How are migraines classified?

**Migraine without aura** (80% of patients)
- Each attack lasts 2 - 72 hours
- The attack has at least 2 of the following characteristics:
  1. unilateral location - most commonly unilateral but may spread to the other side (30-40% of cases are bilateral)
  2. pulsating quality
  3. moderate to severe intensity
  4. pain is aggravated by walking up or down stairs or similar physical activity
- During an attack at least one of the following should be present:
  1. nausea or vomiting
  2. unusual sensitivity to light, noise or odors

**Migraine with aura** (20% of patients)
- Similar to the above but visual, sensory, motor disturbances or aphasia precede the headache by up to 60 minutes

What non-pharmacologic therapies are recommended?

While no well-designed trials have evaluated non-pharmacological treatment, the following may be beneficial: rest in a dark, noise-free room, ice applied to forehead, or sleep. In patients who are volume depleted, fluids should be tried.

What oral agents are effective?

While treatment for migraine is often separated into the treatment of mild, moderate and severe symptoms, clinical trials have not evaluated different drugs on this basis. Effectiveness is defined in most trials as a decrease in pain of 2 points on a scale of 0 to 3, measured one or two hours after drug administration.

**Acetaminophen**

While acetaminophen on its own is often used, there are no well-designed placebo controlled trials demonstrating its effectiveness in adults. Acetaminophen 400 mg in combination with codeine 25 mg has been shown to be as effective as ASA 1000 mg, and acetaminophen 500 mg plus metoclopramide 5mg has been shown to be more effective than placebo.1

**NSAIDs**

A number of trials have shown that NSAIDs are effective in treating migraine headaches. NSAIDs that have been studied include ASA, ibuprofen, naproxen, and diclofenac.

**Oral ergot alkaloids**

Few well-designed clinical trials involving ergotamine are available. Most controlled trials demonstrate little or no benefit with these agents. Although several comparative trials including ergotamine exist, they are of poor quality. A meta-analysis was not able to demonstrate a benefit from oral ergotamine.2 However, parenterally administered dihydroergotamine is effective (see below).

**Dimenhydrinate, domperidone, and metoclopramide**

While dimenhydrinate and metoclopramide are often used, there is no evidence that they are effective on their own when given orally. In a double-blind crossover trial, domperidone 40 mg was more effective than 20 mg in preventing onset of headache in patients with migraine with aura when taken at the first sign of prodrome.3

**Selective serotonin agonists (sumatriptan)**

Oral sumatriptan has been shown to be more effective than placebo at aborting head aches (50-80% versus 20-40%).4,5,6,7,8 Oral doses of 25, 50 and 100 mg of sumatriptan are equally effective in the treatment of acute migraine.7,8 Other similar drugs (rizatriptan, zolmitriptan, eletriptan, naratriptan) may be available soon, although it is unknown what, if any, advantages they will have over currently available agents.
Narcotics & Barbiturates
Few well-designed trials of oral narcotics as single agents have been published, making it difficult to assess the effect of these agents in acute migraine attacks. A combination product containing dextropropoxyphene (65 mg, ASA (500 mg), and phenazone (a salicylate) was superior to ASA (500 mg) alone and similar to ergotamine (1 mg) in preventing progression of headaches. As mentioned, codeine plus acetaminophen has been shown to be as effective as ASA. There are no well-conducted trials evaluating barbiturates.

Is there evidence that some oral agents are superior to others?
NSAIDs vs. Acetaminophen
In children, acetaminophen (15 mg/kg) and ibuprofen (10 mg/kg) have been compared for the treatment of moderate to severe acute migraine. When analyzed under intent-to-treat conditions there was no difference between acetaminophen and ibuprofen. Another trial found ibuprofen 400 mg initially then 400 mg every 4-6 hours to be superior to acetaminophen 900 mg followed by 900 mg every 4-6 hours.

NSAIDs vs. NSAIDs
No well designed comparative trials of different NSAIDs are available.

NSAIDs vs. Ergot Alkaloids
Naproxen 750 mg has been shown to be at least as effective as oral ergotamine 2 mg.

Sumatriptan vs. Other Oral Agents
Oral sumatriptan 100 mg has been shown to be more effective than ergotamine 2 mg plus caffeine 200 mg. Two trials have compared the combination of oral ASA 900 mg plus metoclopramide 10 mg to oral sumatriptan 100 mg in multiple episodes of migraines. One study demonstrated that for two of the three headaches treated, sumatriptan was more effective (59% vs. 38%) but headache recurrence after 24 hours and side effects were more frequent. There was no difference in other endpoints (nausea, vomiting, photophobia, phonophobia).

What injectable agents are effective?
Only one randomized, double-blinded trial comparing parenteral to oral therapy has been published. In this trial intravenous (IV) metoclopramide 10 mg was superior to oral ibuprofen 600 mg (mean pain score 1/10 vs. 6/10 at 1 hour). Fifteen well-conducted trials have demonstrated the superiority of subcutaneously (SC) administered sumatriptan over placebo. However, sumatriptan 6 mg SC administered during the aura phase of migraine does not prevent progression to moderate/severe headache any better than placebo.

There is no evidence that SC route is clinically superior to oral route.
Other therapies which have been demonstrated in randomized, double-blinded trials to be superior to placebo include DHE 0.5-1 mg IV plus prochlorperazine 5-10 mg IV, metoclopramide 10 mg IV, nalbuphine 10 mg intramuscularly (IM).

Is there evidence that some injectable agents are superior to others?
SC sumatriptan 6 mg was found to be more effective than SC dihydroergotamine 0.5-1 mg in relieving pain at 2 hours (78% vs. 57%), although by 4 hours both therapies were equal. By 24 hours, more DHE patients had complete relief than sumatriptan patients (90% vs. 77%). There was significantly less headache recurrence within 24 hours in the DHE group (18% vs. 45%). See Table 1 for other comparative trials. Although no comparison studies of morphine vs. meperidine in acute migraine have been done, morphine is considered the drug of choice in acute and chronic pain.

Table 1: Comparative trials of parenteral agents for acute migraine attacks

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>Comparison</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan 6 mg SC</td>
<td>DHE 0.5 -1 mg SC</td>
<td>See Text</td>
<td>19</td>
</tr>
<tr>
<td>DHE 1 mg IV + Metoclopramide 5 mg IV</td>
<td>Ketorolac 60 mg IM</td>
<td>A &gt; B</td>
<td>20</td>
</tr>
<tr>
<td>DHE 1 mg IV + Metoclopramide 10 mg IV</td>
<td>Meperidine 75 mg IM + hydroxyzine 50 mg IM</td>
<td>A &gt; B</td>
<td>21</td>
</tr>
<tr>
<td>Chlorpromazine 25 mg IV</td>
<td>Meperidine 100 mg IV+ dimenhydrinate 50 mg IV</td>
<td>A &gt; B</td>
<td>22</td>
</tr>
<tr>
<td>Meperidine 75 mg IM</td>
<td>Ketorolac 30 mg IM</td>
<td>A &gt; B</td>
<td>23</td>
</tr>
<tr>
<td>Chlorpromazine 12.5 mg IV q20 min</td>
<td>Lidocaine 50 mg IV q20 min (max 150 mg)</td>
<td>A &gt; B</td>
<td>24</td>
</tr>
<tr>
<td>Chlorpromazine 12.5 mg IV q20 min</td>
<td>DHE 1 mg IV + 1 mg IV in 30 min</td>
<td>A &gt; B</td>
<td>24</td>
</tr>
<tr>
<td>Meperidine 100 mg IM + hydroxyzine 50 mg IM</td>
<td>Ketorolac 60 mg IM</td>
<td>A = B</td>
<td>25</td>
</tr>
<tr>
<td>Chlorpromazine 25 mg IV</td>
<td>Ketorolac 60 mg IM</td>
<td>A = B</td>
<td>26</td>
</tr>
<tr>
<td>Methotrimeprazine 37.5 mg IM</td>
<td>Meperidine 75 mg IM + dimenhydrinate 50 mg IM</td>
<td>A = B</td>
<td>27</td>
</tr>
</tbody>
</table>

>” - efficacy superior to, “=” efficacy equal to
Table 2: Drugs for Migraine

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dose*</th>
<th>Average Cost**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + Codeine</td>
<td>Empracet®, Tylenol 3®, generic</td>
<td>300 mg + 30 mg</td>
<td>$0.05</td>
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<tr>
<td>Ibuprofen</td>
<td>Motrin®, generic</td>
<td>400 - 1200 mg</td>
<td>$0.04 - $0.10</td>
</tr>
<tr>
<td>ASA + Metoclopramide</td>
<td>ASA +, generic</td>
<td>1000 mg +10 mg</td>
<td>$0.08</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Tevino®, generic</td>
<td>750 mg</td>
<td>$0.33</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren®, generic</td>
<td>500 mg</td>
<td>$0.34</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Imitrex®, generic</td>
<td>25 - 100 mg</td>
<td>$6.47 - $15.26</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PARENTERAL</strong></td>
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<td></td>
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</tr>
<tr>
<td>Meperidine/Pethidine</td>
<td>Demecol®, generic</td>
<td>75 - 100 mg IV/SC</td>
<td>$0.33</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Largactil®, generic</td>
<td>25 mg IV</td>
<td>$0.59</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Maxeran®, Reglan®, generic</td>
<td>10 mg IV</td>
<td>$1.20</td>
</tr>
<tr>
<td>DHE</td>
<td>Dihydroergotamine®</td>
<td>0.5 - 1 mg IV/SC</td>
<td>$2.25 - $4.49</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>Nozilan®</td>
<td>10 mg IM</td>
<td>$3.37</td>
</tr>
<tr>
<td>Methotrimeprazine</td>
<td>Toradol®, Imitrex®</td>
<td>37.5 mg IM</td>
<td>$3.70</td>
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<td>Ketorolac</td>
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<td>60 mg IM</td>
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<tr>
<td>Sumatriptan</td>
<td></td>
<td>6 mg SC</td>
<td>$34.65</td>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>INTRANASAL</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DHE</td>
<td>Migranal®</td>
<td>0.5 - 1 mg IN</td>
<td>$1.28 - $2.55</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Stadol NS®, Imitrex®</td>
<td>1 mg IN</td>
<td>$2.55</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td></td>
<td>20 mg IN</td>
<td>$9.72</td>
</tr>
</tbody>
</table>

* Doses listed are those shown to be effective for acute migraine headaches. Some doses have been slightly altered to match available strengths.
** Average or lowest cost alternative (LCA) price in BC (1997 Pharmacare data).

What intranasal therapies are effective?

Intranasal administration of DHE is superior to placebo, but inferior to SC sumatriptan with respect to pain relief and control of nausea. Intranasal sumatriptan 10 mg – 40 mg produces superior headache relief to placebo (75% vs. 32%). Butorphanol, a mixed agonist-antagonist opioid is available in an intranasal dosage form. In the one available randomized, double-blinded, placebo-controlled trial butorphanol was found to be superior to placebo for pain relief. A high rate of dizziness, drowsiness and other CNS adverse effects associated with butorphanol was seen. As with other narcotics, abuse potential does exist. Intranasal lidocaine has been evaluated in one well-conducted trial; it was demonstrated to reduce pain, nausea, and clinical disability compared to placebo while causing minimal adverse effects. At present, no intranasal lidocaine product is available in Canada.

What about headache recurrence with sumatriptan?

Although sumatriptan is effective, some trials found a higher rate of headache recurrence within 24 hours compared to placebo (38-66% for sumatriptan vs. 18-43% placebo). A study of patients with recurrent headache within 24 hours of successful treatment with sumatriptan found that re-treatment with sumatriptan 100 mg PO was superior to placebo at relieving pain (67-69% vs. 17-25%). However, 60% of these patients had a second recurrence. Taking a second 100 mg dose two hours after the initial oral dose does not improve pain relief nor delay the recurrence of headache.5

What about the cardiovascular effects of sumatriptan?

Use of sumatriptan in patients with coronary artery disease (CAD) or at high risk for such disease should be avoided as several cases of cardiac ischemia and myocardial infarction have been associated with its use. On the other hand, in patients with no CAD, the chest or neck tightness sometimes caused by sumatriptan (up to 40% ) has been shown to be unrelated to cardiac ischemia.

Conclusions & Suggestions

1. Non-drug measures may be beneficial.
2. When selecting therapy, first consider using agents to which the patient has previously responded.
3. Oral agents should be tried first if they can be tolerated.
4. The evidence does not support the use of oral ergot alkaloids.
5. A number of NSAIDs are effective although no one NSAID has been shown to be superior. There is less evidence to support the use of acetaminophen.
6. Oral narcotic combination products (e.g. acetaminophen/ASA + codeine) are effective.
7. When narcotics are used alone or parenterally, morphine is the drug of choice. However, aside from meperidine there are few well-conducted trials of parenteral narcotics in acute migraine.
8. ASA 900 mg plus metoclopramide 10 mg PO has been shown in one study to be as effective with fewer side effects than oral sumatriptan 100 mg.
The role of intranasal sumatriptan has not been established, although it appears to be more effective than placebo and less effective than sumatriptan SC. Intranasal sumatriptan is more effective than placebo. These therapies should be reserved for patients who do not respond to oral or SC agents.

Intranasal butorphanol cannot be recommended due to the high incidence of adverse CNS effects and abuse potential.

We would like to acknowledge the neurologists and others whose thoughtful suggestions have greatly assisted in the preparation of the final version of this letter.

References