SIGN on the pharmacological management of migraine

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In February 2018, the Scottish Intercollegiate Guidelines Network (SIGN) published a new guideline on the pharmacological management of migraine (SIGN 155). This article discusses the main recommendations of the guidance and how it compares with other UK headache guidelines, including NICE.

There are now three UK guidelines on the treatment of migraine. In 2010, the British Association for the Study of Headache (BASH) published guidance on the management of migraine, tension-type, cluster and medication-overuse headache, of which migraine accounted for the largest part. A revision was planned for 2016 but has not appeared, presumably because NICE published its guideline on the management of headache in the over-12s in 2012, and updated it in 2015. NICE decided in 2016 not to carry out a major update, so its recommendations still stand. Now, SIGN has produced a guideline with a narrower focus: the drug treatment of migraine, though it also covers the treatment of medication-overuse headache.

This is another example of overlap between SIGN and NICE, despite the two organisations having pledged to reduce duplication. In November 2017, NICE published a guideline on chronic asthma management, marching into an area that had been well served by SIGN and the British Thoracic Society for years, right up to the last update in 2016. The two asthma guidelines have some differences, though none major.

Arguably, it’s not important if there is more than one guideline because commissioners and providers in England and Wales are expected to ‘enable’ the use of NICE guidelines whereas SIGN guidelines are intended for implementation in NHS Scotland. But the border between the two health services is only organisational and clinicians have enough to do without worrying about potentially conflicting recommendations, whether they are based on the same evidence or – as in the case of the migraine guidance – one includes more recent evidence.

SIGN divides its migraine guidance into six main sections: an introduction...
and overview, treatments for acute and chronic migraine, medication-overuse headache, devices for migraine treatment, and information for patients.

**Categorising migraine**

Migraine is categorised as headache with or without aura, and as episodic (low frequency: up to nine days per month, or high frequency: 10–14 days per month) or chronic (≥15 days per month with superimposed migraine on ≥8 days per month for over three months). A detailed definition is included in an appendix to the SIGN guideline. Overall lifetime prevalence of migraine exceeds 90% and it accounts for 4–5% of primary care consultations and 30% of neurology outpatient consultations. Migraine causes 80% of medication-overuse headache, which affects 0.5%–2.6% of people.

Women are twice as likely as men to have migraine, a fact attributable to hormonal changes during the menstrual cycle. Underdiagnosis, misdiagnosis and undertreatment are common. Migraine impacts education, working and social life, and the family. People with migraine say their quality of life is affected by pain, sleep disturbance and restriction of daily activities. They also express concern about the adverse effects of drug treatment and dependence on prophylactic measures.

**Treating acute migraine**

The aim of acute treatment is to abort an attack or reduce the severity of headache and other symptoms. Medication should be taken as soon as the person realises they are developing a migraine (except in the case of triptans, which should be taken at the start of headache, not aura). A response is usually defined as being pain-free at two hours and sustained freedom from pain at 24 hours. The recommended treatments are superior to placebo by these measures but most data in the guideline refer to the two-hour endpoint.

Patients should be offered the choice of a stepped approach to treatment (beginning with mild analgesics then stepping up to a triptan if necessary) or a stratified one (using analgesics for milder headache, triptans for worse pain). Treatment does not always work so patients should have access to rescue medication. The response to triptans is variable and a trial of different agents may be needed to find the most effective one. Migraine may be associated with vomiting, which reduces the absorption of oral and orodispersible medication, and some of the dose of nasally administered drugs; an antiemetic should therefore be considered. Patients should be warned of the risk of medication-overuse headache.

SIGN recommends several options for first-line acute treatment and lists the number needed to treat (NNT) for the outcome of pain free at two hours in patients with moderate to severe pain compared with placebo (see Table 1). Aspirin might be slightly more effective at 24 hours (NNT=6.6 for a dose of 1000mg) than after two hours (NNT=8.1 at a dose of 900–1000mg); it has similar efficacy to sumatriptan 50mg, but sumatriptan 100mg is more effective than aspirin and metoclopramide combined. Aspirin also improves associated symptoms such as nausea, vomiting, photophobia and phonophobia. However, it is contraindicated during the third trimester of pregnancy.

Table 1. Number needed to treat (NNT) for acute migraine therapies to achieve an outcome of pain free at two hours in patients with moderate to severe pain, compared with placebo. Reproduced from: SIGN 155. Pharmacological Management of Migraine. February 2018.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple analgesics</td>
<td></td>
</tr>
<tr>
<td>Aspirin 900mg or 1000mg</td>
<td>8.1</td>
</tr>
<tr>
<td>Diclofenac potassium 50mg</td>
<td>8.9</td>
</tr>
<tr>
<td>Ibuprofen 400mg</td>
<td>7.2</td>
</tr>
<tr>
<td>Ibuprofen 200mg</td>
<td>9.7</td>
</tr>
<tr>
<td>Naproxen 500mg or 825mg</td>
<td>11.1</td>
</tr>
<tr>
<td>Paracetamol 1000mg</td>
<td>12.2</td>
</tr>
<tr>
<td>Oral triptans</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan 50mg</td>
<td>6.1</td>
</tr>
<tr>
<td>Sumatriptan 100mg</td>
<td>4.7</td>
</tr>
<tr>
<td>Zolmitriptan 5mg</td>
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<td>Zolmitriptan 2.5mg</td>
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<td>Nasal triptans</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan 20mg</td>
<td>4.7</td>
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<td>Zolmitriptan 5mg</td>
<td>3.0</td>
</tr>
<tr>
<td>Subcutaneous triptans</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan 6mg</td>
<td>2.3</td>
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<tr>
<td>Combination therapy</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan 50–85mg and naproxen 500mg</td>
<td>4.9</td>
</tr>
</tbody>
</table>
**Diagnosis**
- Consider migraine in any patient presenting with episodic disabling headache
- Patients with episodic disabling headache superimposed on a background of daily or near daily headache are likely to have chronic migraine
- Always ask about acute medication use. If required for more than 2 days a week consider whether there may be medication overuse headache. Headache diaries can help

**Acute therapy**
Avoid opiates and restrict acute medication to 2 days a week
- Simple analgesics: aspirin 900mg or ibuprofen 400–600mg
- Triptans:
  - sumatriptan 50–100 mg is first choice
  - all oral triptans are gastrically absorbed, so may not work if the patient is vomiting
  - triptans only work once headache starts
  - general efficacy is to work for 2 out of 3 attacks
- Add antiemetic: metoclopramide 10mg or prochlorperazine 10mg
- Consider nasal zolmitriptan or subcutaneous sumatriptan

**Lifestyle advice**
For patients with migraine, maintaining a regular routine is important, including the following:
- Encourage regular meals, adequate hydration with water, sleep and exercise
- Avoid specific triggers if known
- Consider activities that encourage relaxation such as mindfulness, yoga or meditation

**Preventative therapy**
- Consider if migraine is disabling and reducing quality of life, eg frequent attacks (>1 per week on average) or prolonged severe attacks
- Which medication to try first depends on patient co-morbidities, other health issues, drug interactions and patient preference
- Anticonvulsants should be avoided in women who may become pregnant
- Start at low dose and gradually increase according to efficacy and tolerability
- Good response is a 50% reduction in severity and frequency of attacks
- Treatment failure is a lack of response to the highest tolerated dose used for 3 months

**Therapies**
- Propranolol: target dose 80mg twice a day
- Topiramate: target dose 50mg twice a day (use if propranolol fails)
- Amitriptyline/other TCA: target dose 30–50mg at night
- Candesartan: target dose 16mg daily

**Other options**
- Sodium valproate: target dose 600mg twice a day (avoid in women who may become pregnant)
- Pizotifen: target dose 3–4.5mg (lacking evidence, but widely used)

**Withdrawal**
If the patient responds well to prophylactic treatment, a trial of gradual drug withdrawal should be considered after six months to one year

**Referral to neurology/headache clinic**
Consider referral if three or more therapies have failed

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tomato cardiovascular and cerebrovascular disease. There is little information about the safety of triptans in people over the age of 65 years.

These recommendations for acute treatment are essentially similar to those of NICE, which otherwise suggests a nasal triptan for 12 to 17-year-olds and advises against using an ergot derivative.

**Migraine prevention**

Most of the evidence on prevention is for episodic rather than chronic migraine and SIGN assumes the two forms respond similarly. Reducing migraine headache severity and/or frequency by about one-third to one-half is regarded as a successful outcome. Deciding when to start prophylaxis depends more on how migraine affects the individual than on headache frequency. Again, the risk of medication overuse should be borne in mind.

Prophylaxis should be used for at least three months at the maximum tolerated dose before deciding if it is effective or not. It may be possible to phase out prophylaxis so the need for treatment should be reconsidered every 6–12 months. Migraine without aura may improve during pregnancy and women should aim to stop prophylaxis before conception; this is not the case for migraine with aura.

The drug of first choice for prophylaxis is propranolol 80–160mg daily. It reduces the frequency of episodic migraine by ≥50% compared with placebo (NNT=4) but comparisons with other preventive drugs are inconclusive due to poor quality. Adverse effects causing discontinuation include nausea and diarrhoea. It should also be used with caution in patients with a history of asthma. Propranolol increases blood levels of rizatriptan, which should not be taken within two hours of the beta-blocker and at a dose no greater than 5mg.

The only other drug SIGN recommends for prophylaxis is topiramate 50–100mg daily, which has efficacy similar to that of propranolol in episodic migraine and may reduce frequency by 25% in chronic migraine. However, it may be associated with nausea, paraesthesia, anorexia, weight loss, cognitive effects and depression. Exposure during the first trimester of pregnancy is associated with an increased risk of abnormal oral cleft development and it should not be used by women who are breastfeeding.

Several other drugs come with weaker endorsement. Tricyclic antidepressants and the calcium-channel blocker flunarizine (not licensed in UK but available from specialist headache services) “should be considered” as a prophylactic treatment for patients with episodic or chronic migraine, and valproate and the angiotensin-receptor blocker candesartan “can be considered”.

Given the high risk of fetal malformation and neurodevelopmental disorders associated with valproate and recent regulatory restrictions on its use in women and girls of childbearing potential, it would seem inappropriate for most women. SIGN concludes that there is insufficient evidence to support the use of pizotifen (NICE identified this issue as a research priority, noting that pizotifen is widely used among young people) and advises against using gabapentin or pregabalin. Evidence is lacking for other antiepileptic drugs, ACE inhibitors and the SSRIs, as well as for occipital nerve block. Trials of calcitonin gene-related peptide monoclonal antibody therapy have reported promising results but SIGN is waiting for assessment from regulatory authorities.

Botulinum toxin type A has been accepted for restricted use in NHS Scotland by the Scottish Medicines Consortium for use in adults with chronic migraine in whom at least three oral prophylactic drugs have failed and where medication overuse has been appropriately managed. SIGN endorses this recommendation but advises against its use in patients with episodic migraine, for which there is a lack of evidence of efficacy.

The NICE guideline recommends propranolol or topiramate as options of first choice for the prophylactic treatment of migraine. Its other recommendations are also consistent with SIGN, but more limited in scope, with the exception of acupuncture as an option when topiramate and propranolol are unsuitable or ineffective.

**Prophylaxis of menstrual migraine**

Menstruation may trigger migraine and symptoms may be worse and less responsive to treatment just before and during menstruation. Migraine may only occur between the two days preceding the onset of bleeding and for three days after. In such cases, a perimenstrual strategy can complement or replace standard prophylaxis (though with an increased risk of medication-overuse headache) provided the woman’s menstrual cycle is regular.

SIGN says frovatriptan 2.5mg twice daily should be considered for prophylaxis of perimenstrual migraine, with zolmitriptan 2.5mg three times daily and naratriptan 2.5mg twice daily as alternatives. There is little evidence to support the use of mefenamic acid or NSAIDs. Oestrogen is effective but associated with rebound headache; there is some evidence to support the use of combined oral contraceptives but it is of poor quality. NICE agrees with SIGN’s recommendations for triptans but advises against the routine use of combined oral contraceptives.

**Medication-overuse headache**

Frequent use of acute migraine treatments – at least 10 days per month for triptans and combined formulations and 15 days per month for analgesics – increases the frequency and intensity of headache (though some patients may in fact have poorly treated migraine). Treatment withdrawal increases symptoms but ultimately reduces both the frequency and severity of headache.

There is a lack of evidence to show whether one management strategy is better than another for medication-overuse headache, so SIGN recommends the choice is tailored to the individual, depending on comorbidities. The options are: abrupt withdrawal considering prophylaxis after a delay; abrupt withdrawal with immediate prophylaxis; and beginning prophylaxis without withdrawal. Naproxen is widely used as a transitional treatment but there is a lack of evidence to support this. Prednisolone is not recommended for routine treatment of medication-overuse headache.
NICE is more directive on this issue. It recommends abruptly stopping the overused medication and considering prophylaxis; inpatient withdrawal is not recommended as routine. Both NICE and SIGN warn that opioids should be withdrawn slowly with, NICE adds, specialist referral or inpatient supervision for people using strong opioids.

**Devices for migraine**

SIGN makes no recommendations on the use of devices for migraine prevention because there is too little evidence to support their use. Interventions now undergoing clinical trials include vagus nerve stimulation, transcutaneous supraorbital nerve stimulation and transcranial magnetic stimulation.

**Patient information**

SIGN has also published a patient version of the guideline, translating the recommendations into a form more easily understood by patients and the public. In addition, the main guidance provides a checklist of points that a GP might cover for each step of the patient’s journey; this is supplemented by an algorithm summarising the approach to drug treatment (see Figure 1). The guidance provides links to organisations that can provide further information about migraine and its treatment. SIGN also updated the guidance in May 2018 with the new MHRA Valproate: Contraception and Pregnancy Prevention information card plus a checklist for female patients prior to treatment with valproate, although it advises that the MHRA website should be checked for updated versions.

**Summary**

The new SIGN guideline is essentially similar to the NICE recommendations that preceded it. It provides more information about the evidence behind the various treatment options for migraine, and perhaps more alternatives for second-line treatment, but the main recommendations are much the same. However, it may help to make management both more rational and more patient-focused by defining the initial approach to treatment as stepped or stratified.

**References**


**Declaration of interests**

None to declare.

*Steve Chaplin is a medical writer specialising in therapeutics*