

## Headache (chronic tension-type)

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### ABSTRACT

**INTRODUCTION:** Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with daily, or very frequent, episodes of headache lasting hours or they may be continuous. It affects up to 4% of the general population, and is more prevalent in women (up to 65% of cases). **METHODS AND OUTCOMES:** We conducted a systematic overview, aiming to answer the following clinical questions: What are the effects of drug treatments for CTTH? What are the effects of non-drug treatments for CTTH? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2013 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). **RESULTS:** At this update, searching of electronic databases retrieved 125 studies. After deduplication, 77 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 56 studies and the further review of 21 full publications. Of the 21 full articles evaluated, three systematic reviews and one RCT were included at this update. We performed a GRADE evaluation for 15 PICO combinations. **CONCLUSIONS:** In this systematic overview, we categorised the efficacy for 12 interventions based on information about the effectiveness and safety of non-drug treatments acupuncture and cognitive behavioural therapy (CBT), as well as the drug treatments amitriptyline, anticonvulsant drugs (sodium valproate, topiramate, or gabapentin), benzodiazepines, botulinum toxin, noradrenergic and specific serotonergic antidepressants (mirtazapine), NSAIDs (e.g. ibuprofen); opioid analgesics (e.g. codeine), paracetamol, serotonin re-uptake inhibitor antidepressants (SSRIs, SNRIs), and tricyclic antidepressants (other than amitriptyline).

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INTERVENTIONS	
<b>DRUG TREATMENTS</b>	
<b>Beneficial</b>	Tricyclic antidepressants (other than amitriptyline) . . . . . 2
Amitriptyline . . . . . 4	<b>Likely to be ineffective or harmful</b>
<b>Likely to be beneficial</b>	Benzodiazepines . . . . . 8
Noradrenergic and specific serotonergic antidepressants (mirtazapine) . . . . . 12	Botulinum toxin . . . . . 9
<b>Unknown effectiveness</b>	NSAIDs (e.g., ibuprofen) . . . . . 11
Anticonvulsant drugs (sodium valproate, topiramate, or gabapentin) . . . . . 7	<b>NON-DRUG TREATMENTS</b>
Opioid analgesics (e.g., codeine) . . . . . 16	<b>Unknown effectiveness</b>
Paracetamol . . . . . 17	Acupuncture . . . . . 22
Serotonin re-uptake inhibitors (SSRI and SNRI antidepressants) . . . . . 17	Cognitive behavioural therapy (CBT) . . . . . 26

### Key points

- Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with headache on 15 or more days per month, lasting hours, or they may be continuous.
  - It affects up to 4% of the general population, and is more prevalent in women (up to 65% of cases).
- We found limited evidence about drug treatments for CTTH.
- Sustained use of **non-steroidal anti-inflammatory drugs (NSAIDs)** (such as ibuprofen) for more than 2 days per week may lead to chronic headache symptoms and reduce the effectiveness of prophylactic treatment.
- We found no evidence from systematic reviews or RCTs on the effectiveness of **paracetamol** and **opioid analgesics**. However, along with NSAIDs, these are likely to cause analgesia overuse headaches.
- Amitriptyline** and **mirtazapine** may be equally effective at reducing the frequency and intensity of CTTH, although amitriptyline may be associated with a less favourable adverse-effect profile.
  - Amitriptyline may be more effective than placebo in reducing headache duration and frequency.
  - High-dose mirtazapine may be more effective than placebo at reducing headache frequency, duration, and intensity. However, low-dose mirtazapine may be no more effective than placebo.
  - We don't know how low-dose mirtazapine and ibuprofen compare at reducing headache symptoms.
- We found no evidence examining the effectiveness of **noradrenergic and specific serotonergic antidepressants** other than mirtazapine in CTTH.

- Sodium valproate, an [anticonvulsant](#), may be no more effective than placebo at reducing headache pain intensity in CTTH, but it may be more effective at reducing headache frequency. However, this is based on limited evidence.  
We found no evidence examining the effectiveness of other anticonvulsants, such as topiramate and gabapentin, in CTTH.
- Results of use of [SSRIs](#) and [tricyclic antidepressants other than amitriptyline](#) are unknown in treating CTTH.
- We don't know whether [benzodiazepines](#) are effective in treating CTTH, and they are commonly associated with significant adverse effects.
- [Botulinum toxin](#) does not seem to be a useful treatment for CTTH. It may be associated with several adverse effects, including facial weakness, difficulty in swallowing, and disturbed local sensation.
- We don't know whether non-drug treatments, specifically [CBT](#) or [acupuncture](#), are effective in treating CTTH.

## Clinical context

### GENERAL BACKGROUND

Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with daily, or very frequent, episodes of headache lasting hours or they may be continuous. The 2004 International Headache Society (IHS) criteria for CTTH are: headaches on 15 or more days a month (180 days/year) for at least 3 months; pain that is bilateral, pressing, or tightening in quality and non-pulsating, of mild or moderate intensity, which does not worsen with routine physical activity (such as walking or climbing stairs); presence of no more than one additional clinical feature (mild nausea, photophobia, or phonophobia); and without moderate/severe nausea or vomiting.

### FOCUS OF THE REVIEW

Tension-type headache is a common disorder, which can cause anxiety and interfere with daily living. If treated incorrectly, it can lead to worsening of symptoms, such as comorbid analgesia overuse headache. Therefore, effective management, which is discussed in this overview, is important to prevent further complications and restore functionality. For non-drug treatments, we focused specifically on acupuncture and CBT as areas where there might be new evidence since the [previous update](#). The authors determined that there was no change in the evidence-base for other non-invasive physical or manual therapies since the previous version, which also included Indian head massage, relaxation or electromyographic biofeedback, and spinal manipulation (chiropractic and osteopathic treatment).

### COMMENTS ON EVIDENCE

There is very limited evidence on prophylactic treatment of CTTH, including for amitriptyline and mirtazapine, which are common treatments for this condition. Most studies are small, short-term in duration, and use different outcome measures. The interpretation of clinical trials in the area of CTTH is further complicated by varying diagnostic expertise, difficulties in obtaining reliable retrospective patient histories, and patient selection.

### SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, March 2007, to December 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 125 studies. After deduplication, 77 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 56 studies and the further review of 21 full publications. Of the 21 full articles evaluated, three systematic reviews and one RCT were included at this update.

### ADDITIONAL INFORMATION

Overall, based on current evidence, the best treatment for CTTH is amitriptyline with lifestyle advice, which should include avoidance of analgesia and caffeine. There is limited evidence to suggest that non-pharmacological treatments, such as relaxation techniques and acupuncture, are of any benefit.

### DEFINITION

Chronic tension-type headache (CTTH) is a disorder that evolves from episodic tension-type headache, with daily, or very frequent, episodes of headache lasting hours or they may be continuous.<sup>[1]</sup> The 2004 International Headache Society (IHS) criteria for CTTH are: headaches on 15 or more days a month (180 days/year) for at least 3 months; pain that is bilateral, pressing, or tightening in quality and non-pulsating, of mild or moderate intensity, which does not worsen with routine physical activity (such as walking or climbing stairs); presence of no more than one additional clinical feature (mild nausea, photophobia, or phonophobia); and without moderate/severe nausea or vomiting.<sup>[1]</sup> CTTH is generally regarded as a featureless headache. Not all experts agree that mild features more typically seen in migraine (photophobia, phonophobia, etc.) should be included in the operational definition of CTTH, and it is often difficult to distinguish mild migraine

headache from tension-type headache. CTTH is to be distinguished from other causes of chronic daily headache that require different treatment strategies (e.g., new daily persistent headache, medication overuse headache, chronic migraine, hemicrania continua). Many people who develop chronic daily headache owing to chronic migraine or medication overuse also develop mild migrainous 'background' headaches that might be mistaken for coincidental CTTH. It is, therefore, extremely important to take a full headache history to elicit the individual features of the headache and look for prodromal or accompanying features that might indicate an alternative diagnosis. In contrast to CTTH, episodic tension-type headache can last from 30 minutes to 7 days, and occurs on less than 180 days a year. The greatest obstacle to studying tension-type headache is the lack of any single proven specific or reliable, clinical, or biological defining characteristic of the disorder. Terms based on assumed mechanisms (muscle contraction headache or tension headache) are not operationally defined. Old studies that used these terms may have included people with many different types of headache. The interpretation of clinical trials in the area of CTTH is complicated by varying diagnostic expertise, difficulties in obtaining reliable retrospective patient histories, and patient selection. As such, in clinical practice, headache practitioners very rarely encounter patients where the diagnosis of 'pure' CTTH is apparent and not complicated by additional headache disorder and/or medication overuse. This has led many headache practitioners to consider that tension type headache might be a relatively featureless form of migraine, especially in those cases where medication overuse is a feature and the CTTH component represents the milder headache days. This should lead to some caution in interpreting results of treatment trials in this area.

<b>INCIDENCE/ PREVALENCE</b>	The prevalence of chronic daily headache from a survey of the general population in the US was 4%. Half of sufferers met the IHS criteria for CTTH. <sup>[2]</sup> In a survey of 2500 undergraduate students in the US, the prevalence of CTTH was 2%. <sup>[3]</sup> The prevalence of CTTH was 2.5% in a Danish population-based survey of 975 individuals. <sup>[4]</sup> One community-based survey in Singapore (2096 people from the general population) found that the prevalence was about 2% in women and 1% in men. <sup>[5]</sup>
<b>AETIOLOGY/ RISK FACTORS</b>	Tension-type headache is more prevalent in women (65% of cases in one survey). <sup>[6]</sup> Symptoms begin before the age of 10 years in 15% of people with CTTH. Prevalence declines with age. <sup>[7]</sup> There is a family history of some form of headache in 40% of people with CTTH, <sup>[8]</sup> although one twin study found that the risk of CTTH was similar for identical and non-identical twins. <sup>[9]</sup>
<b>PROGNOSIS</b>	The prevalence of CTTH declines with age. <sup>[7]</sup>
<b>AIMS OF INTERVENTION</b>	To reduce the frequency, severity, and duration of headache, with minimal adverse effects from treatment.
<b>OUTCOMES</b>	<b>Symptom severity</b> (headache scores [e.g. headache index score], headache frequency, headache intensity, and headache duration); <b>adverse effects</b> .
<b>METHODS</b>	<b>Search strategy</b> <i>BMJ Clinical Evidence</i> search and appraisal date December 2013. Databases used to identify studies for this systematic overview include: Medline 1966 to December 2013, Embase 1980 to December 2013, The Cochrane Database of Systematic Reviews 2013, issue 12 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. <b>Inclusion criteria</b> Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing at least 20 individuals (at least 10 per arm) of whom at least 80% were followed up. There was no minimum length of follow-up. We included adults (aged >16 years) with chronic tension type headache and, where possible, diagnosis according to International Headache Society (any version) — see further detail in definition section above. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. <i>BMJ Clinical Evidence</i> does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. <b>Evidence evaluation</b> A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed <i>a priori</i> with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections (see below). <b>Adverse effects</b> All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although <i>BMJ Clinical Evidence</i> presents data

on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 31 ). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website ([www.clinicalevidence.com](http://www.clinicalevidence.com)).

**QUESTION** What are the effects of drug treatments for chronic tension-type headache?

**OPTION** AMITRIPTYLINE

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- Amitriptyline may be more effective than placebo in reducing headache duration and frequency.
- Amitriptyline and mirtazapine may be equally effective at reducing the frequency and intensity of chronic tension-type headache (CTTH), although amitriptyline may be associated with a less-favourable adverse effect profile.

**Benefits and harms**

**Amitriptyline versus placebo:**

We found two systematic reviews (search date 2009; <sup>[10]</sup> and 1994 <sup>[11]</sup>) and three additional RCTs <sup>[12]</sup> <sup>[13]</sup> <sup>[14]</sup> comparing amitriptyline with placebo (dosage range 10–150 mg; treatment duration 4–32 weeks). The first systematic review <sup>[10]</sup> identified one RCT <sup>[15]</sup> that met *BMJ Clinical Evidence* inclusion criteria. As the systematic review did not carry out a meta-analysis but did report a different analysis from that in the RCT, we have reported from both here. The second systematic review <sup>[11]</sup> identified one RCT, <sup>[16]</sup> and we have reported directly from the RCT here. All but one of the RCTs <sup>[12]</sup> found that amitriptyline significantly improved headache duration and frequency in people with moderate-to-severe, properly-defined CTTH. Most of the recent RCTs were small, of short-term duration, and used different outcome measures.

**Symptom severity**

*Amitriptyline compared with placebo* Amitriptyline may be more effective at reducing headache duration and frequency in people with moderate-to-severe chronic tension-type headache ([low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache scores</b>					
<sup>[16]</sup> RCT 3-armed trial	90 people; diagnosed using Criteria of the Ad Hoc Committee, 1962 <sup>[2]</sup>  In review <sup>[11]</sup>  4-week trial duration	<b>Reduction in mean headache score , 1 week</b> with amitriptyline 10 mg with placebo  Absolute results not reported  The remaining arm compared amitriptyline 25 mg	P <0.001  Mild reduction in headache scores at week 1 with amitriptyline 10 mg		amitriptyline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] RCT <b>3-armed trial</b>	90 people; diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] In review [11] 4-week trial duration	<b>Reduction in mean headache score , 2 and 4 weeks</b> with amitriptyline 10 mg with placebo Absolute results not reported The remaining arm compared amitriptyline 25 mg	No reduction in headache scores at weeks 2 or 4 with amitriptyline 10 mg		
[16] RCT <b>3-armed trial</b>	90 people; diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] In review [11] 4-week trial duration	<b>Reduction in mean headache score , 1, 2, and 4 weeks</b> with amitriptyline 25 mg with placebo Absolute results not reported The other arm compared amitriptyline 10 mg	No difference noted at 1, 2, or 4 weeks with 25 mg dose of amitriptyline		
[15] RCT <b>Crossover design</b> <b>3-armed trial</b>	40 people; diagnosed using IHS criteria [17] In review [10] 32-week trial duration	<b>Reduction in area under headache curve (AUC) , 32 weeks</b> with amitriptyline with placebo Absolute results not reported AUC was calculated as daily headache duration x headache intensity The remaining arm compared citalopram	P = 0.002 for amitriptyline v placebo Results in 34/40 people (85%) who completed the trial Significant result for combined outcome resulted primarily from significant reductions in duration of headache (P = 0.01), rather than headache intensity (P = 0.12)	○○○	amitriptyline
[12] RCT <b>5-armed trial</b>	203 people; diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] 4-week trial duration	<b>Clinically important improvement (50% or more reduction in headache scores) , 4 weeks</b> 34/53 (64%) with amitriptyline 14/48 (29%) with placebo The remaining arms evaluated nortriptyline, stress management, and stress management plus antidepressant drugs	RR 2.19 95% CI 1.35 to 3.57	●●○	amitriptyline
[12] RCT <b>5-armed trial</b>	203 people; diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] 4-week trial duration	<b>Headache index scores , 4 weeks</b> with amitriptyline with placebo Absolute results not reported The remaining arms evaluated nortriptyline, stress management, and stress management plus antidepressant drugs	MD 0.92 95% CI 0.44 to 1.41	○○○	amitriptyline
<b>Headache duration, frequency, or intensity</b>					
[10] Systematic review	40 people; diagnosed using IHS criteria [17] Data from 1 RCT 3-armed crossover RCT	<b>Headache intensity , 32 weeks</b> with amitriptyline with placebo Absolute results not reported The remaining arm evaluated citalopram	SMD +0.06 95% CI -0.42 to +0.53	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[10] Systematic review	40 people; diagnosed using IHS criteria [17] 3-armed crossover RCT	<b>Headache duration , 32 weeks</b> with amitriptyline with placebo Absolute results not reported The remaining arm evaluated citalopram	SMD +0.22 95% CI -0.26 to +0.7	↔	Not significant
[14] RCT Crossover design	27 people; diagnosed using IHS criteria [17] 8-week trial duration	<b>50% reduction in headache frequency or severity</b> with amitriptyline with placebo Absolute results not reported	P <0.001	○○○	amitriptyline
[13] RCT 3-armed trial	203 people; diagnosed using Criteria of the Ad Hoc Committee, 1962 [2] 16-week trial duration	<b>50% or more reduction in headache frequency, duration, and intensity</b> with amitriptyline with amitriptyline-N-oxide with placebo Absolute results not reported	Reported as not significant for both amitriptyline and amitriptyline-N-oxide v placebo	↔	Not significant

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[10] Systematic review	People with tension-type headache	<b>Adverse effects</b> with amitriptyline with placebo Absolute results not reported The review reported that several RCTs reported data on adverse events, which were often minor and comparable in the antidepressant and placebo groups			

No data from the following reference on this outcome. [12] [13] [14] [15] [16]

### Amitriptyline versus SSRI antidepressants:

See option on Serotonin reuptake inhibitors (SSRIs and SNRIs), p 17 .

### Amitriptyline versus mirtazapine:

See option on Noradrenergic and specific serotonergic antidepressants (mirtazapine), p 12 .



## Amitriptyline versus CBT plus relaxation:

See option on CBT, p 26 .

### Further information on studies

<sup>[15]</sup> Similar results for adverse effects have also been found in other studies for amitriptyline.

**Comment:** It has been shown that amitriptyline is effective in reducing the number of headache days, as well as reducing the severity of the headache.

#### Clinical guide

Analgesics need to be reduced or stopped where possible to prevent analgesia overuse headaches.

### OPTION ANTICONVULSANT DRUGS

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 31](#) .
- Sodium valproate may be no more effective than placebo at reducing headache pain intensity, but it may be more effective at reducing headache frequency. However, this is based on limited evidence from one small study.
- We don't know how effective topiramate or gabapentin are compared with placebo in people with chronic tension-type headache (CTTH), as we found no evidence.

### Benefits and harms

#### Anticonvulsant drugs (sodium valproate, topiramate, or gabapentin) versus placebo:

We found one systematic review (search date 2009), <sup>[10]</sup> which identified no RCTs. We found one small additional RCT comparing sodium valproate with placebo. <sup>[18]</sup>

#### Symptom severity

*Anticonvulsant drugs (sodium valproate, topiramate, or gabapentin) compared with placebo* We don't know whether sodium valproate is more effective than placebo at reducing headache pain (assessed by visual analogue scale [VAS]), but it may be more effective at reducing headache frequency ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
<sup>[18]</sup> RCT	41 people with CTTH (diagnostic criteria used were unclear)	<b>Mean general pain (assessed by VAS) , 3 months</b> 4.1 with sodium valproate 4.0 with placebo 23 people in the sodium valproate group, and 18 people in the placebo group	Reported as not significant P value not reported Non-significant between-group differences were also reported at 1 month (P values not reported)	↔	Not significant
<sup>[18]</sup> RCT	41 people with CTTH (diagnostic criteria used were unclear)	<b>Mean maximum pain (assessed by VAS) , 3 months</b> 5.3 with sodium valproate 5.6 with placebo 23 people in the sodium valproate group, and 18 people in the placebo group	Reported as not significant P value not reported Non-significant between-group differences were also reported at 1 month (P values not reported)	↔	Not significant
<sup>[18]</sup> RCT	41 people with CTTH (diagnostic criteria used were unclear)	<b>Pain frequency (mean number of days with pain per month) , 3 months</b> 10.5 with sodium valproate	P <0.05 Significant between-group differences for pain frequency were also observed at 1 month	○○○	sodium valproate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		22.3 with placebo 23 people in the sodium valproate group, and 18 people in the placebo group	in favour of sodium valproate (12.5 days/month with sodium valproate v 22.5 days/month with placebo, P <0.05)		

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[18] RCT	70 people with chronic daily headache (41 with CTTH and 29 with chronic migraine; diagnostic criteria used were unclear)	<b>Adverse effects , 3 months</b> 3/40 (8%) with sodium valproate 1/30 (3%) with placebo  In the sodium valproate group, 1 person had somnolence/tremor, 1 person had impotence, and 1 person had hair loss  In the placebo group, 1 person refused to continue treatment because of dizziness and nausea	Significance not assessed		

### Further information on studies

[18] Randomisation and allocation concealment used in the study were not described. The RCT did not define the diagnostic criteria used for CTTH; however, it did analyse separately those people with chronic migraine (except for adverse effects). Sodium valproate was given once daily for the first week and then twice daily for the next 11 weeks.

**Comment:** None.

## OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- We don't know whether benzodiazepines are effective in treating chronic tension-type headache (CTTH). They are commonly associated with serious adverse effects, such as an increased risk of motor vehicle accidents, falls and fractures, fatal poisonings, depression, dependency, decline in functional status, cognitive decline, confusion, erratic behaviour, and amnesia.

### Benefits and harms

#### Benzodiazepines versus placebo:

We found one systematic review (search date 2009), [10] which identified no RCTs that met our inclusion criteria.



## Further information on studies

<sup>[19]</sup> The adverse effects of benzodiazepines include increased risk of motor vehicle accidents, falls and fractures, fatal poisonings, depression, dependency, decline in functional status, cognitive decline, confusion, erratic behaviour, and amnesia.

**Comment:** We found two RCTs that did not meet our inclusion criteria; one was too small (16 people), and the other did not meet the at least 80% follow-up criteria. Both RCTs found modest short-term improvements in CTTH with benzodiazepines (diazepam or alprazolam).<sup>[20]</sup> <sup>[21]</sup>

## OPTION BOTULINUM TOXIN

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- Botulinum toxin does not seem to be a useful treatment for chronic tension-type headache (CTTH). It may be associated with several adverse effects including facial weakness, neck pain, and disturbed local sensation.

## Benefits and harms

### Botulinum toxin versus placebo:

We found one systematic review (search date 2012),<sup>[22]</sup> which identified nine RCTs. Of the nine RCTs, eight included only people with CTTH and one included a mixed population of people with either chronic or episodic tension-type headaches.

### Symptom severity

*Botulinum toxin compared with placebo* Botulinum toxin may be no more effective than placebo at improving the frequency of CTTH (*low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache frequency</b>					
<sup>[22]</sup> Systematic review	675 people with CTTH 7 RCTs in this analysis See Further information on studies	<b>Headache frequency (mean headaches/month) , 56–120 days</b> with botulinum toxin A with placebo Absolute results not reported 434 people in the botulinum toxin A group, and 241 people in the placebo group	MD -1.43 95% CI -3.13 to +0.27 Heterogeneity: $I^2 = 61.5\%$ ; P = 0.02 See Further information on studies	↔	Not significant
<sup>[22]</sup> Systematic review	447 people with CTTH 3 RCTs in this analysis See Further information on studies	<b>Proportion of people with 50% reduction in headaches per month</b> 53/320 (17%) with botulinum toxin A 23/122 (19%) with placebo	RR 1.00 95% CI 0.57 to 1.76	↔	Not significant

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[22] Systematic review	3097 adults with headache See Further information on studies	<b>Blepharoptosis</b> 136/1797 (8%) with botulinum toxin A 13/1300 (1%) with placebo	RR 9.5 95% CI 4.7 to 18.9		placebo
[22] Systematic review	2783 adults with headache See Further information on studies	<b>Muscle weakness</b> 358/1706 (21%) with botulinum toxin A 25/1077 (2%) with placebo	RR 8.9 95% CI 2.5 to 30.9 Heterogeneity: $I^2 = 85.8\%$ (P value not reported)		placebo
[22] Systematic review	2033 adults with headache See Further information on studies	<b>Neck pain</b> 230/1205 (19%) with botulinum toxin A 30/828 (4%) with placebo	RR 4.7 95% CI 3.2 to 6.9		placebo
[22] Systematic review	767 adults with headache See Further information on studies	<b>Neck stiffness</b> 56/395 (14%) with botulinum toxin A 16/372 (4%) with placebo	RR 3.2 95% CI 1.9 to 5.6		placebo
[22] Systematic review	3110 adults with headache See Further information on studies	<b>Paraesthesia</b> 54/1794 (3%) with botulinum toxin A 18/1316 (1%) with placebo	RR 3.3 95% CI 1.3 to 7.9		placebo
[22] Systematic review	1088 adults with headache See Further information on studies	<b>Skin tightness</b> 30/580 (5%) with botulinum toxin A 7/508 (1%) with placebo	RR 3.6 95% CI 1.6 to 8.3		placebo

### Further information on studies

[22] *Diagnostic criteria* The diagnostic criteria used in each RCT for defining CTTH was not reported in the systematic review. However, the review categorised "chronic headache" as 15 or more headaches per month.

[22] *Heterogeneity* The systematic review carried out sensitivity analyses and found no relationship between quality (Jadad scores), quality items (e.g., ITT, randomisation, industry sponsorship, blinding, attrition), and outcomes. There were no relationships between age, sex, sample size, study duration, botulinum toxin dose or injection strategy (i.e., fixed injection sites, or 'follow the pain' protocols) and study outcomes. All nine RCTs in people with CTTH used a single injection of botulinum only. There was no evidence of publication bias. Also, re-analysis of the data, adjusting for the lack of normality from the small sample sizes of the various studies, produced non-significant results.

[22] *Adverse effects* The analysis of adverse effects included a mixture of studies, including episodic migraine (10 studies), chronic migraine (5 studies), chronic daily headache (3 studies), CTTH (8 studies), and mixed episodic and CTTH (1 study). The review did not specify the studies from which the adverse effects data were derived.

**Comment:** Botulinum toxin has a role in some primary headache disorders; however, its role in CTTH is not established and it may be associated with facial weakness, difficulty swallowing, and disturbed local sensation. Studies so far have been too small to validate its use at present.

**OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)**

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- NSAIDs (ibuprofen) may lead to chronic headache symptoms and reduce the effectiveness of prophylactic treatment.

**Benefits and harms**

**NSAIDs versus placebo:**

We found one systematic review (search date 2009), [10] which identified one four-armed RCT [23] comparing ibuprofen alone, placebo, low-dose mirtazapine plus ibuprofen, and mirtazapine alone (see also option on Noradrenergic and specific serotonergic antidepressants, p 12 ). The review only reported results for headache intensity; therefore, we have reported directly from the RCT.

**Symptom severity**

*NSAIDs compared with placebo* Ibuprofen may be no more effective than placebo at reducing headache frequency and duration at 4 weeks. Moreover, ibuprofen may worsen headache intensity (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache duration, frequency, or intensity</b>					
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria [17]) In review [10]	<b>Headache frequency (days with headache) , from baseline to last 4 weeks of treatment</b>  28–27 with ibuprofen 28–28 with placebo  The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone	Reported as not significant P value not reported	↔	Not significant
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria [17]) In review [10]	<b>Headache duration (hours with headache) , from baseline to last 4 weeks of treatment</b>  248–231 with ibuprofen 371–334 with placebo  The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone	Reported as not significant P value not reported	↔	Not significant
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria [17]) In review [10]	<b>Headache intensity (11-point verbal rating scale, from 0 = headache-free to 10 = worst headache imaginable) , from baseline to last 4 weeks of treatment</b>  4.2–4.4 with ibuprofen 5.0–4.4 with placebo  The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone	P = 0.03	○○○	placebo

**Adverse effects**

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[23] RCT	93 people (diagnosed with IHS criteria [17])	<b>Proportion of people reporting one or more adverse effect</b>	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	In review <sup>[10]</sup>	<p>11/24 (46%) with ibuprofen 10/23 (43%) with placebo</p> <p>Adverse effects reported included drowsiness, weight gain, dry mouth, increased appetite, improved sleep, irritability, dyspepsia, feeling 'zombie-like', and various others, which were not defined</p> <p>The remaining arms evaluated mirtazapine plus ibuprofen, and mirtazapine alone</p>			

### Ibuprofen versus mirtazapine:

See option on Noradrenergic and specific serotonergic antidepressants, p 12 .

### Further information on studies

<sup>[23]</sup> This RCT is also reported in the option on [Noradrenergic and specific serotonergic antidepressants, p 12](#) .

### Comment:

We found one non-systematic review, which identified 29 observational studies (2612 people), and found no evidence of benefit of common analgesia for chronic tension-type headache (CTTH). It found that sustained frequent use (2–3 times/week) of some common analgesics in people with episodic headache was associated with chronic headache and reduced effectiveness of prophylactic treatment. <sup>[24]</sup>

### Clinical guide

Observational studies are difficult to interpret. From a practical, clinical perspective, it seems likely that all types of analgesic, when used on a regular basis, are capable of transforming acute headaches into chronic headaches in predisposed people. This applies to simple analgesics, such as paracetamol and NSAIDs, as well as opiates and compound analgesics containing mixes of different acute-attack medications (often including caffeine). In general, many headache experts advise people to eliminate medication overuse, and stop using acute-attack medications before considering preventative treatment for CTTH or other types of chronic daily headache. Where medication overuse is contributing to chronic daily headache, withdrawal may lead to temporary and short-lived worsening of the headache disorder followed by possible improvement. Caffeine also seems to provide acute relief for some types of headache, although regular use may contribute to perpetuating the headache into a chronic state. It may be helpful for some people to avoid caffeine when faced with chronic daily headaches such as chronic migraine or CTTH.

## OPTION

## NORADRENERGIC AND SPECIFIC SEROTONERGIC ANTIDEPRESSANTS

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 31](#) .
- High-dose mirtazapine may be more effective than placebo at reducing headache frequency, duration, and intensity. However, low-dose mirtazapine may be no more effective than placebo.
- Mirtazapine and amitriptyline may be equally effective at reducing the frequency and intensity of chronic tension-type headache (CTTH), although mirtazapine may be associated with a more favourable adverse effect profile.
- We found no direct information from RCTs about noradrenergic and specific serotonergic antidepressants other than mirtazapine in the treatment of people with CTTH.

## Benefits and harms

### Mirtazapine versus placebo:

We found one systematic review (search date 2009),<sup>[10]</sup> which identified two RCTs.<sup>[25] [23]</sup> The review only reported headache intensity for one RCT<sup>[23]</sup> and no outcomes for the other RCT; therefore, we have reported directly from the RCTs. One RCT examined high-dose mirtazapine (30 mg/day),<sup>[25]</sup> while the other RCT examined low-dose mirtazapine (4.5 mg/day).<sup>[23]</sup>

### Symptom severity

*Mirtazapine compared with placebo* High-dose mirtazapine may be more effective than placebo at reducing headache frequency, duration, and intensity at 8 weeks. However, low-dose mirtazapine may be no more effective than placebo at reducing headache frequency, duration, and intensity (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache duration, frequency, or intensity</b>					
<sup>[25]</sup> RCT Crossover design	24 people (diagnosed with IHS criteria <sup>[17]</sup> ) Total trial duration was 18 weeks	<b>Headache frequency (days with headache) , last 4 weeks of treatment</b> 25.5 with high-dose mirtazapine 28.0 with placebo	P = 0.005 The RCT did not report results before crossover, so results should be interpreted with caution	○○○	mirtazapine
<sup>[25]</sup> RCT Crossover design	24 people (diagnosed with IHS criteria <sup>[17]</sup> ) Total trial duration 18 weeks	<b>Headache duration (hours with headache) , last 4 weeks of treatment</b> 210 with high-dose mirtazapine 288 with placebo	P = 0.03 The RCT did not report results before crossover, so results should be interpreted with caution	○○○	mirtazapine
<sup>[25]</sup> RCT Crossover design	24 people (diagnosed with IHS criteria <sup>[17]</sup> ) Total trial duration 18 weeks	<b>Headache intensity (verbal rating scale 0–10) , last 4 weeks of treatment</b> 4.2 with high-dose mirtazapine 4.3 with placebo	P = 0.03 The RCT did not report results before crossover, so results should be interpreted with caution	○○○	mirtazapine
<sup>[23]</sup> RCT 4-armed trial	93 people (diagnosed with IHS criteria <sup>[17]</sup> )	<b>Headache frequency (change from baseline in days with headache) , last 4 weeks of treatment</b> 28–28 with low-dose mirtazapine 28–28 with placebo The remaining arms evaluated mirtazapine plus ibuprofen and ibuprofen alone	Reported as not significant P value not reported	↔	Not significant
<sup>[23]</sup> RCT 4-armed trial	93 people (diagnosed with IHS criteria <sup>[17]</sup> )	<b>Headache duration (change from baseline in hours with headache) , last 4 weeks of treatment</b> 408–290 with low-dose mirtazapine 371–334 with placebo The remaining arms evaluated mirtazapine plus ibuprofen, and ibuprofen alone	Reported as not significant P value not reported	↔	Not significant
<sup>[23]</sup> RCT 4-armed trial	93 people (diagnosed with IHS criteria <sup>[17]</sup> )	<b>Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache free to 10 = worst headache imaginable) , last 4 weeks of treatment</b> 4.5–4.1 with low-dose mirtazapine 5.0–4.4 with placebo	Reported as not significant P value not reported	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The remaining arms evaluated mirtazapine plus ibuprofen, and ibuprofen alone			

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[25] RCT Crossover design	24 people	<p><b>Proportion of people reporting one or more adverse effect</b></p> <p>24/24 (100%) with high-dose mirtazapine</p> <p>18/24 (75%) with placebo</p> <p>Adverse effects included drowsiness, dizziness, weight gain, dry mouth, increased appetite, oedema in extremities, sleep disturbances, nausea, concentration difficulties, irritability, and various (not defined)</p>	P = 0.39	↔	Not significant
[23] RCT 4-armed trial	93 people	<p><b>Proportion of people reporting one or more adverse effect</b></p> <p>14/23 (61%) with low-dose mirtazapine</p> <p>10/23 (43%) with placebo</p> <p>Adverse effects included drowsiness, weight gain, dry mouth, increased appetite, improved sleep, irritability, dyspepsia, feeling 'zombie-like', and various (not defined)</p> <p>The remaining arms evaluated mirtazapine plus ibuprofen and ibuprofen alone</p>	Significance not assessed		

## Mirtazapine versus ibuprofen:

We found one systematic review (search date 2009),<sup>[10]</sup> which identified one four-armed RCT comparing low-dose mirtazapine (4.5 mg/day), mirtazapine plus ibuprofen, ibuprofen alone, and placebo (see also option on NSAIDs, p 11 ).<sup>[23]</sup> The review only reported results for headache intensity; therefore, we have reported directly from the RCT.

## Symptom severity

*Mirtazapine compared with ibuprofen* We don't know how low-dose mirtazapine and ibuprofen compare at reducing headache frequency, duration, or intensity at 4 weeks (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria <sup>[17]</sup> ) In review <sup>[10]</sup>	<p><b>Headache frequency (change from baseline in days with headache), last 4 weeks of treatment</b></p> <p>28–28 with low-dose mirtazapine</p>	Reported as not significant P value not reported	↔	Not significant



Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		28–27 with ibuprofen The remaining arms evaluated mirtazapine plus ibuprofen and placebo			
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria [17]) In review [10]	<b>Headache duration (change from baseline in hours with headache), last 4 weeks of treatment</b> 408–290 with low-dose mirtazapine 248–231 with ibuprofen The remaining arms evaluated mirtazapine plus ibuprofen and placebo	Reported as not significant P value not reported	↔	Not significant
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria [17]) In review [10]	<b>Headache intensity (change from baseline in 11-point verbal rating scale, from 0 = headache-free to 10 = worst headache imaginable), last 4 weeks of treatment</b> 4.5–4.1 with low-dose mirtazapine 4.2–4.4 with ibuprofen The remaining arms evaluated mirtazapine plus ibuprofen and placebo	Reported as not significant P value not reported	↔	Not significant

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[23] RCT 4-armed trial	93 people (diagnosed with IHS criteria [17]) In review [10]	<b>Proportion of people reporting one or more adverse effect</b> 14/23 (61%) with low-dose mirtazapine 11/24 (46%) with ibuprofen The remaining arms evaluated mirtazapine plus ibuprofen and placebo	Significance not assessed		

### Mirtazapine versus amitriptyline:

We found one systematic review (search date 2009), [10] which identified no RCTs. We found one additional RCT comparing mirtazapine (30 mg/day) with amitriptyline. [26]

### Symptom severity

*Mirtazapine compared with amitriptyline* Mirtazapine and amitriptyline may be equally effective at 6 months at reducing headache frequency and intensity (as measured by visual analogue scale [VAS]) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache scores</b>					
[26] RCT	60 people (diagnosed with IHS criteria [17]) Duration of trial 6 months	<b>Percentage improvement in VAS score (scale 0–10); subjective assessment of combined headache frequency and intensity</b> 65% with mirtazapine 58% with amitriptyline	Reported as not significant P value not reported Both treatments significantly reduced headache frequency and severity from baseline	↔	Not significant

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[26] RCT	60 people (diagnosed with IHS criteria [17])	<b>Overall adverse effects</b> with mirtazapine with amitriptyline Absolute results reported graphically Adverse effects, particularly dry mouth and drowsiness, were frequently reported	Reported as significantly less common with mirtazapine than amitriptyline P <0.001	○○○	mirtazapine

**Comment:** The four-armed RCT [23] reported no significant reduction in headache symptoms with low-dose mirtazapine plus ibuprofen compared to either drug alone. This study is also reported in the option on NSAIDs, p 11 .

## OPTION OPIOID ANALGESICS

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- We found no RCT evidence examining the effectiveness of opioid analgesics (e.g., codeine) in people with chronic tension-type headache (CTTH).
- Use of opioid analgesics may lead to analgesia overuse headaches.

## Benefits and harms

### Opioid analgesics versus placebo:

We found no systematic review or RCTs.

**Comment:** We found one non-systematic review, which identified 29 observational studies (2612 people), and found no evidence of benefit of common analgesia for CTTH. However, it found that sustained frequent use (2–3 times/week) of some common analgesics in people with episodic headache was associated with chronic headache and reduced effectiveness of prophylactic treatment. [24]

## Clinical guide

Observational studies are difficult to interpret. From a practical, clinical perspective, it seems likely that all types of analgesic, when used on a regular basis, are capable of transforming acute headaches into chronic headaches in predisposed people. This applies to simple analgesics, such as paracetamol and NSAIDs, as well as opiates and compound analgesics containing mixes of different acute-attack medications (often including caffeine). In general, many headache experts advise people to eliminate medication overuse, and stop using acute-attack medications before considering preventative treatment for CTTH or other types of chronic daily headache. Where medication overuse is contributing to chronic daily headache, withdrawal may lead to temporary and short-lived worsening of the headache disorder followed by improvement. Caffeine also seems to provide acute relief for some types of headache, although regular use may contribute to perpetuating the headache into a chronic state. It may be helpful for some people to avoid caffeine when faced with chronic daily headaches such as chronic migraine or CTTH.

## OPTION PARACETAMOL

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 31](#) .
- We found no RCT evidence examining the effectiveness of paracetamol in people with chronic tension-type headache (CTTH).
- Use of paracetamol may lead to analgesia overuse headaches.

## Benefits and harms

### Paracetamol versus placebo:

We found no systematic review or RCTs.

### Comment:

We found one non-systematic review, which identified 29 observational studies (2612 people), and found no evidence of benefit of common analgesia for CTTH. It found that sustained frequent use (2–3 times/week) of some common analgesics in people with episodic headache was associated with chronic headache, analgesia overuse headaches, and reduced effectiveness of prophylactic treatment. <sup>[24]</sup>

## Clinical guide

Observational studies are difficult to interpret. From a practical, clinical perspective, it seems likely that all types of analgesic, when used on a regular basis, are capable of transforming acute headaches into chronic headaches in predisposed people. This applies to simple analgesics, such as paracetamol and NSAIDs, as well as opiates and compound analgesics containing mixes of different acute-attack medications (often including caffeine). In general, many headache experts advise people to eliminate medication overuse, and stop using acute-attack medications before considering preventative treatment for CTTH or other types of chronic daily headache. Where medication overuse is contributing to chronic daily headache, withdrawal may lead to temporary and short-lived worsening of the headache disorder followed by improvement. Caffeine also seems to provide acute relief for some types of headache, although regular use may contribute to perpetuating the headache into a chronic state. Patients should avoid caffeine when faced with chronic daily headaches such as chronic migraine or CTTH.

## Drug safety alert

**August 2013, paracetamol (acetaminophen)** The Food and Drug Administration (FDA) has issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen). These skin reactions, known as Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP), can be fatal ([www.fda.gov/](http://www.fda.gov/)).

## OPTION SEROTONIN RE-UPTAKE INHIBITORS

- For GRADE evaluation of interventions for Headache (chronic tension-type), [see table, p 31](#) .
- We don't know whether SSRIs are effective in treating chronic tension-type headache (CTTH).

## Benefits and harms

### SSRI antidepressants versus placebo:

We found two systematic reviews (search date 2009; <sup>[10]</sup> and 2005 <sup>[27]</sup>). The first review <sup>[10]</sup> identified two RCTs. <sup>[15]</sup> <sup>[28]</sup> The second review <sup>[27]</sup> identified one RCT <sup>[15]</sup> that was also identified in the first review. The second review performed a slightly different analysis of the RCT, but found similar results. <sup>[27]</sup> We have, therefore, only reported from the first systematic review.

### Symptom severity

*SSRI antidepressants compared with placebo* We don't know how SSRI antidepressants and placebo compare at reducing headache symptoms (*low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
<sup>[10]</sup> Systematic review	60 people with tension-type headache (diagnosed using IHS criteria <sup>[17]</sup> ) Data from 1 RCT	<b>Headache improvement</b> with sertraline with placebo Absolute results not reported 50 people in this analysis	RR 4.5 95% CI 1.08 to 18.77		sertraline
<sup>[10]</sup> Systematic review	60 people with tension-type headache (diagnosed using IHS criteria <sup>[17]</sup> ) Data from 1 RCT	<b>Headache index</b> with sertraline with placebo Absolute results not reported 50 people in this analysis	SMD 1.66 95% CI 1.01 to 2.3		sertraline
<sup>[10]</sup> Systematic review	40 people (diagnosed with IHS criteria <sup>[17]</sup> ) Data from 1 RCT 3-armed crossover RCT	<b>Headache intensity</b> with citalopram with placebo Absolute results not reported 34 people in this analysis The remaining arm compared amitriptyline	SMD +0.17 95% CI -0.30 to +0.65		Not significant
<sup>[10]</sup> Systematic review	40 people; (diagnosed with IHS criteria <sup>[17]</sup> ) Data from 1 RCT 3-armed crossover RCT	<b>Headache duration</b> with citalopram with placebo Absolute results not reported 34 people in this analysis The remaining arm compared amitriptyline	SMD +0.01 95% CI -0.46 to +0.49		Not significant

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
<sup>[28]</sup> RCT	50 people In review <sup>[10]</sup>	<b>Nausea</b> with sertraline with placebo Absolute results not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Nausea was reported in 6 people taking sertraline and 4 taking placebo			

No data from the following reference on this outcome. <sup>[15]</sup>

### SSRI antidepressants versus amitriptyline:

We found two systematic reviews (search date 2009; <sup>[10]</sup> and 2005 <sup>[27]</sup>), which identified the same two RCTs <sup>[15]</sup> <sup>[29]</sup> (see Further information on studies). The second review meta-analysed the two RCTs, therefore, we have reported from this review. <sup>[27]</sup>

### Symptom severity

*SSRI antidepressants compared with amitriptyline* We don't know how SSRI antidepressants and amitriptyline compare at reducing headache symptoms (*very low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache duration, frequency, or intensity</b>					
<sup>[27]</sup> Systematic review	152 people 2 RCTs in this analysis See Further information on studies regarding RCTs	<b>Headache frequency (mean number of days with headache/month) , 8 weeks</b> with SSRIs (sertraline or citalopram) with amitriptyline Absolute results not reported 75 people received SSRIs (sertraline or citalopram), and 77 received amitriptyline	MD +0.76 95% CI -2.05 to +3.57 P = 0.60	↔	Not significant
<sup>[27]</sup> Systematic review	152 people 2 RCTs in this analysis See Further information on studies regarding RCTs	<b>Headache severity (assessed on a 10-point scale [VAS or ordinal scale]) , 8 weeks</b> with SSRIs (sertraline or citalopram) with amitriptyline Absolute results not reported 75 people received SSRIs (sertraline or citalopram), and 77 received amitriptyline	MD +0.32 95% CI -0.55 to +1.19 P = 0.47 Heterogeneity: $I^2 = 72\%$ ; P = 0.06	↔	Not significant
<sup>[27]</sup> Systematic review	152 people 2 RCTs in this analysis See Further information on studies regarding RCTs	<b>Headache duration (mean hours/day) , 8 weeks</b> with SSRIs (sertraline or citalopram) with amitriptyline Absolute results not reported 75 people received SSRIs (sertraline or citalopram), and 77 received amitriptyline	MD 1.26 95% CI 0.06 to 2.45 P = 0.04	○○○	amitriptyline

### Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[27] Systematic review	40 people Data from 1 RCT 3-armed crossover RCT (see Further information on studies)	<b>Number of people with minor adverse effects</b> 15 with citalopram 33 with amitriptyline The most frequent minor adverse effects were drowsiness and dry mouth in the amitriptyline group	OR 0.13 95% CI 0.05 to 0.36 NNH 8 95% CI 3 to 20		citalopram

### Further information on studies

[27] Of the two reported RCTs in the systematic review, one was a three-armed study (40 people) with crossover design (three 8-week treatment periods with 2-week washout between periods) comparing citalopram, amitriptyline, and placebo, [15] and the other was a single-centre, open-label study (90 people) comparing sertraline with amitriptyline. [29] The review reported that in the three-armed crossover study "carry-over and time period effects were not present. Therefore, this study was analysed as if it were a parallel-group trial, combining data from all treatment periods".

### Comment:

#### SSRI antidepressants, harms

Harms associated with the use of SSRIs are well described (see option on SSRIs in the overview on Depression in adults: drug and physical treatments).

Since the search date of this overview, one of the systematic reviews [27] included above has been updated (search date 2014). [30] The two RCTs added were both included in the other systematic review we identified. [10] The authors of the updated systematic review concluded that "the new included studies have not added high-quality evidence to support the use of SSRIs or venlafaxine (a SNRI) as preventive drugs for tension-type headache". [30]

### OPTION

#### TRICYCLIC ANTIDEPRESSANTS (OTHER THAN AMITRIPTYLINE)

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- We don't know whether tricyclic antidepressants other than amitriptyline are effective in treating chronic tension-type headache (CTTH).

### Benefits and harms

#### Tricyclic antidepressants (other than amitriptyline) versus placebo:

We found one systematic review (search date 2009), [10] which identified two RCTs. [31] [32] The systematic review did not perform a meta-analysis, therefore, we have reported directly from the RCTs where data were unclear or missing in the systematic review.

### Symptom severity

*Tricyclic antidepressants (other than amitriptyline) compared with placebo* We don't know whether maprotiline, clomipramine, or mianserin are more effective than placebo at reducing headache symptoms ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
[31] RCT	30 people (diagnosed with IHS criteria [17])	<b>Reduction in headache intensity (increase in headache-free day)</b>	P <0.001		maprotiline



Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Crossover design</b>	14-week trial duration	with maprotiline with placebo 18/30 (60%) people found maprotiline better than placebo; 7 found it as effective; 3 found placebo better than maprotiline; 2 had no effect from either			
[32] RCT	114 people; diagnosed by criteria of the Ad Hoc Committee 1962 [2] (80% consistent with IHS criteria) 6-week trial duration	<b>More than 50% reduction in intensity , 6 weeks</b> with mianserin with clomipramine with placebo Absolute results not reported	Reported as non-significant reduction in area under curve (AUC) pain scores (calculated by area under the curve from graphed results) between mianserin, clomipramine, and placebo	↔	Not significant
[10] Systematic review	People with tension-type headache; diagnosed by criteria of the Ad Hoc Committee 1962 [2] (80% consistent with IHS criteria) Data from 1 RCT 6-week trial duration	<b>Headache improvement</b> with mianserin with placebo Absolute results not reported At least 56 people in this analysis 3-armed RCT	RR 1.18 95% CI 0.74 to 1.88	↔	Not significant
[10] Systematic review	People with tension-type headache; diagnosed by criteria of the Ad Hoc Committee 1962 [2] (80% consistent with IHS criteria) Data from 1 RCT 6-week trial duration	<b>Headache intensity</b> with mianserin with placebo Absolute results not reported At least 56 people in this analysis 3-armed RCT	SMD 0.51 95% CI 0.00 to 1.01	↔	Not significant

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[31] RCT <b>Crossover design</b>	30 people; diagnosed by IHS criteria [17] 14-week trial duration	<b>Adverse effects</b> with maprotiline with placebo Absolute results not reported Maprotiline was associated with a higher incidence of adverse effects (most notably sedation, dry mouth, and weight gain), but the authors reported these to be mild			
[32]	114 people; diagnosed by	<b>Adverse effects</b>			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
RCT	criteria of the Ad Hoc Committee 1962 [2] (80% consistent with IHS criteria)	with mianserin with clomipramine with placebo Absolute results not reported One person withdrew due to severe leukopenia associated with fever and glandular swelling Other adverse effects were classed 'not serious', but still caused withdrawals			

**Tricyclic antidepressants (other than amitriptyline) versus CBT plus relaxation:**  
See option on CBT, p 26 .

**Comment:** None.

**QUESTION** What are the effects of non-drug treatments for chronic tension-type headache?

**OPTION** ACUPUNCTURE

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- We don't know whether acupuncture is more effective than sham/minimum acupuncture in treating chronic tension-type headache (CTTH), as most studies are in mixed populations of episodic tension-type headache (TTH) and CTTH, and results vary between studies, over time, and with analysis of headache symptoms used.
- Acupuncture may be more effective than no acupuncture at reducing headache symptoms. However, this is based on one small study in a mixed population of episodic TTH and CTTH.

**Benefits and harms**

**Acupuncture versus sham acupuncture/minimum acupuncture:**

We found one systematic review, [33] which identified five RCTs relevant to this comparison. We found one additional RCT. [34] The systematic review included all people with TTH, regardless of how it was defined. We have, therefore, selectively reported those studies that best meet *BMJ Clinical Evidence* inclusion criteria. The review did not report adverse effects, so we have reported these directly from one of the RCTs. [35]

**Symptom severity**

*Acupuncture compared with sham acupuncture/minimum acupuncture* Acupuncture may be more effective than sham acupuncture/minimum acupuncture at improving headache symptoms at 3 to 4 months after randomisation. However, we don't know whether it is more effective in the longer term, and many studies have involved mixed populations with episodic and CTTH (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
[33] Systematic review	People with TTH 4 RCTs in this analysis	<b>Proportion of responders , 3–4 months after randomisation</b> 195/391 (50%) with acupuncture 128/312 (41%) with sham intervention	RR 1.24 95% CI 1.05 to 1.46 P = 0.009		acupuncture

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[33] Systematic review	People with TTH Data from 1 RCT	<b>Proportion of responders , &gt;6 months after randomisation</b> 6/15 (40%) with acupuncture 4/15 (27%) with sham intervention	RR 1.50 95% CI 0.53 to 4.26 P = 0.45	↔	Not significant
[33] Systematic review	People with TTH 4 RCTs in this analysis	<b>Number of headache days , 3–4 months after randomisation</b> with acupuncture with sham intervention Absolute results not reported 653 people in this analysis	MD -1.94 95% CI -3.15 to -0.72 P = 0.002	○○○	acupuncture
[33] Systematic review	People with TTH 4 RCTs in this analysis	<b>Headache intensity , 3–4 months after randomisation</b> with acupuncture with sham intervention Absolute results not reported 623 people in this analysis	SMD -0.12 95% CI -0.28 to +0.04 P = 0.15	↔	Not significant
[33] Systematic review	People with TTH 3 RCTs in this analysis	<b>Headache score , 3–4 months after randomisation</b> with acupuncture with sham intervention Absolute results not reported 205 people in this analysis	SMD -0.11 95% CI -0.40 to +0.18 P = 0.47	↔	Not significant
[34] RCT	50 people with CTTH	<b>Median headache severity (measured by Visual Analogue Scale [VAS]) , 3 months</b> -2 with laser acupuncture 0 with placebo (machine set to 0 output power)	P <0.001 Similar significant differences reported at 1 and 2 months' follow-up (P <0.001)	○○○	laser acupuncture
[34] RCT	50 people with CTTH	<b>Number of days per month with headache , 3 months</b> -8 days/month with laser acupuncture 0 days/month with placebo (machine set to 0 output power)	P <0.001 Similar significant differences reported at 1 and 2 months' follow-up (P <0.001)	○○○	laser acupuncture
[34] RCT	50 people with CTTH	<b>Headache duration , 3 months</b> -4 hours with laser acupuncture 0 hours with placebo (machine set to 0 output power)	P <0.001 Similar significant differences reported at 1 and 2 months' follow-up (P <0.001)	○○○	laser acupuncture

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[35] RCT 3-armed trial	270 people; 124 with CTTH, 146 with episodic TTH	<b>Proportion of people reporting at least 1 adverse effect</b> 23/132 (17%) with acupuncture	Significance not assessed See Further information on studies		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review <sup>[33]</sup>	<p>11/63 (17%) with minimal acupuncture</p> <p>In total, there were 30 adverse effects with acupuncture, and 14 adverse effects with minimal acupuncture</p> <p>Adverse effects included triggering of headache or other pain, haematoma, and dizziness</p> <p>The remaining arm evaluated a waiting list control group (no acupuncture)</p>			

No data from the following reference on this outcome. <sup>[34]</sup>


### Acupuncture versus no acupuncture:

We found one systematic review (search date 2008), <sup>[33]</sup> which identified one RCT <sup>[35]</sup> relevant to this comparison. The review did not report adverse effects, so we have reported these directly from the RCT. <sup>[35]</sup>

### Symptom severity

*Acupuncture compared with no acupuncture* Acupuncture may be more effective than no acupuncture (waiting list control) at increasing the proportion of 'responders' and improving headache intensity, duration, and frequency at 3 to 4 months after randomisation (*low-quality evidence*).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
<sup>[33]</sup> Systematic review	People with TTH and CTTH diagnosed using IHS criteria <sup>[17]</sup>  Data from 1 RCT	<p><b>Proportion of responders , 3–4 months after randomisation</b></p> <p>60/132 (45%) with acupuncture 3/74 (4%) with no acupuncture</p> <p>Responders defined as having "reduction of at least 50% headache days per 4 weeks"</p> <p>3-armed RCT; the remaining arm evaluated minimal acupuncture (superficial needling at non-acupuncture points)</p>	<p>RR 11.36</p> <p>95% 3.69 to 34.98</p> <p>P value not reported</p>		acupuncture
<sup>[33]</sup> Systematic review	People with episodic TTH and CTTH diagnosed using IHS criteria <sup>[17]</sup>  Data from 1 RCT	<p><b>Mean number of headache days , 3–4 months after randomisation</b></p> <p>9.9 with acupuncture 16.3 with no acupuncture</p> <p>181 people in this analysis</p> <p>3-armed RCT; the remaining arm evaluated minimal acupuncture (superficial needling at non-acupuncture points)</p>	<p>MD -6.40</p> <p>95% CI -8.81 to -3.99</p> <p>P value not reported</p>		acupuncture
<sup>[33]</sup> Systematic review	People with episodic TTH and CTTH diagnosed using IHS criteria <sup>[17]</sup>  Data from 1 RCT	<p><b>Mean headache intensity , 3–4 months after randomisation</b></p> <p>2.9 with acupuncture 4.6 with no acupuncture</p> <p>182 people in this analysis</p>	<p>SMD -1.08</p> <p>95% CI -1.41 to -0.76</p> <p>P value not reported</p>		acupuncture

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3-armed RCT; the remaining arm evaluated minimal acupuncture (superficial needling at non-acupuncture points)			
[33] Systematic review	People with episodic TTH and CTTH diagnosed using IHS criteria [17]  Data from 1 RCT	<b>Mean headache score , 3–4 months after randomisation</b> 15.8 with acupuncture 26.4 with no acupuncture 181 people in this analysis  3-armed RCT; the remaining arm evaluated minimal acupuncture (superficial needling at non-acupuncture points)	SMD –0.71 95% CI –1.02 to –0.39 P value not reported		acupuncture

## Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Adverse effects</b>					
[35] RCT <b>3-armed trial</b>	270 people; 124 with CTTH, 146 with episodic tension-type headache  In review [33]	<b>Proportion of people reporting at least 1 adverse effect</b> with acupuncture with no acupuncture  No information given on adverse effects with acupuncture v no treatment  See adverse effects of acupuncture v sham acupuncture above  The remaining arm evaluated minimally penetrating acupuncture  See Further information on studies			

## Further information on studies

[33] *Acupuncture v sham acupuncture* The systematic review reported that one of the four RCTs in the meta-analysis had 14/69 (20%) loss to follow-up at 5 months, and two RCTs were unclear regarding the details of randomisation. Only one RCT (409 people; mixed population of TTH or CTTH diagnosed by IHS) independently found significant differences with regard to proportion of 'responders' and number of headache days at 3 to 4 months after randomisation. As this trial was by far the largest, it dominated the meta-analyses (around 70% weight). The review noted that there was little statistical heterogeneity; however, the analyses still had limited power.

[33] *Acupuncture v no acupuncture* The systematic review noted that the RCT was unblinded but otherwise had a low risk of bias. People in the no-acupuncture group received acupuncture 3 months after randomisation (waiting list condition), so it is only possible to assess short-term effects. The RCT also measured analgesic use, which showed that there were significantly better results in the acupuncture groups compared with the no-acupuncture group at both 8 weeks (181 people, mean 2.1 with acupuncture v 4.2 with no acupuncture; SMD –0.71, 95% CI –1.03 to –0.40) and 3 to 4 months (180 people, mean 1.9 with acupuncture v 4.4 with no acupuncture; SMD –0.74, 95% CI –1.06 to –0.42; P values not reported).

<sup>[35]</sup> The RCT reported two serious adverse events requiring hospital stays within 24 weeks of randomisation in the acupuncture group, and one in the waiting list (no intervention) group, which were considered by the authors to be unrelated to the treatment.

**Comment:** None.

**OPTION COGNITIVE BEHAVIOURAL THERAPY**

- For GRADE evaluation of interventions for Headache (chronic tension-type), see table, p 31 .
- We don't know whether cognitive behavioural therapy (CBT) is effective in treating chronic tension-type headache (CTTH).

**Benefits and harms**

**CBT versus no CBT:**

We found one systematic review (search date 1994), <sup>[11]</sup> which identified three small RCTs.

**Symptom severity**

*CBT compared with no CBT* We don't know whether cognitive therapy is more effective than control at improving headache symptoms ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
<sup>[11]</sup> Systematic review	55 people 3 RCTs in this analysis	<b>Headache symptoms</b> with cognitive therapy with control Absolute results not reported	The review pooled data on cognitive therapy and found significantly greater improvement compared with control treatments (P value not reported)  The RCTs in the review were small and had as few as 8 people in each group; clear conclusions could not be drawn	○○○	cognitive therapy

**Adverse effects**

No data from the following reference on this outcome. <sup>[11]</sup>

**CBT plus relaxation versus placebo:**

We found one systematic review (search date 2009), <sup>[10]</sup> which identified one four-armed RCT. <sup>[12]</sup> The four-armed RCT compared stress management (combination treatment involving instruction on stress management skills, relaxation, and cognitive coping), tricyclic antidepressants (amitriptyline or nortriptyline), combined stress management plus antidepressants, and placebo. <sup>[12]</sup> The review did not report all of the results from the RCT; therefore, we have reported directly from the RCT where necessary.

**Symptom severity**

*CBT plus relaxation compared with placebo* Stress management (which includes cognitive coping and relaxation) may be more effective than placebo at reducing headache index scores at 6 months, but we don't know how it compares at improving frequency of clinically important improvements ([very low-quality evidence](#)).



Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Symptom severity</b>					
[12] RCT 4-armed trial	203 adults In review [10]	<p><b>Headache index score (mean of pain ratings: score 0–10 where 10 is most severe pain, recorded in a diary 4 times/day) , 6 months</b></p> <p>with stress management with placebo</p> <p>Absolute results not reported</p> <p>Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive coping</p> <p>The remaining arms evaluated tricyclic antidepressants plus stress management, and tricyclic antidepressants alone</p>	<p>MD 0.79</p> <p>95% CI 0.30 to 1.28</p>	○ ○ ○ ○	stress management
[12] RCT 4-armed trial	203 adults In review [10]	<p><b>Clinically important improvement (50% or more reduction in headache index score)</b></p> <p>17/49 (35%) with stress management 14/48 (29%) with placebo</p> <p>Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive coping</p> <p>The remaining arms evaluated tricyclic antidepressants plus stress management, and tricyclic antidepressants alone</p>	<p>RR 1.19</p> <p>95% CI 0.66 to 2.13</p>	↔	Not significant

## Adverse effects

No data from the following reference on this outcome. [12]

### CBT plus relaxation versus tricyclic antidepressants (amitriptyline or nortriptyline):

We found one systematic review (search date 2009), [10] which identified one four-armed RCT. [12] The four-armed RCT compared stress management (combination treatment involving instruction on stress management skills, relaxation, and cognitive coping), tricyclic antidepressants (amitriptyline or nortriptyline), combined stress management plus tricyclic antidepressants, and placebo. [12] The review did not report all of the results from the RCT; therefore, we have reported directly from the RCT where necessary.

### Symptom severity

*CBT plus relaxation compared with tricyclic antidepressants* We don't know how stress management (which includes cognitive coping and relaxation) compares with tricyclic antidepressants (amitriptyline or nortriptyline) at reducing headache index scores at 6 months or reducing frequency of clinically important improvements ([very low-quality evidence](#)).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
<b>Headache scores</b>					
[12] RCT 4-armed trial	203 adults In review [10]	<p><b>Headache index score , 6 months</b></p> <p>with stress management</p> <p>with tricyclic antidepressants</p> <p>Absolute results not reported</p> <p>Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive coping</p> <p>Tricyclic antidepressants included amitriptyline or nortriptyline</p> <p>The remaining arms evaluated tricyclic antidepressants plus stress management, and placebo</p>	<p>MD -0.13</p> <p>95% CI -0.61 to +0.35</p>	↔	Not significant
[10] Systematic review	Adults with tension-type headache diagnosed using IHS criteria [17]	<p><b>Clinically important improvement (50% or more reduction in headache index score)</b></p> <p>with stress management</p> <p>with tricyclic antidepressants</p> <p>Absolute results not reported</p> <p>At least 78 people in this analysis</p> <p>Stress management included combination treatment involving instruction on stress management skills, relaxation, and cognitive coping</p> <p>Tricyclic antidepressants included amitriptyline or nortriptyline</p> <p>The remaining arms evaluated tricyclic antidepressants plus stress management, and placebo</p>	<p>RR 1.09</p> <p>95% CI 0.65 to 1.82</p>	↔	Not significant

## Adverse effects

No data from the following reference on this outcome. [12]

**Comment:** The RCT of stress management combining relaxation and cognitive coping is also reported in the options on [Amitriptyline](#), p 4 and [Tricyclic antidepressants \(other than amitriptyline\)](#), p 20 . [12]

### Clinical guide

Although the four-armed RCT comparing stress management (cognitive coping and relaxation), tricyclic antidepressants, combined stress management plus tricyclic antidepressants, and placebo found that the headache index score was reduced with stress management compared with placebo, it found no convincing reduction in the number of people who had a clinically important response. The evidence is too limited to define the role of CBT in the treatment of CTTH.

## GLOSSARY

**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low-quality evidence** Any estimate of effect is very uncertain.

## SUBSTANTIVE CHANGES

**Acupuncture** One systematic review added. <sup>[33]</sup> Categorisation unchanged (unknown effectiveness).

**Amitriptyline** One systematic review added. <sup>[10]</sup> Categorisation unchanged (beneficial).

**Anticonvulsant drugs** One systematic review <sup>[10]</sup> and one RCT <sup>[18]</sup> added. Categorisation unchanged (unknown effectiveness).

**Benzodiazepines** One systematic review added. <sup>[10]</sup> Categorisation unchanged (likely to be ineffective or harmful).

**Botulinum toxin** One systematic review added. <sup>[22]</sup> Categorisation unchanged (likely to be ineffective or harmful).

**Cognitive behavioural therapy** One systematic review added. <sup>[10]</sup> Categorisation unchanged (unknown effectiveness).

**Noradrenergic and specific serotonergic antidepressants** One systematic review added. <sup>[10]</sup> Categorisation unchanged (likely to be beneficial).

**Serotonin re-uptake inhibitors** One systematic review added. <sup>[10]</sup> Categorisation unchanged (unknown effectiveness).

**Tricyclic antidepressants (other than amitriptyline)** One systematic review added. <sup>[10]</sup> Categorisation unchanged (unknown effectiveness).

**Non-steroidal anti-inflammatory drugs (NSAIDs)** Condition re-structured. One systematic review added. <sup>[10]</sup> Categorisation unchanged (likely to be ineffective or harmful).

**Opioid analgesics** Condition restructured. No new evidence. Categorisation unchanged (unknown effectiveness).

**Paracetamol** Condition restructured. No new evidence. Categorisation unchanged (unknown effectiveness).

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# Headache (chronic tension-type)

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**GRADE** Evaluation of interventions for Headache (chronic tension-type).

Important outcomes	Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Symptom severity			GRADE	Comment
						Consistency	Directness	Effect size		
<i>What are the effects of drug treatments for chronic tension-type headache?</i>										
	6 (271) <sup>[10] [12] [13] [14] [15] [16]</sup>	Symptom severity	Amitriptyline versus placebo	4	-1	0	-1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for heterogeneity in outcomes assessed
	1 (41) <sup>[18]</sup>	Symptom severity	Anticonvulsant drugs (sodium valproate, topiramate, or gabapentin) versus placebo	4	-3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods
	At least 3 (at least 442) <sup>[22]</sup>	Symptom severity	Botulinum toxin versus placebo	4	-2	0	0	0	Low	Quality points deducted for incomplete reporting of results and significant heterogeneity in the meta-analysis
	1 (93) <sup>[23]</sup>	Symptom severity	NSAIDs versus placebo	4	-2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
	2 (117) <sup>[25] [23]</sup>	Symptom severity	Mirtazapine versus placebo	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for low dose used in one RCT
	1 (93) <sup>[23]</sup>	Symptom severity	Mirtazapine versus ibuprofen	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for low dose used
	1 (60) <sup>[26]</sup>	Symptom severity	Mirtazapine versus amitriptyline	4	-2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
	2 (100) <sup>[10]</sup>	Symptom severity	SSRI antidepressants versus placebo	4	-2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
	2 (152) <sup>[27]</sup>	Symptom severity	SSRI antidepressants versus amitriptyline	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for narrow range of comparators
	2 (at least 56) <sup>[10] [31] [32]</sup>	Symptom severity	Tricyclic antidepressants (other than amitriptyline) versus placebo	4	-2	-1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; consistency point deducted for conflicting results
<i>What are the effects of non-drug treatments for chronic tension-type headache?</i>										
	At least 5 (at least 653) <sup>[33]</sup>	Symptom severity	Acupuncture versus sham acupuncture/minimum acupuncture	4	-1	0	-1	0	Low	Quality point deducted for incomplete reporting of results; directness point deducted for inclusion of episodic tension-type headache
	1 (at least 181) <sup>[33]</sup>	Symptom severity	Acupuncture versus no acupuncture	4	-1	0	-1	0	Low	Quality point deducted for sparse data; directness point deducted for inclusion of episodic tension-type headache

Important outcomes	Studies (Participants)	Outcome	Comparison	Type of evidence	Symptom severity			Effect size	GRADE	Comment
					Quality	Consistency	Directness			
	3 (55) <sup>[11]</sup>	Symptom severity	CBT versus no CBT	4	-3	0	-1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about clinical significance of result; directness point deducted for unclear control group
	1 (at least 60) <sup>[10]</sup> <sup>[12]</sup>	Symptom severity	CBT plus relaxation versus placebo	4	-2	-1	-1	0	Very low	Quality point deducted for sparse data and incomplete reporting of results; consistency point deducted for lack of consistency in beneficial effects; directness point deducted for multiple interventions used in comparison
	1 (at least 78) <sup>[10]</sup> <sup>[12]</sup>	Symptom severity	CBT plus relaxation versus tricyclic antidepressants (amitriptyline or nortriptyline)	4	-2	0	-1	0	Very low	Quality point deducted for sparse data and incomplete reporting of results; directness point deducted for multiple interventions used in comparison

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [ $<200$  people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.