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META-ANALYSIS

Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions

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Abstract

Background: Ibuprofen and paracetamol have long been used as analgesics in a range of acute, intermittent and chronic pain conditions. Paracetamol is often the first line analgesic recommended, without consensus about which is the better analgesic.
Methods: An overview review of systematic reviews and meta-analyses directly compares ibuprofen and paracetamol at standard doses in particular painful conditions, or uses indirect comparisons against placebo. Electronic searches for systematic reviews were sought published since 1995 using outcomes approximating to ≥50% pain intensity reduction. Painful conditions were acute post-operative pain, dysmenorrhoea, tension-type headache (TTH), migraine, osteoarthritis and rheumatoid arthritis, back pain, cancer and paediatric pain. There was no systematic assessment of harm.
Results: Sixteen systematic reviews and four individual patient data meta-analyses were included. Ibuprofen was consistently superior to paracetamol at conventional doses in a range of painful conditions. Two direct comparisons favoured ibuprofen (acute pain, osteoarthritis). Three of four indirect comparisons favoured ibuprofen (acute pain, migraine, osteoarthritis); one showed no difference (TTH), although there were methodological problems. In five pain conditions (dysmenorrhoea, paediatric pain, cancer pain, back pain and rheumatoid arthritis), there were limited data on paracetamol and ibuprofen.
Conclusions: At standard doses in different painful conditions, ibuprofen was usually superior producing more patients with the degree of pain relief that patients feel worthwhile. Neither of the drugs will be effective for everyone, and both are needed. This overview questions the practice of routinely using paracetamol as a first line analgesic because there is no good evidence for efficacy of paracetamol in many pain conditions.

1. Background

The mainstays of non-prescription and prescription analgesics are paracetamol (acetaminophen) and ibuprofen. Paracetamol was discovered in the 1950s (Axelrod, 2003), closely followed by the patent for ibuprofen in 1962 (Rainsford, 2013). Both drugs were prescribed for a wide range of painful conditions, and by the mid-1980s were available without prescription in many parts of the world. Analgesic combinations of ibuprofen plus paracetamol are effective drugs (Moore et al., 2011).

A long-standing argument concerns which of oral ibuprofen or paracetamol is more effective at standard

What's already known about this topic?
- Paracetamol and ibuprofen are widely used analgesics.
- There is uncertainty over which is better.
- Paracetamol is widely suggested as the first line analgesic in guidelines.

What does this study add?
- Evidence from direct and indirect comparisons from systematic reviews in a number of pain conditions shows ibuprofen to be consistently superior where there are good data.
- There is no good evidence of efficacy of paracetamol in many pain conditions.

doses (Jadad, 1994). The roots of the argument lie in inconsistent results of single-dose trials in acute post-operative pain. For 20 years, this has been known to be a product of the relatively small size of the trials and the large effects of random chance in these small trials (Moore et al., 1998), although trial methods also in use for over 50 years have stood the test of time (McQuay et al., 2012). Systematic reviews of all high-quality randomized trials are needed to overcome variability in effects measures in individual studies, and to obtain the best available data to use to make comparisons sensible.

Rational, evidence-based assessments of relative efficacy take time to become widely accepted. In many 'evidence-based guidelines', paracetamol is frequently cited as a first line treatment, e.g., in UK National Guidance on Osteoarthritis (NICE 2014). The implication is that paracetamol must be a better drug than ibuprofen based on assessment of efficacy or safety.

This is buttressed by studies showing little difference between paracetamol and ibuprofen in non-pain situations, as for symptomatic treatment of respiratory tract infections (Little et al., 2013). Some reviews have questioned the alternative assumption that ibuprofen is superior to paracetamol, e.g., in headache, by examining the few trials where head-to-head (direct) comparisons have been made (Manzano et al., 2010), although limited by small numbers of small trials.

We have therefore sought to examine the 'ibuprofen versus paracetamol' question through a systematic search for systematic reviews of direct or indirect comparisons of efficacy between the two. Indirect comparisons compare interventions with the same comparator, usually placebo, and have been shown often to be superior to direct comparison because there is more information available (Song et al., 2003).

Of at least equal and probably greater importance is the question of potential harm. Paracetamol has long been considered a 'safer' drug than ibuprofen, but now this seems unlikely, based on a systematic review of non-prescription doses taken for 7 days or less (Rainsford et al., 1997), and a large randomized trial directly comparing safety over 3 months (Doherty et al., 2011). Safety in long-term use is much more controversial, particularly because of concerns over cardiovascular harm with non-steroidal anti-inflammatory drugs (NSAIDs). Harm is discussed in relation to efficacy, but was not part of this systematic overview, because a full assessment of harm requires a quite different set of searches, of different study architectures and with quite different outcomes. Moreover, short-term use has to be contrasted with long-term use.

2. Methods

2.1 Searching

We performed a series of electronic searches for systematic reviews or meta-analyses reporting on the analgesic efficacy of oral ibuprofen alone or oral paracetamol alone compared with placebo. We also searched for systematic reviews or meta-analyses reporting direct comparisons of ibuprofen and paracetamol. Searches were conducted using PubMed and the Cochrane Library (CENTRAL) using the generic form of 'pain' [tiab – restriction to title and abstract only] AND 'ibuprofen' [tiab] or 'paracetamol' [tiab] AND 'pain condition' [tiab], with filters of human, systematic review and meta-analysis. Titles and abstracts were screened online, and full reports were obtained for any publication considered possibly useful for this overview. We also obtained any studies relating to individual patient data meta-analyses from pooled studies. There was no language restriction, but we included only studies published since 1995 to ensure that information was reasonably up-to-date; the first quality scoring system for including papers in systematic reviews of pain was in 1996 (Jadad et al., 1996). We excluded reviews that were obviously superseded by subsequent or updated reviews, as in Cochrane reviews.

Pain conditions considered were acute post-operative pain, dysmenorrhoea, tension-type headache (TTH), migraine, osteoarthritis and rheumatoid arthritis, back pain, cancer pain and paediatric pain.

2.2 Outcomes

A systematic review of patients' views indicated that patients with pain want either to have large reduction in their pain (≥50% from baseline), or to be in a low pain state, namely no worse than mild pain (Moore et al., 2013b). Migraine patients want pain to be significantly reduced quickly

without recurrence, and ideally without adverse effects (Lipton et al., 2002). Pain outcomes like these are associated with major improvements in comorbidities, with reduced depression, improved sleep, better functioning, higher quality of life and improved ability to work (Moore et al., 2014d).

We therefore chose to make comparisons between ibuprofen and paracetamol using outcomes approximating those valued by patients, ideally those of, or close to, ≥50% pain intensity reduction over the course of a trial, or being in a low pain state at the end of a trial, ideally defined as having pain intensity below 30% of maximum on any scale.

2.3 Analysis

There was no prior intention to perform new meta-analyses of treatment efficacy, but rather to use data and analyses from published reviews. However, we recognized that not all reviews would perform dichotomous analyses of the outcomes now thought most informative, and that some additional analyses may be needed. We performed analyses only where there was an adequate amount of data, which we defined as at least two trials and 200 patients (Moore et al., 1998). Using dichotomous outcomes, we calculated risk ratio and number needed to treat (NNT) with 95% confidence intervals. Relative benefit or risk was calculated using a fixed effect model (Morris and Gardner, 1995), with no statistically significant difference between treatments assumed when the 95% confidence intervals included unity. NNT was calculated (Cook and Sackett, 1995) using the pooled number of observations only when there was a statistically significant difference of relative benefit or risk.

Statistical differences between NNTs for ibuprofen and paracetamol were calculated using the z-test (Tramer et al., 1997), using two-tailed tests and with a p-value of less than 0.05 indicating statistical significance. Significance tests were performed only when both ibuprofen and paracetamol data sets were of the minimal size for calculating NNT.

2.4 Doses

Both ibuprofen and paracetamol show higher efficacy at higher doses in acute pain (McQuay and Moore, 2007) and probably also in chronic pain, at least for ibuprofen (Gallelli et al., 2012). Typical single oral doses of ibuprofen are between 200 and 400 mg, and for paracetamol between 500 and 1000 mg. We therefore chose to compare these doses in acute pain and headache. Daily doses of ibuprofen are typically about 1200 mg in arthritis, but the licence allows up to 2400 mg daily. Paracetamol is licensed variably between about 3000 and 4000 mg. In chronic pain, we chose therefore to compare daily doses of ibuprofen of 1200 mg and above with daily doses of paracetamol of 3000 mg and above.

These dosing regimens do not apply to treatment of paediatric pain and fever, where doses are usually given according to the weight of the child (mg/kg).

3. Results

Results of the search are given separately for each painful condition examined; no systematic reviews or meta-analyses were found for any other painful condition. In total, 16 systematic reviews were included, together with four individual patient data meta-analyses.

3.1 Excluded studies

Six reviews were excluded. One meta-analysis pooled data for various acute and chronic painful conditions to compare them in children and adults (Pierce and Voss, 2010). It concluded that ibuprofen was as or more efficacious than paracetamol for treatment of pain and fever in adult and pediatric populations and is equally safe, although outcomes and doses were ill defined. A systematic review directly compared ibuprofen and paracetamol for pain and fever in children (Perrott et al., 2004). It used ≥50% maximum pain relief, but their analysis was based on just three trials and used methods developed for adults in different settings, which almost certainly do not apply in these paediatric trials. Another reported only on antipyretic results (Goldman et al., 2004).

Data from Weil et al. (2007) on paracetamol after wisdom tooth removal had been superseded by Toms et al. (2008), which included more data and used a more useful analysis. An analysis of preoperative analgesics for dental procedures in children (Ashley et al., 2012) assembled only five trials with 190 children taking different drugs and was not considered further.

A systematic review in TTH was not considered because the authors used equations derived from acute pain, almost certainly inappropriately, so results were not to be trusted (Yoon et al., 2012).

3.2 Acute post-operative pain

We identified four potentially useful systematic reviews for acute post-operative pain relating to pain relief for removal of wisdom teeth, mostly in adults (Bailey et al., 2013), pain after surgery, mainly third molar extraction, for ibuprofen (Derry et al., 2009) and paracetamol (Toms et al., 2008). We also identified an individual patient data analysis directly comparing ibuprofen and paracetamol (Moore et al., 2011).

For post-operative pain relief in adults, a Cochrane review pooled data from five trials (676 patients) directly comparing single oral doses of ibuprofen 400 mg with paracetamol 1000 mg following third

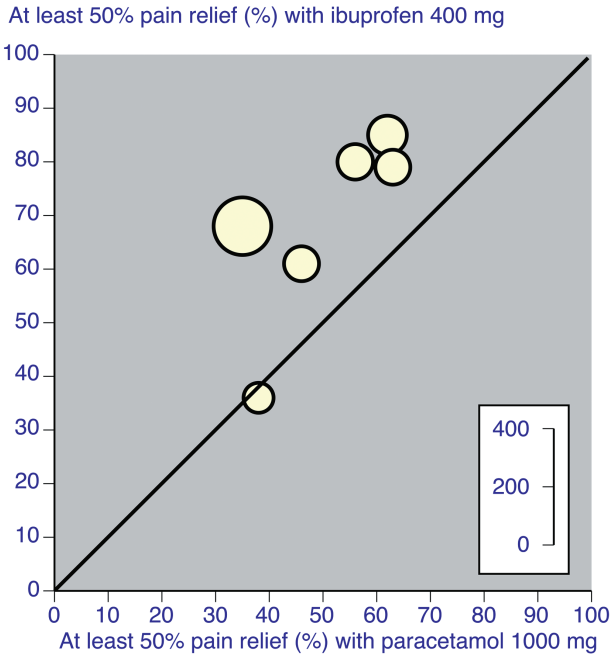

Figure 1 Trials directly comparing ibuprofen 400 mg and paracetamol 1000 mg after third molar extraction. The size of the symbol is proportional to the number of patients in the trial (inset scale). Data sources were a Cochrane review directly comparing single oral doses of ibuprofen with paracetamol (Bailey et al., 2013) with one additional trial (Cooper et al., 1989).

molar removal (Bailey et al., 2013). One trial had unaccountably been omitted (Cooper et al., 1989), and so we recalculated using six trials and 796 patients (Fig. 1). The larger pooled analysis showed ibuprofen 400 mg to provide at least 50% pain relief over 6 h in 19% more patients than paracetamol 1000 mg; the relative benefit for the direct comparison of ibuprofen 400 mg with paracetamol 1000 mg was 1.4 (95% confidence interval 1.3–1.6) and the NNT was 5.1 (3.8–7.8). That meant for every five patients treated with ibuprofen 400 mg compared with paracetamol 1000 mg, one additional patient would have adequate pain relief.

There were insufficient data for a comparison of ibuprofen 200 mg with paracetamol 1000 mg.

Table 1 also shows the results of indirect comparisons of ibuprofen 200 and 400 mg with paracetamol 1000 mg, in which each drug was separately compared with placebo, and the results of those NNTs compared one with another (Toms et al., 2008; Derry et al., 2009). The analysis was split into pain following all surgery, third molar extraction (most of the data) and surgery other than third molar extraction.

For pain after all surgery and third molar extraction, ibuprofen 400 mg was significantly better than ibuprofen 200 mg. Paracetamol at doses between 500 and 1000 mg was significantly worse than either dose of ibuprofen. For other (non-dental) surgery, statistical significance was not usually achieved, perhaps reflecting a smaller data set for the comparisons. About 12% more patients experienced at least 50% pain relief with ibuprofen 400 mg than with paracetamol 1000 mg. A similar magnitude of superiority of ibuprofen 200 and 400 mg over paracetamol 500 and 1000 mg was found in an individual patient data direct comparison, but based on relatively small numbers of patients (Moore et al., 2011).

3.3 Tension-type headache

A systematic review reported comparisons of both ibuprofen 400 mg and paracetamol 1000 mg with placebo. For outcomes of pain free at 2 h, and a patient global assessment equivalent to 'very good' or 'excellent', no significant difference was found (Table 2) (Moore et al., 2014e). The quality and appropriateness of clinical trials in TTH is a matter of some doubt (Moore et al., 2014e).

3.4 Migraine

In migraine, two systematic reviews reported on comparisons of ibuprofen 200 and 400 mg against placebo (Rabbie et al., 2013) and paracetamol 1000 mg against placebo (Derry and Moore, 2013). For the outcome of pain free at 2 h, ibuprofen 400 mg produced the lowest (best) NNT, but it was not significantly different statistically from either ibuprofen 200 mg or paracetamol 1000 mg. For the outcome of mild or no pain at 2 h, ibuprofen 400 mg again produced the lowest NNT, which was significantly better than both ibuprofen 200 mg and paracetamol 1000 mg.

3.5 Dysmenorrhoea

Searches in dysmenorrhoea produced one systematic review in primary dysmenorrhoea (Marjoribanks et al., 2010). It found five studies comparing ibuprofen with placebo, and pooled various dichotomous outcomes to produce a result showing statistical superiority of ibuprofen (400 mg at three to six times daily). Two small trials compared ibuprofen with paracetamol and found no difference between them, but the meaning of the comparisons is unclear because of the small number of patients contributing to this comparison.

An earlier systematic review (Zhang and Li Wan Po, 1998) reported that ibuprofen 400 mg was significantly better than placebo in nine trials (599 women),

Table 1 Summary of indirect comparisons of ibuprofen and paracetamol with placebo in acute post-operative pain: all surgery, dental surgery only and non-dental (other) surgery only. The outcome is the number of patients with at least 50% of maximum possible pain relief over 6 h (≥50% maxTOTPAR).

Drug and dose (mg)	Number of		Percent with outcome with		NNT	Statistically different (two tails of z) from ibuprofen comparator	
	Trials	Patients	Active drug	Placebo	(95% CI)	200 mg	400 mg
Acute post-operative pain: all surgery ≥50% maxTOTPAR							
Ibuprofen 200	20	2690	46	9	2.7 (2.5–3.0)		$z = -2.0$; $p = 0.044$
Ibuprofen 400	61	6475	54	14	2.5 (2.4–2.6)	$z = 2.0$; $p = 0.044$	
Paracetamol 500	6	561	61	32	3.5 (2.7–4.8)	$z = -1.8$; $p = 0.075$	$z = -2.7$; $p = 0.006$
Paracetamol 600/650	19	1886	38	16	4.6 (3.9–5.5)	$z = -5.9$; $p < 0.001$	$z = -8.3$; $p < 0.001$
Paracetamol 1000	28	3232	46	18	3.6 (3.2–4.1)	$z = -4.0$; $p < 0.001$	$z = -6.6$; $p < 0.001$
Acute post-operative pain: dental ≥50% maxTOTPAR							
Ibuprofen 200	18	2470	47	10	2.7 (2.5–3.0)		$z = -3.5$; $p < 0.001$
Ibuprofen 400	49	5428	55	12	2.3 (2.2–2.4)	$z = 3.5$; $p < 0.001$	
Paracetamol 500	3	305	56	30	3.8 (2.7–6.4)	$z = -1.8$; $p = 0.06$	$z = -3.1$; $p = 0.002$
Paracetamol 600/650	10	1276	35	12	4.2 (3.6–5.2)	$z = -4.7$; $p < 0.001$	$z = -7.9$; $p < 0.001$
Paracetamol 1000	19	2157	41	10	3.2 (2.9–3.6)	$z = -2.5$; $p = 0.012$	$z = -6.3$; $p < 0.001$
Acute post-operative pain: other surgery ≥50% maxTOTPAR							
Ibuprofen 200	2	220	39	5	3.0 (2.3–4.2)		$z = 1.4$; $p = 0.17$
Ibuprofen 400	12	1047	48	22	3.9 (3.2–5.0)	$z = -1.4$; $p = 0.17$	
Paracetamol 500	3	256	66	34	3.2 (2.3–5.1)	$z = -0.3$; $p = 0.76$	$z = 0.8$; $p = 0.4$
Paracetamol 600/650	9	610	43	25	5.6 (4.0–9.5)	$z = -2.5$; $p = 0.01$	$z = -1.7$; $p = 0.09$
Paracetamol 1000	10	1075	59	32	3.7 (3.1–4.7)	$z = -1.2$; $p = 0.25$	$z = 0.3$; $p = 0.78$

Source: ibuprofen (Derry et al., 2009) and paracetamol (Toms et al., 2008). NNT, number needed to treat; CI, confidence interval; TOTPAR, total pain relief.

Significantly better than comparator.

Significantly worse than comparator.

Table 2 Summary of indirect comparisons of ibuprofen and paracetamol with placebo in tension-type headache and migraine for the outcomes of pain free at 2 h and mild or no pain at 2 h.

Drug and dose (mg)	Number of		Percent with outcome with		NNT	Statistically different (two tails of z) from ibuprofen	
	Trials	Patients	Active drug	Placebo	(95% CI)	200 mg	400 mg
Tension-type headache							
Pain free at 2 h							
Ibuprofen 400	3	826	29	18	8.9 (5.9–18)		
Paracetamol 1000	5	1387	34	22	8.7 (6.2–15)		z = 0.1; p = 0.94
Global assessment by patient (top two categories)							
Ibuprofen 400	3	774	40	24	6.1 (4.3–10)		
Paracetamol 1000	5	1121	46	35	8.4 (5.7–16)		z = −1.0; p = 0.31
Migraine							
Pain free at 2 h							
Ibuprofen 200	2	777	20	10	9.6 (6.5–18)		z = −1.2; p = 0.23
Ibuprofen 400	6	2575	26	12	7.2 (5.9–9.2)	z = 1.2; p = 0.23	
Paracetamol 1000	3	717	19	10	12 (7.5–32)	z = −0.6; p = 0.55	z = −1.9; p = 0.06
Mild or no pain at 2 h							
Ibuprofen 200	2	777	52	37	6.3 (4.4–11)		z = −3.8; p = 0.002
Ibuprofen 400	7	1815	57	25	3.2 (2.8–3.7)	z = 3.8; p = 0.002	
Paracetamol 1000	3	717	56	36	5.0 (3.7–7.7)	z = 0.9; p = 0.39	z = −2.6; p = 0.008

Source: tension headache (Moore et al., 2014e) and migraine ibuprofen (Rabbie et al., 2013) and paracetamol (Derry and Moore, 2013). NNT, number needed to treat; CI, confidence interval.

Significantly better.

Significantly worse.

but that paracetamol, in one trial, was not. Using data equivalent to at least 50% pain relief, the NNT for ibuprofen 400 mg compared with placebo was 2.6 (2.2–3.2). An individual patient data meta-analysis (Edwards et al., 2004) reported an NNT of 2.4 for the outcome of at least 50% pain over 6 h for ibuprofen 400 mg compared with placebo, but based on data from only 96 women.

3.6 Osteoarthritis

Searches in osteoarthritis produced three systematic reviews (Lee et al., 2004; Towheed et al., 2006; Verkleij et al., 2011).

One (Towheed et al., 2006) related to hip osteoarthritis only. It evaluated a number of NSAIDs together with paracetamol 4000 mg daily. Only a single 4-week trial (184 patients) compared ibuprofen 1200 and 2400 mg daily with paracetamol 4000 mg daily. Five trials (1835 patients) were pooled for a calculation of overall pain comparing paracetamol 4000 mg daily with placebo. Of these, almost 300 patients were in a trial lasting 1 week, 57 in a trial lasting 12 weeks, and the remainder in trials lasting 6 weeks. It demonstrated superiority of paracetamol over placebo of limited clinical significance. The standardized mean difference (standard deviation units) for overall pain of 0.13 (95% confidence interval 0.04–0.22) was lower for paracetamol than placebo, but amounted to just a few millimetres on a 100-mm visual analogue pain scale. The imputation method in the original studies was not mentioned.

The other two systematic reviews examined direct comparisons of NSAIDs with paracetamol in osteoarthritis. The earlier review of seven trials (Lee e1596t al., 2004) included a trial comparing ibuprofen 1200 and 2400 mg with paracetamol 4000 mg daily over 4 weeks. The later review (Verkleij et al., 2011) had an additional trial comparing ibuprofen 1200 mg with paracetamol 3000 mg daily over 2 weeks. In these two trials, ibuprofen was significantly better than paracetamol in two of the three individual comparisons of doses of ibuprofen with doses of paracetamol.

An individual patient data meta-analysis (Moore et al., 2010a) pooled data from seven osteoarthritis trials lasting at least 12 weeks. In two trials with 618 patients, the NNT for ibuprofen 2400 mg daily at 12 weeks compared with placebo for ≥50% reduction in pain intensity was 8.4 (5.1–24), where patients who withdrew from the study for any reason were classed as non-responders. At 6 weeks, the NNT was 6.4 (4.3–12).

3.7 Rheumatoid arthritis

A systematic review (Wienecke and Gotzsche, 2004) found only four older, small studies comparing NSAIDs with paracetamol in rheumatoid arthritis. The largest, a crossover trial with 54 patients, compared ibuprofen 600 mg daily with paracetamol 3000 mg daily, with patients generally preferring ibuprofen.

3.8 Back pain

A systematic review concerned with NSAIDs for back pain (Roelofs et al., 2008) concluded that NSAIDs were better than placebo, but this was based on inclusion of studies of low reporting quality and small size. Only a single small study of reasonable quality directly compared any NSAID with paracetamol, and none compared ibuprofen with paracetamol. NSAIDs were better than placebo for chronic low back pain in an individual patient meta-analysis using the outcome of at least 50% pain relief at the end of a 12-week trial (Moore et al., 2010c).

A systematic review of paracetamol in non-specific low back pain found only two randomized and double-blind trials (Davies et al., 2008). The trials were small, and no conclusions could be drawn.

3.9 Cancer pain

Two systematic reviews examined the efficacy of NSAIDs and paracetamol used as single agents in cancer pain (McNicol et al., 2005; Mercadante and Giarratano, 2013). None of the trials of NSAIDs identified in the reviews included ibuprofen. Of the five small trials of paracetamol 1500–5000 mg daily over 1–7 days, only one found superiority of paracetamol over placebo, and it was clinically insignificant.

3.10 Paediatric pain

We could find no review with useful information on paediatric pain for inclusion.

4. Discussion

In 2013, primary care physicians in England wrote 22 million prescriptions for paracetamol at a cost of £82 million, compared with 4.2 million prescriptions for ibuprofen at a cost of £14 million (Prescription Cost Analysis England 2014). Paracetamol accounts for two-thirds of the over-the-counter painkiller market, with around 200 million packs of paracetamol sold each year in the United Kingdom. Paracetamol is recommended as first line treatment for low back pain (Koes et al., 2010) and osteoarthritis (NICE 2014), and these are typical of many guidelines.

Our overview calls into question this widespread practice of routinely using paracetamol as a first line analgesic in preference to ibuprofen or other analgesics. The same question was also raised by a recent large randomized trial showing no difference between paracetamol and placebo in acute back pain (Williams et al., 2014).

One of the first applications of systematic reviews to pain therapy was to determine differences in efficacy between ibuprofen and paracetamol (Jadad, 1994). This overview of systematic reviews of efficacy used direct and indirect comparisons of ibuprofen and paracetamol, and has demonstrated consistent superiority of ibuprofen for pain relief at conventional doses in a range of painful conditions (Table 3). Two direct comparisons favoured ibuprofen in acute pain and osteoarthritis. Three of four indirect comparisons favoured ibuprofen (acute pain, migraine and osteoarthritis), and one was unable to show any difference (TTH). In five pain conditions (dysmenorrhoea, paediatric pain, cancer pain, back pain and rheumatoid arthritis), there were limited data on either paracetamol or ibuprofen. Where there were data, therefore, they tended to favour ibuprofen.

There are significant limitations in the overview. It is important to stress that it examined evidence comparing the efficacy of ibuprofen and paracetamol at standard doses in different painful conditions using systematic reviews and meta-analyses. It did not set out comprehensively to review harm because that would have required a quite different approach. We did not find a systematic comparison of harm from ibuprofen and paracetamol in our searches. A systematic review of harm would be a helpful addition to the argument; this was outside the scope of our overview and remains a task for future research.

For efficacy, limitations principally concern the lack of data in individual reviews and occasional poor quality of data available. Many older trials were small and did not report outcomes important to patients, and those in chronic pain were often of short duration, which can overestimate treatment effects. All these factors can impart bias, as can the failure to use or report a correct imputation method for study withdrawals (Moore et al., 2010b, 2012). Several of the systematic reviews are in need of updating because they may be out-of-date (Goldman et al., 2004; Lee et al., 2004; Perrott et al., 2004; McNicol et al., 2005; Towheed et al., 2006; Roelofs et al., 2008) or need

Table 3 Summary of results for ibuprofen and paracetamol in direct and indirect comparisons in different painful conditions.

	Ibuprofen versus paracetamol comparison evidence	
Painful condition	Direct comparison	Indirect comparison
Occasional or intermittent use for acute pain (prescribed and non-prescribed)		
Acute post-operative pain	Ibuprofen 400 mg significantly better than paracetamol 1000 mg	Ibuprofen 200 and 400 mg significantly better than paracetamol 500, 650 and 1000 mg
Tension-type headache	No data	No difference between ibuprofen 400 mg and paracetamol 1000 mg
Migraine	No data	Ibuprofen 400 mg, but not 200 mg, better than paracetamol 1000 mg
Dysmenorrhoea	No data	No data available on paracetamol Ibuprofen better than placebo
Occasional or intermittent use for acute pain (mainly prescribed)		
Paediatric pain	No data	No data
Cancer pain	No data	Paracetamol no better than placebo No data on ibuprofen
Ongoing use for chronic pain (mainly prescribed)		
Back pain	No data	No data
Osteoarthritis	Limited data, but at typical daily doses ibuprofen appears to be better than paracetamol	Paracetamol barely distinguished from placebo Ibuprofen clearly better than placebo
Rheumatoid arthritis	No data	No data

Ibuprofen better than paracetamol.
No difference.

methodological upgrading to better reflect outcomes of importance to patients (Marjoribanks et al., 2010) or both.

The need for more or better data may be the perennial conclusion of evidence-based reviews, but we need to make choices between treatments now based on the evidence available. The priority will always be to use available evidence with wisdom, taking into account the conditions in which evidence is to be used and the needs and circumstances of the patient who receives the treatment. Beyond this imperative, we can still use judgement to guide thinking, including acknowledging that both ibuprofen and paracetamol will fail to provide adequate pain relief in some people (Moore et al., 2013a). 'Better' in the assessments made in many of the reviews means that a drug produces good pain relief in more people, not that it produces somewhat greater pain relief in everyone. The experience of the individual is paramount.

In the case of decisions about ibuprofen versus paracetamol, the judgements are determined mainly by duration of use: occasional or intermittent use for acute pain, and ongoing use for chronic pain.

4.1 Occasional or intermittent use for acute pain

The priority in acute pain, including headache and period pain, is for a high degree of pain relief, ideally delivered quickly. These are common conditions, with most people not consulting a professional, but treating their pain with non-prescription medicines. The results here are therefore relevant both to non-prescribed and prescribed analgesic use.

In the context mainly of non-prescription medicines, single doses of ibuprofen 200 and 400 mg typically produce good pain relief in more people than paracetamol 1000 mg in almost all circumstances. The exception was TTH, where a systematic review highlighted inconsistencies in trial design and reporting, including variable designs, poor quality, typically small studies and inconsistent outcome reporting (Moore et al., 2014e). For dysmenorrhoea, ibuprofen 400 mg had a low (good) NNT of 2.6 when compared with placebo, while paracetamol was not significantly different from placebo. Fast-acting ibuprofen formulations have been shown to produce better analgesia than standard acid formulations (Moore et al., 2014b,c), but none of the comparisons here have been made against fast-acting formulations.

There is no obvious evidence of a safety advantage for paracetamol over ibuprofen for non-prescription doses taken for 7 days or less (Rainsford et al., 1997), or for 3 months (Doherty et al., 2011). Adverse event rates in single-dose trials are no different from placebo with ibuprofen or paracetamol (Toms et al., 2008; Derry et al., 2009), although a large randomized trial for common pain in general practice indicated a lower incidence of gastrointestinal adverse events for ibuprofen compared with paracetamol (Moore et al., 2003). There is no evidence of any cardiovascular risk with ibuprofen used at non-prescription doses (Moore

et al., 2014a), but non-overdose paracetamol-exposed liver failure was twice as common than NSAID-exposed liver failure (Gulmez et al., 2013).

Cancer pain and paediatric pain will most often be treated with prescribed analgesics. Cancer pain is included here because of the importance of getting on top of pain. Paracetamol was not significantly different from placebo in cancer pain, and no trials tested ibuprofen in this condition. For paediatric pain, there was insufficient information from systematic reviews.

4.2 Ongoing use for chronic pain

Ongoing therapy for chronic pain like osteoarthritis should produce adequate pain relief, but only about half of those with knee pain taking ibuprofen 1200 mg or paracetamol 3000 mg daily have a result they consider good or excellent in a clinical trial (Doherty et al., 2011). In clinical practice, more often than not, pain relief is inadequate (Conaghan et al., 2014), so people are exposed to possible harms without benefit. In osteoarthritis, some, but not all, people taking standard ibuprofen doses will have adequate pain relief; most of those taking paracetamol will not. On average, paracetamol may produce pain relief equivalent to a few millimetres on a 100-mm visual analogue scale in patients with arthritis over a few weeks (Towheed et al., 2006); for ibuprofen, it is about 8 mm after 12 weeks (Moore et al., 2010a).

The risk of upper gastrointestinal bleeding with ibuprofen was smallest among NSAIDs in a systematic review of good quality studies in the pre-coxib era (Hernandez-Diaz and Rodriguez, 2000), and this risk was also elevated in current users of paracetamol, and very significantly so at doses above 2000 mg daily (Gonzalez-Perez and Rodriguez, 2006). This accords with results from a randomized comparison in which a fall in haemoglobin of at least 20 g/L occurred in similar proportions of patients with ibuprofen and paracetamol (Doherty et al., 2011). Cardiovascular events with NSAIDs are a concern, but ibuprofen use over 2 years was not associated with any cardiovascular risk or change in all-cause mortality in a large Australian study (Mangoni et al., 2010).

These findings are arguably as important for non-prescription use of analgesics as for prescription use. If the United Kingdom is an example, in both circumstances, paracetamol dominates analgesic use, and that is likely to be the case in many parts of the world. Paracetamol may well be a useful analgesic in combination with others, but it has limited efficacy on its own (Moore et al., 2013a). Paracetamol fails to provide adequate analgesia in 65% of people in clinical trials in the best circumstance (Moore et al., 2013a). Promoting analgesic drugs that do not work for most people in most circumstances is a curious strategy.

5. Conclusions

Ibuprofen and paracetamol are both drugs with proven analgesic effect. But at the standard doses used in different painful conditions, ibuprofen is usually superior. This means that ibuprofen provides more patients with a degree of pain relief that patients feel worthwhile. Neither of the drugs will be effective for everyone, and both are needed. But this overview calls into question the widespread practice of routinely using paracetamol as a first line analgesic in preference to ibuprofen or other analgesics. There is no good evidence of clinically relevant efficacy of paracetamol in many pain conditions.

Author contributions

R.A.M. developed the original concept for the study, helped define the broad aims and objectives, performed the searches and extracted data, and was responsible for writing initial and subsequent drafts. S.D. and P.W. checked searches and data extraction, and contributed to the development of the manuscript. S.S. and D.J.A. contributed to the development of the manuscript. All authors discussed the results and commented on the manuscript.

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