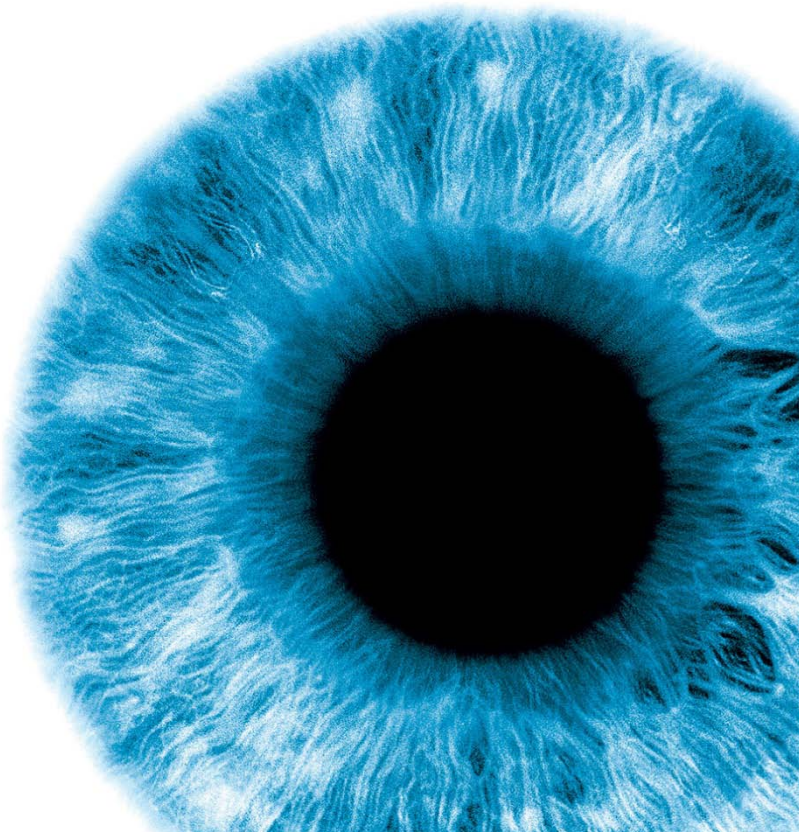
NICE National Institute for Health and Care Excellence

Headaches

Evidence Update October 2014

A summary of selected new evidence relevant to NICE clinical guideline 150 'Diagnosis and management of headaches in young people and adults' (2012)

Evidence Update 67



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Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

[1] **Headaches. NICE clinical guideline 150 (2012)**

A search was conducted for new evidence from 13 March 2012 to 26 March 2014. A total of 7782 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 31 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group (EUAG), which advised on the final list of 13 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base. A final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 150 (NICE CG150). For further information about the review decision see the NICE CG150 webpage. The process of updating NICE guidance is separate from the process of both an Evidence Update and the review proposal.

See the NICE clinical guideline development methods for further information about updating clinical guidelines.

NICE Pathways

NICE pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathways cover advice and recommendations related to this Evidence Update:

- Headaches. NICE Pathway

Quality standards

- Headaches in young people and adults. NICE quality standard 42

[1] NICE-accredited guidance

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE clinical guideline 150 (NICE CG150). Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG150.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Management		
Acute treatment of migraine in children and young people		
• In children and young people aged 12–17 years with migraine, oral triptans[2], with or without a non-steroidal anti-inflammatory drug (NSAID), are more effective than placebo at eliminating migraine pain at 2 hours.		✓
Pharmacological prophylaxis of migraine with antiepileptics in adults		
• Regular prophylactic treatment with topiramate[3] is more effective than placebo at reducing headache frequency in adults with episodic migraine.		✓
• Gabapentin[4] and gabapentin enacarbil[5] are no better than placebo for prophylactic treatment of migraine in adults and are commonly associated with adverse events.	✓*	
• Sodium valproate[5] and valproate semisodium[5] are effective preventive treatments to reduce headache frequency in adults with episodic migraine.		✓
Pharmacological prophylaxis of migraine with other drugs in adults		
• Angiotensin-inhibiting drugs and beta-blockers may be effective options for reducing migraine frequency.	✓*	

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update the guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.

[2] At the time of publication of this Evidence Update, triptans (except nasal sumatriptan) did not have UK marketing authorisation for acute treatment of migraine in children and young people aged under 18 years. Informed consent should be obtained and documented.
[3] At the time of publication of this Evidence Update, topiramate did not have UK marketing authorisation for migraine prophylaxis in children and young people aged under 18 years. Informed consent should be obtained and documented.
[4] At the time of publication of this Evidence Update, gabapentin did not have UK marketing authorisation for migraine prophylaxis. Informed consent should be obtained and documented.
[5] At the time of publication of this Evidence Update, gabapentin enacarbil, sodium valproate and valproate semisodium did not have UK marketing authorisation for migraine prophylaxis and were not considered for NICE CG150.

Key point	Potential impact on guidance: Yes	Potential impact on guidance: No
Pharmacological prophylaxis of migraine in children and young people		
• Limited evidence suggests that prophylactic use of topiramate and trazodone hydrochloride[6] reduces headache frequency in children and young people with episodic migraine, whereas other commonly used drugs, including propranolol, may not be effective.		✓
Non-pharmacological prophylaxis of migraine in children and young people		
• Intensive cognitive behavioural therapy plus amitriptyline[6] is more effective at reducing headache frequency than headache education plus amitriptyline in young people aged 10–17 years with severe chronic migraine.		✓
Treatment of migraine during pregnancy		
• Triptan use during pregnancy is not associated with miscarriage, stillbirth or congenital malformations.		✓
Medication overuse headache		
• Prophylaxis with prednisone[7] or prednisolone[7] during the first few days after headache medication withdrawal is not effective at reducing headache in people with medication overuse headache.		✓
• Inpatient treatment is more effective than outpatient treatment or education alone at achieving medication withdrawal in people with migraine and complicated medication overuse headache.		✓

[6] At the time of publication of this Evidence Update, trazodone hydrochloride and amitriptyline did not have UK marketing authorisation for prophylaxis of migraine in children and young people aged under 18 years, and were not considered for NICE CG150.

[7] At the time of publication of this Evidence Update, prednisone and prednisolone did not have UK marketing authorisation for prophylaxis of medication overuse headache in children and young people aged under 18 years, and were not considered for NICE CG150.

1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from NICE clinical guideline 150 (NICE CG150).

1.1 Assessment

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 Diagnosis

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.3 Management

Acute treatment of migraine in children and young people

NICE CG150 recommends that adults and young people aged 12 years and over who have migraine with or without aura should be offered acute treatment, taking into account the person's preference, comorbidities and risk of adverse events. Combination therapy with an oral triptan[8] and a non-steroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, should be offered first. For young people aged 12–17 years, a nasal triptan should be considered in preference to an oral triptan.

For people who prefer to take only 1 drug, monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol should be considered for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. Because of an association with Reye's syndrome, preparations containing aspirin should not be offered to people aged less than 16 years.

Ho et al. (2012) and **Derosier et al. (2012)** both assessed the efficacy and safety of oral triptans, with or without an NSAID, for acute treatment of migraine in children and young people. Both used a placebo run-in stage to identify and exclude people whose migraine responded to placebo, because placebo response rates are typically high in patients with paediatric migraine.

The randomised, controlled, double-blind trial by Ho et al. (2012) investigated the efficacy and safety of oral rizatriptan[8] for acute treatment of migraine in children and young people aged 6–17 years. People who had a history of migraine that did not respond to NSAIDs or paracetamol were recruited from 191 sites in the USA, Europe, India and Canada.

In stage 1, eligible patients were randomised to placebo or orally disintegrating rizatriptan – 5 mg for those who weighed less than 40 kg and 10 mg for those who weighed 40 kg or more. Patients then took the study treatment in response to a moderate or severe migraine attack. Those who continued to report moderate or severe pain after 15 minutes (non-responders) entered stage 2 of the study. In stage 2, patients who had not responded to placebo randomly received placebo or rizatriptan and those who had not responded to rizatriptan received placebo.

[8] At the time of publication of this Evidence Update, triptans (except nasal sumatriptan) did not have UK marketing authorisation for this indication in children and young people aged under 18 years. Informed consent should be obtained and documented.

The primary outcome was freedom from pain at 2 hours after taking the stage 2 drug in the subgroup of 12–17 year olds (a reduction in pain on the 5-Face Pain Scale from moderate or severe [face 3, 4 or 5] to no pain [face 1]). Tolerability and safety were assessed with adverse event reports and examinations at baseline and 14-day follow-up.

A total of 1382 children and young people aged 6–17 years were randomly assigned to either rizatriptan or placebo in stage 1, 963 used the assigned intervention in stage 1, and 831 used the intervention in stage 2. Young people aged 12–17 years who took rizatriptan in stage 2 (n=284) were more likely to be free from pain 2 hours later than were those who took placebo (n=286; 31% versus 22%, odds ratio [OR]=1.55, 95% confidence interval [CI] 1.06 to 2.26, p<0.05). The incidence of adverse events was similar in the rizatriptan and the placebo groups (24% versus 23% among 12–17 year olds, no statistical analysis for between group difference presented). The most common adverse effects were somnolence, nausea, fatigue, dizziness, upper abdominal pain, and asthenia.

Despite efforts to exclude people who responded to placebo from the efficacy analyses, the rate of placebo response was still relatively high in this study. In addition, the study did not include an active comparator. Another limitation is that the study only included children and young people who had not been successfully treated with NSAIDs or paracetamol, so the findings may not be generalisable to all children and young people with migraine.

Derosier et al. (2012) conducted a randomised, controlled, double-blind trial of combined oral sumatriptan and naproxen sodium[9] (an NSAID) compared with placebo in young people with migraine. Young people aged 12–17 years with a history of moderate-to-severe migraine 2 to 8 times a month for 6 months or more were recruited from 77 sites in the USA.

In the 12-week run-in stage of the study, all participants were instructed to treat 1 moderate-to-severe migraine with placebo. Those who reported pain at 2 hours after treatment were then randomly assigned to placebo or to combined oral sumatriptan/naproxen in a dose of 10/60 mg, 30/180 mg or 85/500 mg. In the second 12-week part of the study, participants treated 1 moderate-to-severe migraine with the allocated study treatment. The primary outcome was the percentage of subjects free from headache pain at 2 hours after treatment.

Of the 976 young people screened for eligibility, 683 completed the first stage of the study and 589 were randomised to placebo (n=176) or to sumatriptan/naproxen 10/60 mg (n=119), 30/180 mg (n=117) or 85/500 mg (n=177) in stage 2. In the modified intention-to-treat population (n=490), participants who received sumatriptan/naproxen were more likely to be free from pain at 2 hours than were those on placebo. A total of 29% of young people taking 10/60 mg sumatriptan/naproxen were free from pain at 2 hours, compared with 27% on 30/180 mg, 24% on 85/500 mg and 10% on placebo (adjusted p=0.003 for all doses versus placebo). Similar proportion of patients were free from pain at 24 hours (9% on placebo, 24% on 10/60 mg sumatriptan/naproxen, 25% on 30/180 mg, 23% on 85/500 mg, adjusted p=0.002 for all doses versus placebo). Post-hoc analyses did not suggest any differences between the efficacy of the 3 doses of sumatriptan/naproxen. The incidence of adverse events was similar in the 4 study groups: 13% with 10/60 mg sumatriptan/naproxen, 9% with 30/180 mg, 13% with 85/500 mg and 8% with placebo (p values not reported).

Limitations of the study included that combined oral sumatriptan/naproxen was not tested against either drug alone. The fixed dose sumatriptan and naproxen sodium combination does not have UK marketing authorisation and is not available in the UK. The exact dose regimen used is not easily replicated using products marketed in the UK.

[9] At the time of publication of this Evidence Update, combined dose sumatriptan and naproxen sodium did not have UK marketing authorisation and was not available in the UK.

Taken together, this evidence indicates that in children and young people aged 12–17 years with migraine, oral triptans, with or without an NSAID, are more effective than placebo at eliminating migraine pain at 2 hours. NICE CG150 recommends treating migraine with an oral or ideally a nasal triptan, alone or with an NSAID or paracetamol, in young people aged 12 years and over. As such, this evidence is unlikely to have an impact on NICE CG150.

Key references

Derosier FJ, Lewis D, Hershey AD et al. (2012) Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine. Pediatrics 129: e1411–20

Ho TW, Pearlman E, Lewis D et al. (2012) Efficacy and tolerability of rizatriptan in pediatric migraineurs: results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design. Cephalalgia 32: 750–65

Pharmacological prophylaxis of migraine with antiepileptics in adults

NICE CG150 recommends offering topiramate[10] or propranolol for the prophylactic treatment of migraine with or without aura in adults and young people aged 12 years or over, according to the person's preference, comorbidities and risk of adverse events. If both topiramate and propranolol are unsuitable or ineffective, healthcare professionals should consider a course of up to 10 sessions of acupuncture over 5–8 weeks or gabapentin[11] (up to 1200 mg per day).

Three Cochrane reviews by Linde et al. assessed the efficacy and tolerability of various antiepileptic drugs for the prevention of episodic migraine in adults:

- topiramate;
- gabapentin, gabapentin enacarbil[12] and pregabalin[12]; and
- valproic acid[12], sodium valproate[12], or a combination of the 2 (valproate semisodium[12]).

In addition, a randomised controlled trial by Silberstein et al. (2013) looked at the efficacy and safety of gabapentin enacarbil for migraine prophylaxis in adults.

Pharmacological prophylaxis with topiramate

NICE CG150 recommends offering topiramate[10] or propranolol for the prophylactic treatment of migraine with or without aura in adults and young people aged 12 years or over, according to the person's preference, comorbidities and risk of adverse events.

The first Cochrane review by **Linde et al. (2013a)** analysed prospective, randomised or pseudo-randomised controlled trials of the effect of prophylactic topiramate on frequency of migraines. Studies were sought of adults with episodic migraine (headache on less than 15 days per month) who self-administered topiramate regularly during headache-free periods to prevent migraines. Trials had to compare topiramate with a placebo, an active control, or a different dose of topiramate and consider migraine frequency (preferably number of migraine attacks), migraine-related quality of life, or both as outcomes. The primary outcome was headache frequency.

A total of 20 papers describing 17 trials met the inclusion criteria. Meta-analysis of 9 trials (n=1737) found that topiramate was more effective than placebo at reducing the number of migraines, resulting in around 1 less headache per month (mean difference [MD] in reduction in number of headaches per month=–1.20, 95% CI –1.59 to –0.80, p<0.00001).

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[10] At the time of publication of this Evidence Update, topiramate did not have UK marketing authorisation for this indication in children and young people aged under 18 years. Informed consent should be obtained and documented.

[11] At the time of publication of this Evidence Update, gabapentin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[12] At the time of publication of this Evidence Update, gabapentin enacarbil, pregabalin, valproic acid, sodium valproate and valproate semisodium did not have UK marketing authorisation for this indication and were not considered for NICE CG150.

The 3 different topiramate doses studied were similarly effective compared with placebo:

- 50 mg: MD=–0.95, 95% CI –1.95 to 0.04, p=0.06 (3 studies, n=520)
- 100 mg: MD=–1.15, 95% CI –1.58 to –0.71, p<0.00001 (6 studies, n=1620)
- 200 mg: MD=–0.94, 95% CI –1.53 to –0.36, p=0.001 (5 studies, n=804).

The response rate – that is, the proportion of people who experienced a 50% or greater reduction in headache frequency – for topiramate was twice as high as that with placebo (47% versus 23%, risk ratio [RR]=2.02, 95% CI 1.57 to 2.6, p<0.00001). Adverse events were reported by a large proportion of study participants treated with topiramate (range across studies 1.5–90%), but these were usually mild.

Limitations of this study include the heterogeneity of the trials analysed: the diagnostic criteria, baseline headache frequency, washout periods for previous medication, rules for rescue medication, and statistical methods and reporting varied considerably. In addition, the authors noted that several of the included studies were 'almost certainly underpowered' and that 9 trials had at least 1 area at high risk of bias (for example, allocation concealment, blinding, or selective reporting).

This evidence shows that regular prophylactic treatment with topiramate is more effective than placebo at reducing headache frequency in adults with episodic migraine. NICE CG150 recommends topiramate as a first-line prophylactic treatment for adults and young people. As such this evidence is consistent with NICE CG150.

Key reference

Linde M, Mulleners WM, Chronicle EP et al. (2013a) Topiramate for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews issue 6: CD010610

Pharmacological prophylaxis with gabapentin, gabapentin enacarbil or pregabalin

NICE CG150 recommends that healthcare professionals should consider gabapentin[13] (up to 1200 mg per day) for migraine prophylaxis in people in whom both topiramate and propranolol are unsuitable or ineffective. The guideline does not make any recommendations on the use of pregabalin for this indication.

The second Cochrane review by **Linde et al. (2013b)** looked for prospective, randomised or pseudo-randomised controlled trials on the prophylactic use of gabapentin, its prodrug gabapentin enacarbil[14], and pregabalin[14]. This review used the same inclusion criteria and outcomes as Linde et al. (2013a).

Six parallel-group trials of gabapentin and gabapentin enacarbil were identified (n=1009); no studies of pregabalin were found. Meta-analysis of 4 of the 5 studies of gabapentin (n=351) found no significant difference between gabapentin and placebo in their effect on monthly frequency of headaches (MD=–0.44, 95% CI –1.43 to 0.56, p=0.39). In addition, the number of responders was no higher with gabapentin than with placebo (OR=1.59, 95% CI 0.57 to 4.46, p=0.38; 2 studies, n=235). The 1 study of gabapentin enacarbil (Silberstein et al. [2013], n=523) did not have sufficient data to determine whether the drug had a greater effect than placebo on monthly frequency of headaches.

The overall risk of adverse events was similar in the gabapentin and the placebo groups (risk difference=0.05, 95% CI –0.04 to 0.14, p=0.28). However, people on gabapentin had a higher risk of dizziness (risk difference=0.15, 95% CI 0.08 to 0.22, p=0.000047; 3 studies, n=382), somnolence (risk difference 0.11, 95% CI 0.03 to 0.18; 2 studies, n=293), and abnormal thinking (risk difference=0.05, 95% CI 0.01 to 0.09, p=0.0075; 3 studies, n=382).

[13] At the time of publication of this Evidence Update, gabapentin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
[14] At the time of publication of this Evidence Update, gabapentin enacarbil and pregabalin did not have UK marketing authorisation for this indication and were not considered for NICE CG150.

Limitations of this analysis include that no trials comparing gabapentin with active comparators were found, and no trials of pregabalin for migraine prophylaxis were identified. In addition, diagnostic criteria, baseline headache frequency, washout periods for previous medication, rules for rescue medication, and the statistical analyses used varied among the 6 studies included. The authors note that these findings contradict those of their previous systematic review of gabapentin (Mulleners and Chronicle 2008) and other published analyses of the drug because of the inclusion of previously confidential research reports that became available because of legal proceedings.

A randomised controlled trial by **Silberstein et al. (2013)** assessed the efficacy and safety of 4 different doses of gabapentin enacarbil for migraine prophylaxis. This study was identified in the Linde at al. (2013b) Cochrane review, but was not 1 of the 4 studies included in the pooled analysis of the effect of gabapentin on headache frequency because it was testing a different compound.

Silberstein et al. (2013) recruited adults who had migraine with or without aura and at least 3 migraine attacks and 4 migraine days a month from multiple sites in the USA and Canada. Participants were randomly assigned to placebo or to gabapentin enacarbil at a dose of 1200 mg, 1800 mg, 2400 mg or 3000 mg. Drug doses were titrated to the assigned target dose or to the maximum tolerated dose over the first 5 weeks of the 20-week treatment period. Doses were then maintained for 12 weeks of treatment then tapered for 3 weeks until discontinued. The primary outcome was mean change from baseline in number of days with headache during the last 4 weeks of treatment before the taper period.

A total of 526 participants were randomised to treatment; the intention-to-treat population comprised 128 patients on placebo and 66 patients on gabapentin enacarbil 1200 mg, 134 on 1800 mg, 133 on 2400 mg and 62 on 3000 mg. Gabapentin enacarbil 1800 mg or 2400 mg – the 2 doses hypothesised to have the best efficacy with the fewest adverse effects – did not reduce the number of days with headache by more than placebo (adjusted MD=0.3, 95% CI –0.6 to 1.1, p=0.579). No 1 dose had a significantly greater effect than placebo (1200 mg: p=0.775; 1800 mg: p>0.999; 2400 mg: p=0.783; and 3000 mg: p=0.987). A similar proportion of patients in each treatment group experienced any adverse event during the entire 20-week study period: 68% of the placebo group, 67% of the 1200 mg gabapentin enacarbil group, 74% of the 1800 mg group, 76% of the 2400 mg group and 79% of the 3000 mg group. The most common adverse events were dizziness, fatigue, nausea and sleepiness.

Limitations of this study include that 53% of patients in the placebo group had a 50% or more reduction in headaches over 4 weeks compared with 53–67% of patients on gabapentin enacarbil. In addition, most of the participants were women (82%) of white ethnicity (83%), so the findings may not be generalisable to other populations.

The evidence suggests that gabapentin and gabapentin enacarbil are no better than placebo for prophylactic treatment of migraine in adults and are commonly associated with adverse events. NICE CG150 recommends gabapentin for prophylactic treatment of migraine in adults and young people in whom topiramate and propranolol are unsuitable or ineffective. This evidence may have a potential impact on NICE CG150, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Key references

Linde M, Mulleners WM, Chronicle EP et al. (2013b) Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews issue 6: CD010609

Silberstein S, Goode-Sellers S, Twomey C et al. (2013) Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia 33: 101–11

Supporting reference

Mulleners W, Chronicle E (2008) Anticonvulsants in migraine prophylaxis: a Cochrane review. Cephalalgia 28: 585–97

Pharmacological prophylaxis with valproic acid, sodium valproate or valproate semisodium

NICE CG150 does not make any recommendations on the use of the antiepileptics valproic acid[15], sodium valproate[15] or valproate semisodium[15] (combined sodium valproate and valproic acid) for prophylactic treatment of migraine in adults.

The third Cochrane review by **Linde et al. (2013c)** analysed prospective, randomised or pseudo-randomised controlled trials of the effect of prophylactic valproic acid, sodium valproate, or a combination of these (valproate semisodium) on frequency of migraines in adults. This review used the same inclusion criteria and outcomes as Linde et al. (2013a).

A total of 10 papers describing 10 trials were identified. Four trials (n=542) compared valproate semisodium with placebo. Not enough data were available from these trials to calculate the effect of this combination on headache frequency. The response rate for valproate semisodium was twice as high as for placebo (42% versus 21%, RR=2.18, 95% CI 1.28 to 3.72, p=0.0042).

Two trials (n=63) found that sodium valproate produced a greater reduction in 28-day headache frequency than placebo (MD=–4.31 headaches, 95% CI –8.32 to −0.30 headaches, p=0.035). One further trial (n=45) compared 3 different doses of sodium valproate. This study found that doses produced that produced lower serum concentrations of valproate (20–50 µg/ml) were associated a slightly lower headache frequency than doses that produced higher serum concentrations (>50 µg/ml; MD=0.80 headaches, 95% CI 0.24 to 1.36 headaches, p value not reported). The remaining 3 trials compared sodium valproate or valproate semisodium with active comparators: flunarizine[16], propranolol and topiramate. None of these studies reported significant differences between sodium valproate or valproate semisodium and the active comparators. The proportion of patients receiving valproate semisodium or sodium valproate who withdrew from trials owing to adverse effects varied from 8% to 19%.

This analysis was also limited by the heterogeneity of the studies included. In addition, 7 of the 10 trials were judged as being at high risk of bias in at least 1 area (for example, random sequence generation, allocation concealment, or blinding).

This evidence suggests that sodium valproate and valproate semisodium are effective preventive treatments to reduce headache frequency in adults with episodic migraine. NICE CG150 does not make any recommendations on sodium valproate or valproate semisodium for prophylactic treatment of migraine, in part because the evidence identified during the guideline production process was of poor quality and largely reported response rates rather than the preferred outcome: change in patient-reported headache frequency. Given that few data on change in headache frequency was reported in the studies analysed by Linde et al. (2013c), this evidence is unlikely to have an impact on NICE CG150.

Key reference

Linde M, Mulleners WM, Chronicle EP et al. (2013c) 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 issue 6: CD010611

[15] At the time of publication of this Evidence Update, valproic acid, sodium valproate and valproate semisodium did not have UK marketing authorisation for this indication and were not considered for NICE CG150.

[16] At the time of publication of this Evidence Update, flunarizine did not have UK marketing authorisation and was not available in the UK.

Pharmacological prophylaxis of migraine with other drugs in adults

NICE CG150 recommends only topiramate, propranolol and gabapentin[17] for pharmacological prophylaxis of migraine in adults, although it adds that riboflavin[18] (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people.

A systematic review and meta-analysis by **Shamliyan et al. (2013)** assessed the effects of several types of prophylactic pharmacological treatments on headache frequency in adults with episodic migraine. The search identified randomised controlled trials and uncontrolled studies of licenced and off-label drugs in community-dwelling adults with episodic migraine (headache less than 15 days per month). The outcomes sought were a 50% or greater reduction in migraine frequency from baseline, complete cessation of migraine attacks, migraine-related disability and quality of life.

A total of 215 randomised controlled trials and 76 non-randomised studies were assessed. The randomised controlled trials looked at 59 drugs, and most were in the USA and western countries. In pooled meta-analyses, the following drugs were more effective than placebo at reducing monthly migraine frequency by more than 50%:

- The antiepileptics topiramate (absolute risk difference=0.29, 95% CI 0.18 to 0.40; 7 studies, n=1422), gabapentin (absolute risk difference =0.17, 95% CI 0.06 to 0.27; 3 studies, n=270) and valproate semisodium[19] (absolute risk difference =0.24, 95% CI 0.10 to 0.38; 3 studies, n=405).
- The beta-blockers propranolol (absolute risk difference =0.22, 95% CI 0.14 to 0.30; 4 studies, n=541), timolol (absolute risk difference =0.27, 95% CI 0.15 to 0.38; 3 studies, n=276) and metoprolol (absolute risk difference =0.20, 95% CI 0.09 to 0.3; 4 studies, n=225).
- The calcium channel blocker nimodipine[19] (absolute risk difference=0.23, 95% CI 00.06 to 0.39; 2 studies, n=126).

Small single randomised controlled trials found that the angiotensin-converting enzyme inhibitor lisinopril[19] and the angiotensin II receptor blocker candesartan[19] were also effective at reducing migraine frequency (lisinopril: absolute risk difference=0.23, 95% CI 0.12 to 0.34, n=120; and candesartan: absolute risk difference=0.35, 95% CI 0.22 to 0.48, n=120).

In a network meta-analysis, angiotensin-inhibiting drugs were the most effective class of drug compared with placebo (OR=5.85, 95% CI 2.53 to 14.65; 5 studies, n=180), followed by the antiadrenergic drug clonidine[20] (OR=3.66, 95% CI 2.04 to 6.49; 7 studies, n=271), beta-blockers (OR=3.37, 95% CI 2.31 to 5.30, 17 studies, n=714) and the antiepileptic drug valproate semisodium (OR=3.24, 95% CI 1.97 to 5.61; 8 studies, n=419). All drugs except beta-blockers were more likely than placebo to cause adverse effects that led to treatment discontinuation.

Limitations of this study include the poor quality of the evidence (as assessed by the authors) for all drugs except topiramate, for which moderate quality evidence was available. The strength of the evidence in individual trials and of pooled data was estimated subjectively

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[17] At the time of publication of this Evidence Update, gabapentin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

[18] At the time of publication of this Evidence Update, riboflavin did not have a UK marketing authorisation for this indication but is available as a food supplement. When advising this option, the prescriber should take relevant professional guidance into account.

[19] At the time of publication of this Evidence Update, valproate semisodium, nimodipine, lisinopril and candesartan did not have UK marketing authorisation for this indication and were not considered for NICE CG150.

[20] Clonidine is licenced for prevention of recurrent migraine in adults. However, the British National Formulary advises that clonidine is not recommended for prophylaxis of migraine because it can aggravate depression and cause insomnia.

according to 6 risk of bias criteria rather than scored with a validated tool. No unpublished data or further information on methodological approaches was sought from the authors of the included studies.

Stovner et al. (2013) conducted a randomised cross-over study to test the efficacy of the angiotensin II blocker candesartan[21] versus propranolol for migraine prophylaxis. People with migraine with or without aura or chronic migraine who had 2 or more headaches per month were recruited from the outpatient clinic of a single hospital in Norway. The study comprised a 4-week baseline period followed by 3 12-week treatment periods with each of placebo, 16 mg candesartan and 160 mg propranolol, with a 4-week wash-out period between each treatment period. The primary outcome was number of days with moderate or severe headache per 4 weeks.

A total of 72 patients were randomly assigned to 1 of 6 treatment sequences that covered all possible chronological sequences of taking the 2 drugs and placebo over the 3 treatment periods. Data for 61 people were available for modified intention-to-treat analyses. Patients had significantly fewer days with migraine per 4 weeks when on candesartan (2.95 days, 95% CI 2.35 to 3.55 days) or propranolol (2.91 days, 95% CI 2.36 to 3.45 days) than on placebo (3.53 days, 95% CI 2.98 to 4.08 days; p=0.02 for both candesartan and propranolol compared with placebo). No difference was seen in the efficacy of candesartan compared with propranolol (p=0.88). The rate of adverse events versus placebo (33%) was significantly higher with propranolol (58%; p=0.006) but not with candesartan (50%; p=0.07). When adverse effects with the active treatments were compared, bodily pain and low pulse at exercise were more common with propranolol and dizziness and paraesthesia were more common with candesartan.

Limitations of this evidence include that the effects of 1 study agent may have been carried over into the next study period, despite the wash-out period. In addition, the small reductions in headache days per month from baseline with each of the study drugs (0.58 days with candesartan and 0.62 days with propranolol) may not be clinically s important. For the sample size estimate, the clinically important difference was set at 0.5 of baseline standard deviation or 1.7 days. When candesartan and propranolol were compared in a per protocol analysis for non-inferiority (n=54), the difference in headache days over four weeks was 0.002 (90% CI –0.48 to 0.49). These data suggest that there is little meaningful difference between the 2 drugs on this outcome.

Taken together, this evidence suggests that angiotensin-inhibiting drugs and beta-blockers may be effective options for reducing migraine frequency. NICE CG150 recommends the beta-blocker propranolol for migraine prophylaxis but does not make any recommendations on angiotensin-inhibiting drugs. The evidence may therefore have a potential impact on NICE CG150, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Key references

Shamliyan TA, Choi JY, Ramakrishnan R et al. (2013) Preventive pharmacologic treatments for episodic migraine in adults. Journal of General Internal Medicine 28: 1225–37

Stovner LJ, Linde M, Gravdahl GB et al. (2013) A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 34: 523–32

[21] At the time of publication of this Evidence Update, candesartan did not have UK marketing authorisation for this indication and was not considered for NICE CG150.

Pharmacological prophylaxis of migraine in children and young people

NICE CG150 recommends offering topiramate[22] or propranolol for the prophylactic treatment of migraine with or without aura in adults and young people aged 12 years or over, or gabapentin (up to 1200 mg per day) if both topiramate and propranolol are unsuitable or ineffective.

A systematic review and meta-analysis by **El-Chammas et al. (2013)** looked at the effectiveness and safety of a range of prophylactic pharmacological treatments for migraine in children and young people. The analysis included randomised controlled trials of headache medication compared with placebo or an active treatment in children and young people less than 18 years old. The primary outcome was the number of headaches per month.

The analysis included 20 trials on episodic migraine (less than 15 headaches per month), plus 1 study on any headache type occurring 15 times or more per month, in children and young people (mean ages in studies 7.8 to 14.2 years). Analyses of the 13 placebo-controlled trials found that topiramate and trazodone hydrochloride[23] were more effective than placebo at reducing the number of headaches per month in episodic migraine (topiramate: weighted mean difference [MD] in headaches per month=–0.71 headaches, 95% CI –1.19 to –0.24 headaches; 2 studies, n=268 and trazodone: weighted MD in headaches a month=–0.60 headaches, 95% CI –1.09 to –0.11 headaches; 1 study, n=40). The following drugs were not significantly better than placebo: clonidine[24], flunarizine[25], piracetam[24], pizotifen, propranolol, sodium valproate[24] and fluoxetine[24]. Topiramate and sodium valproate were associated with more adverse effects than placebo (topiramate: relative risk=1.53, 95% CI 1.05 to 2.24 and valproate: relative risk=1.16, 95% CI 0.93 to 1.44).

Not enough comparative effectiveness data on prophylactic medication for migraine were available to allow a network meta-analysis. However, the 10 studies with comparative effectiveness analyses showed that flunarizine was more effective than piracetam at reducing headache frequency (difference in number of headaches over 16 weeks=–2.20 days, 95% CI –3.93 to –0.47 days; 1 study, n=98) but no better than aspirin (1 study, n=30) or dihydroergotamine[25] (1 study, n=50). Propranolol was as effective as behavioural therapy (difference in number of headaches a month=0.88 days, 95% CI −1.86 to 3.62 days; 1 study, n=43), but no better than valproate (2 studies, n=183), cinnarizine[24] (1 study, n=120) or flunarizine (1 study, n=33).

This analysis is limited by the considerable heterogeneity among the included trials (I^2=70.1%). In addition, the included trials were generally small (mean sample size=70) and short (mean duration=12 weeks), and only 4 trials used intention-to-treat analyses despite mean withdrawal rates of 10%.

Limited evidence suggests that prophylactic use of topiramate and trazodone hydrochloride reduces headache frequency in children and young people with episodic migraine, whereas other commonly used drugs, including propranolol, may not be effective. NICE CG150

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[22] At the time of publication of this Evidence Update, topiramate did not have UK marketing authorisation for this indication in children and young people aged under 18 years. Informed consent should be obtained and documented.

[23] At the time of publication of this Evidence Update, trazodone hydrochloride did not have UK marketing authorisation for this indication in children and young people aged under 18 years, and was not considered for NICE CG150.

[24] At the time of publication of this Evidence Update, clonidine, piracetam, sodium valproate, fluoxetine and cinnarizine did not have UK marketing authorisation for this indication in children and young people aged under 18 years, and were not considered for NICE CG150. Clonidine is licenced for prevention of recurrent migraine in adults. However, the British National Formulary advises that clonidine is not recommended for prophylaxis of migraine because it can aggravate depression and cause insomnia.

[25] At the time of publication of this Evidence Update, flunarizine and dihydroergotamine did not have UK marketing authorisation and were not available in the UK.

recommends offering topiramate or propranolol prophylaxis for young people aged 12 years and over with migraine with or without aura. However given the shortcomings of the studies included in the meta-analysis, this evidence is unlikely to have an impact on NICE CG150.

Key reference

El-Chammas K, Keyes J, Thompson N et al. (2013) Pharmacologic treatment of pediatric headaches: a meta-analysis. JAMA Pediatrics 167: 250–8

Non-pharmacological prophylaxis of migraine in children and young people

Prophylactic non-pharmacological management of migraines with psychological therapies was considered during the development of NICE CG150. However, no studies of cognitive behavioural therapy (CBT) for migraine prophylaxis were identified. Research recommendation 4.4 indicates that a pragmatic randomised controlled trial is needed to assess a psychological intervention such as CBT compared with an active control on headache outcomes in people with chronic headache disorders.

Powers et al. (2013) conducted a randomised controlled trial of CBT compared with headache education alongside medication in young people with chronic migraine. Young people aged 10–17 years with a diagnosis of chronic migraine (15 or more days with headache per month) and at least moderate migraine-related disability were recruited from a single centre in the USA. Participants were randomly assigned to 10 X 1-hour sessions of CBT or headache education, plus 1 mg/kg amitriptyline[26] per day in both groups. The CBT intervention comprised coping skills for paediatric pain, whereas the headache education intervention consisted of discussion of headache-related education topics. Participants and their families were blinded to the psychological intervention received, and 20% of the intervention sessions were reviewed to check integrity (the psychologists received extra training if they deviated from the treatment protocol). The primary outcome was change in the number of days with headache per month between baseline and 20 weeks after treatment.

Of the 398 young people screened for eligibility, 135 (34%) were randomly assigned to CBT plus amitriptyline (n=64) or headache education plus amitriptyline (n=71). More than 95% of participants attended all intervention sessions, and 77% provided prospective headache diary information. In an intention-to-treat analysis, participants in the CBT group had 11.5 fewer days with headache per month compared with a reduction of 6.8 days in the headache education group (MD=4.7 days, 95% CI 1.7 to 7.7 days, p=0.002). Two -thirds (66%) of the CBT group had a 50% or greater reduction in headache days, compared with around one-third (36%) of the headache education group (OR=3.45, 95% CI 1.66 to 7.15, p<0.001).

Limitations include the study's small size and that the study did not include an inactive comparator group to test solely the effect of CBT. In addition, the study looked at a very specific group of paediatric patients: only patients with severe migraine were included, and young people with severe psychiatric comorbidities, contraindications to amitriptyline or baseline disability in the mild-to-none range were excluded. The very specific CBT protocol may be difficult to replicate, and amitriptyline is not licenced for migraine prophylaxis in the UK or recommended by NICE CG150.

This evidence suggests that intensive CBT plus amitriptyline is more effective at reducing headache frequency than headache education plus amitriptyline in young people aged 10–17 years with severe chronic migraine. NICE CG150 does not make any recommendations on CBT for migraine owing to lack of evidence, but this research provides 'proof of concept' that CBT on top of medication may be effective in a subset of young people with chronic migraine. The nature of the population included in this study limits the generalisability of the findings,

[26] At the time of publication of this Evidence Update, amitriptyline did not have UK marketing authorisation for this indication in children and young people aged under 18 years, and was not considered for NICE CG150.

and the intervention may be difficult to replicate in the NHS. As such this evidence, alone, is unlikely to have an impact on NICE CG150.

Further large randomised controlled trials are needed to confirm the efficacy of CBT and other psychological interventions compared with usual care for prophylactic treatment of adults and children with migraine and other forms of chronic headache. Research recommendation 4.4 in NICE CG150 recommends a pragmatic randomised controlled trial to test whether psychological interventions such as CBT improve headache outcomes and quality of life for people with chronic headache disorders.

Key reference

Powers SW, Kashikar-Zuck SM, Allen JR et al. (2013) Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents: a randomized clinical trial. The Journal of the American Medical Association 310: 2622–30

Treatment of migraine during pregnancy

NICE CG150 recommends that pregnant women should be offered paracetamol for the acute treatment of migraine with or without aura. A triptan or an NSAID should be considered after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy. Specialist advice should be sought if prophylactic treatment for migraine is needed during pregnancy.

The full version of NICE CG150 considered 3 prospective cohort studies of triptans for migraine in pregnancy that reported a non-significant increased risk of several fetal adverse events. The adverse events associated with triptan use were: spontaneous and therapeutic abortion; Apgar score less than 7 at 1 minute and at 5 minutes; major birth defects; and death during the first 12 months of life. The Guideline Development Group agreed that the evidence reviewed did not indicate an increased risk associated with the use of triptans during pregnancy. It added that the evidence on the safety of triptans in pregnancy was not conclusive but was reassuring.

Nezvalová-Henriksen et al. (2013) conducted a population-based cohort study to assess the safety of triptans during pregnancy. A group of 181,125 pregnant women were retrospectively identified from the Medical Birth Registry of Norway, which prospectively collects data on pregnancy after the 12th week of gestation and birth for all deliveries in the country. Data for these women were linked to data from the Norwegian Prescription Database on triptans dispensed between 2004 and 2007. Pregnancy outcome data – including foetal death, non-chromosomal congenital malformations, birth weight, and gestational age – were collected from the Medical Birth Registry of Norway.

A total of 1465 women in the cohort redeemed prescriptions for triptans during pregnancy, with sumatriptan, rizatriptan, eletriptan and zolmitriptan being the most commonly used drugs. A further 1095 women redeemed prescriptions for triptans between 7 months and 1 month before pregnancy only (disease comparison group), and the remaining 178,565 did not redeem triptans during the study period (population comparison group). After controlling for maternal age and previous stillbirth or miscarriage, women who redeemed prescriptions for triptans during pregnancy were at no higher risk of miscarriage or stillbirth than those who did not take triptans before or during pregnancy (OR=1.01, 95% CI 0.56 to 1.84). In addition, no link was found between triptan redemption during pregnancy and congenital malformations (OR=1.09, 95% CI 0.87 to 1.36). Women who redeemed triptans during the second trimester of pregnancy (gestational weeks 13–28) had a higher risk of low birth weight infants (birth weight <2500 g; OR=1.68, 95% CI 1.08 to 2.61) and postpartum haemorrhage (OR=1.57, 95% CI 1.19 to 2.07). However, the risk of postpartum haemorrhage was also raised among women in the disease comparison group (OR=1.21, 95% CI 1.03 to 1.42).

Limitations of this study include that the prescription redemption data could not show whether the triptans were taken and at what point in pregnancy. In addition, the overall rate of congenital malformations in the study was low (5.1%), so the analyses may have been underpowered for this outcome.

This evidence suggests that triptan use during pregnancy is not associated with miscarriage, stillbirth or congenital malformations. Given that NICE CG150 recommends the use of triptans during pregnancy, this evidence is consistent with and strengthens the guidance.

Key reference

Nezvalová-Henriksen K, Spigset O, Nordeng H (2013) Triptan safety during pregnancy: a Norwegian population registry study. European Journal of Epidemiology 28: 759–69

Medication overuse headache

Prophylactic treatment

NICE CG150 recommends that people with medication overuse headache should be advised to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually. Prophylactic treatment for the underlying primary headache disorder can be considered in addition to withdrawal of the overused medication.

The full version of NICE CG150 acknowledges that steroids may aid medication withdrawal in some people with medication overuse headache. However, at the time NICE CG150 was produced, insufficient evidence was available to make specific recommendations on the types of prophylactic drugs to aid withdrawal. Research recommendation 4.5 indicates that double-blind randomised controlled trials are needed to establish whether steroids or other pharmacological treatments help people with medication overuse headaches withdraw from medication.

A randomised controlled trial by **Rabe et al. (2013)** investigated the efficacy of prednisone[27] for the treatment of withdrawal headache in people with medication overuse headache. Adults with a diagnosis of migraine or episodic tension-type headache seeking treatment for medication overuse headache were recruited from 3 tertiary referral centres in Germany and 1 in Austria. Participants were randomly assigned to 100 mg prednisone or 100 mg placebo to be taken daily during the first 5 days of the withdrawal period. Patients could undergo withdrawal on either an inpatient or an outpatient basis. All participants also received daily calcium, potassium and ranitidine to minimise the potential harms of the high doses of prednisolone, and were able to take rescue medication in instances of 'unbearable' headache. The primary outcome was a reduction in the number of hours with moderate-to-severe headache over the first 3 days after medication withdrawal.

A total of 96 patients were recruited and randomly assigned to prednisone (n=48) or placebo (n=48); data on the primary endpoint were available for 37 people (77%) in the prednisone group and 41 (85%) in the placebo group. People who received prednisone had a similar number of hours with headache at 3 days following withdrawal as those who received placebo (20.9 hours versus 18.2 hours, p=not significant). Likewise no difference was seen between the 2 treatment groups in the number of hours with headache in the first 5 days after withdrawal (29.6 hours versus 27.7 hours, p=not significant) or during the total 14 days of observation (74.9 hours versus 69.8 hours, p=not significant). People in the prednisone group requested significantly less rescue medication during the first 5 days after withdrawal (1.1 doses versus 2.3 doses, p=0.021), but not during the whole 14-day study period (3.6 doses versus 6.4 doses, p=0.105).

[27] At the time of publication of this Evidence Update, prednisone did not have UK marketing authorisation for this indication and were not considered for NICE CG150.

Limitations of this study include the long recruitment period (2004 to 2009) and high drop-out rate (19%), potentially because some participants found the task of recording headache severity on an hourly basis too onerous. In addition, the majority of patients (71%) went through medication withdrawal on an inpatient basis, an approach that NICE CG150 does not recommend should be used routinely in England.

An earlier randomised controlled study by Bøe et al. (2007) also found that prednisolone[28] did not affect the number of days with headache in people with medication overuse headache undergoing medication withdrawal. In this study, 100 people in Norway with migraine or tension-type headache and probable medication overuse headache were randomly assigned to receive prednisolone (n=51) or placebo (n=49) for the first 6 days after withdrawal. Headache frequency during the first 6 days was similar in both groups (mean number of days with headache=1.48 days, 95% CI 1.28 to 1.68 days versus 1.61 days, CI 1.41 to 1.82 days, p=0.34).

Taken together, these studies suggest that prophylaxis with prednisone or prednisolone during the first few days after headache medication withdrawal is not effective at reducing headache in people with medication overuse headache. NICE CG150 suggests that prophylactic treatment may be considered in people with medication overuse headache undergoing withdrawal of the overused medication. However, the guidance does not make any recommendations specifically to use or not use corticosteroids. As such, this evidence is unlikely to have an impact on NICE CG150.

Key reference

Rabe K, Pageler L, Gaul C et al. (2013) Prednisone for the treatment of withdrawal headache in patients with medication overuse headache: a randomized, double-blind, placebo-controlled study. Cephalalgia 33: 202–7

Supporting reference

Bøe MG, Mygland A, Salvesen R (2007) Prednisolone does not reduce withdrawal headache: a randomized, double-blind study. Neurology 69: 26–31

Inpatient withdrawal

NICE CG150 states: do not routinely offer inpatient withdrawal for medication overuse headache. Specialist referral and/or inpatient withdrawal of overused medication should be considered for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.

A prospective, randomised cohort study by **Rossi et al. (2013)** compared advice alone with structured inpatient and outpatient withdrawal programmes in patients with medication overuse headache. A single specialist headache centre in Italy enrolled adults with migraine and 'complicated' medication overuse headache – that is, a comorbid medical or psychiatric illness; social or environmental issues, such as housing or economic problems; relapse after previous detoxification treatment; or daily use of multiple doses of symptomatic medications. Eligible patients were randomly assigned to receive either:

- Education on medication overuse headache and advice to withdraw the overused medications;
- An outpatient withdrawal programme comprising the same education and advice as the first group plus prednisone and individualised prophylaxis treatment; or
- A 10-day inpatient withdrawal programme with education and advice, steroids, fluid replacement, antiemetics (metoclopramide hydrochloride) and individualised prophylaxis treatment.

[28] At the time of publication of this Evidence Update, prednisolone did not have UK marketing authorisation for this indication and were not considered for NICE CG150.

The primary outcome measures at 2 months after the start of withdrawal were the proportion of responders in each treatment group (participants who took NSAIDS less than 15 days/month or other symptomatic medications less than 10 days/month) and the proportion of responders with headache improvement (patients who experienced more than 50% reduction in headache frequency from baseline).

A total of 141 patients were recruited to the study and 137 were included in the final analyses: 46 who received advice only, 46 who underwent outpatient treatment withdrawal and 45 who did inpatient withdrawal. The proportion of patients who responded to treatment was highest in the inpatient group (88.9%), and the same in the advice group and the outpatient group (60.8%; p compared with inpatient group=0.003). Similarly, the inpatient group had the highest proportion of responders with headache improvement (84.4%), whereas the proportion was roughly equivalent in the education and the outpatient groups (54.3% and 56.5% respectively; p compared with inpatient group=0.003).

Limitations of this study include that the sample size was relatively small and it assessed a highly complex group of patients. In addition, it was conducted at a single tertiary referral centre, and the education and advice component of each treatment may not be reproducible in non-specialised centres.

This evidence shows that inpatient treatment is more effective than outpatient treatment or education alone at achieving medication withdrawal in people with migraine and complicated medication overuse headache. NICE CG150 states that inpatient withdrawal should be reserved for people who are using strong opioids, have relevant comorbidities, or have previously been unsuccessful at withdrawal of overused medication. This evidence is consistent with the current guidance and therefore unlikely to have an impact on NICE CG150.

Key reference

Rossi P, Faroni JV, Tassorelli C et al. (2013) Advice alone versus structured detoxification programmes for complicated medication overuse headache (MOH): a prospective, randomized, open-label trial. The Journal of Headache and Pain 14: 10

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Prophylactic treatment of migraine with or without aura

- Pharmacological treatment of pediatric headaches
- Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults
- Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults
- Cognitive Behavioural Therapy (CBT) for people with chronic headache disorders to improve headache outcomes and quality of life

Further evidence uncertainties for headaches can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Headaches. NICE clinical guideline 150 (2012)

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 13 March 2012 (the end of the search period of NICE CG150) to 26 March 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)

The Evidence Update search strategy replicates the strategy used by NICE CG150 (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with filters for systematic reviews, randomised controlled trials, observational studies, diagnostic studies, qualitative studies and quality of life studies.

Additionally, 2 studies (Silberstein et al. [2013] and Stovner et al. [2013]) were identified outside of the literature search. Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Headache/ (22044)
2	exp Headache Disorders/ or exp Headache Disorders, Primary/ (25937)
3	(headache* or migraine*).ti,ab. (65421)
4	exp Migraine Disorders/ (21060)
5	Tension-Type Headache/ (1485)
6	Cluster Headache/ (2119)
7	((ciliary or migrain* or petrosal or sluder* or spheno-palatine or vidian) adj4 neuralgi*).ti,ab. (134)
8	or/1-7 (76077)
9	limit 8 to ed=20120313-20140311 (6651)
10	limit 9 to english language (5992)
11	"review"/ or review.pt. or review.ti. (1924949)
12	(systematic or evidence* or methodol* or quantitativ*).ti,ab. (1706041)
13	Meta-Analysis/ (45670)
14	Meta-Analysis as Topic/ (13522)
15	(meta-analy* or metanaly* or metaanaly* or meta analy*).ti,ab. (53994)
16	((systematic* or evidence* or methodol* or quantitativ*) adj3 (review* or overview*)).ti,ab. (74273)
17	((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab. (34742)
18	11 and 12 (301299)
19	or/13-18 (385751)
20	randomized controlled trial.pt. (366703)
21	controlled clinical trial.pt. (87802)
22	randomi?ed.ab. (318385)
23	placebo.ab. (143748)
24	randomly.ab. (189528)
25	Clinical Trials as topic.sh. (168638)
26	trial.ti. (114737)
27	or/20-26 (860509)
28	Epidemiologic Studies/ (5862)
29	exp case control studies/ (643886)
30	exp cohort studies/ (1322287)
31	Cross-Sectional Studies/ (169996)
32	case control.ti,ab. (70236)
33	(cohort adj (study or studies or analys*)).ti,ab. (79146)
34	((follow up or observational or uncontrolled or non randomi?ed) adj (study or studies)).ti,ab. (76470)
35	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort*)).ti,ab. (591775)
36	cross sectional.ti,ab. (146927)
37	or/28-36 (1824046)
38	exp "sensitivity and specificity"/ (406554)
39	(sensitivity or specificity).ti,ab. (659632)
40	((pre test or pretest or post test) adj probability).ti,ab. (1391)
41	(predictive value* or PPV or NPV).ti,ab. (65991)
42	likelihood ratio*.ti,ab. (7895)
43	likelihood function/ (16685)
44	(ROC curve* or AUC).ti,ab. (40806)

45	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. (59157)
46	or/38-45 (1031822)
47	gold standard.ab. (29257)
48	quality adjusted life.tw. (5600)
49	(qaly* or qald* or qale* or qtime*).tw. (4648)
50	disability adjusted life.tw. (1090)
51	daly*.tw. (1090)
52	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (14471)
53	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (957)
54	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2391)
55	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (20)
56	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (323)
57	(euroqol or euro qol or eq5d or eq 5d).tw. (3465)
58	(hql or hqol or h qol or hrqol or hr qol).tw. (6891)
59	(hye or hyes).tw. (53)
60	health* equivalent* year*.tw. (1)
61	(hui or hui1 or hui2 or hui3).tw. (814)
62	health utilit*.tw. (1011)
63	disutilit*.tw. (189)
64	rosser.tw. (71)
65	(quality of wellbeing or quality of well being).tw. (321)
66	qwb.tw. (159)
67	willingness to pay.tw. (2031)
68	standard gamble*.tw. (634)
69	time trade off.tw. (690)
70	time tradeoff.tw. (198)
71	tto.tw. (543)
72	or/48-71 (35451)
73	19 or 27 or 37 or 46 or 47 or 72 (3581098)
74	10 and 73 (2686)
75	(red flag* or warning).ti,ab. (12471)
76	((intracranial or key or serious or significant) adj2 (abnormal* or characteristic* or patholog* or cause* or symptom* or feature*)).ti,ab. (83685)
77	exp HIV/ (82755)
78	(human immunodeficiency virus or human immuno-deficiency virus or HIV or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome).ti,ab. (237285)
79	exp Neoplasms/ (2514695)
80	(cancer* or neoplasm* or tumo?r*).ti,ab. (1751601)
81	(early adj3 (day or morning) adj3 (migraine* or headache*)).ti,ab. (22)
82	(new adj3 (onset or daily) adj3 (migraine* or headache*)).ti,ab. (278)
83	exp Questionnaires/ (299789)

84	questionnaire*.ti,ab. (270322)
85	Mass Screening/ (80537)
86	screen*.ti,ab. (419602)
87	(diary or diaries).ti,ab. (14068)
88	(chronicle* or patient log* or daily record* or daily log*).ti,ab. (2399)
89	exp tomography, x-ray computed/ (295325)
90	exp Magnetic Resonance Imaging/ (303718)
91	(neuroimag* or neuro-imag*).ti,ab. (24309)
92	(compute* adj2 tomograph*).ti,ab. (170217)
93	(ct or cat).ti,ab. (269594)
94	((MR or magnetic resonance or NMR) adj2 (imag* or tomograph* or angiograph*)).ti,ab. (171894)
95	MRI.ti,ab. (125412)
96	antiemetics/ or domperidone/ or metoclopramide/ or cinnarizine/ or cyclizine/ (12809) exp Magnetic Resonance Imaging/ (303718)
97	antiemetic*.mp. (9367)
98	Domperidone.mp. (2194)
99	Metoclopramide.mp. (6137)
100	Cinnarizine.mp. (917)
101	Cyclizine.mp. (314)
102	Phenothiazines/ or prochlorperazine/ or perphenazine/ or trifluoperazine/ or promethazine/ (15951)
103	Phenothiazine*.mp. (10947)
104	Prochlorperazine.mp. (1221)
105	Perphenazine.mp. (1796)
106	Trifluoperazine.mp. (4848)
107	Promethazine.mp. (3409)
108	exp Histamine Antagonists/ (54793)
109	antihistamine*.mp. (7931)
110	Cyproheptadine.mp. (2893)
111	migraleve.mp. (8)
112	migramax.mp. (0)
113	paramax.mp. (22)
114	(acetylsalicylic acid or aspirin).mp. (53055)
115	(paracetamol or acetaminophen or panadol).mp. (18761)
116	exp Analgesics, Opioid/ (90334)
117	(Buprenorphine or Codeine or Diamorphine or Dihydrocodeine or Dipipanone or Fentanyl or Hydromorphone or Meptazinol or Morphine or Oxycodone or Papaveretum or Pentazocine or Pethidine or Tramadol).mp. (74259)
118	exp Adrenal Cortex Hormones/ (332212)
119	adrenal cortex hormone*.mp. (52234)
120	exp Steroids/ (693777)
121	(corticosteriod* or glucocorticoid*).mp. (81993)
122	exp Prednisolone/ (43896)
123	exp Dexamethasone/ (43604)
124	(prednisolone or prednisone or dexamethasone).mp. (130269)
125	(ergotamine or dihydroergotamine).mp. (4099)
126	(cafergot or migril).mp. (44)
127	contraceptive agents/ or contraceptive

	agents, female/ or exp contraceptives, oral/ or exp menstruation-inducing agents/ (45636)
128	(Loestrin20 or Mercilon or Femodette or Brevinor or Cilest or Eugynon30 or Loestrin30 or Microgynon30 or Norimin or Norinyl-1 or Ovranette or Ovysmen or Yasmin or Femodene or Marvelon or Minulet or BiNovum or Logynon or Qlaira or Synphase or Triadene or Tri-Minulet or Trinordial or TriNovum or Evra patch or Cerazette or Femulen or Micronor or Microval or Neogest or Norgeston or Noriday or Medroxyprogesterone acetate or Depo-provera or Norethisterone enantate or Noristerat or Etonogestrel-releasing implant or Implanon or Mirena).mp. (7149)
129	((progestogen* or progestin* or progestagen* or estrogen* or oestrogen* or combined) adj3 contraceptive*).ti,ab. (3767)
130	exp Anti-Inflammatory Agents, Non-Steroidal/ (155154)
131	(((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or NSAID*).tw. (31021)
132	(Aceclofenac or Acemetacin or Celecoxib or Dexibuprofen or Dexketoprofen or Diclofenac or Etodolac or Etoricoxib or Fenbufen or Fenoprofen or Flurbiprofen or Ibuprofen or Indometacin or Ketoprofen or Mefenamic acid or Meloxicam or Nabumetone or Naproxen or Piroxicam or Sulindac or Tenoxicam or Tiaprofenic acid or tolfenamic acid or clotam rapid).mp. (35812)
133	Tryptamines/ or Sumatriptan/ (6214)
134	(triptan* or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or

	Zolmitriptan).mp. (4065)
135	(almogran or relpax or migard or naramig or maxalt or imigran or zomig).mp. (83)
136	exp Calcium Channel Blockers/ (71354)
137	(calcium adj3 (blocker* or antagonist* or inhibitor*)).ti,ab. (29243)
138	(nimodipine or diltiazem or verapamil).ti,ab. (27887)
139	(nimodipine or diltiazem or verapamil).ti,ab. (27887)
140	Angiotensin-Converting Enzyme Inhibitors/ (29031)
141	angiotensin receptor antagonists/ or angiotensin ii type 1 receptor blockers/ or angiotensin ii type 2 receptor blockers/ (13932)
142	(Captopril or Cilazapril or Enalapril maleate or Fosinopril sodium or Imidapril hydrochloride or Lisinopril or Moexipril hydrochloride or Perindopril erbumine or Perindopril arginine or Quinapril or Ramipril or Ramipril with felodipine or Trandolapril).mp. (18687)
143	(Angiotensin-Converting Enzyme Inhibitor* or ACE inhibitor* or angiotensin receptor blocker* or ARB or ARBS).ti,ab. (29338)
144	(candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan).ti,ab. (13258)
145	exp Serotonin Uptake Inhibitors/ (30661)
146	(selective serotonin reuptake inhibitor* or selective serotonin uptake inhibitor* or SSRI*).ti,ab. (9790)
147	(paroxetine or citalopram or escitalopram or fluoxetine or fluvoxamine or sertraline or

	mirtazapine).ti,ab. (18717)
148	(SNRI* or serotonin norepinephrine reuptake inhibitor*).ti,ab. (882)
149	venlafaxine.ti,ab. (2497)
150	exp Antidepressive Agents, Tricyclic/ (28791)
151	tricyclic*.ti,ab. (12350)
152	(amitryptyline or amitriptiline or imipramine or nortriptyline or desipramine or dosulepin).ti,ab. (14019)
153	exp Adrenergic beta-Antagonists/ (76539)
154	(beta-blocker* or beta?blocker*).ti,ab. (22605)
155	(propranolol or metoprolol or nadolol or timolol or atenolol).ti,ab. (41283)
156	methysergide/ or pizotyline/ (3012)
157	Ergotamine/ (2088)
158	Cyproheptadine/ (2056)
159	(serotonergic adj2 modulator*).ti,ab. (47)
160	(methysergide or pizotifen or pizotyline or ergotamine or cyproheptadine).ti,ab. (6484)
161	exp Anticonvulsants/ (117422)
162	(anticonvulsant* or antiepileptic or anti-epileptic*).ti,ab. (32137)
163	(sodium valproate or valproic acid or topiramate or gabapentin).ti,ab. (13034)
164	Acupuncture/ (1172)
165	exp Acupuncture Therapy/ (16203)
166	(acupunctur* or needling or electroacupunctur*).ti,ab. (15111)

167	exp Dietary Supplements/ (39394)
168	vitamins/ or vitamin b complex/ or exp riboflavin/ or exp vitamin b 12/ (50942)
169	magnesium compounds/ or magnesium chloride/ or magnesium hydroxide/ or magnesium oxide/ or magnesium sulfate/ (10368)
170	Magnesium/ (60957)
171	exp Ubiquinone/ (6561)
172	(vitamin B12 or vitamin B 12).ti,ab. (14940)
173	(cobalamin* or cyanocobalamin* or cobamide* or hydroxo-cobalamin* or hydroxycobalamin* or hydroxocobalamin*).ti,ab. (4933)
174	(riboflavin or vitamin B2 or vitamin B 2 or vitamin g).ti,ab. (7351)
175	(magnesium adj2 (supplement* or salt* or carbonate or oxide or chloride or sulphate or sulfate or maleate or
176	(coenzyme Q10 or ubiquinone or ubidecarenone).ti,ab. (6769)
177	Herbal Medicine/ or Drugs,chinese herbal/ (28852)
178	Tanacetum parthenium/ (147)
179	Petasites/ (75)
180	Phytotherapy/ (28467)
181	Plants, Medicinal/ (51346)
182	plant preparations/ or plant extracts/ (73172)
183	feverfew*.ti,ab. (204)
184	((chrysanthemum or tanacetum) adj2 parthenium*).ti,ab. (109)
185	(butterbur* or petasite*).ti,ab. (166)
186	exp Exercise Therapy/ (29095)

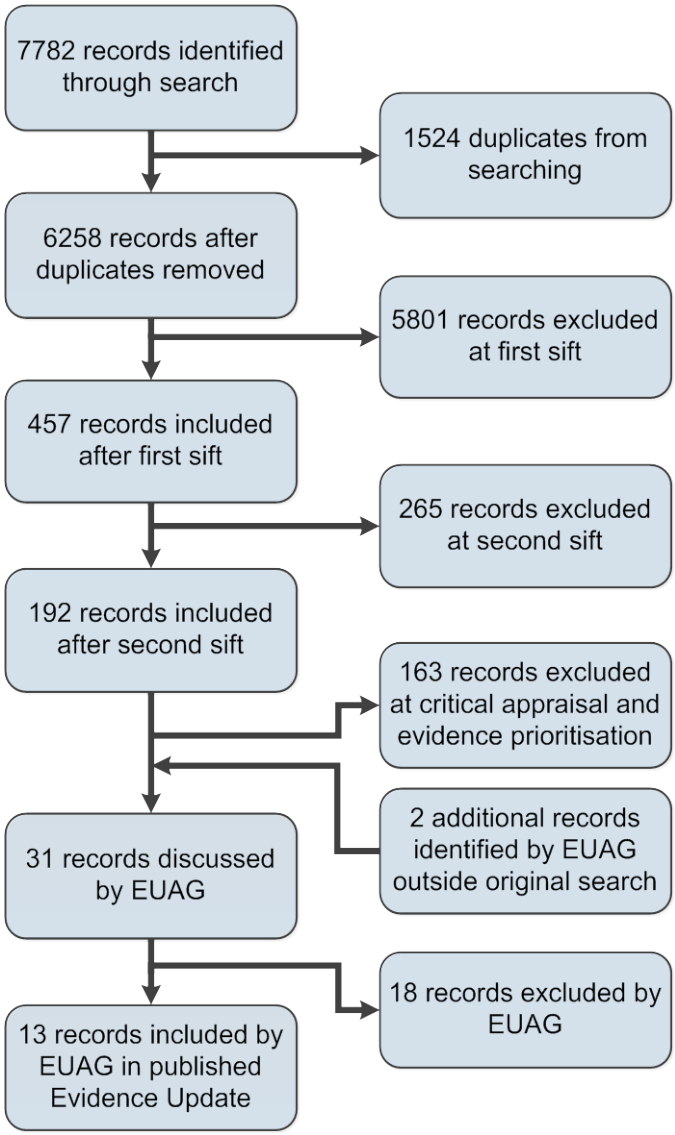
187	exercise/ (65057)
188	"Physical Education and Training"/ (11689)
189	exp Exercise Movement Techniques/ (5086)
190	(exercise adj3 (session* or training or technique* or physical or isometric or aerobic or therap* or program* or class*)).ti,ab. (36590)
191	(tai chi or tai ji or pilates or yoga).ti,ab. (2169)
192	(physical adj2 (training or education or program*)).ti,ab. (10451)
193	exp Musculoskeletal Manipulations/ or "Physical Therapy (Speciality)"/ or Physical Therapy Modalities/ (38403)
194	Chiropractic/ (2981)
195	Manipulation, Orthopedic/ (3394)
196	Osteopathic Medicine/ (2540)
197	((lumbar or cervical or spinal or musculoskeletal) adj2 manipulat*).ti,ab. (1334)
198	(osteopath* or chiropractic* or reflexolog* or massage or acupressure or shiatsu or shiatzu).ti,ab. (13269)
199	((movement or manual or manipulat* or trigger point or motion or passive or cpm) adj2 therap*).ti,ab. (4231)
200	(stretching adj2 (exercise* or relaxed or dynamic or passive or muscle or active or isometric)).ti,ab. (1299)
201	136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 (890388)
202	Self Care/ or Social Support/ or Counseling/ (97112)
203	Self-Help Groups/ or exp Patient participation/ (24989)
204	health education/ or exp consumer health information/ or patient education as topic/ or Communication/ or Health Communication/ (177915)
205	patient education handout/ (3919)
206	teaching/ or exp Programmed Instruction as Topic/ (51665)
207	exp communications media/ or Hotlines/ or exp Internet/ (265403)
208	information centers/ or information services/ or learning/ (60665)
209	Information Dissemination/ or Health Knowledge, Attitudes, Practice/ (79423)
210	(self care or self-care or selfcare or selfhelp or self-help or self help or self-management or self management).ti,ab. (19869)
211	(social support or support group*).ti,ab. (23394)
212	((education* or learn* or training or teach*) adj2 (program* or patient* or consumer* or material* or resource* or aid*)).ti,ab. (85274)
213	(information adj2 (resource* or leaflet* or pamphlet* or handout*)).ti,ab. (3535)
214	(patient adj (information or knowledge or website*)).ti,ab. (5283)
215	(workshop* or counse?ling or seminar* or discussion group*).ti,ab. (84616)
216	(factsheet* or advice line* or advice-line* or help line* or help-line* or

	helpline*).ti,ab. (558)
217	Cognitive Therapy/ (15130)
218	exp Biofeedback, Psychology/ or feedback/ or feedback, psychological/ or autogenic training/ (36617)
219	Breathing Exercises/ (2683)
220	relaxation therapy/ (5657)
221	Muscle Relaxation/ (11366)
222	Relaxation/ (1756)
223	"Imagery (Psychotherapy)"/ (1149)
224	Meditation/ (1481)
225	Mind-Body Therapies/ or Mind-Body Relations, metaphysical/ (2041)
226	Psychotherapy/ (40371)
227	(cognitive adj behavio?r adj (therap* or treatment or technique*)).ti,ab. (1945)
228	(neurofeedback or biofeedback).ti,ab. (4922)
229	((controlled or paced or therap* or exercise*) adj2 breathing).ti,ab. (1593)
230	(respirat* adj3 (training or exercise* or therap*)).ti,ab. (5492)
231	(CBT or qigong).ti,ab. (4562)
232	(guided adj2 (imagery or visuali*)).ti,ab. (523)
233	(mindfulness or meditation or attention* control training).ti,ab. (3043)
234	((finger or hand) adj2 warming).ti,ab. (63)
235	(relaxation adj2 (therap* or training)).ti,ab. (1723)
236	(relaxation adj2 (therap* or training)).ti,ab. (1723)
237	exp Oxygen Inhalation Therapy/

	(21163)
238	oxygen.ti,ab. (278840)
239	or/237-238 (287809)
240	(pregnan* or prenatal).mp. (776542)
241	239 and 240 (6949)
242	Abnormalities, Drug-Induced/ (13733)
243	239 and 242 (84)
244	exp Oxygen Inhalation Therapy/ae, ct [Adverse Effects, Contraindications] (2034)
245	241 or 243 or 244 (8921)
246	Pregnancy Outcome/ (36566)
247	((pregnan* or birth) adj2 outcome*).mp. (45643)
248	exp Pregnancy Complications/ (333704)
249	exp Congenital Abnormalities/ (455201)
250	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp. (240496)
251	or/246-250 (793992)
252	245 and 251 (2938)
253	(pregnan* or prenatal).mp. (776542)
254	Tryptamines/ or Sumatriptan/ (6214)
255	(triptan$ or Almotriptan or Eletriptan or Frovatriptan or Naratriptan or Rizatriptan or Sumatriptan or Zolmitriptan).mp. (4065)
256	(almogran or relpax or migard or naramig or maxalt or imigran or zomig).mp. (83)
257	254 or 255 or 256 (7281)

258	253 and 257 (126)
259	Abnormalities, Drug-Induced/ (13733)
260	257 and 259 (15)
261	Sumatriptan/ae, ct, po, to (439)
262	258 or 260 or 261 (542)
263	Pregnancy Outcome/ (36566)
264	((pregnan* or birth) adj2 outcome*).mp. (45643)
265	exp Pregnancy Complications/ (333704)
266	exp Congenital Abnormalities/ (455201)
267	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp. (240496)
268	or/263-267 (793992)
269	262 and 268 (55)
270	exp Verapamil/ (16638)
271	(Verapamil or Calan or Cordilox or Dexverapamil or Falicard or Finoptin or Iproveratril or Isoptin or Isoptine or Izoptin or Lekoptin).ti,ab. (20232)
272	or/202-203 (118538)
273	(pregnan* or prenatal).mp. (776542)
274	272 and 273 (8736)
275	Abnormalities, Drug-Induced/ (13733)
276	272 and 275 (66)
277	Verapamil/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity] (1194)
278	274 or 276 or 277 (9932)
279	Pregnancy Outcome/ (36566)
280	((pregnan* or birth) adj2 outcome*).mp. (45643)
281	exp Pregnancy Complications/ (333704)
282	exp Congenital Abnormalities/ (455201)
283	((f?etal or f?etus or birth or neonatal or congenital or pregnan*) adj3 (complication* or abnormal* or defect* or malformation*)).mp. (240496)
284	or/279-283 (793992)
285	278 and 284 (3684)
286	or/75-236 (6666316)
287	252 or 269 or 285 (6673)
288	286 or 287 (6668585)
289	74 and 288 (1729)
290	limit 289 to yr="2012 -Current" (1549)

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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