

# Delivery systems for acute migraine medications

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## abstract

**OBJECTIVE** To discuss advantages and disadvantages of various routes of administration and delivery systems for acute migraine medications, and to assist family physicians in optimizing treatment for individual patients.

**QUALITY OF EVIDENCE** A MEDLINE search from January 1966 to October 2000 and a Current Contents search for the year 1999 to October 2000 were conducted. Randomized controlled trials were selected, when available. Also included are guidelines (Canadian), non-blinded trials, systematic reviews, and population-based studies.

**MAIN MESSAGE** Selecting an appropriate way to deliver medication is important in acute migraine therapy. The parenteral route has advantages, such as rapid onset, greater efficacy, and the possibility of use during nausea and vomiting. Disadvantages include local site discomfort, inconvenience, and patients' dislike of needles. Most patients prefer oral therapy, but gastric stasis and nausea and vomiting during a migraine attack might limit its use. The intranasal route usually provides fairly rapid onset, but side effects, such as disturbances in taste, can occur. The rectal route is another option, but absorption is sometimes erratic, rectal irritation can occur, and few migraine medications are available in rectal formulation.

**CONCLUSION** Selection of appropriate medications and suitable delivery systems for individual patients, based on the characteristics of their attacks (eg, severity, speed of progression to severe intensity, degree of associated symptoms), ease of administration, and patient preference, will optimize therapy for acute migraine attacks.

## résumé

**OBJECTIF** Discuter des avantages et des inconvénients de diverses modalités d'administration et de perfusion des médicaments contre la migraine aiguë et aider les médecins de famille à optimiser individuellement la pharmacothérapie chez les patients.

**QUALITÉ DES DONNÉES** Une recension a été effectuée dans MEDLINE de janvier 1966 à octobre 2000 ainsi qu'une revue des sommaires de l'année 1999 jusqu'à octobre 2000. On a retenu les essais aléatoires contrôlés lorsqu'ils étaient disponibles. On a aussi inclus les lignes directrices (canadiennes), les essais sans insu, les revues systématiques et les études fondées sur la population.

**PRINCIPAL MESSAGE** Le choix d'un mode approprié d'administration des médicaments importe beaucoup dans la thérapie contre la migraine aiguë. La voie parentérale comporte des avantages, comme un effet rapide, une plus grande efficacité et la possibilité d'y recourir malgré la nausée ou les vomissements. Au nombre des inconvénients figurent l'inconfort au site d'injection, le caractère non pratique du traitement et l'aversion des patients pour les aiguilles. La plupart des patients préfèrent l'administration par voie orale, mais la stase gastrique ainsi que la nausée et les vomissements durant une attaque de migraine sont susceptibles d'en restreindre l'usage. La voie intranasale procure habituellement un soulagement assez rapide, mais des effets secondaires comme des changements au niveau du goût peuvent se produire. La voie rectale représente une autre option, mais l'absorption est souvent inégale, une irritation rectale peut se produire et peu de médicaments contre la migraine sont disponibles sous forme d'administration par voie rectale.

**CONCLUSION** Le choix des médicaments et des modes de perfusion appropriés en fonction de chaque patient, se fondant sur les caractéristiques de ses attaques (c.-à-d. la sévérité, la rapidité de progression vers une forte intensité, le degré de symptômes connexes), la facilité d'administration et les préférences du patient, permettra d'optimiser la thérapie contre les attaques de migraine aiguë.

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**M**igraine, an underrecognized and undertreated neurologic disorder, has a prevalence of 15% to 17% in women, 5% in men, 5% in children, and 10% in adolescents.<sup>1,3</sup> It is characterized by episodic, unilateral, pulsating or throbbing headaches that are often accompanied by nausea, vomiting, photophobia, and phonophobia (also olfactophobia), and is aggravated by physical activity (Table 1).<sup>4</sup>

Migraine attacks affect the daily lives and well-being of sufferers. The effect of migraine on quality of life is similar to that of chronic conditions, such as osteoarthritis, diabetes, and depression.<sup>5</sup> A Canadian

**Table 1. Criteria for diagnosis of migraine without aura in adults<sup>4</sup>**

- |    |   |
|----|---|
| A. | At least five attacks fulfilling criteria B to D  |
| B. | Each attack lasts 2 to 72 hours (untreated or unsuccessfully treated)   |
| C. | The attack has at least two of the following characteristics: <ul style="list-style-type: none"> <li>• Unilateral location (might be bilateral in 30% to 40% of cases; might begin on one side and spread to other side)</li> <li>• Pulsating quality (&gt;50% of migraine sufferers report non-throbbing pain during some attacks; if pain is throbbing at any phase of attack, consider it pulsating)</li> <li>• Moderate or severe intensity (inhibits or prohibits daily activity)</li> <li>• Pain is aggravated by routine physical activity (eg, walking up and down stairs)</li> </ul> |
| D. | At least one of the following symptoms is present: <ul style="list-style-type: none"> <li>• Nausea or vomiting (not just anorexia)</li> <li>• Photophobia (aversion to light), phonophobia (aversion to sounds or noise), and olfactophobia (aversion to odours)</li> </ul>   |
| E. | No evidence of any other disease that might cause headaches   |

*Note—Migraine with aura: diagnostic criteria are the same as for migraine without aura, with addition of symptoms of neurologic dysfunction (eg, visual disturbance) occurring before or during the attack.*

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population survey determined the effects of headaches on sufferers: regular activities were limited in 78% of migraine attacks, and about one third of sufferers required bed rest; however, only 64% of migraine sufferers had ever sought medical attention. Researchers estimate that about 7 million working days are lost annually in Canada due to migraine.<sup>6</sup> In the United States, estimated annual costs for medical care and lost productivity exceed \$17 billion.<sup>7</sup>

Reducing the burden of migraine can be accomplished by encouraging sufferers to consult physicians, by diagnosing and assessing disability accurately, and by using appropriate nonpharmacologic and pharmacologic treatment strategies.<sup>5</sup> Because many migraine sufferers are managed by family physicians, it is important for family physicians to be aware of current migraine therapy and medication delivery systems. This article focuses on the various routes of administration and delivery systems for acute migraine medications, considering advantages and disadvantages of each. I hope this will aid physicians in selecting appropriate delivery systems for individual patients in order to optimize acute migraine therapy.

### Quality of evidence

Evidence presented in this review is derived from searches of MEDLINE (January 1966 to October 2000) and Current Contents (January 1999 to October 2000). MeSH headings or key words used included "migraine"; "sumatriptan"; "naratriptan"; "zolmitriptan"; "rizatriptan"; "anti-inflammatory agents, nonsteroidal"; "dihydroergotamine"; "ergotamine"; "butorphanol"; and "lidocaine." Randomized controlled trials were selected, when available; other references included guidelines (Canadian), non-blinded trials, systematic reviews, and population-based surveys.

Evidence for the efficacy of newer agents, such as relatively selective serotonin (5-HT) receptor agonists (for receptor subtypes 1B and 1D [5-HT<sub>1B/1D</sub>]), and other acute therapies is derived primarily from randomized controlled trials. However, no evidence is available for the efficacy of older treatments (eg, ergotamine). Recently published (1997) Canadian guidelines for pharmacologic management of migraine have assessed the quality of evidence available.<sup>4</sup>

### Overview

Canadian guidelines for diagnosis and management of migraine, using both pharmacologic and nonpharmacologic therapies, have been published recently.<sup>4,8</sup> Nonpharmacologic therapy involves patient education,

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**Table 2. Recommended acute migraine medications based on severity of attacks for outpatient treatment**

SEVERITY OF ATTACKS	RECOMMENDED ACUTE MEDICATIONS (ORAL, UNLESS OTHERWISE INDICATED)
Mild	Acetylsalicylic acid (not enteric-coated; preferably soluble or effervescent)
	NSAIDs (eg, ibuprofen, naproxen sodium)
	Acetaminophen*
	Adjunctive: dimenhydrinate, domperidone, <sup>†</sup> metoclopramide <sup>‡</sup>
Moderate	NSAIDs (eg, ibuprofen, naproxen sodium, mefenamic acid, diclofenac potassium)
	Serotonin (5-HT <sub>1</sub> ) agonists: DHE (IM, nasal, SC), ergotamine ± caffeine (oral, rectal), <sup>‡</sup> naratriptan, rizatriptan (oral tablet or wafer), sumatriptan (oral, nasal, SC), zolmitriptan
	Combination analgesics <sup>§</sup> : ASA or acetaminophen + codeine ± caffeine; ASA + butalbital + caffeine ± codeine
	Others: lidocaine (nasal)
	Adjunctive: as for mild attacks
Severe	Serotonin (5-HT <sub>1</sub> ) agonists: DHE (IM, nasal, SC), rizatriptan (oral tablet or wafer), sumatriptan (nasal, oral, SC), zolmitriptan
	Opioids: butorphanol (nasal)
	Others: lidocaine (nasal)
	Adjunctive: as for mild attacks

Adapted from Pryse-Phillips et al.<sup>4</sup>

DHE—dihydroergotamine, IM—intramuscular, NSAIDs—nonsteroidal anti-inflammatory agents, SC—subcutaneous.

\*Acetaminophen is considered less effective than ASA or NSAIDs.

<sup>†</sup>Metoclopramide and domperidone might relieve migraine attacks, as well as associated nausea and vomiting.

<sup>‡</sup>Evidence suggests that ergotamine is of limited efficacy and has excessive side effects; frequent use (more than twice weekly) can result in medication-induced headache.

<sup>§</sup>Combination products are not considered first-line therapy; frequent use (more than twice weekly) of analgesics, particularly combination products, can result in medication-induced headache.

avoidance of trigger factors, and various biobehavioural and physical measures (eg, biofeedback, relaxation, cognitive-behavioural therapy).<sup>8</sup> Choice of acute pharmacologic therapy is based on severity of attacks (Table 2).<sup>4</sup> Prophylactic therapy can be considered for patients suffering from frequent or disabling attacks,

or for whom acute therapies are ineffective or are contraindicated.<sup>4</sup>

For many years, the only migraine-specific acute medications available were ergotamine and dihydroergotamine (DHE), which are nonselective serotonin (5-HT<sub>1</sub>) receptor agonists. An analysis of placebo-controlled trials of ergotamine concluded that ergotamine (with or without caffeine) is not significantly more effective than placebo, and it tends to exacerbate nausea and vomiting.<sup>9</sup> The introduction of sumatriptan, the first relatively selective serotonin (5-HT<sub>1B/1D</sub>) receptor agonist, in 1991 revolutionized acute migraine therapy. Recently, several other serotonin (5-HT<sub>1B/1D</sub>) receptor agonists (“triptans”) have been marketed in Canada (eg, naratriptan, rizatriptan, zolmitriptan). Triptans are considered the most efficacious agents for outpatient management of migraine attacks.

### Routes of administration and drug delivery systems

Migraine medications can be administered by five routes (Table 3). Patients generally prefer the oral route, but many migraine sufferers have nausea and vomiting and need to receive their medications by parenteral (intravenous, intramuscular, or subcutaneous), intranasal, rectal, sublingual, or orally disintegrating routes. Speed of onset could be a factor in selecting the best route of administration or formulation for a particular patient. Convenience and ease of administration are also important considerations. Access to convenient formulations of migraine medications might increase earlier treatment of headache and overall compliance.

To determine patient preferences and priorities for migraine treatment, a random-digit telephone survey identified and polled 688 people with migraine. According to migraine sufferers, the most important attributes of migraine medication were complete relief of pain (86%), lack of recurrence (86%), and rapid onset of pain relief (83%). Most sufferers preferred oral tablets or capsules (73%); second choice was tablets that dissolved rapidly in the mouth (51%).<sup>10</sup> When patients considered taking subcutaneous or oral sumatriptan, the main reason for choosing the subcutaneous route was speed of relief; the severity of the attack and having nausea and vomiting also influenced the choice. The oral route was chosen mainly for convenience.<sup>11</sup> Some patients might benefit from access to two or more different delivery systems, depending on the characteristics of their attacks.

**Table 3. Routes of administration of acute migraine medications for outpatient use**

DELIVERY ROUTE	MEDICATIONS
Intranasal	Serotonin (5-HT <sub>1</sub> ) agonists: DHE, sumatriptan, zolmitriptan (recently approved for marketing in Canada) Opioids: butorphanol Local anesthetic: lidocaine
Oral	Analgesics NSAIDs Serotonin (5-HT <sub>1</sub> ) agonists: ergotamine, naratriptan, rizatriptan, sumatriptan, zolmitriptan (recently approved for marketing in Canada)
Oral disintegrating tablet or wafer	Serotonin (5-HT <sub>1</sub> ) agonists: rizatriptan, zolmitriptan (recently approved for marketing in Canada)
Parenteral (SC or IM)	Serotonin (5-HT <sub>1</sub> ) agonists: DHE (SC, IM), sumatriptan (SC)
Rectal	Serotonin (5-HT <sub>1</sub> ) agonists: ergotamine, sumatriptan (not available in Canada)
Sublingual	Serotonin (5-HT <sub>1</sub> ) agonist: ergotamine

DHE—dihydroergotamine, IM—intramuscular, NSAIDs—nonsteroidal anti-inflammatory agents, SC—subcutaneous

**Parenteral route.** Parenteral administration has the advantages of rapid onset of effect and potential use in patients with nausea and vomiting. Intravenous and intramuscular injections, however, must usually be administered in an emergency room or physician's office, and administration can cause local discomfort. Patients can be taught to give themselves injections of medications, such as subcutaneous sumatriptan (supplied with an autoinjector) or subcutaneous or intramuscular DHE.<sup>12-14</sup> The inconvenience and lack of patient acceptance could, however, limit use of the parenteral route.

Sumatriptan is the only triptan available as a subcutaneous injection. It is easier to administer than DHE because it is supplied as an autoinjector. Response to subcutaneous sumatriptan (56% to 88% after 1 hour) is greater than to oral (46% to 67% after 2 hours) or intranasal (55% to 78% after 2 hours) sumatriptan, and it has a more rapid onset of effect (10 to 15 minutes; maximum effect at 1 hour).<sup>15</sup> In a randomized, double-blind, placebo-controlled trial, use of sumatriptan injection was found to reduce migraine-associated

productivity loss by about 50% and to alleviate headache in 69% of patients 1 hour after dosing and in 79% of patients 2 hours after dosing.<sup>16</sup>

Subcutaneous sumatriptan should be considered for patients who fail to respond to any of the oral triptans.<sup>17</sup> The subcutaneous route is also a good choice for patients with severe pain, rapid progression of pain to severe intensity, and (as noted) nausea and vomiting. Adverse effects are common with subcutaneous sumatriptan, however. They include atypical sensations, such as tingling, warmth, heaviness or pressure (in chest, neck, throat, jaw, arms), dizziness, flushing, and discomfort at the injection site; these effects are usually mild and transient.<sup>15</sup>

### Oral route.

**Tablets:** The oral route is convenient, and many patients prefer it. Nausea and vomiting during an attack limit use of tablets, and onset of action is usually slower than with parenteral or intranasal administration. Some new oral triptans (eg, rizatriptan) seem to offer onset of action approaching that of parenteral drugs. Because gastric stasis often occurs during attacks, patients sometimes absorb oral medications slowly. Prokinetic agents (eg, metoclopramide, domperidone) can be administered with oral analgesics to enhance gastric motility and drug absorption and to help control nausea and vomiting associated with attacks.<sup>18,19</sup>

Caffeine is often added to analgesic or ergotamine preparations to increase absorption, and caffeine might have an analgesic effect on its own. Excessive use of caffeine-containing products, however, can result in withdrawal headaches.<sup>20</sup> Enteric-coated preparations are not advisable for acute attacks because they are absorbed slowly. Soluble or effervescent oral medications are ideal for acute migraine attacks because they are rapidly absorbed; however, few medications are available in this format.<sup>4,18</sup>

Low oral bioavailability is a shortcoming of some migraine-specific medications (eg, ergotamine, sumatriptan). Newer triptans are more lipophilic and have better oral bioavailability (Table 4).<sup>21-26</sup> Of the available triptans, naratriptan has the greatest oral bioavailability. Whether better oral bioavailability translates into a more consistent clinical response in individual patients is unclear; further studies are needed.<sup>27</sup> A placebo-controlled study of rizatriptan in multiple migraine attacks demonstrated high consistency for the 10-mg dose (86% of patients responded in two out of three attacks; 60% responded in all three attacks)<sup>28</sup>; this could be attributed to both its bioavailability (45%)

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**Table 4. Pharmacokinetics of serotonin (5-HT<sub>1B/1D</sub>) receptor agonists<sup>21-26</sup>**

CHARACTERISTICS	NARATRIPTAN (AMERGE)	RIZATRIPTAN (MAXALT, MAXALT RPD)	SUMATRIPTAN (IMITREX)	ZOLMITRIPTAN (ZOMIG)
Dosage forms	Oral tablets • 1 mg • 2.5 mg	Oral tablets • 5 mg • 10 mg Wafers (RPD) • 5 mg • 10 mg	Subcutaneous injection • 6 mg Oral tablets • 25 mg • 50 mg • 100 mg Nasal • 5 mg • 20 mg	Oral tablets • 2.5 mg
Bioavailability	74% (women) 63% (men)	45% (tablets and wafers)	Subcutaneous: 96% Oral: 14% Nasal: 16%	40%
Effect of food on oral bioavailability	No important effect	No effect on bioavailability; with tablets, delay to T <sub>max</sub> is about 1 h	No important effect	No important effect
T <sub>max</sub> outside migraine attack	2-5 h	1-1.5 h (tablets) 1.6-2.5 h (wafers)	Subcutaneous: 15 min Oral (100 mg): 0.5-5 h* Nasal: 1-1.5 h	2 h
T <sub>max</sub> during migraine attack	3.5 h	Same as T <sub>max</sub> outside attack	Subcutaneous: no data Oral: 2 h Nasal: no data	4 h or later (11/20 patients) <sup>22</sup>
Elimination half-life	5-8 h	2-3 h	2 h	2.5-3 h

Note: Only one particular triptan can be taken within a 24-hour period (according to manufacturer's product monographs; not evidence-based); however, different formulations of the same triptan can be used within a 24-hour period (eg, sumatriptan subcutaneous, oral, or nasal<sup>25,26</sup>), with an appropriate interval between doses (ie, at least 2 hours).

T<sub>max</sub>—Time to maximum serum concentration.

\* 70% to 80% of maximum serum values (C<sub>max</sub>) are attained within 30 to 45 minutes of dosing.

and relative lipophilic properties compared with sumatriptan.<sup>27</sup>

Time to reach maximum plasma concentrations (T<sub>max</sub>) might correlate with the onset of action. A shorter T<sub>max</sub> is likely to result in an earlier onset of action.<sup>27</sup> For example, the T<sub>max</sub> for rizatriptan tablets is 1 to 1.5 hours, and its onset of action is relatively rapid; however, administration with food delays time to reach peak concentrations by 1 hour. For rizatriptan and sumatriptan, oral absorption and T<sub>max</sub> are not significantly affected during migraine attacks. For naratriptan and zolmitriptan, T<sub>max</sub> is delayed during migraine attacks, presumably due to gastric stasis (Table 4).<sup>21-26</sup>

Some nonsteroidal anti-inflammatory agents (NSAIDs) (eg, naproxen sodium [T<sub>max</sub> 1 h], ibuprofen [T<sub>max</sub> 0.5 to 1.5 h], and diclofenac potassium [T<sub>max</sub> 0.3 to 1 h]) are fairly rapidly absorbed. A double-blind, randomized, crossover study demonstrated that diclofenac potassium (50 mg or 100 mg) was as effective as oral

sumatriptan (100 mg) and had a faster onset of effect.<sup>29</sup> Diclofenac sodium, however, is an enteric-coated preparation with a slower release (T<sub>max</sub> 2 to 3 h), which is more suitable for chronic painful conditions.<sup>29</sup>

Recently, a novel, solubilized formulation (liquigel) of ibuprofen, indicated for the acute treatment of migraine, has been marketed in Canada. Because it is more soluble, it is rapidly absorbed from the gastrointestinal tract and has a rapid onset of action. In a randomized, double-blind, placebo-controlled, dose-ranging study, 729 migraine sufferers evaluated a single 200-, 400-, or 600-mg dose of a liquigel formulation of ibuprofen. All three doses were superior to placebo for "pain-free" at 2 hours and for proportion of patients with mild or no limitation of physical activity (2 to 8 hours).<sup>30</sup>

The median time to first perceptible relief of pain with ibuprofen liquigel in 400- and 600-mg doses was 30 minutes; for 200 mg of ibuprofen, it was 36 minutes

(versus 52 minutes for placebo). Ibuprofen liqigels were generally superior to placebo for reducing photophobia, phonophobia, and nausea; all doses were well tolerated.<sup>31</sup> The onset of action of the liqigel formulation appears to be comparable to that of ibuprofen oral suspension.

**Oral disintegrating tablets.** Rizatriptan is available as both an oral tablet and an oral disintegrating tablet (wafer). The wafer is a novel, freeze-dried formulation that rapidly disintegrates on the tongue (within seconds), is swallowed with saliva, and is absorbed from the gastrointestinal tract; it can be taken without liquids. Absorption is somewhat slower for the wafer ( $T_{max}$  1.6 to 2.5 hours) than for the oral tablet ( $T_{max}$  1 to 1.5 hours).<sup>16</sup> The wafer was developed with the goal of offering patients greater convenience.

Wafers might be an alternative for patients who have difficulty swallowing tablets or liquids or who experience nausea and vomiting with their attacks, for situations where liquids are not readily available, or for patients who simply prefer a convenient and discreet medication (can be taken anywhere and anytime). A placebo-controlled, double-blind study of 555 migraine sufferers demonstrated that the wafer formulation of rizatriptan is convenient and effective and has efficacy comparable to that of oral tablets (from 30 minutes through 2 hours). Most patients found its taste acceptable. Patient preference was 75% for the wafer and 25% for the oral tablet.<sup>32</sup>

In a 6-month, open-label continuation study, 367 patients were given a choice of 10-mg rizatriptan tablets or wafers. Although no group preference was found, individual patients had strong preferences for one preparation over the other. Reasons for wafer preference included administration without water, well tolerated in the presence of nausea, and faster onset of action. Patients who preferred tablets cited a disagreeable taste of the wafer or comfort with "pills."<sup>32</sup>

Zolmitriptan has been marketed in Europe in a fast-dissolving system (OraSolv) that incorporates microencapsulated drug ingredients into tablets that dissolve quickly in the mouth; it recently was approved for marketing in Canada.

**Sublingual route.** The sublingual route of administration is useful for patients who are unable to take oral medications due to nausea and vomiting. Absorption tends to occur faster, provided the medication is absorbed through the oral mucosa. The only migraine medication currently available in sublingual form is ergotamine, and there are no randomized controlled trials demonstrating its efficacy.<sup>9</sup>

**Intranasal route.** The intranasal route of administration is also useful for patients who have nausea and vomiting during their attacks. Because this route tends to bypass the gastrointestinal tract, onset of effect is generally faster than with oral medications. Adverse effects can include local irritation of the nasal mucosa and, possibly, an unpleasant taste if some drug is swallowed.<sup>33</sup> An unpleasant taste might worsen nausea and precipitate vomiting. Although intranasal administration is relatively simple, it is not very discreet.

The migraine-specific agents DHE and sumatriptan are available as nasal sprays. The DHE nasal spray is rapidly absorbed into the systemic circulation ( $T_{max}$  0.9 hours); noticeable relief begins within about 30 minutes.<sup>33</sup> It is well tolerated but is somewhat complicated to use, because it requires opening an ampule and inserting it into a nasal applicator. Intranasal sumatriptan, supplied as a single-dose device (not requiring assembly), is also rapidly absorbed ( $T_{max}$  1 to 1.5 hours). Onset of action occurs in 15 minutes (vs 30 minutes for oral sumatriptan) and maximum effect at 2 hours. Although efficacy is similar to that of oral sumatriptan (at 2 hours), the magnitude of therapeutic effect in the first 30 minutes after intranasal administration is relatively small (compared with subcutaneous sumatriptan).<sup>15,33,34</sup> Interestingly, a substantial amount of nasally administered drug appears to be absorbed by the gastrointestinal tract (44% to 75%), whereas 25% to 56% is apparently absorbed by the nasal mucosa (personal communication from Diane Drolet, Project Leader, Medical Affairs, Glaxo Wellcome Canada; October 1999). Taste disturbance is a common, dose-related adverse effect.<sup>35</sup>

In a survey of migraine sufferers who had had previous experience with subcutaneous or oral sumatriptan, nasal sumatriptan was rated as more user-friendly than subcutaneous or oral sumatriptan. Although it was considered less effective than subcutaneous sumatriptan, fewer adverse effects were noted (most commonly, a bitter taste).<sup>36</sup> In a comparative study, sumatriptan nasal spray demonstrated a faster onset of action and greater efficacy than DHE nasal spray.<sup>37</sup>

Butorphanol, a synthetic opioid agonist-antagonist, is also available as a nasal spray. It could be an alternative for severe attacks in patients who do not tolerate, or have contraindications to, migraine-specific medications, or when other medications have failed. Because sedation is an important side effect, intranasal butorphanol might be appropriate for use

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at night. Onset of action is rapid, generally within 15 minutes; in one clinical trial, 60% of patients experienced relief of headache within 2 hours.<sup>38</sup> However, butorphanol is associated with many adverse effects and has the potential for abuse. It should be prescribed with great caution and used no more than 2 days weekly, to avoid medication-induced headache.<sup>33</sup>

Lidocaine, a local anesthetic, has also been administered intranasally for acute migraine, although no commercially available intranasal form exists. A 4% topical solution can be instilled into the nostril (same side as headache), using a specific technique, which anesthetizes the sphenopalatine ganglion (inflammation of this area might be involved in the pathophysiology of migraine). The technique is somewhat complicated and might require the assistance of another person. Intranasal lidocaine has a rapid onset of effect (55% response rate at 15 minutes); however, the relapse rate after successful treatment is high (42% within 1 hour).<sup>39</sup>

**Rectal route.** The rectal route of administration is yet another option for patients with nausea or vomiting or with pronounced gastric stasis during an attack. Disadvantages of this route include lower patient acceptance compared with other routes, possible irritation of the rectal mucosa, and sometimes, erratic absorption. The only migraine-specific medication available as a rectal suppository in Canada is ergotamine, and there are no randomized controlled trials demonstrating its efficacy.<sup>9</sup> Sumatriptan has been shown to be well tolerated and fairly rapidly absorbed ( $T_{max}$  1 to 2.5 hours) from a rectal suppository formulation.<sup>40</sup> Rectal sumatriptan is not currently available in Canada. Prochlorperazine suppositories (25 mg) have been shown to be useful for treating severe migraine in emergency departments.<sup>41</sup>

### Conclusion

Acute migraine medications should be selected on the basis of severity of attacks and associated symptoms (eg, nausea). Various medications can be prescribed for mild, moderate, or severe attacks. Selecting a suitable route of administration and delivery system is also important and should be based on the characteristics of an attack (eg, speed of progression to severe intensity, degree of associated symptoms), ease of administration, and patient preference. Although patients might prefer

### Editor's key points

- Choosing the route for giving medications for migraine headaches depends on the severity and speed of the attack, associated symptoms, and patient preference.
- Parenteral administration has the obvious advantages of rapid onset and the possibility of use during nausea and vomiting. Oral treatment is suitable for attacks without nausea and vomiting; a disintegrating wafer could be a useful option.
- The nasal route is a good alternative to the oral route with rapid onset of action. The rectal route is possible but unreliable.

### Points de repère du rédacteur

- Le choix du mode d'administration des médicaments contre les migraines dépend de la gravité et de la rapidité des attaques, des symptômes associés et de la préférence du patient.
- L'administration par voie parentérale comporte des avantages évidents en matière de soulagement rapide et de possibilité d'utilisation durant la nausée et les vomissements. Le traitement par voie orale convient aux attaques sans nausée ou vomissement; un cachet désintégrant pourrait constituer une option utile.
- La voie nasale est une bonne alternative à l'administration par voie orale et procure une rapidité d'action. La voie rectale est une autre possibilité, mais elle n'est pas fiable.

a particular delivery system for various reasons, efficacy of the preparation is an important consideration. It might be useful for patients to have access to at least two different delivery systems, enabling them to choose the most suitable method for a particular attack. ❀

### Competing interests

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