Current practice and future directions in the prevention and acute management of migraine

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Migraine is a common and disabling brain disorder with a strong inherited component. Because patients with migraine have severe and disabling attacks usually of headache with other symptoms of sensory disturbance (eg, light and sound sensitivity), medical treatment is often required. Patients can be managed by use of acute attack therapies (eg, simple analgesics or non-steroidal anti-inflammatory drugs) or specific agents with vasoconstrictor properties (ie, triptans or ergot derivatives). Future non-vasoconstrictor approaches include calcitonin gene-related peptide receptor antagonists. Preventive therapy is probably indicated in about a third of patients with migraine, and a broad range of pharmaceutical and non-pharmaceutical options exist. Medication overuse is an important concern in migraine therapeutics and needs to be identified and managed. In most patients, migraine can be improved with careful attention to the details of therapy, and in those for whom it cannot, neuromodulation approaches, such as occipital nerve stimulation, are currently being actively studied and offer much promise.

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Introduction

Migraine is a complex, common, and disabling disorder of the brain, whose mechanisms are only now being unravelled.[1–3] It is characterised by sensory symptoms: pain and sensitivity to normal afferent information, such as light, sound, and head movement. The attack manifestations are defined by the International Headache Society,[4] although the diagnostic criteria do not include common considerations such as the familial nature of the disorder.[5] Migraine is one of the primary headache disorders in which headache is part of the clinical phenotype of the syndrome, in contrast to secondary headaches in which head pain is a consequence and a symptom of another disorder. Episodic migraine, by definition, occurs on fewer than 15 days per month and chronic migraine occurs on 15 days or more per month.[6]

In terms of acute treatment, migraine can be managed with available substance groups such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), ergotamine derivatives, and triptans, with their different modes of administration. New strategies in acute treatment are very promising and the calcitonin gene-related peptide (CGRP) receptor antagonists and serotonin 5-HT_{1F} agonists are in the late stages of development. Preventive treatment can be divided into pharmacological and non-pharmacological therapies; one approach certainly does not exclude the use of the other, and a combination of pharmacological and non-pharmacological approaches, such as patient education, acupuncture, biofeedback, and exercise, can be useful in clinical practice. Medication-overuse headache (MOH),[7] which is caused by the regular use of analgesics or specific anti-migraine treatments that can increase headache frequency, is very much a problem in migraine management.[8]

In this Review, the subject of migraine treatment alone is covered. A more detailed coverage of the pathophysiology and diagnosis of headache disorders can be found elsewhere.[3,9–13] Available and awaited future approaches to migraine treatment will be outlined and, where possible, the evidence base is cited, although many care strategies remain to be rigorously tested. We discuss both acute and preventive treatment, as well as strategies for the management of medication overuse.

General treatment principles

Once the diagnosis has been confirmed, one usually starts the management process by explaining the condition to provide an understanding of the problem and to set realistic expectations. This is helpful for patients because it engages them in their own care, which in turn facilitates management. A headache diary will often be very instructive in the planning and evaluation of therapy. Recording affected days, pain severity, and medication use and response, as well as obvious triggers (eg, days of menstrual flow) can be extremely helpful to determine the need for preventive strategies and for considering therapeutic outcomes. Migraine-related disability is also an important factor and can be assessed using the very pragmatic and useful migraine disability assessment score,[14] or a similar approach. Together, these aspects help to determine the need and choice of acute and preventive treatments. For example, attacks that last for days and are highly disabling and refractory to acute attack therapy might require a preventive approach. Patients who typically have more than two or three migraine attacks per month might also benefit from preventive treatment,[15] although the frequency is arbitrary and a matter of debate.

Acute attack treatment

Current attack treatments fall into two categories: disease non-specific—analgesics and NSAIDS; and more disease specific—ergot-related compounds and triptans. Of note, specificity is relative, because triptans, for example, are also effective in the acute treatment of cluster headache,[16] and perhaps other types of primary or even secondary headache.[17,18] To avoid medication overuse, patients need to be counselled on the frequency of use of acute attack medicines,[19] and even simple analgesics such as paracetamol (acetaminophen) can be troublesome in this context.[7]

Analgesics and NSAIDs

Because drugs such as aspirin 900–1000 mg and paracetamol 1000 mg are cheap and can be effective, their use should be considered.[20–22] It is almost inconceivable that a patient with disabling headache would not have tried these approaches before seeking a neurological opinion. However, dosing might have been inadequate. Naproxen (500–1000 mg orally or rectally, with an anti-emetic),[23–26] ibuprofen (400–800 mg orally),[27,28] or tolfenamic acid (200 mg orally)[29] can be extremely effective in migraine if used adequately. Selective cyclo-oxygenase 2 inhibitors have also proven effective in migraine treatment with similar efficacy to NSAIDs.[30] However, the best-studied drug, rofecoxib, is no longer available. The debate over the cardiovascular safety of both unselective (NSAIDs) and selective cyclo-oxygenase inhibitors continues, and patients should be made aware of potential side-effects. Moreover, patients with a high risk profile in terms of cardiovascular disease should not use cyclo-oxygenase inhibitors frequently.

The addition of anti-emetics or prokinetics, such as domperidone (10 mg orally)[31–33] or metoclopramide (10 mg orally),[34,35] to analgesics or NSAIDs might improve the efficacy of these drugs with an independent anti-nociceptive effect and help patients to deal with migraine-associated nausea. However, the evidence base for their additional use is weak, and is largely based on their combination with other treatments.[36,37] Compound analgesics (ie, those containing aspirin, paracetamol, and caffeine) have been shown to be more effective than single analgesics.[38,39] However, these drugs, particularly caffeine-containing analgesics,[40] might carry an increased risk of MOH, although no prospective studies have been done.

Ergot derivatives and triptans

When analgesic measures fail to avert disability, more specific and more effective anti-migraine treatments are required.[41] Ergotamine, previously the mainstay of acute treatment, can no longer be considered the treatment of choice in acute migraine.[42] There are particular situations in which ergotamine is very helpful, such as in the treatment of very long attacks with headache recurrence, but dosing must be carefully monitored because ergotamine overuse can produce severe headache in addition to many vascular problems.[43] Dihydroergotamine is usually better tolerated than ergotamine (less nausea and vasoconstriction), but has a poor oral bioavailability.[44] Dihydroergotamine administered via a nasal spray has a better bioavailability of about 40%, but the onset of action is relatively slow and it has been shown to be inferior to nasal and subcutaneous sumatriptan.[45,46] Injectable dihydroergotamine (intravenous or intramuscular) is more effective, but produces more side-effects and the mode of administration is less convenient. In the near future, dihydroergotamine might go through its second incarnation as a new orally inhaled formulation that seems to be very promising in terms of headache relief and tolerability.[47]

The triptans, which are serotonin 5-$HT_{1B/1D}$ receptor agonists, have revolutionised the lives of many patients with severe migraine attacks, and are clearly the most powerful option available to stop a migraine attack. They can be rationally applied by considering their pharmacological, physicochemical, and pharmacokinetic features,[48] and are available in various formulations (tablet, nasal spray, subcutaneous injection, suppositories).[41] Although head-to-head comparisons between triptans are not exhaustive,[49] it is widely acknowledged that the seven licensed compounds differ with regard to their effectiveness, side-effect rate, and frequency of headache recurrence (table 1).[50] By determining the clinical problem, such as failure of analgesics or NSAIDs, nausea issues, or headache recurrence, a physician can tailor the choice of triptan to the patient's need (panel).

Widespread clinical experience suggests that failure with one triptan does not predict failure with another.[51,52] Indeed, each triptan should probably be tried for three attacks, because after three unsuccessful trials, the probability of success will be low, based on extrapolation from consistency studies.[53,54] There is no firm evidence base on which to decide how many oral triptans to try before switching formulation, although there is evidence that switching from one to another after failure results in effective treatment.[51,52] From a pragmatic position, one could suggest switching to a nasal or injectable formulation after a patient has failed three oral triptans. Some patients feel they can improve their responsiveness to triptans by switching from one substance to another between attacks, although this approach has never been formally investigated.

The combination of triptans with anti-emetics has been rarely studied, with only small studies indicating the benefits of such an approach.[55] Although one might expect this combination to be helpful, the reasons are not clinically obvious. The main concern for triptans is their rare, but serious, cardiovascular side-effects,[56] which necessitates that they are not used in patients with cerebrovascular or cardiovascular contraindications.

Treatment considerations

Pregnancy and lactation

Although triptans are contraindicated during pregnancy, data from pregnancy registries indicate that sumatriptan is largely safe in terms of teratogenicity when used during the first trimester, although their use might lead to an increase in preterm births.[57] Therefore, women who were unaware of their pregnancy when they took a triptan can be reassured. However, triptans should not be deliberately used during pregnancy owing to insufficient data being available. In general, lactation is also a contraindication to triptan use, although very little sumatriptan has been found in breastmilk.[58] As an alternative, injectable sumatriptan (which has a short

terminal half-life) can be used.[59] Mothers can then pump and discard milk after using injectable sumatriptan and use formula or previously pumped breastmilk for the next feed. Breastfeeding can be resumed 12 h after sumatriptan use.

Serotonin syndrome

Caution has also been advised with the combination of triptans and selective serotonin reuptake inhibitors (SSRIs) owing to the possible production of the potentially life-threatening serotonin syndrome, with symptoms such as tremor, palpitations, flushing, hypertension, and agitation.[60,61] To date, 11 cases have been described with suspected serotonin syndrome attributed to triptan monotherapy,[61] although the investigators did not apply strict diagnostic criteria.[62] 27 cases of serotonin syndrome during concomitant use of SSRIs, selective norepinephrine reuptake inhibitors (SNRIs), and triptans were reported in a US Food and Drug Administration (FDA) alert,[63] with one more case reported subsequently.[64] However, only seven of the cases reported by the FDA actually fulfilled Sternbach's criteria of serotonin syndrome.[65] About 700 000 patients are taking SSRIs or SNRIs with triptans annually in the USA.[66] Thus, considering the very low number of reported cases, triptans rarely precipitate serotonin syndrome when administered with SSRIs or SNRIs.[65] Because of the continuing debate, patients who have been appropriately selected to use a combination of such drugs should be made aware of the possibility of serotonin syndrome. Possible symptoms should be discussed so that they seek medical attention if required. Moreover, new cases of serotonin syndrome should be reported.

Allodynia

A recent issue has been the extent to which the presence of allodynia, the production of the sensation of pain from normally non-painful stimuli, can influence outcome. Allodynia is an extremely common phenomenon in migraine, occurring in about two-thirds of patients in population-based studies,[67,68] and was first recognised at least 50 years ago.[69] An initial uncontrolled study suggested that the presence of allodynia was associated with a poor outcome on triptans,[70] consistent with the development of central sensitisation in an inflammatory model of trigeminal nociception.[71] However, randomised controlled trials (RCTs) on the use of triptans when pain is mild, the attack is not fully developed, and allodynia is already present failed to support this concept.[72,73] A recent study suggested that pain intensity rather than allodynia influences outcome measures.[74] Taken together, these findings suggest that patients can be encouraged to use triptans before allodynia has developed, but there is not enough evidence to stop them from taking triptans when allodynia is present.

	Initial 2 h relief	Sustained pain-free	Consistency	Tolerability
Sumatriptan				
50 mg	ND	ND	ND/–	ND
25 mg	–	ND/–	–	+
Zolmitriptan				
2·5 mg	ND	ND	ND	ND
5 mg	ND	ND	ND	ND
Naratriptan				
2·5 mg	–	–	–	++
Rizatriptan				
5 mg	ND	ND	ND	ND
10 mg	+	+	++	ND
Eletriptan				
20 mg	–	–	–	ND
40 mg	ND/+	ND/+	ND	ND
80 mg	+(+)	+	ND	–
Almotriptan				
12·5 mg	ND	+	+	++

ND=no difference compared with sumatriptan. +=better than sumatriptan. –=inferior to sumatriptan. Adapted from Ferrari and colleagues,[50] with permission from Elsevier.

Table 1: **Comparison of the main efficacy and tolerability measures for the oral triptans versus 100 mg sumatriptan**

Maximum monthly use

Another controversial issue relates to the maximum monthly use of triptans. The manufacturers' dosing recommendations for triptans state that the safety of treating an average of more than three to four headaches in a 30-day period has not been established. However, even daily triptan use has been reported to be relatively safe.[75] Because triptan use on 10 days or more is believed to carry the risk of MOH,[1] we advise our patients to use triptans on fewer than 10 days per month, while calling their attention to the fact that safety has only been determined for up to three to four headaches per month.

Early treatment

Almotriptan 12·5 mg has been shown to abate migraine attacks more effectively when taken early in the attack (ie, within 1 h) when the pain is still mild than when taken later in the attack when the pain is moderate or severe.[73] This is also very likely to be true for other triptans, analgesics, and NSAIDs, although similar studies are not available. Some fear that patients could take triptans for headaches that would not eventually evolve into full-blown migraine and thereby increase the risk of MOH. However, treatment of migraine pain when early or mild was associated with a reduction in pain recurrence compared with treatment when moderate or severe,[76] so one could argue that this might reduce the monthly use of triptans. We advise our patients to take triptans as early as possible when the

***Panel:* Stratification of acute migraine-specific treatment options for various clinical situations**

Unresponsive to analgesics/NSAIDs

First tier

- Sumatriptan (50 mg or 100 mg)
- Almotriptan (12·5 mg)
- Rizatriptan (10 mg)
- Eletriptan (40 mg)
- Zolmitriptan (2·5 mg)

Slower effect/better tolerability

- Naratriptan (2·5 mg)
- Frovatriptan (2·5 mg)

Infrequent headache

- Ergotamine (1–2 mg)
- Dihydroergotamine (2 mg) nasal spray

Early nausea/vomiting or difficulties taking tablets

- Zolmitriptan (5 mg) nasal spray
- Sumatriptan (20 mg) nasal spray
- Sumatriptan (6 mg) subcutaneously
- Sumatriptan (25 mg) suppository
- Rizatriptan (10 mg) rapidly dissolving wafer

Headache recurrence

- Ergotamine (2 mg), most effective rectally/usually with caffeine
- Naratriptan (2·5 mg)
- Almotriptan (12·5 mg)
- Eletriptan (40 mg)

Tolerating acute treatments poorly

- Naratriptan (2·5 mg)
- Frovatriptan (2·5 mg)
- Almotriptan (12·5 mg)

Menstrual-related headache

Prevention (perimenstrual use for 5–6 days)

- Ergotamine (every night)
- Frovatriptan (2·5 mg twice daily)
- Naratriptan (1 mg twice daily)
- Naproxen (500 mg twice daily)
- Estrogens (data are conflicting)

Acute treatment

- Triptans, if not used for prevention
- Dihydroergotamine nasal spray, if triptans or ergotamine not used for prevention

Very rapidly developing symptoms

- Zolmitriptan (5 mg) nasal spray
- Sumatriptan (6 mg) subcutaneously
- Dihydroergotamine (1 mg) intramuscularly

All drugs are taken orally, unless stated otherwise. NSAIDs=non-steroidal anti-inflammatory drugs.

pain is still mild to moderate, but when they are reasonably sure they are developing their typical migrainous pain.

Choice of acute treatment

Most headache authorities suggest stratified care by attack, which is what patients often do when they have the available options: for example, patients use analgesics or NSAIDs for their less severe attacks, relying on triptans or ergot derivatives when their attacks or circumstances demand them, or when the other options do not provide relief (panel). Recent data suggest that combining a triptan (eg, sumatriptan 85 mg) with an NSAID (eg, naproxen 500 mg) can improve efficacy and reduce headache recurrence by about a third.[23] Such an approach is attractive if headaches are infrequent, although whether there is an increased risk of MOH still needs to be determined. If nausea is a major issue, analgesics, NSAIDs, and sumatriptan can be taken as suppositories. For such patients, sumatriptan and zolmitriptan are also available as nasal sprays, and an iontophoretic transdermal preparation of sumatriptan is in late phase 3 development.[77] Injectable sumatriptan is another alternative, and can be helpful if a rapid onset of action is desired by the patient. A needle-free sumatriptan injection device has recently been approved by the FDA.[78]

There are no evidence-based therapies for the acute treatment of aura; thus, prevention is the best option, although an uncontrolled study with ketamine does suggest one possible way forward.[79] Such an approach is based on the pharmacology of cortical spreading depression (CSD), the animal equivalent of human aura,[80] which can be blocked by NMDA receptor antagonists.[81] However, an RCT in patients with migraine is needed.

Recent developments in acute therapy

Although triptans currently remain the most effective option for acute attack therapy, outstanding issues exist. First, not all patients respond to treatment. Response rates after oral administration are 30–40% for pain-free outcomes at 2 h.[50] Second, of those who do respond, about one in three experience headache recurrence within 24 h.[82] Third, whereas most patients are not particularly troubled by the side-effects of triptans, which they rate well below efficacy considerations,[83] the fact that triptans constrict cranial blood vessels through activation of serotonin 5-HT_{1B} receptors produces an important problem.[84] These receptors are predominantly found in the cranial circulation, although, unfortunately, they are also found in small concentrations on coronary vessels where they mediate vasoconstriction.[85] As a consequence, substantial effort has been expended to search for non-vasoconstrictor therapies for acute migraine.[86]

CGRP receptor antagonists

Possible future candidates for migraine treatment include CGRP receptor antagonists,[87,88] nitric-oxide-synthase inhibitors,[89] vanilloid transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor antagonists,[90,91] AMPA, kainate,[92] and pure kainate

receptor antagonists,[93] and 5-HT$_{1F}$ receptor agonists.[94] Of these, the CGRP receptor antagonist class is probably the most advanced. The intravenous antagonist olcegepant and the orally available antagonist telcagepant have shown clear effects in phase 1 and 2 RCTs,[95,96] and telcagepant has recently undergone two phase 3 studies (figure) without cardiovascular liability.[97–99] A phase 2 trial on another CGRP receptor antagonist, BI 44370, has been completed and results are awaited.[100]

CGRP receptor antagonists have shown some promise in terms of reduced headache recurrence,[96,101] and there is also hope that this group of compounds contains a lower risk of inducing MOH than do triptans. The clinical tolerability of these drugs in terms of CNS and vascular side-effects seems to be more favourable than for triptans. However, concerns about possible liver toxicity remain. The development programme of one compound, MK3207, which was undergoing phase 2 evaluation, has been discontinued because of delayed liver test abnormalities.[102] Moreover, in a migraine prevention study of daily telcagepant over 3 months, increases in transaminases were observed in a few patients.[103] FDA filing for telcagepant has thus been delayed to allow a review of additional safety data.[104]

Serotonin receptor agonists

The announcement of the success of a phase 2 dose-ranging proof-of-concept study with the 5-HT$_{1F}$ receptor agonist COL-144[104] offers another prospect for a non-vasoconstrictor acute anti-migraine therapy. Unlike the triptans, COL-144 does not act at 5-HT$_{1B/D}$ receptors and therefore does not cause vasoconstriction. 130 patients with migraine received doses of between 2·5 mg and 45 mg COL-144 or placebo administered intravenously.[105] The drug was well tolerated and did not produce triptan-like chest symptoms. At effective doses of COL-144, a higher proportion of patients showed a headache response at 2 h than those on placebo.[105] An orally bioavailable formulation of COL-144 is now in phase 2 testing.[106] The success of CGRP receptor antagonists and 5-HT$_{1F}$ receptor agonists reinforce the need for a neurally based approach to migraine and emphasise that migraine is a brain disorder.

Preventive treatment

Preventive therapy is a crucial component of the management strategy to reduce migraine disability, and is indicated in about a third of patients with migraine.[107] Unfortunately, the mechanisms of action of current preventive treatments are not well understood. One potential mechanism could be the suppression of CSD,[80] as most preventive medicines seem to inhibit CSD.[108] Silent CSD might occur during migraine without aura,[109] and its suppression would explain the effectiveness of migraine prophylactics. However, much more research is needed to confirm this hypothesis.

Although attack frequency is usually the main impetus for prevention, sometimes intractability is the problem.

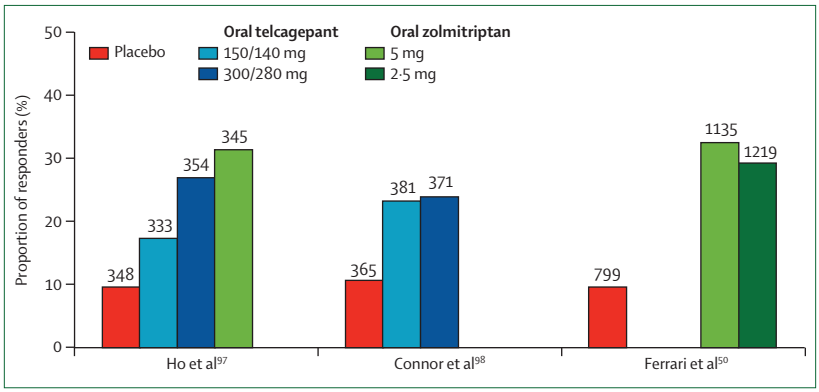

Figure: **Efficacy of CGRP receptor antagonists in migraine**
Results of two double-blind, randomised, placebo-controlled studies on oral telcagepant,[97,98] and a meta-analysis by Ferrari and colleagues.[50] Total numbers of patients in each group are shown above the bars. Data are shown for the endpoint pain freedom at 2 h. CGRP=calcitonin gene-related peptide.

Consensus guidelines differ substantially with regard to recommendations about when to start pharmacological migraine prophylaxis. In the US guidelines,[110] treatment is recommended when attacks regularly exceed two times per week, whereas European guidelines suggest migraine prophylaxis for two attacks or more per month.[15] Patient preference is certainly a major factor in deciding whether to start a preventive treatment.

Current pharmacological approaches

The choice of migraine preventive agent is based on effectiveness, side-effect profile, knowledge of previous efficacious or unsuccessful treatment trials, and the comorbidities of the individual patient. With regard to the efficacy of preventive agents in studies, a 25% increase in responders (ie, patients with a 50% reduction in migraine days) can typically be expected in the active drug group compared with those on placebo.[111] In clinical practice, this translates into a 50% reduction in migraine days for half the patients who use them,[112] and usually a more obvious reduction in severity with some concomitant opportunity to provide better control of residual attacks. Preventive agents are, of course, only helpful if they are actually taken, so it is important that the patient is engaged in this process and knows what to expect.

Another issue relates to the optimum duration of prophylactic treatment. For topiramate, a positive treatment effect can be maintained over a period of at least 12–14 months.[113,114] However, there seems to be a prolonged benefit after cessation of a 6-month treatment period with topiramate.[113] In light of these results, one could conclude that, after a 6-month treatment period with a stable therapeutic effect, tapering of the preventive medication should be tried in patients without (or with few) comorbid conditions such as fibromyalgia, depression, or anxiety disorder, whereas it should be continued over a longer period of time (>12 months) in patients in whom comorbidities are clinically pre-eminent and who have risk factors for migraine

	Dose	Common side-effects
Beta-blockers		
Propranolol[118-120]	40–120 mg twice daily	Reduced energy, tiredness, postural symptoms; contraindicated in asthma
Metoprolol	25–100 mg twice daily	Reduced energy, tiredness, postural symptoms; contraindicated in asthma
Anticonvulsants		
Valproate[121-123]	400–600 mg twice daily	Drowsiness, weight gain, tremor, hair loss, fetal abnormalities, haematological or liver abnormalities
Topiramate[118,124,125]	50–200 mg daily	Paraesthesiae, cognitive dysfunction, weight loss, care with a family history of glaucoma, nephrolithiasis
Gabapentin[126]†	900–3600 mg daily	Dizziness, sedation
Calcium channel blockers		
Flunarizine[127,128]	5–15 mg daily	Drowsiness, weight gain, depression, parkinsonism
Antidepressants		
Amitriptyline,‡ dosulepin (dothiepin), nortriptyline[129]‡	25–75 mg every night	Drowsiness, urinary retention, arrhythmias; note that some patients are very sensitive and might only need a total dose of 10 mg, although generally 1–1·5 mg/kg bodyweight is required
Venlafaxine[130,131]	75–150 mg daily	Drowsiness, urinary retention, arrhythmias
Serotonin antagonists		
Pizotifen[132]	0·5–2 mg daily	Weight gain, drowsiness
Methysergide[133]	1–6 mg daily	Drowsiness, leg cramps, hair loss, retroperitoneal fibrosis; 1 month drug holiday is required every 6 months
Other compounds§		
Lisinopril[134]	20 mg daily	Cough, dizziness
Candesartan[135]	16 mg daily	Birth defects and fetal death
Nutraceuticals¶		
Riboflavin[136]	400 mg daily	..
Coenzyme Q10[137]	100 mg three times daily or 75 mg twice daily	Gastrointestinal upset
Butterbur (*Petasites hybridus*)[138]	50–75 mg twice daily	Elevation of transaminases
Feverfew (*Tanacetum parthenium*)[139-142]	6·25 mg three times daily	Skin rash

No convincing controlled evidence has been found for verapamil.[143-145] Controlled trials in the following drugs have shown no effect: nimodipine,[146] clonidine,[147] and the SSRI fluoxetine.[148] *The local national formulary should be consulted for detailed information on dose, side-effects, and contraindications. †Supported more by experience because the cited study did not achieve the primary endpoint on an intention-to-treat basis. ‡A small study, although a very widely used treatment. §Compounds not widely considered mainstream but with a positive RCT. ¶Non-pharmaceuticals with at least one positive RCT. RCT=randomised placebo-controlled trial. SSRI=selective serotonin reuptake inhibitor.

Table 2*: Preventive treatments in migraine

progression (ie, high attack frequency, history of head injuries or obesity).[115,116] Patient preference is important in this decision. Preliminary evidence suggests that, when re-introducing a migraine preventive treatment in patients who have previously used prophylactic medication, one should switch to a different group of preventive drugs even if previous treatment trials were effective.[117]

Table 2 shows the treatments that have proven effective in the preventive management of migraine. These broadly comprise substances from groups including beta-blockers, antidepressants, anticonvulsants, calcium-channel blockers, serotonin antagonists, and nutraceuticals (ie, dietary supplements with pharmacological properties). In our view, the beta-blockers propranolol and metoprolol, the antiepileptic drugs valproate and topiramate, and the calcium-channel blocker flunarizine can be considered to be first-choice drugs. Each of these drugs has proven efficacy in reducing migraine attack frequency in RCTs.[118,121,123–125,127] Flunarizine is not available in many countries and verapamil could be used as an alternative, although the evidence is much less clear for this drug with positive effects only in very small studies (table 2).[143,144] Relatively new drugs with some promise for the treatment of migraine include the antidepressant venlafaxine,[130,131] as well as the inhibitor of angiotensin-converting enzyme lisinopril and the antagonist of angiotensin II receptor candesartan.[134,135]

Although chronic migraine is represented by a large group of patients who present with disabling headache in secondary care, treatments have only recently been studied in this group. Several RCTs have shown that topiramate 100 mg reduces attack frequency in chronic migraine,[149–151] and converts chronic migraine into episodic migraine.[151] Its effect is similar to propranolol 160 mg daily.[150] In one study, inclusion of patients with medication overuse did not inhibit the useful effects of topiramate 100 mg,[150] although patients on topiramate did not reduce their acute medication overuse. However, in a subgroup analysis of patients with medication overuse in a similar study in the USA, those on topiramate did only slightly better than those on placebo, with the difference between the groups not being significant ($p=0·059$).[149,152] Because of the somewhat inconsistent evidence, the results from the former study should not be taken to suggest that all patients with medication overuse should be treated with preventive drugs as opposed to encouraging medication withdrawal first, as the data suggest that only a subgroup of patients might benefit from immediate preventive therapy.

Recent developments in preventive therapy

CSD inhibitors

Similar to the available preventive agents, tonabersat, a novel potential preventive agent that has recently been investigated in three phase 2 studies, also inhibits CSD.[153] In addition, it reduces CSD-induced nitric-oxide release and trigeminovascular responses in the laboratory.[154] Unfortunately, two small RCTs and a larger, well powered study (Tonabersat Evaluation in Migraine Prevention in the United States [TEMPUS]) were negative in terms of prevention of migraine without aura.[155–157] One of these studies had an interesting design and recruited only patients who had migraine attacks with frequent aura.[155] In addition to the primary endpoint of a reduction in migraine headache days with or without aura, which was not met, a co-primary endpoint of this cross-over study was the number of aura attacks. The investigators found a significant reduction in this co-primary endpoint in patients during tonabersat treatment compared with

during placebo treatment period. This result is in agreement with the view that CSD is the experimental equivalent of aura, and substances effective in CSD are also effective in aura. However, this study challenges the view that silent CSD triggers migraine attacks without aura. Together, these results suggest that, although tonabersat is unlikely to be a major step forward for the treatment of patients with migraine without aura, it could be an option for the management of patients with aura.

Neuromodulation

Neuromodulatory approaches are currently focusing on the stimulation of the greater occipital nerve (GON). Low-frequency electrical stimulation has been shown to inhibit nociceptive processing with effects outlasting the conditioning electrical stimulation.[158] In the case of GON stimulation, the targeted synapses and neurons are located in the trigeminocervical complex and receive convergent input from the GON as well as from the trigeminal nerve.[159] Stimulation of the GON is thus expected to modulate excitability to the GON as well as dural afferent input, and this has been confirmed in animal experiments.[160] Moreover, functional imaging studies have shown that central processing of migraine pain signals in the thalamus could be modified by GON stimulation.[161]

The use of occipital nerve stimulation for the treatment of intractable head pain in human beings was first proposed in 1999, when a series of cases of intractable occipital neuralgia responding to occipital nerve stimulation were reported.[162] Detailed phenotyping of these cases in the context of a functional imaging study showed that almost all patients had chronic migraine, and that the stimulation approach was very successful.[161] Two RCTs are now complete (PRecision Implantable Stimulator for Migraine [PRISM] and Occipital Nerve Stimulation for the Treatment of Intractable chronic Migraine [ONSTIM]),[163,164] and have been published in abstract form.[165,166]

The PRISM study was completed by 125 treatment-refractory migraine patients with or without medication overuse. In the overall group, the primary endpoint (reduction in migraine days at 12 weeks after implantation compared with baseline) was not met, although there was a trend towards greater efficacy in the treatment group than in the control group. This trend was driven by the patients without medication overuse (reduction of 5·9 migraine days per month in the active groups *vs* –2·6 migraine days in the control group), whereas in the group with medication overuse, outcomes of active and control stimulation were similar (–5·0 *vs* –4·8 migraine days per month). With regard to the subgroup without medication overuse, the study was probably underpowered to detect a significant effect of the stimulation. Moreover, stimulation settings were probably not optimised.

66 patients completed the ONSTIM study. The responder rate was significantly higher in the group with adjustable stimulation than in patients with preset stimulation or medical management. The effectiveness of a diagnostic occipital nerve block did not predict stimulation efficacy. However, the primary endpoint of the study (percentage reduction in headache days per month) was not met, although there was a trend in favour of stimulation.[166] As an alternative to stimulation of only the occipital nerve, combined stimulation of the occipital and supraorbital nerves has been suggested and showed some promise in an open study.[167] This is a developing area of research,[168] and with optimised stimulation settings, peripheral nerve stimulation might be a useful treatment strategy, particularly for medically treatment-refractory patients without medication overuse, although further studies are awaited before this technique can be used outside clinical trials. Initial results in cluster headache are promising.[169,170]

Botulinum toxin type A

Botulinum toxin type A (onabotulinum toxin A; BTA) inhibits the release of acetylcholine at motor nerve terminals.[171] This action led to its use in the treatment of movement disorders, such as dystonia,[172] and in cosmetic use for forehead and other facial wrinkles. Open-label experience from its cosmetic use suggested potential benefits in headache. Basic experimental studies showed anti-nociceptive properties in some standard models, such as rats with formalin-induced pain,[173] which provided the rationale for its development in headache prevention.[174] However, the evidence regarding possible anti-nociceptive properties of BTA in human models of experimental pain remains inconclusive.[175–179] Initially, an RCT by Silberstein and colleagues[180] showed a positive effect for a 25 U dose in the prevention of episodic migraine, but no response at 75 U compared with placebo. Of eight subsequent double-blind RCTs with a total of 1728 patients, all but one small study with 30 patients were negative.[181–188] Accordingly, a recent meta-analysis of these studies concluded that BTA is not significantly better than placebo for the preventive treatment of episodic migraine.[189]

With regard to chronic daily headaches, two large studies (total 1057 patients) have been reported, and both were negative on the primary endpoint of headache days.[190,191] Recently, two phase 3 studies of BTA in chronic migraine have been completed (Phase III REsearch Evaluating Migraine Prophylaxis Therapy with Botulinum Toxin Type A [PREEMPT1] in North America and PREEMPT2 in North America and Europe).[192] In PREEMPT1, the primary endpoint (change in number of headache episodes from baseline) was similar in the BTA group and controls (–5·2 *vs* –5·3 episodes), although the secondary endpoint (reduction of headache days) differed between the two groups (–7·8 *vs* –6·4 headache days). The investigators attributed the negative outcome regarding the primary endpoint to a baseline imbalance in headache episodes between the treatment and placebo groups. Subsequently, in PREEMT2, the sponsor changed

the primary endpoint from change in number of headache episodes to change in number of headache days. PREEMPT2 was reported to be successful with regard to primary and secondary endpoints, with a reduction of 9·0 headache days in the BTA group and 6·7 days in the placebo group. The injections were well tolerated in both studies. A pooled analysis of data from PREEMPT1 and PREEMPT2 also showed a significant benefit of BTA over placebo with regard to headache days and headache episodes,[193] and BTA was also reported to be effective in a subgroup of patients with medication overuse.[194]

Taking into account the experience from BTA studies on episodic migraine, the results in chronic migraine were challenging. A separate study confirming the results of PREEMPT1 or PREEMPT2 is therefore necessary. From a mechanistic point of view, it could be that pathophysiological processes such as central sensitisation might have a more prominent role in preventive treatment of chronic migraine than that of episodic migraine, and are targeted by BTA as indicated by a BTA-induced size reduction in the zone of secondary hyperalgesia in human experimental pain models.[178,195] The results for chronic migraine from the PREEMPT1 and PREEMPT2 studies are only applicable to patients without continuous headaches, because such patients were excluded from these studies.

Patent foramen ovale closure

An epidemiological relation seems to exist between patent foramen ovale (PFO) and migraine with aura, but not migraine without aura.[196] Open-label studies suggested that PFO closure could cure or substantially improve migraine.[197] In accordance with this hypothesis, the primary endpoint of an RCT in migraineurs with aura in Europe (Migraine Intervention with STARFlex Technology [MIST]-I)[198] was the cessation of migraine headaches 91–180 days after the procedure. This endpoint was reached in only three (4%) of 74 patients in the implant group versus three (4%) of 73 patients in the control group (p=0·51). Secondary endpoints were also negative.[198] The US study, MIST-II,[199] was halted by the sponsor with enrolment problems and a reallocation of funds to a PFO closure study in stroke stated as the reasons.[200] PFO closure has important associated risks, including arrhythmia and cardiac tamponade, and thus any potential benefit needs to outweigh those risks. At this time, there is no justification whatsoever for PFO closure to be used in migraine outside a clinical trial.

Alternative management strategies

Migraine is clearly an inherited disposition to headache that is triggered by change: too much or too little sleep, skipping meals, weather change, change in exertion patterns, or change in stress. Thus a balanced, regular lifestyle seems desirable, although it has not been proven by evidence-based medicine that education of patients and other adjustments to lifestyle truly reduce the frequency or severity of headaches. The same applies to the careful intake of recognised aggravating substances, such as caffeine.[201]

Obesity has been shown to be a risk factor for the progression from episodic to chronic migraine.[202,203] Although no studies have specifically investigated weight reduction as a therapeutic intervention in migraine, its use is plausible in obese patients with chronic migraine. In obese patients with episodic migraine, weight reduction might prevent the progression to chronic migraine.

No RCTs to date have assessed the effectiveness of exercise as a single intervention in migraine prevention, and a recent qualitative systematic review concluded that the published studies, mostly of poor quality, only suggest a reduction in pain intensity rather than a reduction in headache frequency or duration.[204] It is certainly not wrong to recommend some degree of aerobic exercise to patients with migraine, because the effectiveness in other common disorders, namely cardiovascular disease, has been broadly shown. However, patients should be aware that exercise itself might be a potential headache trigger, which is also true for exercise-related weight loss and dehydration. In contrast to exercise, there is some evidence for efficacy of behavioural techniques such as biofeedback, relaxation, and cognitive therapy for the prevention of migraine.[205,206]

Two large multicentre RCTs of acupuncture for the prevention of migraine have now been done.[207,208] One study showed similar effectiveness of the acupuncture interventions to standard medical treatment with beta-blockers, calcium-channel blockers, or antiepileptic drugs.[207] However, there was no difference between verum and sham acupuncture, indicating that exact adherence to the traditional acupuncture concepts might not be important. The other study also showed no difference between verum and sham acupuncture, but both interventions were clearly superior to a waiting-list group.[208] Therefore, there are good reasons to include acupuncture in a multimodal setting of migraine prevention. By contrast, there is no evidence to recommend homoeopathy.[209] One study recently suggested that acupuncture might also be useful for the treatment of acute migraine attacks, and showed verum acupuncture to be superior to sham acupuncture in the acute setting.[210] However, the absolute treatment effect was small (a reduction of 1 point on a 10-point visual analogue scale), and it is questionable whether this can be considered clinically relevant.

Taken together, there is increasing evidence for the efficacy of some non-pharmacological approaches. These interventions are usually very well tolerated and provide an important measure to combine with pharmacological approaches in multidisciplinary care to achieve optimum responses.[211–213] Integrated care extends these concepts of multidisciplinary treatment to structured cooperation and interaction between neurologists in private practice and tertiary-care

headache centres with harmonisation of treatment approaches.[214] It is hoped that such organisational structures can further improve patient care, but a careful cost-benefit evaluation will be necessary before such approaches are widely adopted.

Management of medication overuse

Medication overuse is effectively defined as the consumption of triptans, ergotamines, opioids, or combination analgesics on 10 days or more per month, with the International Headache Society allowing 15 days per month for simple analgesics.[7] It seems essential that analgesic overuse should be reduced and eliminated to determine the underlying headache phenotype and to start managing the problem effectively.[215] There is no universally accepted, evidence-based approach to the management of MOH. The best that can be done is to offer some observations, modulated by our experience, which will necessarily be imperfect. This is an area that desperately needs more research.

Withdrawal treatment

Although abrupt drug withdrawal is often regarded as the treatment of choice,[216] patients can also reduce their use by, for example, 10% every week or every 2 weeks, because abrupt cessation often produces withdrawal headache. Either approach can be facilitated by first keeping a careful diary for 1–2 months to focus all parties' minds on the issue. A small dose of an NSAID, such as naproxen 500 mg twice daily if tolerated, will take the edge off the pain as analgesic use is reduced, as will a GON injection.[217] Some experts advocate corticosteroids to facilitate the withdrawal process,[218] but clinical trials have been short and the results are conflicting.[219,220] Moreover, late-onset rebound headache might complicate such a strategy.

When the patient has reduced their analgesic use substantially, a preventive agent should be introduced (table 2) if headache frequency remains a problem. The sequence of withdrawal and introduction of a preventive agent is still a matter for debate. As noted above, topiramate has been shown to be effective in some patients even before withdrawal.[150] However, patients who are unresponsive to preventive treatment during continuing medication overuse can respond better when overuse is stopped.[221] At this point, it could be reasoned to first withdraw patients whenever they are willing. A preventive therapy can then be introduced as a second step if necessary after withdrawal. In patients who refuse to withdraw, preventive treatment can be introduced while they are still overusing medication. In the latter scenario, it is useful to advise patients of the likely higher prospect of failure of the preventive agent. Future studies will hopefully clarify this issue.

Because non-pharmacological approaches, such as behavioural treatment and acupuncture, have been shown to be effective in the treatment of episodic migraine, these techniques might also be helpful in chronic migraine complicated by medication overuse. Current evidence indicates that these techniques are particularly valuable in maintaining improvement over longer time periods.[212]

Search strategy and selection criteria

We searched PubMed with the keywords "migraine", "treatment", "randomized controlled", and "trial". All papers published from 1966 to November, 2009, in English or German, were considered if they described a controlled trial. Abstracts located by this search were reviewed and, if appropriate, the full articles obtained. References cited within selected articles were also considered. In addition, review books, abstracts, and articles that had previously come to the attention of the authors were included.

Hospital admission

We believe that some patients with medication overuse will require admission to hospital for detoxification. However, not all headache experts take this view, and practice varies substantially from country to country and even within countries. In general, patients who require admission to hospital could include those who fail drug withdrawal as outpatients, those who have a significant complicating medical condition (eg, unstable insulin-dependent diabetes mellitus or less well controlled epilepsy), or those on complicating medicines (eg, opioids or barbiturates), for which withdrawal might be problematic as an outpatient. Approaches vary from multidisciplinary to largely medicine based, but have not been rigorously compared.[213]

Antidopaminergic anti-emetics (ie, domperidone, metoclopramide [also acts at 5-HT_4 and 5-HT_3 receptors]) or 5-HT_3 receptor antagonists (ie, ondansetron or granisetron) can be given as required, as oral, suppository, or intravenous formulations. The same applies to fluids. In addition, clonidine can be given for opioid withdrawal symptoms. Some clinicians use clomipramine or acamprosate for withdrawal symptoms, although data on their effectiveness are limited.[222,223] For acute, intolerable pain, we have found intravenous aspirin 1 g to be very useful and remarkably well tolerated in the setting of medication withdrawal (Goadsby PJ, unpublished). At night, oral or intramuscular chlorpromazine is helpful both for pain and for its sedative effect after ensuring adequate hydration. If the patient does not settle over 3–5 days, a course of intravenous dihydroergotamine can be used.[224] The above-mentioned anti-emetics will be required with dihydroergotamine to ensure that treatment is well tolerated.[225]

Conclusions

Effective migraine management is possible in most patients. However, much work remains to be done to

improve the evidence base of the current approaches, particularly in the management of chronic migraine, and to elucidate their mechanisms of action. Medical therapy is still the mainstay of migraine treatment, but migraine is a complex disorder for which comorbidities and patient preferences have to be taken into account. Non-pharmacological treatments can certainly help to reduce the disease burden and to improve patient satisfaction. An individualised approach to migraine management is thus warranted and will be appreciated by the patient. Future pharmacological developments for the treatment of acute migraine attacks, such as new triptan formulations, non-vasoconstrictor CGRP receptor antagonists, and 5-HT_{1F} agonists, will hopefully further improve the care of these often severely affected patients.

Contributors

PJG and TS participated equally in the writing and editing of the Review. Both authors have read and approved the final manuscript.

Conflicts of interest

In the past 3 years, PJG has consulted for, advised, or collaborated with Advanced Bionics, Allergan, Almirall, Autonomic Technologies Inc, AstraZeneca, Belgian Research Council, Boehringer-Ingelheim, Bristol-Myers Squibb, Boston Scientific, Colucid, Eli-Lilly, Fidelity Foundation, GlaxoSmithKline, Johnson & Johnson, Kalypsys, Medtronic, MAP Pharmaceuticals, Migraine Research Foundation, Migraine Trust, Minster, UK Medical Research Council, Merck Sharp and Dohme, US National Institutes of Neurological Diseases and Stroke, Netherlands Research Council, Neuralieve, Neuraxon, NeuroTherapeutics Pharma, UK Organisation for Understanding Cluster Headache, and Pfizer. TS has given talks for Pfizer.

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