National Medicines Information Centre
ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • www.nmic.ie
VOLUME 24
NUMBER 5
2018

MANAGEMENT OF MIGRAINE

- **Migraine is the most common neurological disorder and a leading cause of disability**
- **Migraine is often underdiagnosed, misdiagnosed and undertreated**
- **The management of migraine is complex and needs to be individualised to the patient**
- **Preventive therapy should be considered for patients with frequent attacks that interfere with their quality of life and cause at least moderately severe disability**

INTRODUCTION

Migraine is a common primary headache disorder, typically characterised by recurrent episodes of head pain with associated neurological, gastrointestinal and autonomic symptoms, alone or in combination.[1-3] Migraine attacks are usually preceded by a prodromal phase and up to 30% of patients with migraine experience aura (transient focal neurological symptoms).[4] It is most prevalent between the ages of 15 and 49 years, and has been reported to affect 10% of school-aged children.[1-6] The incidence of migraine is roughly equal in males and females prior to puberty, and is strongly associated with abdominal pain in childhood.[1,7] However, it increases significantly in females following puberty.[3,8,8] Migraine is three times more common in females, with a lifetime prevalence of 43% in females.[10] **Migraine is a leading cause of disability worldwide**; the WHO Global Burden of Diseases (2016) study ranks migraine as the second most common cause of disability worldwide for non-fatal conditions, and the first in those aged <50 years.[11,12] **Migraine has a considerable impact on quality of life and is a substantial burden on the entire family unit.**[1,3,5] It is associated with an increased risk of other disorders including fibromyalgia, anxiety, depression, ischaemic stroke (particularly in migraine with aura) and cardiovascular disease.[1,3,5,13] **Migraine is often underdiagnosed, misdiagnosed (e.g. tension-type headache and sinusitis) and undertreated in both primary and secondary care.**[1,8,12]
This bulletin will outline the current management options for migraine.

PATHOPHYSIOLOGY

Migraine is a complex neurological disorder involving neurons in cortical, subcortical and brainstem areas that regulate autonomic, affective, cognitive and sensory functions.[1,4,9] The **prodromal phase,** which may occur up to 3 days before the headache, involves regions including the hypothalamus and brainstem nuclei.[1,14] The **aura phase** in migraine is associated with cortical spreading depression (CSD),[1,14] which is accompanied by alterations in regional cerebral blood flow.[9,14] The **headache phase** involves activation of trigeminal sensory pathways, which convey nociceptive information from the meninges to central areas of the brain and subsequently to the cortex.[1,14] The neuropeptide **calcitonin gene-related peptide (CGRP)** is increased in patients with migraine and is believed to activate a number of these pathways.[14] The underlying **cause of migraine is not completely understood**; however genetic and environmental factors are thought to play a role.[4,14] Many patients have first-degree relatives who also suffer from migraine.[4,9,14] **Triggers for migraine attacks include stress, female hormonal changes, change in lifestyle (e.g. skipped meals, lack of sleep), strong odours (e.g. perfumes, paints), environmental factors (e.g. bright light, weather), caffeine intake, excessive alcohol, and medications (including oral contraceptives and nasal decongestants).**[5,15,16] Migraine attacks are more common before, and during the first 3 days, of the menstrual cycle;[5] it is thought that the drop in oestrogen during the luteal phase is associated with triggering migraine.[10]

CLASSIFICATION

The International Classification of Headache Disorders (ICHD) has established diagnostic criteria for migraine; the most recent version (ICHD-3) was published in 2018.[2]
Migraine has two major subtypes, as shown in table 1; a) **migraine without aura** which is characterised by headache and associated symptoms and b) **migraine with aura** which is characterised by transient focal neurological symptoms that usually precede or sometimes accompany the headache.[2]

Table 1: Diagnostic criteria for migraine[2]

Migraine without aura	Migraine with aura
A. At least five attacks fulfilling criteria B-D (see below) B. Headache attacks lasting 4 to 72 hours (when untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: a. Unilateral location b. Pulsating quality c. Moderate or severe pain intensity d. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) D. During headache at least one of the following: a. Nausea and/or vomiting b. Photophobia and phonophobia E. Not better accounted for by another diagnosis	A. At least two attacks fulfilling criteria B and C (see below) B. One or more of the following reversible aura symptoms: a. Visual b. Sensory c. Speech and/or language d. Motor e. Brainstem f. Retinal C. At least three of the following six characteristics: a. At least one aura symptom which spreads gradually over ≥5 minutes b. Two or more symptoms occurring in succession c. Each individual aura symptom lasts 5 to 60 minutes d. At least one aura symptom which is unilateral e. At least one aura symptom which is positive f. The aura is accompanied or followed within 60 minutes by headache D. Not better accounted for by another headache diagnosis and transient ischaemic attack has been excluded

Migraine may be **episodic,** defined as headache occurring on <15 days per month, or **chronic** which is headache (migraine-like or tension-type) occurring on ≥15 days per month for >3 months, with features of migraine on at least 8 days per month.[1,2,5] **Chronic migraine is associated with more significant disability and a greater use of healthcare resources than episodic migraine.**[1]

CLINICAL FEATURES

Prodromal symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness/pain and may occur up to 3 days before the migraine and persist during and after the attack.[1,2,5] **Migraine aura** may occur before, during or in the absence of headache, usually lasting up to 60 minutes.[1,2] **Visual aura is the most common type of aura** (occurring in over 90% of patients) and may present as unformed flashes of light, partial loss of vision (scotoma) or fortification phenomena.[1,2,10] Sensory disturbances are the next most frequent aura. This includes paraesthesiae (e.g. numbness or tingling), moving from a point of origin and affecting a greater or smaller part of one side of the body, face and/or tongue; they usually occur in association with a visual aura.[1,2,5] Speech disturbances are less frequent aura presentations,[1,2,5] and symptoms that are thought to reflect brainstem dysfunction (e.g. vertigo, dysarthria, ataxia and diplopia) can also occur.[1,4] Hemiplegic migraine is a rare subtype of migraine which is associated with motor deficits.[1] Many patients who experience migraine with aura may also have attacks of migraine without aura.[2]

Migraine headaches are classically described as severe, unilateral (60%), throbbing (50%) and aggravated by physical activity (90%). However, they may also be moderate, bilateral (especially in children and adolescents) and constant in quality.[1,2,5] The headache can occur anytime and may involve any part of the head (including the posterior cervical region). It may be accompanied by neck pain and typically reaches peak intensity after 1 hour and has a median duration of 24 hours.[1] **Additional features of migraine**, which may assist diagnosis, include photophobia (94%), phonophobia (91%), dizziness (72%), cutaneous allodynia (70%) and gastrointestinal symptoms (e.g. nausea, vomiting and diarrhoea).[1,2,5] Patients may also experience a **postdromal phase** (e.g. fatigue) following the headache.[17]

Medication overuse and medication-overuse headache (MOH) are complications of migraine and typically occur in patients who experience frequent attacks; at least 50% of people with chronic migraine overuse acute medications.[1,8] **MOH is defined as headache occurring on ≥15 days per month developing as a consequence of regular overuse of acute headache medication** (combination analgesics, opioids or triptans on ≥10 days/month or paracetamol or non-steroidal anti-inflammatory drugs [NSAIDs] on ≥15 days/month) for >3 months.[2,18] **Patients with migraine should be counselled about the risk of medication overuse and MOH, which usually resolves after the overuse has stopped.**[2,8]

DIAGNOSIS

Migraine is the most common diagnosis in patients who present with headache to primary care physicians. However, it is underdiagnosed and often misdiagnosed. It should be carefully considered in patients presenting with recurrent moderate/severe headaches with normal neurological findings, after secondary causes are excluded.[18] **History and physical examination** are usually sufficient to make a diagnosis of migraine; completion of patients' diaries should be included in the assessment.[19] Table 2 summarises aspects to consider when assessing a patient presenting with a headache for the first time or for those who have a change in headache pattern.[18] In general, neuroimaging is not required for patients with migraine,[15,18] however, brain imaging with MRI is generally indicated for patients with aura.[20]

Table 2: Assessment of patient with headache[18]

Clinical history should include details of:*	Physical examination should include:
• headache onset (e.g. thunderclap, head or neck trauma), previous attacks, duration of attacks • pain location (e.g. unilateral, bilateral, associated neck pain) • headache-associated symptoms (e.g. nausea, vomiting, photophobia) • relationship of headache attacks to precipitating factors • headache severity and effect on work and family activities • acute and preventive medications tried • the presence of coexistent conditions that might influence treatment (e.g. insomnia, depression, anxiety, hypertension, asthma and history of heart disease or stroke)	• blood pressure measurement • neck examination (e.g. posture, range of movement and palpation for muscle tender points) • a screening neurological examination with: ○ assessment of mental status, cranial nerve examination (e.g. fundoscopy, pupils, eye movements, visual fields, evaluation of facial movements for asymmetry and weakness) • assessment for limb weakness and reflex asymmetry • assessment of gait • examination for temporomandibular disorders if indicated by associated jaw complaints

*history should include site, radiation, character, severity, duration and frequency, aggravating and relieving factors and associated phenomena[17]

Referral for further assessment and investigations including MRIs should be considered if a patient has signs suggestive of secondary causes of headache – see table 3.[18]

Table 3: Red flag features as potential indicators of secondary headache[18]

Emergency (address immediately)	Urgent (address within hours to days)	Other possible indicators of secondary headache (less urgent) include:
Thunderclap onset Fever and meningismus Papilloedema with focal signs or reduced level of consciousness Acute glaucoma	Temporal arteritis Papilloedema without focal signs or reduced level of consciousness Relevant systemic illness Elderly patient: new headache with cognitive change	Unexplained focal signs Atypical headaches Unusual headache precipitants and/or aura symptoms Onset after aged 50 years Aggravation by neck movement Jaw symptoms

MANAGEMENT

The management of migraine includes non-pharmacological management including conservative strategies (e.g. lifestyle changes), non-pharmacological therapies and pharmacological management.

NON-PHARMACOLOGICAL MANAGEMENT

Most headache experts advocate **lifestyle modifications** in order to improve or prevent migraine. The general advice is to: 1) reduce stress, 2) avoid skipping meals, 3) reduce caffeine, 4) get adequate sleep and 5) exercise regularly.[5] Patients should be educated to **recognise prodromal migraine symptoms** so that they can initiate treatment as soon as pain begins or just before.[5] **Patients should be encouraged to keep a headache diary** in order to: 1) record the frequency, duration, severity of the headaches, and any associated symptoms (including aura symptoms), 2) identify possible triggers and 3) assess the effectiveness of headache interventions (including prescribed and over the counter medications).[17,19] **The education of patients with frequent migraine attacks about the potential for medication overuse and MOH** is important, including advice to minimise overuse of simple analgesics.[1,5,7,58] Non-pharmacological therapies including **cognitive behavioural therapy (CBT) and acupuncture may be beneficial in migraine prevention**.[20-22]

PHARMACOLOGICAL MANAGEMENT

Pharmacological management of migraine includes both acute and preventive medications.

Acute pharmacological management of migraine

Practical aspects to consider: the objectives of acute treatment are to: 1) treat attacks early, 2) achieve quick, complete pain relief and 3) reduce the incidence of adverse events.[1,5,23] **Acute migraine medication should be used no more than 6 to 8 days per month in order to avoid medication overuse.**[17] The treatment needs to be individualised to the patient. Patients may choose **a stepped-care approach** by first using simple analgesics (e.g. aspirin or ibuprofen) and stepping up to a migraine-specific medication (e.g. triptans) if the pain progresses, or **a stratified approach** to use simple analgesics for mild headaches and migraine-specific medication for moderate to severe pain.[1,8,24] Patients with **moderate to severe headaches** may require a combination of acute medications with different mechanisms of action; for example there is evidence that combining sumatriptan with naproxen provides greater efficacy than using either drug alone.[24] The addition of an antiemetic should be considered even in the absence of nausea and vomiting.[19] A non-oral route of administration (e.g. nasal sumatriptan, rectal diclofenac) may be beneficial for patients awakened by moderate to severe attacks or whose pain peaks rapidly (i.e. within 30 minutes) and for those with nausea or vomiting during the prodromal phase or early during the attack.[1,17] **Routine use of codeine-containing analgesics or opioids (including tramadol) should be avoided due to the high incidence of adverse events, the risk of dependence and tolerance, and the risk of developing MOH.**[1,8,17,19]

Acute pharmacotherapy

This includes both simple analgesics (e.g. NSAIDs and paracetamol) and migraine-specific medicines such as the triptans. Antiemetics (which also have prokinetic effects) are also used for the relief of associated symptoms such as nausea. **Prescribers should refer to the Summary of Product Characteristics for full prescribing information including doses, contraindications, adverse effects and drug interactions**.

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen, naproxen and diclofenac are effective in relieving migraine pain.[25,26] Aspirin has relatively rapid absorption[24] and the efficacy is improved by combining it with an antiemetic such as metoclopramide.[8] Ibuprofen and naproxen have also been shown to be effective in relieving migraine-associated symptoms including nausea, photophobia and phonophobia.[8] NSAIDs are generally recommended as a first-line option.[8] Caution is advised in patients with conditions including uncontrolled hypertension, cardiovascular disease (CVD) and patients with risk factors for CVD; aspirin should not be used in patients <16 years.[8,27] Adverse events include gastric irritation.

Paracetamol is also effective in relieving pain in acute migraine and is generally considered effective for attacks of mild to moderate severity.[24] The efficacy is increased when used in combination with an antiemetic.[8,28] A recent review found that a combination of paracetamol 1,000mg plus metoclopramide 10mg had similar efficacy to sumatriptan 100mg at 2 hours.[8,24] **Paracetamol is recommended as treatment for patients with acute migraine who are unable to take other acute therapies.**[8,28]

Triptans are highly selective 5-HT_{1B} and 5-HT_{1D} receptor agonists.[1,24] The triptans currently available in Ireland include sumatriptan (of note the 50mg formulation is now available as pharmacy only), zolmitriptan, frovatriptan, eletriptan, almotriptan and naratriptan.[29-36] Evidence has shown that triptans are effective for acute migraine, including migraine associated with menstruation.[19,24] Triptans are recommended as a first-line option, unless contraindications exist;[1,8,37] contraindications include history of myocardial infarction, cerebrovascular disease, uncontrolled hypertension and use of monoamine oxidase inhibitors.[29-36] Triptans are generally recommended at the start of the headache phase of a migraine attack;[15,22] **there is increasing evidence of greater efficacy when triptans are taken when the pain is mild**.[15,22] **Individual patients respond to different triptans in profoundly different ways** in terms of effectiveness for pain relief and adverse effects.[1,8,24] In patients with severe acute migraine or early vomiting, nasal or subcutaneous (currently not licensed in Ireland) sumatriptan should be considered.[1,8,38,39] If nausea is mild, orodispersible formulations (e.g. zolmitriptan) may be helpful.[24] Adverse events include flushing and sensations of heaviness; these are usually transient affecting any part of the body including the chest and throat.[29-36]

Antiemetics such as prochlorperazine or metoclopramide (oral or parenteral formulations) are used for the treatment of migraine headache, usually in combination with simple analgesics. They are also recommended for patients presenting with migraine associated symptoms of nausea or vomiting.[8] Metoclopramide should not be used regularly due to the risk of extrapyramidal side effects;[8] a minimum of 6 hours between administrations is required.[40]

Preventive pharmacological management of migraine

Practical aspects to consider: The decision about when to start preventive therapy for migraine should be made on an individual basis and is best guided by establishing the impact of migraine on the individual patient.[5,8] Most experts recommend that it should be considered when migraine symptoms occur on at least 8 to 10 days per month and cause at least moderate disability to the patient.[1,17] **Preventive therapy should be considered for individuals whose attacks interfere with their quality of life**, despite appropriate use of acute medications and lifestyle modification strategies, or if contraindications, treatment resistance or adverse events preclude the use of effective acute medications.[1] A patient's medical co-morbidities should be considered and the aim should be to use a single medication that may treat multiple disorders if possible.[17] When starting preventive treatment, a low dose should be used and the dose gradually increased every 2 to 8 weeks; patients should be given an adequate trial for 2 to 3 months at the maximum tolerated dose, and the need for continued therapy reassessed, with the help of a migraine diary after 3 to 6 months.[8,17,19] Adverse effects are common for most of the preventive treatments and adherence to treatment is generally poor.[1,5]

Preventive pharmacotherapy

Antiepileptic drugs (AEDs) including topiramate and valproate have been shown to reduce migraine frequency by approximately 50%.[41,42] **Topiramate (licensed for migraine prevention) is associated with teratogenic effects**. Approximately 50% of pregnancies are unplanned,[43] therefore appropriate contraception is advised in women of childbearing potential (of note, topiramate is an enzyme inducer and may affect the efficacy of oral contraceptives).[44] Current guidelines recommend that patients who have migraine with aura should not use combined hormonal contraceptives in view of the increased risk of ischaemic stroke.[20,45-49] **Valproate, which is not licensed for migraine, should be absolutely avoided for migraine prophylaxis in women of childbearing potential** in view of the high risk of serious developmental disorders and congenital malformations associated with its use.[17,42,50] There is a lack of evidence to support the use of

other AEDs including pregabalin, gabapentin, lamotrigine and oxcarbazepine for migraine prevention.[51,52]

Antidepressants: Tricyclic antidepressants, in particular amitriptyline (and nortriptyline), have been shown to reduce migraine frequency by up to 50% (in particular, in patients with higher headache frequencies) and are recommended as an option for migraine prevention.[8,17,53] Adverse effects include weight gain and drowsiness. The evidence is not robust to support the use of selective serotonin reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors for migraine prevention.[17,54] One study found venlafaxine had similar efficacy to amitriptyline (with less adverse effects) and it may be useful for patients with depression and migraine.[1,17,18]

Antihypertensives are also used for migraine prevention. ***Beta blockers*** including propranolol, metoprolol and atenolol have been shown to reduce the frequency of episodic migraine by up to 50%, although the individual trials are rated of low quality and short duration (<3 months).[8] Propranolol and metoprolol are authorised for prevention of migraine.[55,56]

Angiotensin II receptor blockers (e.g. candesartan – unauthorised indication) and ***angiotensin-converting enzyme inhibitors*** (e.g. lisinopril – unauthorised indication) have also shown some benefit in migraine prevention, however the evidence base is small.[1,8,18] Candesartan is widely used in practice;[17] a small study showed it to have similar efficacy to propranolol.[8,17,57] ***Calcium-channel blockers*** including flunarizine and verapamil (unauthorised indication) have been shown to have some benefit in migraine prevention.[8] Flunarizine seems to have similar efficacy to propranolol and topiramate,[8] and is usually helpful in hemiplegic migraine.[17] Adverse effects include weight gain, depression and insomnia.[58]

Pizotifen (a serotonin antagonist) is long-established and widely used in migraine prevention.[22,27] There is insufficient evidence to support its use;[22,27] adverse effects include weight gain.[59]

Other preventive therapies

For women with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, use of a long acting triptan (such as naratriptan or frovatriptan, unauthorised for this indication) on the days that migraine is expected (total of 3 to 5 days) may be considered as preventive therapy.[8,10,17,19] In specialist centres, **greater occipital nerve (GON) blocks** are also used to reduce the frequency of migraine headaches in patients with chronic migraine.[8,17,22] **Botulinum toxin A** has been shown to **reduce migraine frequency in patients with chronic migraine,**[60] but it is not effective for episodic migraine.[8] It should only be administered in specialist centres with expertise in its use[8,61] and in patients who have failed to respond to ≥3 preventive therapies.[8] There is limited evidence to support the use of non-prescription items including riboflavin, coenzyme Q10 and magnesium for migraine prevention and further evidence is required.[5,17,22]

Emerging therapies: The role of calcitonin gene-related peptide (CGRP) in the pathogenesis of migraine has led to the development of monoclonal antibodies targeting CGRP.[1] Subcutaneously administered CGRP antibodies targeting the peptide or its receptor have been shown to be efficacious for the prevention of episodic and chronic migraine in pivotal trials.[1,8] **Erenumab** is the first monoclonal antibody to target the CGRP pathway authorised in the EU for the prevention of episodic and chronic migraine (currently not reimbursed in Ireland).[62,63]

SUMMARY

Table 4 summarises the management of migraine. **The Irish College of General Practitioners (ICGP)** is currently in the process of publishing a Quick Reference Guide (QRG) on "Migraine: Diagnosis and Management from a GP Perspective".[17] In addition, the Migraine Association of Ireland have information for patients and healthcare professionals on their website (www.migraine.ie).

Table 4: Summary of management of migraine[8,17]

Diagnosis of migraine
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 and consider the possibility of MOH
Consider the use of headache diaries

↓ ↓

Non-pharmacological therapy
Manage stress appropriately
Patients should be encouraged to maintain a regular routine including:
- Regular meals and adequate hydration with water, regular sleep and exercise, caffeine reduction
- Avoidance of specific triggers if known

Recommend activities that encourage relaxation (e.g. mindfulness, yoga or meditation)
Consider CBT and acupuncture

↓ ↓

Acute therapy	**Preventive therapy**
Restrict medication to 1 to 2 days a week (**avoid opioids**) Simple analgesics: aspirin or ibuprofen Triptans (all oral triptans are gastrically absorbed, therefore may not work if patient is vomiting; consider nasal sumatriptan or orodispersible zolmitriptan) Triptans only work once headache starts Early or persistent vomiting (or no vomiting) • Add antiemetic – metoclopramide or prochlorperazine No response to acute therapy • Try other triptans • Try triptan and NSAID combinations	Consider if the migraine is impacting on the patient's lifestyle • Topiramate • Amitriptyline • Beta blockers – propranolol or metoprolol • Flunarizine • Pizotifen • Candesartan* Consider specialist referral to neurology/headache clinic if 3 or more therapies have failed If the patient responds well to prophylactic treatment a trial of gradual drug withdrawal should be considered after 6 months to one year

MOH – medication overuse headache; CBT – cognitive behavioural therapy; NSAID – non-steroidal anti-inflammatory drug
*not authorised for migraine prevention

List of references available on request. Date of preparation: Nov 2018

Migraine – final references Vol.24 .No.5 2018

1. Dodick D, Migraine, Lancet 2018;391:1315-30
2. Headache Classification Committee of the International Headache Society, The International Classification of Headache Disorders, 3rd edition, Cephalgia 2018;38(1):1-211, downloaded from http://www.ihs-headache.org/ichd-guidelines on the 16th October 2018
3. Adelborg K et al, Migraine and risk of cardiovascular diseases: Danish population based matched cohort study, BMJ 2018;360:k96
4. Burstein R et al, Migraine: multiple processes, complex pathophysiology, Journal of Neuroscience 2015;35(17):6619-6629
5. Charles A, Migraine, NEJM 2017;377:553-61
6. Steiner TJ et al, Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain 2018;19(1):17-018-0846-2
7. Angus-Leppan H et al, Abdominal migraine, BMJ 2018;360:k179
8. SIGN 155: Pharmacological management of migraine February 2018 downloaded from www.sign.ac.uk on the 13th September 2018
9. Goadsby T, Migraine pathophysiology, Headache 2005;45 [Suppl 1]:S14-S24
10. Todd C et al, Women and migraine: the role of hormones, Current Neurology and Neuroscience Report 2018;18:42 (1-6)
11. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators*, Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet 2017;390:1211-1259
12. Steiner T et al, Editorial: migraine is the first cause of disability in under 50s: will health politicians now take notice? The Journal of Headache and Pain 2018;19:17 (1-4)
13. Mahmoud A et al, Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1,152,407 subjects, BMJ Open 2018;8:e020498
14. Dodick D, A phase by phase review of migraine pathophysiology, Headache 2018;58:4-16
15. BASH, Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type headache, cluster headache, medication-overuse headache, 3rd Edition (1st revision) 2010, British Association for the Study of Headache accessed 23rd October 2018
16. Kelman L, The triggers or precipitants of the acute migraine attack, Cephalalgia 2007;27:394-402
17. Kearney M, Ruttledge M, Tomkins E, Migraine: Diagnosis & Management from a GP perspective (Quick Reference Guide), Quality in Practice Committee, Irish College of General Practitioners, available on www.icgp.ie (date of publication to be confirmed)
18. Becker W et al, Clinical Review: guideline for primary care management of headache in adults, Canadian Family Physician 2015;61:670-679
19. NICE Clinical guideline: Headaches in over 12s: diagnosis and management, published 19 September 2012 available on www.nice.org.uk/guidance/cg150 (accessed 26th September 2018)
20. Mitsikostas D et al, European headache federation consensus on technical investigation for primary headache disorders, The Journal of Headache and Pain 2016;17:5 DOI. 10.1186/s10194-016-0596-y / SIGN 107: Diagnosis and management of headache in adults, November 2008 downloaded from www.sign.ac.uk on the 27th September 2018
21. Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, Vickers A, White AR, Acupuncture for the prevention of episodic migraine, Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD001218. DOI:10.1002/14651858.CD001218.pub3
22. Sinclair A et al, Headache management: pharmacological approaches, Pract Neurol 2015;15:411-423`

23. Silberstein S, Current management: migraime headache, CNS Spectrums 2017;22:4-12
24. Becker W, Acute migraine treatment in adults, Headache 2015;55:778-793
25. Rabbie R, Derry S, Moore RA, Ibuprofen with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD008039. DOI:10.1002/14651858.CD008039.pub3
26. Derry S, Rabbie R, Moore RA, diclofenac with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD008783. DOI:10.1002/14651858.CD008793.pub3
27. British National Formulary: treatment of migraine, downloaded from www.medicinescomplete.com on the 23rd October 2018
28. Derry S, Moore RA, Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD008040. DOI:10.1002/14651858.CD008040.pub3
29. SmPC Imigran® (sumatriptan) downloaded from www.hpra.ie September 2018
30. SmPC Imigran® Nasal Spray (sumatriptan) downloaded from www.hpra.ie September 2018
31. SmPC Zomig® (zolmitriptan) downloaded from www.hpra.ie September 2018
32. SmPC Frovex® (frovatriptan) downloaded from www.hpra.ie September 2018
33. SmPC Relpax® (eletriptan) downloaded from www.hpra.ie September 2018
34. SmPC Almogran® (almotriptan) downloaded from www.hpra.ie September 2018
35. SmPC Naraverg® (naratriptan) downloaded from www.hpra.ie September 2018
36. SmPC (sumatriptan 50mg) downloaded from www.hpra.ie September 2018
37. Derry CJ, Derry S, Moore RA, Sumatriptan (oral route of administration) for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008615. DOI:10.1002/14651858.CD008615.pub2
38. Derry CJ, Derry S, Moore RA, Sumatriptan (subcutaneous route of administration) for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD009665. DOI:10.1002/14651858.CD009665
39. Derry CJ, Derry S, Moore RA, Sumatriptan (intranasal route of administration) for acute migraine headaches in adults. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD009663. DOI:10.1002/14651858.CD009663
40. SmPC metoclopramide downloaded from www.hpra.ie October 2018
41. Linde M, Mulleners WM, Chronicle EP, McCrory DC, Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010610. DOI:10.1002/14651858.CD010610
42. Linde M, Mulleners WM, Chronicle EP, McCrory DC, Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010611. DOI:10.1002/14651858.CD010611
43. Centre for Maternal and Child Enquiries, Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006-2008, BJOG 2011;118 (Suppl 1)
44. SmPC Topamax® (topiramate) downloaded from www.hpra.ie September 2018
45. Faculty of Sexual and Reproductive Healthcare Clinical Guidance, UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2016), downloaded from www.fsrh.org/ on the 26th November 2018
46. John Guillebaud and Anne MacGregor, Contraception – your questions answered, Seventh Edition, Published by Elsevier 2017
47. SmPC Marviol downloaded from www.hpra.ie on the 26th November 2018
48. SmPC Yasmin downloaded from www.hpra.ie on the 26th November 2018
49. Summary chart of US medical eligibility criteria use for contraceptive use (updated 2017) downloaded from https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf on the 26th November 2018

50. Vatzaki E et al, Latest clinical recommendations on valproate use for migraine prophylaxis in women of childbearing age: overview from European Medicines Agency and European Headache Federation, Journal of Headache and Pain 2018;19:68
51. Linde M, Mulleners WM, Chronicle EP, McCrory DC, Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010609. DOI:10.1002/14651858.CD010609
52. Linde M, Mulleners WM, Chronicle EP, McCrory DC, Antiepileptics other than gabapentin, pregabalin, topiramate and valproate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD010608. DOI:10.1002/14651858.CD010608
53. SmPC amitriptyline downloaded from www.hpra.ie September 2018
54. Banzi R, Cusi C, Randazzo C, Sterzi R, Tedesco D, Moja L, Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for the prevention migraine in adults. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD002919. DOI:10.1002/14651858.CD002919.pub3
55. SmPC Beta-Prograne® (propranolol) downloaded from www.hpra.ie September 2018
56. SmPC Metocor® (metoprolol) downloaded from www.hpra.ie September 2018
57. Stovner LJ et al, A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study, Cephalalgia 2014 June;34(7):523-532.
58. SmPC Sibelium® (flunarizine) downloaded from www.hpra.ie September 2018
59. SmPC sanomigran® (pizotifen) downloaded from www.hpra.ie September 2018
60. Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, Clarke CE, Sincalir A, Botulinum toxins for the prevention migraine in adults. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD011616. DOI:10.1002/14651858.CD011616.pub2
61. SmPC Botox® downloaded from www.hpra.ie September 2018
62. SmPC Aimovig® (erenumab) downloaded from www.hpra.ie October 2018
63. National Centre for Pharmacoeconomics website re Aimovig® www.ncpe accessed September 2018