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Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults (Review)

Derry S, Moore RA

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[Intervention Review]

Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 11, 2010 (Derry 2010). Migraine is a common, disabling condition and a burden for the individual, health services and society. Many sufferers choose not to, or are unable to, seek professional help and rely on over-the-counter analgesics. Co-therapy with an antiemetic should help to reduce nausea and vomiting, which are commonly associated with migraine.

Objectives

To determine the efficacy and tolerability of paracetamol (acetaminophen), alone or in combination with an antiemetic, compared with placebo and other active interventions in the treatment of acute migraine in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and the Oxford Pain Relief Database for studies through 4 October 2010 for the original review, and to 13 February 2013 for the update. Two clinical trials registers (ClinicalTrials.gov and gsk-clinicalstudyregister.com) were also searched on both occasions.

Selection criteria

We included randomised, double-blind, placebo- or active-controlled studies using self-administered paracetamol to treat a migraine headache episode, with at least 10 participants per treatment arm.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Numbers of participants achieving each outcome were used to calculate relative risk and numbers needed to treat (NNT) or harm (NNH) compared with placebo or other active treatment.

Main results

Searches for the update identified one additional study for inclusion. Eleven studies (2942 participants, 5109 attacks) compared paracetamol 1000 mg, alone or in combination with an antiemetic, with placebo or other active comparators, mainly sumatriptan 100 mg. For all efficacy outcomes paracetamol was superior to placebo, with NNTs of 12 (19% response with paracetamol, 10% with placebo), 5.0 (56% response with paracetamol, 36% with placebo) and 5.2 (39% response with paracetamol, 20% with placebo) for 2-hour pain-free and 2- and 1-hour headache relief, respectively, when medication was taken for moderate to severe pain.

Paracetamol 1000 mg plus metoclopramide 10 mg was not significantly different from oral sumatriptan 100 mg for 2-hour headache relief; there were no 2-hour pain-free data.

Adverse event rates were similar between paracetamol and placebo, and between paracetamol plus metoclopramide and sumatriptan. No serious adverse events occurred with paracetamol alone, but more serious and/or severe adverse events occurred with sumatriptan than with the combination therapy (NNH 32).

Authors' conclusions

Paracetamol 1000 mg alone is statistically superior to placebo in the treatment of acute migraine, but the NNT of 12 for pain-free response at two hours is inferior to at of other commonly used analgesics. Given the low cost and wide availability of paracetamol, it may be a useful first choice drug for acute migraine in those with contraindications to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. The addition of 10 mg metoclopramide gives short-term efficacy equivalent to oral sumatriptan 100 mg. Adverse events with paracetamol did not differ from placebo; serious and/or severe adverse events were slightly more common with sumatriptan than with paracetamol plus metoclopramide.

PLAIN LANGUAGE SUMMARY

Paracetamol (acetaminophen) with or without an antiemetic for acute migraine in adults

This is an updated version of the original Cochrane review published in Issue 11, 2010 (Derry 2010). New searches identified one additional study for inclusion; this study compared paracetamol with etodolac and did not contribute to any of the analyses in the review.

A single oral dose of paracetamol 1000 mg will reduce headache pain from moderate or severe to none by 2 hours in 1 in 5 people (19%) taking paracetamol, compared with 1 in 10 (10%) taking placebo. Pain will be reduced from moderate or severe to no worse than mild pain by 2 hours in about 1 in 2 people (56%) taking paracetamol, compared with about 1 in 3 (36%) taking placebo. Too few data were available to assess efficacy beyond 2 hours.

Paracetamol 1000 mg plus metoclopramide 10 mg and oral sumatriptan 100 mg provide similar levels of headache relief at 2 hours. There was insufficient information to compare paracetamol, alone or in combination, with other active treatments.

Adverse events do not differ significantly between paracetamol and placebo. Slightly more serious and/or severe adverse events occur with sumatriptan 100 mg than with paracetamol 1000 mg plus metoclopramide 10 mg.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Paracetamol 1000 mg compared with placebo for migraine headache

Patient or population: adults with migraine headache - moderate or severe pain

Settings: community

Intervention: paracetamol 1000 mg

Comparison: placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	NNT or NNH (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
Pain free response at 2 h	190 in 1000	100 in 1000	NNT 12 (7.5 to 32)	3 studies, 717 attacks, 104 events	Low ¹	
Headache relief at 2 h	560 in 1000	360 in 1000	NNT 5.0 (3.7 to 7.7)	3 studies, 717 attacks, 334 events	Low ¹	
Headache relief at 1 h	390 in 1000	200 in 1000	NNT 5.2 (3.8 to 8.1)	2 studies, 655 attacks, 189 vents	Low ¹	
At least one AE	180 in 1000	230 in 1000	NNH 21 (11 to 300)	4 studies, 1293 attacks, 261 events	Low ¹	
Sustained pain-free at 24 h	no data					
Sustained headache relief at 24 h	no data					
Serious AE	insufficient data					

CI: Confidence interval; **NNT:** number needed to treat; **NNH:** number needed to harm

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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: We are very uncertain about the estimate.

1 - Quality of evidence downgraded from high because of threat from potential publication bias with modest effect size and numbers of events

BACKGROUND

Description of the condition

Migraine is a common, disabling headache disorder, ranked seventh highest among specific causes of disability globally (Steiner 2013), with considerable social and economic impact (Hazard 2009). Recent surveys found a one-year prevalence of 15% globally (Vos 2012) and for adults in European countries (Stovner 2010), 13% for all ages in the United States (US) (Victor 2010), 21% in Russia (Ayzenberg 2012) and 9% for adults in China (Yu 2012). Migraine is more prevalent in women than in men (by a factor of two to three), and in the age range 30 to 50 years.

The International Headache Society (IHS) classifies two major subtypes (IHS 2004). Migraine without aura is the most common subtype. It is characterised by attacks lasting 4 to 72 hours that are typically of moderate to severe pain intensity, unilateral, pulsating, aggravated by normal physical activity and associated with nausea and/or photophobia and phonophobia. Migraine with aura is characterised by reversible focal neurological symptoms that develop over a period of 5 to 20 minutes and last for less than 60 minutes, followed by headache with the features of migraine without aura. In some cases the headache may lack migrainous features or be absent altogether.

A recent large prevalence study in the US found that over half of migraineurs had severe impairment or required bed rest during attacks. Despite this high level of disability and a strong desire for successful treatment, only a proportion of migraine sufferers seek professional advice for the treatment of attacks. The majority were not taking any preventive medication, although one-third met guideline criteria for offering or considering it. Nearly all (98%) migraineurs used acute treatments for attacks, with 49% using over-the-counter (OTC) medication only, 20% using prescription medication, and 29% using both. OTC medication included aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen) and paracetamol with caffeine (Bigal 2008, Diamond 2007; Lipton 2007). Similar findings have been reported from other large studies in France and Germany (Lucas 2006; Radtke 2009).

The significant impact of migraine with regard to pain, functional health and well-being is well documented (Buse 2011; Leonardi 2005; Vos 2012). A cross-sectional survey of eight European U countries (representing 55% of the adult population) has estimated an annual direct and indirect cost of migraine per person of €1222, and a total annual cost for the EU of €111 billion for adults aged 18 to 65 years (Linde 2012). Costs are substantially greater for the minority with chronic migraine compared with episodic migraine; they also vary between countries, probably due to differences in available therapies and they way they are delivered, and to structural differences in healthcare systems (Bloudek 2012). In the US, the average annual direct cost per person has been estimated at \$1757 for episodic migraine and \$7750 for chronic migraine (Munakata 2009). Whatever the exact direct and indirect costs are for each country, it is clear that migraine presents a significant economic burden. Successful treatment of acute migraine attacks not only benefits patients by reducing their disability and improving health-related quality of life, but also has the potential to reduce the need for healthcare resources and increase economic productivity. Migraine is ranked in the top 10 disorders for global years lived with disability (Vos 2012).

Description of the intervention

Paracetamol (acetaminophen) was first identified as the active metabolite of two older antipyretic drugs, acetanilide and phenacetin, in the late nineteenth century. It became available in the United Kingdom (UK) on prescription in 1956, and OTC in 1963 (PIC 2009). Since then it has become one of the most popular antipyretic and analgesic drugs worldwide, and is often also used in combination with other drugs. OTC medications are less expensive, more accessible, and have favourable safety profiles relative to many prescription treatments.

Despite a low incidence of adverse effects, paracetamol has a recognised potential for hepatotoxicity and is thought to be responsible for approximately half of all cases of liver failure in the UK (Hawton 2001), and about 40% in the US (Norris 2008). Acute paracetamol hepatotoxicity at therapeutic doses is extremely unlikely despite reports of so-called therapeutic misadventure (Prescott 2000). In recent years legislative changes restricting pack sizes and the maximum number of tablets permitted in OTC sales were introduced in the UK (CSM 1997) on the basis of evidence that poisoning is lower in countries that restrict availability (Gunnell 1997; Hawton 2001). The contribution of these changes, which are inconvenient and costly (particularly to chronic pain sufferers), to any observed reductions in incidence of liver failure or death, remains uncertain (Hawkins 2007). There have been concerns over the safety of paracetamol in patients with compromised hepatic function (those with severe alcoholism, cirrhosis or hepatitis), but these have not been substantiated (Dart 2000; PIC 2009).

Oral paracetamol, used appropriately, has the potential to reduce unnecessary pain in a variety of conditions. Paracetamol is the analgesic of choice for adult patients in whom salicylates or other NSAIDs are contraindicated. Such patients include about one in five asthmatics, those with salicylate allergies and those with a history of peptic ulcer.

In order to establish whether paracetamol is an effective analgesic at a specified dose in acute migraine attacks, it is necessary to study its effects in circumstances that permit detection of pain relief. Such studies are carried out in individuals with established pain of moderate to severe intensity, using single doses of the interventions. Participants who experience an inadequate response with either placebo or active treatment are permitted to use rescue medication, and the intervention is considered to have failed in those individuals. In clinical practice, however, individuals would not normally wait until pain is of at least moderate severity, and may take a second dose of medication if the first dose does not provide adequate relief. Once analgesic efficacy is established in studies using single doses in established pain, further studies may investigate different treatment strategies and patient preferences. These are likely to include treating the migraine attack early while pain is mild, and using a low dose initially, with a second dose if response is inadequate.

How the intervention might work

The lack of significant anti-inflammatory activity of paracetamol implies a mode of action distinct from that of NSAIDs; yet, despite years of use and research, the mechanisms of action of paracetamol are not fully understood. NSAIDs act by inhibiting the activity of cyclooxygenase (COX), now recognised to consist of two isoforms (COX-1 and COX-2), which catalyses

the production of prostaglandins responsible for pain and inflammation. Paracetamol has previously been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but is now being considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis', wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (Botting 2000; Chandrasekharan 2002), now has little credibility, and a central mode action of paracetamol is thought to be likely (Graham 2005).

The efficacy of oral medications is reduced in many migraineurs because of impaired gastrointestinal motility, which is associated with nausea, and because of non-absorption of the drug due to vomiting (Volans 1974). The addition of an antiemetic may improve outcomes by alleviating the often incapacitating symptoms of nausea and vomiting, and (at least potentially) by enhancing the bioavailability of the co-administered analgesic. In particular, prokinetic antiemetics such as metoclopramide, which stimulate gastric emptying, may improve outcomes by increasing absorption of the analgesic. This has been investigated for metoclopramide and aspirin (Ross-Lee 1983; Volans 1975). It has been claimed that treatment with intravenous metoclopramide alone can reduce pain in severe migraine (Friedman 2005; Salazar-Tortolero 2008), but this claim requires further investigation, since metoclopramide has not been shown to be an analgesic in classical pain studies. The present review will seek to determine whether treatment of acute migraine attacks with paracetamol plus an antiemetic is in any way superior to treatment with paracetamol alone.

Why it is important to do this review

Population surveys show that paracetamol is frequently used to treat migraine headaches, but we could find no systematic review of the efficacy of this intervention in adults. It is important to know where this widely available and inexpensive drug fits in the range of therapeutic options for migraine therapy. For many migraineurs, non-prescription therapies offer convenience, and may be the only ones available or affordable.

This review is one of a series examining the efficacy of OTC treatments for migraine, including aspirin (Kirithi 2013) ibuprofen (Rabbie 2013), and diclofenac (Derry 2013), as well as oral sumatriptan (Derry 2012b), which is available without prescription in some countries.

OBJECTIVES

The objective of the review is to determine the efficacy and tolerability of paracetamol, alone or in combination with an antiemetic, compared with placebo and other active interventions in the treatment of acute migraine headaches in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, double blind, placebo- or active-controlled studies using paracetamol to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of

the outcomes specified. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. We accepted cross-over studies if there was adequate (at least 24 hours) washout between treatments.

Types of participants

Studies included adults (at least 18 years of age) with migraine. We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although other definitions were considered if they conformed in general to IHS diagnostic criteria. There were no restrictions on migraine frequency, duration or type (with or without aura). We accepted studies that included participants taking stable prophylactic therapy to reduce the frequency of migraine attacks. If reported, details on any prophylactic therapy prescribed or allowed are provided in the [Characteristics of included studies](#) table.

Types of interventions

We included studies using a single dose of paracetamol to treat a migraine headache episode when pain was of moderate to severe intensity, or investigating different dosing strategies or timing of the first dose, or both, in relation to headache intensity. There were no restrictions on dose or route of administration, provided the medication was self-administered.

Included studies could use either paracetamol alone, or paracetamol plus an antiemetic. The antiemetic had to be taken either combined with paracetamol in a single formulation, or separately not more than 30 minutes before paracetamol, and had to be self-administered.

A placebo comparator is essential to demonstrate that paracetamol is effective in this condition. We considered active-controlled trials without a placebo as secondary evidence. We excluded studies designed to demonstrate prophylactic efficacy in reducing the frequency of migraine attacks.

Types of outcome measures

In selecting the main outcome measures for this review, we considered scientific rigour, availability of data and patient preferences (Lipton 1999). Patients with acute migraine headaches have rated complete pain relief, no headache recurrence, rapid onset of pain relief, and no side effects as the four most important outcomes (Lipton 1999).

In view of these patient preferences, and in line with the guidelines for controlled trials of drugs in migraine issued by the IHS (IHS 2000), the main outcomes to be considered were:

Primary outcomes

- Pain-free at two hours, without the use of rescue medication (PF2).
- Reduction in headache pain ('headache relief') at two hours (HR2) - pain reduced from moderate or severe to none or mild without the use of rescue medication.

Data for pain-free and headache relief at earlier time points were collected when reported and relevant.

Secondary outcomes

- Sustained pain-free during 24 hours (SPF24) - pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.
- Sustained pain reduction over 24 hours (SHR24) - headache relief at two hours, sustained for 24 hours, with no use of rescue medication or second dose of study medication.
- Adverse events: participants with any adverse event during 24 hours postdose; serious adverse events; adverse events leading to withdrawal.

Pain intensity or pain relief had to be measured by the patient (not the investigator or care provider). Pain measures accepted for the primary outcomes were:

- Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm visual analogue scale (VAS), where < 30 mm was considered equivalent to mild or no pain and ≥ 30 mm equivalent to moderate or severe pain (Collins 1997);
- Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS, where < 30 mm was considered equivalent to none or a little, and ≥ 30 mm equivalent to some, a lot or complete.

We considered only data obtained directly from the patient.

Other outcomes

In the earlier review we reviewed a number of other secondary outcomes.

- Use of rescue medication.
- Relief of headache-associated symptoms.
- Relief of functional disability.

These are not now reported in detail in Results but have been moved to an appendix (see [Differences between protocol and review](#)).

Definitions of important terms, including all measured outcomes, are provided in [Appendix 1](#).

Search methods for identification of studies

Electronic searches

The following databases were searched for the original review to 4 October 2010:

- The Cochrane Central Register of Controlled Trials (CENTRAL).
- MEDLINE (via Ovid).
- EMBASE (via Ovid).
- Oxford Pain Relief Database (Jadad 1996a).

For the update we searched:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2013);
- MEDLINE (via Ovid) from 1 January 2010 to 13 February 2013;
- EMBASE (via Ovid) from 1 January 2010 to 13 February 2013.

See [Appendix 2](#) for the search strategy for MEDLINE, [Appendix 3](#) for the search strategy for EMBASE, and [Appendix 4](#) for the search strategy for CENTRAL. There were no language restrictions.

Searching other resources

Reference lists of retrieved studies and review articles were searched for additional studies, as were two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com). Grey literature and abstracts were not searched. Glaxo-Smith Kline provided additional detail relating to two studies for which a summary of results has been published online.

Data collection and analysis

Selection of studies

Two review authors independently carried out the searches and selected studies for inclusion. We viewed titles and abstracts of all studies identified by electronic searches on screen, and excluded any that clearly did not satisfy inclusion criteria. We read full copies of the remaining studies to identify those suitable for inclusion. Disagreements were settled by discussion with a third review author.

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. Disagreements were settled by discussion with a third review author. One author entered data for the original review into RevMan 5.0, and one author entered information for the update (RevMan 2012).

Assessment of risk of bias in included studies

We used the Oxford Quality Score (Jadad 1996b) as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum. The scores for each study are reported in the '[Characteristics of included studies](#)' table.

Two authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study:

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) were excluded.
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). Studies that did not conceal allocation (e.g. open list) were excluded.

3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). Studies that were not double-blind were excluded.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (< 10% of participants provided no data without acceptable reason - e.g. they were randomised but did not have a qualifying headache). Studies with high data loss were excluded.

Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We used relative risks (or 'risk ratios', RR) to establish statistical difference. We used numbers needed to treat (NNT) and pooled percentages as absolute measures of benefit or harm.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occur with paracetamol than with control (placebo or active) we use the term 'the number needed to treat to prevent one event' (NNTp).
- When significantly more adverse outcomes occur with paracetamol compared with control (placebo or active) we use the term 'the number needed to harm or cause one event' (NNH).

Unit of analysis issues

The unit of analysis was the individual patient.

Dealing with missing data

The most likely source of missing data was cross-over studies; we planned to use only first-period data where possible, but where that was not provided, we treated the results as if they were parallel group results. Where there were substantial missing data in any study, we would comment on this and perform sensitivity analyses to investigate their effect.

For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat basis, i.e. we included all participants who were randomised and received an intervention. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We would exclude data from outcomes where results from $\geq 10\%$ of participants were missing with no acceptable reason provided or apparent.

Assessment of heterogeneity

We assessed heterogeneity of response rates using L'Abbé plots, a visual method for assessing differences in results of individual

studies. (L'Abbé 1987). Where data could be pooled, we report the I^2 statistic.

Data synthesis

We analysed studies using a single dose of paracetamol in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.

We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998). We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CIs were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995) when there was a statistically significant difference from control. A statistically significant difference from control is assumed when the 95% CI of the relative risk of benefit or harm did not include the number one.

We used the z test to determine significant differences between NNT, NNTp and NNH for different doses of active treatment, or between groups in the sensitivity analyses (Tramer 1997).

We describe data from comparisons and outcomes with only one study or fewer than 200 participants in the text and summary tables where appropriate for information and comparison, but they are not analysed quantitatively.

Subgroup analysis and investigation of heterogeneity

Issues for potential subgroup analysis were dose, monotherapy or combination with an antiemetic, formulation, and route of administration. For combined treatment with an antiemetic, we planned to compare different antiemetics if there were sufficient data.

Sensitivity analysis

We planned sensitivity analysis for study quality (Oxford Quality Score of 2 versus 3 or more), and for migraine type (with aura versus without aura). A minimum of two studies, with 200 participants in total, had to be available for any sensitivity analysis.

RESULTS

Description of studies

Included studies

Eleven studies fulfilled the inclusion criteria for this review; nine were published in full in peer-reviewed journals (Dexter 1985; Dowson 2000; Freitag 2008; Hoernecke 1993; Lipton 2000; MacGregor 1993; Norrelund 1989; Oztürk 2012; Prior 2010), and two were available as Results Summaries on the manufacturer's website (GL/MIG/001/92; GL/MIG/001A/92). No further details were provided by the manufacturer for these two studies.

All 11 studies recruited participants between 18 and 65 or 70 years of age (mean ages ranging from 33 to 49 years; one study (Hoernecke 1993) included one participant aged 75 years). Seven studies used IHS criteria (IHS 1988; IHS 2004) to diagnose migraine or other criteria that we considered compatible (Ad Hoc 1962; Soyka 1988); four studies (Dexter 1985; Dowson 2000; GL/MIG/001/92; GL/MIG/001A/92) did not report criteria for diagnosis, and we

planned to include them, with a sensitivity analysis to determine their effect on results. In fact [Dexter 1985](#) did not provide any usable efficacy data, and the others did not evaluate any of the same treatment comparisons as those that did report diagnostic criteria. Most studies reported a history at study entry of migraine headaches for at least six months, one year or two years, with between one attack every two months to eight attacks per month of moderate to severe intensity if untreated. Participants were most commonly recruited through attendance at specialised migraine clinics or through primary care practices, although [Lipton 2000](#) used telephone recruitment, and [Prior 2010](#) used a combination of clinic patients and advertising.

Three studies excluded people who had recently used prophylactic medication ([Dexter 1985](#); [GL/MIG/001/92](#); [GL/MIG/001A/92](#)), and three permitted stable prophylactic medication, provided it remained constant ([Dowson 2000](#); [Oztürk 2012](#); [Prior 2010](#)). The implication in other studies was that prophylactic medication was not permitted. [Lipton 2000](#) and [Prior 2010](#) excluded anyone who needed bed rest in at least 50% of attacks, or experienced vomiting in at least 20% of attacks, while [Oztürk 2012](#) excluded anyone who had severe nausea and/or vomiting for at least 25% of attacks.

The 11 studies reported on 14 different treatment comparisons:

- Four studies compared paracetamol 1000 mg alone with placebo ([Freitag 2008](#); [Hoernecke 1993](#); [Lipton 2000](#); [Prior 2010](#); 1293 participants in the comparison).
- One study compared paracetamol 500 mg plus the antiemetic metoclopramide 5 mg with placebo, but did not provide any usable efficacy data ([Dexter 1985](#); 47 participants).
- One study compared paracetamol 1000 mg plus a different antiemetic, domperidone 20 mg or 30 mg, with paracetamol 1000 mg alone ([MacGregor 1993](#); 46 participants in a cross-over study).
- Two studies compared paracetamol 1000 mg plus metoclopramide 10 mg with sumatriptan 100 mg ([GL/MIG/001/92](#); [GL/MIG/001A/92](#); 721 participants).
- One study compared paracetamol 1000 mg plus domperidone 20 mg with sumatriptan 50 mg ([Dowson 2000](#); 120 participants in a cross-over study).
- One study compared paracetamol 1000 mg plus dihydroergotamine 2 mg with paracetamol 1000 mg alone and with dihydroergotamine 2 mg alone ([Hoernecke 1993](#); 288 participants in a cross-over study).
- One study compared paracetamol 1000 mg plus rizatriptan 10 mg with paracetamol 1000 mg alone and rizatriptan 10 mg alone ([Freitag 2008](#); 173 participants).
- One study compared paracetamol 1000 mg with tolafenamic acid 400 mg ([Norrelund 1989](#); 116 participants in a cross-over study).

- One study compared paracetamol 1000 mg with etodolac 400 mg and etodolac 800 mg ([Oztürk 2012](#); 173 participants in a cross-over study).

All treatments were administered orally, either at the onset of an attack when pain intensity was usually still mild ([Dexter 1985](#); [Hoernecke 1993](#); [MacGregor 1993](#); [Norrelund 1989](#)), or when pain intensity was moderate or severe ([Dowson 2000](#); [Freitag 2008](#); [GL/MIG/001/92](#); [GL/MIG/001A/92](#); [Lipton 2000](#); [Oztürk 2012](#); [Prior 2010](#)). Six studies used a parallel-group design ([Dexter 1985](#); [Freitag 2008](#); [GL/MIG/001/92](#); [GL/MIG/001A/92](#); [Lipton 2000](#); [Prior 2010](#)) and the remainder a cross-over design. None of the cross-over studies reported data for the first attack only, and in four ([Dowson 2000](#); [MacGregor 1993](#); [Norrelund 1989](#); [Oztürk 2012](#)) the attrition rate was 20% to 25%, while in another ([Hoernecke 1993](#)) only the number completing all four attacks was reported (completer analysis). Some participants would have been excluded because they did not experience the requisite number of qualifying headaches in the specified study period; none of the studies contributed to meta-analyses of efficacy data.

Most studies used a particular medication to treat a single attack (participants in cross-over studies treated each attack with a different medication), but four studies treated three ([GL/MIG/001/92](#); [GL/MIG/001A/92](#); [Oztürk 2012](#)) or four ([Dexter 1985](#)) attacks with the same medication. [GL/MIG/001/92](#) and [GL/MIG/001A/92](#) reported data separately for each attack, and first attack data are used for the primary analysis. [Dexter 1985](#) did not provide any usable data for the primary analysis, and [Oztürk 2012](#) reported data for up to three attacks per treatment period/intervention, but did not contribute data to any analyses.

Excluded studies

Three studies were excluded after reading the full paper ([Diamond 1976](#); [Diener 2005](#); [Larsen 1990](#)). Details are provided in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Studies were of good methodological quality, with six scoring 5/5, three scoring 4/5, and two scoring 3/5 on the Oxford Quality Scale. Points were lost primarily due to failure to adequately describe the methods of randomisation and blinding, but one study [Oztürk 2012](#) did not adequately account for drop outs.

A Risk of bias table was completed for randomisation, allocation concealment, blinding, incomplete outcome assessment, and size. Only three studies adequately reported allocation concealment ([GL/MIG/001/92](#); [GL/MIG/001A/92](#); [Lipton 2000](#); [Prior 2010](#)), two were considered at high risk of bias due to incomplete outcome assessment ([Dexter 1985](#); [MacGregor 1993](#)), and three were considered at high risk due to small size ([Dexter 1985](#); [Freitag 2008](#); [MacGregor 1993](#)) ([Figure 1](#)). [Dexter 1985](#) and [MacGregor 1993](#) did not contribute to any pooled analyses in this review.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Five studies used a cross-over design. None reported data for the first phase separately, and three (Dowson 2000; Hoernecke 1993; Norrelund 1989) reported only on participants who took each of the study medications. Two cross-over studies excluded significant (> 10%) numbers of participants because they did not treat attacks with each study medication; Dowson 2000 excluded 41/161 (25%) participants, and Hoernecke 1993 excluded 186/474 (39%) participants, mostly because they did not report four separate attacks. While this is a significant loss of data from these studies, there is no reason to think that there was any systematic bias involved. Neither study contributed data to any pooled analysis. MacGregor 1993 did not exclude two participants who had invalid data for two of three treatments. Oztürk 2012 reported combined data for up to three attacks treated with each of three interventions, but did not comment on numbers of participants who did not experience three attacks per treatment or otherwise explain drop-outs.

Effects of interventions

See: [Summary of findings for the main comparison](#)

Although 11 studies were identified for inclusion in this review, few compared paracetamol, with or without an antiemetic, with either placebo or the same active comparator, when taken either at onset of pain (while pain intensity was usually mild) or once pain

intensity was moderate or severe. Consequently, few studies could be combined, and there were few data available for meta-analysis. We have reported on all comparisons with at least 200 participants and have analysed quantitatively all those involving at least two studies and 200 participants or treated attacks.

Details of outcomes in individual studies are provided in [Appendix 5](#) (efficacy) and [Appendix 6](#) (adverse events and withdrawals).

Results for the primary analyses are summarised in Summary of results A.

Pain-free at two hours

Paracetamol 1000 mg versus placebo

Three studies (717 participants) provided data for pain-free response at two hours when medication was taken for moderate to severe pain (Freitag 2008; Lipton 2000; Prior 2010).

- The proportion of participants pain-free at two hours with paracetamol 1000 mg was 19% (68/367; range 14% to 26%).
- The proportion of participants pain-free at two hours with placebo was 10% (36/350; range 8% to 15%).
- The relative benefit of treatment compared with placebo was 1.8 (95% CI 1.2 to 2.6); the NNT was 12 (7.5 to 32) ([Analysis 1.1](#); [Figure 2](#)).

Figure 2. Forest plot of comparison: 1 Paracetamol 1000 mg versus placebo, outcome: 1.1 Pain-free at 2 hours.

One other study (576 attacks) provided data equivalent to pain-free response at two hours (pain 0 or 1 on scale 0 to 9) when medication was taken at the onset of attack and the pain not necessarily moderate or severe (Hoernecke 1993). Thirty-one percent (31%; 89/288) of attacks were pain-free at two hours with paracetamol 1000 mg compared with 19% (65/288) with placebo (Analysis 1.1).

Paracetamol 1000 mg versus dihydroergotamine 2 mg

In addition to providing data for comparison of paracetamol 1000 mg with placebo (above), Hoernecke 1993 also provided data for comparison with dihydroergotamine 2 mg, with medication taken at the onset of attack and the pain not necessarily moderate or severe. Thirty-one percent (31%; 89/288) of attacks were pain-free at two hours with paracetamol 1000 mg compared with 25% (72/288) with dihydroergotamine 2 mg.

Paracetamol 1000 mg versus etodolac 400 mg and 800 mg

One study provided data for comparison of paracetamol 1000 mg with etodolac 400 mg and 800 mg (Oztürk 2012); 19% (64/344)

of attacks were pain-free at two hours with paracetamol 1000 mg compared with 19% (63/327) with etodolac 400 mg and 24% (84/349) with etodolac 800 mg. This study did not have a placebo control group for internal sensitivity.

Headache relief at two hours

Paracetamol 1000 mg versus placebo

Three studies (717 participants) provided data for headache relief at two hours when medication was taken for moderate to severe pain (Freitag 2008; Lipton 2000; Prior 2010).

- The proportion of participants with headache relief at two hours with paracetamol 1000 mg was 56% (207/367; range 52% to 70%).
- The proportion of participants with headache relief at two hours with placebo was 36% (127/350; range 32% to 46%).
- The relative benefit of treatment compared with placebo was 1.6 (1.3 to 1.8); the NNT was 5.0 (3.7 to 7.7) (Analysis 1.3; Figure 3).

Figure 3. Forest plot of comparison: 1 Paracetamol 1000 mg versus placebo, outcome: 1.3 Headache relief at 2 hours.

One other study (Hoernecke 1993) treated at onset of attack when pain was not necessarily moderate or severe. At two hours, 109/288 (38%) attacks had mild or no pain with paracetamol 1000 mg and 56/288 (20%) with placebo (Analysis 1.3). This cross-over study reported efficacy data only for participants who treated all four attacks, each with a different intervention. The attrition rate over the course of the study is not known.

Paracetamol 1000 mg versus dihydroergotamine 2 mg

One study (Hoernecke 1993) treated at onset of attack when pain was not necessarily moderate or severe. At two hours, 109/288 (38%) attacks had mild or no pain with paracetamol 1000 mg and 82/288 (28%) with dihydroergotamine 2 mg. This cross-over study reported efficacy data only for participants who treated all four attacks, each with a different intervention. The attrition rate over the course of the study is not known.

Paracetamol 1000 mg versus etodolac 400 mg and 800 mg

One study provided data for comparison of paracetamol 1000 mg with etodolac 400 mg and 800 mg (Oztürk 2012); 44% (150/344) of attacks had headache relief at two hours with paracetamol 1000 mg compared with 48% (158/327) with etodolac 400 mg and 46% (161/349) with etodolac 800 mg. This study did not have a placebo control group for internal sensitivity.

Paracetamol 500 mg plus domperidone 20 mg versus sumatriptan 50 mg

Only one study provided data for this comparison, with medication taken for moderate to severe pain (Dowson 2000): 44/120 (36%) of attacks had headache relief at two hours with paracetamol 500 mg plus domperidone 20 mg, compared with 40/120 (33%) with sumatriptan 50 mg. Twenty-five percent of study participants did not treat both attacks and are not included in any analysis. This study did not have a placebo control group for internal sensitivity and did not report the criteria used for diagnosis.

Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg

Two studies (1140 participants) provided data for these treatments, with medication taken for moderate to severe pain (GL/MIG/001/92; GL/MIG/001A/92). Data for the first of three attacks treated are used for this analysis. These studies did not have placebo control groups for internal sensitivity and did not report the criteria used for diagnosis.

- The proportion of participants with headache relief at two hours with paracetamol 1000 mg plus metoclopramide 10 mg was 39% (225/580; range 36% to 41%).
- The proportion of participants with headache relief at two hours with sumatriptan 100 mg was 42% (233/560; range 41% to 42%).
- The relative benefit of the combination compared with sumatriptan was 0.93 (0.81 to 1.1; Analysis 2.1). The NNT was not calculated.

Headache relief at one hour

Paracetamol 1000 mg versus placebo

Two studies (635 participants) provided data for headache relief at one hour when medication was taken for moderate to severe pain (Lipton 2000; Prior 2010).

- The proportion of participants with headache relief at one hour with paracetamol 1000 mg was 39% (127/324; range 37% to 42%).
- The proportion of participants with headache relief at one hour with placebo was 20% (62/311; range 17% to 23%).
- The relative benefit of treatment compared with placebo was 2.0 (1.5 to 2.6; Analysis 1.2); the NNT was 5.2 (3.8 to 8.1).

Paracetamol 1000 mg versus etodolac 400 mg and 800 mg

One study provided data for comparison of paracetamol 1000 mg with etodolac 400 mg and 800 mg (Oztürk 2012); 26% (85/327) of attacks had headache relief at one hour with paracetamol

1000 mg compared with 30% (96/321) with etodolac 400 mg and 31% (104/340) with etodolac 800 mg. This study did not have a placebo control group for internal sensitivity, and the reported denominators differ from those reported for 2-hour outcomes.

Sustained pain-free at 24 hours

Only one study ([Freitag 2008](#)) comparing paracetamol 1000 mg with placebo and rizatriptan 10 mg reported this outcome; 16% (7/43) of participants had a sustained pain-free response with paracetamol, 8% (3/39) with placebo, and 23% (10/43) with rizatriptan.

Sustained headache relief at 24 hours

Only one study ([Freitag 2008](#)) comparing paracetamol 1000 mg with placebo and Practipan 10 mg reported this outcome; 42% (18/43) of participants had sustained headache relief with paracetamol, 15% (6/39) with placebo, and 53% (23/43) with rizatriptan.

Two studies ([GL/MIG/001/92](#); [GL/MIG/001A/92](#)) comparing paracetamol 1000 mg plus metoclopramide 10 mg with sumatriptan 100 mg reported sustained headache relief at 48 hours; 27% (78/286) experienced the outcome with paracetamol plus metoclopramide and 41% (118/288) with sumatriptan.

Subgroup analyses

All included studies used paracetamol at a dose of 1000 mg, but different comparator doses have been analysed separately. There were no data to compare paracetamol with and without an antiemetic, and insufficient data to compare different antiemetics (metoclopramide and domperidone). All medication was administered orally as standard formulations (e.g. not soluble, effervescent).

Studies treating at onset of a migraine attack have been analysed separately from those treating once pain is moderate or severe; there were insufficient data for any pooled analysis of studies treating at onset. There were insufficient data for analysis of studies using multiple dosing strategies.

Sensitivity analyses

No sensitivity analysis could be carried out for methodological quality or migraine subtype, as all studies scored 3 or more on the Oxford Quality Scale, and no study analysed migraine subtypes separately.

Summary of results A: Pain-free and headache relief							
	Baseline pain intensity	Studies	Participants or attacks treated	Treatment (%)	Placebo or comparator (%)	RR (95% CI)	NNT (95% CI)
Pain-free at 2 h							
Paracetamol 1000 mg versus placebo	Moderate/severe	3	717	19	10	1.8 (1.2 to 2.6)	12 (7.5 to 32)
Paracetamol 1000 mg versus placebo	Onset	1	576	31	19	-	-
Paracetamol 1000 mg versus dihydroergotamine 2 mg	Onset	1	576	31	25	-	-
Paracetamol 1000 mg versus etodolac 400 mg	Moderate/severe	1	671	19	19	-	-
Paracetamol 1000 mg versus etodolac 800 mg	Moderate/severe	1	693	19	24	-	-
Headache relief at 2 h							
Paracetamol 1000 mg versus placebo	Moderate/severe	3	717	56	36	1.6 (1.3 to 1.8)	5.0 (3.7 to 7.7)
Paracetamol 1000 mg versus placebo	Onset	1	576	38	20	-	-
Paracetamol 1000 mg versus dihydroergotamine 2 mg	Onset	1	576	28	20	-	-
Paracetamol 1000 mg versus etodolac 400 mg	Moderate/severe	1	671	44	48	-	-
Paracetamol 1000 mg versus etodolac 800 mg	Moderate/severe	1	693	44	46	-	-
Paracetamol 1000 mg + domperidone 20 mg versus sumatriptan 50 mg	Moderate/severe	1	240	36	33	-	-
Paracetamol 1000 mg + metoclopramide 10 mg versus sumatriptan 100 mg	Moderate/severe	2	1140	39	42	0.93 (0.81 to 1.1)	Not calculated
Headache relief at 1 h							
Paracetamol 1000 mg versus placebo	Moderate/severe	2	635	39	20	2.0 (1.5 to 2.6)	5.2 (3.8 to 8.1)

Paracetamol 1000 mg versus etodolac 400 mg	Moderate/severe	1	648	26	30	-	-
Paracetamol 1000 mg versus etodolac 800 mg	Moderate/severe	1	667	26	31	-	-

Adverse events

Any adverse event

All included studies made some mention of adverse events, but did not always report the numbers of participants in each treatment group who experienced at least one adverse event. The incidence of adverse events varied considerably between studies, and probably reflects whether all events were recorded, or just those that were treatment-emergent, not part of the migraine attack (i.e. not migraine-associated symptoms) or considered drug-related. Differences in the methods used to collect data (e.g. diary vs. spontaneous reporting) may also influence recorded incidence. In addition, it was not always stated whether data continued to be collected after use of rescue medication, which may cause its own adverse events. Where reported, adverse events were described as mostly of mild or moderate intensity, and transient.

One study comparing paracetamol 1000 mg with placebo reported the number of participants with at least one adverse event before use of rescue medication and within 24 hours (Freitag 2008), two reported within six hours (Lipton 2000; Prior 2010), and one within two hours (Hoernecke 1993). These studies were combined for analysis (1293 participants).

- The proportion of attacks experiencing adverse events with paracetamol 1000 mg was 18% (117/655; range 1% to 34%).
- The proportion of attacks experiencing adverse events with placebo was 23% (144/638; range 3% to 46%).
- The relative risk with treatment compared with placebo was 0.78 (0.64 to 0.95; Analysis 1.4). There were more adverse events with placebo than with paracetamol; the NNTp was 21 (11 to 300) for paracetamol compared with placebo.

In the two studies with high rates of adverse events (Lipton 2000; Prior 2010), most were migraine-associated symptoms.

One study comparing paracetamol 1000 mg plus metoclopramide 10 mg with sumatriptan 100 mg reported the numbers of participants with "major" and "minor" adverse events (GL/MIG/001/92), and a similar study reported numbers with any adverse events (GL/MIG/001A/92). We assumed for analysis that major and minor categories are mutually exclusive (which may slightly overestimate the event rate) and combined the studies for analysis.

- The proportion of participants experiencing adverse events with paracetamol 1000 mg plus metoclopramide 10 mg was 28% (191/675; range 25% to 32%).
- The proportion of participants experiencing adverse events with sumatriptan 100 mg was 47% (304/653; range 41% to 53%).
- The relative risk with paracetamol plus metoclopramide compared with sumatriptan was 0.61 (0.53 to 0.71; Analysis 2.2); the NNTp was 5.5 (4.3 to 7.6) for paracetamol plus metoclopramide compared with sumatriptan.

There were insufficient data for analysis of other comparisons (Appendix 6).

Specific adverse events

Not all studies reported on numbers of participants with specific adverse events. Some reported the most common events, or those occurring in a given percentage of any treatment arm, while others

reported "drug-related adverse events" or "side effects". Most reported events affected the digestive system (abdominal pain, nausea, vomiting), special senses (sensitivity to stimuli), or the central nervous system (dizziness), and many were likely to be symptoms associated with the migraine attack itself, rather than an adverse effect of the medication. There were too few events for detailed analysis.

Serious adverse events

One study (Norrelund 1989) did not report on serious adverse events. No study reported any serious adverse events in participants treated with paracetamol 1000 mg alone or paracetamol 1000 mg plus domperidone 20 mg.

Two studies comparing paracetamol 1000 mg plus metoclopramide 10 mg or sumatriptan 100 mg (GL/MIG/001/92; GL/MIG/001A/92) reported on "major" adverse events, which were defined as "serious adverse events or clinical abnormalities that led to withdrawal". These appear to include severe (a measure of intensity) adverse events necessitating withdrawal in addition to any serious events (usually defined as having significant medical consequences such as death, prolonged hospitalisation, permanent disability, or congenital anomaly).

- The proportion of participants experiencing major adverse events with paracetamol 1000 mg plus metoclopramide 10 mg was 3% (21/675).
- The proportion of participants experiencing major adverse events with sumatriptan 100 mg was 6% (41/653; range 5% to 8%).
- The relative risk with paracetamol plus metoclopramide compared with sumatriptan was 0.50 (0.30 to 0.83; Analysis 2.3); the NNH was 32 (18 to 112).

In GL/MIG/001/92 only two types of "major" adverse events were reported by more than 1% of participants: 5/305 reported dizziness and 4/305 reported nausea with sumatriptan 100 mg. One participant reported chest pain with sumatriptan 100 mg. In GL/MIG/001A/92 only one "major" adverse event was reported by more than 1% of participants: 4/348 reported chest pain with sumatriptan 100 mg. There were no "major" adverse events occurring in more than 1% of participants with paracetamol plus metoclopramide in either study.

Withdrawals

Adverse event withdrawals

Eight studies reported on withdrawals due to adverse events. In four there were no withdrawals in any treatment arm (Freitag 2008; Hoernecke 1993; Lipton 2000; MacGregor 1993). In Dexter 1985 there were two withdrawals due to nausea with paracetamol plus metoclopramide, and in Prior 2010 there were two withdrawals with paracetamol and one with placebo, all due to migraine-associated symptoms. In GL/MIG/001/92 and GL/MIG/001A/92 there were five and eight withdrawals, respectively, with paracetamol plus metoclopramide, and 18 and 13, respectively, with sumatriptan 100 mg, with no reasons for withdrawal given.

Other withdrawals and exclusions

Some participants were excluded from analyses because they vomited within 30 minutes of taking study medication, were lost

to follow-up or had major protocol violations. Generally these numbers were small and equally distributed between treatment arms. One four-period cross-over study ([Hoernecke 1993](#)) and three studies treating more than one attack with the same medication ([Dexter 1985](#); [GL/MIG/001/92](#); [GL/MIG/001A/92](#)) reported small numbers of participants who withdrew between treatment periods due to lack of efficacy. Lack of efficacy during a single attack should be captured by Use of rescue medication ([Appendix 7](#)), although there were limited data reported for this outcome.

DISCUSSION

Summary of main results

This review included 11 randomised, double-blind, controlled studies with 2942 participants (5109 attacks). Medication was taken either at the onset of an attack or once pain intensity was moderate or severe, and most studies investigated the effects of a single dose of medication for an attack. Only one dose of paracetamol, 1000 mg, was used. Five different active comparators were evaluated (sumatriptan 50 mg and 100 mg, dihydroergotamine 2 mg, rizatriptan 25 mg, tolfenamic acid 400 mg, and etodolac 400 mg and 800 mg), plus two in combination with paracetamol (dihydroergotamine and rizatriptan), and two different antiemetics (metoclopramide 10 mg and domperidone 20 and 30 mg) were combined with paracetamol, but there were sufficient data to compare only paracetamol with placebo, and paracetamol plus metoclopramide with sumatriptan. Outcomes were not consistently reported, and only one small study reported on 24-hour sustained efficacy. There were insufficient data to compare treating an attack at onset with treating once pain has become moderate or severe, or to compare single with multiple dosing regimens.

For the IHS preferred outcome of pain-free at two hours, paracetamol 1000 mg was better than placebo, with an NNT of 12, when baseline pain was moderate or severe (three studies; 717 participants). Around 1 in 5 participants achieved this outcome with paracetamol compared with 1 in 10 with placebo. For headache relief at one hour and two hours, paracetamol was also better than placebo, with NNTs of 5 when baseline pain was moderate or severe. Over half of participants achieved relief at two hours with paracetamol, compared with about 1 in 3 with placebo.

There were no data for pain-free at two hours for the combination of paracetamol 1000 mg and metoclopramide 10 mg versus sumatriptan 100 mg, but for headache relief at two hours, there was no significant difference between the two treatments when baseline pain was moderate or severe (two studies; 1140 participants). About 2 in 5 participants achieved this outcome in these studies.

Adverse events were poorly reported, but there was no evidence of an increase in the number of participants experiencing any adverse events with paracetamol 1000 mg compared with placebo, and no serious adverse events were reported with paracetamol alone. Significantly fewer participants experienced any adverse event with the combination of paracetamol plus metoclopramide compared with sumatriptan 1000 mg, and there were more "major" adverse events with sumatriptan (6% versus 3%).

Additional analyses ([Appendix 7](#)) show that for relief of migraine-associated symptoms of nausea, photophobia and phonophobia,

about 10% to 15% more participants achieved relief within two hours with paracetamol than with placebo, with NNTs of 7 to 11. There was no significant difference between paracetamol 1000 mg plus metoclopramide 10 mg and sumatriptan 100 mg for relief of "light/noise sensitivity" at two hours.

In the three studies that reported functional disability, most participants were experiencing some degree of disability when they took study medication, and significantly more were free of disability at two hours with paracetamol than with placebo, with an NNT of 10. About 1 in 4 of those with disability at the time of treatment were free of disability at two hours with paracetamol compared with 1 in 7 with placebo. Fewer participants needed to use rescue medication over six hours with paracetamol than with placebo (NNT 6), but more needed it over 24 hours with paracetamol than with sumatriptan (NNH 17).

Overall completeness and applicability of evidence

Included studies did not always report our prespecified outcomes of interest, and for some outcomes (such as adverse events) data were not reported consistently, making it difficult to combine data for analysis. There were insufficient data for most drug comparisons or treatment protocols to allow analysis, so that evidence is limited to the comparison of a single dose of paracetamol (1000 mg) with placebo, and a single dose of the combination of paracetamol plus metoclopramide (1000/10 mg) with sumatriptan 100 mg, both taken when pain intensity was moderate or severe. Even for these comparisons, not all of the prespecified outcomes were reported. Of particular note is that only one small study reported on 24-hour sustained response (relief or pain-free) in comparisons with placebo, so that no conclusions can be drawn about whether paracetamol can prevent recurrence of the attack.

Participants in most studies had a diagnosis of migraine according to IHS or comparable criteria, but four studies did not report criteria. Of these four, [Dexter 1985](#) and [Dowson 2000](#) did not contribute to any efficacy analyses; data for the other two studies ([GL/MIG/001/92](#); [GL/MIG/001A/92](#)) were taken from a manufacturer's Summary of Results sheet, which did not report details of methods, but it is very likely that IHS diagnostic criteria from 1988 were used in these trials. These two studies did provide data for analysis, but it was not possible to compare their results with those from studies that reported diagnostic criteria.

Participants were mostly recruited from migraine clinics or primary care, which might lead to under-representation of individuals with milder headaches. [Lipton 2000](#) and [Prior 2010](#) excluded those who usually required bed rest or who vomited during more than 20% of attacks, and [Prior 2010](#) included only those who had also previously used OTC medications. These two studies contributed almost 90% of the data for the primary outcomes for paracetamol compared with placebo. [Oztürk 2012](#) excluded those who had severe nausea and/or vomiting for at least 25% of attacks, but did not contribute to analyses. Some individuals with very severe or difficult-to-treat migraine headaches may have been excluded in these two studies, and limits on the frequency of attacks would exclude those with very frequent attacks, but otherwise the population in this review was probably representative, in terms of migraine headaches, of those who seek help for the condition. Most studies specified that participants were required to be "in good general health" or excluded those with significant co-morbidities

(including, for example uncontrolled hypertension, renal or hepatic disease, cardiovascular and cerebrovascular disease). This may mean that the population studied may differ from the general public who choose to self-medicate with OTC paracetamol.

The amount of information available for active comparators was small, so that direct comparisons could not be made except for paracetamol plus metoclopramide versus sumatriptan, and there were insufficient data to compare paracetamol plus an antiemetic with placebo.

Individual studies are underpowered to determine differences between treatments for adverse events, and even pooling studies may not provide adequate numbers of events to demonstrate differences or allow confidence in the size of the effect. Analysis of adverse events in these studies was further compromised by incomplete and inconsistent reporting, but there was no evidence of increased numbers of adverse events, or any serious adverse events, with paracetamol 1000 mg alone or in combination with metoclopramide 10 mg.

Quality of the evidence

Included studies were of adequate or good methodological quality and validity; reporting of details of the methods of randomisation and allocation concealment tended to be better in more recent studies.

Potential biases in the review process

The main area of concern was that the numbers of participants and events were small and divided between many different comparators. For cross-over studies we have used data from each phase, which may introduce unknown biases (Elbourne 2002).

We consider that NNTs of 8 for the outcome pain-free at two hours (13% benefit over comparator), and 6 for headache relief at two hours (17% benefit over comparator), are working limits of clinical utility in this condition. For pain-free at two hours paracetamol is already outside the limit of utility, so the calculation of the quantity of additional data with null effect that would be required to reach that point could not be done (Moore 2008), and even a small body of unidentified evidence showing no effect would affect interpretation of results for this outcome. For headache relief at two hours we calculate that only 143 participants would be needed in unidentified studies showing no effect of paracetamol over placebo to increase the NNT to the limit of utility. It is not unlikely that this quantity of null data exists. While it is unlikely that the result would be overturned, the size of the effect should be interpreted with caution.

Agreements and disagreements with other studies or reviews

A systematic review of interventions for acute migraine with a literature search to 2000 found no trials using paracetamol that satisfied inclusion criteria and provided primary efficacy data

(Oldman 2002). A review of OTC drugs for acute migraine with a search up to 2002 (Wenzel 2003) found that paracetamol was more effective than placebo for headache relief at two hours, and recommended OTC products (paracetamol, aspirin, ibuprofen and combination products) as "a feasible option" for those who experience disability with fewer than 50% of attacks and/or vomiting with fewer than 20% of attacks. Earlier reviews have also recommended OTC products, together with an antiemetic, for mild migraine attacks (e.g. Diener 1998). Recent guidelines on the drug treatment of migraine headaches (Evers 2009) acknowledge that paracetamol has shown efficacy in acute treatment in one RCT. This review includes new studies, presenting more robust estimates of efficacy for a number of standard and validated outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

For individuals who have contraindications to, or are unable to tolerate, aspirin or NSAIDs, paracetamol 1000 mg alone may be a useful first-line treatment for migraine headaches that do not cause severe disability. In combination with metoclopramide, paracetamol may offer similar efficacy to oral sumatriptan 100 mg, but with fewer adverse events. If tolerated, other therapies, such as aspirin or ibuprofen, are effective in more individuals.

Implications for research

Studies are needed to investigate further whether the addition of an antiemetic, such as metoclopramide, to paracetamol can improve either pain relief or migraine-associated symptoms, and also to investigate potential benefits of different dosing strategies such as treating when pain is still mild or multiple dosing regimens. Studies should assess whether efficacy at early time points is sustained. Head-to-head studies with active comparators, particularly other OTC medications, would allow direct comparison between treatments. Ideally these studies would include a placebo comparator for internal validity.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dexter 1985

Methods	R, DB, PC, parallel-group
	Four attacks treated. Medication (2 tablets) taken at onset of attack, repeated after 1 and 4 h if necessary (maximum 6 tablets in 24 h). Rescue medication (aspirin 600 mg) after 4 h if necessary

Dexter 1985 (Continued)

Participants	Common or classical migraine (≥ 2 years). Aged 20-50 years. Frequency 2 to 8 per month. Excluded: prophylactic treatment within 4 weeks N = 49 (42 completed 4 attacks) M 16, F 33 Mean age 33 years
Interventions	Paracetamol + metoclopramide 2 x 500/5 mg Placebo
Outcomes	Severity and duration of attacks Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4 Predates IHS diagnostic criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matched placebo"
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Study size	High risk	< 50 participants per treatment group

Dowson 2000

Methods	R, DB, DD, AC, cross-over Two attacks treated with single doses of each of two study medications. Medication taken when pain was moderate or severe. Rescue medication after 4 h if necessary Severity assessed at 0, 1, 2, 4, 24, 48, 72 h
Participants	Migraine $\pm$ aura (diagnostic criteria not reported). Aged 18 to 65 years. Duration of condition > 1 year. Frequency ≥ 2 every 12 weeks. Prophylactic therapy (pizotifen, clonidine, β -blockers, calcium channel blockers) allowed if stable for ≥ 3 months and kept constant N = 161 (120 took both treatments and were analysed for efficacy) M 9, F 111

Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults (Review)

Dowson 2000 (Continued)

	Mean age 43 years
Interventions	Paracetamol + domperidone 1000/20 mg + placebo Sumatriptan 50 mg + placebo
Outcomes	Headache relief at 2 h Presence of nausea and vomiting Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebos"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy data analysed for participants taking both interventions. Safety data included all participants taking any intervention
Study size	Unclear risk	50 to 200 participants per treatment group

Freitag 2008

Methods	Multicentre, R, DD, AC and PC, parallel-group Single attack treated with a single dose of study medication. Medication taken when pain was moderate or severe. Rescue medication after 2 h if necessary Assessments at 0, 0.5, 1, 1.5, 2, 3, 4, 24 h
Participants	Migraine ± aura (IHS 2004). Aged ≥ 18 years. Frequency 0.5 to 6 per month. Untreated severity ≥ moderate. Excluded: >10 headache days per month or used analgesics regularly > 3 days per week N = 173 M 21, F 152 Mean age 43 years
Interventions	Paracetamol 1000 mg, n = 43 Rizatriptan 10 mg, n = 43 Rizatriptan + paracetamol 10/1000 mg, n = 48

Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults (Review)

Freitag 2008 (Continued)

Placebo, n = 39

Outcomes	Pain-free at 2 h Headache relief at 2 h 24 h sustained relief 24 h sustained pain-free Relief of nausea, photophobia, phonophobia, functional disability Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy, "matched placebos"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs described
Study size	High risk	< 50 participants per treatment group

GL/MIG/001/92

Methods	Multicentre, R, DB, parallel-group Three attacks treated with same medication. Second dose of sumatriptan or placebo paracetamol + domperidone allowed after 2 h if necessary. Rescue medication after 4 hours if necessary
Participants	Migraine ± aura (diagnostic criteria not reported). Aged 20 to 65 years. Duration of condition > 1 year. Frequency ≥ 1 every 8 weeks. Excluded: prophylactic treatment within 2 weeks, IHD, chronic analgesic use for other condition N = 607 M 98, F 509 Mean age 39 years
Interventions	Paracetamol + metoclopramide 1000/10 mg, n = 302

GL/MIG/001/92 (Continued)

Sumatriptan 100 mg, n = 305

Outcomes	Headache relief at 2 h 24 h sustained relief Relief of nausea, vomiting, photophobia/phonophobia Use of rescue medication Adverse events Withdrawals
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Notes	Oxford Quality Score: R2, DB2, W1. Total = 5
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Investigators provided with a sealed envelope for each patient - to be returned unopened at the end of the trial, or patient discontinued from trial
Blinding (performance bias and detection bias) All outcomes	Low risk	Each active treatment had a matched placebo tablet (triple dummy)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs described
Study size	Low risk	> 200 participants per treatment group

GL/MIG/001A/92

Methods	Multicentre, R, DB, parallel-group Three attacks treated with single doses of the same medication. Rescue medication after 4 hours if necessary
Participants	Migraine ± aura (diagnostic criteria not reported). Aged 20 to 65 years. Duration of condition > 1 year. Frequency ≥ 1 every 8 weeks. Excluded: prophylactic treatment within 2 weeks, IHD, chronic analgesic use for other condition N = 721 M 124, F 597 Mean age 40 years
Interventions	Paracetamol + metoclopramide 1000/10 mg, n = 373 Sumatriptan 100 mg, n = 348
Outcomes	Headache relief at 2 h

GL/MIG/001A/92 (Continued)

24 h sustained relief

Relief of photophobia/phonophobia

Use of rescue medication

Adverse events

Withdrawals

Notes Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Investigators provided with a sealed envelope for each patient - to be returned unopened at the end of the trial, or patient discontinued from trial
Blinding (performance bias and detection bias) All outcomes	Low risk	Each active treatment had a matched placebo tablet (triple dummy)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs described
Study size	Low risk	> 200 participants per treatment group

Hoernecke 1993

Methods	Multicentre, R, DB, PC and AC, four-way cross-over
	Four consecutive attacks treated with single doses of each test medication
Participants	"Simple" migraine (criteria of Soyka). Aged 18-70 years (included one patient aged 75 years). Prior attacks uniform with regard to headache intensity and duration
	N = 288 (completed 4 attacks)
	M 55, F 233
	Mean age 42 years
Interventions	Paracetamol 1000 mg
	Dihydroergotamine 2 mg
	Paracetamol + dihydroergotamine 1000/2 mg
	Placebo
Outcomes	Pain-free at 2 h
	Headache relief at 1 h and 2 h
	≤ 50% pain relief at 1 h and 2 h

Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults (Review)

Hoernecke 1993 (Continued)

Presence of nausea, vomiting, photophobia, phonophobia

Use of rescue medication

Adverse events

Withdrawals

Notes Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised order in the form of a Latin square"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Study size	Low risk	> 200 participants per treatment group

Lipton 2000

Methods	<p>Multicentre, R, DB, PC, parallel-group</p> <p>Single attack treated with a single dose of study medication. Medication taken when pain was moderate or severe. Rescue medication after 2 h if necessary</p> <p>Assessments at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 h</p>
Participants	<p>Migraine ± aura (IHS 1988). Aged ≥ 18 years. Frequency 0.5 to 6 per month. Untreated severity ≥ moderate. Excluded: require bedrest for >50%, or vomiting with >20% of attacks</p> <p>N = 289</p> <p>M 58, F 231</p> <p>Mean age 37 years</p> <p>15% with aura</p>
Interventions	<p>Paracetamol 1000 mg, n = 147</p> <p>Placebo, n = 142</p>
Outcomes	<p>Pain-free at 2 h</p> <p>Headache relief at 1 h and 2 h</p> <p>Relief of nausea, photophobia, phonophobia, functional disability</p>

Lipton 2000 (Continued)

Use of rescue medication

Adverse events

Withdrawals

Notes Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	"all information kept in a blinded form until after database was locked"
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical appearing placebo tablets"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs described
Study size	Unclear risk	50 to 200 participants per treatment group

MacGregor 1993

Methods	R, DB, PC, cross-over Three attacks treated, each with a single dose of each of three study medications. Medication taken at onset of attack, repeated every 4 h (maximum four doses). Rescue medication after 1 h if necessary Severity assessed at 0, 0.5, 1, 2, 4, 8, 24 h
Participants	Migraine ± aura (IHS 1988). Aged 18 to 70 years N = 58 M 8, F 50 Median age 43 years Aura: 43%
Interventions	Paracetamol + domperidone 1000/20 mg, n = 44 Paracetamol + domperidone 1000/30 mg, n = 46 Paracetamol 1000 mg + placebo, n = 44
Outcomes	Use of rescue medication Adverse events Withdrawals

MacGregor 1993 (Continued)

Notes Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"predetermined randomized code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matched placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	High risk	< 50 participants per treatment group

Norrelund 1989

Methods	R, DB, AC, cross-over Two attacks treated, each with a single dose of each study medication. Mediastion taken at onset. Rescue medication (usual) after 3 h if necessary	
Participants	Migraine (ad hoc criteria). Aged 18 to 70 years. Frequency 1 to 6 attacks per month N = 149 (116 used both treatments) M 16, F 100 Mean age 45 years	
Interventions	Paracetamol 1000 mg, n = 116 Tolfenamic acid 400 mg, n = 116	
Outcomes	Adverse events	
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Low risk	"identical sealed packages containing two capsules of each drug"

Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults (Review)

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Norrelund 1989 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completer analysis (treating both attacks), but adequate reasons for exclusion given for all others
Study size	Unclear risk	50 to 200 participants per treatment group

Oztürk 2012

Methods	R, DB, AC, cross-over Three attacks treated, each with a single dose of each study medication. Mediacion taken when pain moderate or severe. Rescue medication (usual) if no relief within 4 h or recurrence Pain intensity assessed at 1, 2, 4, 24 h	
Participants	Migraine (ICHD-II criteria). Aged 18 to 65 years. Frequency 1 to 8 attacks per month N = 173 (1047 attacks, 118 participants used all three treatments) M 23%, F 77% Mean age 34 years	
Interventions	Paracetamol 1000 mg, n = 350 attacks evaluated Etodolac 400 mg, n = 339 attacks evaluated Etodolac 800 mg, n = 358 attacks evaluated	
Outcomes	Pain-free at 2 h Headache relief at 1 h and 2 h 24-h sustained pain-free Adverse events	
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Treatment drugs were dispensed as 2 pills of similar coating to keep the blindness"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs not adequately accounted for - possibly lack of qualifying headache
Study size	Low risk	> 200 attacks per treatment group

Prior 2010

Methods	<p>Multicentre, R, DB, PC, parallel-group</p> <p>Single attack treated with a single dose of study medication. Medication taken when pain was moderate or severe. Rescue medication after 2 h if necessary</p> <p>Assessments at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 h</p>
Participants	<p>Episodic migraine $\pm$ aura (IHS 2004). Age $\geq$ 18 years. History of 0.5 to 6 attacks/month in past year and previous treatment with OTC medication. Untreated severity $\geq$ moderate. Excluded: require bedrest for > 50%, or vomiting with > 20% of attacks</p> <p>N = 346</p> <p>M 58, F 288</p> <p>Mean age 39 years</p> <p>22% with aura</p>
Interventions	<p>Paracetamol 1000 mg, n = 177</p> <p>Placebo, n = 169</p> <p>Prophylactic medication continued unchanged</p>
Outcomes	<p>Pain-free at 2 h</p> <p>Headache relief at 1 h and 2 h</p> <p>Relief of nausea, photophobia, phonophobia, functional disability</p> <p>Use of rescue medication</p> <p>Adverse events</p> <p>Withdrawals</p>
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	"blister cards with winged 2-piece code label including treatment assignment according to sponsor-generated randomization code"
Blinding (performance bias and detection bias) All outcomes	Low risk	"tablets identical in shape, size and color"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate reasons for exclusion given for all others.
Study size	Unclear risk	50 to 200 participants per treatment group

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Diamond 1976	No usable single dose data. No diagnostic criteria.
Diener 2005	Mixed migraine and tension headache.
Larsen 1990	Up to 8 attacks treated/participant, but total number of attacks/treatments not reported, so denominator unknown.

DATA AND ANALYSES

Comparison 1. Paracetamol 1000 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 hours	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Moderate/severe pain	3	717	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.24, 2.62]
1.2 Onset of attack	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.04, 1.80]
2 Headache relief at 1 hour	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Moderate/severe pain	2	635	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.52, 2.55]
3 Headache relief at 2 hours	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Moderate/severe pain	3	717	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.32, 1.83]
3.2 Onset of attack	1	576	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.47, 2.57]
4 Any adverse event	4	1293	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.64, 0.95]
5 Use of rescue medication at 6 h	2	635	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.47, 0.74]
6 Relief of associated symptoms at 2 hours	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Nausea	2	536	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.17, 1.61]
6.2 Photophobia	3	985	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.19, 1.64]
6.3 Phonophobia	3	944	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.21, 1.67]
7 Relief of functional disability at 2 hours	2	610	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.24, 2.48]

Analysis 1.1. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 1 Pain-free at 2 hours.

Analysis 1.2. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 2 Headache relief at 1 hour.

Analysis 1.3. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 3 Headache relief at 2 hours.

Analysis 1.4. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 4 Any adverse event.

Analysis 1.5. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 5 Use of rescue medication at 6 h.

Analysis 1.6. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 6 Relief of associated symptoms at 2 hours.

Analysis 1.7. Comparison 1 Paracetamol 1000 mg versus placebo, Outcome 7 Relief of functional disability at 2 hours.

Comparison 2. Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 hours	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.81, 1.07]
2 Any adverse event	2	1328	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.53, 0.71]
3 Major adverse event	2	1328	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Use of rescue medication at 24 h	2	1243	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.01, 1.36]
5 Relief of light/noise sensitivity at 2 hours	2	1001	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.21]

Analysis 2.1. Comparison 2 Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg, Outcome 1 Headache relief at 2 hours.

Analysis 2.2. Comparison 2 Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg, Outcome 2 Any adverse event.

Analysis 2.3. Comparison 2 Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg, Outcome 3 Major adverse event.

Analysis 2.4. Comparison 2 Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg, Outcome 4 Use of rescue medication at 24 h.

Analysis 2.5. Comparison 2 Paracetamol 1000 mg plus metoclopramide 10 mg versus sumatriptan 100 mg, Outcome 5 Relief of light/noise sensitivity at 2 hours.

APPENDICES

Appendix 1. Definitions

All terms relating to primary efficacy outcomes are defined according to the effect of the treatment on headache pain, measured using a four-point pain intensity scale (ranging from 0 to 3 or none, mild, moderate, and severe).

- Baseline pain intensity - level of pain participant must be experiencing in order to receive study medication, either 1 (mild pain) or 2/3 (moderate or severe pain).

- Pain-free at two hours - number of participants with a pain intensity of 0 (none) at two hours after administration of study medication, expressed as a fraction of the treated participants with the appropriate baseline pain.
- Headache relief at two hours - number of participants with a reduction in pain intensity from 2/3 (moderate/severe) to 0/1 (none/mild) at two hours after administration of study medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- 24-hour sustained headache relief - number of participants with a reduction in pain intensity from 2/3 (moderate/severe) to 0/1 (none/mild) at two hours after administration of study medication which is then sustained between 2 and 24 hours without recurrence of headache or use of rescue medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- 24-hour sustained pain-free - number of participants with a pain intensity of 0 (none) at two hours after administration of study medication which is then sustained between 2 and 24 hours without recurrence of headache or use of rescue medication expressed as a fraction of the treated participants with the appropriate baseline pain.
- Use of rescue medication - number of participants requiring the use of additional medication to treat either recurrence of headache or an inadequate response to study medication, provided that the additional medication is not, or does not include, the study drug.
- Relief of associated symptoms - number of participants with an absence of a headache-associated symptom (nausea, vomiting, photophobia, or phonophobia) at two hours after administration of study medication, expressed as a fraction of the treated participants for whom the symptom was present at baseline.
- Relief of functional disability - reduction in the level of functional disability, measured using a four-point scale, from moderate or severe disability (grade 2/3) at baseline to mild or none (grade 1/0) at two hours after administration of study medication, expressed as a fraction of the treated participants with moderate or severe functional disability at baseline.

Appendix 2. Search strategy for MEDLINE (via Ovid)

1. Acetaminophen/
2. (acetaminophen OR paracetamol OR Paramax OR Migraeflux OR Metomax).mp.
3. 1 OR 2
4. Headache/ OR exp Headache Disorders/
5. exp Migraine Disorders/
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
- 10.randomized.ab.
- 11.placebo.ab.
- 12.drug therapy.fs.
- 13.randomly.ab.
- 14.trial.ab.
- 15.groups.ab.
- 16.OR/8-15
- 17.3 AND 7 AND 16

Appendix 3. Search strategy for EMBASE (via Ovid)

1. Paracetamol/
2. (acetaminophen OR paracetamol OR Paramax OR Migraeflux OR Metomax).mp.
3. 1 OR 2
4. exp Headache and facial pain
5. exp migraine
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. clinical trials.sh.
9. controlled clinical trials.sh.
- 10.randomized controlled trial.sh.
- 11.double-blind procedure.sh.
- 12.(clin* adj25 trial*).ab.

- 13.((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.
- 14.placebo*.ab.
- 15.random*.ab.
- 16.OR/8-15
- 17.3 AND 7 AND 16

Appendix 4. Search strategy for CENTRAL

1. MeSH descriptor Acetaminophen
2. (acetaminophen OR paracetamol OR Paramax OR Migraeflux OR Metomax):ti,ab,kw.
3. 1 OR 2
4. MeSH descriptor Headache/ OR MeSH descriptor Headache Disorders explode all trees
5. MeSH descriptor Migraine Disorders explode all trees
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw.
7. 4 OR 5 OR 6
8. Randomized controlled trial:pt
9. MESH descriptor Double-blind Method
- 10.random*:ti,ab,kw.
- 11.OR/8-10
- 12.3 AND 7 AND 11
- 13.Limit 12 to Clinical Trials (CENTRAL)

Appendix 5. Summary of efficacy outcomes: headache relief, pain-free, and use of rescue medication

Study ID	Treatment	HR 1 h	HR 2 h	PF 2 h	24 h SHR	24 h SPF	Use of rescue medication
Dexter 1985	(1) Paracetamol + metoclopramide 500/5 mg, n = 22 (18 analysed for efficacy) (2) Placebo, n = 27 (24 analysed for efficacy)	No data	No data	No data	No data	No data	Over 24 h: (1) 9/18 (2) 18/24 Up to 3 doses of study medication taken
Dowson 2000	(1) Paracetamol + domperidone 1000/20 mg + placebo (2) Sumatriptan 50 mg + placebo 161 participants took medication, 120 completed both attacks and analysed for efficacy	No data	(1) 44/120 (2) 40/120	No data	No data	No data	No data
Freitag 2008	(1) Paracetamol 1000 mg, n = 43 (2) Rizatriptan 10 mg, n = 43 (3) Rizatriptan + paracetamol 10/1000 mg, n = 48 (4) Placebo, n = 39	No data	(1) 30/43 (2) 33/43 (3) 43/48 (4) 18/39	(1) 11/43 (2) 17/43 (3) 26/48 (4) 6/39	(1) 18/43 (2) 23/43 (3) 30/48 (4) 6/39	(1) 7/43 (2) 10/43 (3) 15/48 (4) 3/39	No usable data
GL/MIG/001/92	(1) Paracetamol + metoclopramide 1000/10 mg, n = 302 (2) Sumatriptan 100 mg, n = 305	No data	Moderate/severe baseline pain Attack 1: (1) 103/227 (2) 118/242 After 2nd dose: (1) 71/138, (2) 75/143 Attack 2: (1) 89/219, (2) 114/207	No data	No 24 h data 48 h, any baseline pain: Attack 1: (1) 78/286 (2) 118/288 Attack 2: (1) 82/260, (2) 118/258 Attack 3:	No data	Over 24 h, any baseline pain: Attack 1: (1) 91/286 (2) 79/288 Attack 2: (1) 93/260 (2) 53/250 Attack 3: (1) 88/228 (2) 59/221

(Continued)

			Attack 3: (1) 65/193, (2) 92/188		(1) 56/228, (2) 72/221		
GL/ MIG/001A/92	(1) Paracetamol + metoclopramide 1000/10 mg, n = 373 (2) Sumatriptan 100 mg, n = 348	No data	Moderate/severe baseline pain Attack 1: (1) 122/294 (2) 115/272 Attack 2: (1) 105/263, (2) 90/236 Attack 3: (1) 73/231, (2) 79/174	No data	No 24 h data 48 h, any base- line pain: Attack 1: (1) 87/351 (2) 105/318 Attack 2: (1) 73/312, (2) 94/276 Attack 3: (1) 77/264, (2) 69/211	No data	Over 24 h, any base- line pain: Attack 1: (1) 154/351 (2) 119/318 Attack 2: (1) 135/312 (2) 114/276 Attack 3: (1) 137/264 (2) 79/211
Hoernecke 1993	(1) Paracetamol 1000 mg (2) Dihydroergotamine 2 mg (3) Paracetamol + dihydroergota- mine 1000/2 mg (4) Placebo 288 participants completed all four treatments	No data	(1) 109/288 (2) 82/288 (3) 130/288 (4) 56/288	Pain free or score of 1 (scale 0-9): (1) 89/288 (2) 72/288 (3) 113/288 (4) 65/288	No data	No data	Over 2 h: (1) 81/288 (2) 92/288 (3) 74/288 (4) 112/288
Lipton 2000	(1) Paracetamol 1000 mg, n = 147 (2) Placebo, n = 142	(1) 62/147 (2) 33/142	(1) 85/147 (2) 55/142	(1) 33/147 (2) 16/142	No data	No data	Over 6 h: (1) 21/147 (2) 46/142
MacGregor 1993	(1) Paracetamol + domperidone 1000/20 mg (2) Paracetamol + domperidone 1000/30 mg (3) Paracetamol 1000 mg + placebo	No data	No data	No data	No data	No data	Over 24 h: (1) 18/44 (2) 15/46 (3) 21/44

(Continued)

	46 participants treated at least 1 attack, 44 treated all 3 attacks						Up to 4 doses of study medication taken
Norrelund 1989	(1) Paracetamol 1000 mg (2) Tolfenamic acid 400 mg 116 participants treated both attacks	No data	No data	No data	No data	No data	No significant difference but paracetamol numerically better than placebo
Oztürk 2012	(1) Paracetamol 1000 mg (2) Etodolac 400 mg (3) Etodolac 800 mg	≤ 3 attacks combined (1) 85/327 (2) 96/321 (3) 104/340	≤ 3 attacks combined (1) 150/334 (2) 158/327 (3) 161/349	≤ 3 attacks combined (1) 64/334 (2) 63/327 (3) 84/349	No data	≤ 3 attacks combined (1) 37/108 (2) 44/115 (3) 46/112 Note - only about 1/3 total attacks in denominator	No usable data
Prior 2010	(1) Paracetamol 1000 mg, n = 177 (2) Placebo, n = 169	(1) 65/177 (2) 29/169	(1) 92/177 (2) 54/169	(1) 24/177 (2) 14/169	No data at 6 h: (1) 98/17, (2) 56/169	No data at 6 h: (1) 62/17, (2) 35/169	Over 6 h: (1) 58/177 (2) 83/169

Appendix 6. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Any AE	Specific AEs	Serious AEs	AE Withdrawal	Other Withdrawals/Exclusions
Dexter 1985	(1) Paracetamol + metoclopramide 500/5 mg, n = 22 (18 analysed for efficacy) (2) Placebo, n = 27 (24 analysed for efficacy)	No "adverse reactions" reported	None	None	(1) 2/22 (nausea) (2) 0/27	Excluded: (1) 2 (lost to follow-up), (2) 3 (LoE, attacks stopped, did not like treatment)
Dowson 2000	(1) Paracetamol + domperidone 1000/20 mg + placebo (2) Sumatriptan 50 mg + placebo 161 participants took medication, 120 completed both attacks and analysed for efficacy	<15% had "side effects" with either treatment	Dizziness: (1) 6, (2) 7 Nausea: (1) 4, (2) 2 Denominator unknown	None	No data	Excluded: 41 pts took at least one treatment, but did experience a second attack during the study.
Freitag 2008	(1) Paracetamol 1000 mg, n = 43 (2) Rizatriptan 10 mg, n = 43 (3) Rizatriptan + paracetamol 10/1000 mg, n = 48 (4) Placebo, n = 39	Before rescue medication: (1) 8/43 (2) 13/43 (3) 16/48 (4) 7/39	Dizziness: (1) 2/43, (2) 2/43, (3) 5/48, (4) 1/39 Nausea: (1) 0/43, (2) 1/43, (3) 3/48, (4) 2/39 Chest discomfort in 2 placebo pts	None	None	Excluded: (1) 2 lost to follow-up, (2) 2 lost to follow-up, 1 withdrew consent, (3) 1 lost to follow-up, (4) 3 lost to follow-up, 1 withdrew consent Discontinued: (1) 3/43, (2) 3/43, (3) 6/48, (4) 6/39 No reasons given for discontinuation
GL/MIG/001/92	(1) Paracetamol + metoclopramide 1000/10 mg, n = 302 (2) Sumatriptan 100 mg, n = 305 Data for all three attacks	"Minor" + "major" over 48 hours: (1) 98/302 (2) 162/305	Most common: Dizziness: (1) 13/302, (2) 22/305 Drowsiness: (1) 5/302, (2) 7/305 Tiredness: (1) 9/302, (2) 4/305 Nausea: (1) 5/302, (2) 44/305 Light headed: (1) 1/302, (2) 16/305	"Major" - any serious AE or clinical or laboratory AE leading to withdrawal: (1) 9/302 (2) 24/305 1 pt had chest pain (major AE)	(1) 5/302 (2) 18/305	Withdrawals: (1) 42/302 (8 LoE, 34 other), (2) 35/305 (other) "Other" probably includes pts who did not have 2nd or 3rd attacks - data for 1st attack used for efficacy

(Continued)

				with suma- triptan		
GL/ MIG/001A/92	(1) Paracetamol + metoclopramide 1000/10 mg, n = 373 (2) Sumatriptan 100 mg, n = 348 Data for all three at- tacks	Over 48 h: (1) 93/373 (2) 142/348	Most common: Dizziness (1) 7/373, (2) 22/348 Drowsiness (1) 4/373, (2) 4/348 Tiredness (1) 3/373, (2) 4/348 Nausea: (1) 3/373, (2) 27/348 Light headed: (1) 1/302, (2) 16/305	"Major" - any serious AE or clin- ical or lab- oratory AE leading to withdraw- al: (1) 12/373 (2) 17/348 4 pts had chest pain (major AE) with suma- triptan	(1) 8/373 (2) 13/348	Withdrawals: (1) 92/373 (11 LoE, 83 other), (2) 95/348 (11 LoE, 90 other) "Other" probably includes pts who did not have 2nd or 3rd attacks - data for 1st attack used for efficacy
Hoernecke 1993	(1) Paracetamol 1000 mg (2) Dihydroergota- mine 2 mg (3) Paracetamol + dihydroergotamine 1000/2 mg (4) Placebo 288 participants completed all four treatments	Over 2 h: (1) 2/288 (2) 5/288 (3) 7/288 (4) 8/288 All tran- sient	Most common: Tiredness: (1) 0/288, (2) 2/288, (3) 4/288, (4) 2/288 Drowsiness: (1) 0/288, (2) 0/288, (3) 0/288, (4) 1/288 Nausea: (1) 0/288, (2) 0/288, (3) 1/288, (4) 1/288	None	None	Excluded: 186 due to miss- ing data or protocol viola- tions Withdrawal after treat- ment: (1) 14 (2) 20 (3) 19 (4) 16 Denominator unknown, since number of partici- pants taking each treat- ment not reported Overall 85 participants dis- continued: 72 had non- medical reasons (attacks not frequent enough, study ended), 7 LoE (1 withdrew after the combi- nation, 2 each after parac- etamol, DHE, and place- bo), in 6 cases there were 'no useful data'
Lipton 2000	(1) Paracetamol 1000 mg, n = 147 (2) Placebo, n = 142	Over 6 h: (1) 47/147 (2) 52/142	Digestive system: (1) 31/147, (2) 31/142 Special senses: (1) 25/147, (2) 33/142 Nervous system: (1) 5/147, (2) 3/142	None	None	Withdrawals: (1) 7/147 (5 vomited within 0.5 h, 2 other), (2) 3/142 (1 vomit- ed within 0.5 h, 2 other)

(Continued)

CV system: (1) 0/147, (2) 3/142						
MacGregor 1993	(1) Paracetamol + domperidone 1000/20 mg (2) Paracetamol + domperidone 1000/30 mg (3) Paracetamol 1000 mg + placebo 46 participants treated at least 1 attack, 44 treated all 3 attacks	Over 24 h: (1) 2/44 (2) 1/46 (3) 1/44	(1) indigestion, dizziness (2) tiredness (3) drowsiness	None	None	Excluded after initial visit: 12/58 pts (10 lost to follow-up, 1 had no qualifying attack, 1 withdrew consent). Unclear whether they took any medication 2 excluded from analyses for (1) and (3) because treated attacks without adequate washout
Norrelund 1989	(1) Paracetamol 1000 mg (2) Tolfenamic acid 400 mg 116 participants treated both attacks	Over 3 h: (1) 7/116 (2) 5/116	No data	No data	No data	Excluded: 7 had only 1 attack
Oztürk 2012	(1) Paracetamol 1000 mg (2) Etodolac 400 mg (3) Etodolac 800 mg	Pts reporting AE in treatment period (1) 8/148 (2) 9/150 (3) 9/151	Dry mouth: (1) 1/148, (2) 1/150, (3) 0/151 Nausea: (1) 3/148, (2) 5/150, (3) 5/151 GI: (1) 8/148, (2) 4/150, (3) 6/151 Drowsiness: (1) 2/148, (2) 2/150, (3) 0/151 Allergic rash, palpitation, tiredness each in 1/151 in (3)	None	No data	No data
Prior 2010	(1) Paracetamol 1000 mg, n = 177 (2) Placebo, n = 169	Over 6 h: (1) 60/177 (2) 77/169	Dizziness: (1) 2/177, (2) 2/169 Nausea: (1) 26/177, (2) 44/169 Vomiting: (1) 4/177, (2) 9/169 Somnolence: (1) 1/177, (2) 2/169	None	(1) 2/177 (2) 1/169 (nausea, vomiting, sensitivity to light and noise)	Withdrawn: (1) 3/177 (1 vomited within 0.5 h, 2 fell asleep), (2) 5/169 (vomited within 0.5 h)

Appendix 7. Other outcomes

Use of rescue medication

Use of rescue medication was permitted after two hours in most studies using single dosing regimens, after 1 to 4 hours in those allowing repeat dose(s), and not reported in [GL/MIG/001/92](#); [GL/MIG/001A/92](#). The time post medication at which use was reported varied between studies, further limiting analysis.

Two studies (635 participants) comparing paracetamol 1000 mg with placebo, with medication taken for moderate to severe pain, permitted use of rescue medication after two hours and reported on use within six hours ([Lipton 2000](#), [Prior 2010](#)).

- The proportion of participants using rescue medication within six hours with paracetamol 1000 mg was 24% (79/324; range 14% to 33%).
- The proportion of participants using rescue medication within six hours with placebo was 41% (129/311; range 32% to 49%).
- The relative risk of treatment compared with placebo was 0.59 (0.47 to 0.74; [Analysis 1.5](#)); the NNTp was 5.9 (4.1 to 10).

A further two studies (1243 participants) comparing paracetamol 1000 mg plus metoclopramide 10 mg with sumatriptan 100 mg, with medication taken for moderate to severe pain, reported on use within 24 hours ([GL/MIG/001/92](#); [GL/MIG/001A/92](#)).

- The proportion of participants using rescue medication within 24 hours with paracetamol 1000 mg plus metoclopramide 10 mg was 38% (245/637; range 32% to 44%).
- The proportion of participants using rescue medication within 24 hours with sumatriptan 100 mg was 33% (198/606; range 27% to 37%).
- The relative risk of treatment with paracetamol plus metoclopramide compared with sumatriptan was 1.2 (1.0 to 1.4; [Analysis 2.4](#)); the NNH was 17 (9.0 to 210) for paracetamol compared with sumatriptan 100 mg.

Relief of migraine-associated symptoms

Reporting of migraine-associated symptoms such as nausea, vomiting, phonophobia and photophobia was inconsistent, with few studies contributing data for analysis. In the five studies that reported on vomiting ([Dowson 2000](#); [GL/MIG/001/92](#); [Hoernecke 1993](#); [Lipton 2000](#); [Prior 2010](#)), too few attacks had vomiting at baseline to allow any analysis. Information about other symptoms is summarised in the table below. We combined data from [Hoernecke 1993](#), in which treatment was taken at the onset of an attack, with data from studies in which treatment was taken when pain intensity was moderate or severe. The response rate in the study where medication was taken at the onset of an attack was higher (in both active and placebo groups) than in the study where it was taken when pain intensity was moderate or severe. Overall, paracetamol 1000 mg was better than placebo for relief of nausea, photophobia and phonophobia, with an additional 10% to 15% of participants experiencing relief at two hours compared with placebo, giving NNTs of 7 to 9 ([Analysis 1.6](#)). There was no clear difference between paracetamol 1000 mg plus metoclopramide 10 mg and sumatriptan 100 mg, taken when pain intensity was moderate or severe, for relief of light and noise sensitivity during the first attack ([Analysis 2.5](#)). When data from all three attacks were combined, this outcome just reached statistical significance in favour of sumatriptan over paracetamol plus metoclopramide.

Summary of results: Relief of associated symptoms 2 hours after taking study medication

Intervention	Studies	Attacks with Symptom Present	Treatment (%)	Placebo (%)	Relative Risk (95% CI)	NNT/NNH
Relief of nausea						
Paracetamol 1000 mg versus placebo	2	536	59	44	1.4 (1.2 to 1.6)	6.7 (4.3 to 15)
Paracetamol 1000 mg versus dihydroergotamine 2 mg	1	341	70	69	-	-
Relief of photophobia						
Paracetamol 1000 mg versus placebo	3	985	41	30	1.4 (1.2 to 1.6)	9.2 (6.0 to 20)

(Continued)

Paracetamol 1000 mg versus placebo, treatment when pain moderate or severe	2	609	25	16	1.6 (1.1 to 2.1)	11 (6.5 to 39)
Relief of phonophobia						
Paracetamol 1000 mg versus placebo	3	944	43	30	1.4 (1.2 to 1.7)	8.1 (5.4 to 16)
Paracetamol 1000 mg versus placebo, treatment when pain moderate or severe	2	588	28	17	1.6 (1.2 to 2.2)	9.5 (5.8 to 26)
Relief of "light/noise sensitivity"						
Paracetamol + metoclopramide 1000 + 10 mg versus sumatriptan 100 mg (1st attack)	2	1001	32	32	1.0 (0.84 to 1.2)	not calculated
Paracetamol + metoclopramide 1000 + 10 mg versus sumatriptan 100 mg (all 3 attacks)	2	2617	28	33	0.87 (0.77 to 0.98)	22 (12 to 91)

Functional disability

Two studies ([Lipton 2000](#); [Prior 2010](#), 610 participants) reported data from which the numbers free of disability following treatment were calculated; 24% (74/309) participants had relief of functional disability at two hours with paracetamol 1000 mg, and 14% (41/301) with placebo. The relative risk for treatment compared with placebo was 1.8 (1.2 to 2.5; [Analysis 1.7](#)); the NNT was 9.7 (6.1 to 24).

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 11, 2010

Date	Event	Description
6 September 2017	Review declared as stable	See Published notes .
7 May 2013	Review declared as stable	This review will be assessed for further updating in 2018.
15 February 2013	New citation required but conclusions have not changed	One new study identified that did not contribute to any analyses
15 February 2013	New search has been performed	New searches carried out, Risk of bias tables expanded and updated, Summary of findings table added.

CONTRIBUTIONS OF AUTHORS

All authors were involved with planning and writing the protocol. For the full review, SD and RAM carried out the searches, identified studies for inclusion, extracted data and performed analyses. HJM acted as arbitrator. All authors were involved with writing the full review.

For the update SD carried out the searches and data extraction, and entered data into RevMan. RAM checked it. Both authors wrote the update.

DECLARATIONS OF INTEREST

RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. RAM and SD have received research support from charities, government and industry sources at various times. The Oxford Pain Research Trust, the NHS Cochrane Collaboration Programme Grant Scheme, and the NIHR Biomedical Research Centre Programme provided support for the original review. The Oxford Pain Research Trust provided support for the update. None had any input into the review at any stage.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Trust, UK.

General institution support

External sources

- International Headache Society, UK.

Support for the editorial process

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After discussion with headache specialists and editorial staff, and in line with Cochrane recommendations, we decided to limit our outcomes for acute migraine headache reviews in order to focus attention on the most important outcomes and to make them more readable for both clinicians and patients. For the majority of interventions we will now include 2-hour pain-free and headache relief (PF2 and HR2) as primary outcomes, and 24-hour sustained pain-free and headache relief (SPF24 and SHR24) and adverse events as secondary outcomes. In this update we have moved results for use of rescue medication and relief of headache-associated symptoms and functional disability to [Appendix 7](#).

In the update we have expanded the Risk of bias table; this review uses the new criteria for analysis. We have also included an assessment of publication bias, which was not included in the protocol or original review. This assessment is now being added routinely to all our reviews as a measure of reliability and robustness of the results.

NOTES

A restricted search in September 2017 did not identify any potentially relevant studies. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [adverse effects] [*therapeutic use]; Acute Disease; Analgesics, Non-Narcotic [adverse effects] [*therapeutic use]; Antiemetics [adverse effects] [*therapeutic use]; Drug Therapy, Combination [methods]; Hyperacusis [drug therapy]; Metoclopramide [adverse effects] [therapeutic use]; Migraine Disorders [*drug therapy]; Photophobia [drug therapy]; Randomized Controlled Trials as Topic; Sumatriptan [adverse effects] [therapeutic use]

MeSH check words

Adult; Humans