Pharmacologic treatment of migraine
Comparison of guidelines

A. Schuurmans, MD  C. van Weel, FRCGP

ABSTRACT

OBJECTIVE To compare guidelines (not the primary studies) for pharmacologic treatment of migraine as to methods of guideline development; recommendations, particularly on triptans; and quality of supporting evidence (with emphasis on comparative studies of triptans versus ergot alkaloids and nonsteroidal anti-inflammatory drugs [NSAIDs]).

DATA SOURCES We searched MEDLINE via PubMed for guidelines on migraine management published since 1990 in any language; in addition, we browsed the Internet for information.

STUDY SELECTION We found nine clinical guidelines on migraine; one guideline, not supported by references, was excluded.

SYNTHESIS Preference for triptans is not well founded and is largely based on comparisons with placebo. Too few studies compared new drugs with established ones (NSAIDs or dihydroergotamine). Guidelines that propose a hierarchy for selection of drugs are opinion-based rather than evidence-based.

CONCLUSION The current lack of evidence from comparative studies seriously limits development of evidence-based clinical practice guidelines for pharmacologic treatment of migraine.

RÉSUMÉ

OBJECTIF Comparer les directives (et non les études primaires) concernant le traitement pharmacologique de la migraine, sous l’aspect particulier des méthodes de développement de ces directives, des recommandations émises, notamment pour les triptans, et de la qualité des preuves à l’appui (notamment pour les études comparant les triptans aux alcaloïdes de l’ergot et aux anti-inflammatoires non stéroïdiens [AINS]).

SOURCES DES DONNÉES On a utilisé PubMed pour identifier dans MEDLINE les directives publiées dans toutes les langues depuis 1990 sur le traitement de la migraine; on a également consulté Internet.

CHOIX DES ÉTUDES Neuf lignes directrices de pratique sur la migraine ont été repérées; une directive sans support bibliographique a été exclue.

SYNTHÈSE La préférence pour les triptans n’est pas bien fondée, reposant principalement sur des comparaisons avec placebo. Trop peu d’études ont comparé les nouveaux médicaments aux médicaments traditionnels (AINS ou dihydroergotamine). Les directives préconisant un ordre de préférence pour les médicaments reposent sur des opinions plutôt que sur des preuves.

CONCLUSION À l’heure actuelle, il n’y a pas assez d’études comparatives sur le traitement pharmacologique de la migraine pour permettre l’émission de lignes directrices de pratique fondées sur des preuves.
Several guidelines on diagnosis and treatment of migraine headache have been developed since the introduction of sumatriptan, the first drug in its class, around 1990. Until that time, ergot alkaloids were known to be effective against migraine, and nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were often prescribed.

Sumatriptan seemed to mark the beginning of a new period in migraine treatment. The efficacy of sumatriptan was self-evident, but by the time it was introduced, the essential question was whether the much more expensive sumatriptan was cost-effective compared with “simple” analgesics, such as acetaminophen, NSAIDs, or ergot alkaloids. Another issue was sumatriptan’s safety for chronic use. This required studies that compared sumatriptan with available (reference) medications, a general problem in introducing new drugs. In comparing migraine treatment guidelines published since 1990, we were particularly interested in the role these guidelines defined for triptans and the evidence to support this role (particularly in comparing triptans with reference medications).

One problem for family physicians is that different guidelines deal with the same clinical topic. This can lead to information overload or even conflicting guidance. This is why we decided to compare guidelines on migraine management.

Sources of information
In our systematic search for published guidelines on migraine treatment, we used MEDLINE through PubMed. The point of departure for the search was the occurrence of the word “migraine” in the title. In keeping with this, we specified that publications should include the key terms guideline, guidelines, or consensus and that the key terms pharmacotherapy or drug therapy had to occur. In view of the small number of publications, no limitations were applied with regard to the target group (first line) of the guidelines. As we were particularly interested in the position of triptans, we restricted the search to guidelines published after 1990.

In addition, we browsed the Internet via AltaVista using the terms “clinical guidelines,” “practice guidelines,” and “medical guidelines.” The websites of institutes known to participate in guideline development were also searched. We also looked in a few relevant and recent reviews for references to other guidelines.

We summarized and subdivided recommendations found in the guidelines into first-, second-, and third-choice medications according to the guidelines or to our best judgment. Special emphasis was placed on the role of triptans and their position in comparison with acetaminophen, NSAIDs, and ergot alkaloids.

Results
The search produced 32 articles; nine were clinical guidelines for migraine management.2–10 We could not use one guideline because the recommendations were not supported by references.2 A summary of recommendations from the guidelines investigated is shown in Table 1.2–10 Some guidelines3,4,6,9 recommend a stepwise approach: acute attacks are treated initially with the safest, least expensive therapies with a switch to migraine-specific medication only if initial treatment fails. Stratified management, on the other hand, specifies migraine severity and recommends migraine-specific agents for severe attacks.7

The remaining guidelines,5,7,10 which do not make recommendations in order of preference, give each investigated drug a place based on all references. Table 12–4,6–22 shows medications in order of preference, partly as stated by the guidelines,3,4,6,7,9 and partly (a somewhat arbitrary arrangement) according to our best judgment.5,8,10 Table 22–4,6–22 summarizes the position of triptans and (dihydro-)ergotamine in relation to NSAIDs and ergot alkaloids (only key studies are presented). There are few comparative studies; most recommendations mention the effectiveness of sumatriptan among other triptans. Most

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Pharmacologic treatment of migraine guidelines, however, emphasize the lack of research on ergotamine and, to a lesser degree, dihydroergotamine.

Discussion
The guidelines we investigated differ greatly in thoroughness and content. The AGREE instrument is an internationally accepted tool for assessing guidelines, but unfortunately it does not enable users to grade the quality of guidelines. The guidelines we studied ranged from the American guideline, which gives each investigated drug a place based on all published studies, to the German guideline, which recommends a stepwise approach with conventional medication but has only weak support for this recommendation. Use of levels of evidence is relatively common. The guidelines that make no use of them mostly discuss and evaluate the references they cite.

Table 1. Summary of recommendations from investigated guidelines: Where no evidence is listed in the Table, none had been presented in the guideline.

<table>
<thead>
<tr>
<th>GUIDELINE</th>
<th>FIRST-CHOICE TREATMENT (LEVEL OF EVIDENCE)</th>
<th>SECOND-CHOICE TREATMENT (LEVEL OF EVIDENCE)</th>
<th>THIRD-CHOICE TREATMENT (LEVEL OF EVIDENCE)</th>
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</thead>
<tbody>
<tr>
<td>The Netherlands. NHG. (1999) Stepwise approach</td>
<td>Antiemetic combined with acetaminophen or ASA</td>
<td>Antiemetic combined with NSAID Ergotamine, sumatriptan, DHE</td>
<td>Sumatriptan, ergotamine</td>
</tr>
<tr>
<td>The Netherlands. Quality-control committee of the Netherlands Society for Neurology (1997) Stepwise approach</td>
<td>Acetaminophen, ASA, or NSAID combined with an antiemetic if necessary</td>
<td>Sumatriptan (I)</td>
<td>Ergotamine (I, III)</td>
</tr>
<tr>
<td>United States. American Academy of Family Physicians and American College of Physicians–American Society of Internal Medicine (2002) Stepwise approach</td>
<td>NSAIDs (ASA, ibuprofen, naproxen, tolfenamic acid, or a combination) (I, II)</td>
<td>Intranasal DHE (I) eg. naratriptan, sumatriptan, zolmitriptan</td>
<td>Intrasal opiate (I) or intravenous antiemetic (II)</td>
</tr>
<tr>
<td>Germany. German Migraine and Headache Society (1998) Stepwise approach</td>
<td>Antiemetic combined with ASA, acetaminophen, or NSAID</td>
<td>Ergotamine, DHE</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Canada. Canadian Headache Society (1997) Stratified approach</td>
<td>ASA (I), acetaminophen (III); NSAID (ibuprofen, naproxen) (I); antiemetic (III)</td>
<td>NSAID (ibuprofen, naproxen, mefenamic acid) (I), sumatriptan (I), DHE (I), ergotamine (II)</td>
<td>Intravenous antiemetic (I), NSAID (ketorolac) (I), intravenous phenothiazine (I), sumatriptan (I), DHE (I), intranasal opiate (I), corticosteroid (II)</td>
</tr>
<tr>
<td>Canada. Therapeutics Initiative (1997) Without ranking</td>
<td>Intravenous antiemetic (II), acetaminophen (II), NSAID (I, II) (ASA, ibuprofen, naproxen, tolfenamic acid), phenothiazine (I),* intranasal or subcutaneous DHE (I, II), sumatriptan (I), naratriptan (I), rizatriptan (I), zolmitriptan (I)</td>
<td>Ergotamine (II), NSAID (intramuscular ketorolac) (II)</td>
<td>Barbiturate (II, III), opiate (I), corticosteroid (III)</td>
</tr>
<tr>
<td>Canada. Canadian Association of Emergency Physicians (1999) (Only serious migraine emergency) Without ranking</td>
<td>Intravenous antiemetic (I), intravenous phenothiazine (I),* NSAID (I), sumatriptan (I), DHE (II)</td>
<td>Haloperidol (III), intranasal lidocaine (I), intranasal opiate (I), corticosteroid (II)</td>
<td></td>
</tr>
<tr>
<td>Canada. Therapeutics Initiative (1997) Without ranking</td>
<td>Acetaminophen, ASA, NSAID (ibuprofen, naproxen, diclofenac) combined with an antiemetic, oral sumatriptan</td>
<td>Intravenous antiemetic, phenothiazine,* DHE, NSAID (ketorolac), subcutaneous sumatriptan, opiate</td>
<td>DHE, opiate, intranasal sumatriptan</td>
</tr>
</tbody>
</table>

ASA—acetylsalicylic acid, DHE—dihydroergotamine, NHG—Netherlands College of General Practitioners, NSAID—nonsteroidal anti-inflammatory drug.

Levels of evidence: I—At least one properly conducted randomized controlled trial, systematic review, or meta-analysis; II—Other comparison trials or non-randomized cohort, case-control, or epidemiologic studies, preferably with more than one study; III—Expert opinion or consensus statements.

* Not as an antiemetic.
Orders of preference in guidelines are opinion-based, but this is not always mentioned. One guideline classifies migraine headache on the basis of its severity without mentioning that this classification is not based on the reference studies. Another guideline mentions that the question of which approach is best (stepwise or stratified management) is still unresolved.

The place of triptans varies enormously (Table 1). This is at least remarkable, given the sparse international literature and the fact that all guidelines were based on (systematic) searches of

### Table 2. Role of triptans: Comparative studies with NSAIDs and ergot alkaloids, and the role of (dihydro-)ergotamine.

<table>
<thead>
<tr>
<th>GUIDELINE</th>
<th>RESULTS OF TRIALS (LEVEL OF EVIDENCE, WHERE GIVEN)</th>
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<tbody>
<tr>
<td>The Netherlands. NHG, 3 (1999)</td>
<td>Sumatriptan compared with:</td>
</tr>
<tr>
<td></td>
<td>• NSAIDs: equally effective 1,12</td>
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<td></td>
<td>• Ergotamine: sumatriptan more effective, but headaches recurred sooner 13</td>
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<tr>
<td></td>
<td>• DHE: sumatriptan works somewhat faster, but headaches recurred sooner 16</td>
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<td></td>
<td>Ergotamine: effectiveness demonstrated 15,16</td>
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<tr>
<td>The Netherlands. Quality-control committee of the Netherlands Society for Neurology, 4 (1997)</td>
<td>Sumatriptan compared with other medications: records the small number of studies, not the conclusions 12,13 (I)</td>
</tr>
<tr>
<td></td>
<td>Ergotamine and DHE: conclusions based mainly on clinical experience 16,17 (II)</td>
</tr>
<tr>
<td>United States. American Academy of Family Physicians and American College of Physicians—American Society of Internal Medicine, 6 (2002)</td>
<td>Oral sumatriptan compared with:</td>
</tr>
<tr>
<td></td>
<td>• NSAIDs: equally effective 11,12,18 (I)</td>
</tr>
<tr>
<td></td>
<td>• Ergot or caffeine: sumatriptan more effective 13 (I)</td>
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<td></td>
<td>Subcutaneous sumatriptan compared with subcutaneous and intranasal DHE: sumatriptan more effective, but headaches recurred sooner 14,19 (I)</td>
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<td>Intramuscular sumatriptan compared with intravenous chlorpromazine: equally effective 29 (III)</td>
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<td></td>
<td>Ergotamine: inconsistent results 17 (III)</td>
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<tr>
<td></td>
<td>• Subcutaneous, intravenous, and intramuscular DHE: no studies demonstrate effectiveness as monotherapy 17 (III)</td>
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<tr>
<td></td>
<td>• Intranasal DHE: less effective than subcutaneous sumatriptan 19 (II)</td>
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<td></td>
<td>• Subcutaneous DHE: after 3 hours equally effective as subcutaneous sumatriptan 14 (I)</td>
</tr>
<tr>
<td>Germany. German Migraine and Headache Society, 4 (1998)</td>
<td>Oral sumatriptan compared with NSAIDs: not reviewed 12</td>
</tr>
<tr>
<td></td>
<td>Ergotamine and DHE: effectiveness mentioned but not supported 22</td>
</tr>
<tr>
<td>Canada. Canadian Headache Society, 7 (1997)</td>
<td>Oral and subcutaneous sumatriptan compared with:</td>
</tr>
<tr>
<td></td>
<td>• NSAID: equally effective 11 (I)</td>
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<td></td>
<td>• DHE: sumatriptan more effective 14 (I)</td>
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<td>Ergotamine: effectiveness not demonstrated 12,17 (I)</td>
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<td>Subcutaneous, intravenous, intramuscular, and intranasal DHE: equally effective 14 (I)</td>
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<td></td>
<td>Subcutaneous sumatriptan compared with:</td>
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<td>• Subcutaneous DHE: sumatriptan faster, but more recurrence of headaches 14 (I)</td>
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<td></td>
<td>• Intranasal DHE: sumatriptan more effective, but shorter acting 29 (II)</td>
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<tr>
<td></td>
<td>DHE: few studies, no conclusions 27 (III)</td>
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<tr>
<td></td>
<td>Intranasal DHE: effective 29 (II)</td>
</tr>
<tr>
<td>Canada. Therapeutics Initiative, 10 (1997)</td>
<td>Oral sumatriptan compared with ergotamine and ASA: no visible difference 11,13</td>
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<td>Subcutaneous sumatriptan compared with:</td>
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<td>Intranasal DHE: effective 19</td>
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</tbody>
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this literature. National medicopolitical differences might have a role here, as only a few guidelines consider costs in their recommendations.2,3 Given the many assumptions in the articles focusing on costs, it seems that cost-effectiveness calculations are somewhat theoretical.26,27

A factor that hampers development of high-quality guidelines for migraine treatment is that recently developed drugs, such as the triptans, have been the subject of more studies and more publications than old ones. Consequently, all guidelines list sumatriptan with supporting evidence. This, however, is evidence against placebo because there are only few comparisons with other effective drugs (Table 2). Recommendations on ergot alkaloids are, to a large extent, based on opinion or consensus.

Although the side effects of ergotamine (particularly vasoconstriction, nausea, and vomiting) are well known,16 triptans also have side effects (such as chest pain).28,29 Lack of data on the relative long-term safety of triptans has led to the conclusion that they are equal to the older drugs in terms of side effects. Again this is opinion, rather than evidence-based information.

Limitations

This study was limited by the time frame chosen for selecting guidelines, but more information from recent reviews28,32 and results of studies comparing sumatriptan and NSAIDs33,34 do not essentially change the findings of this study.

Conclusion

Guidelines should support medical practitioners in pursuing the highest quality of care for their patients. But family physicians who turn to the guidelines on migraine for support for pharmacotherapy will probably not find much help. Different guidelines recommend different approaches, even when they are written for the same clinical care setting, such as primary care. Actual guideline-prescribed care will depend to a large extent on which guideline has been used. This introduces an unsatisfactory element of chance.

A comparison of the effectiveness and safety of all available migraine drugs, over all stages of migraine severity, would benefit family physicians. As long as these data are unavailable, guidelines will have little to offer. As long as new drugs are not tested before they are introduced in studies that compare their therapeutic value in the practical settings in which patients are usually treated, important information is unavailable to those who have to design guidelines. We would welcome a policy in which new medicines are accepted only when they have an evidence-based value over existing standard therapy.

Competing interests

None declared

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