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The acute treatment of migraine

Update of the MIPCA evidence-based guidelines, including the treatment of menstrual migraine

Introduction

The MIPCA (www.mipca.org.uk) evidence-based guidelines for the acute treatment of migraine were first published a decade ago,[1] and have not been revised for several years.[2] In the interim, new treatments have been developed, and there is much new data on existing treatments. In addition, we now have much more information on the treatment of menstrual migraine. This newsletter summarises this new data and aims to demonstrate how existing treatments can be tailored to the needs of the individual patient. In addition, we look at the new treatments that are likely to become available in the next few years, and how they might be used to evolve treatment further.

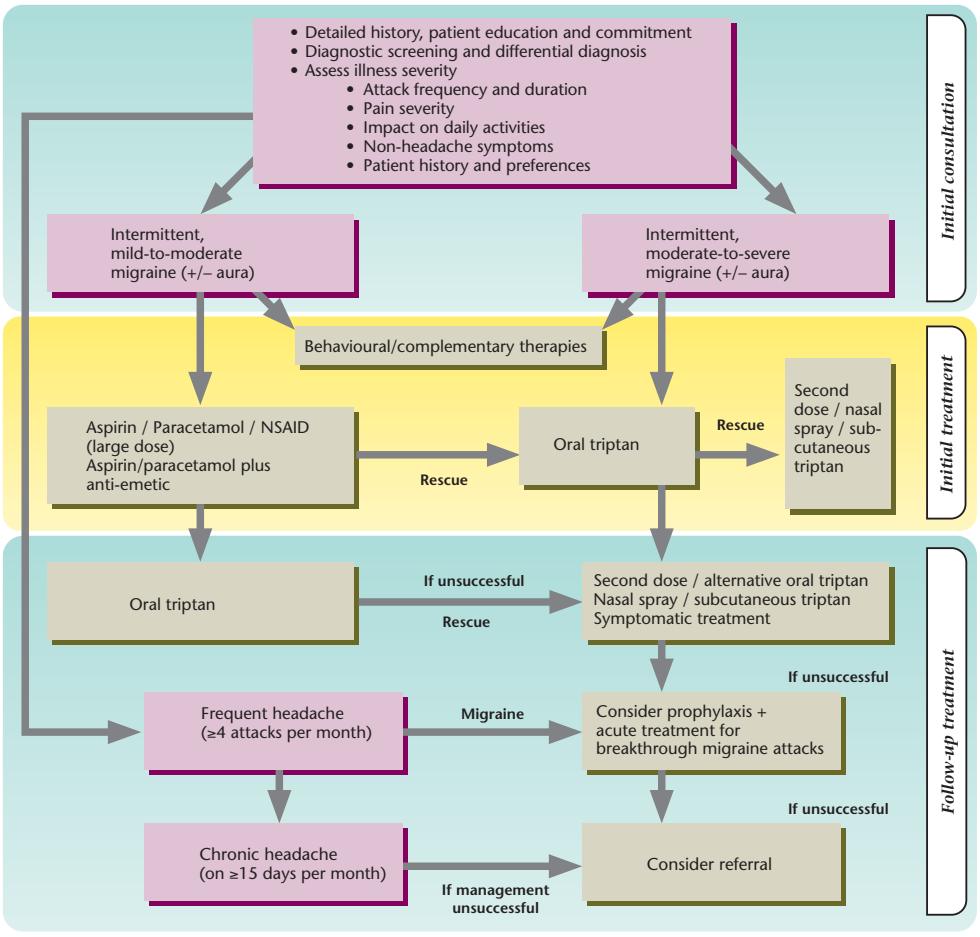
Principles of acute migraine management

The principles underlying the MIPCA guidelines remain essentially unaltered:[1-3]

- Conduct specific consultations for headache.
- From the outset, institute systems of detailed history taking, patient education and eliciting their commitment to care.
- Use a screening algorithm for the differential diagnosis of headache.[1] The final diagnosis can then be confirmed by further questioning, if necessary.
- Select an acute treatment that is tailored to the needs of the individual patient, using a management algorithm (Figure 1).[1,3] Assessing the impact of headache on the patient's daily life with the MIDAS[4] or HIT-6[5] questionnaire is a key aspect of diagnosis and management.
- Only prescribe treatments that have objective evidence of good efficacy and tolerability.[6]
- Use prospective follow-up procedures and questionnaires (e.g. the Migraine-ACT questionnaire[7]) to monitor the success of treatment.
- Organise a team approach to headache management in primary care, using GP and referral services, together with community-based healthcare services (e.g. pharmacists, dentists, opticians and other professionals).[1]

Further details of these principles of care can be found in MIPCA Newsletter Number 8, available to download from the MIPCA website (www.mipca.org.uk).[2]

Figure 1. MIPCA management algorithm for the treatment of migraine.[1,3]



Choice of initial acute treatment[1-3,6]

- All patients should be provided with behavioural and/or physical therapies, such as relaxation, biofeedback, stress reduction strategies, cervical manipulation, massage, exercise and the avoidance of migraine triggers.
- Analgesic-based treatments, e.g. aspirin and NSAIDs in large doses, paracetamol plus domperidone or aspirin or paracetamol plus metoclopramide, are recommended for mild to moderate migraine. These drugs should be taken as early as possible and before the headache develops, including during the aura. However, codeine-based treatments (e.g. Solpadeine) should be avoided due to their known potential for overuse.
- Oral triptans are recommended for moderate to severe migraine, and should be taken as soon as possible after the headache starts, preferably when it is mild in intensity. Oral triptans remain the gold standard for acute migraine treatment.
- The intake of all acute treatments should be monitored, due to the risk of overuse and the development of medication overuse headache (MOH) and chronic headaches.

Initial medication	Choice of rescue or follow-up medication if initial therapy fails
Analgesic-based therapies	Try a second dose Triptan tablets (conventional tablets or orally disintegrating tablets [ODT])
Oral triptans (conventional tablets or ODT)	Try a second dose Alternative triptan tablets Triptan delivered by nasal spray or subcutaneous injection
Nasal spray triptans	Try a second dose Subcutaneous sumatriptan
Subcutaneous sumatriptan	Try a second dose Symptomatic treatments (e.g. antiemetics, strong analgesics)

Table 1. Appropriate medications to use when the initial migraine therapy fails.[1-3]

Evaluating the oral triptans

Clinical evidence on the oral triptans is of universally high quality, with multiple Grade A clinical studies conducted for all seven drugs currently licensed.[6] Figure 2 shows a summary of the data obtained from placebo-controlled studies with the oral triptan conventional tablets.

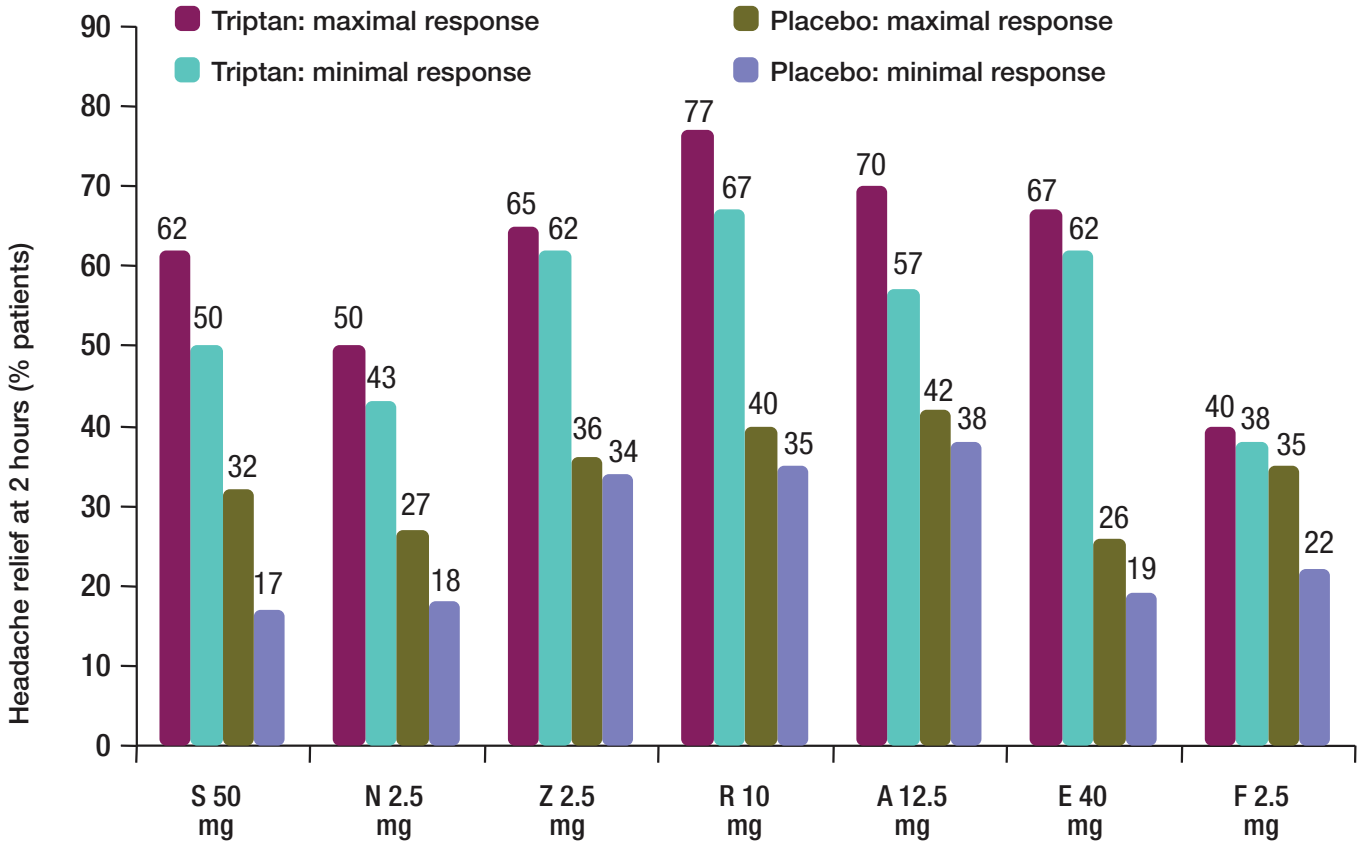


Figure 2. A summary of data from Grade A placebo-controlled studies with the oral triptan tablets: proportion of patients reporting headache relief (improvement from severe or moderate headache to mild or no headache) at 2 hours after treatment.[6] (S = sumatriptan; N = naratriptan; Z = zolmitriptan; R = rizatriptan; A = almotriptan; E = eletriptan; F = frovatriptan)

General conclusions from these data:

- All the triptan drugs evaluated in these studies were significantly superior to placebo in terms of headache relief, and therefore possess Grade A evidence of efficacy.
- The placebo response rate was highly variable, ranging from <20% to >40%.
- Most of the oral triptan formulations provided broadly similar levels of headache relief, although efficacy varied in different studies of the same drug.
- Naratriptan and frovatriptan may have lower reported 2-hour efficacy rates compared with the other oral triptans. However, the longer half-life of frovatriptan my result in reduced headache recurrence and the requirement for a second dose.

Efficacy of the ODT and non-oral triptans

The rizatriptan 10 mg[8] and zolmitriptan 2.5 mg[9] ODT triptan formulations demonstrated similar efficacy compared with the conventional tablet formulations (Figure 3).

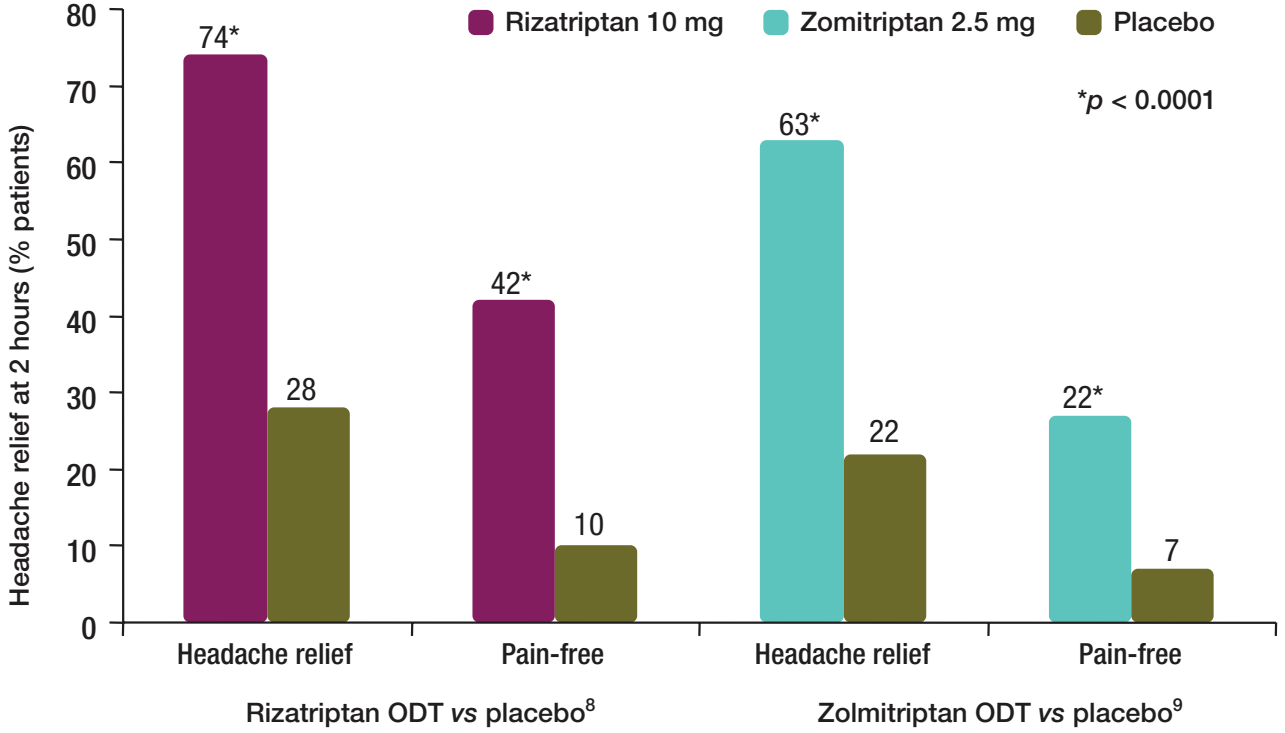


Figure 3. A summary of data from Grade A placebo-controlled studies with the ODT triptans: proportion of patients reporting headache relief or pain-free (improvement from severe or moderate headache to mild or no headache, or to no headache), at 2 hours after treatment.[8,9]

A new fast-disintegrating, rapid-release formulation of sumatriptan tablets was developed to improve absorption and speed of response to the drug. For the 50 mg dose, 67% of patients receiving sumatriptan reported headache relief at 2 hours compared with 42% with placebo ($p<0.001$).[10] These data are similar to those for the conventional tablet[6] (see Figure 2), although onset of action was reported rapidly, within 30 minutes of dosing. It needs to be remembered that this tablet still has to be swallowed, unlike the ODT formulations which dissolve in the mouth.

Efficacy data on the non-oral triptan formulations is shown in Figure 4. Subcutaneous sumatriptan 6 mg is the most effective and rapid-acting of the triptans, onset of action being reported within 10 minutes.[11] Clinical data indicate that zolmitriptan nasal spray 5 mg is slightly more effective than the tablet formulations, both in maximum effect and time to onset of action (within 15 minutes).[12] Data are similar for sumatriptan nasal spray 20 mg, with an onset of action within 15 minutes, although the maximum effect is not markedly different from that of the oral formulation.[13]

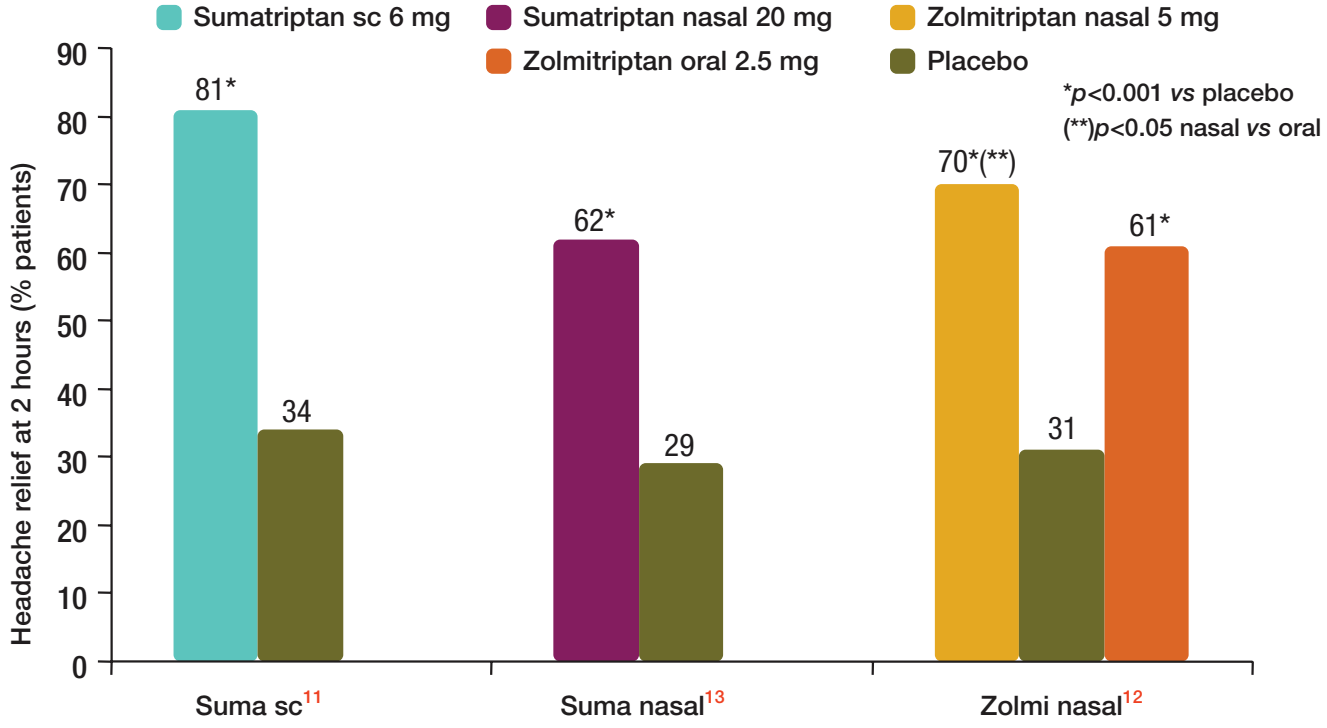


Figure 4. A summary of data from Grade A placebo-controlled studies with the non-oral triptans: proportion of patients reporting headache relief (improvement from severe or moderate headache to mild or no headache) at 2 hours after treatment.[11-13]

Comparator data with the triptans

Head-to-head clinical trials conducted between oral triptans and non-triptan comparator drugs indicated that triptans were significantly superior to ergotamine-based combination drug regimes.[6] Triptans provided similar levels of efficacy as medications based on aspirin or NSAIDs for the primary endpoint of headache relief, but tended to show superiority for other endpoints.[6]

Meta-analyses conducted over a decade ago indicated that the different oral triptans had similar clinical profiles,[14,15] but concluded that rizatriptan 10 mg and almotriptan 12.5 mg provided the highest likelihood of consistent efficacy. Eletriptan 80 mg (twice the usually prescribed dose) had superior efficacy to, but was tolerated worse than, the other triptans. More recent meta-analyses have been conducted on almotriptan,[16] and zolmitriptan.[17] Almotriptan 12.5 mg was as effective as sumatriptan 100 mg and zolmitriptan 2.5 mg, but was better tolerated than sumatriptan 100 mg. Zolmitriptan 2.5 mg was as effective as almotriptan 12.5 mg, eletriptan 40 mg, and sumatriptan 50 mg, was somewhat more effective than naratriptan 2.5 mg but slightly less effective than rizatriptan 10 mg.

Similar data have been obtained from head-to-head clinical trials with the oral triptans (Table 2).[6,18-20]

Sumatriptan comparator studies

Study	Proportion of patients (%)			
	Comparator drug	Sumatriptan	Placebo	*p*-value (active comparators)
Zolmitriptan 5 mg vs. Sumatriptan 100 mg[6] (*n*=1,058)	59	61	44	NS
Zolmitriptan 2.5 mg vs. Sumatriptan 50 mg[6] (*n*=1,522)	63	67	None	NS
Rizatriptan 10 mg vs. Sumatriptan 100 mg[6] (*n*=1,268)	67	62	40	NS
Rizatriptan 10 mg vs. Sumatriptan 50 mg[6] (*n*=1,329)	72	68	38	NS
Eletriptan 40 mg vs. Sumatriptan 100 mg[6] (*n*=692)	65	55	24	NS
Eletriptan 40 mg vs. Sumatriptan 100 mg[6] (*n*=2,113)	67	59	26	<0.001
Naratriptan 1-10 mg vs. Sumatriptan 100 mg[6] (*n*=643)	52-59	60	31	NS
Almotriptan 12.5 mg vs. Sumatriptan 50 mg[6] (*n*=1,173)	58	57	None	NS
Almotriptan 12.5 mg vs. Sumatriptan 100 mg[6] (*n*=668)	57	64	42	NS

Eletriptan comparator studies

Study	Proportion of patients (%)			
	Comparator drug	Eletriptan	Placebo	*p*-value (active comparators)
Zolmitriptan 2.5 mg vs. eletriptan 40 mg[6] (*n*=1,312)	60	64	22	NS

Naratriptan comparator studies

Study	Proportion of patients (%)			
	Comparator drug	Naratriptan	Placebo	*p*-value (active comparators)
Rizatriptan 10 mg vs. Naratriptan 2.5 mg[6] (*n*=522)	45	21	None	<0.001
Eletriptan 40 mg vs. Naratriptan 2.5 mg[6] (*n*=548)	56	42	31	<0.01

Frovatriptan comparator studies

Study	Proportion of patients (%)			
	Comparator drug	Frovatriptan	Placebo	*p*-value (active comparators)
Zolmitriptan 2.5 mg vs. Frovatriptan 2.5 mg[18] (*n*=133)	58	57	None	NS
Rizatriptan 10 mg vs. Frovatriptan 2.5 mg[19] (*n*=148)	62	55	None	NS
Almotriptan 12.5 mg vs. Frovatriptan 2.5 mg[20] (*n*=133)	56	54	None	NS

NS = not significant

Table 2. Summary of the efficacy of the marketed oral triptans from randomised, controlled, direct comparator clinical studies: proportion of patients reporting headache relief (improvement from severe or moderate to mild or no headache pain) at 2 hours after treatment.[6,18-20]

These data indicate that all the oral triptans, with the exception of naratriptan 2.5 mg, have similar efficacy profiles when compared with each other in randomised clinical trials and meta-analyses. However, the triptans do differ from each other in some respects:

1. Tolerability profiles: all the oral triptans are generally well tolerated, although almotriptan, frovatriptan and naratriptan have fewer associated adverse events than the other triptans.
2. Headache recurrence: this is a feature of treatment with triptans, where, following an initial response, the headache returns within 24 or 48 hours of treatment. This frequently necessitates the use of a second dose of medication. Research indicates that predicting factors for recurrence include female gender, age ≥35 years and severe baseline pain.[21] Frovatriptan[18-20] is associated with a reduced incidence of recurrence compared to the other oral triptans, possibly due to its longer plasma half-life.

Choosing the appropriate triptan in clinical practice

As described above, the clinician should select an initial acute treatment that is tailored to the needs of the individual patient. Determining the severity of the migraine is a key assessment in assessing the patient's needs, and the MIDAS[4] or HIT-6[5] questionnaire can be used for this.

- Patients with mild-to-moderate migraine may be effectively treated with a simple analgesic, on its own or in combination with other compounds.
- Patients with moderate-to-severe migraine, and those that have previously failed on analgesic-based therapy, should be prescribed an oral triptan from the start.
- Figure 5 shows some features of the individual triptans that may help guide the clinician in selecting an appropriate initial treatment for their patients.

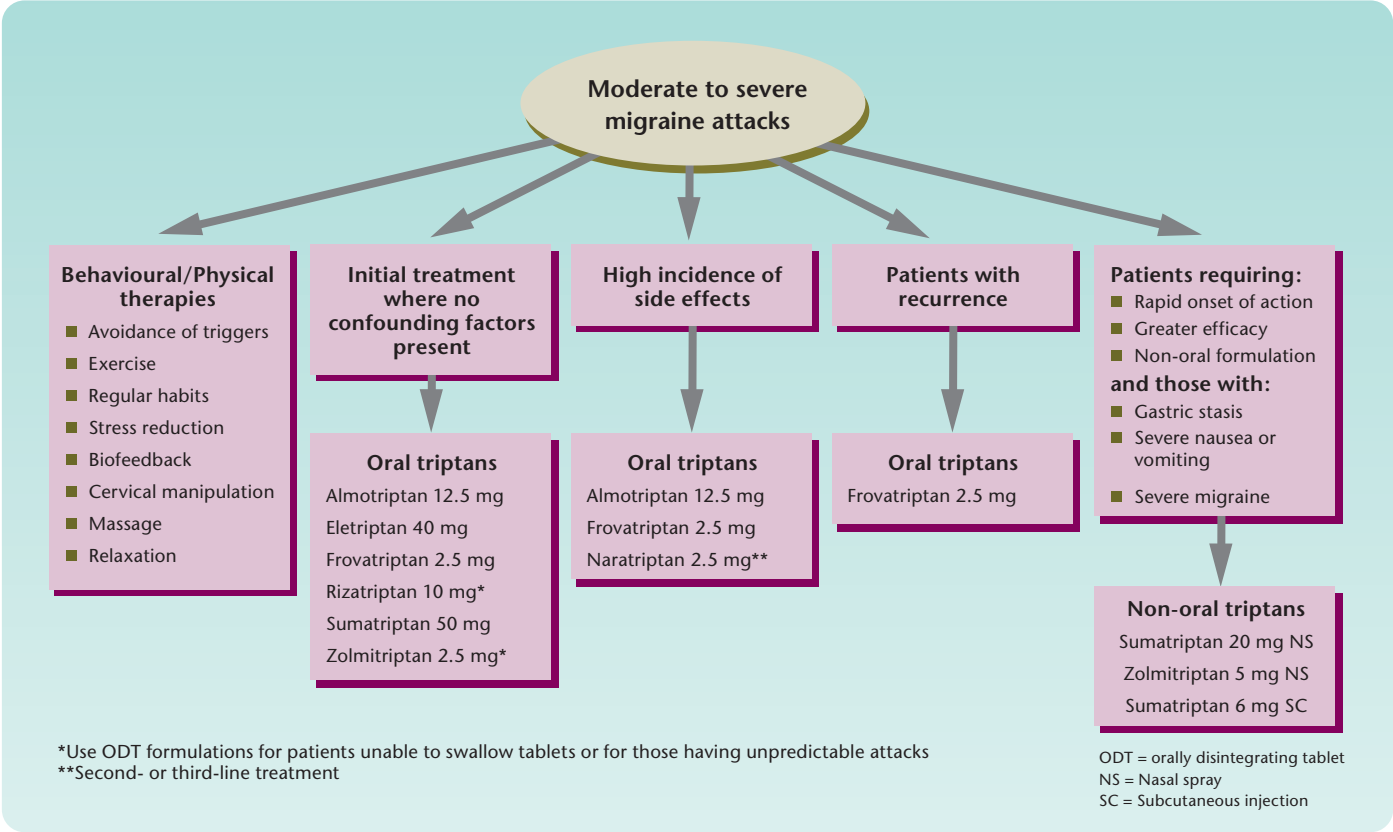


Figure 5. Guidelines for the acute treatment of migraine with triptans: Initial treatment

Conclusions

In summary, all the oral triptans except for naratriptan are suitable first-line treatments for most migraine patients. The choice of triptan should be based on its efficacy, tolerability and rate of recurrence, and on the personal requirements of the individual patient.

- Patients frequently reporting headache recurrence may benefit from frovatriptan 2.5 mg.
- Those unable to tolerate other oral triptans may benefit from almotriptan 12.5 mg, naratriptan 2.5 mg or frovatriptan 2.5 mg.
- Patients that have unpredictable attacks may benefit from the ODT (although they are not absorbed in the mouth), or nasal spray formulations.
- Patients with particularly severe attacks, those with a need for rapid response and those with nausea and (especially) vomiting may require the nasal spray or subcutaneous formulations.

Looking to the future

New acute treatments based on innovative delivery systems are currently under investigation and, in some cases, are already available in some countries. Many of these new formulations are designed to overcome the poor gastric absorption and emptying (gastric stasis) associated with migraine that frequently limits the oral delivery of migraine drugs.[22]

- The combination of sumatriptan 85 mg and naproxen 500 mg is available in the USA. This combines the rapid efficacy of the triptan with the long action of the NSAID.
- A needle-free formulation of sumatriptan 6 mg subcutaneous injection, in which compressed nitrogen pushes the drug subcutaneously, was launched recently in the USA. While there is no advantage of this formulation over the conventional injection in terms of efficacy and safety, it may be accepted better by some patients.
- A sumatriptan iontophoretic dermal patch was also launched recently in the USA. Potential advantages of this formulation include the avoidance of gastrointestinal absorption and therefore gastric stasis, and a sustained delivery. Available data indicate that the dermal patch has a similar efficacy to the conventional tablet formulation.
- Other sumatriptan formulations in development include an intranasal dry powder and a lingual spray.
- A new formulation of dihydroergotamine (DHE) has been developed for oral inhalation. Data from a Phase III study demonstrated that inhaled DHE had a favourable efficacy profile and a sustained action over the 48 hours after treatment (Figure 6).[23]

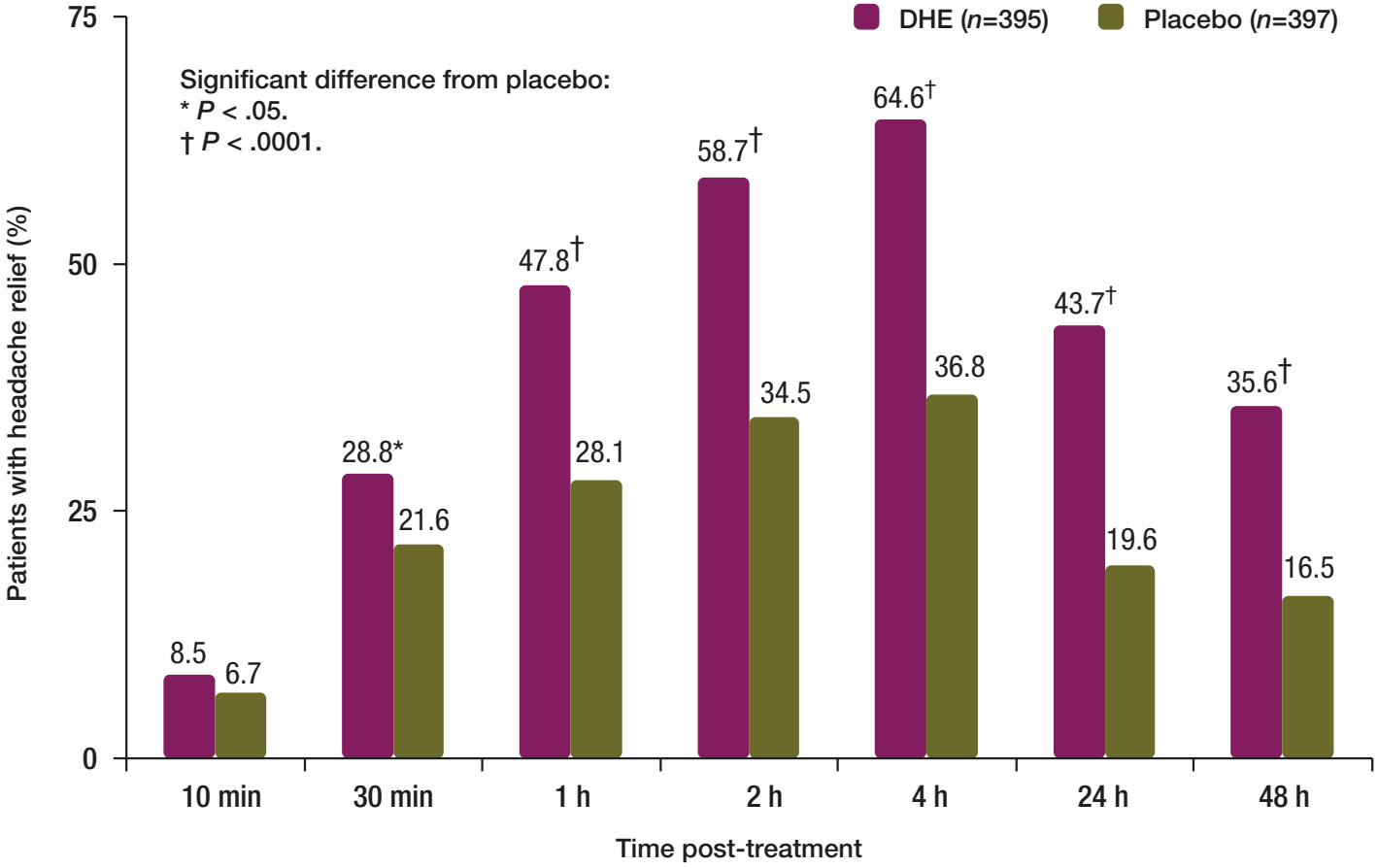


Figure 6. Proportion of patients reporting headache relief (improvement from severe or moderate to mild or no headache pain) from 10 minutes to 48 hours after treatment with inhaled DHE or placebo.[23]

- Dissolvable sachets of diclofenac have been developed to improve absorption of the drug, and this formulation is now available in the USA.

Treatment of menstrual migraine

MIPCA last addressed menstrual migraine in Newsletter 17, published in March 2008.[24] The main conclusions were as follows:

- A high proportion of female patients on a GP's list will suffer from attacks of menstrual migraine (defined as attacks occurring between two days before the onset of menstruation and the first three days of bleeding).
- Attacks of menstrual migraine are usually more frequent and more severe than those occurring at other times.
- Management strategies for menstrual migraine are the same as those for general migraine, and there should be few problems in managing all migraine attacks experienced by women in primary care.

Further relevant updates from 2008 to date are summarised below.

- An evidence-based review[25] of treatments for menstrual migraine concluded that:
- Sumatriptan 50 mg and 100 mg, mefenamic acid 500 mg, rizatriptan 10 mg[26-28] and the sumatriptan 85 mg / naproxen 500 mg combination[29] were all effective and had acceptable safety profiles.[25] Further studies have demonstrated that almotriptan 12.5 mg,[30,31] frovatriptan[32,33] and

zolmitriptan[31,33] are also effective and well-tolerated for menstrual migraine.

- Predictable menstrual attacks may be managed by perimenstrual prophylaxis with transcutaneous estradiol 1.5 mg,[25] frovatriptan 2.5 mg bd[34-36] and naratriptan 1 mg bd.[25] Zolmitriptan 2.5 mg bd also showed efficacy in this indication.[37]
- Strategies using contraception may be used to treat menstrual migraine in those requiring effective birth control.[25]
- Initial head-to-head clinical trials conducted between different triptans for menstrual migraine have now been published (Figure 7).

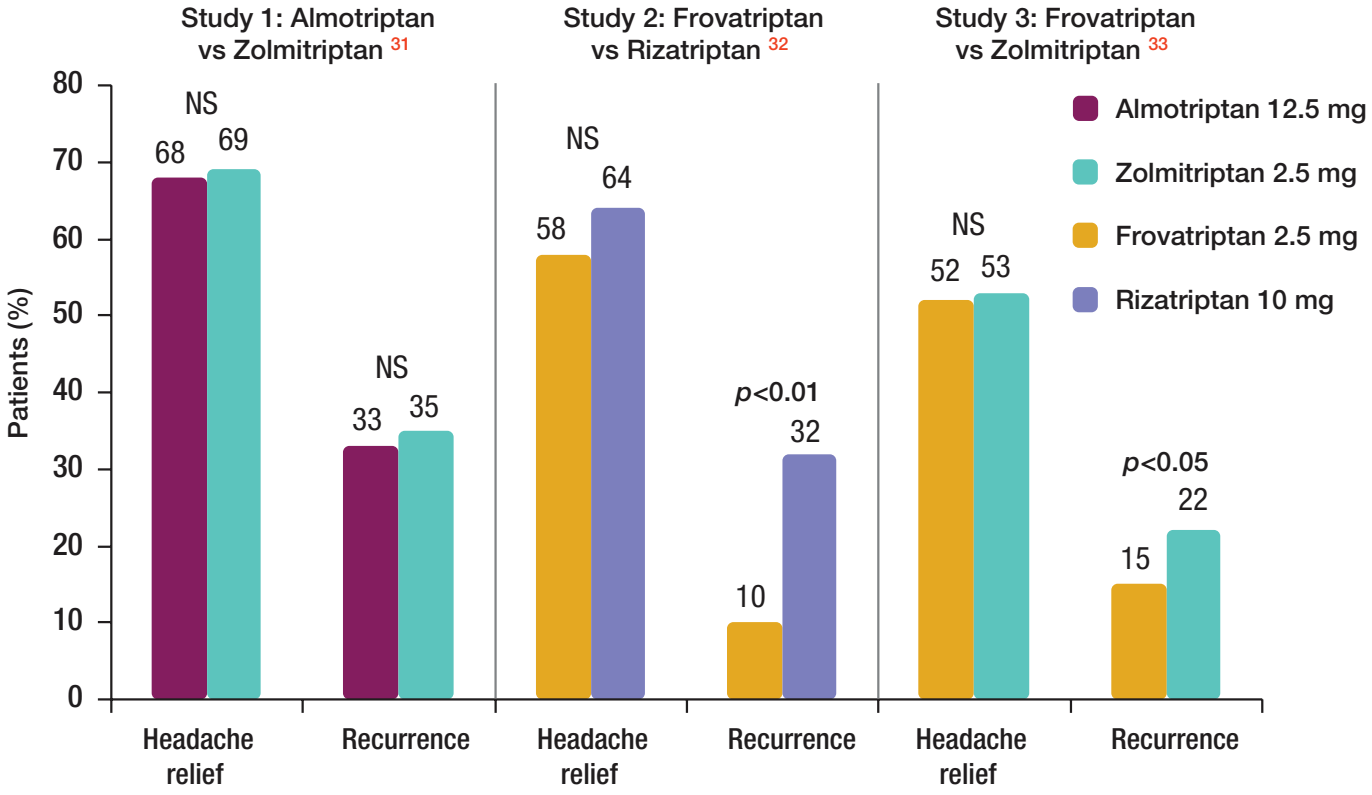


Figure 7. Comparator studies with oral triptan tablets in the treatment of menstrual migraine attacks. Study 1: almotriptan 12.5 mg vs zolmitriptan 2.5 mg[31]; Study 2: frovatriptan 2.5 mg vs rizatriptan 10 mg[32]; Study 3: frovatriptan 2.5 mg vs zolmitriptan 2.5 mg.[33] Proportion of patients reporting headache relief (improvement from severe or moderate to mild or no headache pain) at 2 hours and headache recurrence (return of moderate or severe headache after initial headache relief) at 24 hours after treatment.

These data suggest that, as in the treatment of general migraine attacks, all the oral triptan tablets may be effective in the acute treatment of menstrual migraine attacks. Frovatriptan appears to be associated with a lower incidence of headache recurrence compared with rizatriptan and zolmitriptan. However, these results require confirmation in large double-blind studies.

Overall conclusion

The oral triptans remain the gold standard as first-choice acute treatments for migraine. Evidence indicates that all of them, except for naratriptan 2.5 mg, have similar clinical profiles. However, the clinician can choose an appropriate initial triptan based on the chemical and clinical features of the drugs and the needs of the individual patient.

Acknowledgements

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