹ Patients treated a single moderate or severe migraine attack with placebo, naproxen sodium 500 mg, sumatriptan 50 mg, or a combination of sumatriptan 50 mg and naproxen sodium 500 mg; in the latter two treatment arms, sumatriptan tablets were encapsulated in order to achieve blinding of the study. The primary endpoint was 24-h “sustained pain response” (pain no greater than mild at 2 h post-dose, taking no rescue medications for 24 h post-dose, and having no recurrence of moderate or severe pain within 24 h of the initial dose). In the sumatriptan plus naproxen sodium group, 46% of subjects achieved a 24-h sustained pain response, which was significantly more effective than sumatriptan alone (29%), naproxen sodium alone (25%), or placebo (17%; p<0.001). There was no significant increase in the incidence of adverse effects with the combination compared to monotherapy with sumatriptan. Encapsulation of sumatriptan for blinding purposes may have altered its pharmacokinetic profile and thereby, possibly decreased efficacy responses.¹⁹

The superiority of fixed-combination sumatriptan/naproxen sodium (85/500 mg; not currently available in Canada) vs. sumatriptan 85 mg (monotherapy) or naproxen sodium 500 mg (monotherapy) was demonstrated in a publication reporting the results of two identically designed randomized, placebo-controlled trials (n=3413).²⁰ In both studies, the fixed-combination resulted in a significantly higher 2-h headache relief rate (defined as pain reduction from moderate or severe to mild or no pain) than sumatriptan monotherapy (65% vs. 55%, respectively, p=0.009 in study 1; 57% vs. 50%, p=0.02 in study 2).

Two replicate, multicentre, randomized, double-blind, placebo-controlled, 2-attack, crossover trials (n=144, study 1; n=139, study 2) evaluated the efficacy of a fixed-dose formulation of sumatriptan 85 mg and naproxen sodium 500 mg (vs. placebo) in migraineurs who had discontinued treatment with a short-acting triptan in the past year because of poor response or intolerance (note: fixed-dose formulation is not available in Canada).²¹ Patients had discontinued an average of 3.3 triptans before study entry. Patients were instructed to treat

Table 3: Individual triptan meta-analyses [part 1] 45,83-88

Drug & route (publication date); number of trials included; number of participants (n); types of participants	Objective	Efficacy outcomes and main results	Conclusions and limitations
<p>Sumatriptan oral (2012)⁸⁵</p> <p>61 RCTs (24 vs. placebo only; 13 vs. active comparator only; 24 vs. placebo & active comparator) n=37,250</p> <p>Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed</p>	<p>To determine efficacy & tolerability of oral sumatriptan vs. placebo & other active interventions in treatment of acute migraine attacks in adults</p>	<p>Primary efficacy outcomes: pain-free at 1 h & 2 h (no rescue medication); headache relief at 1 h & 2 h; sustained pain-free during 24 h post-dose (pain-free at 2 h & no use of rescue medication or recurrence of moderate to severe pain within 24 h); sustained headache relief during 24 h post-dose (headache relief at 2 h, sustained for 24 h, with no use of rescue medication or second dose of study medication)</p> <p>Direct comparisons with other active treatments: other triptans, acetaminophen, ASA, NSAIDs, & ergotamine combinations</p> <p>Main results: For sumatriptan 50 mg vs. placebo: Pain-free at 2 h: 28% vs. 11% (NNT=6.1) Headache relief at 2 h: 57% vs. 32% (NNT=4.0) Sustained pain-free (24 h): 17% vs. 7% (NNT = 9.5)</p> <p>For sumatriptan 100 mg vs. placebo: Pain-free at 2 h: 32% vs. 11% (NNT=4.7) Headache relief at 2 h: 61% vs. 32% (NNT=3.5) Sustained pain-free (24 h): 24% vs. 8% (NNT=6.5)</p> <p>For sumatriptan 50 mg vs. effervescent ASA 1,000 mg: Pain-free at 2 h: 32% vs. 26% (NS)</p> <p>For sumatriptan 100 mg vs. ASA 900 mg + metoclopramide 10 mg: Pain-free at 2 h: 26% vs. 16%; NNT=10 in favour of sumatriptan</p> <p>For sumatriptan 50 mg vs. rizatriptan 10 mg: Pain-free at 2h: 35% vs. 39% (NS)</p> <p>For sumatriptan 100 mg vs. rizatriptan 10 mg: Pain-free at 2 h: 31% vs. 37%; NNT=16 in favour of rizatriptan</p> <p>For sumatriptan 50 mg vs. eletriptan 40 mg: Pain-free at 2 h: 18% vs. 24%; NNT=16 in favour of eletriptan</p> <p>For sumatriptan 100 mg vs. eletriptan 40 mg: Pain-free at 2 h: 24% vs. 32%; NNT=12 in favour of eletriptan</p> <p>For sumatriptan 100 mg vs. almotriptan 12.5 mg: Pain-free at 2 h: 33% vs. 28% (NS)</p>	<p>Oral sumatriptan is effective as an abortive treatment for acute migraine attacks, relieving pain, nausea, photophobia, phonophobia, & functional disability but is associated with increased AEs vs. placebo.</p> <p>Results for 25 mg dose were similar to 50 mg dose, while 100 mg dose was significantly better than 50 mg for pain-free and headache relief at 2 h.</p> <p>Data support general guideline to use 50 mg as starting dose, with increases to 100 mg, if necessary & tolerated (some patients may find a 25 mg dose is sufficient).</p> <p>Treating early, during mild pain phase, gave significantly better NNTs for pain-free at 2 h and sustained pain-free at 24 h than did treating established attacks with moderate or severe pain intensity.</p> <p>AEs: mostly mild to moderate severity, self-limiting; clear dose response relationship (25 mg to 100 mg); serious AEs uncommon</p> <p>Limitations: most studies industry-sponsored using brand name; no generic sumatriptan trials found; limited data on sustained pain relief or pain-free (24 or 48 h); more early intervention studies needed</p>
<p>Sumatriptan subcutaneous (SC) (2012)⁸³</p> <p>35 RCTs (28 vs. placebo; 3 vs. active comparator only; 4 vs. placebo & active comparator) n=9365</p> <p>Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed</p>	<p>To determine efficacy & tolerability of SC sumatriptan vs. placebo and other active interventions in treatment of acute migraine attacks in adults</p>	<p>Primary efficacy outcomes: pain-free at 1 h & 2 h (no rescue medication); headache relief at 1 h & 2 h; sustained pain-free during 24 h post-dose (pain-free at 2 h & no use of rescue medication or recurrence of moderate to severe pain within 24 h); sustained headache relief during 24 h post-dose (headache relief at 2 h, sustained for 24 h, with no use of rescue medication or second dose of study medication)</p> <p>Main results: For sumatriptan 6 mg SC vs. placebo: Pain-free at 1 h: 41% vs. 7% (NNT=2.9) Pain-free at 2 h: 59% vs. 15% (NNT=2.3) Headache relief at 1 h: 71% vs. 26% (NNT=2.2) Headache relief at 2 h: 79% vs. 31% (NNT=2.1) Sustained pain-free (24 h): 31% vs. 15% (NNT=6.1)</p> <p>Sumatriptan SC vs. active comparators [SC naratriptan (not available in Canada); IV ASA (not available in Canada); oral effervescent ASA + metoclopramide; IN & SC DHE] – insufficient data for a pooled analysis</p> <p>AEs: mostly mild to moderate, self-limiting; serious AEs (overall) = 0.25%; for sumatriptan 6 mg vs. placebo: NNH=4.9</p>	<p>SC sumatriptan is an effective abortive treatment for acute migraine attacks, quickly relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased AEs vs. placebo.</p> <p>Most data is for 6 mg dose; data suggest a 4 mg dose (where available) may be a sensible starting dose, with increase to 6 mg, if response is inadequate & higher dose is tolerated.</p> <p>No evidence that taking second dose of sumatriptan 6 mg in event of inadequate response 1 h after initial dose has significant impact on headache relief by 2 h.</p> <p>AEs: mostly mild to moderate & short duration; serious AEs uncommon</p> <p>Limitations: only 5 studies provided 24 h sustained efficacy data; no early intervention studies when pain is mild</p>
<p>Sumatriptan intranasal (IN) (2012)⁸⁴</p> <p>12 RCTs (10 vs. placebo only; 2 vs. active comparators) n=4755</p> <p>Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed</p>	<p>To determine efficacy & tolerability of IN sumatriptan compared to placebo & other active interventions in the treatment of acute migraine attacks in adults</p>	<p>Primary efficacy outcomes: pain-free at 1 h & 2 h (no rescue medication); headache relief at 1 h & 2 h; sustained pain-free during 24 h post-dose (pain-free at 2 h & no use of rescue medication or recurrence of moderate to severe pain within 24 h); sustained headache relief during 24 h post-dose (headache relief at 2 h, sustained for 24 h, with no use of rescue medication or second dose of study medication)</p> <p>Main results: Sumatriptan 20 mg vs. placebo: Pain-free at 2 h: 32% vs. 11% (NNT=4.7) Headache relief at 1 h: 46% vs. 25% (NNT=4.9) Headache relief at 2 h: 61% vs. 32% (NNT=3.5)</p> <p>Active comparators (2 trials): sumatriptan 20 mg IN vs. DHE 1 mg: no usable data; sumatriptan 20 mg IN vs. rizatriptan (ODT) 10 mg: rizatriptan had higher % headache relief at 2 h (71% vs. 65%) & relief of associated symptoms at 2 h</p> <p>AEs: mild to moderate severity, self-limiting; serious AEs uncommon; taste disturbance significantly higher incidence for sumatriptan IN 10/20 mg vs. placebo (22-30% vs. 1%; NNH=3.5 & 4.8, respectively)</p>	<p>IN sumatriptan is effective as an abortive treatment for acute migraine attacks, relieving pain, nausea, photophobia, phonophobia, & functional disability, with single doses of 10 mg or more providing clinically useful levels of relief, but is associated with increased AEs vs. placebo.</p> <p>Data suggest that a 10 mg dose may be a sensible starting dose (depending on availability; 5-mg and 20-mg strengths are available in Canada), with increase to 20 mg, if there is an inadequate response.</p> <p>AEs: increased vs. placebo; most AEs mild & of short duration.</p> <p>Limitations: insufficient evidence to address several important primary & secondary outcomes (e.g., 24 h sustained efficacy; 1 h pain-free); lack of early interventions studies when pain is mild</p>

Table 3: Individual triptan meta-analyses [part 2] continued

<p>Zolmitriptan oral, intranasal (2008)⁸⁵</p> <p>24 RCTs; n=15,408 (ages 12-65)</p> <p>Types of participants: adults (18-65 years) and/or adolescents (12-17 years); IHS criteria for migraine diagnosis</p>	<p>To assess relative efficacy and tolerability of different formulations of zolmitriptan compared with placebo, active comparators, or different dosage forms of zolmitriptan in acute migraine attacks</p>	<p>Efficacy outcomes*: % of pts with: (1) headache relief at 1 h and 2 h post-dose; (2) pain-free at 1 h and 2 h post-dose; (3) sustained pain-free response over 24 h post-dose; primary outcomes: headache relief and pain-free responses at 2 h post-dose</p> <p>Results: All 3 formulations of zolmitriptan were significantly more effective vs. placebo for all efficacy outcomes.</p> <p>For 2-h pain free rates: zolmitriptan 2.5 mg tablet was as effective as almotriptan 12.5 mg, eletriptan 40 mg, sumatriptan 50 & 100 mg, and more effective than naratriptan 2.5 mg.</p> <p>Zolmitriptan 5 mg nasal spray had faster onset of action and greater efficacy vs. zolmitriptan 2.5 mg tablet.</p> <p>Zolmitriptan 2.5 mg had lower risks of AEs than eletriptan 80 mg, but higher risks than naratriptan 2.5 mg or rizatriptan 10 mg.</p>	<p>Zolmitriptan is an effective treatment for acute migraine attacks. For pain-free at 2 h, zolmitriptan 2.5 mg tablet showed similar efficacy to almotriptan 12.5 mg, eletriptan 40 mg, and sumatriptan 50 mg, and greater efficacy vs. naratriptan 2.5 mg.</p> <p>Zolmitriptan 2.5 mg showed similar efficacy to rizatriptan 10 mg for headache relief and pain-free response, but was less effective for sustained pain-free response.</p> <p>Nasal spray (5 mg) had faster onset of action and greater efficacy vs. zolmitriptan 2.5 mg oral tablet.</p>
<p>Naratriptan oral (2004)⁸⁶</p> <p>10 RCTs (9 DB) n=4499 (ages 18-65)</p> <p>Types of participants: adults (18-65 years); IHS criteria for migraine diagnosis</p>	<p>To evaluate comparative efficacy and tolerability of naratriptan in acute migraine attacks</p>	<p>Efficacy outcomes**: (1) headache relief at 2 h and 4 h post-dose; (2) pain-free at 2 h and 4 h post-dose; (3) sustained relief over 24 h</p> <p>Results: Pooled RRs vs. placebo for pain-free response at 2 h and 4 h for naratriptan 2.5 mg: 2.52 (95% CI: 1.78-3.57), and 2.58 (95% CI: 1.99-3.35).</p> <p>Naratriptan 2.5 mg more effective vs. naratriptan 1 mg: RRs for pain-free response at 2 h and 4 h were 1.64 (95% CI: 1.28-1.86), and 1.35 (95% CI: 1.20-1.51).</p> <p>Naratriptan 2.5 mg less effective in pain-free response vs. rizatriptan 10 mg at 4 h (RR: 0.68; 95% CI: 0.55-0.85) or sumatriptan 100 mg at 4 h (RR: 0.79; 95% CI: 0.79; 95% CI: 0.67-0.93).</p> <p>Significantly fewer pts had AEs with naratriptan 2.5 mg vs. rizatriptan 10 mg (RR: 0.73; 95% CI: 0.56-0.97) or sumatriptan 100 mg (RR: 0.68; 95% CI: 0.55-0.86).</p>	<p>Naratriptan is effective and well-tolerated for acute migraine attacks; 2.5 mg dose is significantly more effective vs. 1 mg dose.</p> <p>Rizatriptan 10 mg and sumatriptan 100 mg are superior to naratriptan for headache relief.</p> <p>Zolmitriptan 2.5 mg is comparable in efficacy to naratriptan 2.5 mg (note: this was based on one trial, which was stopped early due to supply problems).</p> <p>Naratriptan is associated with lower incidence of AEs vs. rizatriptan, sumatriptan, and zolmitriptan; overall rate of AEs for naratriptan is similar to placebo.</p>
<p>Frovatriptan oral (2005)⁸⁷</p> <p>5 RCTs n=2866</p> <p>Types of participants: moderate or severe migraine attacks</p>	<p>To evaluate efficacy and tolerability of frovatriptan in acute migraine</p>	<p>Frovatriptan 2.5 mg more effective vs. placebo for pain-free (RR 3.70; 95% CI: 2.59-5.29; $p<0.0001$ at 2 h, and 2.67; 95% CI: 2.21-3.22, $p<0.0001$ at 4 h).</p> <p>Frovatriptan also superior to placebo in reducing headache severity: pooled RR 1.66 at 2 h (95% CI: 1.48-1.88; $p<0.0001$), and 1.83 at 4 h (95% CI: 1.66-2.00; $p<0.0001$).</p> <p>Risk of headache recurrence reduced by 26% with frovatriptan vs. placebo (RR 0.74; 95% CI: 0.59-0.93; $p=0.009$).</p> <p>Frovatriptan also superior vs. placebo in improving symptoms associated with migraine (nausea, photophobia, phonophobia).</p> <p>Frovatriptan caused more AEs vs. placebo (RR 1.31; 95% CI: 1.07-1.62; $p=0.01$).</p>	<p>Frovatriptan is more effective but may cause more AEs than placebo in acute moderate to severe migraine.</p>
<p>Almotriptan oral (2007)⁸⁸</p> <p>8 RCTs n=4995</p> <p>Types of participants: adults; IHS criteria for migraine diagnosis</p>	<p>To evaluate comparative efficacy and safety of almotriptan in acute migraine attacks</p>	<p>Almotriptan 12.5 mg significantly more effective vs. placebo for all efficacy outcomes (RRs ranged from 1.47 to 2.15; ARDs ranged from 0.01 to 0.28); no significant differences in any safety outcomes.</p> <p>No significant differences in efficacy outcomes comparing almotriptan 12.5 mg vs. sumatriptan 100 mg & vs. zolmitriptan 2.5 mg.</p> <p>Almotriptan 12.5 mg associated with significantly fewer AEs vs. sumatriptan 100 mg (RR: 0.39; 95% CI: 0.23, 0.67); however, no significant differences between almotriptan and sumatriptan for clinically important AEs (e.g., dizziness, somnolence, asthenia, chest tightness).</p>	<p>Almotriptan 12.5 mg is an effective treatment for acute migraine attacks; found to be as effective as sumatriptan 100 mg & zolmitriptan 2.5 mg for 2-h headache relief and pain-free</p> <p>Risk of AEs for almotriptan 12.5 mg was similar to placebo & significantly lower than sumatriptan 100 mg.</p>

*Headache relief defined as decrease from initial moderate or severe headache to mild or none; pain-free response defined as reduction in headache severity from mild, moderate, or severe to no pain; sustained pain-free response defined as pain-free at 2 h post-dose, no pain from 2 to 24 h as well as use of no rescue medication or a second dose of study drug. **Headache relief defined as decrease from initial moderate or severe headache to none or mild at 2 and 4 h post-dose; pain-free defined as headache reduced from moderate or severe to none at 2 and 4 h post-dose; sustained relief over 24 h defined as headache relief at 4 h post-dose, maintained for 24 h after treatment (i.e., pain did not return to moderate or severe), with no use of rescue medication or a second dose of study medication. RCTs = randomized; controlled trials; IHS = International Headache Society; CI = confidence interval; AEs = adverse events; ODT = orally disintegrating tablet; RR (risk ratio) for efficacy = proportion of patients achieving outcome in treatment group relative to control group; CI = confidence interval; RR for AEs = relative risk; RRs = pooled rate ratios; ARDs = absolute rate differences; NNT = number-needed-to-treat; NNH = number-needed-to-harm; NS = not significant

within one hour, while pain was mild. Sumatriptan/naproxen was superior ($p<0.001$) to placebo for 2- through 24-h sustained pain-free response (primary endpoint) (study 1: 26% vs. 8%; study 2: 31% vs. 8%), and for pain-free response at 2 h (study 1: 40% vs. 17%; study 2: 44% vs. 14%). Sumatriptan/naproxen was generally well tolerated.

Triptan non-responders (switching triptans)

Oral triptan therapy does not provide headache relief in approximately one-third of patients.¹⁴ Since response to a single triptan is not predictable in an individual patient, it may be useful to test a range of different triptans in an individual, in order to select the “ideal triptan” in terms of effectiveness and tolerability

for that patient. Evidence from clinical trials indicates that patients with a poor response to one triptan can benefit from subsequent treatment with a different triptan.²²⁻²⁶ When switching to another triptan, it is generally recommended (according to Product Monographs) to wait 24 hours before using a different triptan.

A multiple attack study evaluated the efficacy and tolerability of five triptans commercially available in Italy (zolmitriptan 2.5 mg, rizatriptan 10 mg, sumatriptan 100 mg, almotriptan 12.5 mg, and eletriptan 40 mg); 30 patients completed the study.²² For a total of 30 attacks, patients used a different triptan or placebo for every five consecutive attacks. Different sequences of the five triptans and of the placebo were used. The primary endpoints evaluated were: headache response at 2 h, pain-free at 2 h, and sustained pain-free (at 24 h); intra-patient consistency (percentage of patients obtaining relief in one or three or five of five consecutively treated attacks), and tolerability. No substantial difference in terms of efficacy of the triptans was noted, and all were well tolerated. Although results of this study are of clinical interest, with the small number of subjects (n=30), this study would have limited power to detect differences among triptans.

A study evaluated the efficacy and tolerability of almotriptan 12.5 mg in migraine patients who responded poorly to oral sumatriptan 50 mg (at least two unsatisfactory responses). Patients treated their first attack with open-label sumatriptan 50 mg. Of the 198 sumatriptan non-responders who treated their second attack (99 almotriptan, 99 placebo), 2-h pain relief rates were significantly higher with almotriptan compared to placebo (47.5 vs. 23.2%, $p<0.001$); a significant difference was also seen in pain-free rates at 2 h (33.3 vs. 14.1%, $p<0.005$). The authors concluded that almotriptan 12.5 mg is an effective and well tolerated alternative for patients who respond poorly to sumatriptan 50 mg.²⁴

In a double-blind, placebo-controlled, parallel group, multicentre study, the tolerability and efficacy of eletriptan was studied in patients (n=446) who had discontinued oral sumatriptan due to lack of efficacy or intolerable adverse events. Patients were randomized to eletriptan 40 mg (E40) or 80 mg (E80), or placebo for treatment of up to three migraine attacks. Two-hour response rates (first-dose, first-attack data) were 59% for eletriptan 40 mg, 70% for eletriptan 80 mg, and 30% for placebo ($p<0.0001$ for both doses of eletriptan vs. placebo; $p<0.05$ for E80 vs. E40). Onset of action was rapid, with 1-h headache response rates significantly superior for E40 and E80 compared to placebo. Both E40 and E80 demonstrated significant consistency of response compared to placebo in at least two of three attacks. Adverse events were mild to moderate in severity and dose-related. The authors concluded that eletriptan (40 mg or 80 mg) produced an effective response in patients who had previously discontinued treatment with sumatriptan.²⁵

In a randomized, double-blind, placebo-controlled study of naratriptan in 347 migraine sufferers non-responsive to sumatriptan (self-described), patients' poor response was confirmed by a single-blind assessment with sumatriptan 50 mg for the treatment of one moderate to severe migraine attack. Patients confirmed as non-responsive (no pain relief at 4 h; non-response confirmed in 63.4% of patients) were randomized to

naratriptan 2.5 mg or placebo for treatment of the next migraine attack. Naratriptan was found to be statistically superior to placebo for relief of headache pain at 4 h (41% vs. 19%; $p<0.001$), and superior to placebo for pain-free at 4 h (22% vs. 10%; $p=0.005$).²⁶

Although the above trials indicate that for patients responding poorly to a given triptan, another triptan is able to show efficacy superior to placebo, none of the trials included the original triptan in blinded fashion for comparison in the placebo-controlled portion of the trial. It is therefore impossible to determine from this data whether, had the original triptan been included in the trial, the second triptan would have been superior to it. Nevertheless, the data available does suggest, as does clinical experience, that many patients benefit from switching triptans if the response to the first triptan is not optimal.

Early intervention

There is considerable evidence from prospective, randomized, controlled trials of triptans that early intervention when pain is still mild results in higher pain-free and sustained pain-free rates, and more rapid return to normal functioning. Placebo-controlled early intervention trials have been done with zolmitriptan (2.5 mg), frovatriptan (2.5 mg), sumatriptan (50 and 100 mg), eletriptan (20 and 40 mg), sumatriptan fast disintegrating tablets (50 and 100 mg), and rizatriptan (10 mg) (see Table 6).²⁷⁻³³ These early intervention trials generally produced higher 2-h pain-free rates than clinical trials in which the headache was not treated until it had become of moderate or severe intensity. In the early treatment studies, methodologies differed from trial to trial, so that they cannot all be directly compared. However, very high 2-h pain-free rates were reported for many trials, including: 57% for zolmitriptan 2.5 mg when patients were treated within 15 minutes of headache onset, 57% for sumatriptan 100 mg, 47% for eletriptan 40 mg, 59% for rizatriptan 10 mg, and 66% for the sumatriptan 100 mg fast disintegrating tablet. These 2-h pain-free rates cannot be directly compared, not only because of differing trial methodologies, but also because the trials had different placebo pain-free rates. Please consult Table 6 for more details.

It is of interest, that early treatment also appears to result in higher 24-h sustained pain-free rates, which were reported for example at 48% for rizatriptan 10 mg.³² Whether or not treatment during the migraine aura phase is advisable is discussed in Section 3.

Headache recurrence

Return of headache within 24 hours after initial treatment success (i.e., recurrence) occurs in approximately one-third of triptan-treated attacks.³⁴ In case of headache recurrence, a second dose of triptan may be taken after an appropriate time interval (i.e., 2 h for most triptans, except 4 h for frovatriptan and naratriptan; the product monograph limits eletriptan 40 mg to one dose per day in Canada, although in some other countries the 80 mg dose is also available; see Section 3 of guideline).

Clinical data derived from 31 triptan, placebo-controlled efficacy trials used in a previous meta-analysis¹⁵ concluded that triptans with longer half-lives and greater 5-HT_{1B} receptor potency had the lowest rate of headache recurrence. Mean

headache recurrence rates were lowest for frovatriptan (17%), eletriptan (24%), and naratriptan (25%).³⁵ However, it is problematic to compare recurrence rates among triptans, as a headache can only recur if it responded to the triptan in the first place.

Recommendations (triptans)

1. **Strong recommendation, high quality evidence:** Triptans (*almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan*) are recommended for the acute treatment of migraine attacks that are likely to become moderate or severe.
2. **Strong recommendation, moderate quality evidence:** If a patient does not respond well to one triptan or tolerates it poorly, other triptans should be tried over time in subsequent attacks. It is recommended that patients wait 24 hours before trying another triptan.
3. **Strong recommendation, high quality evidence:** If migraine response to sumatriptan is inadequate, consider use of naproxen sodium 500 mg to be given simultaneously with the triptan.
4. **Strong recommendation, low quality evidence:** If migraine response to other triptans (other than sumatriptan) is inadequate, consider the addition of an NSAID (e.g., naproxen sodium) to be given simultaneously with the triptan.
5. **Strong recommendation, high quality evidence:** Patients with migraine attacks that are usually moderate or severe in intensity should be advised to take triptans early during their migraine attacks while pain is mild (caution the patient regarding medication overuse headache – see Section 3).

Ergot Derivatives

Overview

The ergot derivatives are older drugs, and clinical trials are generally of poor quality. There are very few randomized, placebo-controlled trials on efficacy of ergot derivatives in acute migraine treatment.³⁶ The ergot derivatives, like the triptans, are vasoconstrictors, and are contraindicated in patients with cardiovascular disease. Because they are less specific than the triptans and affect a greater variety of receptors, they generally have more side effects, such as nausea. The ergot derivatives are divided into dihydroergotamine (DHE), which is available in an injectable and an intranasal formulation, and ergotamine, which is available in oral tablet form only (in combination with caffeine).

a) Dihydroergotamine (DHE)

Evidence Summary

Intranasal (IN): The IN formulation of DHE has shown variable to superior efficacy compared with placebo in acute migraine^{37,38}; however, it was less effective than IN or SC sumatriptan.^{39,40} In a multicentre, randomized, double-blind, double-dummy, crossover study (n=368, treating two attacks), significantly more patients obtained headache relief at 60 minutes after treatment with IN sumatriptan 20 mg (as a single dose in one nostril) than with IN DHE 1 mg (given as one 0.5 mg

spray in each nostril plus optional 0.5 mg in each nostril, 30 min after first dose) (53% vs. 41%; $p<0.001$).³⁹ In a multicentre, randomized, double-blind, double-dummy, crossover study (n=266), SC sumatriptan (6 mg) was significantly better than IN DHE (1 mg plus optional 1 mg) at providing headache relief and resolution of headache at all time points from 15 minutes to 2 hours ($p<0.001$ at all time points); SC sumatriptan had a faster onset of action than IN DHE. Headache relief was achieved and maintained for 24 hours in 54% of sumatriptan-treated patients compared with 39% of DHE IN-treated patients ($p<0.001$). However, more patients reported headache recurrence after treatment with SC sumatriptan (31%) than after IN DHE (17%).⁴⁰

Subcutaneous: In a multicentre, randomized, double-blind clinical trial (n=295), headache relief with SC DHE (1 mg) was similar to that of SC sumatriptan 6 mg (85.5% vs. 83.3% by 4 hours, respectively); DHE had a slower onset of action but fewer headache recurrences compared with sumatriptan (17.7% vs. 45%, respectively; $p\leq 0.001$).⁴¹

Recommendation (dihydroergotamine)

1. **Weak recommendation, moderate quality evidence:** Dihydroergotamine (intranasal or subcutaneous self-injection) may be considered for the acute treatment of moderate or severe migraine attacks.

b) Ergotamine

Overview

Ergotamine use is problematic in migraine because of poor oral absorption, vasoconstrictive side effects, and the frequent occurrence of dose limiting side effects such as nausea, which make it difficult to achieve a therapeutic dose in many patients. However, the cost of ergotamine is much lower than that of triptans, and it may be an option in selected patients who do not respond to triptans or are unable to pay for triptans.

Evidence Summary (comparative studies with triptans)

In a multicentre, randomized, double-blind, double-dummy, parallel-group trial (n=580), oral ergotamine (2 mg plus caffeine 200 mg) was inferior to oral sumatriptan (100 mg dispersible tablet) for 2 h headache relief (48% vs. 66%, respectively; $p<0.001$) and 2 h pain-free (13% vs. 35%, respectively; $p<0.001$).⁴² However, 41% of patients in the sumatriptan group had headache recurrence within 48 hours compared with 30% in the ergotamine/caffeine group ($p=0.009$). In another multicentre, randomized, placebo-controlled, double-blind trial, parallel-group study (n=733), oral ergotamine (2 mg plus caffeine 200 mg) was inferior to oral eletriptan 40 mg and 80 mg for 2-h headache response (33% vs. 54% for eletriptan 40 mg; $p<0.001$) and 2-h pain-free (10% vs. 28% for eletriptan 40 mg vs. 5% for placebo; $p<0.001$).⁴³ In a third trial, almotriptan was more effective than caffeine/ergotamine, with significantly more patients becoming pain-free at 2 h post-dose (21% vs. 14%, respectively; $p<0.05$); 2-h pain-relief rate was 58% vs. 45%, respectively ($p<0.01$).⁴⁴

A meta-analysis of oral sumatriptan concluded that ergotamine (plus caffeine) was significantly less effective than oral sumatriptan.⁴⁵

Recommendations (ergotamine)

1. **Strong recommendation, moderate quality evidence:** Ergotamine should not be used routinely for acute migraine attacks, due to inferior efficacy compared to the triptans, and the potential for more side effects.
2. **Weak recommendation, moderate quality evidence:** Ergotamine may be considered for use in some patients, for example when triptans are not available to the patient or not effective.

2. NON-SPECIFIC AGENTS

Simple Analgesics and NSAIDs

Overview

Over-the-counter (OTC) analgesics are used exclusively for migraine attacks by about 60% of patients. However, most trials of OTC medications have systematically excluded patients with severe disability (e.g., requiring bed rest) during 50% or more of attacks, or vomiting with more than 20% of attacks. When data from 11 adequately designed trials were combined in a systematic review (in 2003), OTC analgesics [e.g., acetaminophen (alone or in combination with caffeine), ASA (alone or in combination with either caffeine and/or acetaminophen), ibuprofen] were more effective than placebo for headache relief within 2 h, and a significant minority of patients achieved pain-free status within 2 h. Up to 76% of patients returned to normal functioning, particularly if their symptoms and disability were mild to moderate. The authors concluded that OTC medications are only indicated in patients with mild to moderate migraine symptoms, and patients who experience disability during most attacks and/or vomiting in more than 20% of attacks are poor candidates for OTC-exclusive therapy.⁴⁶

Various NSAIDs including ibuprofen, naproxen sodium, diclofenac potassium, and others have been studied in acute migraine. There appear to be no significant differences in efficacy among the various NSAIDs; however, there is a lack of head-to-head comparisons. NSAIDs appear to be effective for mild to moderate attacks (and perhaps in severe attacks in some patients); however, they are associated with a risk for gastrointestinal adverse effects, including bleeding. NSAIDs should be avoided in patients with peptic ulceration, history of gastrointestinal bleed, or ASA-induced asthma. Trials with rofecoxib, a COX-2 inhibitor, have also demonstrated efficacy in migraine^{47,48}; however, rofecoxib is no longer available on the market, due to a risk of cardiovascular adverse effects.

a) Acetylsalicylic Acid (ASA)

Evidence Summary

ASA with or without Metoclopramide (see Table 7)

A Cochrane systematic review (2010) of 13 trials comparing ASA (900 or 1,000 mg) alone (pain-free at 2 h: 24% vs. 11% for placebo; NNT=8.1) or in combination with metoclopramide (10 mg) (pain-free at 2 h: 18% vs. 7% for placebo; NNT=8.8), with placebo or other active comparators (mainly sumatriptan 50 or 100 mg) concluded that ASA 1,000 mg is an effective treatment for acute migraine in adults, with efficacy similar to that of sumatriptan 50 mg or 100 mg; the addition of metoclopramide 10 mg improved relief of nausea and vomiting.

Sumatriptan 100 mg was superior to ASA (900 mg) plus metoclopramide (10 mg) for pain-free at 2 h (28% vs. 18%, respectively; relative benefit of ASA + metoclopramide vs. sumatriptan was 0.63, giving an NNT of 9.8). Adverse effects were mainly mild and transient, were slightly more common with ASA than placebo, but less common than with sumatriptan 100 mg. However, further head-to-head studies are needed to establish the efficacy of ASA compared to other triptans and NSAIDs.⁴⁹

Effervescent ASA (see Table 7)

An individual patient data meta-analysis (2007) of three randomized, controlled trials of effervescent ASA (eASA) concluded that eASA 1,000 mg is as effective as sumatriptan 50 mg (pain-free at 2 h: 27.1% vs. 29%, respectively, vs. 15.1% for placebo) for the treatment of acute migraine attacks (including severe attacks), and has a better side effect profile.⁵⁰

Recommendation (ASA)

1. **Strong recommendation, high quality evidence:** ASA (975-1,000 mg tablets or effervescent formulation), given with oral metoclopramide (10 mg) if nausea is present, is recommended for the acute treatment of migraine attacks of all severities.

b) Ibuprofen

Evidence Summary (see Table 7)

A systematic review/meta-analysis (2007) of five trials of low-dose ibuprofen concluded that ibuprofen (200 and 400 mg) is effective in reducing headache intensity and rendering adult patients pain-free at 2 h compared to placebo (NNT for pain-free at 2 h=13 for 200 mg, and =9 for 400 mg); photophobia and phonophobia improved with the 400 mg dose only. Adverse effects were similar for ibuprofen and placebo.⁵¹

A Cochrane systematic review (2010) determined the efficacy and tolerability of ibuprofen alone or in combination with an antiemetic, compared to placebo and other active interventions in the treatment of acute migraine headaches in adults.⁵² Nine studies (4273 participants, 5223 attacks) fulfilled entry criteria, and were included in the analysis; none of the studies combined ibuprofen with a self-administered antiemetic. All studies utilized single doses of medication. For ibuprofen 400 mg versus placebo, NNTs for 2-h pain-free (26% vs. 12%, respectively), 2-h headache relief (57% vs. 25% respectively), and 24-h sustained headache relief (45% vs. 19%, respectively) were 7.2, 3.2 and 4.0, respectively. For ibuprofen 200 mg versus placebo, NNTs for 2-h pain-free (20% vs. 10%, respectively) and 2-h headache relief (52% vs. 37%, respectively) were 9.7 and 6.3, respectively. The 400 mg dose was significantly better for 2-h headache relief than 200 mg. Solubilized formulations of ibuprofen 400 mg (e.g., liquid containing capsules⁵³) were significantly superior to standard tablets for 1-h (but not 2-h) headache relief (NNT=3.9 for solubilized formulations vs. NNT=8.3 for regular tablets for 1-h headache response; p=0.0114). However, there are no studies directly comparing solubilized formulations with standard formulations. The Cochrane review concluded that ibuprofen is an effective treatment for acute migraine headache, providing pain relief in about half of sufferers; however, it only provided

complete relief from pain (approximately 1 in 4 patients taking ibuprofen 400 mg) and associated symptoms in a minority of sufferers. For all efficacy outcomes, NNTs were better with 400 mg than 200 mg (compared to placebo) but the 400 mg dose achieved statistical significance only for headache relief at 2 h. Soluble formulations provided more rapid relief. Adverse effects with ibuprofen were generally mild and transient.

In a randomized, placebo-controlled trial comparing ibuprofen (400 mg) with rizatriptan (10 mg), rizatriptan was superior in 2-h headache relief (73% vs. 53.8%; $p=0.0001$) and in use of rescue medication, but not for 2-h pain-free and 24-h headache relapse.⁵⁴

Recommendation (ibuprofen)

- 1. Strong recommendation, high quality evidence:** *Ibuprofen [400 mg tablet or solubilized (liquid containing capsules) formulation] is recommended for the acute treatment of migraine attacks of all severities.*
- 2. Strong recommendation, moderate quality evidence:** *Ibuprofen (400 mg) in solubilized formulation (liquid containing capsules) is recommended for the acute treatment of migraine attacks of all severities for patients desiring a faster onset of therapeutic effect as compared to the regular ibuprofen tablets.*

c) Naproxen Sodium

Evidence Summary (see Table 7)

A systematic review/meta-analysis (2010) of four trials (one paper reported results of two trials, and was treated as two separate trials) of naproxen sodium concluded that it was more effective than placebo in reducing pain intensity and providing pain-free within 2 h in adults with moderate or severe migraine attacks [pooled risk ratio for headache relief at 2 h = 1.58 ($p<0.00001$), and pain-free at 2 h = 2.22 ($p=0.0002$)].⁵⁵ Three of the studies used 500 mg doses of naproxen sodium, and one study used 825 mg. Pain-free at 2 h was relatively better with naproxen sodium 825 mg than 500 mg (RR 4.26, 95% CI 1.96-9.27 vs. RR 1.83, 95% CI 1.42-2.36), as well as sustained pain-free response (RR 4.44, 95% CI 1.91-10.32 vs. RR 1.55, 95% CI 1.15-2.09). In Europe, 825 mg is the highest recommended dose for acute migraine, whereas lower doses are generally recommended in North America (i.e., 275-550 mg). There was no significant difference in headache recurrence rate between naproxen sodium and placebo. Naproxen sodium generally relieved nausea, photophobia, and phonophobia significantly better than placebo. Adverse events commonly associated with naproxen sodium were nausea, dizziness, dyspepsia, and abdominal pain. The efficacy of naproxen sodium relative to other acute therapies requires head-to-head clinical trials. Naproxen sodium is preferred over naproxen (base) for acute migraine due to its faster onset of action. However, controlled release formulations of naproxen sodium would not be appropriate for acute migraine treatment.

Recommendation (naproxen sodium)

- 1. Strong recommendation, high quality evidence:** *Naproxen sodium in immediate release formulation (500 or 550 mg; up to 825 mg, if needed and tolerated) is*

recommended for the acute treatment of migraine attacks of all severities.

d) Diclofenac Potassium

Overview

Diclofenac sodium is available in Canada only as an enteric-coated or extended-release tablet with a prolonged release of active drug, and is indicated for chronic pain. Because of a slow onset of action, these preparations would not be suitable for the acute treatment of migraine attacks in most patients.⁵⁶ Diclofenac potassium is available as an immediate-release tablet, providing a rapid onset of action for the treatment of acute pain conditions. Diclofenac potassium for oral solution, a novel, water-soluble buffered powder formulation, has been available in other countries, and has been recently approved for use in Canada specifically for the acute treatment of migraine attacks in adults. It has a time to maximum plasma concentration (T_{max}) of approximately 15 minutes, suggesting the potential for a rapid onset of effect.^{57,58}

Evidence Summary

A Cochrane systematic review (2012) included five studies in adults ($n=1356$) comparing oral diclofenac potassium with placebo, and also with sumatriptan in one study (none of the studies combined diclofenac with an antiemetic).⁵⁹ The review concluded that based on limited data, oral diclofenac potassium 50 mg is an effective treatment for acute migraine, reducing moderate to severe pain to no more than mild pain (headache relief) in about 55% (NNT=6.2) of those treated, to no pain (pain-free) at 2 h in approximately 22% (NNT=8.9), and to no pain sustained to 24 h (pain-free at 24 h) in approximately 19% (NNT=9.5). There were insufficient data to evaluate other doses of oral diclofenac (e.g., 100 mg), or to compare different formulations or different dosing regimens. Adverse effects of diclofenac potassium were mostly mild to moderate intensity and self-limiting, and were not significantly different from placebo over the short term. Only one study compared oral diclofenac with an active comparator (oral sumatriptan 100 mg).⁶⁰ This study used a primary efficacy criterion of migraine headache pain recorded on a 100 mm visual analog scale (VAS) 2 h after dosing. Diclofenac potassium was more effective than placebo in reducing headache pain at 2 h ($p<0.001$; 50 mg and 100 mg doses had similar efficacy); no statistically significant difference was found between either dose of diclofenac potassium and sumatriptan 100 mg. Both doses of diclofenac potassium were significantly better than placebo and sumatriptan in reducing nausea at 2 h. Further head-to-head trials are needed to establish the place in therapy for diclofenac potassium relative to alternative acute treatments for migraine.

A multicentre (Europe), randomized, controlled, double-blind, double-dummy, cross-over trial compared single doses of diclofenac potassium 50 mg sachets (powdered formulation for oral solution) and 50 mg tablets with placebo in 328 patients with migraine pain (888 attacks).⁶¹ For the primary endpoint (pain-free at 2 h), 24.7% of patients were pain-free at 2 h post-dose with diclofenac sachets, 18.5% with diclofenac tablets, and 11.7% with placebo. Treatment differences were significant for sachets vs. placebo ($p<0.0001$), tablets vs. placebo ($p=0.004$),

Table 4: Triptans - Randomized, double-blind, comparative trials versus other triptans* [part 1]⁸⁹⁻¹⁰³

Drugs, doses, dosage form	Study design, # pts included in analysis (n), primary endpoints	Results (primary endpoints)	Conclusions/comments
Zolmitriptan 2.5/ 5 mg vs. sumatriptan 25/ 50 mg; oral tablets ⁸⁹	PG, MC; up to 6 attacks treated over 6 months; n=1212 (treated at least 2 attacks) 2-h headache response**	2-h headache response: Z-2.5 mg: 67.1%; Z-5 mg: 64.8% S-25 mg: 59.6%; S-50 mg: 63.8% Z-2.5 mg significantly more effective vs. S-25/50 mg ($p<0.001$); Z-5 mg significantly more effective vs. S-25 mg ($p<0.001$)	Z- 2.5/5 mg at least as effective as S-25/50 mg for all parameters studied; Z- 2.5 mg significantly more effective vs. S-50 mg for 2 h & 4 h headache response; Z-2.5/5 mg significantly more likely to have pain relief over 24 h vs. S (Note: Z-5 mg is not available in Canada)
Zolmitriptan 2.5/5mg vs. sumatriptan 50 mg; oral tablets ⁹⁰	PG, DD, MC; 1:1:1 ratio; up to 6 attacks treated; n=1522 (treated at least 2 attacks) 2-h headache response**	2-h headache response: Z-2.5 mg: 62.9%; Z-5 mg: 65.7%; S-50 mg: 66.6% (NS difference between Z-2.5/5mg vs. S-50 mg)	Similar efficacy for Z-2.5/5 mg vs. S-50 mg; similar rates of meaningful migraine relief (1, 2, or 4 h) & sustained (24 h) pain relief (Note: Z-5mg is not available in Canada)
Rizatriptan 10 mg vs. naratriptan 2.5 mg; oral tablets ⁹¹	PC, MC, single attack; n=522 Time to headache relief within 2 h*	Time to headache relief within 2 h: R superior to N (hazard ratio 1.62, $p<0.001$)	R more effective than N & provided earlier headache relief than N; more patients pain-free at 2 h with R vs. N (44.8% vs. 20.7%, $p<0.001$); earlier relief of associated symptoms & return to normal function in 2 h with R vs. N ($p<0.001$); similar overall pain relief over 24 h for R & N
Rizatriptan 10/20/40 mg vs. sumatriptan 100 mg; oral tablets ⁹²	PC, PG, MC, dose-ranging study; n=449 2-h headache response**	2-h headache response: S-100 mg: 46%; R-10 mg: 52%; R-20 mg: 56%; R-40 mg: 67%; P: 18%; R-40 mg significantly better vs. S-100 mg; R-10/20 mg similar to S-100 mg	Efficacy of R-10/20 mg comparable to S-100 mg; R-40 mg superior to S-100 mg but high frequency of ADRs with R-40 mg (Note: R-20/40 mg not available in Canada)
Rizatriptan 5/10 mg vs. sumatriptan 25/50 mg; oral tablets ⁹³	PC, CO, MC, 2 attack trial, 5 sequence groups; active vs. placebo ratio 2:1; n=1329 (treated at least one attack) Time to pain relief within 2 h**	Time to pain relief within 2 h: R superior to S; R-10 mg vs. S-50 mg: hazard ratio 1.14 ($p<0.05$)	R-5/10 mg provided faster relief of headache pain & greater relief of migraine symptoms (esp. nausea) than S-25/50 mg; response to R better on other measures (e.g., functional disability, satisfaction)
Rizatriptan 5/10 mg vs. sumatriptan 100 mg; oral tablets ⁹⁴	PC, PG, TD, MC, single-dose study; n=1091 Time to pain relief within 2 h** for R-10 mg vs. S-100mg	Time to pain relief within 2 h: R-10 mg had earlier onset than S-100 mg [$p=0.032$; hazard ratio 1.21 after age-adjusted analysis (since pts in R group were younger vs. S group)]	R-10 mg has faster onset than S-100 mg; R-10 mg superior to S-100 mg for pain-free response ($p=0.032$), reduction in functional disability ($p=0.015$) & relief of nausea ($p=0.010$) at 2 h; significantly fewer AEs with R-10 mg vs. S-100 mg (33% vs. 41%, $p=0.014$)
Rizatriptan 5/10 mg vs. sumatriptan 25/50 mg; oral tablets ⁹⁵	PC, 2-attack, CO, 6 treatment sequences; n=1447 (treated at least one attack) Time to pain relief within 2 h**	Time to pain relief within 2 h: R-10 mg vs. S-50 mg (NS); R-5 mg superior to S-25 mg (OR 1.22; $p=0.007$)	Faster onset of pain relief (at 1 h) with R-10 mg vs. S-50 mg (but no difference at 2 h); secondary endpoints favoured R over S
Almotriptan 12.5 mg vs. sumatriptan 50 mg; oral tablets (encapsulated) ⁹⁶	PC, PG, MC, single-dose; n=1173 2-h headache relief**	2-h headache relief: A: 58%, S: 57.3% (NS) Headache freedom (i.e., pain-free) at 2 h (secondary): A: 17.9%, S: 24.6% ($p=0.005$)	Study compared optimum doses of both drugs; similar efficacy; less chest pain with A vs. S
Eletriptan 40 mg vs. sumatriptan 100 mg; oral tablets (encapsulated) ⁹⁷	PG, DD, MC, single attack, 1:2:1 ratio; n= 2072 2-h headache relief**	2-h headache relief: E: 67%, S: 59% ($p<0.01$) 2-h pain-free (secondary): E: 36%, S: 27% ($p<0.0001$)	Greater efficacy for E vs. S (primary and secondary endpoints); E: rapid headache response (1 h) & better sustained response (24 h) vs. S
Eletriptan 40/80 mg vs. sumatriptan 50/100 mg; oral tablets (encapsulated) ⁹⁸	PC, DD, PG, MC, multiple attack; n=774 1-h headache response** (first attack)	1-h headache response: E-80 mg: 37% vs. S-50 mg: 24% ($p<0.05$) E-40 mg: 30% (superior to P) S-100 mg: 27% vs. E-80 mg: 37% (NS)	E-80 mg significantly better vs. S-50 mg (but similar to S-100 mg) for 1 h headache response; E-80 mg significantly superior consistency of response across multiple attacks vs. S-50/100 mg (Note: E-80 mg is not an approved dose in Canada)
Almotriptan 12.5 mg vs. zolmitriptan 2.5 mg; oral tablets (encapsulated) ⁹⁹	DB, PG, MC, (not PC), single attack; n=1103 Composite endpoint: sustained pain-free +no adverse events (SNAE)	No significant difference in SNAE (A: 29.2% vs. Z: 31.8%) Significantly lower incidence of triptan-associated AEs for A group vs. Z group	A & Z associated with similar efficacy & overall tolerability; A associated with significantly lower rate of triptan-associated AEs
Eletriptan 80 mg (& 40 mg) vs. zolmitriptan 2.5 mg ¹⁰⁰ ; oral tablets	DB, DD, PC, PG, MC, single attack; n=1312 2-h headache response**	2-h headache response: E-80 mg: 74%; E-40 mg: 64%; Z-2.5 mg: 60% ($p<0.0001$ vs. E-80 mg), and 22% for P ($p<0.0001$ vs. all active treatments)	E-80 mg significantly better than Z-2.5 mg; E-40 mg similar efficacy to Z-2.5 mg (secondary endpoint) AEs more frequent with E-80 mg (Note: E-80 mg is not an approved dose in Canada)

and for sachets vs. tablets ($p=0.0035$). The NNTs compared with placebo to achieve pain-free at 2 h were 7.75 (95% CI 5.46, 13.35) for sachets, and 15.83 (95% CI 8.63, 96.20) for tablets. Sachets were also superior to tablets for sustained headache response, sustained pain-free, and reduction in headache intensity within the first 2 h post-dose (measured on visual analog scale) ($p < 0.05$). The onset of analgesic effect was 15 minutes for sachet versus 60 minutes for tablets.

In the IMPACT study, the efficacy of diclofenac potassium 50 mg for oral solution (dissolved in approximately two ounces

of water) was assessed in a multicentre (U.S.), randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-attack trial in adult sufferers with migraine (moderate or severe attacks).⁵⁸ Subjects with vomiting in 20% of migraine attacks or who required bed rest during attacks were excluded. There were four co-primary endpoints. Compared to placebo ($n=347$), significantly more subjects treated with diclofenac potassium for oral solution ($n=343$) achieved a 2-h pain-free response (25% vs. 10% for placebo; $p<0.001$), no nausea (65% vs. 53%; $p=0.002$), no photophobia (41% vs. 27%;

Table 4: Triptans - Randomized, double-blind, comparative trials versus other triptans* [part 2] continued

Frovatriptan 2.5 mg vs. rizatriptan 10 mg ¹⁰¹ ; oral tablets	DB, MC, CO; 1-3 attacks; each treatment period not > 3 months n=125 (ITT) 2-h pain-free (PF) 2-h pain relief (PR)** 48-h SPF***	Primary (preference to one treatment via questionnaire with score 0-5): NS difference (2.9 for F vs. 3.2 for R) Secondary (F vs. R): 2-h pain-free: 33% vs. 39% (NS) 2-h pain relief: 55% vs. 62% (NS) Recurrent episodes within 48 h: 21% vs. 43% ($p<0.001$) SPF at 48 h: 26% vs. 22% (NS) AEs: NS difference	Frovatriptan 2.5 mg has similar efficacy vs. rizatriptan 10 mg, but has a significantly lower rate of recurrent episodes within 48 h; both are similarly preferred by patients
Frovatriptan 2.5 mg vs. zolmitriptan 2.5 mg ¹⁰² ; oral tablets	DB, MC, CO; 1-3 attacks; each treatment period not > 3 months n=107 (ITT) 2-h pain-free (PF) 2-h pain relief (PR)** 48-h SPF***	Primary (preference to one treatment via questionnaire with score 0-5): NS difference (2.9 for F vs. 3.0 for Z) Secondary (F vs. Z): 2-h pain-free: 26% vs. 31% (NS) 2-h pain relief: 57% vs. 58% (NS) Recurrence rate within 48h: 21% vs. 24% (NS) SPF at 48h: 18% vs. 22% (NS) AEs: less for F ($p<0.05$)	Frovatriptan 2.5 mg has similar efficacy vs. zolmitriptan 2.5 mg, with some advantages in terms of tolerability and recurrence; both are similarly preferred by patients
Frovatriptan 2.5 mg vs. almotriptan 12.5 mg ¹⁰³ ; oral tablets	DB, MC, CO; 1-3 attacks; each treatment period not > 3 months n=114 (ITT) 2-h pain-free (PF) 2-h pain relief (PR)** 48-h SPF***	Primary (preference to one treatment via questionnaire with score 0-5): NS difference (3.1 for F vs. 3.4 for A) Secondary (F vs. A): 2-h pain-free: 30% vs. 32% (NS) 2-h pain relief: 54% vs. 56% (NS) (4-h pain-free & pain relief: also NS differences) Recurrence rate within 48 h: 30% vs. 44% ($p<0.05$) SPF: 21% vs. 18% (NS) AEs: NS differences	Frovatriptan 2.5 mg has similar efficacy vs. almotriptan 12.5 mg, but has a significantly lower recurrence rate at 48 h; both are similarly preferred by patients

*Note: Some of the trials listed in this table are also included in meta-analyses in Table 3. **2-h/1-h headache response/pain relief/headache relief: reduction in pain from moderate/severe (Grade 2/3) to no/mild pain (Grade 0/1) within 2 hours/1 hour of treatment. ***48-h SPF = sustained pain-free episodes within 48 h (migraine attack pain-free at 2 h, not recurring and not requiring use of rescue medication or a second study drug dose within 48 h. RCT = randomized, controlled trial; AEs = adverse events; P= placebo; Z = zolmitriptan; S= sumatriptan; R = rizatriptan; N= naratriptan; A = almotriptan; E = eletriptan; F = frovatriptan; CO = cross-over; DD = double-dummy; TD = triple-dummy; PC = placebo-controlled; PG = parallel-group; MC = multicentre; NS = not statistically significant; OR = odds ratio; ITT = intention-to-treat; NS = not significant; SPF = sustained pain-free.

$p<0.001$), and no phonophobia (44% vs. 27%; $p<0.001$). Pain intensity differences between treatments were significantly lower in the diclofenac potassium group, starting at 30 minutes post-treatment ($p=0.013$), with significant differences at all time points, thereafter ($p<0.001$). The most common treatment related adverse event was nausea (4.6% for diclofenac potassium vs. 4.3% for placebo).

Recommendations (diclofenac potassium)

- Strong recommendation, high quality evidence:**
Diclofenac potassium (50 mg tablet or powder for oral solution) is recommended for the acute treatment of migraine attacks of all severities.
- Strong recommendation, moderate quality evidence:**
Diclofenac potassium powder for oral solution (50 mg) is recommended for the acute treatment of migraine attacks of all severities for patients desiring a faster onset of therapeutic effect as compared to the diclofenac oral tablet formulation.

e) Acetaminophen

Evidence Summary

In a multicentre, randomized, placebo-controlled trial of acetaminophen in adults with migraine, 1,000 mg doses produced pain relief in 57.8% of moderate attacks within 2 h (vs.

38.7% for placebo; $p=0.002$); 22.4% of patients were pain-free at 2 h (vs. 11.3% for placebo; $p=0.01$). This trial excluded patients with disabling headaches (requiring bed rest or precluding daily activities more than 50% of the time), or those with vomiting in more than 20% of attacks.⁶² In another, multicenter, randomized, placebo-controlled trial ($n=346$ adults with migraine), significantly more patients treated with acetaminophen (1,000 mg) had pain relieved after 2 h (52.0%) compared to those treated with placebo (32.0%; $p=0.001$). However, acetaminophen was not significantly better than placebo for pain-free at 2 h. Patients were excluded if they had a history of severely incapacitating migraines with more than 50% of episodes requiring bed rest (or prohibiting performance of daily activities), or more than 20% of episodes included vomiting.⁶³

A Cochrane systematic review (2010) of acetaminophen for acute migraine headaches in adults ($n=2769$; 4062 attacks; see Table 7), which included ten trials (including the two trials discussed above, which contributed almost 99% of the data for primary outcomes), concluded that acetaminophen 1,000 mg alone may be a useful first-line treatment for individuals with migraine headache that do not cause severe disability. Acetaminophen was superior to placebo, with NNTs of 12.0, 5.2 and 5.0 for 2-h pain-free and 1- and 2-h headache relief, respectively.⁶⁴ When combined with metoclopramide, acetaminophen provided similar efficacy to oral sumatriptan

Table 5: Triptans – Randomized, double-blind comparative studies versus NSAIDs/analgesic combinations*^{77,79,81,104-108}

Drugs, doses, # pts included in analysis (n)	Study design, # pts included in analysis (n), primary endpoints	Results	Conclusions/comments
Sumatriptan (S) 100 mg vs. lysine acetylsalicylate 1620 mg + metoclopramide (LAS + M) 10 mg ⁷⁹	PC, PG, MC, 2 attack trial; n=421 2-h headache response**	2-h headache response (1st attack): S: 57%; LAS + M: 53% (NS); 2-h pain-free (secondary) 1 st attack: S: 30%; LAS + M: 22% (NS)	Both S & LAS + M superior to P; similar efficacy for S and LAS + M; LAS + M significantly more effective for nausea relief than S & better tolerated. (Note: lysine acetylsalicylate is not available in Canada)
Sumatriptan (S) 100 mg vs. tolfenamic acid (TA) 200 mg ¹⁰⁴	PC, PG, 2 attack trial; n=141 2-h headache response**; Difference in headache severity at 2 h after 1 st dose	2-h headache response, attack 1: S: 79%; TA: 77% (NS); attack 2: S: 64%; TA 70% (NS); Difference in headache severity at 2h: NS 2-h pain-free (secondary), attack 1: S:50%; TA: 37% (NS); attack 2: S: 26%; TA 16% (NS)	Both S & TA superior to P; similar efficacy for TA and S; similar frequency of AEs Note: tolfenamic acid is not available in Canada
Sumatriptan (S) 100 mg vs. diclofenac-potassium (DP) 50/100 mg ¹⁰⁵	DD, CO, MC, with-in patient trial, 4 attack trial, 4 treatment sequences; n=144. Pain intensity via visual analogue scale (VAS) at 2 h (0 = no pain; 100 = excruciating pain & bed rest)	2-h VAS: NS difference between S & DP (both doses similarly effective); DP provided significant pain relief from 60 min after dose (S: from 90 min after dose); DP superior to S in reducing nausea	DP is effective, fast-acting and well tolerated and some advantages over S; no advantage of DP 100 mg vs. DP 50 mg; unable to evaluate headache response or pain-free response from VAS
Sumatriptan (S) 100 mg vs. ASA 900 mg + metoclopramide (A + M) 10 mg (n=358) ¹⁰⁶	PG, MC, 3 attack trial; n=358 2-h headache response**	2-h headache response (1st attack): S: 56%; A + M: 45% (NS); S superior to A + M for secondary endpoints: 2-h headache response (attacks 2 & 3), 2-h pain-free (attacks 1 & 3) & global ratings	66% of S patients vs. 45% of A + M patients rated therapy as reasonable, good or excellent (p<0.001)
Sumatriptan (S) 50 mg (encapsulated) vs. effervescent ASA 1000 mg vs. ibuprofen (I) 400 mg ¹⁰⁷	PC, DD, MC, 3-fold CO; n=192 2-h headache response**	2-h headache response: ASA: 52.5%; I: 60.2%; S: 55.8% (NS)	Effervescent ASA 1,000 mg is as effective as S-50 mg and I-400 mg but S more effective for pain-free at 2 h
Sumatriptan (S) 50 mg vs. AAC (acetaminophen 500 mg, ASA 500 mg, caffeine 130 mg); all encapsulated ¹⁰⁸	PC, MC; 2:2:1 randomization; drugs taken at first sign of migraine attack; n=171 Sum of pain intensity differences from baseline at 4 h post-dose (SPID4)	SPID4: significantly greater in AAC group vs. S group	AAC significantly superior to S taken at first sign of attack; encapsulation may affect kinetics; excluded patients with vomiting >20% of attacks or bed rest >50% of attacks (Note: AAC combination is not available in Canada)
Sumatriptan (S) 50 mg (encapsulated) vs. domperidone (DO) 10 mg + acetaminophen (AC) 500 mg (fixed combination) (n=161) ⁸¹	DD, PC, CO, MC, 2 attack trial; n=171 2-h headache response**	2-h headache response: S: 33.3%; DO/AC: 36.4% (NS); NS difference for nausea/vomiting reduction by both	Similar efficacy for both; low 2-h response rates for both (reason unknown); (Note: DO/AC fixed combination is not available in Canada)
Zolmitriptan (Z) 2.5 mg vs. ASA 900 mg + metoclopramide (A + M) 10 mg ⁷⁷	MC, PG, 3 attacks; n=666 2-h headache response**	2-h headache response (3 of 3 attacks): Z: 33.4%; A + M: 32.9% (NS); Pain-free at 2 h (secondary): Z: 10.7%; A + M: 5.3% (significant)	Possible selection bias (mostly good responders to A + M; mostly triptan-naïve); both well-tolerated; higher pt satisfaction with Z vs. A + M (83% vs. 75%, p=0.03)

*Note: some of the trials listed in this table are also included in meta-analyses in Tables 3 and 7. ** 2-h headache response: reduction in pain from severe/moderate to mild/no pain within 2 hours of treatment. P = placebo; PC = placebo-controlled; DD = double-dummy; PG = parallel group; MC = multicentre, CO = cross-over; NS = not statistically significant; AEs = adverse events

Table 6: Triptans - Early intervention: randomized, double-blind, prospective trials²⁷⁻³³

Drug and dose	Study design, # patients included in analysis (n), primary endpoints	Results	Comments/conclusions
Zolmitriptan 2.5 mg oral ²⁷	RA, DB, PC, PG; n=280 Pain-free at 2 h: attacks treated during mild phase within 4 h of onset (time to treatment was recorded) vs. placebo	Pain-free at 2h (all pts): Z: 43.4%; P: 18.4% ($p<0.0001$) Pain-free at 2 h (treated within 15 min of onset): Z: 57%; P: 20% ($p<0.001$)	Most pts treated early (> 50% within 30 min of onset); high pain-free rates with treatment while pain is mild & ↓ progression to more severe migraine; lower incidence of adverse effects with early treatment
Frovatriptan 2.5 mg oral (2 attacks) ²⁸	RA, DB, PC, two-way crossover: Dose 1 taken at onset of mild headache pain; Dose 2 could be taken from 2 h after Dose 1, only if headache progresses to moderate or severe (one dose active, other placebo; dosing order reversed for attack 2); n=241 Pain-free at 2 h (Dose 1); use of Dose 2 and/or rescue meds, pain severity, functional impairment, headache recurrence	Pain-free at 2 h: F: 28%; P: 20% ($p=0.04$); benefit sustained up to 4 h post-dose ($p=0.003$) Sustained pain-free: 40% with early use of F vs. 31% with later use ($p<0.05$) Early use of F: sign. ↓ re-medication ($p<0.001$), prevented headache progression ($p<0.001$), ↓ pain burden & functional disability ($p\leq 0.001$)	Early use of F resulted in higher, earlier and sustained pain-free response, prevented progression to moderate/severe headache and ↓ pain burden & functional disability; long half-life of F – suitability for early intervention
Sumatriptan 50/100 mg oral ³³	RA, DB, DD, PC, PG (2 identical trials); 1:1:1 ratio S-50 mg, S-100 mg, P; pts treated attacks at first sign of pain, while mild pain (not more than 2 h after onset); n=354 (study 1); n=337 (study 2) Pain-free at 2 h (S-50 mg vs. P) (primary endpoint)	Pain-free at 2 h (pooled results): S-50 mg: 50%; P: 29% ($p<0.001$) S-100 mg: 57%; P: 29% ($p<0.001$)	Treatment of migraine at first sign of pain with S-50/100 mg provides superior pain-free relief at 2 & 4 h vs. P; S provided freedom from migraine-associated symptoms in most patients at 2 h
Eletriptan 20/40 mg oral ²⁹	RA, DB, PC, PG (33 centres); n=565 1:1:1 ratio E-20 mg, E-40 mg, P; patients treated attacks as soon as sure they had typical migraine headache (after aura phase ended) & encouraged (not required) to take study med when pain was mild Pain-free at 2 h	Pain-free at 2 h (all patients; treated at any baseline severity): E-20 mg: 35%; P: 22% ($p<0.01$) E-40 mg: 47%; P: 22% ($p<0.0001$) Pain-free at 2 h (treated when pain was mild): E-40 mg: 68%; P: 25% ($p<0.0001$) (for E-20 mg: NS)	Early treatment with E-40 mg when pain was mild resulted in higher pain-free and sustained pain-free rates; sustained pain-free maintained over 24 h post-dose with E vs. P
Sumatriptan oral fast-disintegrating 50/100 mg ³⁰	RA, DB, PC, PG (54 centres); n=432 1:1:1 ratio S-50 mg, S-100 mg, P; patients treated attack within 1h of onset of mild pain & only while pain was mild Pain-free at 2 h	Pain-free at 2 h: S-50 mg: 51%; P: 20% ($p<0.001$) S-100 mg: 66%; P: 20% ($p<0.001$) Normal function restored in sign. greater % pts ($p<0.05$) treated with S vs. P from 45 min post-dose for S-100 mg & 1 h post-dose for S-50 mg Median lost time equivalents (during 24 h post-dose; paid work & activities outside paid work) sign. lower in each S group vs. P	S fast disintegrating oral formulation confers rapid, sustained restoration of functional ability
Sumatriptan 50/100 mg oral ³¹	RA, DB, PC, PG (25 centres); n=361 1:1:1 ratio S-50 mg, S-100 mg, P; patients treated attack within 2 h of first sign of migraine pain & only while pain was mild. Pain-free at 2 h	Pain-free at 2 h: S-50 mg: 40%; S-100 mg: 50%; P: 16% ($p<0.001$, active groups vs. P)	Both doses of S significantly superior to P for 2-h pain-free; higher pain-free rates when S taken while headache was mild vs. older trials (taken when moderate or severe pain)
Rizatriptan 10 mg oral ³²	Two studies (TAME1, TAME2): RA, DB, PC, PG (46 centres); n=1030; 2:1 ratio R 10 mg vs. P; patients treated within 1 h of migraine onset, while pain was mild Pain-free at 2 h & sustained pain-free at 24 h	TAME1: Pain-free at 2 h: R: 57.3%; P: 31.1% ($p<0.001$) Sustained pain-free at 24 h: R: 42.6%; P: 23.2% ($p<0.001$) TAME2: Pain-free at 2 h: R: 58.9%; P: 31.1% ($p<0.001$) Sustained pain-free at 24 h: R: 48.0%; P: 24.6% ($p<0.001$)	R 10 mg significantly superior to P when treating migraine early, while pain is mild

P = placebo; Z = zolmitriptan; F = frovatriptan; S = sumatriptan; E = eletriptan; RA = randomized; CO = controlled; DB = double-blind; PC = placebo-controlled; PG = parallel group; DD = double dummy; NS = not statistically significant

100 mg for 2 h headache relief (no pain-free data), and relief of photophobia and phonophobia, but with fewer adverse effects than sumatriptan.⁶⁴

Recommendation (acetaminophen)

1. Strong recommendation, high quality evidence: Acetaminophen (1,000 mg), alone or in combination with oral metoclopramide (10 mg), is recommended for the acute treatment of mild or moderate migraine attacks.

Opioid- and Tramadol-containing Products

a) Oral Opioid-containing Products

Overview

Opioids are associated with significant adverse effects including sedation, dizziness, constipation, tolerance, dependence, and abuse potential. There is also a significant risk of medication overuse headache with frequent use of opioid-containing combination products.^{1,65}

Evidence Summary

Oral opioids (e.g., codeine, morphine, hydromorphone, meperidine) and opioid-containing combination products (e.g., ASA/acetaminophen plus codeine) may relieve acute migraine pain in some patients; however, they may aggravate migraine-associated nausea and vomiting. There is a lack of randomized, controlled trials assessing the efficacy of oral opioids and combination products for the symptomatic treatment of migraine. One randomized, double-blind, placebo-controlled trial which compared an acetaminophen-codeine combination to ASA, found no significant difference, although both were superior to placebo in the treatment of acute migraine attacks.⁶⁶

b) Intranasal Butorphanol

Overview

Butorphanol tartrate is a potent, synthetic mixed agonist-antagonist opioid analgesic for use in the relief of moderate to severe pain. Although butorphanol is not a pure agonist and, theoretically, may have less addiction potential than pure agonists (e.g., hydromorphone, morphine, meperidine), it is associated with similar adverse effects, and the potential for medication overuse headache and abuse/dependence. There have been widespread reports of abuse and dependence, primarily in migraine patients. Butorphanol has effects at the kappa opioid receptor, which can produce unpleasant emotional sensations and dysphoria.⁶⁷

Evidence Summary

At the time of marketing, clinical trial experience with butorphanol nasal spray in migraineurs was limited. Subjects with frequent or refractory headache, or those with a prior history of substance abuse, were excluded from butorphanol trials.⁶⁷ Butorphanol nasal spray has been shown to be effective in rapidly relieving pain associated with acute migraine (moderate to severe) in two randomized, double-blind, placebo-controlled trials.^{68,69} In a randomized, controlled, double-blind, parallel-group trial (n=275 in efficacy analysis), butorphanol

1 mg nasal spray was compared to a combination of butalbital 50 mg, caffeine 40 mg, ASA 325 mg, and codeine phosphate 30 mg in patients with moderate to severe migraine.⁶⁹ Butorphanol nasal spray was more effective than the butalbital-containing combination in treating migraine pain (primary efficacy measure was pain intensity difference during first two hours); butorphanol had a rapid time to onset of 15 minutes; however, it was associated with more side effects than the butalbital-containing product.

c) Oral Tramadol plus Acetaminophen

Overview

Tramadol is an analgesic that binds weakly to μ -opioid receptors, and also inhibits serotonin and norepinephrine reuptake. As with opioids, tramadol use is associated with adverse effects such as central nervous system (CNS) depression and respiratory depression, dependence, withdrawal reactions, and the potential for abuse (less potential for abuse than opioids).⁷⁰⁻⁷²

Evidence Summary

There is one published randomized, multicentre, placebo-controlled trial of oral tramadol and acetaminophen combination (2 tablets: total dose 75 mg/650 mg; n=305) in acute migraine.⁷³ At 2 h after dosing, the treatment response (i.e., headache relief; primary endpoint) for tramadol/acetaminophen was 55.8% vs. 33.8% for placebo (p<0.001); subjects in the tramadol/acetaminophen group were more likely than those in the placebo group to be pain-free at 2 h (22.1% vs. 9.3%; p≤0.007). Photophobia and phonophobia were significantly less common with tramadol/acetaminophen than placebo at 2 h, but not migraine-related nausea. Treatment-related adverse events included nausea, dizziness, vomiting, and somnolence.

Recommendations (opioids and tramadol)

- 1. Strong recommendation, low quality evidence:** Oral opioids, including codeine, are not recommended for routine use in migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and triptans), and the risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation.
- 2. Weak recommendation, low quality evidence:** Codeine-containing combination analgesics may be considered for patients with moderate or severe migraine attacks when triptan and/or NSAIDs are ineffective or contraindicated, and for occasional use as rescue medication when the patient's regular medication has failed. Frequency of use should be closely monitored, preferably with use of headache diaries.
- 3. Strong recommendation, low quality evidence:** Tramadol alone or in combination with acetaminophen is not recommended for routine use in migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and triptans), and the risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation.

4. **Weak recommendation, moderate quality evidence:** *Tramadol in combination with acetaminophen may be considered for patients with moderate or severe migraine attacks when triptans and/or NSAIDs are ineffective or contraindicated, and for occasional use as rescue medication when the patient's regular medication has failed. Frequency of use should be closely monitored, preferably with use of headache diaries.*
5. **Strong recommendation, low quality evidence:** *Butorphanol nasal spray, although effective for acute migraine, should be avoided (except in exceptional circumstances) for the acute treatment of migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and / or triptans), risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation. When used, frequency of use should be closely monitored, preferably with use of headache diaries.*

Barbiturate (Butalbital)-containing Products

Overview

Butalbital-containing products are associated with significant adverse effects (e.g., sedation, intoxication similar to that produced by alcohol), risk of dependence, abuse potential, risk of medication-overuse headache with frequent use, and a severe withdrawal syndrome (including seizures) on discontinuation of high doses.^{1,65,74,75}

Evidence Summary

A qualitative systematic search (1966-2001) concluded that although butalbital-containing products are commonly prescribed for migraine, no evidence in the literature has demonstrated their benefit over other agents or placebo.⁷⁴ In a randomized, controlled trial (n=275 in efficacy analysis) comparing butorphanol nasal spray to a combination of butalbital 50 mg, caffeine 40 mg, ASA 325 mg, and codeine phosphate 30 mg, the butalbital-containing combination was inferior to butorphanol in treating migraine pain.⁶⁹

In a recent, randomized, double-blind, placebo-controlled trial (n=442), a butalbital-acetaminophen-caffeine containing combination analgesic was compared to a sumatriptan-naproxen sodium combination.⁷⁶ For inclusion, all patients were required to have used butalbital compounds in the past (butalbital responders), and in fact 88% of subjects who entered the study reported current use of butalbital compounds. The study population may have been biased, therefore, in favour of subjects who respond to butalbital-containing analgesics. Despite this, although both the butalbital-containing analgesic and the sumatriptan-naproxen sodium compound were superior to placebo, the sumatriptan-naproxen sodium compound was superior to the butalbital compound on most secondary endpoints, although not for the primary endpoint of sustained pain-free, where there was no significant difference. This study demonstrated that butalbital-containing analgesics may have efficacy in the treatment of acute migraine attacks, but are not superior to an NSAID-triptan combination.⁷⁶ Therefore, given the potential problems with butalbital-containing compounds, it

would seem difficult to justify their use in acute migraine except for exceptional circumstances.

Recommendation (barbiturates)

1. **Strong recommendation, low quality evidence:** *Barbiturate (i.e., butalbital)-containing combination analgesics should be avoided (except in exceptional circumstances) for the acute treatment of migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and / or triptans), risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation of high doses.*

3. Adjunctive Drugs

Overview

Adjunctive therapies may be used to relieve associated symptoms of migraine (e.g., nausea, vomiting), enhance gastric emptying, or to improve efficacy of acute migraine therapies. Parenteral dopamine antagonists (e.g., metoclopramide, prochlorperazine; administered in the emergency room), used as monotherapy, are effective in relieving migraine-associated nausea, as well as headache (not included in this guideline). In outpatient practice, adjunctive drugs are often used in combination with other effective migraine treatments.¹ There are randomized controlled trials for oral metoclopramide and domperidone as adjunctive drugs in the outpatient setting. Oral or rectal prochlorperazine may be used for relief of migraine-associated nausea and vomiting but there is a lack of RCTs. Although dimenhydrinate is often used by patients for nausea and vomiting associated with migraine, there are no RCTs to support its use, and metoclopramide would appear to be a better choice for most patients based on evidence for efficacy.

Evidence Summary

a) Metoclopramide

Metoclopramide has shown efficacy in combination with other acute therapies.⁷⁷⁻⁷⁹ A Cochrane systematic review of ASA with or without metoclopramide (see Acetylsalicylic Acid section and Table 7) concluded that the addition of oral metoclopramide (10 mg) to ASA 1,000 mg improves relief of nausea and vomiting.⁴⁹ Limitations of metoclopramide include adverse effects such as sedation, extrapyramidal effects, and the relatively uncommon risk of tardive dyskinesia.

Metoclopramide may improve the efficacy of triptans. In a small, double-blind, randomized, crossover study of 16 adult migraineurs who had failed to receive adequate relief from triptans (i.e., adequate doses of at least two separate trials of the same triptan, or at least two trials involving different triptans) treated one migraine with each treatment: sumatriptan 50 mg plus metoclopramide 10 mg, or sumatriptan 50 mg plus placebo. Patients treated their migraines when they were moderate or severe in intensity. Meaningful relief was attained in 10 (63%) of 16 migraines treated with the combination of sumatriptan plus metoclopramide, compared with 5 (31%) of 16 migraines treated with sumatriptan plus placebo. The combination was well tolerated. Whether initiating therapy when pain was mild or

Table 7: Meta-analyses/systematic reviews of acetaminophen, ASA and NSAIDs for acute migraine treatment [part 1]^{31,32,49,50,55,59,64}

Drug (publication date); number of trials included; number of participants (n); types of participants	Objective	Efficacy outcomes and main results	Conclusions and limitations
Acetaminophen (2010) ⁶⁴ 10 RCTs n=2769 (4062 attacks) Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed	To determine efficacy and tolerability of acetaminophen, alone or in combination with antiemetic vs. placebo or other active interventions in treatment of acute migraine in adults	Primary efficacy outcomes: pain-free at 2 h, without use of rescue medications; headache relief* at 1 h & 2 h; sustained pain-free** over 24 h; sustained pain reduction*** over 24 h Main results: Acetaminophen 1,000 mg vs. placebo: 2-h pain-free: 19% vs. 10% (NNT=12) 1-h headache relief: 39% vs. 20% (NNT=5.2) 2-h headache relief: 56% vs. 36% (NNT=5) Nausea photophobia & phonophobia reduced more with acetaminophen vs. placebo at 2 h (NNTs of 7-11); more individuals were free of functional disability at 2 h with acetaminophen (NNT=10) & fewer needed rescue medication over 6 h (NNT=6) Acetaminophen 1,000 mg + metoclopramide 10 mg vs. sumatriptan 100 mg: 2-h headache relief: 39% vs. 42% (NS; NNT not calculated); no 2-h pain-free data; NS difference in relief of photophobia & phonophobia at 2h) AE rates similar for acetaminophen vs. placebo, and between acetaminophen + metoclopramide & sumatriptan; more "major" adverse events occurred with sumatriptan (NNH=32)	Acetaminophen 1,000 mg alone is an effective treatment for acute migraine headaches; the addition of metoclopramide 10 mg gives short-term efficacy equivalent to oral sumatriptan 100 mg. AEs with acetaminophen did not differ from placebo; "major" AEs were slightly more common with sumatriptan than with acetaminophen + metoclopramide. Note: potential for hepatotoxicity with acetaminophen Limitations: data not reported consistently for some outcomes; single-dose comparisons; no data on prevention of recurrence with acetaminophen; 2 studies ^{62,63} contributed almost 90% of data for primary outcomes; some individuals with very severe or difficult-to-treat migraine attacks may have been excluded, and limits on frequency of attacks would exclude those with very frequent attacks; patients with significant co-morbidities were excluded from most studies; limited data with respect to active comparators other than sumatriptan
Ibuprofen (2007) ⁵¹ 5 RCTs n=1353 (pain relief) n=2161 (pain-free) Types of participants: age ≥ 16 years; moderate to severe migraine attacks	To evaluate efficacy of low-dose ibuprofen (200 or 400 mg) for treatment of acute migraine attack	200 mg dose: NNT = 8 (95% CI 5-20) for pain relief at 2 h & NNT = 13 (95% CI 8-50) for pain-free 400 mg dose: NNT = 4 (95% CI 3-7) for pain relief at 2 h & NNT = 9 (95% CI 5-20) for pain-free 24-h sustained pain-free for ibuprofen was no better than placebo 400 mg dose: relief in photophobia = 30% (95% CI 8-57; p<0.01) & phonophobia = 49% (95% CI 23-81; p<0.0001)	Ibuprofen (200 & 400 mg) is effective in reducing headache intensity & rendering adult patients pain-free at 2 h; photophobia & phonophobia improved with 400 mg dose only AEs were similar for ibuprofen & placebo. Limitations: individual study designs/small sample size; inconsistencies in descriptions of outcomes; too few studies to allow sub-group analysis
Ibuprofen (2010) ⁶² 9 RCTs (1 RCT used liquisol formulation) n=4373 (5223 attacks) Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed	To determine safety and efficacy of ibuprofen, alone or in combination with antiemetic, compared to placebo and other active interventions in treatment of acute migraine headaches in adults	Primary efficacy outcomes: pain-free at 2 h without use of rescue medications; headache relief* at 1 h & 2 h; sustained pain-free** over 24 h; sustained pain reduction*** over 24 h Main results: Ibuprofen 400 mg vs. placebo: 2-h pain-free (26% vs. 12%): NNT=7.2 2-h headache relief (57% vs. 25%) NNT=3.2 24-h sustained headache relief (45% vs. 19%): NNT=4.0 Ibuprofen 200 mg vs. placebo: 2-h pain-free (20% vs. 10%): NNT=9.7 2-h headache relief (52% vs. 37%): NNT=6.3 Ibuprofen 400 mg solubilized vs. standard tablets (no head-to-head trials): 1-h headache relief: NNT= 3.9 vs. NNT=8.3 (p=0.0114). 2-h headache relief: NS difference Significant relief of migraine associated symptoms after 2 h with ibuprofen vs. placebo (trend to lower NNT with 400 mg vs. 200 mg ibuprofen) in 4 studies AEs mostly mild and transient, with similar rate to placebo; 2 serious AEs with ibuprofen (perforation of duodenal ulcer; death due to sepsis – not related to study medication)	Ibuprofen is an effective treatment for acute migraine headaches, providing pain relief in about half of sufferers, but complete relief from pain and associated symptoms for only a minority; NNT for ibuprofen 400 mg significantly superior to 200 mg for 2-h pain relief only. Results are similar to those for ASA 900 mg or 1000 mg, with ibuprofen 400 mg performing slightly better than ASA, and ibuprofen 200 mg slightly worse [see ASA ± antiemetic (2010; below)]. Solubilized formulations (e.g., liquisol) were superior for 1-h but not 2-h headache relief vs. standard tablets. AEs were mostly mild and transient with ibuprofen. Limitations: small number of events used to calculate some results, particularly for specific AEs and for presence and relief of vomiting at 2 h (fewer than 100 participants had vomiting at baseline)
Naproxen Sodium (2010) ⁵⁵ 4 RCTs n=2168 Types of participants: adults; moderate to severe attacks	To assess efficacy & safety of naproxen sodium in treatment of acute migraine attacks Naproxen sodium dose was 500 mg in 3 trials; 825 mg in one trial	Naproxen sodium was more effective than placebo: pooled risk ratios were 1.58 (95% CI 1.41-1.77, p<0.00001), and 2.22 (95% CI 1.46-3.37, p=0.0002), respectively, for headache relief at 2 h and pain-free at 2 h No significant difference in headache recurrence between naproxen sodium & placebo Risk of any AE was greater with naproxen sodium than placebo (pooled risk ratio 1.29, 96% CI 1.04-1.60, p=0.02); most common AEs with naproxen sodium were nausea, dizziness, dyspepsia, abdominal pain	Naproxen sodium is more effective but may cause more adverse events than placebo in moderate to severe migraine; it is effective in reducing headache intensity, rendering pain-free at 2 h & improving migraine-associated symptoms. Limitations: one study had small number of patients; inconsistencies in descriptions of outcomes adopted by individual trials (but all trials were high quality)
ASA ± antiemetic (metoclopramide) (2010) ⁴⁹ 13 RCTs n=4222 (treating 5261 migraine headaches of moderate to severe intensity) Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed	To determine efficacy & tolerability of ASA (900 or 1,000 mg), alone or in combination with metoclopramide (10 mg), compared to placebo & other active comparators (sumatriptan) in treatment of acute migraine headaches in adults	Primary efficacy outcomes: pain-free at 2 h, without use of rescue medications; headache relief* at 1 h & 2 h; sustained pain-free** over 24 h; sustained pain reduction*** over 24 h Main results: ASA 900 mg or 1,000 mg vs. placebo: 2-h pain-free: 24% vs. 11% (NNT=8.1) 2-h headache relief: 52% vs. 32% (NNT=4.9) 24-h sustained headache relief: 39% vs. 24% (NNT=6.6) ASA 900 mg + metoclopramide 10 mg vs. placebo: 2-h pain-free: 18% vs. 7% (NNT=8.8) 2-h headache relief: 57% vs. 26% (NNT=3.3) 24-h sustained headache relief: 37% vs. 17% (NNT=6.2) No data for 24-h sustained pain-free Sumatriptan 50 mg did not differ from ASA alone for 2-h pain-free and headache relief, while sumatriptan 100 mg was better than ASA + metoclopramide for 2-h pain-free (but not headache relief); there was no data for 24-h headache relief	ASA 1,000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 or 100 mg, with reduction in both pain & associated symptoms such as nausea & photophobia; addition of metoclopramide 10 mg improves relief of nausea & vomiting; sumatriptan 100 mg was superior to ASA/metoclopramide for pain-free at 2 h. AEs mainly mild & transient, & slightly more common with ASA than placebo, but less common than with sumatriptan 100 mg. Further studies are needed to establish efficacy of ASA compared to other triptans & NSAIDs Limitations: small number of actual events used to calculate some results (e.g., small number of vomiting episodes) in estimations of efficacy concerning relief of associated symptoms

Table 7: Meta-analyses/systematic reviews of acetaminophen, ASA and NSAIDs for acute migraine treatment [part 2] continued

		Associated symptoms (nausea, vomiting, photophobia & phonophobia) were reduced with ASA vs. placebo; addition of metoclopramide significantly reduced nausea ($p<0.00006$) & vomiting ($p=0.002$) vs. ASA alone AEs mostly mild & transient, occurring slightly more often with ASA vs. placebo	
ASA effervescent (eASA) (2007)⁵⁰ 3 single-dose RCTs (individual patient data meta-analysis) e ASA: n=392; sumatriptan 50 mg: n=221; placebo: n=378 Total of 991 attacks Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; history of migraine at least 1 year; 1-6 attacks per month	To evaluate efficacy & safety eASA 1,000 mg in comparison with sumatriptan 50 mg & placebo	Pain (i.e., headache) relief at 2 h: eASA: 51.5% (95% CI: 46.6-56.5%) Sumatriptan: 46.6% (95% CI: 40.0-53.2%) Placebo: 33.9% (95% CI: 29.1-38.6%) Pain-free at 2 h: eASA: 27.1% (95% CI: 22.6-31.4%) Sumatriptan: 29% (95% CI: 23.0-34.9%) Placebo: 15.1% (95% CI: 11.5-18.7%) Sustained pain-free up to 24 h: eASA: 23.5% (95% CI: 19.3-27.7%) Sumatriptan: 22.2% (95% CI: 17.7-27.6%) Placebo: 14.6% (95% CI: 11.0-18.1%) Lower frequency of AEs (including gastrointestinal) in eASA vs. sumatriptan group (12.0% vs. 16.2%)	Effervescent ASA 1,000 mg is as effective as sumatriptan 50 mg for treatment of acute migraine attacks (including severe attacks) & has better side effect profile Limitations: meta-analysis is based on single-dose studies, which may have resulted in lower frequency of adverse events for eASA vs. sumatriptan
Diclofenac potassium (2012)⁵⁹ 5 RCTs n=1356 Types of participants: adults (≥ 18 years); IHS criteria for migraine diagnosis; stable prophylactic therapy allowed	To determine efficacy & tolerability of diclofenac alone or in combination with an antiemetic, compared to placebo and other active interventions in treatment of acute migraine headaches in adults	Primary efficacy outcomes: pain-free at 1 h & 2 h, without use of rescue medication; headache relief* at 1 h & 2 h; sustained pain-free** during 24 h post-dose (pain-free at 2 h & no use of rescue medication or recurrence of moderate to severe pain within 24 h); sustained headache relief*** during 24 h post-dose For single dose studies of diclofenac potassium vs. placebo (2 studies): 2-h headache relief: 55% vs. 39% (NNT = 6.2) 2-h pain-free: 22% vs. 11% (NNT = 8.9) Sustained pain-free (24 h): 19% vs. 8.2% (NNT = 9.5) Comparison with sumatriptan 100 mg oral: Diclofenac potassium was more effective vs. placebo in reducing headache pain at 2 h using VAS ($p<0.001$; 50 mg & 100 mg doses had similar efficacy); no statistically significant difference between either dose of diclofenac potassium & sumatriptan 100 mg. AEs mostly mild to moderate and transient with diclofenac potassium; same rate as placebo	Oral diclofenac potassium 50 mg is an effective treatment for acute migraine, providing relief from pain and associated symptoms; only a minority of patients achieved pain-free responses. AEs are mostly mild and transient (same rate as placebo); further head-to-head studies with other acute treatments are needed Limitations: studies used different doses and formulations of diclofenac, different dosing regimens (single dose or with optional second dose) & different levels of baseline pain; insufficient data for analysis of 100 mg dose; single dose studies may not reveal rare but potentially serious AEs

*Headache relief: pain reduced from moderate or severe to none or mild, without use of rescue medication. **Sustained pain-free over 24 h: pain-free within 2 h, with no use of rescue medication or recurrence within 24 h. ***Sustained pain reduction/headache relief over 24 h: headache relief at 2 h, sustained for 24 h, with no use of rescue medication or a second dose of study medication. RCTs = randomized, controlled trials; IHS = International Headache Society; NNT = number-needed-to treat; NNH = number-needed-to-harm; NS = non-statistically significant; AEs = adverse events; CI = confidence interval

using a higher dose of sumatriptan (e.g., 100 mg) would have provided additional benefit is unknown.⁸⁰

b) Domperidone

There is some evidence for efficacy of domperidone combined with acetaminophen for acute migraine.^{81,82} A randomized, double-blind, crossover study compared the fixed combination (not available in Canada) of acetaminophen 500 mg and domperidone 10 mg with sumatriptan 50 mg.⁸¹ There was no significant difference in headache relief at 2 h between the two treatments (36.4% vs. 33.3%, respectively), and improvement in nausea was the same with both. However, fewer side effects were reported with the acetaminophen and domperidone combination. Domperidone has an advantage over metoclopramide in that it is not associated with extrapyramidal effects or tardive dyskinesia. However, it can cause QT prolongation, which may lead to serious ventricular arrhythmias and sudden cardiac death, especially in patients older than 60 years-of-age and with daily doses greater than 30 mg (Health Canada Endorsed Important Safety Information on Domperidone Maleate, March 2, 2012).

Recommendations (adjunctive drugs)

- Strong recommendation, moderate quality evidence:** *Metoclopramide (10 mg orally) is recommended for use with acute migraine medications for migraine attacks to improve relief of nausea.*
- Strong recommendation, low quality evidence:** *Domperidone (10 mg orally) is recommended for use with acute migraine medications for migraine attacks to improve relief of nausea.*

CONCLUSIONS

In this targeted review, strong recommendations for use in acute migraine therapy have been made for 7 triptans, 4 NSAIDs (including ASA), and acetaminophen. All of these had high quality evidence supporting their use. Another medication, dihydroergotamine (intranasal or SC self-injection), received a weak recommendation for use related to the balance between efficacy and side effects, based on moderate quality evidence. Three other medications, all of which were not recommended for routine use, received weak recommendations for use:

Table 8: Summary of Recommendations for Medications for Acute Migraine Treatment *

Drug & route(s)	Recommendation	Quality of Evidence
Recommended for use in episodic migraine** (Use)		
Triptans and other migraine-specific medications:		
Almotriptan (oral)	Strong	High
Eletriptan (oral)	Strong	High
Frovatriptan (oral)	Strong	High
Naratriptan (oral)	Strong	High
Rizatriptan (oral)	Strong	High
Sumatriptan (SC, oral, intranasal)	Strong	High
Zolmitriptan (oral, intranasal)	Strong	High
Dihydroergotamine (intranasal, SC self-injection)	Weak	Moderate
Ergotamine (oral)	Weak (not recommended for routine use)	Moderate
ASA / NSAIDs:		
ASA (oral)	Strong	High
Diclofenac potassium (oral)	Strong	High
Ibuprofen (oral)	Strong	High
Naproxen sodium (oral)	Strong	High
Other:		
Acetaminophen (oral)	Strong	High
Opioids and Tramadol (not recommended for routine use):		
Opioid (i.e., codeine)- containing medications (oral)	Weak	Low
Tramadol-containing medications (oral)	Weak	Moderate
Anti-emetics:		
Domperidone (oral)	Strong	Low
Metoclopramide (oral)	Strong	Moderate
Not recommended for use in episodic migraine** (Do not use)***		
Butalbital-containing medications (oral)	Strong	Low
Butorphanol (intranasal)	Strong	Low

*Utilizing GRADE criteria. **Migraine with headache on less than 15 days a month. ***Except under exceptional circumstances

ergotamine, codeine-containing combination analgesics, and tramadol-containing analgesics. Supporting evidence for use for these three medications ranged from low to moderate quality evidence.

Two anti-emetics, metoclopramide and domperidone, received strong recommendations for use, with moderate quality evidence for metoclopramide and low quality evidence for domperidone.

Two medications received strong “do not use” recommendation (except for use in exceptional circumstances): butalbital-containing medications and butorphanol (intranasal), supported by low quality evidence. The above recommendations are summarized in Table 8.

Choice of an acute medication for a specific patient must be individualized, based on evidence for efficacy, potential drug side effects, co-existent medical and psychiatric illnesses, and patient preference. It also needs to be recognized that patient response to acute migraine medications is idiosyncratic and often cannot be predicted in advance. Therefore, multiple treatment options may need to be tried before an excellent medication for the patient is found.

Patient preference may also include considerations of cost, and cost may be a societal consideration as well. However, it

must be kept in mind that most of the costs associated with migraine are indirect costs related to missed work and other activities, and these are often much larger than the direct costs which include medication costs.

The principles of acute migraine therapy are discussed further in Section 1 of this guideline, and acute medication choice for individual patients is discussed in greater detail in Section 3.

REFERENCES

1. Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society.[see comment][erratum appears in CMAJ 1997 Nov 15;157(10):1354]. [Review] [160 refs]. CMAJ. 1997;156:1273-87.
2. Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache. 1999;39:S20-6.
3. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.
4. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008; 336:995-8.
5. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64: 401-6.

6. Cuello Garcia CA, Pacheco Alvarado KP, Perez Gaxiola G. Grading recommendations in clinical practice guidelines: randomised experimental evaluation of four different systems. *Arch Dis Child*. 2011;96:723-8.
7. Brozek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. *Allergy*. 2011;66:588-95.
8. Oldman AD, Smith LA, McQuay HJ, Moore RA. Pharmacological treatments for acute migraine: quantitative systematic review. *Pain*. 2002;97:247-57.
9. Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs*. 2010;70:1505-18.
10. Dodick D, Lipton RB, Martin V, et al. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. [Review] [66 refs]. *Headache*. 2004;44:414-25.
11. Tepper SJ, Millson D. Safety profile of the triptans. [Review] [51 refs]. *Expert Opin Drug Saf*. 2003;2:123-32.
12. Wenzel RG, Tepper S, Korab WE, Freitag F. Serotonin syndrome risks when combining SSRI/SNRI drugs and triptans: is the FDA's alert warranted? *Ann Pharmacother*. 2008;42:1692-6.
13. Gillman PK. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review. *Headache*. 2010;50:264-72.
14. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. [see comment] [erratum appears in *Cephalalgia*. 2003 Feb;23(1):71-]. *Cephalalgia*. 2002;22:633-58.
15. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials. [see comment]. *Lancet*. 2001;358:1668-75.
16. Pascual J, Mateos V, Roig C, Sanchez-Del-Rio M, Jimenez D. Marketed oral triptans in the acute treatment of migraine: a systematic review on efficacy and tolerability. *Headache*. 2007;47:1152-68.
17. Gawel MJ, Worthington I, Maggiano A. A systematic review of the use of triptans in acute migraine. [see comment]. [Review] [74 refs]. *Can J Neurol Sci*. 2001;28:30-41.
18. Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. [Review] [35 refs]. *Cephalalgia*. 2004;24:321-32.
19. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache*. 2005;45:983-91.
20. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA*. 2007;297:1443-54.
21. Mathew NT, Landy S, Stark S, et al. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache*. 2009;49:971-82.
22. Vollono C, Capuano A, Mei D, et al. Multiple attack study on the available triptans in Italy versus placebo. *Eur J Neurol*. 2005;12:557-63.
23. Dodick DW. Triptan nonresponder studies: implications for clinical practice. *Headache*. 2005;45:156-62.
24. Diener HC, Gendolla A, Gebert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. *Eur Neurol*. 2005;53:41-8.
25. Farkkila M, Olesen J, Dahlof C, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to oral sumatriptan. *Cephalalgia*. 2003;23:463-71.
26. Stark S, Spierings EL, McNeal S, Putnam GP, Bolden-Watson CP, O'Quinn S. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. *Headache*. 2000;40:513-20.
27. Klapper J, Lucas C, Rosjo O, Charlesworth B, ZODIAC study g. Benefits of treating highly disabled migraine patients with zolmitriptan while pain is mild. [see comment]. *Cephalalgia*. 2004;24:918-24.
28. Cady R, Elkind A, Goldstein J, Keywood C. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack versus dosing after the headache has become moderate or severe. *Curr Med Res Opin*. 2004;20:1465-72.
29. Brandes JL, Kudrow D, Cady R, Tiseo PJ, Sun W, Sikes CR. Eletriptan in the early treatment of acute migraine: influence of pain intensity and time of dosing. *Cephalalgia*. 2005;25:735-42.
30. Barbanti P, Carpay JA, Kwong WJ, Ahmad F, Boswell D. Effects of a fast disintegrating/rapid release oral formulation of sumatriptan on functional ability in patients with migraine. *Curr Med Res Opin*. 2004;20:2021-9.
31. Jelinski SE, Becker WJ, Christie SN, Ahmad FE, Pryse-Phillips W, Simpson SD. Pain free efficacy of sumatriptan in the early treatment of migraine. *Can J Neur Sci*. 2006;33:73-9.
32. Cady R, Martin V, Mausek A, et al. Efficacy of Rizatriptan 10 mg administered early in a migraine attack. *Headache*. 2006;46:914-24.
33. Winner P, Mannix LK, Putnam DG, et al. Pain-free results with sumatriptan taken at the first sign of migraine pain: 2 randomized, double-blind, placebo-controlled studies. *Mayo Clin Proc*. 2003;78:1214-22.
34. Loder E. Triptan therapy in migraine. *N Engl J Med*. 2010;363:63-70.
35. Geraud G, Keywood C, Senard JM. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. *Headache*. 2003;43:376-88.
36. Tfelt-Hansen P, Saxena PR, Dahlof C, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. [Review] [84 refs]. *Brain*. 2000;123:9-18.
37. Anonymous. Efficacy, safety, and tolerability of dihydroergotamine nasal spray as monotherapy in the treatment of acute migraine. Dihydroergotamine Nasal Spray Multicenter Investigators. *Headache*. 1995;35:177-84.
38. Treves TA, Kuritzky A, Hering R, Korczyn AD. Dihydroergotamine nasal spray in the treatment of acute migraine. *Headache*. 1998;38:614-7.
39. Boureau F, Kappos L, Schoenen J, Esperanca P, Ashford E. A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine. *Int J Clin Pract*. 2000;54:281-6.
40. Touchon J, Bertin L, Pilgrim AJ, Ashford E, Bes A. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology*. 1996;47:361-5.
41. Winner P, Ricalde O, Le Force B, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. [see comment]. *Arch Neurol*. 1996;53:180-4.
42. Anonymous. A randomized, double-blind comparison of sumatriptan and Cafegot in the acute treatment of migraine. The Multinational Oral Sumatriptan and Cafegot Comparative Study Group. *Eur Neurol*. 1991;31:314-22.
43. Diener HC, Jansen JP, Reches A, et al. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafegot) in the acute treatment of migraine: a multicentre, randomised, double-blind, placebo-controlled comparison. *Eur Neurol*. 2002;47:99-107.
44. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan is an effective and well-tolerated treatment for migraine pain: results of a randomized, double-blind, placebo-controlled clinical trial. *Cephalalgia*. 2002;22:453-61.
45. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database of Systematic Reviews*. 2012;2:008615.
46. Wenzel RG, Sarvis CA, Krause ML. Over-the-counter drugs for acute migraine attacks: literature review and recommendations. *Pharmacotherapy*. 2003;23:494-505.
47. Silberstein S, Tepper S, Brandes J, et al. Randomized, placebo-controlled trial of rofecoxib in the acute treatment of migraine. *Neurology*. 2004;62:1552-7.
48. Misra UK, Jose M, Kalita J. Rofecoxib versus ibuprofen for acute treatment of migraine: a randomised placebo controlled trial. *Postgrad Med J*. 2004;80:720-3.
49. Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2010;4:008041.

50. Lampl C, Voelker M, Diener HC. Efficacy and safety of 1,000 mg effervescent aspirin: individual patient data meta-analysis of three trials in migraine headache and migraine accompanying symptoms. *J Neurol*. 2007;254:705-12.
51. Suthisisang C, Poolsup N, Kittikulsuth W, Pudchakan P, Wiwatpanich P. Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. *Ann Pharmacother*. 2007;41:1782-91.
52. Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2010;008039.
53. Kellstein DE, Lipton RB, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. *Cephalalgia*. 2000;20:233-43.
54. Misra UK, Kalita J, Yadav RK. Rizatriptan vs. ibuprofen in migraine: a randomised placebo-controlled trial. *J Headache Pain*. 2007;8:175-9.
55. Suthisisang C, Poolsup N, Suksomboon N, Lertpipometha V, Tepwitukgid B. Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. *Headache*. 2010;50:808-18.
56. McNeely W, Goa KL. Diclofenac-potassium in migraine: a review. *Drugs*. 1999;57:991-1003.
57. Diener HC, Montagna P, Gacs G, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. *Cephalalgia*. 2006;26:537-47.
58. Lipton RB, Grosberg B, Singer RP, et al. Efficacy and tolerability of a new powdered formulation of diclofenac potassium for oral solution for the acute treatment of migraine: results from the International Migraine Pain Assessment Clinical Trial (IMPACT). *Cephalalgia*. 2010;30:1336-45.
59. Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2012;2:008783.
60. Anonymous. Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. The Diclofenac-K/Sumatriptan Migraine Study Group. *Cephalalgia*. 1999;19:232-40.
61. Diener HC, Montagna P, Gacs G, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. *Cephalalgia*. 2006;26:537-47.
62. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med*. 2000;160:3486-92.
63. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. *Headache*. 2010;50:819-33.
64. Derry S, Moore RA, McQuay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010;008040.
65. Silberstein SD, McCrory DC. Butalbital in the treatment of headache: history, pharmacology, and efficacy. [Review] [44 refs]. *Headache*. 2001;41:953-67.
66. Boureau F, Joubert JM, Lasserre V, Prum B, Delecoeuillerie G. Double-blind comparison of an acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. *Cephalalgia*. 1994;14:156-61.
67. Loder E. Post-marketing experience with an opioid nasal spray for migraine: lessons for the future. *Cephalalgia*. 2006;26:89-97.
68. Hoffert MJ, Couch JR, Diamond S, et al. Transnasal butorphanol in the treatment of acute migraine. *Headache*. 1995;35:65-9.
69. Goldstein J, Gawel MJ, Winner P, et al. Comparison of butorphanol nasal spray and Fiorinal with codeine in the treatment of migraine. *Headache*. 1998;38:516-22.
70. Senay EC, Adams EH, Geller A, et al. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug Alcohol Depend*. 2003;69:233-41.
71. Raffa RB. Basic pharmacology relevant to drug abuse assessment: tramadol as example. *J Clin Pharm Ther*. 2008;33:101-8.
72. Tjaderborn M, Jonsson AK, Ahlner J, Hagg S. Tramadol dependence: a survey of spontaneously reported cases in Sweden. *Pharmacoepidemiol Drug Saf*. 2009;18:1192-8.
73. Silberstein SD, Freitag FG, Rozen TD, et al. Tramadol/acetaminophen for the treatment of acute migraine pain: findings of a randomized, placebo-controlled trial. *Headache*. 2005;45:1317-27.
74. Wenzel RG, Sarvis CA. Do butalbital-containing products have a role in the management of migraine? [Review] [55 refs]. *Pharmacotherapy*. 2002;22:1029-35.
75. Raja M, Altavista MC, Azzoni A, Albanese A. Severe barbiturate withdrawal syndrome in migrainous patients. *Headache*. 1996;36:119-21.
76. Derosier F, Sheftell F, Silberstein S, et al. Sumatriptan-naproxen and butalbital: A double-blind, placebo-controlled crossover study. *Headache*. 2012;52:530-43.
77. Geraud G, Compagnon A, Rossi A, COZAM Study G. Zolmitriptan versus a combination of acetylsalicylic acid and metoclopramide in the acute oral treatment of migraine: a double-blind, randomised, three-attack study. *Eur Neurol*. 2002;47:88-98.
78. Chabriat H, Joire JE, Danchot J, Gripon P, Bousser MG. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicentre double-blind placebo-controlled study. *Cephalalgia*. 1994;14:297-300.
79. Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. [see comment]. *Lancet*. 1995;346:923-6.
80. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. [see comment]. *Headache*. 2003;43:729-33.
81. Dowson A, Ball K, Haworth D. Comparison of a fixed combination of domperidone and paracetamol (Domperamol) with sumatriptan 50 mg in moderate to severe migraine: a randomised UK primary care study. *Curr Med Res Opin*. 2000;16:190-7.
82. MacGregor EA, Wilkinson M, Bancroft K. Domperidone plus paracetamol in the treatment of migraine. *Cephalalgia*. 1993;13:124-7.
83. Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012;2:009665.
84. Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012;2:009663.
85. Chen LC, Ashcroft DM. Meta-analysis of the efficacy and safety of zolmitriptan in the acute treatment of migraine. *Headache*. 2008;48:236-47.
86. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials. *Pharmacoepidemiol Drug Saf*. 2004;13:73-82.
87. Poolsup N, Leelasangaluk V, Jittangtrong J, Rithlamlert C, Ratanapantamane N, Khanthong M. Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J Clin Pharm Ther*. 2005;30:521-32.
88. Chen LC, Ashcroft DM. Meta-analysis examining the efficacy and safety of almotriptan in the acute treatment of migraine. *Headache*. 2007;47:1169-77.
89. Gallagher RM, Dennish G, Spierings EL, Chitra R. A comparative trial of zolmitriptan and sumatriptan for the acute oral treatment of migraine. [see comment]. *Headache*. 2000;40:119-28.
90. Gruffyd-Jones K, Kies B, Middleton A, Mulder LJ, Rosjo O, Millson DS. Zolmitriptan versus sumatriptan for the acute oral treatment of migraine: a randomized, double-blind, international study. *Eur J Neurol*. 2001;8:237-45.
91. Bomhof M, Paz J, Legg N, Allen C, Vandormael K, Patel K. Comparison of rizatriptan 10 mg vs. naratriptan 2.5 mg in migraine. *Eur Neurol*. 1999;42:173-9.

92. Visser WH, Terwindt GM, Reines SA, Jiang K, Lines CR, Ferrari MD. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Dutch/US Rizatriptan Study Group. *Arch Neurol*. 1996;53:1132-7.
93. Goldstein J, Ryan R, Jiang K, et al. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Rizatriptan Protocol 046 Study Group. [see comment]. *Headache*. 1998;38:737-47.
94. Tfelt-Hansen P, Teall J, Rodriguez F, et al. Oral rizatriptan versus oral sumatriptan: a direct comparative study in the acute treatment of migraine. Rizatriptan 030 Study Group. [see comment]. *Headache*. 1998;38:748-55.
95. Kolodny A, Polis A, Battisti WP, Johnson-Pratt L, Skobieranda F, Rizatriptan Protocol 052 Study G. Comparison of rizatriptan 5 mg and 10 mg tablets and sumatriptan 25 mg and 50 mg tablets. *Cephalalgia*. 2004;24:540-6.
96. Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, Jirgens KJ. Oral almotriptan vs. oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. *Arch Neurol* 2001; 58:944-50.
97. Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. [see comment]. *Headache*. 2003;43:214-22.
98. Sandrini G, Farkkila M, Burgess G, Forster E, Haughie S, Eletriptan Steering C. Eletriptan vs sumatriptan: a double-blind, placebo-controlled, multiple migraine attack study. [see comment]. *Neurology*. 2002;59:1210-7.
99. Goadsby PJ, Massiou H, Pascual J, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurol Scand*. 2007;115:34-40.
100. Steiner TJ, Diener HC, MacGregor EA, Schoenen J, Muirheads N, Sikes CR. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. *Cephalalgia*. 2003;23:942-52.
101. Savi L, Omboni S, Lisotto C, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus rizatriptan for the acute treatment of migraine. *J Headache Pain*. 2011;12:219-26.
102. Tullo V, Allais G, Ferrari MD, et al. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. *Neurol Sci*. 2010;31: S51-4.
103. Bartolini M, Giamberardino MA, Lisotto C, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. *J Headache Pain*. 2011;12:361-8.
104. Myllyla VV, Havanka H, Herrala L, et al. Tolfenamic acid rapid release versus sumatriptan in the acute treatment of migraine: comparable effect in a double-blind, randomized, controlled, parallel-group study. *Headache*. 1998;38:201-7.
105. Anonymous Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. The Diclofenac-K/Sumatriptan Migraine Study Group. *Cephalalgia*. 1999;19:232-40.
106. Anonymous A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. *Eur Neurol*. 1992;32:177-84.
107. Diener HC, Bussone G, de Liano H, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia*. 2004;24:947-54.
108. Goldstein J, Silberstein SD, Saper JR, et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: results from the ASSET trial. *Headache*. 2005;45:973-82.

Pharmacological Acute Migraine Treatment Strategies: Choosing the Right Drug for a Specific Patient

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ABSTRACT: Background: In our targeted review (Section 2), 12 acute medications received a strong recommendation for use in acute migraine therapy while four received a weak recommendation for use. Strong recommendations were made to avoid use of two other medications, except for exceptional circumstances. Two anti-emetics received strong recommendations for use as needed. **Objective:** To organize the available acute migraine medications into acute migraine treatment strategies in order to assist the practitioner in choosing a specific medication(s) for an individual patient. **Methods:** Acute migraine treatment strategies were developed based on the targeted literature review used for the development of this guideline (Section 2), and a general literature review. Expert consensus groups were used to refine and validate these strategies. **Results:** Based on evidence for drug efficacy, drug side effects, migraine severity, and co-existent medical disorders, our analysis resulted in the formulation of eight general acute migraine treatment strategies. These could be grouped into four categories: 1) two mild-moderate attack strategies, 2) two moderate-severe attack or NSAID failure strategies, 3) three refractory migraine strategies, and 4) a vasoconstrictor unresponsive-contraindicated strategy. In addition, strategies were developed for menstrual migraine, migraine during pregnancy, and migraine during lactation. The eight general treatment strategies were coordinated with a “combined acute medication approach” to therapy which used features of both the “stratified” and the “step care across attacks” approaches to acute migraine management. **Conclusions:** The available medications for acute migraine treatment can be organized into a series of strategies based on patient clinical features. These strategies may help practitioners make appropriate acute medication choices for patients with migraine.

RÉSUMÉ: Stratégies de traitement pharmacologique de la crise aiguë de migraine : choisir la bonne médication pour un patient donné.
Contexte : Dans notre révision ciblée (section 2), 12 médicaments de phase aiguë ont reçu une forte recommandation pour leur utilisation dans le traitement de la crise aiguë de migraine et 4 ont reçu une recommandation faible. Une forte recommandation a été émise contre l'utilisation de 2 autres médicaments, sauf dans des circonstances exceptionnelles. Deux médicaments antiémétiques sont fortement recommandés pour utilisation au besoin. **Objectif :** Le but de l'étude était d'organiser la médication disponible pour le traitement de la crise aiguë de migraine en stratégies de traitement afin d'aider le médecin à choisir un médicament spécifique pour un patient donné. **Méthode :** Une revue ciblée de la littérature ainsi qu'une revue générale de la littérature ont été utilisées pour développer des stratégies de traitement de la crise aiguë de migraine et pour élaborer ces lignes directrices (section 2). Des groupes de consensus expert ont été utilisés pour raffiner et valider ces stratégies. **Résultats :** L'élaboration de 8 stratégies générales de traitement de la crise aiguë de migraine résulte de notre analyse basée sur des preuves de l'efficacité de la médication et de ses effets secondaires, la sévérité de la migraine et la présence de comorbidités. Elles peuvent être regroupées en 4 catégories : 1) deux stratégies pour les crises légères à modérées ; 2) deux stratégies pour les crises modérées à sévères ou si échec des AINS ; 3) trois stratégies pour la migraine réfractaire et 4) une stratégie si échec ou contre-indication au traitement par un vasoconstricteur. De plus, des stratégies ont été élaborées pour la migraine menstruelle, la migraine pendant la grossesse et pendant la lactation. Les 8 stratégies de traitement général ont été coordonnées avec une approche combinée pour la médication de phase aiguë qui utilisait des caractéristiques de l'approche stratifiée et de l'approche par étapes pour toute crise pour le traitement de la crise aiguë de migraine. **Conclusions :** Les médicaments qui sont disponibles pour traiter la crise aiguë de migraine peuvent être organisés en stratégies de traitement basées sur le tableau clinique que présente le patient. Ces stratégies peuvent aider le médecin à faire des choix appropriés de médication pour traiter les patients qui souffrent de migraine.

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Finding an effective acute medication may be relatively simple for many patients with migraine, particularly those with attacks of mild or moderate severity. They may find, for example, that ibuprofen works well for them. Others may need to try a number of prescription medications before they find one that is satisfactory.

In Section 2, 18 acute migraine medications and two adjunctive medications were evaluated. Twelve acute

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medications received a strong recommendation for use in acute migraine therapy (Table 1). Four acute medications received a weak recommendation for use, with three of these NOT recommended for routine use (ergotamine, opioids including codeine-containing medications, and tramadol-containing medications). Strong recommendations were made to avoid use of butorphanol nasal spray and butalbital-containing medications, with use only under exceptional circumstances. Two oral anti-emetics, metoclopramide and domperidone, received a strong recommendation for use with acute migraine attack medications where necessary.

Acute Migraine Treatment Approaches and Strategies

The goal of this section of the guideline is to provide additional guidance to the practitioner in choosing a medication for a specific patient, based upon the evidence-based review presented in Section 2, a general literature review, and expert consensus based on clinical experience.

Table 1: Medications for Acute Migraine Treatment Assessed in Section 2*

Class, drug, (route)	Recommendation
Recommended for use in episodic migraine** (Use)	
Triptans and other migraine-specific medications:	
Almotriptan (oral)	Strong
Eletriptan (oral)	Strong
Frovatriptan (oral)	Strong
Naratriptan (oral)	Strong
Rizatriptan (oral)	Strong
Sumatriptan (SC, oral, intranasal)	Strong
Zolmitriptan (oral, intranasal)	Strong
Dihydroergotamine (DHE) (intranasal, SC self-injection)	Weak
Ergotamine (oral)	Weak (not recommended for routine use)
ASA / NSAIDs:	
ASA (oral)	Strong
Diclofenac potassium (oral)	Strong
Ibuprofen (oral)	Strong
Naproxen sodium (oral)	Strong
Other:	
Acetaminophen (oral)	Strong
Opioids and Tramadol:	
Opioid (i.e., codeine)-containing medications (oral)	Weak (not recommended for routine use)
Tramadol-containing medications (oral)	Weak (not recommended for routine use)
Anti-emetics:	
Domperidone (oral)	Strong
Metoclopramide (oral)	Strong
Not recommended for use in episodic migraine** (Do not use)***:	
Butalbital-containing medications (oral)	Strong
Butorphanol (intranasal)	Strong

*Utilizing GRADE criteria; **Migraine with headache on less than 15 days per month; ***Except under exceptional circumstances

Medication choice for a patient with migraine must be individualized, and various treatment approaches are proposed in the literature.¹ In this guideline, we propose that the “stratified care” approach may be most appropriate for many patients with severe migraine attacks; while a modified “step care across attacks” approach may be more appropriate for many others with migraine. We have called this overall approach a “combined acute medication approach”. Because it bases choice of acute migraine medication upon the patient’s clinical features, and flexibly combines features of both the “stratified” and “step care across attacks” approaches, we feel it may be the best overall acute migraine treatment approach.

Although the term “strategy” has been used for “stratified”, “step-care across attacks”, and “step-care within attacks” approaches, we feel the term “approach” is more appropriate than “strategy” for these very general approaches to acute treatment. We use the term “strategy” in this guideline for more specific components of the therapeutic choices that must be made. Each of the strategies discussed in this guideline relates directly to a specific clinical situation, and to specific drugs (Table 2). In this way, we hope to provide therapeutic guidance beyond the three treatment approaches that have already been discussed in the medical literature.¹

The factors that need to be considered when an acute medication is recommended for a patient are shown in Table 3. Some of these have already been mentioned in Section 1 under “General Principles of Acute Migraine Therapy”.

“Stratified” versus “step care” approaches

Treatment approaches have already been defined and discussed in Section 1. “Stratified care”, where the first acute medication recommended is tailored to the patient’s attack severity or degree of disability, has been promoted as the best way to find the right medication for the patient quickly. This likely reduces the number of patients who become discouraged and become “lapsed consulters”. A potential disadvantage of this approach is that a more expensive medication (e.g., a triptan) may be used long term by the patient when a less expensive medication (e.g., an NSAID) might have been effective.

Table 2: Acute Migraine Treatment Strategies

1. Mild-moderate attack strategies:
 - a. Acetaminophen strategy
 - b. NSAID strategy
2. Moderate-severe attack or NSAID failure strategies:
 - a. NSAID with triptan rescue strategy
 - b. Triptan strategy
3. Refractory migraine strategies:
 - a. Triptan – NSAID combination strategy
 - b. Triptan – NSAID combination with rescue medication strategy
 - c. Dihydroergotamine strategy
4. Vasoconstrictor unresponsive-contraindicated strategy
5. Menstrual migraine strategy
6. Migraine during pregnancy strategy
7. Migraine during lactation strategy

The “step care across attacks” approach usually involves using “simple” analgesics (e.g., acetaminophen or NSAIDs) first, and “stepping up” to the triptans if necessary. This approach may result in more lapsed consulters, and in needless suffering as various ineffective medications are tried in turn.

In the “step care within attacks” approach, the patient takes a non-steroidal anti-inflammatory drug (NSAID) or acetaminophen early in an attack, and “moves up” to a triptan several hours later if the first medication is ineffective. As all acute migraine medications are more likely to be effective if taken early in the attack, this can be a self-defeating approach, although some patients with slowly developing migraine attacks and those who can predict the severity of an oncoming attack with some degree of certainty may find it useful.

It is likely that no single treatment approach is ideal for all patients. In practice, many patients have already tried several non-prescription medications before consulting a physician, so a

“step care across attacks” approach has already been started. For those who have not, careful patient education and the streaming of patients into an appropriate treatment approach and strategy based upon their clinical features may be most effective. Described below is a “combined” treatment approach. It includes an acute medication treatment “ladder” for those streamed to “step care across attacks”. For each component or step, more details may be found regarding the medications recommended by going to the relevant strategy description later in this section.

Combined acute medication approach for migraine attacks

In this approach, treatment recommendations are based on attack severity and response to previously tried medications. Note that some patients may have more than one attack severity. In addition to attack severity, the overall structural features of the patient’s usual migraine attack need to be considered when planning management (Table 3). These include:

Table 3: Factors to be considered when recommending an acute migraine medication

Factor	Comment
Patient response	The response of a specific patient to medications cannot be predicted with certainty. Responses to medications used in the past can help guide therapy.
Evidence for efficacy	The quality of evidence available varies greatly for different medications.
Tolerability	Side effects differ between different medications.
Co-existent medical and psychiatric disorders	These may result in contraindications to some acute medications (e.g., vascular disease and vasoconstrictors).
Pain intensity	Patients with disabling pain intensity are more likely to require a “stratified approach” with early use of triptans or triptan-NSAID combination. If pain builds up rapidly and peaks early in the attack, a medication with rapid absorption may be necessary (e.g., SC sumatriptan, intranasal zolmitriptan, oral rizatriptan, etc). This may be particularly important for attacks that are fully developed upon awakening.
Attack duration	Patients with long-lasting migraine attacks (lasting beyond 24 hours untreated) may be more prone to headache recurrence. A triptan with a lower rate of headache recurrence (eletriptan, frovatriptan) or a triptan combined with an NSAID with a longer half-life (e.g., naproxen sodium) may be helpful.
Associated migraine symptoms – nausea and / or vomiting	These may indicate the need for a non-oral medication formulation, and / or an anti-emetic. This is particularly important for patients with nausea and / or vomiting early in the attack.
Early treatment	All acute medications appear to be more effective when taken early in the migraine attack. A potentially effective medication may be considered ineffective by the patient if it is taken only after the attack is fully developed. This becomes especially important if a “step care within attacks” approach is being considered. The benefits of early treatment must be balanced against the risk of medication overuse in patients with frequent migraine attacks.
Consistency of response	For patients with severe attacks, if the patient’s, primary acute medication is not effective for every attack, a rescue medication should be considered for when their regular medication fails.
Avoidance of patient discouragement and “Lapsed Consulters”	Rigid adherence to a “step care across attacks” approach may result in ineffective recommendations initially. The patient may withdraw from care and rely on “over the counter” medications. This may increase the risk of poor medication efficacy and medication overuse.
Medication cost	Although cost is an important factor, less expensive but also less effective medications may result in increased indirect costs (missed work, etc), and therefore greater overall costs.
Opioid avoidance	Opioid-containing analgesics are best avoided for acute migraine where possible. They are often no more effective than ASA / NSAIDs ⁸³ , they are often overused ¹⁵³ , and overuse often results in medication overuse headache. ^{21,85}
Avoidance of medication overuse	Relatively ineffective medications may result in more frequent medication use, and may result in medication overuse headache. Opioid- and barbiturate-containing combination analgesics appear particularly problematic with regard to medication overuse.

- Whether the pain builds up quickly and peaks early in the attack, or only later in the attack.
- Whether significant nausea occurs early in the attack where it may impede the effectiveness of oral medications, or only later in the attack.
- Whether the attack comes on during the day where it can be treated early, or is present in a fully developed form (often with nausea or early vomiting) upon awakening.
- The usual duration of the patient's attacks. Patients with attacks of long duration may be more prone to pain recurrence after initial acute treatment.
- Whether the patient has a migraine aura. This may allow for early treatment of the migraine attack, although for triptans there is evidence that treatment at pain onset is most effective (see later section, "Timing of triptan use in migraine with aura").

Many of these features are also considered in more detail in the individual treatment strategies discussed later in this document.

Combined acute medication treatment approach

1. Patients who present with severe attacks that often require bed rest should be given a triptan, with an anti-nauseant, if necessary, consistent with the stratified approach (see strategy 2b: Triptan strategy).
2. Patients whose attacks are usually less severe than those above, and who have not had adequate trials of non triptans can be considered for a "step care across attacks" approach as outlined below. They should be educated carefully about the options for acute migraine treatment and the treatment plan. Patient follow-up is important. For all acute medications, treatment early in the attack is generally more effective, but it is important that patients with frequent attacks avoid medication overuse.
 - i. **Step 1:** ASA 1,000 mg, ibuprofen 400 mg, diclofenac potassium 50 mg or naproxen sodium 500 - 550 mg (up to 825 mg can be used). Acetaminophen 1,000 mg can be used for patients intolerant of NSAIDs. For patients desiring a more rapid onset of action, solubilized ibuprofen, diclofenac potassium in a powdered formulation (for oral solution) or effervescent ASA can be used. Metoclopramide 10 mg (or domperidone 10 mg) can be added if nausea is present. These may improve absorption, and therefore efficacy of the NSAID or acetaminophen (see strategy 1a: Acetaminophen strategy; Strategy 1b: NSAID strategy). For patients with relatively severe attacks in whom an NSAID is being tried, a triptan can also be prescribed at the same time as a rescue medication (see strategy 2a: NSAID with triptan rescue strategy). This strategy can also be used for patients who are found to generally respond well to their NSAID, but who do have treatment failure from time to time (for example, if they take their medication too late in their attack).
 - ii. **Step 2:** A triptan should be recommended as primary therapy, with the addition of an anti-nauseant (e.g., metoclopramide 10 mg), if necessary, for patients who do not respond well to NSAIDs or acetaminophen. Several

different triptans should be tried in different attacks if the response to the first triptan is not excellent (see strategy 2b: triptan strategy). When a different triptan is tried, product monographs recommend that it not be used within 24 hours of the previous triptan.

- iii. **Step 3:** For patients whose usual response to triptans remains inadequate in most attacks, or who sometimes respond well but have relatively frequent triptan failures, an NSAID (e.g., naproxen sodium 500 - 550 mg) should be given simultaneously with their triptan (see strategy 3a: triptan-NSAID combination strategy).
- iv. **Step 4:** For patients with relatively severe attacks who usually respond well to their triptan-NSAID combination, the need for a further "rescue" medication should be considered for when the usual medication fails if the patient does not respond in every attack (see strategy 3b: triptan-NSAID combination with rescue medication strategy).
- v. **Step 5:** For patients who do not respond satisfactorily to either NSAIDs or triptans or combinations of these, the feasibility of using dihydroergotamine (DHE) either by nasal spray or if necessary by self-injection (subcutaneous or intramuscular) should be considered in the absence of contraindications. Concomitant use of an anti-nauseant (metoclopramide 10 mg orally) should be considered, especially with DHE by injection (see strategy 3c: dihydroergotamine strategy).
- vi. **Step 6:** Opioid analgesics (e.g., acetaminophen with tramadol or codeine) remain an option for patients without a satisfactory response to earlier treatment steps, but their frequency of use should be closely monitored and behavioural and pharmacological preventive treatment options should be explored. These medications are also an option for patients with contraindications to vasoconstrictor drugs and who do not respond to NSAIDs or non-opioid combination analgesics (see strategy 4: vasoconstrictor unresponsive-contraindicated strategy).

EXPERT CONSENSUS

- i. *Patients with severe attacks that often require bed rest:*
 - a. *Should be given a triptan (with an anti-nauseant, if necessary), consistent with the stratified approach.*
 - b. *Subcutaneous sumatriptan 6 mg may be the preferred triptan for severe attacks with early vomiting, or for severe attacks which do not respond to other triptan formulations.*
- ii. *Patients with less severe attacks and who have not had adequate trials of non triptans:*
 - a. *Should be educated about acute treatment options.*
 - b. *An anti-emetic (metoclopramide 10 mg or domperidone 10 mg) can be added to acute migraine medications if needed for nausea.*
 - c. *A "step care across attacks" strategy as outlined below can be initiated with careful patient follow-up.*

Step 1: ASA 1,000 mg, ibuprofen 400 mg, diclofenac potassium 50 mg, naproxen sodium 550 mg, or acetaminophen 1,000 mg if NSAID intolerant. For patients with relatively severe attacks (but not usually requiring bed rest), a triptan can be

prescribed at the same time. The triptan can be used as a rescue medication by the patient as necessary if the NSAID or acetaminophen occasionally fails, or can be adopted as the patient's primary acute migraine medication if the NSAID or acetaminophen proves unhelpful (see step 2 below).

Step 2: For patients not responding well to NSAIDs, use a triptan as the primary medication for acute migraine therapy:

- a. At least three different triptans should be tried (in different attacks) if the response to the first triptan is not excellent. An excellent response is defined as pain free or almost pain free with the ability to resume usual activities at 2 h post-dose, and no significant side effects.
- b. A triptan should be used to treat approximately three separate migraine attacks before being judged effective or ineffective.
- c. Intranasal triptans which are partially absorbed through the nasal mucosa (e.g., zolmitriptan 5 mg) may be preferred to oral triptans for patients with nausea. It is important that patients administer them according to the product monograph to allow for maximum nasal drug absorption.
- d. Orally dissolving tablets (wafers) may be the preferred oral triptan for patients with nausea exacerbated by taking fluids.
- e. For patients with more than one migraine attack severity, providing medications from two different classes should be considered (e.g., a triptan and NSAID).

Step 3: For patients whose response to triptans remains inadequate because of incomplete relief or frequent treatment failure, an NSAID (e.g., naproxen sodium 500 - 550 mg) should be used simultaneously with their triptan.

Step 4: For patients with a good response to their triptan-NSAID combination therapy but who experience occasional treatment failure, consider the need for a rescue medication. Rescue medications can include additional NSAIDs (oral, rectal, or injectable with oral metoclopramide), prochlorperazine (oral, rectal), corticosteroids, and acetaminophen with tramadol or codeine (not for routine use; monitor frequency of use carefully).

Step 5: For patients who do not respond satisfactorily to an NSAID-triptan combination, the use of dihydroergotamine (nasal spray or self-injection), combined with oral meto-clopramide (if needed), can be considered.

Step 6: Although not recommended for routine use in migraine, opioid analgesics (e.g., acetaminophen with codeine or tramadol) remain an option for patients without a satisfactory response to earlier treatment steps, but:

- a. their frequency of use should be closely monitored (using a headache diary).
- b. behavioural and pharmacological preventive treatment options should be explored.
- c. these medications are also a treatment option for patients with contraindications to vasoconstrictor drugs and who do not respond to NSAIDs.

Acute Migraine Treatment Strategies

There are many drugs available for acute migraine treatment. These need to be chosen based upon patient clinical characteristics, and each needs to be used appropriately. The

medications are organized here into a number of treatment strategies, and are discussed below. Once the clinical data on a specific patient has been gathered, including past medication use and response, an appropriate strategy should be chosen and implemented. Depending upon the patient's response to the chosen pharmacological treatment strategy, the same strategy can be continued, or a new strategy can be implemented.

The primary drugs for acute migraine attack treatment are the NSAIDs (including ASA) and the triptans. Acetaminophen is widely used, but is considered less effective than the NSAIDs, and suitable mainly for attacks of mild to moderate severity. In the treatment strategies discussed below, metoclopramide is recommended when an anti-nauseant is needed, as more evidence is available for efficacy for this drug than for the related medication, domperidone. Domperidone can also be used, and may have fewer side effects; however, domperidone may be associated with QT prolongation in some patients.

1. Mild to moderate attack strategies

For patients with attacks that are not disabling (i.e., attacks do not require bed rest, and do not stop participation in activities, although it may be somewhat difficult for the patient to continue), the following two strategies may be most appropriate:

a. Acetaminophen strategy

This strategy simply involves the use of acetaminophen 1,000 mg, as needed. It can be used alone, or in combination with metoclopramide 10 mg (or domperidone 10 mg). Acetaminophen has the advantage of fewer gastrointestinal side effects than NSAIDs, and has been shown to be superior to placebo in the acute treatment of migraine attacks.^{2,3} Acetaminophen is considered to be less effective than NSAIDs for acute migraine treatment; and there is some limited randomized controlled data to support this in pediatric patients⁴, and in adults.⁵

Acetaminophen is thought to act primarily centrally, and inhibits prostaglandin synthesis in neurons. Because it is unable to inhibit prostaglandin synthesis in leukocytes and platelets, it does not have anti-inflammatory or anti-platelet activity. Acetaminophen-induced analgesia is blocked by CB1 receptor antagonists, suggesting that it also acts through cannabinoid receptors.⁶ It has a relatively short elimination half-life of 2 - 3 h, so repeated dosing may be necessary for a sustained analgesic effect. Maximum plasma concentrations of acetaminophen are reached within 30 - 60 minutes. The usual recommended dose for analgesia is 650 - 1,000 mg (a dose of 1,000 mg is recommended for migraine). This can be repeated every four to six hours, with a maximum of 4,000 mg per 24 hours.

EXPERT CONSENSUS

i. Acetaminophen is an effective option for acute migraine therapy for some patients with attacks of mild to moderate intensity.

b. NSAID strategy

A number of commonly used NSAIDs have high quality evidence for efficacy for acute migraine treatment. These include ASA, ibuprofen, naproxen sodium, and diclofenac potassium.

Table 4: Non-Steroidal Anti-Inflammatory Drugs: Pharmacokinetics and Dosage

Drug	T _{max} (hours)	Elimination half-life (hours)	Dose (mg)*	Dosage interval (if repeated) & maximum daily dose*
Acetylsalicylic acid (ASA) (tablet)	1 - 2	ASA: 0.25 Salicylate (active): 5-6 (after 1 g dose)	975 - 1,000	every 4-6 h; max: 5.4 g/day (varies depending on indication)
Acetylsalicylic acid (ASA)(effervescent)	~20 min	as above	975 - 1,000	every 4 h; max: 8 (325 mg) tablets
Ibuprofen (tablet)	1 - 2	2	400	every 4 h; max: 2,400 mg
Ibuprofen (solubilized)	< 1	2	400	every 4 h; max: 2,400 mg
Naproxen sodium**	2	14	500 - 550 (up to 825 mg)	twice a day; max: 1,375 mg
Diclofenac potassium (tablet)	< 1	2	50	3-4 times a day; max: 150 mg
Diclofenac potassium (powder for oral solution)	15 min	2	50	single dose recommended for migraine attack
Ketorolac (tablet)***	< 1	5	10	3-4 times a day; max: 40 mg

T_{max} = time to maximum plasma concentration; *Note: for acute migraine treatment, only one or two doses are usually recommended; doses are for adults; **Absorbed more quickly than naproxen; ***No controlled trial evidence for efficacy in migraine

Other NSAIDs (e.g., oral ketorolac) lack randomized controlled trial studies in migraine. It would appear most prudent to utilize NSAIDs with good evidence for efficacy, although it is possible that other NSAIDs might be more effective in selected patients. The NSAID can be used alone or with metoclopramide.

In choosing an NSAID, the pharmacokinetic properties of the drug should be considered. Rapid absorption provides the opportunity for a rapid onset of action for quick migraine relief, and this may be important for patients with migraine attacks that increase rapidly in intensity. For patients with relatively prolonged migraine attacks, an NSAID with a longer half-life (e.g., naproxen) may reduce the likelihood of headache recurrence. NSAIDs currently used for migraine have quite different pharmacokinetic properties (Table 4).

Rapidity of absorption of NSAIDs does depend in part on tablet dissolution times, and solubilized formulations of ibuprofen, effervescent ASA, and diclofenac potassium powder for oral solution may be especially useful because of more rapid oral absorption (see Table 4).

There is probably no ideal NSAID for migraine, and it is often worthwhile for patients to try several if their response to their initial NSAID is not ideal. Numbers needed to treat (NNTs) for various NSAIDs (the number of patients who will need to be treated to achieve a pain relief endpoint in one patient over and above the placebo response) as available are given in Table 5.

Ibuprofen appears to be the most commonly used NSAID for migraine in Canada, perhaps in part because it is widely available without prescription.⁷ Its relatively short elimination half-life (2 h) may result in the need for repeated dosing in many patients. Ibuprofen is preferred by many patients, perhaps because of its rapid onset of action. It may produce less gastric irritation than ASA, and the NNT for a positive response as compared to placebo is at least as good if not better than for ASA in migraine. In controlled clinical trials, doses greater than 400 mg were no more effective than the 400 mg dose for acute migraine attacks.

Ibuprofen has shown good efficacy in acute migraine^{8,9}, and appears to have similar efficacy compared to other acute

Table 5: Number needed to treat (NNT) for simple analgesics/NSAIDs in the acute treatment of migraine^{9,11,14,154,155}

Analgesic or NSAID (tablets)	NNT (2-h headache relief)	NNT (2-h pain-free)
Acetaminophen 1,000 mg ¹⁵⁴	5.0	12.0
ASA 900-1,000 mg ¹⁴	4.9	8.1
ASA 900 mg + metoclopramide 10 mg ¹⁴	3.3	8.8
Ibuprofen 400 mg ⁹	3.2	7.2
Naproxen sodium 500-825 mg ¹¹	7.0	15.0
Diclofenac potassium (tablet) ¹²	6.2	8.9
Diclofenac potassium powder for oral solution ^{13,155}	4.5	7.1

migraine drugs. In one large, double-blind, cross-over trial, the percentage of patients with a reduction in headache severity from moderate or severe to mild or no pain at 2 h (primary endpoint) was 52.5% for effervescent ASA 1,000 mg, 60.2% for ibuprofen tablets 400 mg, 55.8% for sumatriptan 50 mg, and 30.6% for placebo. All active treatments were superior to placebo ($p < 0.0001$), whereas the active treatments were not statistically different from one another.¹⁰ Ibuprofen is, therefore, a well-established acute migraine headache treatment. Its strengths include a short time to maximal plasma concentrations and a rapid onset of action, with the solubilized formulation being somewhat faster than the regular tablets. Its main shortcoming is its relatively short half-life. When repeated dosing is necessary, the patient may respond better to an NSAID with a longer duration of action (e.g., naproxen sodium).

Naproxen sodium also has good evidence for efficacy in migraine¹¹, and is widely used. Naproxen sodium (immediate release formulation) is preferred to naproxen due to its faster onset of action, and there is some evidence (one clinical trial) that the 825 mg dose is more effective than the 500 mg dose.¹¹ Naproxen sodium may be used up to twice daily, if necessary, and its long half-life may be an advantage over other NSAIDs in some patients.

There is good evidence supporting the use of diclofenac potassium for the acute treatment of migraine.¹² As the sodium salt of diclofenac is only available in Canada as enteric-coated or sustained release tablets, diclofenac potassium should be used in migraine because of a faster onset of action. Although doses greater than 50 mg (i.e., 100 mg) have not been shown to be superior to the 50 mg dose, it is possible that higher doses may benefit individual patients. Diclofenac potassium has recently become available as a powder (50 mg) for oral solution. It has a T_{max} of 15 minutes, and has shown superiority over the regular tablet at the same dose for the pain-free at two hours endpoint in one study ($p=0.0035$).¹³ The plasma half-life for diclofenac potassium is relatively short and similar to that of ibuprofen.

ASA in doses of 975 to 1,000 mg with or without metoclopramide also has good evidence for efficacy in acute migraine; addition of metoclopramide 10 mg improves relief of nausea.¹⁴ Effervescent ASA has a faster onset of action than regular tablets (Table 4), and has shown similar efficacy to sumatriptan 50 mg for the treatment of acute migraine attacks (including severe attacks).¹⁵

EXPERT CONSENSUS

- i. NSAIDs (including ASA) are helpful for many patients with migraine. Although it cannot be predicted which NSAID will be best for a specific patient, pharmacokinetic differences between them should be considered when treatment recommendations are made.
- ii. For patients with migraine attacks that increase in intensity rapidly, diclofenac potassium powder for oral solution, effervescent ASA, and solubilized ibuprofen capsules have a rapid onset of action and may be particularly helpful.
- iii. For patients with migraine attacks that increase in intensity rapidly, diclofenac potassium tablets have the most rapid onset of action for tablet formulations of NSAIDs (note: diclofenac potassium powder for oral

solution has a more rapid oral absorption than tablets).

- iv. The long plasma half-life of naproxen sodium may make it particularly helpful for patients with prolonged migraine attacks.

2. Moderate-severe attack or NSAID failure strategies

a. NSAID with triptan rescue strategy

Clinical trials indicate that NSAIDs may be helpful for patients with migraine of any severity, although many of the NSAID clinical trials excluded patients who frequently required bed rest for their attacks. For the patient with relatively severe migraine attacks, when an NSAID is tried, it may be useful to provide a triptan as a rescue medication, should the NSAID prove unsatisfactory. The triptan in this “step-care within attack” mode of use may also not prove entirely satisfactory as it will be taken relatively late in the attack, but nevertheless it should give the patient some relief, and perhaps help avoid the patient becoming a “lapsed consumer”. Patients can then decide over time whether it is necessary to make the triptan their primary acute medication rather than the NSAID, in which case they can start to take it early in the attack.

Another situation where the “NSAID with triptan rescue” strategy can be useful is if the patient’s attacks usually do respond well to an NSAID, but the NSAID occasionally fails. The patient will then use the triptan for only a relatively small proportion of attacks. If patients have attacks of varying severity and are able to predict the eventual intensity of a developing migraine attack, they may choose to take a triptan early only for those attacks that they think will become severe, and an NSAID for those that will likely be of mild or moderate intensity. If they are unable to predict the intensity of the developing migraine attack, the “NSAID with triptan rescue” strategy may be more satisfactory for them.

More details on triptan use are provided in the next section below.

b. Triptan strategy

This section will provide a detailed description of triptan pharmacology and adverse events, as the triptans are very important acute migraine medications and many physicians are not as familiar with them as they are with NSAIDs. Clinical use of the triptan strategy will then be summarized. Triptans can be used with or without metoclopramide.

Triptan pharmacology

Triptans are serotonin agonists with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors, and act on the trigeminovascular system. Through activation of the 5-HT_{1D} receptor, they may block the release of vasoactive peptides from perivascular trigeminal nociceptive nerve terminals, and also inhibit synaptic transmission from primary to secondary sensory neurons in the trigeminocervical complex. Selective vasoconstrictor effects on intracranial blood vessels through activation of 5-HT_{1B} receptors on vascular smooth muscle also may be important in their migraine-abortive efficacy. Triptans may also facilitate descending pain inhibitory systems.^{16,17} Almotriptan is also an agonist at the 5-HT_{1F} receptor (shown to be effective in aborting migraine)¹⁸, and frovatriptan at the 5-HT₇ receptor (clinical

relevance unknown). Triptans not only relieve migraine pain, and but also relieve associated symptoms including nausea, vomiting, photophobia, and phonophobia.

A major advantage of triptans over most other alternatives (e.g., ergots, analgesics) is their more specific mechanism of action and favourable side effect profile. However, it is estimated that up to one-third of patients fail to achieve adequate pain relief with oral triptans.^{17,19}

Triptans and treatment early in the attack

Although triptans can be effective at any time during a migraine attack, their efficacy is better when they are taken early in an attack (when headache pain is still mild).²⁰ However, early intake can lead to frequent medication use and medication overuse headache in some patients. In epidemiological studies, the risk for migraine chronification became significant with triptan intake at 12 days per month.²¹

Triptan formulations

Seven triptans are currently available in Canada: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. All are available in oral dosage forms, two as intranasal sprays (sumatriptan, zolmitriptan), and one as a subcutaneous (SC) injection (sumatriptan). Rizatriptan and zolmitriptan are also available as orally dissolving tablets (wafers).

The route of administration of a triptan can affect its efficacy, tolerability, and speed of onset. Injections (SC) and nasal sprays generally have a faster onset of action and higher efficacy compared to orally administered medications. Subcutaneous sumatriptan (6 mg) has the highest response rates; up to 80% of patients have pain relief after 2 h.^{22,23} It has a therapeutic gain of 51 percentage points (70% response with active treatment vs. 19% with placebo), which is the largest for all available triptans.²⁴ However, oral tablets are often preferred by patients even though they have a slower onset of action. The oral route may not be feasible in the presence of significant nausea and/or

Table 6: Triptans - pharmacokinetics^{19,23,29,31,156,157}

	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Bioavailability	70%	50%	Males:20% Females: 30%	Males: 63% Females: 74%	45%	SC: 96% Oral: 14% Nasal: 16%	Oral: 40% Nasal: 41%
T_{max}	1 - 3 h	1 - 2 h	2 - 4 h	2 - 3 h	Oral: 1 - 1.5 h ODT: 1.6 - 2.5 h	SC: 15 min Oral: 2.5 h Nasal: 1 - 1.5 h	Oral/ODT: 2 h Nasal: 2 h
Onset	0.5 - 2 h	0.5 - 1 h	precise data not available; slow onset for most patients	1 - 3 h	0.5 - 1 h	SC: 10 - 15 min Oral (fast dissolving): 30 min. Nasal: 15 min	Oral/ODT: 45 min Nasal: 10 - 15 min
Elimination half-life	3 - 4 h	3.8 h	~26 h	5 - 8 h	2 - 3 h	2 h	2.5 - 3 h
Metabolism & elimination	MAO-A, CYP3A4, CYP2D6; inactive metabolites; 40% unchanged in urine	CYP3A4; active N-demethylated metabolite; 90% non-renal clearance	CYP1A2; several metabolites; active desmethyl frovatriptan	CYP 450 (various isoenzymes); inactive metabolites; 50% unchanged in urine	MAO-A; inactive & one active metabolites; 8 -16% unchanged in urine	MAO-A; inactive metabolites	CYP1A2, MAO-A; inactive & one active metabolites; 8% unchanged in urine
Significant drug interactions*	None	CYP 3A4 inhibitors: E contraindicated within 72 h of potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole)	None (CYP1A2 inhibitors have minimal potential to affect kinetics of frovatriptan)	None	MAOIs (avoid use within 14 days) Propranolol (↑ AUC of R.; max. 5 mg single doses & 10 mg/24 h of R)	MAOIs (avoid use within 14 days)	MAOIs (avoid use within 14 days) CYP 1A2 inhibitors (e.g., cimetidine, fluvoxamine, ciprofloxacin); ↑ AUC & t _{1/2} of Z; max. 5 mg/24 h of Z)

*All triptans: do not use within 24 hours of an ergot derivative (e.g., ergotamine, DHE) or another triptan (due to possibility of additive vasoconstriction); there is a theoretical possibility of serotonin syndrome (rare) when combined with other serotonergic drugs (e.g., SSRIs, lithium) - however, this is controversial; AUC = area under the curve; MAOI = monoamine oxidase inhibitor; E = eletriptan; R = rizatriptan; Z = zolmitriptan; ODT = orally disintegrating tablet

vomiting. Patients may need access to more than one triptan formulation, based on attack characteristics.^{25,26}

Triptan choice and patient preference

Although the triptans are chemically related drugs, in clinical practice it is a common experience that some patients will prefer one triptan to another. This may relate to a perceived difference in efficacy, differences in the side effects experienced, or both. Which triptan a patient will prefer cannot be predicted. It is generally accepted that the differences between patients are greater than the differences between triptans, and no one triptan is superior to the others for all patients. With regard to individual patients this has led to the adage that the best triptan “is the one that works best for the patient”. The different triptans do have different pharmacokinetic properties, and also to some extent show differences in side effects. Triptan choice can therefore be tailored to some extent to the individual patient. Rapidity of pain relief, the probability of pain relief, the probability of headache recurrence, and the probability of adverse events all are potential contributors to how satisfactory the patient’s response will be to any given triptan.^{17,27,28}

Pharmacokinetic differences among triptans and onset of pain relief

The pharmacokinetic differences among the triptans (Table 6) may be clinically relevant for individual patients.^{19,23,28,29} Subcutaneous sumatriptan has the most rapid onset of action (approximately 10 min) compared to oral or intranasal triptans.³⁰ Intranasal zolmitriptan also has a relatively rapid onset of action (10-15 min).^{29,31} Of the oral triptans, rizatriptan and eletriptan have a relatively fast onset of action (approximately 30 min). Naratriptan and frovatriptan have the slowest onset of action (up to 4 h). There is no evidence that orally dissolving tablets/wafers act more quickly than regular tablets.

Subcutaneous sumatriptan with its rapid absorption and onset of action, coupled with no interference with absorption due to nausea or vomiting, gives it a unique therapeutic role. Although it is not as widely used as the oral triptans because of the need for an injection and also because of increased side effects, it should be considered where other formulations have proven less effective than desired, or where early vomiting in the attack renders other formulations ineffective.

Among the oral tablets, frovatriptan and naratriptan stand out as having a slower absorption, and a longer time to T_{max} . The remaining triptans show less differentiation, with rizatriptan having perhaps the fastest time to T_{max} , indicating the potential for a rapid onset of action.

The probability of pain relief

Table 7 shows the number needed to treat (NNT) for the “pain free at two hours” endpoint. This is the number of patients that need to be treated to render one patient pain free at two hours over and above the placebo response. Subcutaneous sumatriptan (6 mg) has the lowest NNT, indication the best efficacy for this endpoint. Among the oral triptans, rizatriptan provides the lowest NNT.

Table 7: Triptans – Number Needed to Treat (NNT) for pain-free response at 2 h in migraine^{*31,158-162}

Drug and dosage	Route	NNT (for 2-h pain-free vs. placebo)**
Sumatriptan 6 mg	subcutaneous	2.3 ¹⁵⁸
Sumatriptan 20 mg	intranasal	4.7 ¹⁵⁹
Zolmitriptan 5 mg	intranasal	4.6 ³¹
Almotriptan 12.5	oral	4.3 ¹⁶⁰
Eletriptan 20 mg	oral	10
Eletriptan 40 mg	oral	4.5
Frovatriptan 2.5 mg	oral	8.5 ¹⁶¹
Naratriptan 2.5 mg	oral	8.2
Rizatriptan 10 mg	oral	3.1
Sumatriptan 50 mg	oral	6.1 ¹⁶²
Sumatriptan 100 mg	oral	4.7 ¹⁶²
Zolmitriptan 2.5 mg	oral	5.9

* Adapted from: Bandolier (<http://www.medicine.ox.ac.uk/bandolier>) except as noted; ** Note: Migraine attacks were treated at moderate or severe intensity. NNTs may be lower for individual drugs when treatment is taken early in the migraine attack.

Adverse events

Adverse events also vary greatly from patient to patient, with one patient tolerating one triptan much better than another, while a second patient may show the reverse. Although the differences between the oral triptans are not large, almotriptan appears to have the lowest absolute adverse event rate.³² Triptan safety during pregnancy and lactation has not been established, but available information on triptan use during pregnancy and lactation is discussed below under the “Migraine during pregnancy strategy” and the “Migraine during lactation strategy”.

a) Cardiovascular safety

Concerns about the cardiovascular safety of triptans are due, in part, to adverse effects experienced by some patients, which are referred to as “triptan sensations”. These effects, including burning, tingling or tightness in the face, neck, limbs or chest, have been reported in approximately 1-7% of patients in clinical trials. Triptan-associated chest symptoms are generally mild and transient, and are not associated with electrocardiographic or enzymatic evidence of myocardial ischemia. However, because 5-HT_{1B} receptors are located on coronary arteries, triptans can constrict coronary arteries to a small extent, which is insignificant in patients without underlying coronary artery disease. Triptans do not appear to differ from one another in this regard.²³ The Triptan Cardiovascular Safety Expert Panel, a multidisciplinary panel convened by the American Headache Society, concluded that while serious cardiovascular adverse events have occurred after the use of triptans, the frequency in both clinical trials and in clinical practice appeared to be very low (less than one per one million exposed).³³ All triptans exhibit a similar safety profile when prescribed appropriately.

Triptans are contraindicated in patients with ischemic heart disease, coronary vasospasm, previous myocardial infarction, cardiac arrhythmias, cerebral or peripheral vascular disease, or uncontrolled or severe hypertension; they should be used with caution in hemiplegic migraine.

b) Serotonin syndrome

Migraine and depression are common, co-morbid, chronic illnesses.^{34,35} Triptans and SSRIs (selective serotonin reuptake inhibitors)/SNRIs (serotonin/norepinephrine reuptake inhibitors) have been taken in combination by millions of patients without resulting serotonin syndrome.³⁶ In July 2006, the United States (U.S.) Food and Drug Administration (FDA) issued an alert regarding the potential for life-threatening serotonin syndrome in patients taking triptans concomitantly with SSRIs or SNRIs, based on 29 case reports of serotonin syndrome. The FDA recommended that patients receiving these drugs concomitantly be informed of the possible risk of serotonin syndrome.

The American Headache Society (AHS) has issued a position paper regarding the FDA alert on the use of triptans combined with SSRIs/SNRIs.³⁷ Using the Sternbach Criteria for Serotonin Syndrome or the Hunter Serotonin Toxicity Criteria, the AHS assessed the 29 cases in the FDA report, as well as a more recently published review of 11 cases of serotonin syndrome resulting from triptan monotherapy.³⁸ Of the 29 cases obtained from the FDA, only 10 cases met the Sternbach Criteria for diagnosing serotonin syndrome, and none met the Hunter Criteria. Case reports of serotonin syndrome involving triptan monotherapy do not have sufficient details to confirm the diagnosis. The AHS concluded that inadequate data are available to determine the risk of serotonin syndrome with combined use of a triptan and SSRI/SNRI, or with triptan monotherapy. Furthermore, the currently available evidence does not support limiting the use of triptans with SSRIs/SNRIs, or the use of triptan monotherapy, due to concerns of serotonin syndrome. Patients taking both a triptan and an SSRI/SNRI should be informed of the symptoms of serotonin syndrome (although rare), and instructed to inform their physician immediately should such symptoms occur, in order to ensure prompt treatment.³⁷ Symptoms of serotonin syndrome include tachycardia, muscle twitching, tremor, sweating, and agitation.

The triptan strategy and overall triptan choice

This section will summarize several aspects of triptan use. For more information on headache recurrence and headache persistence after triptan use, please see specific sections below which deal with these issues. Table 8 shows the triptans available in Canada, and the doses usually used.

Treatment early in the attack

Like all acute migraine medications, triptans are more effective if taken early in the migraine attack (see a later section “The timing of triptan use in migraine with aura” for more information on migraine with aura). Patients should be advised to take them early in migraine without aura if they anticipate a migraine attack of at least moderate severity. For patients with relatively frequent migraine attacks this advice may need to be tempered with a caution that when triptans are taken on ten days a month or more (triptan overuse), patients may be at risk for more frequent headache attacks (triptan overuse headache).³⁹

Choosing a triptan formulation

The response of an individual patient to a specific triptan cannot be predicted with accuracy, but some attempt can be made to tailor the triptan to the patient’s needs. This requires an adequate headache history, and information about how quickly the patient’s attacks build up in intensity and how disabling the attacks are may be helpful. In general, for the oral triptans, if speed of onset and a high response rate are considered important by the patient, rizatriptan and eletriptan would be good choices overall. If headache recurrence is an issue, eletriptan and frovatriptan could have an advantage. If side effects are an issue, almotriptan would appear to have an advantage, and still couples this advantage with a good response rate and good headache recurrence profile.³²

If nausea is present, the nasal sprays can be useful, particularly zolmitriptan 5 mg which shows significant nasal drug absorption, and a rapid onset of action.^{40,41} If nausea is milder but exacerbated by taking liquids, the two oral wafers, rizatriptan and zolmitriptan, can be useful. They are not absorbed through the oral mucosa, and are therefore basically

Table 8: Triptan formulations available in Canada, with doses most commonly used*

Medication	Formulation and dose (mg)			
	Tablet	Wafer**	Nasal spray	Injection
Sumatriptan	50, 100		20	6
Zolmitriptan	2.5	2.5	5	
Rizatriptan	10	10		
Naratriptan	2.5			
Eletriptan	40			
Almotriptan	12.5			
Frovatriptan	2.5			

*See Table 9 for more detailed information regarding clinical use; **Orally disintegrating tablet

equivalent to the corresponding oral tablets except that water is not required for ingestion.⁴²

Sumatriptan (6 mg) by SC self-injection remains the triptan formulation with the highest overall headache response rate, and is the only formulation which guarantees complete absorption of the administered dose in the presence of vomiting. It also produces peak serum levels more rapidly than the other triptan formulations. It should be considered when patients awaken with fully developed migraine attacks that do not respond to oral triptans, when patients vomit early in the attack, or in general when migraine attacks do not respond well to other triptan formulations. Zolmitriptan nasal spray can also be considered in these situations, particularly in patients who are reluctant to use an injectable formulation. The triptan formulations available in Canada are shown in Table 8. Because individual patients respond differently in an unpredictable fashion, patients should if necessary try several other triptans over time, if the response to their current triptan is not optimal.

Patients with a history of sulfonamide (sulfa) allergies usually tolerate triptans well, including those that contain a sulfonamide moiety or sulfonyl group. If previous reactions to sulfa drugs have been severe, there is the option of choosing triptans without a sulfonamide or sulfonyl group in their chemical structure. Zolmitriptan, rizatriptan, and frovatriptan do not have a sulfonamide moiety or sulfonyl group, whereas almotriptan and eletriptan both have a sulfonyl group, and naratriptan and sumatriptan have a sulphonamide moiety.

Triptan use with an anti-emetic

Although the triptans will often treat associated symptoms like nausea quite satisfactorily at the same time as they relieve the headache, there are two situations where the addition of an anti-emetic (metoclopramide or domperidone), to be taken simultaneously with the triptan, can be helpful. The first is if nausea is so pronounced that additional medication is required to control this symptom. The second is if the response to the triptan is not fully satisfactory, perhaps because of gastric stasis and delayed absorption of the triptan. It has been demonstrated that migraineurs suffer from gastric stasis during an acute migraine attack, and also interictally between migraine attacks.^{43,44}

Although parenteral metoclopramide is used to treat the headache component of the migraine attack in the emergency department, metoclopramide in oral form seems much less effective for that purpose, and is used primarily to treat migraine-related nausea and to improve gastric motility. Either metoclopramide or domperidone can be used. Metoclopramide is used much more widely in migraine, and has more evidence for efficacy. Domperidone penetrates the CNS less, and therefore has less potential for extrapyramidal side effects. Domperidone in high doses, particularly in older individuals, has been linked to QT prolongation and serious cardiac arrhythmias.^{45,46}

Does metoclopramide increase the rapidity of drug absorption in migraine? In a small study involving ten patients, the time to reach peak plasma concentration of effervescent acetaminophen and the peak concentration reached were not changed by metoclopramide.⁴⁷ However, other studies have shown an effect on drug absorption. Metoclopramide pre-treatment in migraine attacks increased the serum concentration of tolfenamic acid at

1.5 h, but its peak concentration, time to peak concentration and the AUC_{0-5 h} remained unchanged as compared with the values obtained with tolfenamic acid alone.⁴⁸

Another study concluded that the impairment of absorption of effervescent ASA during migraine attacks is related to impaired gastro-intestinal motility with delayed gastric emptying, and this impaired motility can be overcome by parenteral metoclopramide.⁴⁹ A clinical trial in which domperidone 20 mg was added to acetaminophen concluded that domperidone shortens the duration of a migraine attack, and may help reduce headache and associated symptoms compared to acetaminophen alone.⁵⁰ In a study involving patients who had failed to obtain adequate relief from a triptan used alone, it was found that sumatriptan 50 mg plus metoclopramide 10 mg provided better relief than sumatriptan alone. It could not be differentiated whether this was due to central dopamine receptor antagonism or to better sumatriptan absorption.⁵¹

Metoclopramide is a substituted benzamide dopamine D₂ antagonist, and at higher doses also a 5-HT₃ antagonist. It is also a gastrointestinal pro-kinetic agent through mechanisms that are not fully understood. In addition to metoclopramide and domperidone, other anti-emetics that have been used in migraine include prochlorperazine (a phenothiazine dopamine D₂ receptor antagonist), and ondansetron (a 5-HT₃ antagonist). Prochlorperazine intravenously is widely used in the emergency room setting for migraine treatment. It is also used orally (10 mg) and rectally (10 - 25 mg) as an anti-emetic in migraine, but the evidence base for its use is much smaller than that for metoclopramide, and it is more likely to cause extra-pyramidal side effects. The evidence base for use of ondansetron as an anti-emetic in migraine is very limited.

Dimenhydrinate is widely available and often used by patients for nausea. It is a complex formulation containing diphenhydramine (an H₁ antagonist that mediates the anti-emetic effect), and a theophylline derivative (a CNS stimulant related to caffeine). Dimenhydrinate has some abuse potential. Given the lack of evidence for its efficacy in migraine, metoclopramide, domperidone, and possibly prochlorperazine would appear to be better choices for treatment of migraine-related nausea.

EXPERT CONSENSUS

- i. It should be recognized that the response of an individual patient to a specific triptan cannot be predicted with accuracy. Patients with a less than optimal response to their current triptan should be encouraged to try several other triptans in different migraine attacks to determine if they will obtain better relief.*
- ii. Patients should be encouraged to take their triptan early in their attacks while pain is still mild, although caution may need to be exercised in patients with frequent attacks to avoid medication overuse.*
- iii. For severe migraine attacks with early vomiting, the use of subcutaneous sumatriptan 6 mg should be considered. Zolmitriptan nasal spray 5 mg may be an alternative choice for some patients. These formulations should also be considered for all patients with severe nausea, particularly those who have nausea early in their attacks, and for attacks not responsive to oral triptan medications.*

- iv. For patients with moderate or severe migraine attacks who require triptan therapy, and whose attacks build up rapidly in intensity, rizatriptan 10 mg tablets, eletriptan 40 mg tablets, zolmitriptan 5 mg nasal spray, and sumatriptan 6 mg SC injection should be considered.
- v. For patients with moderate or severe attacks who experience side effects on other triptans, almotriptan should be considered.
- vi. For patients who experience frequent headache recurrence on triptan therapy, the use of eletriptan or frovatriptan should be considered, or the addition of naproxen sodium to the patient's current triptan.
- vii. For patients with nausea or vomiting who require an additional anti-emetic, metoclopramide, domperidone, or if necessary, prochlorperazine can be considered, to be taken with the triptan or triptan-NSAID combination.

Headache Recurrence on Triptans

The return of headache within 24 hours after initial relief is a difficult parameter to study objectively, because in order to experience headache recurrence patients must have first experienced relief, and the proportion of patients experiencing headache relief varies from drug to drug. If they produce initial headache relief, frovatriptan, naratriptan, and eletriptan may have some advantage in terms of a lower rate of headache recurrence.

Headache recurrence is experienced by 15-40% of patients taking an oral triptan; in most cases, a second dose of triptan is effective.⁵² Combining a triptan with an NSAID (e.g., sumatriptan plus naproxen sodium) reduces headache recurrence.⁵³ In a review of data derived from 31 placebo-controlled major efficacy trials of triptans, it was concluded that triptans with longer half-lives and greater 5-HT_{1B} receptor potency had the lowest rates of headache recurrence.⁵⁴ Mean headache recurrence rates ranged from 17% for frovatriptan to 40% for rizatriptan. Dihydroergotamine (DHE), another acute migraine treatment with a long half-life, is also known to have a low headache recurrence rate.⁵⁵

If patients do experience headache recurrence after initial relief from a triptan; the best practice is for the patient to take a second dose of the same triptan. For example, in a study with rizatriptan where headache recurrences were treated with either rizatriptan 10 mg or placebo (median time to recurrence 12 hours), the recurrent headache responded to a second dose of rizatriptan 10 mg in 82% of patients, versus 44% for placebo.⁵⁶

EXPERT CONSENSUS

- i. When patients experience recurrence of a migraine headache attack after initial headache relief from a triptan, a second dose of the triptan should be recommended.
- ii. For patients who experience frequent headache recurrence on triptan therapy, the use of eletriptan, frovatriptan, or dihydroergotamine (DHE) should be considered instead of the patient's current triptan, or the addition of naproxen sodium to the patient's current triptan.

Headache Persistence (triptan failure)

A related issue is what to advise if the patient's usual triptan dose fails to provide relief during some attacks. The usual advice is that if the initial dose has not provided relief, a second dose will also not be helpful. This is based on two types of evidence. First of all, in a study that tested the ability of zolmitriptan 5 mg, 2.5 mg and placebo to successfully treat a moderate or severe persistent headache 2 h after an initial dose of zolmitriptan 2.5 mg, neither dose of zolmitriptan was superior to placebo for headache response. The placebo response rate at 2 h after treatment for persistent headache was high at 51.6%, suggesting perhaps that the initial dose of zolmitriptan was still active in reducing headache severity. However, the second dose of zolmitriptan which had been used to treat the persistent headache was clearly no better, with a response rate at 2 h of 51.6% for the 5 mg dose, and 49.7% for the 2.5 mg dose. These results therefore suggested that a second triptan dose two hours after the first dose was no more effective than placebo at providing headache relief.⁵⁷

The other line of evidence comes from dose ranging triptan efficacy trials. Many of these suggest that as the dose of a triptan is increased, after a certain point headache response rates do not increase further. In one trial, for example, 2-h headache response rates for eletriptan 40 mg, and 80 mg were 62%, and 59% respectively, and at 4 h were 76%, and 79%, respectively.⁵⁸ In another study, the 2-h headache response rates for zolmitriptan 2.5 mg, 5 mg, and 10 mg were 65%, 67%, and 67%, respectively, again showing essentially no increase in headache response rates as the dose was increased over the usual therapeutic dose.⁵⁹ Both these types of data suggest that adding a second triptan dose within a few hours if the first dose is not successful in providing headache relief is not helpful, in sharp contradistinction to the good response that is seen with a second triptan dose when it is taken for headache recurrence. In clinical practice some patients do report relief after taking a second triptan dose for persistent headache, but given the very high placebo response rate observed in this therapeutic situation as discussed above, such anecdotal observations are difficult to interpret. It would seem prudent to use a non-triptan rescue medication if a patient's triptan medication has failed.

EXPERT CONSENSUS

- i. When patients experience occasional triptan failure with headache persistence two hours after taking a triptan, a rescue medication from another drug class should be considered, as opposed to dosing again with their triptan.

Timing of Triptan use in Migraine with Aura

Triptans are known vasoconstrictors, but triptan use during typical migraine auras appears safe. As migraine aura symptoms are likely due to a neurophysiological phenomenon (cortical spreading activation followed by depression) rather than vasoconstriction, it is not surprising that triptans do not seem to affect a typical migraine aura. In a study where 88 patients used subcutaneous sumatriptan 6 mg during their aura, it was found that sumatriptan given during the aura did not prolong or alter the nature of the migraine aura.⁶⁰

A number of clinical trials have shown greater efficacy when a triptan is taken early in the migraine attack. It would seem logical, therefore, to extend this observation and recommend that patients take their triptan during the migraine aura. Two randomized controlled trials, however, suggest that this is not advantageous. When subcutaneous sumatriptan was given during the migraine aura, 68% of patients went on to develop a moderate or severe headache within six hours, as compared to 75% of patients with placebo.⁶⁰ This difference was not statistically significant, although the study had only just over 80 patients in each group, and may therefore have been underpowered to detect a difference. Similarly, a study comparing eletriptan 80 mg given during the aura phase with placebo found no significant difference in the proportion of patients developing moderate-to-severe headache within six hours (eletriptan (61%) versus placebo (46%).⁶¹ This study was also relatively small, with just over 40 patients in each patient group. A third small crossover study using zolmitriptan 20 mg given during the aura found that a migraine headache did not follow the aura in three out of 16 patients, whereas the headache followed the aura in all patients who took placebo.⁶² This small study was interpreted as showing some promise for taking a triptan during the aura, although the response rate is clearly much lower than has been found in other studies when zolmitriptan is taken early in the pain phase of the headache. In summary, although all three of these small randomized studies showed no significant benefit as compared to placebo when a triptan is taken during the aura, none showed any adverse effects of the triptan on the aura.

Patients do anecdotally report success with taking a triptan during their migraine aura. These observations are difficult to interpret, given that in the eletriptan study, 54% of patients given placebo did not develop a headache afterwards, and similarly in the sumatriptan study 25% did not develop a headache after placebo. The randomized clinical studies would suggest that triptan treatment during the aura is not beneficial, and that patients should be advised to take their triptan after the aura during the initial part of the pain phase of their migraine. A small recent open label study, however, has suggested that at least for some patients, treatment during the aura may be advantageous. Using sumatriptan RT (fast dissolving formulation), treatment during the aura prevented the development of headache in 89% of attacks, while treatment during the pain phase within one hour of pain onset in the same patients rendered 79% of attacks pain free.⁶³

Triptan product monographs typically state that they are contraindicated in patients with hemiplegic, ophthalmoplegic, and basilar migraine. These contraindications are theoretical and presumably based on the vasoconstrictor actions of triptans, rather than on data. Given that migraine auras appear related to neurophysiological factors and not direct vasoconstriction and the lack of evidence regarding triptan use in these syndromes, the risk which triptans pose is unclear. Clinicians need to be aware of these contraindications. Anecdotally, where they have been tried, patients with hemiplegic migraine do seem to tolerate triptans safely and find them effective.^{64,65}

In summary, although small randomized double-blind placebo controlled trials have given no support for triptan use during the migraine aura, this practice appears safe in patients with a typical aura. It would seem appropriate to recommend that

patients take their triptan early at onset of the pain phase, but if they find taking their triptan during their aura consistently effective in preventing their headaches, there is no reason to discourage this practice.

EXPERT CONSENSUS

- i. Patients with migraine with aura should be advised to take their triptan at the onset of the pain phase, although triptan treatment during typical migraine aura is safe, and if patients find that treatment during the aura is effective, there is no reason to discourage this practice.*

3. Refractory migraine strategies

a. Triptan-NSAID combination strategy

The use of sumatriptan and naproxen sodium simultaneously to treat migraine attacks is based on several randomized controlled trials which have shown that the combination is more effective than either drug used alone.^{66,67} Naproxen sodium 500 mg was used in these trials, and was combined with several different sumatriptan dosages.

A sumatriptan-naproxen sodium combination tablet (not available in Canada) has also been compared to placebo in a patient population that had discontinued a short-acting triptan in the previous year because of poor effectiveness or intolerance. In these randomized double-blind, placebo-controlled, two-attack crossover trials the sumatriptan-naproxen combination tablet provided 2-h pain free results in 40 and 44% of patients in the two trials, versus 17 and 14% for placebo.⁶⁸

It would appear reasonable to apply the principle that early treatment during a migraine attack increases effectiveness of the sumatriptan-naproxen combination. In pooled data from two placebo-controlled trials, sumatriptan 85 mg combined with naproxen sodium 500 mg taken early in the attack provided 2-h pain free results in 51.5% of patients, versus 16% for placebo.⁶⁹

The sumatriptan-naproxen sodium combination has also been shown to reduce the headache recurrence rate as compared to sumatriptan taken alone.⁷⁰

Although the evidence available is largely confined to sumatriptan-naproxen sodium combinations, it would seem reasonable to generalize from this evidence to other triptan-NSAID combinations. Among NSAIDs, naproxen sodium may be particularly suited for combining with most triptans, given its long half-life and duration of action, but other triptan-NSAID combinations may also be effective. Table 9 provides information (doses, cautions, etc) for many medications used for acute migraine treatment.

b. Triptan-NSAID combination with rescue medication strategy

For some patients, triptans are effective for virtually every attack, particularly if they are taken early when the pain is still of mild intensity. When patients do experience occasional triptan failure, a rescue medication can be helpful and may in some cases prevent emergency department visits. For most patients, it would appear best to use the triptan-NSAID combination strategy before resorting to other rescue medications, although there may be exceptions if patients have only the very occasional triptan failure.

Table 9: Acute pharmacologic therapies for migraine^{2,3,8,11,12,14,15,19,23,154,157,163}

Drug class/drug	Dosage (adults)	Selected adverse effects	Comments
Triptans:			
Almotriptan (oral tablets)	6.25 or 12.5 mg (optimal dose 12.5 mg); may repeat once after 2 h* (max. 25 mg/24 h)	<i>All triptans:</i> Chest/neck/jaw discomfort or tightness (“triptan sensations”); paresthesias	<i>All triptans:</i> To avoid MOH, limit use to not more than 9 days/month
Eletriptan (oral tablets)	20 or 40 mg (optimal dose 40 mg); may repeat 20 mg dose once after 2 h*; a 2 nd 40 mg dose is not recommended by product monograph (max. 40 mg/24 h in Canada; 80 mg/24 h in U.S.)	If chest discomfort persists or appears to be cardiac in origin, consult physician immediately	Contraindicated in cardiovascular, cerebrovascular, peripheral vascular disorders, uncontrolled hypertension
Frovatriptan (oral tablets)	2.5 mg; may repeat once in 4-24 h* (max. 5 mg/24 h)		If no response to first dose of triptan, do not repeat for that attack; may repeat dose if partial effect from first dose (after appropriate interval) or if headache recurs after successful initial response
Naratriptan (oral tablets)	1 or 2.5 mg (optimal dose 2.5 mg); may repeat once after 4 h* (max. 5 mg/24 h)		
Rizatriptan [oral tablets, orally dispersible tablets (RPD®)]	5 or 10 mg (optimal dose 10 mg); may repeat after 2 h* (max. 20 mg/24 h)		<i>Rizatriptan:</i> Propranolol inhibits metabolism of rizatriptan; a dose of 5 mg is recommended for patients on propranolol.
Sumatriptan [oral tablets, fast-disintegrating tablets (DF), nasal spray, SC injection]	<i>Oral:</i> 25, 50 or 100 mg (optimal dose 100 mg); may repeat once after 2 h* (max. 200 mg/24 h) <i>Nasal:</i> 5 or 20 mg (optimal dose 20 mg) in one nostril; may repeat after 2 h (max. 40 mg/24 h) <i>SC:</i> 6 mg; may repeat once in 1 h (max. 12 mg/24 h)		
Zolmitriptan [oral tablets, orally dispersible tablets (Rapimelt®), nasal spray]	<i>Oral:</i> 1 mg or 2.5 mg (optimal dose 2.5 mg), may repeat once after 2 h* (max. 10 mg/24 h) <i>Nasal:</i> 2.5 mg or 5 mg (optimal dose 5 mg) in one nostril; may repeat once after 2 h* (max. 10 mg/24 h)		
Ergot derivatives:			
Ergotamine (+ caffeine) (oral tablets)	<i>Oral:</i> 0.5 to 2 mg at onset; then 1 mg q1 h prn X 3 doses (max. 6 mg/24 h); once an effective and tolerated dose has been established (usually between 0.5 and 2 mg), the whole dose should be taken at one time early in the attack	<i>Ergotamine:</i> nausea, vomiting, paresthesias, cramps, vasoconstriction, ergot dependence, ergotism	<i>Ergotamine:</i> Very limited role for ergotamine; to avoid MOH, limit use to not more than 9 days/month
Dihydroergotamine (DHE) (nasal spray, injection)	<i>Nasal:</i> 0.5 mg (1 spray) in each nostril; repeat in 15 min if no effect (max. 4 mg/24 h) <i>SC/IM:</i> 0.5 or 1 mg; may repeat in 1 h (max. 3 mg/24 h); maybe given IV (in hospital)	<i>DHE:</i> same as for ergotamine but less potent vasoconstriction <i>DHE nasal:</i> rhinitis, nausea, taste disturbance	<i>All ergot derivatives:</i> Many contraindications (e.g., cardiovascular, peripheral vascular disorders; pregnancy) Avoid concomitant use with potent CYP3A4 inhibitors (e.g., macrolide antibiotics, protease inhibitors) Avoid concomitant use with other vasoconstrictors Caution in elderly (due to vasoconstriction) Antiemetic (e.g., metoclopramide) may be required with parenteral DHE
Analgesics/NSAIDs:			
Acetaminophen	1,000 mg (max. 4 g/day)	<i>Acetaminophen:</i> Hepatotoxicity with acute overdose or chronic use of high doses (> 4 g/day)	<i>Simple analgesics/NSAIDs:</i> To avoid MOH, limit use of simple analgesics or NSAIDs to not more than 14 days/month
Acetylsalicylic acid (ASA)	975 – 1,000 mg		
Ibuprofen	400 mg	<i>ASA/NSAIDs:</i> GI irritation, renal toxicity, hypertension; avoid if ASA-induced asthma or GI ulcers	
Naproxen sodium	500 or 550 mg (up to 825 mg)		
Diclofenac potassium	50 mg (max. 100 mg)		
Opioid- and/or barbiturate (i.e., butalbital)-containing products:			
Butorphanol nasal spray (not recommended - use in exceptional cases only)	1 mg (1 spray) in one nostril; may repeat once in 60-90 min, if adequate pain relief is not achieved; this 2-dose sequence can be repeated in 4-6 h, if necessary	<i>All opioids:</i> CNS depression, sedation, respiratory depression, tolerance, dependence, abuse, possible addiction	<i>All opioids:</i> Limit use of opioid-containing products to refractory cases, with close monitoring of usage. Butorphanol: limit use to not more than 7 days/month
<i>Opioid combination products:</i> (e.g., acetaminophen + tramadol; acetaminophen/ASA + caffeine + codeine;	<i>Opioid combination products:</i> Individualized dosing (use lowest effective dose)		<i>Tramadol and codeine-containing products:</i> limit use to no more than 9 days a month

Table 9: continued

<i>Butalbital-containing products:</i> (i.e., ASA + butalbital + caffeine ± codeine) (not recommended – use in exceptional cases only)	<i>Butalbital-containing products:</i> Individualized dosing (use lowest effective dose)	<i>Butalbital-containing products:</i> sedation, dependence, abuse, possible addiction; withdrawal syndrome after discontinuing high doses	<i>Butalbital)-containing products:</i> Little evidence for efficacy; strong risk of overuse; avoid except in exceptional circumstances, with close monitoring of usage; suggest limiting use to not more than 7 days/month
Adjunctive drugs:			
Metoclopramide	10 mg orally (may repeat up to 4 doses/24 h); single doses of 20 mg may be used, if necessary.	<i>Metoclopramide:</i> drowsiness, extrapyramidal effects	May be combined with acute therapies
Domperidone	10 mg orally (may repeat up to 4 doses/24 h); single doses of 20 mg may be used, if necessary.	<i>Domperidone:</i> QT prolongation	
Prochlorperazine	10 mg orally (may repeat up to 4 doses/24 h) or 10-20 mg rectally** (may repeat up to 4 doses of 10 mg or 2 doses of 20 mg/24 h)	<i>Prochlorperazine:</i> drowsiness, dizziness, extrapyramidal effects	

MOH = medication overuse headache; GI = gastrointestinal; * Second dose may be taken if headache recurs after initial relief or if partial response to first dose (after specified time interval); if there is no response to first dose, 2nd dose should not be taken for that attack (may take drug for subsequent attacks); ** Rectal prochlorperazine is available in 10 mg strength only

There are several issues which make selection of an effective rescue medication for refractory migraine attacks difficult.

These include:

1. Many migraine sufferers with a refractory migraine attack have nausea and/or vomiting to a degree which may make it difficult to take oral medications effectively.
2. Many medications are more effective when given parenterally, particularly intravenously (e.g., metoclopramide, prochlorperazine, chlorpromazine, and ketorolac). Intravenous medications are not an option in the home setting, although patients can be trained to give themselves subcutaneous or intramuscular injections. Delivery of medication rectally (by suppository) in patients with vomiting (e.g., prochlorperazine) is also an option.
3. There is concern that opioid use may result in long term receptor changes in patients with migraine and lead to less responsiveness to other drugs (triptans and NSAIDs). It was found in a small case series that migraine patients with prior opioid exposure did not respond as well to intravenous ketorolac 30 mg than patients with no prior history of opioid treatment.⁷¹ Nevertheless, it remains unclear how clinically important receptor changes related to occasional opioid use might be in the long term in migraine management. There is also concern about the propensity of opioids to lead to escalation of use over time, and to medication overuse headache. Opioids should therefore not be used routinely in migraine, but are one option for rescue medication for occasional use when a patient's triptan fails.

Choosing a rescue medication for triptan failure is problematic in that triptans are vasoconstrictors, and as a result other vasoconstrictors (other triptans, dihydroergotamine, and ergotamine) are not recommended within 24 hours of the previous triptan dose (according to product information for triptans). The rescue medication choices that remain are somewhat limited. Available options for use at home include several classes of medications:

1. **NSAIDs** (oral and injectable): Oral NSAIDs are unlikely to provide adequate pain relief in patients who have failed triptan therapy, but may provide some relief, and may be useful in combination with dopamine antagonists. Among the NSAIDs, when patients have severe nausea or vomiting, intramuscular (IM) ketorolac is most likely to be helpful in the home setting provided that it can be administered safely. Ketorolac 60 mg IM has been shown to be as effective as a combination of meperidine 50-100 mg with an anti-emetic. Ketorolac 30 mg IM appears to be less effective.⁷² Whether IM ketorolac 60 mg can be used safely at home has been studied. In an open label clinical trial, 16 patients with episodic migraine administered 61 separate injections of ketorolac at home. The authors found that after appropriate training, patients were able to administer the ketorolac safely. Sixty-four percent of ketorolac injections in this open-label studies provided relief classified as "good". All patients had a history of frequent emergency room visits, and improvement was sufficient in 87% of ketorolac administrations in the study that an emergency room visit could be avoided. Of interest, 13 of the 16 patients had previously been IM dihydroergotamine treatment failures. For safety reasons, patients with a history of gastritis, ulcer, esophagitis, renal

insufficiency, or sensitivity to any non-steroidal were excluded.⁷³ Self-injection of ketorolac has not been widely used in Canada, but this small study suggests that it is an option which can be considered as a rescue medication in patients with triptan failure. If patients have already taken naproxen sodium or another NSAID as part of the triptan-NSAID combination strategy, consideration will need to be given to the time elapsed since the last NSAID dose, as ketorolac is also an NSAID.

As many migraine patients with refractory attacks will have nausea or even vomiting, an IM medication is an attractive option for home rescue. Rapidity of drug absorption is also an important factor, and with IM ketorolac, peak blood levels occur within 45 minutes. Combining it with an anti-emetic (e.g., rectal prochlorperazine) may be helpful.

Indomethacin is another option for rescue therapy in refractory migraine when triptans have failed. It has been studied as a combination drug with caffeine and prochlorperazine). In a double-blind randomized controlled study without placebo, an oral formulation of the three drugs (indomethacin 25 mg, prochlorperazine 2 mg, and caffeine 75 mg) was as effective as sumatriptan 50 mg for the 2-h pain free endpoint in migraine. Interestingly, when taken as a rescue medication at 2 h because of treatment failure, it appeared more efficacious than sumatriptan 50 mg.⁷⁴ In another study using suppository formulations for both the three-drug combination (indomethacin 25 mg, prochlorperazine 4 mg, and caffeine 75 mg) and for sumatriptan 25 mg, the three-drug combination provided a 2-h pain-free rate of 47% versus 35% for sumatriptan, and a 48-h sustained pain free response of 39% versus 32% for sumatriptan.⁷⁵ In summary, indomethacin in combination with prochlorperazine might be a useful rescue medication in patients with triptan failure. The combination medications used in the studies referenced above are not available in Canada, but indomethacin suppositories and prochlorperazine tablets and suppositories are individually available, and the suppositories could be used even in the presence of vomiting. In the context of a rescue medication, doses of indomethacin 50 mg and prochlorperazine 10 mg orally would appear appropriate. If suppositories are used, indomethacin 50 to 100 mg and prochlorperazine 10 to 25 mg might be useful (but see below re doses available in Canada).

2. Dopamine antagonists (prochlorperazine, meto-clopramide, and chlorpromazine): The effectiveness of a number of dopamine antagonists given intravenously in refractory migraine attacks has been well established.⁷⁶ Given orally, these medications are helpful as anti-emetics, but much less useful in actually aborting the migraine attack. Prochlorperazine given as a suppository in a dose of 10 - 25 mg can be helpful, particularly if the migraine attack is accompanied by nausea and vomiting. The efficacy of prochlorperazine 25 mg suppositories in acute migraine has been studied in an emergency department in a randomized, double-blinded, placebo-controlled study. Prochlorperazine was statistically superior to placebo, and the authors concluded that the 25 mg rectal suppository provided excellent pain relief within 2 h in patients with acute migraine.⁷⁷ The 25 mg suppository can be given twice a day. In Canada, only the 10 mg prochlorperazine suppository is available, but two can be used simultaneously to approximate doses used in the study above. A related drug, chlorpromazine, could also be considered,

as chlorpromazine both intravenously⁷⁶ and intramuscularly⁷⁸ has been reported to be helpful in acute migraine. Like prochlorperazine, it is a powerful antiemetic, and its sedative effects may also be helpful. No published studies on chlorpromazine suppositories in acute migraine treatment have been located, and chlorpromazine suppositories are not generally available in Canada.

3. Corticosteroids: Short-term high dose steroid treatment has a time-honoured place in the treatment of status migrainosus (or status migraine), although there is a lack of randomized controlled trials. It might therefore be considered for a refractory migraine attack that has failed to respond to the patient's usual acute medication. Reviews on this subject typically state that corticosteroids are commonly used as therapy for status migraine, and that short courses of rapidly tapering doses of oral corticosteroids (prednisone or dexamethasone) are thought to alleviate status migraine.⁷⁹ By extension, a short course of prednisone or dexamethasone (starting with a high dose of prednisone 50 or 60 mg on the first day and tapering over two or three additional days, or dexamethasone 8 mg on the first day, and tapering over two or three days) might be helpful as a rescue medication in a refractory migraine attack. Frequency of use should be limited to once a month or less.

Much of the research in this area has been done in emergency departments where dexamethasone has been assessed for its ability to prevent headache recurrence after acute migraine attack treatment with other drugs. A meta-analysis of available data concluded (in 2008) that when added to standard abortive therapy for migraine headache in the emergency room, a single parenteral dose of dexamethasone is associated with a 26% relative reduction in headache recurrence (NNT=9) within 72 hours.⁸⁰

Whether dexamethasone alone can reduce migraine intensity is less clear, but there is some evidence that it can. In a double-blind, randomized controlled study involving 190 patients in an emergency department, it was found that dexamethasone 8 mg IV reduced headache intensity more at 60 minutes and 24 hours post intervention than a relatively small dose of morphine (0.1 mg/kg) IV.⁸¹ Perhaps the best evidence that dexamethasone is potentially useful as a rescue medication in acute migraine attacks is data from a randomized, double-blind, cross-over study which compared rizatriptan 10 mg alone to dexamethasone 4 mg orally alone and to the combination of rizatriptan 10 mg and dexamethasone 4 mg in patients with menstrually related migraine attacks. The combination of the two medications was superior for both 24-h sustained pain relief and 24-h sustained pain free endpoints. For attacks treated with dexamethasone alone, the 24-h sustained pain relief endpoint was met in 33.3% of attacks. The significance of this result is difficult to assess in the absence of a placebo group, but the authors concluded that the use of dexamethasone alone in the treatment of menstrually related migraine attacks was not justified by their data.⁸² In patients who received the rizatriptan 10 mg - dexamethasone 4 mg combination, 50.7% met the 24-h sustained pain-free endpoint, versus only 32.2% of those who received rizatriptan alone ($p < 0.05$). Therefore, it might be expected, although not proven, that dexamethasone 4 mg taken several hours after a failed triptan treatment might confer clinically significant benefit.

4. *Opioids and opioid-containing combination analgesics:*

There are many reasons to avoid opioids in migraine therapy including:

- a. Not many comparison trials between oral opioids and other acute medications for migraine have been done, but clinical trials that are available including those using parenteral medications have shown that opioids are generally not superior in headache relief as compared to many other acute pharmacological therapies.^{72,83}
- b. Recent opioid use may render migraine specific medications less effective. In a post-hoc pooled analysis of rizatriptan trials, patients with prior opioid use within several months prior to taking rizatriptan showed a lower response rate to rizatriptan.⁸⁴ In a study with intravenous ketorolac given relatively late in the migraine attack, patients with a history of prior opioid use tended not to become pain free as compared to patients without a history of prior opioid use.⁷¹
- c. Among acute migraine medications, opioids place patients at relatively high risk for medication overuse headache, particularly with use at frequencies of eight days a month or more.⁸⁵ There is evidence that opioids induce persistent pronociceptive trigeminal neural adaptations, which may be of concern in patients with migraine.⁸⁶

Nevertheless, opioids are widely (and often inappropriately) used in Canada as acute migraine medications. In 2005, in a nation-wide population-based sample of Canadians with migraine, 21% listed a combination analgesic which contained codeine as their primary acute migraine medication.⁷ Combination analgesics with acetaminophen, codeine, and caffeine, although not recommended for routine use, are an option for occasional use as a rescue medication, with the reservations noted above. If opioid-containing combination analgesics are used, tramadol may be a better choice than codeine, given its dual mode of action with binding to μ -opioid receptors, and serotonin and norepinephrine reuptake inhibition. The use of codeine is potentially problematic as it is a relatively inactive pro-drug, and its analgesic effect is dependent upon its conversion into morphine (via CYP2D6). As a result, it is ineffective in 7 to 10% of the white population because of homozygosity for the nonfunctional mutants of the CYP2D6 alleles. On the other hand, many individuals, depending on ethnic background (ranging from 2-3% in Europe to 40% in North Africa) are ultra-rapid metabolizers of codeine and experience a much greater effect of the drug (including both analgesic effects and side effects), because larger amounts of morphine are produced.⁸⁷ Tramadol has some direct analgesic effect from the parent drug. Because it also has an active metabolite which is more potent on the μ opioid receptor than tramadol itself, those who have higher CYP2D6 activity will have an increased analgesic effect, while those with less CYP2D6 activity will experience less analgesia.⁸⁸

Combination analgesics with barbiturates (with or without opioids) are best avoided because of risk of medication overuse headache which may occur at relatively low frequencies of use (as low as five days of use a month).⁸⁹ If they are used under exceptional circumstances, careful monitoring of frequency of use both by patient diary and by prescriptions is highly recommended.

Strong oral opioids (e.g., morphine, hydromorphone, oxycodone) are best avoided in migraine, if possible, but they may be an option for infrequent use (suggest limiting use to not more than seven days per month) as a rescue medication for the occasional patient (including oxycodone-acetaminophen combinations). Careful patient selection is important, and monitoring of frequency of use with headache diaries is recommended (Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain available at: <http://nationalpaincentre.mcmaster.ca/opioid/>).

Although not recommended for routine use, intranasal butorphanol is another opioid option for occasional use (suggest limiting use to not more than seven days per month) as a rescue medication when the patient's regular medication fails. It has the advantage that, as a nasal spray, it can be used during severe attacks even if the patient is vomiting. It may therefore reduce the need to attend an emergency department for parenteral medications. Intranasal butorphanol does have a significant risk for drug dependency⁹⁰, and can cause significant sedation and dysphoria. The usual dosage is 1 mg (one spray) in one nostril, with a second dose (1 mg) taken in 60 to 90 minutes, if adequate pain relief is not achieved. This two-dose sequence can be repeated in four hours, if necessary. If used at all, butorphanol should be considered only for carefully selected patients, and careful monitoring of use by the prescribing physician is essential to ensure that escalation in frequency of use is not occurring.

Sleep often helps to terminate a migraine attack and if opioids help to induce sleep, this has the potential to be beneficial. Barbiturate-containing combination analgesics are not recommended, however, because of risk of sedation, cognitive side effects and medication overuse headache.⁹¹ Of interest, however, in a randomized double-blind placebo-controlled trial in patients discharged after treatment in the emergency department, secobarbital 100 mg to be taken on arrival at home, with a second dose to be taken an hour later if not asleep, resulted in a sustained 24-h headache relief of 94%, as compared to 50% for placebo.⁹² However, based on minimal evidence for efficacy and the high risk of side effects and overuse, barbiturates are not recommended as a treatment option for acute migraine.

In summary, finding an effective rescue medication for refractory attacks in patients where their usual triptan medication or triptan-NSAID combination has failed can be problematic. A number of potential options, many of them without an adequate evidence base, are listed in Table 10. Anecdotally, occipital nerve blockade with local anesthetics can also be helpful in terminating acute migraine attacks, but controlled trials are lacking, and it is not a practical option for home use.

EXPERT CONSENSUS

- i. *For patients whose response to triptans alone is inadequate, an NSAID (e.g., naproxen sodium 500 - 550 mg) should be used simultaneously with their triptan.*
- ii. *For patients with nausea, or where poor drug absorption is suspected, oral metoclopramide 10 mg or domperidone 10 mg can be given with the triptan.*
- iii. *For patients with severe migraine attacks where their triptan or triptan-NSAID combination occasionally fails to provide adequate relief, a rescue plan should be*

discussed with the patient. This may include a rescue medication to be taken at home when their usual medication fails.

- iv. In providing a rescue medication, the patient needs to be carefully assessed, and the medication tailored as much as possible to the patient's needs. For parenteral formulations, careful patient training is essential, and consideration should be given as to whether the patient can safely administer the medication.
- v. For many rescue medications, in particular opioids and dexamethasone, frequency of use should be carefully monitored to ensure patient safety, and in the case of opioids to avoid medication overuse headache, abuse, dependence and possible addiction.
- vi. Rescue medications that can be considered, either alone or in combination, include:
 - a. NSAIDs with or without an anti-emetic, including ketorolac 60 mg by IM self-injection and rectal indomethacin
 - b. Dopamine antagonists including prochlorperazine suppositories
 - c. Oral dexamethasone or another steroid, either as a single dose or a short steroid taper over several days

d. Tramadol or codeine-containing combination analgesics (limit use to not more than 9 days a month)

e. Other opioids (suggest limiting use to not more than seven days per month)

- vii. Migraine attack preventive management options, both pharmacological and behavioural, should be considered for all patients where acute therapy is not adequately successful or the patient is at risk of medication overuse headache.

c. Dihydroergotamine strategy

Dihydroergotamine (DHE)

Dihydroergotamine (DHE) has a similar mode of action to the triptans, and is a 5HT_{1B} and 5HT_{1D} agonist. Unlike the triptans, it also acts on a number of other receptor subtypes, and this may be why some patients who do not respond well to the triptans respond to DHE. Dihydroergotamine is also associated with a lower headache recurrence rate than most triptans. Because DHE, like other ergotamines, is a vasoconstrictor, it is not an option as a rescue medication for triptan failure unless 24 hours have elapsed since the triptan was last taken.⁹³⁻⁹⁵

Dihydroergotamine is an option for primary therapy for patients without contraindications who do not respond well to

Table 10: Potential rescue medications in patients with occasional triptan failure (or failure of triptan-NSAID combination therapy)*

Medication	Comments
NSAIDs:	
Oral naproxen sodium, ibuprofen, or diclofenac potassium (all may be combined with oral metoclopramide or oral/rectal prochlorperazine)	Less likely to be effective as a rescue medication
Ketorolac (60 mg) IM	Requires patient training in safe injection technique
Indomethacin oral or rectal with or without prochlorperazine	Limited evidence
Dopamine antagonists:	
Prochlorperazine oral or rectal	May be used in combination with NSAIDs
Chlorpromazine oral	Sedation and anti-emetic properties may be useful
Steroids:	
Dexamethasone / prednisone oral	Limited evidence. Limit to short courses (single dose or several days), and limit frequency of use.
Opioids:	
Combination analgesics with tramadol	Monitor use – risk of medication overuse – limit to 9 days a month or less
Combination analgesics with codeine	Monitor use – risk of medication overuse – limit to 9 days a month or less
Intranasal butorphanol	Best avoided - monitor frequency of use closely – high risk of addiction, medication overuse – select patients carefully, limit use to no more than 7 days a month
Combination analgesics with barbiturates	Best avoided, use only in exceptional circumstances – monitor use – high risk of addiction, medication overuse
Strong opioids (morphine, hydromorphone, oxycodone)	Best avoided, use only in exceptional circumstances – monitor use – high risk of addiction, medication overuse, limit to no more than 7 days a month

*For additional information on drug dosages, etc, see discussion of Strategy 3b: Triptan-NSAID combination with rescue medication strategy.

the triptans, but unfortunately is not readily absorbed after oral administration. It is therefore only available as a nasal spray and by injection. The side effects of DHE and other ergots reflect their agonist activity at 5-HT_{1A} (nausea, dysphoria), 5-HT_{2A} (peripheral vaso-constriction), and dopamine D₂ (nausea, vomiting) receptors.⁹³ Idiosyncratic fibrotic complications involving the lung, heart, and retroperitoneum are serious but very rare side effects which appear to be linked to 5-HT₂ agonism.⁹⁶

Dihydroergotamine is associated with less potent vasoconstriction (peripheral arteries), less nausea and vomiting, and a lower risk of medication overuse headache compared with ergotamine.⁹⁷ However, both ergotamine and DHE were comparable in terms of vasoconstriction in human coronary arteries.⁹⁸ DHE has a central effect in the brainstem, which may result in enhanced efficacy in migraine.⁹⁹ It is available in intranasal (IN) and parenteral formulations [for intravenous (IV), intramuscular (IM) or subcutaneous (SC) use]. Oral DHE is not available in Canada.

Peak plasma DHE levels occur in 30-60 min with the IN formulation.⁹³ An orally inhaled form (delivered with a novel inhaler using a breath-triggered, synchronized mechanism) is currently being studied in phase III clinical trials; it appears to be promising.⁹⁶ IV DHE, usually given with an IV antiemetic, is useful for severe attacks in the emergency department. The IV route will not be discussed further in this guideline. DHE may also be self-injected (IM or SC) by patients at home¹⁰⁰⁻¹⁰², but individual patient instruction in proper injection technique is required as an auto-injector is not available. Peak plasma levels occur within 24 minutes with IM or SC administration.⁹⁶

Nasal DHE is typically administered as follows: One spray (0.5 mg) in each nostril, repeated after 15-30 minutes. Not all the medication is absorbed, and therefore the total dose is 2 mg, as compared to the usual 1 mg dose when DHE is used by injection. It is recommended that patients not use more than eight sprays in 24 hours or 24 sprays in one week. Subcutaneous or intramuscular self-injection of DHE provides more certain drug absorption than the intranasal route. Patients are typically trained to administer the DHE injections in the lateral thigh. The usual dose is 1 mg of DHE, but this can be reduced to 0.5 mg if nausea is a problem. Metoclopramide 10 mg taken orally 30 minutes before the DHE injection is often used routinely to reduce nausea. If injection-site burning is a problem, patients can be shown how to dilute the DHE by adding 0.5 ml of normal saline to 1 mL of DHE solution.¹⁰⁰ Patients should be cautioned to reduce the dose or discontinue DHE if leg cramps become a problem, or if they experience coldness or tingling in the hands and feet in association with the injections. An information sheet instructing patients how to self-administer DHE by subcutaneous injection has been published.¹⁰³

Dihydroergotamine injections can be used on an as needed basis, similar to the triptans. Similar to triptans and ergotamine, it is best not to exceed use on nine days a month, although, unlike other acute headache medications, DHE may not cause medication overuse headache.⁹⁴ For prolonged refractory migraine attacks, or if the DHE is used as a bridging medication during detoxification from medication overuse, the DHE can be administered by self-injection twice daily for three or four days, occasionally longer, and then on an as needed basis. Patients

should monitor carefully for side effects, as DHE used in this way exceeds the usual dosage recommendations. The usual recommended dose for subcutaneous or intramuscular use is 1 mg, and this can be repeated, as needed, at one hour intervals to a total dose of 3 mg in a 24 hour period. It is recommended that the total weekly dosage not exceed 6 mg. Nevertheless, headache specialists have for many years administered DHE for a number of days at dosages from 0.5 to 1 mg three times a day in inpatient settings, thereby exceeding the recommended maximum weekly dose.^{104,105}

To summarize, when DHE is used on an outpatient basis by self-injection, the dose should likely be limited to no more than 3 mg per day, administered in 1 mg doses if tolerated. Although daily injections can be used for several days if necessary in responsible patients with refractory headache attacks who are able to monitor for side effects, this should be limited to preferably two or a maximum of three 1 mg injections per day, usually for a maximum period of three to four days. However, in refractory patients longer courses of daily injections are sometimes used. Dihydroergotamine can be used on an as needed basis thereafter. It would appear prudent to limit long term DHE use to nine days a month, although it is unclear whether DHE causes medication overuse headache in migraine sufferers. As all other acute medications do, caution with regard to frequency of DHE use is advised.

Ergotamine

Ergotamine, introduced in the early 1900s, was the first migraine-specific agent. It is a potent serotonin 5-HT_{1B/1D} receptor agonist¹⁰⁶, and has also been shown to inhibit neurogenic inflammation in animals.⁹³ Rectal and sublingual dosage forms are no longer available in Canada, with only an oral tablet formulation (in combination with caffeine) currently available. Oral bioavailability of ergotamine is very poor due to extensive first pass metabolism. Caffeine is believed to enhance absorption of ergotamine.¹⁰⁷ Use of oral ergotamine is limited by side effects (in particular nausea), and limited efficacy. It is difficult to titrate oral ergotamine to an effective but sub-nauseating dose.⁹⁶ Ergotamine is a potent vasoconstrictor (alpha-adrenergic effect) and is associated with peripheral and coronary vasoconstriction. It is also associated with a risk of ergotism, and a high risk of medication overuse headache. Its use must be limited to less than ten days per month.¹⁰⁸ A meta-analysis of studies has concluded that the adverse effects of ergotamine outweigh any benefits.^{95,109}

Because ergotamine is not recommended for routine use, we have not provided an ergotamine strategy in this guideline. An expert consensus panel which reviewed the use of ergotamine (in the year 2000) concluded that there remains a place for ergotamine in modern clinical practice but only when used carefully.⁹⁵ The authors concluded that it remains useful for a limited number of migraine sufferers who have prolonged attacks or in whom headache recurrence is a substantial issue. It was felt that a triptan was a better option for most migraine sufferers requiring migraine specific medication both from an efficacy and side effect perspective. Given that there are more triptans available today than there were in 2000, it is likely that the place of ergotamine in migraine therapy today is even more limited. The same authors recommended a dose of 0.5 to 2 mg,

and once the patient's dosage is established, the whole dose should be taken at one time as early in the attack as practical. The objective is to find a dose which is effective but which has as few side effects as possible. A smaller dose can be tried initially, and this can be increased in subsequent attacks to determine the dose required to produce headache relief. Ergotamine can also be tested for tolerability with regard to nausea between attacks to assist in the process of finding the correct dose for the patient.

EXPERT CONSENSUS

- i. *Dihydroergotamine (DHE) by nasal spray [one spray (0.5 mg) in each nostril, repeated once after 15 - 30 minutes; maximum daily dose eight sprays] or self-injection (0.5 - 1 mg; maximum daily dose 3 mg) is an option for acute migraine therapy for patients who do not respond well to triptan-NSAID combination therapy (but not as a rescue therapy as it is also a vasoconstrictor).*
- ii. *DHE self-injection (SC or IM) requires individual patient training in safe injection techniques, but provides more reliable drug absorption than the intranasal route.*
- iii. *Oral ergotamine is not recommended for routine use, but remains an option for a small proportion of patients with prolonged headache attacks and / or frequent headache recurrence who do not respond well to the triptans and for whom DHE is not an option. When used, once an effective and tolerated dose has been determined (usually between 0.5 and 2 mg), the entire dose should be taken early in the headache attack to maximize effectiveness.*

4. Vasoconstrictor unresponsive or contraindicated strategy

The triptans and DHE are the most effective medications for many patients with severe migraine attacks, but a significant proportion of patients with migraine do not respond to these medications. For others, these medications may be contraindicated, primarily because of cardiovascular disease. The treatment options for both of these patient groups are similar, although for healthy migraine patients without cardiovascular disease, cardiovascular safety of NSAIDs will be less of an issue. The discussion below will focus on patients with contraindications to triptans, but options are similar for healthy patients who are triptan-DHE unresponsive.

For patients with contraindications to vasoconstrictors, the NSAIDs (including ASA) and acetaminophen, with or without metoclopramide, remain first line therapy (see strategy 1a: acetaminophen strategy and strategy 1b: NSAID strategy). If these are unsuccessful, combinations of NSAIDs, acetaminophen, and caffeine can be tried. It has been shown that combination analgesics with acetaminophen-acetylsalicylic acid (ASA)-caffeine are superior in providing headache relief as compared to the ASA-acetaminophen combination without caffeine ($p=0.0181$), to ASA alone ($p=0.0398$), acetaminophen alone ($p=0.0016$), caffeine alone ($p<0.0001$), and placebo ($p<0.0001$).¹¹⁰ This combination analgesic is not available in Canada, but patients could be provided with 500 mg of ASA, 500 mg of acetaminophen, and 50 to 100 mg of caffeine to be taken simultaneously. Metoclopramide 10 mg orally could be added as well. Even in patients with severe headache attacks, a fixed combination of ASA 500 mg, acetaminophen 400 mg, and caffeine 100 mg was found to be efficacious as compared to

placebo.¹¹¹ Although caffeine might interfere with sleep if the patient needs to rest, it does seem to confer a definite benefit in analgesia when taken with analgesics like ASA or acetaminophen. In a major review of this subject, it was concluded that caffeine made a significant contribution to analgesia, and that to obtain the same amount of analgesia without caffeine required an increase of 40% in the dose of the other analgesics in the combination tablet.¹¹² Combinations of ASA, acetaminophen, and caffeine taken together, with or without metoclopramide, can be considered for acute migraine treatment when simpler analgesic or NSAID regimens are not successful.

Many NSAIDs have been associated with an increased risk of cardiovascular events (myocardial infarction and stroke), and this may be a concern in patients with migraine and contraindications to triptans because of vascular disease. Even short-term use (< 90 days) of ibuprofen, diclofenac and celecoxib appears to lead to an increased risk of serious coronary artery disease. Naproxen, on the other hand, does not appear to result in increased cardiovascular risk.¹¹³ Another study also concluded that naproxen had a relatively safe cardiovascular profile, in contrast to diclofenac which had a higher risk.¹¹⁴ The relevance of these studies on NSAIDs and cardiovascular risk to patients with migraine who may use these drugs only occasionally is unknown, but if effective, naproxen sodium might be considered the NSAID of choice in patients with cardiovascular disease.

For patients with contraindications to vasoconstrictors who do not respond to NSAIDs, acetaminophen, and combinations of these with caffeine, the options for acute migraine treatment are limited primarily to analgesic combinations containing opioids (including tramadol), unless another solution (e.g., dopamine antagonists) can be found. Occasional use of steroids (e.g., dexamethasone) may also be an option for some patients. The options for patients in the "vasoconstrictor- unresponsive-contraindicated strategy" are similar to the options discussed above for rescue medications under the "triptan-NSAID combination with rescue medication strategy" (see Table 10). More caution with many of the available medications is needed, however, in that the patient using the "vasoconstrictor-contraindicated strategy" may be taking the medications on a regular basis, rather than only occasionally when their usual medication fails.

Although they are not recommended for routine use, in this circumstance combination analgesics containing codeine or tramadol may be necessary. In patients with severe attacks, stronger opioids and barbiturate-containing combination analgesics may also be a consideration in exceptional cases. The use of the opioid and barbiturate-containing analgesics should be very carefully monitored to avoid escalation of use and the development of medication overuse headache, dependence, abuse, and/or possible addiction. A headache diary which records medication use can be very helpful for this purpose.

As for all patients with migraine, whenever there is difficulty controlling migraine attacks satisfactorily with acute medications, non-pharmacological treatment approaches and pharmacological prophylactic drug therapy should be strongly considered. A multi-disciplinary treatment program may be helpful and should be pursued, if possible.¹¹⁵

EXPERT CONSENSUS

- i. *For patients with contraindications to vasoconstrictors or who have proven unresponsive to vasoconstrictors (triptans, DHE, and / or ergotamine), acetaminophen, NSAIDs (including ASA), acetaminophen-NSAID-caffeine combinations, dopamine antagonists (e.g., prochlorperazine), occasional steroid use, and opioid-containing combination analgesics can be considered.*
- ii. *Consideration needs to be given to the safety of NSAIDs in patients with cardiovascular disease. Because of a relatively benign cardiovascular profile, naproxen sodium may be the NSAID of choice, if effective, for patients with cardiovascular disease, particularly in patients who require relatively frequent use.*
- iii. *If use of tramadol or codeine-containing combination analgesics is necessary, frequency of use should be carefully monitored and limited to use on 9 days a month or less.*
- iv. *If, in exceptional cases, use of strong opioids or barbiturate-containing analgesics is considered, their frequency of use should be carefully monitored to avoid medication overuse headache, dependence, abuse, and possible addiction. Use should be limited to not more than seven days per month.*
- v. *Behavioural treatment strategies and pharmacological prophylaxis may need to be maximized if a satisfactory pharmacological acute treatment cannot be established.*

5. Menstrual migraine strategy

Women may have migraine attacks only at the time of menstruation (pure menstrual migraine), or they may have recurring attacks clearly related to menstruation but also have attacks during other parts of the menstrual cycle as well (menstrually related migraine). By definition, patients with menstrually related migraine (MRM) have migraine without aura attacks that occur during the time period starting two days before menstruation onset to three days after onset in at least two out of three menstrual cycles and additionally at other times of the cycle (Appendix A 1.1 http://ihs-classification.org/en/02_klassifikation/05_anhang/01.01.02_anhang.html).

It has long been a clinical impression that, at least in some women, MRM attacks are more severe and more difficult to treat than attacks occurring during other portions of the menstrual cycle. A recent study did to some extent confirm this clinical impression, in that MRM episodes were more impairing, longer lasting, and more likely to relapse than non-MRM episodes in a selected population of women with frequent menstrual migraine.¹¹⁶ Nevertheless, many studies have shown that MRM attacks appear to respond to triptans just as well as other migraine attacks do. A post hoc analysis of a major almotriptan trial, for example, found that almotriptan was similarly effective in relieving migraine symptoms and improving functional disability in MRM attacks as compared to non-MRM attacks.¹¹⁷ Many triptans have been shown to have good efficacy in treating MRM attacks.¹¹⁸⁻¹²⁰

It may be that clinical trials such as those cited above excluded patients with particularly severe menstrual migraine through their inclusion / exclusion criteria. However, it does

seem clear that the first step in the treatment of menstrual migraine attacks is to treat them in the same manner as other migraine attacks. If the response is less than optimal, treatment can be advanced to the use of triptan-naproxen sodium combinations. There is evidence that a sumatriptan-naproxen combination is efficacious in menstrual migraine.¹²¹ There is also evidence that adding dexamethasone (4 mg) to rizatriptan (10 mg) improves efficacy for menstrual migraine attacks above that of rizatriptan alone.⁸²

Nevertheless, there are patients with severe MRM attacks who do not respond well to acute attack treatment with triptans. Some of these patients do not have a sufficient number of attacks per month to justify a daily prophylactic medication, or may not have responded to such medications. In these cases, short-term prophylaxis with a triptan around the period of headache vulnerability can provide benefit. Typically such regimens involve taking a triptan twice daily for six or seven days, starting two days prior to the anticipated onset of a menstrual migraine attack. Regular periods are essential for this mode of therapy to be effective. Efficacy for such a regimen has been shown for frovatriptan 2.5 mg once or twice daily, naratriptan 1 mg twice daily, and zolmitriptan 2.5 mg twice or three times daily.¹²²⁻¹²⁵

Other options that have been researched for the short-term prophylactic treatment of problematic menstrual migraine include naproxen¹²⁶, and percutaneous estrogen. Percutaneous estrogen has been used on the basis that it may blunt the large reduction in estrogen that occurs naturally at the onset of menstruation. An evidence-based review published in 2008 gave grade B recommendations for the perimenstrual use of transcutaneous estrogen 1.5 mg, frovatriptan 2.5 mg twice daily, and naratriptan 1 mg twice daily for the preventive treatment of MRM.¹²⁰ However, recent controlled trials with estrogen have been plagued with post-dosing migraine attacks immediately after the estrogen treatment was stopped due to deferred estrogen withdrawal¹²⁷, or have been unable to show a benefit (with 100 mcg estradiol) over that provided by placebo.¹²⁸ On balance, it would appear that the best option available for short-term monthly menstrual migraine prophylaxis is frovatriptan 2.5 mg twice daily for at least six days. It has the best evidence, and among the triptans may be the preferred choice for short-term prophylaxis because of its long half-life (26 hours). Although medication overuse headache is a concern, taking an acute medication in a concentrated fashion over a short time period, with long medication free intervals during the remainder of the month may be less likely to lead to medication overuse headache than the same number of acute medication days spread more evenly throughout the month.

Other options for short term prophylaxis of MRM that have been evaluated by double-blind placebo controlled trials include magnesium pyroglutamate 360 mg daily started on the 15th day of the menstrual cycle and continued until menstruation started, and mefenamic acid 500 mg three times daily started at the onset of the MRM and continued for the duration of menstrual bleeding.^{129,130} In an evidence-based review, because of the poor quality of these studies, it was concluded that there was insufficient evidence to recommend for or against using magnesium for short term prophylaxis of MRM.¹²⁰ Given the nature of the mefenamic acid study, it was considered a symptomatic therapy study. The strength of

evidence supporting its use was considered fair, and mefenamic acid was recommended for routine use.¹²⁰

Continuous use of combined oral contraceptives (COCs) without interruption for a number of months in order to reduce the number of menstrual periods and, therefore, the number of MRM attacks has also been recommended. A detailed discussion on the use of extended COCs for menstrual migraine is beyond the scope of this guideline, and the evidence for efficacy in menstrual migraine is very limited. Several studies have shown that continuous use of low-dose COCs is safe for up to one year¹³¹ and two years¹³², although these studies were conducted in the general population, and not specifically in women with migraine. Headache symptoms including those during the period of hormone withdrawal, although headache type was not determined, have also been reported to improve with continuous use of COCs in open label studies.^{133,134}

Migraine with aura is a risk factor for stroke, and is often considered a contraindication to the use of COCs¹³⁵, although it has been questioned whether currently used COCs with low estrogen dosage pose a risk.¹³⁶ A recent review, however, concluded that use of low-dose COCs is associated with a two-fold increased risk of ischemic stroke compared with nonusers, and that given the availability of other contraceptive methods; it is difficult to justify exposing women with migraine with aura to these risks solely for contraception.¹³⁷ In otherwise healthy young females without other cardiovascular risk factors, however, the risks are small. In patients with disabling MRM, the risk/benefit ratio of using continuous low dose COCs for a period of time would need to be considered on a case by case basis. MRM migraine attacks are usually migraine without aura attacks.

It has been concluded that hormonal treatment of migraine is not a first-line strategy for most women with migraine, including menstrual migraine.¹³⁵ While use of COCs for extended time periods without interruption may be helpful in selected women with refractory menstrual migraine, other treatment regimens should be tried first.

EXPERT CONSENSUS

- i. *In most patients, acute treatment of menstrual migraine attacks is similar to acute treatment of attacks occurring at other times during the menstrual cycle.*
- ii. *For patients with refractory menstrual migraine who have a sufficient migraine attack frequency to justify general prophylactic therapy, this may be the best option.*
- iii. *For selected patients with refractory menstrual migraine with predictable timing of menstrual cycles, short-term monthly prophylaxis can be considered. Among the available options (frovatriptan, zolmitriptan, naratriptan, and naproxen), frovatriptan 2.5 mg twice a day starting two days before menstruation onset and continuing for six days has the strongest evidence for efficacy.*
- iv. *In selected patients, hormonal manipulation including estrogen supplementation around the time of menstruation, and continuous use of combination oral contraceptives can be considered but other treatment options should be tried first. If continuous use of combined oral contraceptives is being considered, contraindications and cautions for these (e.g., smoking, migraine aura, etc)*

should be observed (see discussion with regard to migraine with aura above).

6. Migraine during pregnancy strategy

Medication use should be minimized during pregnancy, and use of behavioural approaches which have no potential side effects for the fetus should be maximized. Although there are no controlled drug trials indicating the level of safety of individual acute migraine medications, sufficient data exists to show that some of the drugs used for acute migraine therapy are relatively safe during pregnancy. In general, dosages and frequency of use during pregnancy should be kept as low as possible. Both patients and practitioners may find the “Motherisk” website helpful (<http://www.motherisk.org/women/drugs.jsp>) when there are questions about medication use during pregnancy. Further advice from Motherisk is available by telephone (416-813-6780).

Acetaminophen

Although no drug has been “proven” to be safe during pregnancy, through long experience acetaminophen is considered the safest of all acute migraine drugs and the analgesic of choice during pregnancy. Unfortunately, its efficacy in migraine is somewhat limited.

Acetaminophen with codeine

Acetaminophen with codeine is also considered relatively safe. The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine have given codeine an “A” rating for use during pregnancy. An “A” rating is given to “drugs that have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed”.¹³⁸ It does need to be recognized, however, that prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate and is best avoided.

The relative safety of codeine use during pregnancy has recently been confirmed by data from the Norwegian Mother and Child Cohort Study.¹³⁹ Pregnancy outcomes of 2,666 women who used codeine during pregnancy were compared with 65,316 women who used no opioids during pregnancy. No significant differences were found in the survival rate or the congenital malformation rate between codeine exposed and unexposed infants. Codeine use anytime during pregnancy was associated with planned Caesarean delivery (adjusted OR 1.4, 95% CI 1.2-1.7; $p < 0.0001$). Third-trimester use was associated with acute Caesarean delivery (adjusted OR 1.5, 95% CI 1.3-1.8; $p < 0.0001$), and postpartum hemorrhage (adjusted OR 1.3, 95% CI 1.1-1.5; $p < 0.0001$). The authors concluded that no effects of maternal codeine intake during pregnancy were observed on infant survival or congenital malformation rate, but the association with acute Caesarean delivery and postpartum hemorrhage may justify caution when administering codeine toward the end of pregnancy.

Other opioids

Other opioids have been given a “C” rating, which includes them among drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible, and in the case of the strong opioids include respiratory depression in the newborn infant and withdrawal symptoms in newborn infants after prolonged use.¹³⁸

ASA and other NSAIDs

Acetylsalicylic acid (ASA) is best avoided during pregnancy, although it does not seem to cause malformations. When given late in pregnancy, it may cause premature closure of the fetal ductus arteriosus, and delay labour and birth. ASA increases the bleeding time both in the newborn infant and in the mother because of its irreversible antiplatelet effects. Products containing ASA should be avoided in the first trimester because of a possible increased risk of spontaneous abortion, and certainly during the last trimester for the reasons given above.

Other NSAIDs are preferable to ASA during pregnancy because of less prolonged effects on platelet function, but should also be avoided in the first trimester because of an increased risk of spontaneous abortion, and should be stopped before the 32nd week of gestation because of effects on the ductus arteriosus. During the latter part of pregnancy, they may also cause fetal renal impairment, inhibition of platelet aggregation and delayed labour and birth.¹³⁸

Ergotamines

Ergotamines must be avoided during pregnancy due to uterotonc effects.⁹⁵

Triptans

The role of the triptans during pregnancy remains controversial, but is becoming clarified as more data becomes available. Among the triptans, experience during pregnancy is by far the greatest with sumatriptan, and this is the triptan which should be used if triptan use is considered necessary. This might be the case, for example, in a patient with severe attacks that do not respond to acetaminophen or acetaminophen with codeine, especially if vomiting is present with the threat of dehydration. Data from the Norwegian Mother and Child Cohort Study has provided significant reassurance that sumatriptan is relatively safe during pregnancy.¹⁴⁰ This was a large, observational, prospective cohort study which evaluated fetal outcomes following exposure to triptans during pregnancy. In this study, 1535 women who used triptans during pregnancy (95% during the first trimester, and 65% during the second and third trimester) were compared with 375 migraine controls that had used triptans only prior to pregnancy, and to 68 021 non-migraine controls that had never used triptans. Among the triptan users during pregnancy, approximately half had used sumatriptan, and the remainder had taken one of the others. No significant associations between triptan therapy during the first trimester and major congenital malformations or other adverse pregnancy outcomes were found. Triptan therapy during the second and/or third trimesters was, however, significantly associated with

atonic uterus (adjusted OR: 1.4; 95% CI 1.1-1.8), and blood loss > 500 mL during labor (adjusted OR: 1.3; 95% CI 1.1-1.5).

The evidence from this study and from others suggests that sumatriptan is a relatively safe therapeutic option for the treatment of migraine attacks in pregnant women, but more studies are needed to confirm the safety of the other triptans in pregnancy. The practical application of these data is that women who suffer from migraine headaches which often render them unable to carry out tasks of daily living can use sumatriptan during pregnancy with relative safety, and without fear of harming their unborn baby.¹⁴¹

Anti-emetics

Several anti-emetics are considered safe during pregnancy. Metoclopramide would be considered the anti-emetic of choice. The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine gives it an “A” rating, and also gives this rating to use of dimenhydrinate, and diphenhydramine during pregnancy.¹³⁸ Domperidone is considered less safe, and was given a B2 rating (drugs that have been taken by only a limited number of pregnant women and women of child bearing age, but no malformations or other harmful effects on the fetus have been observed; and animal studies are inadequate for assessment of risk). Phenothiazines (e.g., prochlorperazine) are given a “C” rating, because when given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the infant. Drugs with a “C” rating are not known to cause fetal malformations.¹³⁸

In summary, the application of all this information, some of it quite new, is summarized in the expert consensus statements below.

EXPERT CONSENSUS

- i. *Avoid use of medications during pregnancy if possible, especially during the first trimester, and consider use of non-pharmacologic strategies (e.g., trigger avoidance, relaxation exercises, etc).*
- ii. *Acetaminophen is generally regarded as the safest analgesic for use during pregnancy.*
- iii. *Alternatives to acetaminophen when acetaminophen is not adequate that may be considered for use during pregnancy include acetaminophen plus codeine combination products (intermittent use).*
- iv. *Sumatriptan is also a potential option for acute migraine treatment in pregnancy, but is not recommended for routine use. There is significant evidence that the risks of sumatriptan use in pregnancy are minimal. It may be considered when migraine headaches are severe with significant disability and/or vomiting, other medications have failed during similar attacks, and the benefits appear to outweigh potential risks. There is much less information available regarding the safety of the other triptans during pregnancy; therefore, they should be avoided.*
- v. *NSAIDs (e.g., ibuprofen, naproxen sodium) should be used with caution during pregnancy (possible increased risk of spontaneous abortion in first trimester), and should be discontinued before week 32.*

- vi. *Because of the long-lasting effects of ASA on platelet function, other NSAIDs are preferred to ASA for use during pregnancy.*
- vii. *Metoclopramide has not been associated with birth defects, and may be used during pregnancy. Dimenhydrinate is considered relatively safe for use as an anti-emetic during pregnancy (but there is no controlled trial evidence for efficacy in migraine). Domperidone should be avoided, as there is a lack of data with regard to its use during pregnancy.*
- viii. *Ergot alkaloids are contraindicated during pregnancy.*

7. Migraine during lactation strategy

Maternal plasma levels, which are dose dependant, are an important determinant of drug levels in breast milk. High lipid solubility, low molecular weight, low protein binding and the unionised state all favour secretion into breast milk.

Acetaminophen

Acetaminophen is considered safe, as there have been no reports of adverse effects, and levels in breast milk are a fraction of the recommended neonatal doses.¹³⁸

ASA and other NSAIDs

Acetylsalicylic acid in analgesic doses for the mother are not considered safe, as salicylates are eliminated slowly by the neonate, cause platelet dysfunction, and have been associated with Reye's syndrome.

Among other NSAIDs, ibuprofen is preferred as it has a low transfer rate into breast milk, is short-acting, is free of active metabolites, and has the best documented safety. Short-term or occasional use of diclofenac and ketorolac is considered compatible with breast feeding. The safety of naproxen is less clear, but it is also considered compatible with breast feeding.¹³⁸

Triptans

Data on triptans and breastfeeding is scarce, but the infant dose after maternal ingestion of sumatriptan would appear to be small. The American Academy of Pediatrics has considered maternal sumatriptan use to be compatible with breast feeding.¹⁴²

Opioids

The short-term use of opioids is generally considered relatively safe during lactation as most opioids are secreted into breast milk in low doses, but they should be used with caution, especially if the infant is premature or less than four weeks old. The infant should be monitored for sedation and other adverse effects including episodes of cyanosis. Morphine has been considered the opioid of choice if potent analgesia is required in breastfeeding mothers. Although it is transferred into breast milk, the oral availability in the infant is low (about 25%). Although codeine is generally considered safe, infant toxicity and death has been reported in a breastfed neonate whose mother was an ultra-fast metabolizer of codeine.¹³⁸ In mothers who are breastfeeding, avoiding codeine for long-term therapy seems reasonable as it has a highly variable metabolism, and has been associated with one reported death and multiple cases of toxicity

in nursing infants. Five to forty percent of individuals, depending on ethnic background, have duplications of the CYP2D6 gene and, therefore, are ultra-rapid metabolizers of codeine. These patients may produce more morphine than is predicted when treated with codeine, and the morphine may in turn enter the breast milk. If opioid therapy is necessary during breastfeeding, there are better alternatives. Infant toxicity from maternal morphine use during breastfeeding has not been reported.¹⁴³ If nursing mothers are taking opioids, the breast milk should be discarded if the mother experiences significant sedation. The majority of adverse events occurred in very young infants in the first month of life, so particular caution should be exercised during this time period.

Anti-emetics

Metoclopramide, domperidone, dimenhydrinate, and prochlorperazine are all considered safe in breastfeeding.¹³⁸

EXPERT CONSENSUS

- i. *Acetaminophen is considered safe during lactation.*
- ii. *Ibuprofen is the NSAID of choice during breast feeding. Diclofenac, ketorolac, and naproxen are also considered compatible with breast feeding, but with less data. ASA should be avoided.*
- iii. *Sumatriptan is considered compatible with breast feeding.*
- iv. *Metoclopramide, domperidone, dimenhydrinate, and prochlorperazine are all considered safe in breastfeeding.*
- v. *If pain medication is necessary in a breastfeeding mother, the safest drugs are acetaminophen and the NSAIDs. If opioids are considered necessary:*
 - a. *Morphine is considered the opioid of choice if potent analgesia is required in breastfeeding mothers.*
 - b. *Codeine in occasional doses is considered generally safe, although serious toxicity has been reported in maternal ultra-fast metabolizers (caution if premature infant or neonate less than four weeks old).*
 - c. *Avoid codeine for long-term therapy because of its variable maternal metabolism, because multiple cases of neonatal toxicity have been reported, and more effective opioid choices are available.*
 - d. *Avoid high doses of opioids in breastfeeding women.*
 - e. *For all opioids, exercise particular caution if the breastfeeding infant is under one month old.*

Premonitory Symptoms and Migraine Treatment

Premonitory symptoms precede the other symptoms of the migraine attack by 2 to 48 hours. They occur before the aura in migraine with aura, and before the onset of pain in migraine without aura.¹⁴⁴ Many different premonitory symptoms have been reported by patients with migraine including fatigue, mood changes, and gastrointestinal symptoms.¹⁴⁵⁻¹⁴⁷ Depending on how the data is collected, between 33 and 80% of migraine sufferers in clinic-based patient samples report premonitory symptoms.^{145,146} In selected patient populations it has been found that patients are able to predict with reasonable accuracy whether a symptom they experience as a possible premonitory symptom is likely to be followed by a migraine headache or not.¹⁴⁸ In summary, it would appear that a significant number of patients

with migraine have premonitory symptoms; many have at least several hours of warning before their headache attack starts, and for an uncertain minority of these patients the premonitory symptoms are reasonably reliable predictors of the oncoming attack.

Much more research is needed before firm recommendations can be made regarding therapy of migraine attacks by giving acute medications during the premonitory phase. Several clinical trials have been done in highly selected patient populations, and have led to the following conclusions:¹⁴⁹⁻¹⁵¹

1. Naratriptan 2.5 mg can prevent some migraine attacks when taken during the premonitory period (open label evidence).
2. Domperidone 30-40 mg can prevent some migraine attacks when taken during the premonitory period (double-blind placebo-controlled cross-over evidence)
3. Both drugs appear to work better when taken early (at least two hours) before headache onset.

Warnings have recently been issued regarding domperidone doses of this magnitude and cardiac arrhythmias (Health Canada Endorsed Important Safety Information on Domperidone Maleate, March 2, 2012), so use of domperidone in this context may be problematic. With regard to triptan use, if the premonitory period represents a time of heightened migraine vulnerability, analogous to what occurs just prior to menstruation in women with menstrual migraine, it might be logical to use a triptan with a relatively long half-life, like

frovatriptan, during the premonitory period in selected patients, but more evidence is needed.¹⁵²

EXPERT CONSENSUS

- i. *There is insufficient evidence to make recommendations regarding the treatment of migraine during the premonitory period. In selected patients with clear cut and reliable premonitory symptoms, a trial of a triptan with a long half-life (e.g., frovatriptan) in a pre-emptive fashion could be considered.*

CONCLUSION AND SUMMARY

Pharmacological acute migraine treatment is complex, and the treatment strategies discussed above may be helpful to practitioners when considering which treatment to recommend for a specific patient. Tables 11A and 11B summarize the treatment strategies and the component medications of each strategy. As with all pharmacological therapies, evidence for efficacy, side effects, and contraindications need to be considered. An additional consideration in acute migraine pharmacological treatment is the potential complication of medication overuse headache, which may complicate the use of any acute medication for migraine attacks (with the exception of dopamine antagonists and possibly dihydroergotamine) when they are used beyond the recommended days per month.

Table 11A: Acute migraine treatment strategies and medication summary: General Strategies

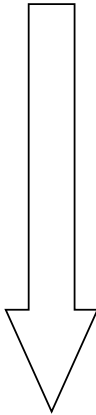
	Clinical Phenotype	Strategy	Medications
Increasing migraine severity - Refractoriness to therapy 	Mild – moderate attack strategies	1.a Acetaminophen	Acetaminophen ± metoclopramide
		1.b NSAID	Ibuprofen, diclofenac potassium, naproxen sodium, ASA, all ± metoclopramide
	Moderate – severe attack /NSAID failure strategies	2.a NSAID with triptan rescue	NSAID ± metoclopramide + a triptan later for rescue if necessary
		2.b Triptan	Triptan ± metoclopramide Sumatriptan (SC injection, nasal, oral) Zolmitriptan (nasal, oral, wafer) Rizatriptan (oral, wafer) Naratriptan (oral) Eletriptan (oral) Almotriptan (oral) Frovatriptan (oral)
	Refractory migraine strategies	3.a Triptan – NSAID combination	Triptan + NSAID taken simultaneously ± metoclopramide
		3.b Triptan – NSAID combination with rescue	Triptan + NSAID taken simultaneously ± metoclopramide + one or more for rescue later (as necessary) of: Ketorolac IM Indomethacin (oral or rectal) Prochlorperazine (oral or rectal) Chlorpromazine (oral) Dexamethasone or prednisone Opioid combination analgesic
		3.c Dihydroergotamine	Dihydroergotamine (nasal or SC or IM self-injection) ± metoclopramide

Table 11B: Acute migraine treatment strategies and medication summary: Special Strategies

Clinical phenotype / strategy	Medication options
Vasoconstrictor unresponsive or contraindicated strategy	<ol style="list-style-type: none"> 1. One of: acetaminophen, ibuprofen, diclofenac potassium, naproxen sodium, or ASA, all \pm metoclopramide 2. Combinations of acetaminophen, ASA, and caffeine (note: combination product not available in Canada but can use individual components) \pm metoclopramide 3. One or more of: <ul style="list-style-type: none"> ➤ ketorolac IM (self-injection) ➤ indomethacin (oral or rectal) ➤ prochlorperazine (oral or rectal) ➤ chlorpromazine (oral) ➤ dexamethasone or prednisone (short course) ➤ opioid (including tramadol) combination analgesics (monitor use closely) 4. One of: butalbital-containing analgesics, or butorphanol nasal spray (both: exceptional circumstances only – monitor use closely)
Menstrual migraine strategy	<ol style="list-style-type: none"> 1. Acute therapy: General strategies 1 through 3c 2. Short term prophylaxis with one of: frovatriptan, zolmitriptan, naratriptan, or naproxen (frovatriptan recommended) 3. Short term prophylaxis with percutaneous estrogen 4. Continuous oral contraceptives (observe contraindications) 5. Less proven options for short term prophylaxis: magnesium, mefenamic acid
Migraine during pregnancy strategy	<p>Avoid medication where possible</p> <ol style="list-style-type: none"> 1. acetaminophen \pm metoclopramide 2. acetaminophen with codeine \pm metoclopramide 3. ibuprofen (avoid 1st trimester and at /after 32nd week gestation) \pm metoclopramide 4. sumatriptan (if benefits outweigh risks – limited data but relatively safe) \pm metoclopramide
Migraine during lactation strategy	<p>Avoid medication where possible</p> <ol style="list-style-type: none"> 1. acetaminophen \pm metoclopramide 2. ibuprofen \pm metoclopramide 3. sumatriptan \pm metoclopramide 4. morphine (exceptional circumstances only - avoid high doses, maternal sedation, avoid when infant is premature, and use caution if infant under 1 month of age)

REFERENCES

1. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP, Disability in Strategies of Care Study group. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial.[see comment]. *JAMA*. 2000;284:2599-605.
2. Lipton RB, Baggish JS, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med*. 2000;160:3486-92.
3. Prior MJ, Codispoti JR, Fu M. A randomized, placebo-controlled trial of acetaminophen for treatment of migraine headache. *Headache*. 2010;50:819-33.
4. Hamalainen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. *Neurology*. 1997;48:103-7.
5. Larsen BH, Christiansen LV, Andersen B, Olesen J. Randomized double-blind comparison of tolfenamic acid and paracetamol in migraine. *Acta Neurol Scand*. 1990;81:464-7.
6. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol*. 2006;531:280-1.
7. Cooke LJ, Becker WJ. Migraine prevalence, treatment and impact: the canadian women and migraine study. *Can J Neurol Sci*. 2010; 37:580-7.
8. Suthisisang C, Poolsup N, Kittikuluth W, Pudchakan P, Wiwatpanich P. Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. *Ann Pharmacother*. 2007;41:1782-91.
9. Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2010;008039.
10. Diener HC, Bussone G, de Liano H, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia*. 2004;24:947-54.
11. Suthisisang C, Poolsup N, Suksomboon N, Lertpipopmetha V, Tepwitukgid B. Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine. *Headache*. 2010;50:808-18.
12. Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2012;2:008783.
13. Diener HC, Montagna P, Gacs G, et al. Efficacy and tolerability of diclofenac potassium sachets in migraine: a randomized, double-blind, cross-over study in comparison with diclofenac potassium tablets and placebo. *Cephalalgia*. 2006;26:537-47.
14. Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2010;4:008041.
15. Lampl C, Voelker M, Diener HC. Efficacy and safety of 1,000 mg effervescent aspirin: individual patient data meta-analysis of

- three trials in migraine headache and migraine accompanying symptoms. *J Neurol.* 2007;254:705-12.
16. Shields KG, Goadsby PJ. Serotonin receptors modulate trigeminovascular responses in ventroposteromedial nucleus of thalamus: a migraine target? *Neurobiol Dis.* 2006;23:491-501.
 17. Loder E. Triptan therapy in migraine. *N Engl J Med.* 2010;363:63-70.
 18. Goldstein DJ, Roon KI, Offen WW, et al. Selective serotonin 1F (5-HT_{1F}) receptor agonist LY334370 for acute migraine: a randomised controlled trial. *Lancet.* 2001;358:1230-4.
 19. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials.[see comment][erratum appears in *Cephalalgia.* 2003 Feb;23(1):71.]. *Cephalalgia.* 2002;22:633-58.
 20. Cady RK, Freitag FG, Mathew NT, et al. Allodynia-associated symptoms, pain intensity and time to treatment: predicting treatment response in acute migraine intervention. *Headache.* 2009;49:350-63.
 21. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache.* 2008;48:1157-68.
 22. Anonymous Treatment of migraine attacks with sumatriptan. The Subcutaneous Sumatriptan International Study Group. *N Engl J Med.* 1991;325:316-21.
 23. Gawel MJ, Worthington I, Maggisano A. A systematic review of the use of triptans in acute migraine.[see comment]. [Review] [74 refs]. *Can J Neurol Sci.* 2001;28:30-41.
 24. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs.* 2000;60:1259-87.
 25. Gladstone JP, Gawel M. Newer formulations of the triptans: advances in migraine management. [Review] [116 refs]. *Drugs.* 2003;63:2285-305.
 26. Rapoport AM, Tepper SJ, Bigal ME, Sheftell FD. The triptan formulations : how to match patients and products. [Review] [75 refs]. *CNS Drugs.* 2003;17:431-47.
 27. Dodick DW, Lipton RB, Ferrari MD, et al. Prioritizing treatment attributes and their impact on selecting an oral triptan: results from the TRIPSTAR Project. [Review] [41 refs]. *Curr Pain Headache Rep.* 2004;8:435-42.
 28. Ferrari MD. Current perspectives on effective migraine treatments: are small clinical differences important for patients? [Review] [9 refs]. *Med Actual.* 2003;39:37-41.
 29. Gawel M, Aschoff J, May A, Charlesworth BR, REALIZE Study T. Zolmitriptan 5 mg nasal spray: efficacy and onset of action in the acute treatment of migraine--results from phase 1 of the REALIZE Study. *Headache.* 2005;45:7-16.
 30. Tfelt-Hansen P. Sumatriptan for the treatment of migraine attacks--a review of controlled clinical trials. *Cephalalgia.* 1993;13:238-44.
 31. Dodick D, Brandes J, Elkind A, Mathew N, Rodichok L. Speed of onset, efficacy and tolerability of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled study. *CNS Drugs.* 2005;19:125-36.
 32. Dodick DW, Sandrini G, Williams P. Use of the sustained pain-free plus no adverse events endpoint in clinical trials of triptans in acute migraine. *CNS Drugs.* 2007;21:73-82.
 33. Dodick D, Lipton RB, Martin V, et al. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. [Review] [66 refs]. *Headache.* 2004;44:414-25.
 34. Modgill G, Jette N, Wang JL, Becker WJ, Patten SB. A population-based longitudinal community study of major depression and migraine. *Headache.* 2012;52:422-32.
 35. Jelinski SE, Magnusson JE, Becker WJ, CHORD Study G. Factors associated with depression in patients referred to headache specialists. *Neurology.* 2007;68:489-95.
 36. Wenzel RG, Tepper S, Korab WE, Freitag F. Serotonin syndrome risks when combining SSRI/SNRI drugs and triptans: is the FDA's alert warranted? *Ann Pharmacother.* 2008;42:1692-6.
 37. Evans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. *Headache.* 2010;50:1089-99.
 38. Soldin OP, Tønning JM; Obstetric-Fetal Pharmacology Research Unit Network. Serotonin syndrome associated with triptan monotherapy. *N Engl J Med.* 2008 May 15;358(20):2185-6.
 39. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24:9-160.
 40. Yates R, Sorensen J, Bergstrom M, et al. Distribution of intranasal C-zolmitriptan assessed by positron emission tomography. *Cephalalgia.* 2005;25:1103-9.
 41. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs.* 2003;17:653-67.
 42. Ahrens SP, Farmer MV, Williams DL, et al. Efficacy and safety of rizatriptan wafer for the acute treatment of migraine. Rizatriptan Wafer Protocol 049 Study Group. *Cephalalgia.* 1999;19:525-30.
 43. Aurora S, Kori S, Barrodale P, Nelsen A, McDonald S. Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. *Headache.* 2007;47:1443-6.
 44. Aurora SK, Kori SH, Barrodale P, McDonald SA, Haseley D. Gastric stasis in migraine: more than just a paroxysmal abnormality during a migraine attack. *Headache.* 2006;46:57-63.
 45. Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. *Pharmacoepidemiol Drug Saf.* 2010;19:881-8.
 46. van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Safety.* 2010;33:1003-14.
 47. Tokola RA. The effect of metoclopramide and prochlorperazine on the absorption of effervescent paracetamol in migraine. *Cephalalgia.* 1988;8:139-47.
 48. Tokola RA, Neuvonen PJ. Effects of migraine attack and metoclopramide on the absorption of tolfenamic acid. *Br J Clin Pharmacol.* 1984;17:67-75.
 49. Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *Br J Clin Pharmacol.* 1975;2:57-63.
 50. MacGregor EA, Wilkinson M, Bancroft K. Domperidone plus paracetamol in the treatment of migraine. *Cephalalgia.* 1993;13:124-7.
 51. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. [see comment]. *Headache.* 2003;43:729-33.
 52. Ferrari MD, James MH, Bates D, et al. Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia.* 1994;14:330-8.
 53. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA.* 2007;297:1443-54.
 54. Geraud G, Keywood C, Senard JM. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. *Headache.* 2003;43:376-88.
 55. Winner P, Ricalde O, Le Force B, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. [see comment]. *Arch Neurol.* 1996;53:180-4.
 56. Teall J, Tuchman M, Cutler N, et al. Rizatriptan (MAXALT) for the acute treatment of migraine and migraine recurrence. A placebo-controlled, outpatient study. Rizatriptan 022 Study Group. *Headache.* 1998;38:281-7.
 57. Tepper SJ, Donnan GA, Dowson AJ, et al. A long-term study to maximise migraine relief with zolmitriptan. *Curr Med Res Opin.* 1999;15:254-71.

58. Sheftell F, Ryan R, Pitman V, Eletriptan Steering C. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache*. 2003;43:202-13.
59. Rapoport AM, Ramadan NM, Adelman JU, et al. Optimizing the dose of zolmitriptan (Zomig, 311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. The 017 Clinical Trial Study Group. *Neurology*. 1997;49:1210-8.
60. Bates D, Ashford E, Dawson R, et al. Subcutaneous sumatriptan during the migraine aura. Sumatriptan Aura Study Group. *Neurology*. 1994;44:1587-92.
61. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. *Eur J Neurol*. 2004;11:671-7.
62. Dowson A. Can oral 311C90, a novel 5-HT_{1D} agonist, prevent migraine headache when taken during an aura? *Eur Neurol*. 1996;36:28-31.
63. Aurora SK, Barrodale PM, McDonald SA, Jakubowski M, Burstein R. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. *Headache*. 2009;49:1001-4.
64. Arto V, Nissila M, Wessman M, Palotie A, Farkkila M, Kallela M. Treatment of hemiplegic migraine with triptans. *Eur J Neurol*. 2007;14:1053-6.
65. Klapper J, Mathew N, Nett R. Triptans in the treatment of basilar migraine and migraine with prolonged aura. *Headache*. 2001;41:981-4.
66. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA*. 2007;297:1443-54.
67. Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache*. 2005;45:983-91.
68. Mathew NT, Landy S, Stark S, et al. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. *Headache*. 2009;49:971-82.
69. Silberstein SD, Mannix LK, Goldstein J, et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. *Neurology*. 2008;71:114-21.
70. Krymchantowski AV. Naproxen sodium decreases migraine recurrence when administered with sumatriptan. *Arq Neuropsiquiatr*. 2000;58:428-30.
71. Jakubowski M, Levy D, Goor-Aryeh I, Collins B, Bajwa Z, Burstein R. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. *Headache*. 2005;45:850-61.
72. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 3: opioids, NSAIDs, steroids, and post-discharge medications. *Headache*. 2012;52:467-82.
73. Turkewitz LJ, Casaly JS, Dawson GA, Wirth O, Hurst RJ, Gillette PL. Self-administration of parenteral ketorolac tromethamine for head pain. *Headache*. 1992;32:452-4.
74. Sandrini G, Cerbo R, Del Bene E, et al. Efficacy of dosing and re-dosing of two oral fixed combinations of indomethacin, prochlorperazine and caffeine compared with oral sumatriptan in the acute treatment of multiple migraine attacks: a double-blind, double-dummy, randomised, parallel group, multicentre study. *Int J Clin Pract*. 2007;61:1256-69.
75. Di Monda V, Nicolodi M, Aloisio A, et al. Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine versus sumatriptan in acute treatment of multiple migraine attacks: a multicenter, randomized, crossover trial. *Headache*. 2003;43:835-44.
76. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 2: neuroleptics, antihistamines, and others. *Headache*. 2012;52:292-306.
77. Jones EB, Gonzalez ER, Boggs JG, Grillo JA, Elswick RK, Jr. Safety and efficacy of rectal prochlorperazine for the treatment of migraine in the emergency department. *Ann Emerg Med*. 1994;24:237-41.
78. McEwen JI, O'Connor HM, Dinsdale HB. Treatment of migraine with intramuscular chlorpromazine. *Ann Emerg Med*. 1987;16:758-63.
79. Rozen TD. Migraine headache: immunosuppressant therapy. *Curr Treat Options Neurol*. 2002;4:395-401.
80. Colman I, Friedman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. *BMJ*. 2008;336:1359-61.
81. Taheraghdam AA, Amiri H, Shojaan H, Shamsvahdati S, Houshyar Y. Intravenous dexamethasone versus morphine in relieving of acute migraine headache. *Pak J Biol Sci*. 2011;14:682-7.
82. Bigal M, Sheftell F, Tepper S, Tepper D, Ho TW, Rapoport A. A randomized double-blind study comparing rizatriptan, dexamethasone, and the combination of both in the acute treatment of menstrually related migraine. *Headache*. 2008;48:1286-93.
83. Boureau F, Joubert JM, Lasserre V, Prum B, Delecoeuillerie G. Double-blind comparison of an acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. *Cephalalgia*. 1994;14:156-61.
84. Ho TW, Rodgers A, Bigal ME. Impact of recent prior opioid use on rizatriptan efficacy. A post hoc pooled analysis. *Headache*. 2009;49:395-403.
85. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. *Neurology*. 2008;71:1821-8.
86. De Felice M, Porreca F. Opiate-induced persistent pronociceptive trigeminal neural adaptations: potential relevance to opiate-induced medication overuse headache. *Cephalalgia*. 2009;29:1277-84.
87. Madadi P, Koren G. Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use. *Pharmacogenomics*. 2008;9:1267-84.
88. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004;43:879-923.
89. Tepper SJ. Medication-overuse headache. *CONTINUUM: Lifelong Learning in Neurology*. 2012;18:807-22.
90. Fisher MA, Glass S. Butorphanol (Stadol): a study in problems of current drug information and control. *Neurology*. 1997;48:1156-60.
91. Bigal ME, Lipton RB. Acute treatment of migraine headache. *Curr Treat Options Neurol*. 2003;5:423-30.
92. Gerhardt RT, Hermstad E, Crawford DM, Rayfield J, Pfaff J, Hunter CJ. Postdischarge secobarbital after ED migraine treatment decreases pain and improves resolution. *Am J Emerg Med*. 2011;29:86-90.
93. Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. *Headache*. 2003;43:144-66.
94. Lipton RB. Ergotamine tartrate and dihydroergotamine mesylate: safety profiles. *Headache*. 1997;37:S33-41.
95. Tfelt-Hansen P, Saxena PR, Dahlof C, et al. Ergotamine in the acute treatment of migraine: a review and European consensus. [Review] [84 refs]. *Brain*. 2000;123:9-18.
96. Baron EP, Tepper SJ. Revisiting the role of ergots in the treatment of migraine and headache. *Headache*. 2010;50:1353-61.
97. Bigal ME, Tepper SJ. Ergotamine and dihydroergotamine: a review. *Curr Pain Headache Rep*. 2003;7:55-62.
98. MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. *Circulation*. 1998;98:25-30.
99. Hoskin KL, Kaube H, Goadsby PJ. Central activation of the trigeminovascular pathway in the cat is inhibited by dihydroergotamine. A c-Fos and electrophysiological study. *Brain*. 1996;119:249-56.
100. Becker WJ, Riess CM, Hoag J. Effectiveness of subcutaneous dihydroergotamine by home injection for migraine. *Headache*. 1996;36:144-8.
101. Weisz MA, el-Raheb M, Blumenthal HJ. Home administration of intramuscular DHE for the treatment of acute migraine headache. *Headache*. 1994;34:371-3.
102. Klapper JA, Stanton J. Clinical experience with patient administered subcutaneous dihydroergotamine mesylate in refractory headaches. *Headache*. 1992;32:21-3.
103. Rothrock JF. Patient information regarding subcutaneous self-administration of dihydroergotamine (DHE). *Headache*. 2007;47:740.

104. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. *Neurology*. 1986;36:995-7.
105. Silberstein SD, Schulman EA, Hopkins MM. Repetitive intravenous DHE in the treatment of refractory headache. *Headache*. 1990;30:334-9.
106. Eadie MJ. Ergot of rye-the first specific for migraine. *J Clin Neurosci*. 2004;11:4-7.
107. Schmidt R, Fanchamps A. Effect of caffeine on intestinal absorption of ergotamine in man. *Eur J Clin Pharmacol*. 1974;7:213-6.
108. Evers S, Gralow I, Bauer B, et al. Sumatriptan and ergotamine overuse and drug-induced headache: a clinicoepidemiologic study. *Clin Neuropharmacol*. 1999;22:201-6.
109. Dahlof C. Placebo-controlled clinical trials with ergotamine in the acute treatment of migraine. [Review] [18 refs]. *Cephalalgia*. 1993;13:166-71.
110. Diener HC, Pfaffenrath V, Pageler L, Peil H, Aicher B. The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia*. 2005;25:776-87.
111. Diener HC, Peil H, Aicher B. The efficacy and tolerability of a fixed combination of acetylsalicylic acid, paracetamol, and caffeine in patients with severe headache: a post-hoc subgroup analysis from a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia*. 2011;31:1466-76.
112. Laska EM, Sunshine A, Mueller F, Elvers WB, Siegel C, Rubin A. Caffeine as an analgesic adjuvant. *JAMA*. 1984;251:1711-8.
113. Ray WA, Varas-Lorenzo C, Chung CP, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circulation. Circ Cardiovasc Qual Outcomes*. 2009;2:155-63.
114. Fosbol EL, Folke F, Jacobsen S, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. *Circulation. Circ Cardiovasc Qual Outcomes*. 2010;3:395-405.
115. Sauro KM, Becker WJ. Multidisciplinary treatment for headache in the Canadian healthcare setting. *Can J Neurol Sci*. 2008;35:46-56.
116. MacGregor EA, Victor TW, Hu X, et al. Characteristics of menstrual vs nonmenstrual migraine: a post hoc, within-woman analysis of the usual-care phase of a nonrandomized menstrual migraine clinical trial. *Headache*. 2010;50:528-38.
117. Diamond ML, Cady RK, Mao L, et al. Characteristics of migraine attacks and responses to almotriptan treatment: a comparison of menstrually related and nonmenstrually related migraines. *Headache*. 2008;48:248-58.
118. Mannix LK, Loder E, Nett R, et al. Rizatriptan for the acute treatment of ICHD-II proposed menstrual migraine: two prospective, randomized, placebo-controlled, double-blind studies. *Cephalalgia*. 2007;27:414-21.
119. Tuchman M, Hee A, Emeribe U, Silberstein S. Efficacy and tolerability of zolmitriptan oral tablet in the acute treatment of menstrual migraine. *CNS Drugs*. 2006;20:1019-26.
120. Pringsheim T, Davenport WJ, Dodick D. Acute treatment and prevention of menstrually related migraine headache: evidence-based review. *Neurology*. 2008;70:1555-63.
121. Mannix LK, Martin VT, Cady RK, et al. Combination treatment for menstrual migraine and dysmenorrhea using sumatriptan-naproxen: two randomized controlled trials. *Obstet Gynecol*. 2009;114:106-13.
122. Brandes JL, Poole A, Kallela M, et al. Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks. *Cephalalgia*. 2009;29:1133-48.
123. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology*. 2004;63:261-9.
124. Tuchman MM, Hee A, Emeribe U, Silberstein S. Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. *CNS Drugs*. 2008;22:877-86.
125. Mannix LK, Savani N, Landy S, et al. Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. *Headache*. 2007;47:1037-49.
126. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache*. 1990;30:705-9.
127. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology*. 2006;67:2159-63.
128. Almen-Christensson A, Hammar M, Lindh-Astrand L, Landtblom AM, Brynhildsen J. Prevention of menstrual migraine with perimenstrual transdermal 17-beta-estradiol: a randomized, placebo-controlled, double-blind crossover study. *Fertil Steril*. 2011;96:498-500.e1.
129. Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. *Headache*. 1991;31:298-301.
130. Al-Waili NS. Treatment of menstrual migraine with prostaglandin synthesis inhibitor mefenamic acid: double-blind study with placebo. *Eur J Med Res*. 2000;5:176-82.
131. Teichmann A, Apter D, Emerich J, et al. Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. *Contraception*. 2009;80:504-11.
132. Reid RL, Fortier MP, Smith L, Mirkin S, Grubb GS, Constantine GD. Safety and bleeding profile of continuous levonorgestrel 90 mcg/ethinyl estradiol 20 mcg based on 2 years of clinical trial data in Canada. *Contraception*. 2010;82:497-502.
133. Coffee AL, Sulak PJ, Kuehl TJ. Long-term assessment of symptomatology and satisfaction of an extended oral contraceptive regimen. *Contraception*. 2007;75:444-9.
134. Sulak P, Willis S, Kuehl T, Coffee A, Clark J. Headaches and oral contraceptives: impact of eliminating the standard 7-day placebo interval. *Headache*. 2007;47:27-37.
135. Loder E, Rizzoli P, Golub J. Hormonal management of migraine associated with menses and the menopause: a clinical review. *Headache*. 2007;47:329-40.
136. Calhoun A. Combined hormonal contraceptives: is it time to reassess their role in migraine? *Headache*. 2012;52:648-60.
137. MacGregor EA. Contraception and headache. *Headache*. 2013;53:247-76.
138. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM, APM: SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. Melbourne: ANZA and FPM, 2010.
139. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: Results from a large population-based cohort study. *Eur J Clin Pharmacol*. 2011;67:1253-61.
140. Nezvalova-Henriksen K, Spigset O, Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. *Headache*. 2010;50:563-75.
141. Duong S, Bozzo P, Nordeng H, Einarson A. Safety of triptans for migraine headaches during pregnancy and breastfeeding. *Can Fam Physician*. 2010;56:537-9.
142. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108:776-89.
143. Hendrickson RG, McKeown NJ. Is maternal opioid use hazardous to breast-fed infants? *Clin Toxicol (Phila)*. 2012;50:1-14.
144. Rossi P, Ambrosini A, Buzzi MG. Prodromes and predictors of migraine attack. *Funct Neurol*. 2005;20:185-91.
145. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache*. 2004;44:865-72.
146. Schoonman GG, Evers DJ, Terwindt GM, van Dijk JG, Ferrari MD. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia*. 2006;26:1209-13.

147. Quintela E, Castillo J, Munoz P, Pascual J. Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. *Cephalalgia*. 2006;26:1051-60.
148. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology* 2003;60:935-40.
149. Waelkens J. Dopamine blockade with domperidone: bridge between prophylactic and abortive treatment of migraine? A dose-finding study. *Cephalalgia*. 1984;4:85-90.
150. Luciani R, Carter D, Mannix L, Hemphill M, Diamond M, Cady R. Prevention of migraine during prodrome with naratriptan. *Cephalalgia*. 2000;20:122-6.
151. Waelkens J. Domperidone in the prevention of complete classical migraine. *Br Med J (Clin Res Ed)*. 1982;284:944.
152. Becker WJ. The premonitory phase of migraine and migraine management. *Cephalalgia*. 2012 Feb 15;[Epub ahead of print].
153. Jelinski SE, Becker WJ, Christie SN, et al. Clinical features and pharmacological treatment of migraine patients referred to headache specialists in Canada. *Cephalalgia*. 2006;26:578-88.
154. Derry S, Moore RA, McQuay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2010;008040.
155. Lipton RB, Grosberg B, Singer RP, et al. Efficacy and tolerability of a new powdered formulation of diclofenac potassium for oral solution for the acute treatment of migraine: results from the International Migraine Pain Assessment Clinical Trial (IMPACT). *Cephalalgia*. 2010;30:1336-45.
156. Buchan P, Keywood C, Wade A, Ward C. Clinical pharmacokinetics of frovatriptan. *Headache*. 2002;42:S54-62.
157. Johnston MM, Rapoport AM. Triptans for the management of migraine. *Drugs*. 2010;70:1505-18.
158. Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012;2:009665.
159. Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012;2:009663.
160. Pascual J, Falk RM, Piessens F, et al. Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2000;20:588-96.
161. Rapoport A, Ryan R, Goldstein J, Keywood C. Dose range-finding studies with frovatriptan in the acute treatment of migraine. *Headache*. 2002;42:S74-83.
162. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database Syst Rev*. 2012;2:008615.
163. Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. [see comment][erratum appears in *CMAJ* 1997 Nov 15;157(10):1354]. [Review] [160 refs]. *CMAJ*. 1997;156:1273-87.

Guideline Summary for Primary Care Physicians

Werner J. Becker¹ and Irene Worthington² on behalf of the Canadian Headache Society Acute Migraine Treatment Guideline Development Group

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Many of the recommendations in this guideline are summarized here to provide a compact source of information for the primary care physician. More detailed discussion can be found in the main guideline document. Tables 2, 11A and 11B in Section 3 of the main guideline document list all the acute treatment strategies, and the medications used in each one. Table 9 in Section 3 summarizes medications dosages and side effects. Recommendations related to the efficacy of individual drugs are based on a comprehensive targeted review. Expert consensus statements regarding other aspects of acute migraine treatment are based on a general literature review and expert opinion. All patients for whom acute migraine medications are being prescribed should be educated regarding the common migraine triggers and the important lifestyle factors that may potentially influence their migraine disorder.

OBJECTIVE

The primary objective of this guideline is to assist the physician in choosing an appropriate acute medication for an individual with migraine, and to assist the physician in using the chosen medication in the most effective manner.

Goals of acute migraine therapy

The goal is to render the patient pain free within two hours after treatment. Not all patients can achieve this goal with current acute treatment options, but if a patient is not reaching this goal, or at least able to function reasonably well at two hours, another therapeutic option should be tried if possible.

- i. *Several acute medication trials may be necessary before an appropriate acute medication is found for a specific patient. Some patients with attacks of varying severity may need access to more than one medication for successful migraine management.*

Avoiding medication overuse

- i. *When initiating treatment with acute migraine medications, the patient should be educated with regard to medication overuse headache. Patients should avoid use of ASA, NSAIDs and acetaminophen on more than 14 days per month, and use of triptans, ergots, opioids, or combination analgesics on more than 9 days a month. Patients taking different acute medications on different days should limit their total use of acute medications to 9 days a month if one of their medications is a triptan, a combination analgesic, an ergotamine, or an opioid.*
- ii. *Patients should be advised to monitor their acute*

medication use if their attacks are frequent, preferably with a headache diary, in order to reduce the risk of medication overuse headache.

- iii. *Pharmacological prophylaxis should be considered for patients with frequent migraine attacks that may be at risk of medication overuse.*

Which acute migraine medication should be used?

An acute medication should be chosen based on evidence for efficacy, side effect profile, migraine attack severity, presence of co-existing medical or psychiatric disorders, and patient preference. A number of acute medications have evidence for efficacy. Acute medications can be divided into those with a strong recommendation for use, and those with a weak recommendation. A strong recommendation means that the medication could be used for most patients, and that the benefits of therapy outweigh the potential risks (although contraindications still need to be observed). A weak recommendation indicates that the intervention could still be useful, but it would not be appropriate for many patients, often because of potential side effects. With a weak recommendation, the balance between risks and benefits is closer or more uncertain,

MAY BE USED FOR MOST PATIENTS: The following acute medications for migraine received a **strong recommendation** for use:

1. **High quality evidence:** *Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) are recommended for the acute treatment of migraine attacks that are likely to become moderate or severe.*
2. **High quality evidence:** *ASA (975-1,000 mg tablets or effervescent formulation), given with oral metoclopramide (10 mg) if nausea is present, is recommended for the acute treatment of migraine attacks of all severities.*

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3. **High quality evidence:** *Ibuprofen [400 mg tablet or solubilized (liquid containing capsules) formulation] is recommended for the acute treatment of migraine attacks of all severities.*
4. **Moderate quality evidence:** *Ibuprofen (400 mg) in solubilized formulation (liquid containing capsules) is recommended for the acute treatment of migraine attacks of all severities for patients desiring a faster onset of therapeutic effect as compared to the regular ibuprofen tablets.*
5. **High quality evidence:** *Naproxen sodium in immediate release formulation (500 or 550 mg; up to 825 mg, if needed and tolerated) is recommended for the acute treatment of migraine attacks of all severities.*
6. **High quality evidence:** *Diclofenac potassium (50 mg tablet or powder for oral solution) is recommended for the acute treatment of migraine attacks of all severities.*
7. **Moderate quality evidence:** *Diclofenac potassium powder for oral solution (50 mg) is recommended for the acute treatment of migraine attacks of all severities for patients desiring a faster onset of therapeutic effect as compared to the diclofenac oral tablet formulation.*
8. **High quality evidence:** *Acetaminophen (1,000 mg), alone or in combination with oral metoclopramide (10 mg), is recommended for the acute treatment of mild or moderate migraine attacks.*
9. **High quality evidence:** *If migraine response to sumatriptan is inadequate, consider use of naproxen sodium 500 mg to be given simultaneously with the triptan.*
10. **Low quality evidence:** *If migraine response to other triptans (other than sumatriptan) is inadequate, consider the addition of an NSAID (e.g., naproxen sodium) to be given simultaneously with the triptan.*

MAY BE USED FOR SOME PATIENTS: The following acute medications for migraine received a **weak recommendation** for use:

1. **Moderate quality evidence:** *Dihydroergotamine (intranasal or subcutaneous self-injection) may be considered for the acute treatment of moderate or severe migraine attacks.*
2. **Moderate quality evidence:** *(Not for routine use) Ergotamine may be considered for use in some patients, for example when triptans are not available to the patient or not effective.*
3. **Moderate quality evidence:** *(Not for routine use) Tramadol in combination with acetaminophen may be considered for patients with moderate or severe migraine attacks when triptans and/or NSAIDs are ineffective or contraindicated and for occasional use as rescue medication when the patient's regular medication has failed. Frequency of use should be closely monitored, preferably with use of headache diaries.*
4. **Low quality evidence:** *(Not for routine use) Codeine-containing combination analgesics may be considered for patients with moderate or severe migraine attacks when triptan and/or NSAIDs are ineffective or contraindicated and for occasional use as rescue medication when the*

patient's regular medication has failed. Frequency of use should be closely monitored, preferably with use of headache diaries.

DON'T USE ROUTINELY: The following medications received a **strong recommendation that they should NOT** be used routinely for the acute treatment of migraine

1. **Moderate quality evidence:** *Ergotamine should not be used routinely for acute migraine attacks, due to inferior efficacy compared to the triptans, and because of the potential for more side effects.*
2. **Low quality evidence:** *Oral opioids, including codeine, are not recommended for routine use in migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and triptans), and the risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation.*
3. **Low quality evidence:** *Tramadol alone or in combination with acetaminophen is not recommended for routine use in migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and triptans), and the risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation.*

DON'T USE: The following medications received a **strong recommendation that they should NOT** be used for acute migraine therapy (except perhaps under very exceptional circumstances):

1. **Low quality evidence:** *Butorphanol nasal spray, although effective for acute migraine, should be avoided (except in exceptional circumstances) for the acute treatment of migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and / or triptans), risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation. When used, frequency of use should be closely monitored, preferably with use of headache diaries.*
2. **Low quality evidence:** *Barbiturate (i.e., butalbital)-containing combination analgesics should be avoided (except in exceptional circumstances) for the acute treatment of migraine, due to lack of evidence for superiority to standard drugs (NSAIDs and / or triptans), risk of dependence/abuse, potential for development of medication overuse headache, and the possibility of a withdrawal syndrome following discontinuation of high doses.*

The following anti-emetics received a **strong recommendation** for use in conjunction with acute migraine medications (there is inadequate evidence to make a recommendation for the use of dimenhydrinate or ondansetron):

1. **Moderate quality evidence:** *Metoclopramide (10 mg orally) is recommended for use with acute migraine medications for migraine attacks to improve relief of nausea.*

2. **Low quality evidence:** Domperidone (10 mg orally) is recommended for use with acute migraine medications for migraine attacks to improve relief of nausea.

Based on evidence from randomized controlled trials, meta-analyses, and systematic reviews, the following additional **strong recommendations** were made for acute migraine therapy:

Try another triptan if the patient response is not excellent:

1. **Moderate quality evidence:** If a patient does not respond well to one triptan or tolerates it poorly, other triptans should be tried over time in subsequent attacks. It is recommended that patients wait 24 hours before trying another triptan.

Treat early if possible:

2. **High quality evidence:** Patients with migraine attacks that usually peak at moderate or severe intensity should be advised to take triptans early during their migraine attacks while pain intensity is still mild (caution the patient regarding medication overuse headache).

Approach to the individual patient

An acute medication should be chosen for a specific patient based on migraine attack severity and on the patient history of response to previously tried acute medications. The following expert consensus statements outline such an approach.

- i. *Patients with severe attacks that often require bed rest:*
- Should be given a triptan (with an anti-nauseant, if necessary), consistent with the stratified treatment approach.
 - Subcutaneous sumatriptan 6 mg may be the preferred triptan for severe attacks with early vomiting, or for severe attacks which do not respond to other triptan formulations.
- ii. *Patients with less severe attacks and who have not had adequate trials of non triptans:*
- Should be educated about acute treatment options.
 - An anti-emetic (metoclopramide 10 mg or domperidone 10 mg) can be added to acute migraine medications if needed for nausea.
 - A “step care across attacks” strategy as outlined below can be initiated with careful patient follow up.

Step 1: ASA 1,000 mg, ibuprofen 400 mg, diclofenac potassium 50 mg, naproxen sodium 550 mg, or acetaminophen 1,000 mg if NSAID intolerant. For patients with relatively severe attacks (but not usually requiring bed rest), a triptan can be prescribed at the same time. The triptan can be used as a rescue medication by the patient as necessary if the NSAID or acetaminophen occasionally fails, or can be adopted as the patient’s primary acute migraine medication if the NSAID or acetaminophen proves unhelpful (see step 2 below).

Step 2: For patients not responding well to NSAIDs, use a triptan as the primary medication for acute migraine therapy:

- At least three different triptans should be tried (in different attacks) if the response to the first triptan is not excellent.

An excellent response is defined as pain free or almost pain free with the ability to resume usual activities at 2 h post-dose, and no significant side effects

- A triptan should be used to treat approximately three separate migraine attacks before being judged effective or ineffective.
- Intranasal triptans which are partially absorbed through the nasal mucosa (e.g., zolmitriptan 5 mg) may be preferred to oral triptans for patients with nausea.
- Orally dissolving tablets (wafers) may be the preferred oral triptan for patients with nausea exacerbated by taking fluids.
- For patients with more than one migraine attack severity, providing medications from two different classes should be considered (e.g., a triptan and NSAID).

Step 3: For patients whose response to triptans remains inadequate because of incomplete relief or frequent treatment failure, an NSAID (e.g., naproxen sodium 500 - 550 mg) should be used simultaneously with their triptan.

Step 4: For patients with a good response to their triptan-NSAID combination therapy but who experience occasional treatment failure, consider the need for a rescue medication. Rescue medications can include additional NSAIDs (oral, rectal, or injectable with oral metoclopramide), prochlorperazine (oral, rectal), corticosteroids, and acetaminophen with tramadol or codeine (not for routine use; monitor frequency of use carefully).

Step 5: For patients who do not respond satisfactorily to an NSAID-triptan combination, the use of dihydroergotamine (nasal spray or self-injection), combined with oral metoclopramide (if needed), can be considered.

Step 6: Although not recommended for routine use in migraine, opioid analgesics (e.g., acetaminophen with codeine or tramadol) remain an option for patients without a satisfactory response to earlier treatment steps, but:

- their frequency of use should be closely monitored (using a headache diary)
- behavioural and pharmacological preventive treatment options should be explored
- these medications are also a treatment option for patients with contraindications to vasoconstrictor drugs and who do not respond to NSAIDs

Acute treatment strategies to guide acute medication choice

There are many drugs available for acute migraine treatment. These need to be chosen based upon patient clinical characteristics, and each needs to be used appropriately. The medications are organized here into a number of treatment strategies. Once the clinical data on a specific patient has been gathered, including attack severity and past medication use and response, an appropriate strategy can be chosen and implemented. Depending upon the patient’s response to the chosen pharmacological treatment strategy, the same strategy can be continued, or a new strategy can be implemented.

The primary drugs for acute migraine attack treatment are the NSAIDs (including ASA) and the triptans. Acetaminophen is widely used, but is considered less effective than the NSAIDs, and is suitable mainly for attacks of mild to moderate severity. Metoclopramide is recommended when an anti-nauseant is needed, as more evidence is available for efficacy for this drug

than for the related medication, domperidone. Domperidone may have fewer side effects; however, domperidone may be associated with QT prolongation in some patients.

1. Mild to moderate attack strategies: These are for patients with attacks that are not disabling (i.e., attacks do not require bed rest, and do not stop participation in activities, although it may be somewhat difficult for the patient to continue).

a. Acetaminophen strategy:

i. Acetaminophen is an effective option for acute migraine therapy for some patients with attacks of mild to moderate intensity.

b. NSAID strategy:

i. NSAIDs (including ASA) are helpful for many patients with migraine. Although it cannot be predicted which NSAID will be best for a specific patient, pharmacokinetic differences between them should be considered when treatment recommendations are made.

ii. For patients with migraine attacks that increase in intensity rapidly, diclofenac potassium powder for oral solution, effervescent ASA, and solubilized ibuprofen capsules have a rapid onset of action and may be particularly helpful.

iii. For patients with migraine attacks that increase in intensity rapidly, diclofenac potassium tablets have the most rapid onset of action for tablet formulations of NSAIDs (note: diclofenac potassium powder for oral solution has a more rapid oral absorption than tablets).

iv. The long plasma half-life of naproxen sodium may make it particularly helpful for patients with prolonged migraine attacks.

2. Moderate-severe attack or NSAID failure strategies

a. NSAID with triptan rescue strategy:

i. For patients with relatively severe attacks (but not usually requiring bed rest), an NSAID can be tried (if not tried and failed previously), and a triptan can be prescribed at the same time. The triptan can be used as a rescue medication by the patient as necessary if the NSAID occasionally fails, or can be adopted as the patient's primary acute migraine medication if the NSAID proves unhelpful.

b. Triptan strategy:

i. It should be recognized that the response of an individual patient to a specific triptan cannot be predicted with accuracy. Patients with a less than optimal response to their current triptan should be encouraged to try several other triptans in different migraine attacks to determine if they will obtain better relief.

ii. Patients should be encouraged to take their triptan early in their attacks while pain is still mild, although caution may need to be exercised in patients with frequent attacks to avoid medication overuse.

iii. For severe migraine attacks with early vomiting, the use of subcutaneous sumatriptan 6 mg should be considered. Zolmitriptan nasal spray 5 mg may be an alternative choice for some patients. These formulations should also be considered for all patients with severe nausea, particularly those who have nausea early in their attacks, and for attacks not responsive to oral triptan medications.

iv. For patients with moderate or severe migraine attacks who require triptan therapy, and whose attacks build up rapidly in intensity, rizatriptan 10 mg tablets, eletriptan 40 mg tablets, zolmitriptan 5 mg nasal spray, and sumatriptan 6 mg SC injection should be considered.

v. For patients with moderate or severe attacks who experience side effects on other triptans, almotriptan 12.5 mg tablets should be considered.

vi. For patients who experience frequent headache recurrence on triptan therapy, the use of eletriptan 40 mg or frovatriptan 2.5 mg tablets should be considered, or the addition of naproxen sodium to the patient's current triptan.

vii. For patients with nausea or vomiting who require an additional anti-emetic, metoclopramide, domperidone, or if necessary, prochlorperazine can be considered, to be taken with the triptan or triptan-NSAID combination.

For patients on the triptan strategy with headache recurrence within 24 hours after successful acute treatment:

i. When patients experience recurrence of a migraine headache attack after initial headache relief from a triptan, a second dose of the triptan should be recommended.

ii. For patients who experience frequent headache recurrence on triptan therapy, the use of eletriptan, frovatriptan, or dihydroergotamine (DHE) should be considered instead of the patient's current triptan, or the addition of naproxen sodium to the patient's current triptan.

For patients on the triptan strategy who have occasional treatment failure (but not often enough to move on to the triptan-NSAID combined strategy):

i. When patients experience occasional triptan failure with headache persistence two hours after taking a triptan, a rescue medication from another drug class should be considered, as opposed to dosing again with their triptan.

Timing of triptan use in patients with migraine with aura:

i. Patients with migraine with aura should be advised to take their triptan at the onset of the pain phase, although triptan treatment during typical migraine aura is safe, and if patients find that treatment during the aura is effective, there is no reason to discourage this practice.

3. Refractory migraine strategies

These are patients who have not responded satisfactorily to NSAIDs and / or triptans.

a. Triptan-NSAID combination strategy:

- i. For patients whose response to triptans alone is inadequate, an NSAID (e.g., naproxen sodium 500 - 550 mg) should be used simultaneously with their triptan.
- ii. For patients with nausea, or where poor drug absorption is suspected, oral metoclopramide 10 mg or domperidone 10 mg can be given with the triptan.

b. Triptan-NSAID combination with rescue medication strategy:

- i. For patients with severe migraine attacks where their triptan or triptan-NSAID combination occasionally fails to provide adequate relief, a rescue plan should be discussed with the patient. This may include a rescue medication to be taken at home when their usual medication fails.
- ii. In providing a rescue medication, the patient needs to be carefully assessed, and the medication tailored as much as possible to the patient's needs. For parenteral formulations, careful patient training is essential, and consideration should be given as to whether the patient can safely administer the medication.
- iii. For many rescue medications, in particular opioids and dexamethasone, frequency of use should be carefully monitored to ensure patient safety, and in the case of opioids to avoid medication overuse headache, abuse, dependence and possible addiction.
- iv. Rescue medications that can be considered, either alone or in combination, include:
 - a. NSAIDs with or without an anti-emetic, including ketorolac 60 mg by IM self-injection and rectal indomethacin
 - b. Dopamine antagonists including prochlorperazine suppositories
 - c. Oral dexamethasone or another steroid, either as a single dose or a short steroid taper over several days
 - d. Tramadol or codeine-containing combination analgesics (limit use to not more than nine days a month)
 - e. Other opioids (suggest limiting use to not more than seven days per month)
- v. Migraine attack preventive management options, both pharmacological and behavioural, should be considered for all patients where acute therapy is not adequately successful or the patient is at risk of medication overuse headache.

c. Dihydroergotamine strategy:

- i. Dihydroergotamine (DHE) by nasal spray [one spray (0.5 mg) in each nostril, repeated once after 15 - 30 minutes; maximum daily dose eight sprays) or self-injection (0.5 - 1 mg; maximum daily dose 3 mg) is an option for acute migraine therapy for patients who do not respond well to triptan-NSAID combination therapy (but not as a rescue therapy as it is also a vasoconstrictor).
- ii. DHE self-injection (SC or IM) requires individual patient training in safe injection techniques, but provides more reliable drug absorption than the intranasal route.

4. Vasoconstrictor unresponsive or contraindicated strategy:

- i. For patients with contraindications to vasoconstrictors or who have proven unresponsive to vasoconstrictors (triptans, DHE, and / or ergotamine), acetaminophen, NSAIDs (including ASA), acetaminophen-NSAID-caffeine combinations (not available in Canada as combination products), dopamine antagonists (e.g., prochlorperazine), occasional steroid use, and opioid-containing combination analgesics can be considered.
- ii. Consideration needs to be given to the safety of NSAIDs in patients with cardiovascular disease. Because of a relatively benign cardiovascular profile, naproxen sodium may be the NSAID of choice, if effective, for patients with cardiovascular disease, particularly in patients who require relatively frequent use.
- iii. If use of tramadol or codeine-containing combination analgesics is necessary, frequency of use should be carefully monitored and limited to use on 9 days a month or less.
- iv. If, in exceptional cases, use of strong opioids or barbiturate-containing analgesics is considered, their frequency of use should be carefully monitored to avoid medication overuse headache, dependence, abuse, and possible addiction. Suggest limiting use to not more than seven days per month.
- v. Behavioural treatment strategies and pharmacological prophylaxis may need to be maximized if a satisfactory pharmacological acute treatment cannot be established.

Special acute treatment strategies**5. Menstrual migraine strategy:**

- i. In most patients, acute treatment of menstrual migraine attacks is similar to acute treatment of attacks occurring at other times during the menstrual cycle.
- ii. For patients with refractory menstrual migraine who have a sufficient migraine attack frequency to justify general prophylactic therapy, this may be the best option.
- iii. For selected patients with refractory menstrual migraine with predictable timing of menstrual cycles, short-term monthly prophylaxis can be considered. Among the available options (frovatriptan, zolmitriptan, naratriptan, and naproxen), frovatriptan 2.5 mg twice a day starting two days before menstruation onset and continuing for six days has the strongest evidence for efficacy.
- iv. In selected patients, hormonal manipulation including estrogen supplementation around the time of menstruation, and continuous use of combination oral contraceptives can be considered but other treatment options should be tried first. If continuous use of combined oral contraceptives is being considered, contraindications and cautions for these (e.g., smoking, migraine aura, etc) should be observed (see discussion with regard to migraine with aura in Section 3, main guideline document).

6. Migraine during pregnancy strategy:

- i. Avoid use of medications during pregnancy if possible, especially during the first trimester, and consider use of

- non-pharmacologic strategies (e.g., trigger avoidance, relaxation exercises, etc).*
- ii. Acetaminophen is generally regarded as the safest analgesic for use during pregnancy.
 - iii. Alternatives to acetaminophen when acetaminophen is not adequate that may be considered for use during pregnancy include acetaminophen plus codeine combination products (intermittent use).
 - iv. Sumatriptan is also a potential option for acute migraine treatment in pregnancy, but is not recommended for routine use. There is significant evidence that the risks of sumatriptan use in pregnancy are minimal. It may be considered when migraine headaches are severe with significant disability and/or vomiting, other medications have failed during similar attacks, and the benefits appear to outweigh potential risks. There is much less information available regarding the safety of the other triptans during pregnancy; therefore, they should be avoided.
 - v. NSAIDs (e.g., ibuprofen, naproxen sodium) should be used with caution during pregnancy (possible increased risk of spontaneous abortion in first trimester), and should be discontinued before week 32.
 - vi. Because of the long-lasting effects of ASA on platelet function, other NSAIDs are preferred to ASA for use during pregnancy.
 - vii. Metoclopramide has not been associated with birth defects, and may be used during pregnancy. Dimenhydrinate is considered relatively safe for use as an anti-emetic during pregnancy (but there is no controlled trial evidence for efficacy in migraine). Domperidone should be avoided, as there is a lack of data with regard to its use during pregnancy.
 - viii. Ergot alkaloids are contraindicated during pregnancy.

7. Migraine during lactation strategy:

- i. Acetaminophen is considered safe during lactation.
- ii. Ibuprofen is the NSAID of choice during breast feeding. Diclofenac, ketorolac, and naproxen are also considered compatible with breast feeding, but with less data. ASA should be avoided.

- iii. Sumatriptan is considered compatible with breast feeding.
- iv. Metoclopramide, domperidone, dimenhydrinate, and prochlorperazine are all considered safe in breastfeeding.
- v. If pain medication is necessary in a breastfeeding mother, the safest drugs are acetaminophen and the NSAIDs. If opioids are considered necessary:
 - a. Morphine is considered the opioid of choice if potent analgesia is required in breastfeeding mothers (however, there is lack of evidence for efficacy of oral morphine in migraine).
 - b. Codeine in occasional doses is considered generally safe, although serious toxicity has been reported in maternal ultra-fast metabolizers (caution if premature infant or neonate less than 4 weeks old).
 - c. Avoid codeine for long-term therapy because of its variable maternal metabolism, because multiple cases of neonatal toxicity have been reported, and more effective opioid choices are available.
 - d. Avoid high doses of opioids in breastfeeding women.
 - e. For all opioids, exercise particular caution if the breastfeeding infant is under one month old.

CONCLUSION

There are many options for acute migraine therapy, but the NSAIDs (including ASA) and the triptans are the primary medications for acute migraine treatment, with or without the addition of an anti-emetic such as metoclopramide or domperidone. For patients with severe attacks which often render them bed ridden, it is important to try a triptan quickly to increase the likelihood of obtaining a good therapeutic response. For patients with attacks of lesser severity who have not tried NSAIDs, it is recommended that these be tried first. It is important, though, to inform patients that other options are available to prevent patients from becoming discouraged lapsed consulters who feels that nothing more can be done for them. Acute migraine treatment needs to be individualized for each patient, and consideration of appropriate formulation/route of administration is important.

Guideline Summary for Patients and Their Families

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This acute migraine treatment guideline is summarized here to provide information for patients with migraine and their families. Acute migraine medications are used to treat individual migraine attacks at the time of the attack. Most patients with migraine will use an acute medication, but patients with migraine, especially if they have frequent attacks, should also consider whether they could change lifestyle factors which might be making their headache more frequent (skipping meals, not enough sleep, etc), or whether they need a migraine preventive medication. Preventive (or prophylactic) medications are quite different from acute medications. Preventive medications are taken daily to reduce the frequency (number) of migraine attacks, while acute medications are used to reduce or stop the pain of a migraine attack once it has started. It is important that acute medications not be taken too often.

OBJECTIVE

The objective of this guideline is to help in choosing the best acute medication for an individual with migraine, and to assist in using the chosen medication in the most effective way.

Goals of acute migraine therapy

The goal is for the patient to be pain free within two hours after treatment without medication side effects (or minimal side effects). Not all patients can achieve this goal with medications that are available at this time, but if patients are not reaching this goal, or not able to do their usual activities reasonably well at two hours, another medication should be tried if possible.

Avoiding medication overuse

Taking acute medications for migraine too often can result in more and more frequent headaches, even to the point where the patient is having headaches every day. This is called medication overuse headache.

To avoid medication overuse headache, ASA, anti-inflammatory medications or NSAIDs (for example ibuprofen, naproxen, diclofenac) and acetaminophen should not be taken on more than 14 days per month. In the same way, triptans, ergots (such as ergotamine), opioids (for example codeine), or combination analgesics (for example acetaminophen with caffeine and codeine) should not be taken on more than nine days a month. Patients taking different acute medications on different days should limit their total use of acute medications to not more than nine days a month if one of their medications is a triptan, a combination analgesic, an ergotamine, or an opioid.

If patients have frequent migraine attacks, it is very useful to record use of acute medications, preferably with a headache

diary. Preventive medications can also be helpful. If they reduce migraine attack frequency, patients will not need their acute medications as often.

Which acute migraine medications should be used?

Many medications have been proven to be helpful for the acute treatment of migraine attacks. These include:

1. **The triptans:** these are listed below with the usual doses used. The triptans can be taken with naproxen sodium 550 mg if they are not effective enough by themselves. They can also be taken with a medication for nausea if necessary (metoclopramide 10 mg or domperidone 10 mg tablets).

- a. Almotriptan 12.5 mg tablets
- b. Eletriptan 40 mg tablets
- c. Frovatriptan 2.5 mg tablets
- d. Naratriptan 2.5 mg tablets
- e. Rizatriptan 10 mg tablets or wafers
- f. Sumatriptan 100 mg tablets, nasal spray 20 mg, and injection 6 mg
- g. Zolmitriptan 2.5 mg tablets or wafers, and nasal spray 5 mg

2. **Several non-steroidal anti-inflammatory drugs (NSAIDs):** these are listed below with the usual doses used. These medications can be taken with a medication for nausea if necessary (metoclopramide 10 mg, or domperidone 10 mg tablets):

- a. ASA 975-1,000 mg in tablet form, or as an effervescent liquid (the effervescent liquid may work more quickly)
- b. Ibuprofen 400 mg in tablet form, or in a liquid-containing capsule which may work more quickly.
- c. Naproxen sodium 500 - 550 mg in tablet form
- d. Diclofenac 50 mg in tablet form or as a powder dissolved in water which works faster than the tablets.

3. **Acetaminophen** 1000 mg in tablet form. Acetaminophen is helpful mainly for attacks of mild or moderate severity. It can be taken with a medication for nausea if necessary (metoclopramide 10 mg or domperidone 10 mg tablets).

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4. *Dihydroergotamine* as a nasal spray (2 mg) or a subcutaneous or intramuscular injection (1 mg). This medication is not available as a tablet. It can be taken with a medication for nausea (metoclopramide 10 mg, or domperidone 10 mg tablets).

5. *Ergotamine* (with caffeine) tablets: Although these can be helpful, they have many side effects, and the triptans usually work better.

Some medications that are sometimes used to treat migraine attacks are best avoided, if possible. They should not be used routinely. These include:

1. Painkillers (analgesics) that contain tramadol, usually in combination with acetaminophen.
2. Painkillers (analgesics) that contain codeine, usually in combination with acetaminophen or ASA and caffeine.

These medications are best avoided because they do not usually work very well for migraine, and they often lead to frequent use and medication overuse headache. If these medications are used, patients should monitor and record how often they use them with a headache diary.

These medications may be necessary in some patients, for example in those who have had a heart attack or stroke and cannot take triptans, or in patients who don't respond to NSAIDs or triptans. They may also be helpful for occasional use as a "rescue" medication when the patient's triptan fails to work.

There are several other medications that are sometimes used for migraine that are best avoided and used only in exceptional circumstances because of their tendency to lead to medication overuse headache and addiction. These include:

1. Butorphanol nasal spray and other strong opioids like oxycodone
2. Barbiturate (butalbital)-containing painkillers (analgesics), either with or without codeine.

In summary, the main medications for acute migraine treatment are the NSAIDs and the triptans. Acetaminophen can also be used for attacks of mild or moderate severity, and metoclopramide and domperidone can be added to help control nausea or vomiting.

Treating early

Patients with migraine attacks that are usually moderate or severe in intensity should be advised to take their acute medication early during their migraine attacks while pain is still mild. Acute medications usually work better when taken early in the attack, although patients need to be careful that they don't take the medication often enough to cause medication overuse headache.

Choosing an acute medication for a specific patient

Patients with migraine can be divided into a number of groups based on the severity of their migraine attacks, the medications they have tried before, and how well the medications that they have tried have worked for them. In this way, one can decide which medication would be best for an individual patient at a particular time.

Situation 1: For patients with severe attacks that often require bed rest it is best to try a triptan (with a medication to treat

nausea if necessary). Subcutaneous sumatriptan 6 mg is often best for severe attacks with early vomiting, or for severe attacks that do not respond to triptan tablets.

Situation 2: Patients with less severe attacks and who have not taken medications before for their migraines can try medications according to the following plan. For those who have tried some medications, they can be fitted into the plan after the first step or two, depending on what has been tried and how well it has worked. If a medication works quite well, there is no need to go on to the next steps. It is also important for patients to:

- a. Learn about the various treatment options that are available, so they don't become discouraged when something they try does not work.
- b. Understand that a medication for nausea (metoclopramide 10 mg or domperidone 10 mg) can be added to all the acute migraine medications if needed for nausea.

Step 1: Individuals who have developed migraine for the first time can try one of ASA 1,000 mg, ibuprofen 400 mg, diclofenac potassium 50 mg, or naproxen sodium 500 - 550 mg. If they have a history of stomach ulcers or find that the NSAIDs cause side effects for them, they can try acetaminophen 1,000 mg. For patients with relatively severe attacks (but not usually requiring bed rest), a triptan can be prescribed by the doctor at the same time. The triptan can then be used as a rescue medication by the patient as necessary if the NSAID or acetaminophen occasionally fails. If the patient finds that the NSAID usually does not work well, the NSAID can be stopped and the triptan can become the patient's main medication.

Step 2: For patients who do not respond well to NSAIDs, a triptan is usually the best medication for use as their main acute migraine treatment. Some important points:

- a. At least three different triptans should be tried (in different attacks) if the first triptan the patient tries does not work well. If it is working well, the patient should be pain free or almost pain free two hours after taking the medication, and be able to do usual activities with no significant side effects.
- b. A triptan should be used to treat approximately three separate migraine attacks before deciding whether it is going to work well or not.
- c. Intranasal triptans which are partially absorbed through the lining of the nose (for example zolmitriptan 5 mg) may work better than tablets for patients with nausea.
- d. Orally dissolving tablets (wafers) may work better than regular tablets for patients with nausea that is worsened by using water to swallow regular tablets.
- e. Triptans usually work best when taken early in the migraine attack while pain is still mild, although too frequent use (use on ten days a month or more) should be avoided. Patients with migraine with aura usually find it most helpful to take their triptan when the headache starts rather than during the aura itself, although triptan treatment during a typical migraine aura is safe. If patients find that taking a triptan during the aura is effective in treating their headache, they can continue to use their triptan in that way.

- f. When patients have relief of their migraine attack with a triptan, but the headache comes back within the next 24 hours, a second dose of the triptan usually works well.
- g. If patients find that their headache often comes back within 24 hours after it has been relieved by a triptan, it may be helpful to switch to eletriptan, frovatriptan, or dihydroergotamine (DHE) from their current triptan. It may also be helpful to take 500-550 mg of naproxen sodium together with the triptan that they are using.
- h. Patients with some severe migraine attacks and others that are less severe may find it helpful to use an NSAID for some attacks and a triptan for others.

Step 3: If triptans do not work very well for a patient, it may be helpful if the patient takes naproxen sodium (500 - 550 mg) together with the triptan.

Step 4: For patients with severe attacks who usually respond well to a triptan-naproxen sodium combination, but have an occasional treatment failure, a rescue plan which may include a different rescue medication for use at those times may be helpful. Rescue medications that can be used include: prochlorperazine tablets or suppositories, occasional use of corticosteroids (such as prednisone), and occasional use of acetaminophen with tramadol or codeine. It is best for patients to discuss rescue medication options with their physician.

Step 5: For patients who do not respond satisfactorily to a triptan-naproxen sodium combination, the use of dihydroergotamine (nasal spray or self-injection), in future attacks combined with oral metoclopramide (if needed), may be helpful.

Step 6: Although not recommended for routine use in migraine, opioid analgesics (for example acetaminophen with codeine or tramadol) remain an option for patients who do not respond well to earlier treatment steps. These medications are also a treatment option for patients who do not respond to NSAIDs and who cannot take triptans because they have had a heart attack or stroke. Patients using medications with codeine or tramadol should:

- a. Closely monitor how often they use them (using a headache diary).
- b. Learn how to find and avoid their migraine attack triggers, and what lifestyle changes might make their migraines less frequent.
- c. Consider whether a migraine preventive medication might be helpful for them.

In summary, by going through these steps patients can see where they fit in, and what medication they should try next.

Menstrual migraine attacks

Menstrual migraine attacks are migraine attacks that occur around the time of menstruation. For some women, these are their most severe attacks, and the ones that are the most difficult to treat. The treatment of menstrual migraine attacks may include:

- a. The same treatments that are used for migraine attacks at any time, as discussed above. If the patient has many attacks at other times during the menstrual cycle as well, the usual preventive medications can be used.

- b. If patients have their migraine attacks mainly just before and during menstruation and don't respond well to NSAIDs or triptans used in the usual way, they can use naproxen sodium (500 - 550 mg) or frovatriptan (2.5 mg) twice a day for six days, starting 2 days before menstruation is expected to start in order to prevent their menstrual migraine attacks.
- c. If none of the options described above are effective, several types of hormonal treatments can be tried, but these are best discussed with the physician.

Migraine during pregnancy

Many patients with migraine improve during pregnancy, but medications are still often necessary. The best strategy is, however, to avoid use of medications during pregnancy if possible, especially during the first trimester, to avoid affecting the unborn baby. Non-medication treatments like avoiding migraine triggers (for example too much stress or too little sleep) and using relaxation exercises may be helpful. Patients who have questions about medication use in pregnancy can check the Motherisk website (www.motherisk.org/) or call Motherisk at the Hospital for Children (tel: 416-813-6780 or 1-877-439-2744). With regard to medications:

- a. Acetaminophen is considered to be the safest painkiller for use during pregnancy. If acetaminophen is not helpful, occasional use of acetaminophen with codeine is also considered relatively safe.
- b. NSAIDs (for example ibuprofen, naproxen sodium) should be used with caution during pregnancy. In the first three months of pregnancy, they may increase the risk of a miscarriage slightly. They should be avoided in the last three months because of effects on the baby. ASA should be avoided during pregnancy.
- c. Triptans are relatively new drugs, and not recommended for routine use during pregnancy. Sumatriptan does seem relatively safe, with no effects on the baby, although it may increase bleeding during delivery. As experience is greatest with sumatriptan, if a triptan is being considered for use during pregnancy, sumatriptan is the one to use. It may be considered when other medications have failed, and migraine headaches are severe with major disability and/or vomiting.
- d. Metoclopramide has not been associated with birth defects, and may be used during pregnancy. Domperidone should be avoided.
- e. Ergotamine and dihydroergotamine should not be used during pregnancy.

Migraine during breastfeeding

Drugs are best avoided during breast feeding as well, but many medications are safe as outlined below.

- a. Acetaminophen is considered safe during breastfeeding.
- b. Ibuprofen is considered the safest NSAID during breast feeding. Diclofenac, ketorolac, and naproxen are also considered relatively safe, but ASA should be avoided.
- c. Among the triptans, sumatriptan is considered safe during breast feeding.

- d. Among medications for nausea, metoclopramide, domperidone, dimenhydrinate, and prochlorperazine are all considered safe in breastfeeding.
- e. Codeine in occasional doses is considered relatively safe, although it is best avoided if possible, especially if the infant is premature or less than one month old. It has on rare occasions caused serious problems for breast feeding infants.

CONCLUSIONS

There are many medications that can be helpful for acute migraine treatment. Treatment needs to be tailored for each patient. Sometimes several different medications need to be tried in order to find one that works best for a patient without causing too many side effects. It is best if patients learn about the treatment options and when to use them so that they can partner better with their physicians and pharmacists in the management of their headaches. The more patients learn about migraine treatment, the more successful they are likely to be. The Headache Network Canada website (www.headachenetwork.ca) is a very good source of information for patients with migraine.

Guideline Development Summary

Werner J. Becker on behalf of the Canadian Headache Society Acute Migraine Treatment Guideline Development Group

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The development of this guideline for the acute pharmacological treatment of migraine is described in this appendix, using the 23 items of the AGREE instrument for the appraisal of practice guidelines as a framework.¹

1. Objectives:

To assist the practitioner to:

- a. Choose an appropriate acute medication for an individual with migraine, based on current evidence in the medical literature.
- b. Use the chosen medication in the most effective manner.
- c. Reduce the headache-related disability suffered by individuals with migraine.
- d. Use the best evidence in the medical literature in the clinical context of overall migraine treatment.

2. The clinical question addressed:

- a) Which acute medication should be prescribed for an individual patient in a specific clinical situation?

3. The target population:

- a) Adults with episodic migraine (patients who experience migraine headache attacks on less than 15 days/month). It does not include recommendations for pediatric patients and for the emergency room management of acute migraine. Although this guideline may have relevance to patients with chronic migraine (headache on 15 days a month or more, with diagnostic criteria for migraine met on at least eight days a month), many of the clinical trials reviewed for this guideline did not include patients with headache frequencies of this magnitude.

4. Professional groups involved in the creation of these guidelines:

- a) These guidelines were produced by the Canadian Headache Society. Health professionals involved in development of the guideline included neurologists, pharmacists, family physicians, and nurses with a special interest in headache.

5. Patient views and preferences:

- a) Patient expectations, views and preferences were obtained from the medical literature. A published patient survey indicated that an overwhelming majority of patients consider complete relief of head pain, no recurrence, and rapid onset of action as important or very important attributes of acute migraine therapy.² Generally, patients want a drug that provides complete headache relief.³

These patient values were considered in the production of this guideline, and many clinical trials use endpoints which made this possible.

- b) Patient views and experiences were also obtained at the Canadian Migraine Forum⁴⁻⁶, which was hosted by the Canadian Headache Society prior to the development of these guidelines.

6. The target users for this guideline:

- a) This guideline is intended primarily for physicians who treat patients with migraine, including both family physicians, and specialists. Other health professionals who treat patients with migraine may also find this guideline helpful.
- b) Although they are not the primary target users of this guideline, this guideline may also be helpful to patients with migraine and their families.

7. Pre-testing of the guidelines:

These guidelines have not been specifically pre-tested among the intended end users. They have however been created by experienced clinicians with extensive experience in medication use for migraine. This experience has been utilized to make the guidelines as clear and practical as possible.

8. Systematic methods were used to search for evidence with regard to the individual drugs assessed:

The recommendations for individual drugs in the Guideline are based on a targeted review (Section 2 of the Guideline). Primarily meta-analyses and systematic reviews were included. Where these were not available for a drug or were out of date, individual clinical trial reports were utilized. Only double-blind randomized clinical trials with placebo or active drug controls were included in the analysis for the targeted review provided in Section 2. For other aspects of the guideline document which deal with more general questions pertinent to acute migraine treatment where randomized trials do not exist, a general literature review was done and expert opinion was used to draw conclusions regarding suggested management. These conclusions are clearly labelled as "Expert consensus" rather than "Recommendations" in order to avoid confusion.

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For the targeted review, a detailed search strategy was employed to find relevant published clinical trials of drugs used in Canada for the acute treatment of migraine in adults.

- a) A MEDLINE search of the English language literature for analgesics, NSAIDs, ergot derivatives, and triptans was performed. Only randomized, controlled trials (RCTs) and meta-analyses/systematic reviews of acute migraine medications in adults were included. The initial search was limited to the years 1996 - May 2006 (first Canadian migraine guidelines were published in 1997). The search was updated in May 2010, and again in May 2012.
- b) The Cochrane Collaboration® and EMBASE were also searched for systematic reviews/meta-analyses.
- c) Search terms used were:
 - i. exp. migraine disorders, and
 - ii. sumatriptan or almotriptan or eletriptan or naratriptan or rizatriptan or zolmitriptan or frovatriptan or “triptan”, or
 - iii. exp. anti-inflammatory agents, non-steroidal, or
 - iv. exp. aspirin, or acetaminophen, or exp. analgesics, or
 - v. ergotamine or dihydroergotamine, or
 - vi. exp. barbiturates or butalbital, or
 - vii. metoclopramide or domperidone or dimenhydrinate or exp. antiemetics
 - viii. limits: human, adults, English, randomized controlled trial (RCT) or meta-analysis

9. Criteria used for including / excluding evidence identified by the search:

- a) Studies were required to be prospective, randomized, double blind, controlled trials of drugs used for acute migraine treatment.
- b) Trials comparing treatments to placebo or an active comparator were included.
- c) Both parallel group and cross-over designs were acceptable.
- d) Study participants had to be adults and meet IHS⁷ or Ad Hoc Committee on Classification of Headache (JAMA. 1962; 179:717-8) criteria for the diagnosis of migraine headache, or provide sufficient detail of the headache characteristics to support the diagnosis of migraine (for studies conducted prior to development of Ad Hoc criteria).
- e) The literature search was limited to agents commonly used in clinical practice, as explained in the text.
- f) Trials of patients with chronic daily headache (headache on ≥ 15 days per month), chronic tension type headache or transformed migraine were not included.

10. Methods used to formulate the recommendations:

- a) Abstracts of studies and meta-analyses identified by the literature search were screened for eligibility by two independent reviewers. Papers that could not be excluded with certainty from this process were reviewed in full. Papers passing the initial screening process were retrieved and the full text was reviewed.
- b) Recommendations were graded based on the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.^{8,9}

- c) Papers were reviewed independently by two reviewers and graded with regard to methodological quality. The literature review, and draft recommendations were presented by IW, and WJB to a group of six experts from the Canadian Headache Society on Oct 29, 2011 in Montreal, and consensus reached through discussion and mutual agreement. The recommendations were graded according to the Grade criteria, and levels of evidence were assigned to the recommendations.
- d) The guidelines were presented by IW and WJB and further discussed and validated with a group of four Canadian headache experts on June 7, 2012 in Ottawa, in conjunction with the Canadian Neurological Sciences Federation.
- e) The draft guideline was then extensively circulated by e-mail to the entire guideline development group (including all the authors) and extensive commentary and feedback was obtained from many. The drafts were then updated for external review.
- f) The guidelines were sent to two external reviewers who had not been involved in the guideline development to that point, a family physician with a special interest in headache and pain, and a pharmacist with special expertise in pain management. All their suggestions were considered by the guideline authors, and the great majority incorporated into the guideline document.

11. Health benefits, side effects, and risks of the recommendations were considered:

- a) The main outcome measures used were pain freedom (pain-free) at two hours and headache relief (pain reduced from severe or moderate to mild or none) at two hours. These outcomes are important to patients, (2) and were also the main outcomes used in many clinical trials. Other outcomes important to patients including headache recurrence rates and adverse events were also considered.
- b) The prevalence of adverse events was analyzed in the studies reviewed, and these were considered in the recommendations. The recommendation grading system used (GRADE) considers adverse events in the grading of recommendations.

12. The link between the recommendations and the evidence on which they are based:

- a) In Section 2 of the guidelines, each drug and the evidence for its efficacy are presented and discussed. All the references on which the recommendation for that drug is based are provided. Tables are provided which summarize the evidence contained in the references.

13. External review of the guideline:

- a) The guidelines were externally reviewed by two experts not involved in the Guideline Development Group. Reviewers were asked to critically review the guidelines, and their feedback was considered. These reviewers included:
 - i) A family physician with special expertise in headache and pain
 - ii) A pharmacist with special expertise in pain

14. The Guidelines were developed on behalf of the Canadian Headache Society. The executive of the Society has undertaken to review and update the guidelines every three years.

15. Every attempt has been made to provide a concrete and precise description of which management is appropriate in a given clinical situation and in a particular patient group, as permitted by the body of evidence:

- a) In addition to the evidence-based targeted review for each acute drug, several sections were added to the guidelines to clarify which management is appropriate in which clinical situation.
- b) Section 1 of the guideline includes a section on “General principles of acute migraine therapy” that discusses the available medication formulations (tablets, injections, etc) and the various general treatment approaches which are available. This section also discusses how to choose between treatment options.
- c) Section 3 provides a detailed approach on how to choose a medication for a specific patient. The available acute treatments have been organized into treatment strategies, and the specific clinical situations in which each strategy should be considered are outlined in detail.
- d) As the evidence for some of the required decision making is limited, it is clearly stated when a general literature review and expert opinion is the basis for a conclusion. To avoid confusion, when non-randomized studies and expert opinion is the basis for a conclusion regarding how patients in specific clinical situations should be managed, the suggested management is labelled “Expert consensus” rather than a recommendation. The term “recommendation” is reserved for recommendations based on evidence from randomized double blind controlled clinical trials.

16. Different possible treatment options for the reduction of migraine frequency in addition to pharmacological prophylaxis are mentioned:

- a) The great majority of patients with migraine in Canada utilize an acute medication for treatment of their migraine attacks.¹⁰ These are not sufficient for some patients, however, and in Section 1, it is clearly stated that for patients with frequent attacks who are at risk of medication overuse headache because they require their acute medication too frequently, behavioural approaches to migraine management and prophylactic medications should be considered in addition to acute medications. This message is reinforced for migraine management in general in Section 3 which deals with treatment strategies in detail.

17. The guideline is structured so that users may find the most relevant recommendations easily:

- a) All the recommendations and expert consensus statements are numbered in the document, and printed so that they stand out from the rest of the text.
- b) Table 8, Section 2 provides a list of all the drugs reviewed, the strength of the recommendations for their use, and the level of evidence supporting that recommendation.

- c) Table 2, Section 3 lists all the acute treatment strategies, and Tables 11a and 11b list all the drugs involved in each treatment strategy.
- d) Table 9, Section 3 provides a list of all the drugs recommended, dosages, formulations, their contraindications, and their adverse effects.
- e) A list of the various sections and appendices included in this guideline is given under the heading “Guideline structure” in order to assist the reader to access any section of interest easily.

18. Tools have been made available to assist in dissemination and implementation:

- a) A summary document for family physicians has been included (Section 4).
- b) Tables 11a and 11b in Section 3 summarize the acute migraine treatment strategies, including the medications used in each. They also indicate when each strategy should be used.
- c) A guideline summary for patients and the public has been included (Section 5).
- d) A patient leaflet which describes acute migraine treatment has been included (Appendix 2).
- e) A patient headache diary sheet together with instructions for completion is provided (Appendix 3).

19. Organizational barriers to applying the recommendations of this guideline have been addressed below:

- a) Individuals with migraine who currently seek medical attention usually do so through the offices of family physicians and specialists, primarily neurologists. Both these groups are able to prescribe medications, so no significant organizational barriers exist to the prescribing of acute medications as recommended in these guidelines.
- b) The prescription of acute migraine medications does require patient follow up for optimal benefit to be achieved. This guideline might reduce the burden of this follow up if physicians are more likely to choose the best drug for the patient first as a result of these guidelines.
- c) Individuals with migraine may also seek over-the-counter treatment in pharmacies. Pharmacists are one of the most accessible of health care professionals. This guideline may assist pharmacists in recommending over-the-counter drugs when appropriate, or referring patients to their physician when prescription medications are required or the patient may be suffering from medication overuse headache. This may help reduce the burden of migraine.

20. Potential effects of these guidelines on the need for additional resources:

- a) This guideline might potentially increase triptan use as compared to the less expensive codeine containing analgesics which are commonly used or over-used in Canada. It is possible that they might increase the overall costs of drugs used for migraine, but as the triptans are more effective than the combination analgesics for most patients, the indirect costs of migraine, such as missed

work, should be reduced much more. The indirect costs of migraine (missed work, etc) are much greater than the direct costs (medications, etc).¹¹

- b) This guideline may also reduce the prevalence of medication overuse headache, a condition which imposes a huge economic and social burden on patients and society.¹¹

21. Options for measuring guideline adherence:

- a) There are a number of options which could be considered to measure guideline adherence in a medical practice. Practice audits could be done to see if patients were treated according to the appropriate treatment strategy. These could also assess what proportion of patients with migraine were receiving acute medications with strong recommendations for use, as opposed to drugs with weak recommendations and drugs not recommended for routine use. Finally, some drugs have strong recommendations against their use. Use of these drugs could also be assessed.
- b) Guideline adherence at a regional level could also be evaluated through an analysis of prescriptions for patients with migraine. NSAID and triptan use, for example could be compared with the use of drugs not recommended for routine use such as opiate-containing combination analgesics.

22. Guideline development and external funding:

- a) This guideline was developed without external funding. All participants volunteered their time. Some minor travel expenses were paid by the Canadian Headache Society.

23. All members of the guideline development group have declared any existing conflict of interest. This has been done in the title page of the guidelines.

REFERENCES

1. AGREE C. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care*. 2003 Feb; 12(1):18-23.
2. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? *Headache*. 2002; 42:3-9.
3. Malik SN, Hopkins M, Young WB, Silberstein SD. Acute migraine treatment: patterns of use and satisfaction in a clinical population. *Headache*. 2006;46:773-80.
4. Becker WJ, Gladstone JP, Aube M. Migraine prevalence, diagnosis, and disability. *Can J Neurol Sci*. 2007;34:S3-9.
5. Becker WJ, Gawel M, Mackie G, South V, Christie SN. Migraine treatment. *Can J Neurol Sci*. 2007;34:S10-9.
6. Becker WJ, Giammarco R, Wiebe V. Moving forward to improve migraine management in Canada. *Can J Neurol Sci*. 2007;34: S20-6.
7. Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders: 2nd edition*. Cephalalgia. 2004;24:9-160.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
9. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008;336:995-8.
10. Cooke LJ, Becker WJ. Migraine prevalence, treatment and impact: the canadian women and migraine study. *Can J Neurol Sci*. 2010;37:580-7.
11. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. *Eur J Neurol*. 2012; 19:703-11.

Acute Migraine Treatment - Information for Patients

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What is acute migraine treatment?

Acute migraine treatment usually involves taking medications to reduce the pain and other symptoms of a migraine attack. Non-medication treatment can also be used, like ice packs and relaxation or meditation, but most patients with migraine also take some sort of medication for their attacks when they happen.

Acute medications (sometimes called symptomatic medications) are used to treat individual migraine attacks when they happen, and are quite different from preventive or prophylactic medications. Preventive medications are meant to be taken daily in order to make migraine attacks less frequent. Acute medications are an entirely different class of medications, and are taken only when the attack actually happens. It is important to know that acute medications can make migraine headaches more frequent if they are taken too often.

Which acute medications can I use for my migraine attacks?

Many medications are used to treat migraine attacks. For milder attacks, acetaminophen may be sufficient. It does not work well for most patients with migraine, however, and the non-steroidal anti-inflammatory drugs (NSAIDs) are usually more effective. NSAIDs that have been proven to help many patients with migraine include ibuprofen (400 mg), naproxen sodium (550 mg), diclofenac (50 mg), and ASA (aspirin) 1,000 mg. Ibuprofen and diclofenac will often start to work very quickly, but you may need to repeat your dose because their effects wear off quickly (in about four hours). They may stop the attack, however, and it may not come back. Naproxen sodium usually lasts longer, up to 12 hours.

If your attacks are severe and especially if they are bad enough that you have to lie down, the NSAIDs may not work well for you. The triptans are medications that are often more effective for more severe attacks (as well as less severe attacks). There are seven triptans available in Canada. They are all a little different, and one may work better for you than the others. It is therefore worthwhile for you to try at least three or four of them if you are not having an excellent response to the one you are taking. An excellent response means that you are free of pain, or at least have improved enough so that you can go about your usual activities two hours after taking the medication, and that you don't have uncomfortable side effects.

The triptans come as tablets, wafers, nasal sprays, and injections. The wafers dissolve in your mouth, so you don't need water to take them. They can be helpful if you find that drinking water with your tablets makes you more nauseated, or causes vomiting. The nasal sprays are absorbed partially through the

lining of the nose, so they can be helpful if you have a lot of nausea, or may vomit with your migraines. Because some of the medication enters the bloodstream quickly through the lining of the nose, they may work very quickly in relieving your migraine. Much of the medication from nasal sprays is still absorbed through the stomach, so if you are vomiting, they may not work that well for you. In that case, the injection is a better option for you, as all the medication will stay in your body. Sumatriptan comes in an auto injector, which is easy to use at home. If the tablets, wafers, or nasal sprays don't work that well for you, you may find that the injection works much better.

How should I choose my acute medication?

There are several things to consider when choosing an acute medication. First of all, how severe are your migraine attacks? If they are quite severe, and force you to go to bed, it is best to try one of the triptans, as it is unlikely that the other medications like the NSAIDs will work for you. If your attacks are milder, the NSAIDs may be a good choice for you. If they are quite mild, even acetaminophen may work well.

Secondly, your past experience with medications is important. If you have tried acetaminophen and ibuprofen, and neither one has worked well for you, then it is likely time to try a triptan, although it is still possible that one of the other NSAIDs may be helpful, like diclofenac or naproxen.

Medications with codeine or tramadol, like acetaminophen with codeine tablets or acetaminophen with tramadol, are not recommended for routine use with migraine attacks. They often don't work all that well, and they lead to medication overuse headache in many people, especially if their migraine attacks are frequent. They may be options if you do respond to other acute migraine medications or cannot take them for some reason. In that case, they should not be taken on more than nine days per month.

If your headache increases in severity rapidly and you need your acute medication to work quickly, there are several special medications which may be helpful. The liquid ibuprofen capsules 400 mg (for example, Advil® Liquigels), diclofenac

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powder for oral solution 50 mg (Cambia®), and effervescent aspirin 900 mg (for example, Alka-Seltzer®) can work more quickly than the regular tablets. Among the triptans, the sumatriptan injection is the fastest (Imitrex® 6 mg). The zolmitriptan nasal spray 5 mg (Zomig®) also has a fast onset of action. Among the triptan tablets, rizatriptan 10 mg (Maxalt®) and eletriptan 40 mg (Relpax®) tend to work quickly. If your headache tends to come back on the same day after you treat it with a triptan, you may find that frovatriptan 2.5 mg (Frova®) or eletriptan 40 mg (Relpax®) will work best for you with less chance that the headache will return after treatment. If the triptans give you side effects that are a nuisance, then you may find that almotriptan 12.5 mg (Axert®) will give you fewer problems and still treat your migraine headaches well.

If drinking water with your tablets makes your nausea worse or makes you vomit, then a wafer which dissolves in your mouth may be best (Maxalt RPD® 10 mg, Zomig Rapimelt® 2.5 mg). If you have a lot of nausea or vomiting, or if you attacks just don't respond well to triptan tablets or wafers, the sumatriptan injection (Imitrex® 6 mg, or the zolmitriptan nasal spray (Zomig® 5 mg) may work better for you. Also, if you have a lot of nausea, you can take a medication for nausea (metoclopramide 10 mg, or domperidone 10 mg) with your triptan or NSAID to get a better treatment result.

Finally, if your attacks are not responding as well as you would like to your triptan, you can try taking naproxen sodium 550 mg with the triptan. This combination often works better than either medication by itself.

What is the best way to take my acute medication?

All the acute migraine medications seem to work better if they are taken early in the attack rather than once the pain becomes severe. So early treatment, if you are confident that the attack is going to build up to a moderate or severe headache if you don't treat it, is usually best. If your migraine attacks are quite frequent, however, you will need to be careful as you don't want to take you acute medication so often that you are at risk for medication overuse headache.

If you have migraine with aura, you may find that if you take your medication during the aura it will prevent the headache from coming on. If this is the case for you, you may do this, as taking acute medications, including the triptans, during the aura is safe. The triptans, however, do seem to work best for many patients when they are taken at the start of the headache pain, rather than during the aura.

Are there any risks in using acute migraine medications?

Like most other medications, the medications used for acute migraine treatment can have side effects. The NSAIDs can be hard on the stomach, and should not be used by patients who have had stomach or duodenal (intestinal) ulcers. They are best taken with food to avoid stomach irritation. Acetaminophen and the triptans are much easier on the stomach. The triptans temporarily narrow (constrict) blood vessels including those in the heart. While this is not a problem for healthy people, it can be for patients with vascular or heart disease. People with a history of heart attacks, a stroke, or serious circulation problems in the legs should not take triptans or dihydroergotamine.

The most common problem with acute migraine medications, however, is medication overuse headache. When they are taken too often, all acute migraine medications can cause medication overuse headache. How often is too often? Patients using NSAIDs and acetaminophen need to keep their medication use to less than 15 days a month. Patients taking the triptans, or ergotamines, or pain killers with codeine or tramadol need to keep use of these medications to less than ten days a month. If they take acute medications above these monthly limits, patients with migraine run the risk of developing more and more frequent headaches. This is called medication overuse headache, and can sometimes lead to daily headaches. When this happens, the medication overuse must be stopped, and a preventive medication started. Referral to a neurologist or headache specialist may be needed.

CONCLUSION

Many acute migraine medications are available, and most patients can find one that works well for them. It is important to know what is available, and that these medications should not be used too often. Patients with frequent migraine attacks need to be especially careful, and they should speak to their doctor about which lifestyle changes they could make to reduce their migraine frequency. If necessary, they should also consider going on a preventive medication to reduce their migraine frequency, and therefore their need for acute medications. Preventive medications are meant to be taken daily, and do not cause medication overuse headache.

Diary Completion Instructions

Werner J. Becker¹ and Irene Worthington² on behalf of the Canadian Headache Society Acute Migraine Treatment Guideline Development Group

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Headache severity

Please record your greatest headache severity during each of the segments of the day: morning, afternoon, and evening / night. Use the scale provided just below the boxes. If you find it too demanding to fill out the diary three times a day, you could leave it in your bedroom, and fill in the diary at the end of the day while your experience of that day is still fresh in your mind.

Acute medications

These are medications which you take to treat individual headache attacks. Once you have placed the names of your acute medications in the left-hand column, simply place in the appropriate box the number of tablets you took that day for each medication. Record also the “overall” relief you received from each medication that you took that day. A scale is provided just below the acute medication section for your use.

Preventive medications

Place the names of each of your preventive medications in the left hand column, along with your tablet size in milligrams. Then each day record how many tablets you took of each medication. There is no “Overall relief” section here, as preventive medications are taken to reduce migraine frequency, not to provide short term relief.

Menstrual periods

Place an “x” on each day that you experience menstrual bleeding. This will help to show whether your headaches are triggered by menstruation, and this in turn may help determine which treatments are best for you.

Disability for the day

Here you can indicate how much your migraine impacted your activities that day. Use a number from the scale provided.

Triggers

Migraine triggers are things that you experience which seem to bring on a headache at least some of the time. They include things like stress, weather changes, certain foods, and many others.

See following page for Diary

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Headache Diary

HNC-CHR Website (headachenetwork.ca)

Name: _____

Month: _____

Year: _____

Headache Severity	Scale of 0-10 No pain = 0 10 = Pain as bad as it could be																																
	DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Morning																																	
Afternoon																																	
Evening/Night																																	

ACUTE MEDICATIONS (Tablets/injections per day) (Medications taken to treat a headache eg. Triptans, painkillers, etc.)

Name: _____ / _____ mg																																	
Overall relief																																	
Name: _____ / _____ mg																																	
Overall relief																																	
Name: _____ / _____ mg																																	
Overall relief																																	
Name: _____ / _____ mg																																	
Overall relief																																	

Relief: 0 = None 1 = Slight Relief 2 = Moderate Relief 3 = Complete Relief

PREVENTIVE MEDICATIONS (Daily medications taken to prevent or decrease your headache tendency eg. Amitriptyline)

Name: _____ / _____ mg																																
Name: _____ / _____ mg																																

MENSTRUAL PERIODS

DISABILITY FOR THE DAY

0 = None 1 = Able to carry out usual activities fairly well 2 = Difficulty with usual activity, may cancel less important ones 3 = Have to miss work (all or part of day) or go to bed for part of day

TRIGGERS

Please code trigger with a number and give details below. Record trigger number in table above on the appropriate date where you feel that trigger contributed to your headache.

