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Oral valdecoxib and injected parecoxib for acute postoperative pain: a quantitative systematic review

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Abstract

Background: Clinical trials suggest that cyclo-oxygenase-2 specific inhibitors (coxibs) are an effective treatment for acute postoperative pain. The aims of this systematic review were to examine the evidence for oral valdecoxib and injected parecoxib, and quantify efficacy and adverse effects.

Methods: Information from randomized, double-blind studies in acute postoperative pain was sought. The area under the pain relief versus time curve over four to six hours was dichotomized using validated equations to derive the proportion of patients with treatment and placebo with at least 50% pain relief over four to six hours and calculate the number-needed-to-treat (NNT). Information on duration of analgesia and adverse events was also collected.

Results: The NNT for one patient to experience at least 50% relief over six hours following a single oral dose of valdecoxib 20 mg and 40 mg was 1.7 (1.4 to 2.0) and 1.6 (1.4 to 1.8) respectively. The NNT for one patient to have at least 50% relief over four to six hours with parecoxib 20 mg IV and 40 mg IV was 3.0 (2.3 to 4.1) and 2.3 (2.0 to 2.6) respectively. Mean time to remedication (weighted by trial size) was >24 hours with valdecoxib 40 mg, 8.7 hours with parecoxib 40 mg IV and 1.7 to 1.8 hours with placebo. There were no statistical differences between treatment and placebo for any adverse effect.

Conclusion: Both oral valdecoxib and injected parecoxib are effective treatments for acute postoperative pain.

Background

Several new cyclo-oxygenase-2 specific inhibitors have been tested in acute pain. Known as 'coxibs', these drugs specifically inhibit only one of the two cyclo-oxygenase isoforms inhibited by older NSAIDs [1,2], and are thought to provide comparative efficacy but fewer gastrointestinal adverse events in chronic dosing [3,4]. A systematic review of rofecoxib demonstrated that a 50 mg

dose was effective in treating acute postoperative pain [5]. Not only did rofecoxib 50 mg show four to six hour efficacy at least equivalent to ibuprofen 400 mg and diclofenac 50 mg, but also a much longer duration as measured by time to next analgesia. This duration of analgesia was seen primarily in the context of third molar extractions, and, of course, reflects the high single dose of rofecoxib in acute pain of 50 mg – twice to four times the

daily chronic pain dose, reflecting an increased safety of coxibs over older NSAIDs. Other coxibs have yet to be evaluated in this way for acute pain.

Valdecoxib is an orally administered coxib [6]. Parecoxib is the sulphonamide-based pro-drug of valdecoxib and, for the moment, the only parenterally administered coxib available [7,8]. There is no evidence that injected NSAIDs provide any greater degree of pain relief than the same drugs administered orally [9]. Parenteral preparations may, however, be particularly useful in the immediate postoperative period when patients are unable to take oral medication or are nauseated and vomiting.

Random chance poses a threat to the accuracy and precision of efficacy estimates from individual trial reports. Although single clinical trials can demonstrate statistical superiority of analgesic over placebo, random variation means that, if small, they provide a poor estimate of effect size [10]. Combining results from appropriate trials in a meta-analysis means that more patients are included, giving a more accurate and reliable estimate of the extent of analgesia [10,11].

Individual trials in acute dental, gynaecologic and orthopaedic pain suggest that valdecoxib and parecoxib are both efficacious and well tolerated. The aims of this systematic review were to combine appropriate data to quantify the efficacy, duration of analgesia and associated adverse effects for single dose valdecoxib and parecoxib in the treatment of acute postoperative pain.

Methods

QUORUM guidelines were followed [12]. Possible studies for inclusion were sought through searching PubMed (Dec 2002) and the Cochrane Library (2002 issue 4) using parecoxib and valdecoxib as free text terms. Pfizer and Pharmacia were asked to provide copies of relevant abstracts and posters. Reference lists and review articles were examined for possible additional references, and in-house databases also checked for papers.

Abstracts were examined for possible inclusion if they were randomized trials conducted in an acute pain setting and used valdecoxib or parecoxib and a matched placebo (with or without an active comparator). Criteria for inclusion were: randomized controlled trials which included single dose treatment groups of valdecoxib or parecoxib, double blind design, baseline postoperative pain of moderate to severe intensity, patients over 15 years of age, at least 10 patients per group, and the pain outcome measures of total pain relief (TOTPAR) or summed pain intensity difference (SPID) over 4–6 hours or sufficient data provided to allow their calculation. Posters and abstracts were accepted provided all criteria could be met. Pain

measures allowed for the calculation of TOTPAR or SPID were a standard five point pain relief scale (none, slight, moderate, good, complete), a standard four point pain intensity scale (none, mild, moderate, severe) or a standard visual analogue scale (VAS) for pain relief or pain intensity. The dichotomous information from the number of patients reporting 'good' and 'excellent' on a standard global scale (poor, fair, good, very good, excellent) were also accepted [13]. Also of interest was information on the time to remedication. For adverse events, the primary outcome sought was the proportion of patients experiencing any adverse event, with secondary outcomes of patients experiencing particular adverse events.

Each report which could possibly be described as a randomized controlled trial was read independently by at least two authors and scored using a commonly-used three item, 1–5 score, quality scale [14]. Consensus was then achieved. The maximum score of an included study was 5 and the minimum score was 2. Authors were not blinded because they already knew the literature.

For each trial, mean TOTPAR, SPID, VASTOTPAR or VASSPID values for the first dose from each drug group were converted to %maxTOTPAR by division into the calculated maximum value [15]. The proportion of patients in each treatment group who achieved at least 50%maxTOTPAR was calculated using valid equations [16–18]. The number of patients with at least 50%maxTOTPAR was then used to calculate relative benefit and NNT for treatment versus placebo. The same methods were used for adverse events.

Relative benefit and relative risk estimates were calculated with 95% confidence intervals using a fixed effects model [19]. Heterogeneity tests were not used as they have previously been shown to be unhelpful [20,21] though homogeneity was examined visually [22]. Publication bias was not assessed using funnel plots as these tests have been shown to be unhelpful [23,24]. The number needed to treat or harm (NNT and NNH) with confidence intervals was calculated by the method of Cook and Sackett [25] from the sum of all events and patients for treatment and placebo.

Relative benefit or risk was considered to be statistically significant when the 95% confidence interval did not include 1. NNT or NNH values were only calculated when the relative risk or benefit was statistically significant, and are reported with the 95% confidence interval. Statistical significance of any difference between numbers needed to treat was assumed if there was no overlap of the confidence intervals and statistically quantified using the z test

[26]. Calculations were performed using Microsoft Excel 2001 on a Power Macintosh G3.

Results
Valdecoxib

Two fully published reports of three trials [27,28] and one poster [29] were included in the analyses. All four trials were funded either by Pfizer or Pharmacia, the manufacturers of valdecoxib. Details of the design, numbers of patients, outcomes, analgesic results, adverse events and quality scores are given in additional file 1. Details of excluded reports are given in additional file 2. All trials were in dental pain following third molar extraction. Including active comparators there were 859 patients included across the four trials; 101 patients were treated with valdecoxib 20 mg, 279 with valdecoxib 40 mg and 194 with placebo. Comparator analgesics were rofecoxib 50 mg (183 patients in two trials [27,29].) and oxycodone 10 mg plus paracetamol 1000 mg (102 patients in two tri-

als [28]). Quality scores were 5 for one report (including two trials), 3 for one report and 2 for one report.

At least 50% pain relief

All three reports provided data that permitted the calculation of six hour TOTPAR and derivation of the number of patients with at least 50%maxTOTPAR. Visual assessment of homogeneity showed all the studies to be in good agreement and all trials showed statistical benefit of valdecoxib 20 mg and 40 mg over placebo (Figure 1). Overall 69/101 patients (68%) given valdecoxib 20 mg experienced at least 50% maxTOTPAR over six hours compared with 8/103 patients (8%) treated with placebo in direct comparisons. The NNT for one patient to have at least half pain relief over six hours was 1.7 (1.4 to 2.0). For valdecoxib 40 mg, 204/279 patients (73%) experienced at least 50% maxTOTPAR over six hours compared to 19/194 patients (10%) with placebo in direct comparisons, the NNT for one patient to have at least half pain relief over six hours with was 1.6 (1.4 to 1.8) (Table 1).

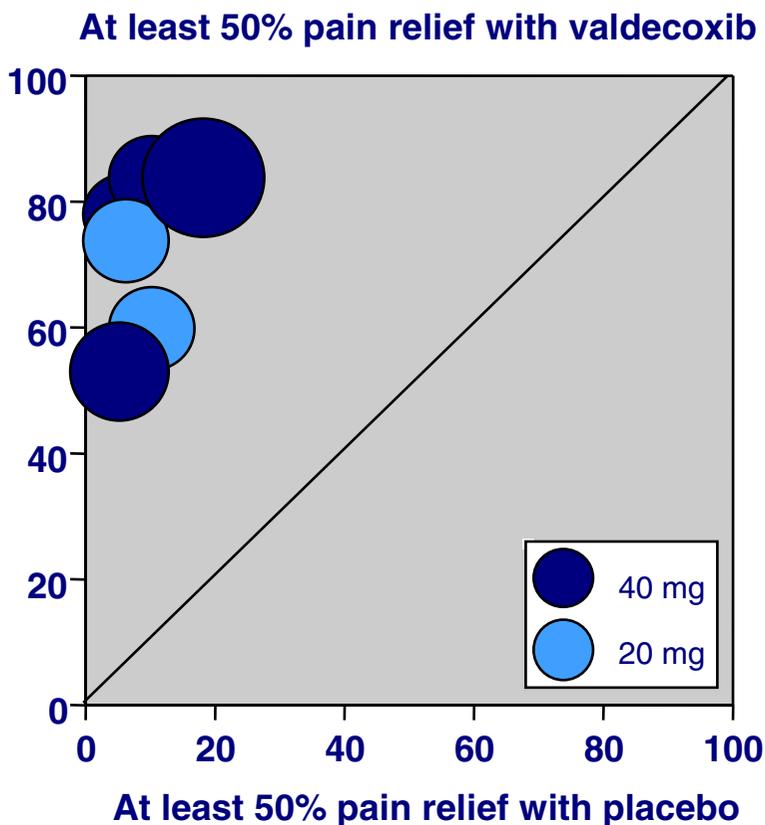


Figure 1
L'Abbe plot showing trials of valdecoxib 20 mg and 40 mg.

Table 1: Efficacy results

Drug and dose	Number of trials	Number (%) of patients with at least 50% pain relief		Relative benefit (95% CI)	NNT (95% CI)	Route
		Active	Placebo			
Valdecoxib 20 mg	2	69/101 (68)	8/103 (8)	8.8 (4.5 to 17.3)	1.7 (1.4 to 2.0)	Oral
Valdecoxib 40 mg	4	204/279 (73)	19/194 (10)	7.3 (4.8 to 11.2)	1.6 (1.4 to 1.8)	Oral
Parecoxib 20 mg	4	85/170 (50)	29/176 (16)	3.1 (2.2 to 4.5)	3.0 (2.3 to 4.1)	Intravenous
Parecoxib 40 mg	4	109/173 (63)	29/176 (16)	3.8 (2.7 to 5.5)	2.2 (1.8 to 2.7)	Intravenous
Parecoxib 20 mg	1	32/51 (63)	2/51 (4)	16 (4.1 to 63.3)	1.7 (1.4 to 2.3)	Intramuscular
Parecoxib 40 mg	1	39/50 (78)	2/51 (4)	19.9 (5.1 to 78)	1.4 (1.2 to 1.6)	Intramuscular

Table 2: Adverse effects

Adverse effect	Number (%) of patients with adverse effects				
	Parecoxib 20 mg (IV)	Parecoxib 40 mg (IV)	Placebo	Valdecoxib 40 mg (oral)	Placebo
Any effect	86/132 (65)	77/131 (59)	73/132 (55)	63/180 (35)	76/144 (53)
Headache	15/132 (11)	14/131 (11)	17/132 (13)	18/180 (10)	36/144 (25)
Nausea	32/132 (24)	25/131 (19)	31/132 (23)	21/180 (12)	30/144 (21)
Vomiting	16/132 (12)	13/131 (10)	11/132 (8)	15/180 (12)	15/144 (10)

Remedication time

Median time to remedication was reported in three reports. The data from one trial [27] did not permit pooling as the design allowed an additional dose of valdecoxib before patients were classed as having remedicated. For placebo, the weighted median time to remedication from 153 patients was 1.7 hours. For valdecoxib 20 mg the weighted median time to remedication based on 101 patients was greater than 17.5 hours. For valdecoxib 40 mg the weighted mean time to remedication based on 199 patients was greater than 24 hours. For oxycodone 10 mg plus paracetamol 1000 mg the weighted mean time to remedication was 8.8 hours from 102 patients. For rofecoxib 50 mg the median time to remedication reported in one trial [29] was greater than 24 hours.

Adverse effects

No patient was withdrawn as a result of adverse effects. Adverse effect data for the two trials published in one report was already pooled [28]. Data from the study with the unconventional remedication regimen were included. Pooled analysis of 324 patients comparing valdecoxib 40 mg to placebo did not reveal any statistically significant differences for 'nausea', 'vomiting', 'dizziness', 'headache' or 'any event'. The absolute proportions of patients experiencing adverse effects were higher with placebo than

with valdecoxib 40 mg, except for 'vomiting' (Table 2). No pooled analysis was possible for valdecoxib 20 mg but the number of patients reporting adverse effects following a single dose was consistently lower than for placebo.

Parecoxib

Overall, three fully published reports [30–32] and one poster [33] were included in the analyses. All four trials were funded by Pharmacia the manufacturers of parecoxib. Details of the design, numbers of patients, outcomes, analgesic results, adverse effects and quality scores are given in additional file 1 (exclusions detailed in additional file 2). One other poster met the inclusion criteria but it was not possible to extract relevant data due to poor print quality and no alternative source of information was available at the time of writing [34].

One trial in dental pain followed third molar extraction [30], two were in pain the day after laparotomy [32,33], and one the day after orthopaedic surgery [31]. Three of the four trials were conducted following the discontinuation of patient-controlled analgesia [31–33]. Including active comparators there were 917 patients included across the four trials; 221 were treated with parecoxib 20 mg, 223 with parecoxib 40 mg and 176 with placebo. All four studies used intravenous (IV) parecoxib. One study

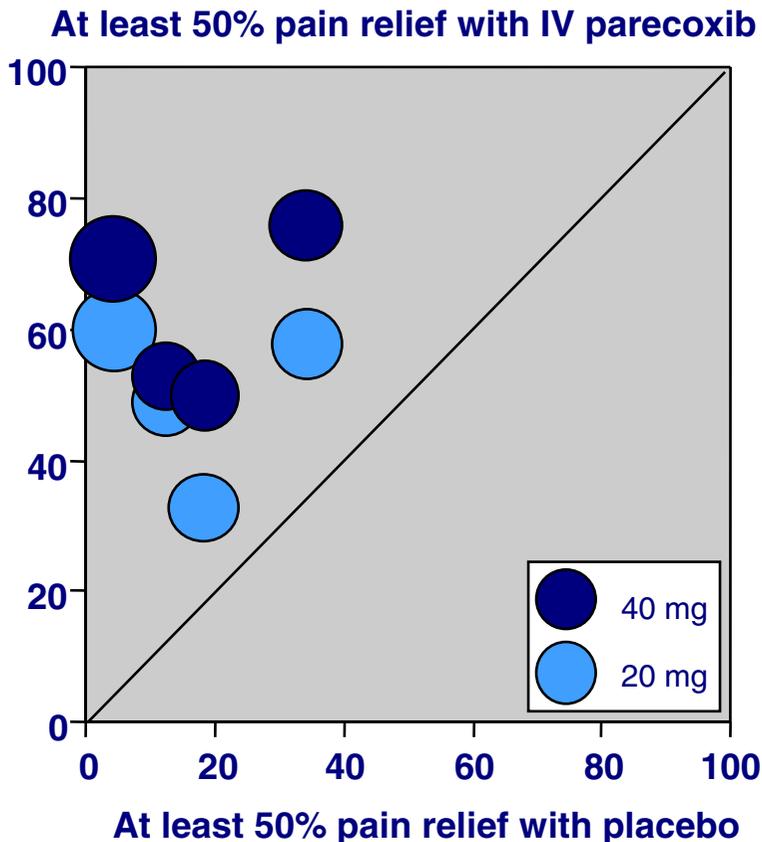


Figure 2
L'Abbe plot showing trials of parecoxib 20 mg and 40 mg.

[30] also reported the results of intramuscular (IM) administration using the same doses. Comparator analgesics incorporated into study design were ketorolac IV or IM (30 mg or 60 mg) in four studies and morphine (4 mg IV) in three studies. Quality scores were 5 for one study, 4 for two studies and 3 for one study.

At least 50% pain relief

All four studies provided data that permitted the calculation of six hour TOTPAR and derivation of the number of patients with at least 50%maxTOTPAR. Visual assessment of homogeneity showed all the studies to be in good agreement, all trials showed statistical benefit of parecoxib 20 mg IV and 40 mg IV over placebo (Figure 2). One trial [30] also showed statistical benefit of parecoxib 20 mg IM and 40 mg IM over placebo. Overall 85/170 patients (50%) given parecoxib 20 mg IV experienced at least 50% maxTOTPAR over six hours compared with 29/

176 patients (16%) with placebo in direct comparison. The NNT for one patient to have at least 50% pain relief over six hours was 3.0 (2.3 to 4.1). For parecoxib 40 mg IV, 109/173 patients (63%) experienced at least 50% maxTOTPAR over six hours compared with 29/176 patients (16%) with placebo in direct comparison. The NNT for one patient to have at least half pain relief over six hours was 2.3 (2.0 to 2.6). The NNTs for both doses given intramuscularly were lower (better) but patient numbers, at about 100 in the comparison, were too small to exclude the effects of chance (Table 1). Sensitivity analyses between dental and postsurgical pain models showed significant differences for both parecoxib 20 mg ($z = 3.36, p = 0.00067$) and 40 mg ($z = 3.15, p = 0.00137$). Significantly fewer patients with moderate to severe postsurgical pain experienced 50% pain relief compared to patients with moderate to severe dental pain.

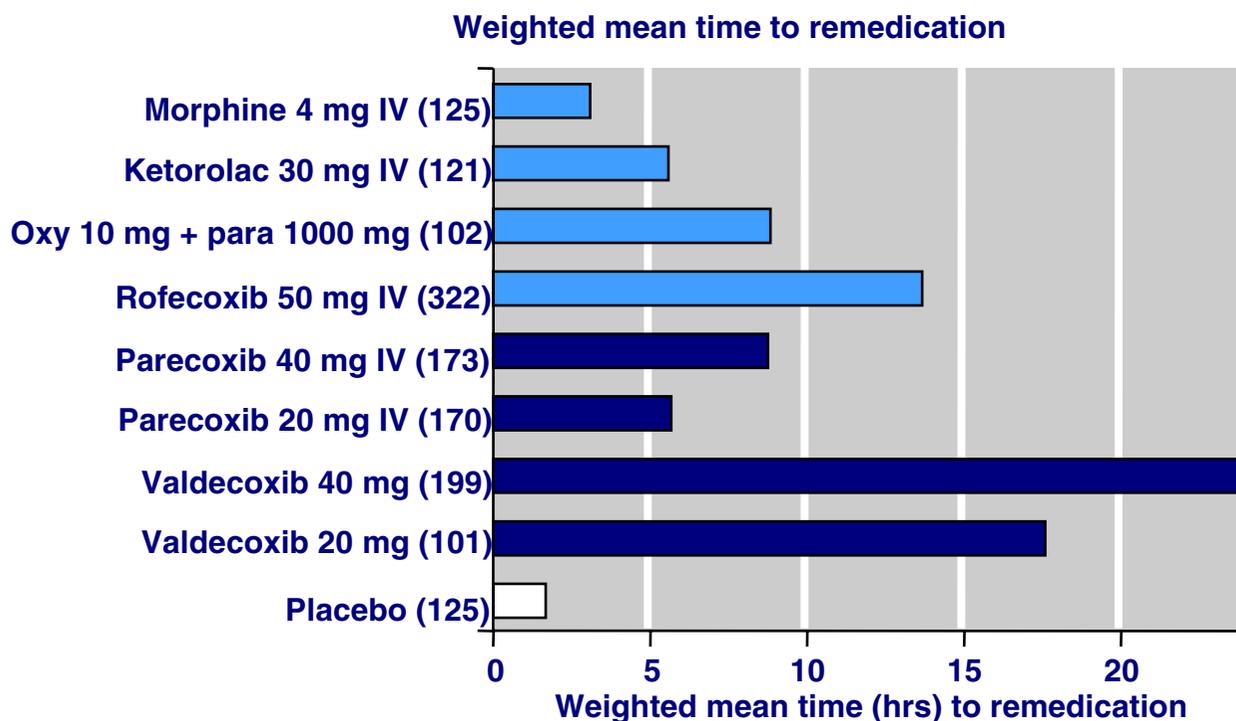


Figure 3
Median time to remediation (weighted by number of patients) for valdecoxib, parecoxib and other analgesics.

Remediation time

Trials discouraged remediation within the first 90 minutes but seven patients withdrew before completing the first hour assessment [32,33]. The median time to remediation was reported in all four studies. For placebo the weighted median time to remediation from 125 patients was 1.6 hours. For parecoxib 20 mg IV the weighted median time to remediation based on 170 patients was 5.6 hours, for parecoxib 40 mg IV the weighted median time to remediation from 173 patients was 8.7 hours. The one report of parecoxib 40 mg in dental pain gave a greater median time to remediation of 15.4 hours (11.1 hours to >24 hours) (additional file 1). The weighted mean time to remediation for ketorolac 30 mg IV was 5.5 hours (based on 121 patients) and for morphine 4 mg IV 3 hours (Figure 3).

Adverse effects

An adverse effect of some type was reported by 55% (73/132) of patients on placebo, 65% (86/132) of patients on parecoxib 20 mg IV and 55% (73/132) of patients on parecoxib 40 mg IV. Three trial reports included the proportion of patients experiencing different adverse events (additional file 1). Pooled analyses of available data for headache, nausea and vomiting revealed no significant differences between either dose of parecoxib IV and placebo (Table 2). The absolute proportions of patients experiencing adverse effects were highest with parecoxib 40 mg IV or placebo. There was no mention of adverse reactions or irritation at injection site.

Discussion

The meta-analyses included in this review combined data from randomised, double-blind trials that used the same methods, the same outcomes, the same patients over the

same period of time to ensure quality and credibility whilst minimising the threat of bias. Compared with placebo the NNT for at least 50% pain relief with a single dose of valdecoxib 40 mg over six hours was 1.6 (1.4 to 1.8) and 1.7 (1.4 to 2.0) for valdecoxib 20 mg. There was no significant difference in efficacy over 4 to 6 hours between valdecoxib 20 mg and 40 mg, though the 40 mg dose provided a longer duration of action (Figure 3). The NNT for parecoxib 40 mg IV was 2.2 (1.8 to 2.7) and 3.0 (2.3 to 4.1) for parecoxib 20 mg IV. These differences in efficacy were again not significant and the 40 mg IV dose resulted in a slightly extended duration of action (Figure 3). The difference between pain models was based on one dental trial compared with one laparotomy and two orthopaedic trials, and while a statistically significant difference was obtained, little weight can be given to this result without substantially more data. Adverse effects did not occur any more frequently with valdecoxib or parecoxib than with placebo however these results do not necessarily extrapolate to other scenarios, particularly chronic dosing [3,35].

The methods of this review are well-established and clinical homogeneity assured by the inclusion criteria. It is therefore legitimate to compare these results with reviews of other oral and parenteral analgesics conducted in the same way [38,39]. Both doses of valdecoxib had slightly lower (better) NNTs than other oral comparators (Table 3). The extended duration of analgesia, afforded particularly by valdecoxib 40 mg after third molar extraction, would seem worthwhile and exceeds that of other oral

comparators (the weighted median time to remedication for ibuprofen 400 mg is 7.4 hours [5], the weighted median time to remedication for diclofenac 50 mg is 6.7 hours [38]). Parecoxib 20 mg IV had a lower (better) NNT than ketorolac 30 mg IM, parecoxib 40 mg IV had a lower (better) NNT than morphine 10 mg IM. Again, extended duration of action would seem to be a potential benefit. Parecoxib 20 mg IV was comparable with ketorolac 30 mg IV but the duration of parecoxib 40 mg IV exceeded that of ketorolac 30 mg, providing an additional three to four hours pain relief (though the duration of analgesia with ketorolac 60 mg IV was not available for further comparison).

Longer duration of analgesia is an important benefit seen here with oral valdecoxib 20 mg and 40 mg and injected parecoxib 20 mg and 40 mg, and seen previously for oral rofecoxib 50 mg (Figure 3). One reason for this longer duration of action is that doses of coxibs used to achieve this are between one and four times the usual daily dose (usually 10 mg or 20 mg for valdecoxib, and 12.5 mg or 25 mg for rofecoxib). Compare this with, say, diclofenac, where an acute pain dose might be 25 mg or 50 mg, some one-sixth to one-third of the maximum daily dose of 150 mg. There should also be a note of caution. Clearly the very long duration of action after third molar extraction – up to 24 hours with valdecoxib 40 mg – is better than older NSAIDs [5]. After other types of surgery the same long duration was not achieved to the same extent. Duration of analgesia may relate both to dose and specific clinical circumstance.

Table 3: NNT League table showing valdecoxib and parecoxib alongside other analgesics

Oral analgesics		
Drug and dose	Number of patients in comparison	NNT (95% CI)
Valdecoxib 40 mg	473	1.6 (1.4 to 1.8)
Valdecoxib 20 mg	204	1.7 (1.4 to 2.0)
Rofecoxib 50 mg ¹	675	2.3 (2.0 to 2.6)
Diclofenac 50 mg ²	738	2.3 (2.0 to 2.7)
Ibuprofen 400 mg ²	4703	2.4 (2.3 to 2.6)
Parenteral analgesics		
Drug and dose	Number of patients in comparison	NNT (95% CI)
Parecoxib 40 mg IV	349	2.2 (1.8 to 2.7)
Morphine 10 mg IM ³	946	2.9 (2.6 to 3.6)
Parecoxib 20 mg IV	346	3.0 (2.3 to 4.1)
Ketorolac 30 mg IM ⁴	359	3.4 (2.5 to 4.9)

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Perhaps the greatest advantage of meta-analysis is that by combining appropriate data the threat of random chance associated with small patient numbers is reduced. Methodological research has demonstrated that data from about 200 patients will be needed for credible estimates when the NNT is 2 and about 1,000 patients when the NNT is 3 to be 95% confident that the NNT is true \pm 0.5 of the observed value [10,11](The numbers of trials (and patients) included in the other analyses, though small compared to other published systematic reviews [38,39], is large enough to justify a certain degree of confidence in the conclusions.

Conclusions

The comparisons between valdecoxib and parecoxib are important and address potentially significant methodological issues for pain research around the coxibs. Valdecoxib is a highly effective oral analgesic with an extended duration of action in dental pain. Parecoxib is also highly effective with a duration comparable with older NSAIDs. The difference between the two drugs is in target usage. Valdecoxib is more efficacious and has a longer duration of action than other oral NSAIDs and coxibs; parecoxib brings the benefits of an injectable coxib drug to the peri-operative and immediate post-operative period as well as to patients who are unable to swallow or are nauseated and vomiting.

Competing interests

RAM & HJM have consulted for various pharmaceutical companies. RAM, HJM & JE have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. All authors have received research support from charities, government and industry sources at various times, but no such support was received for this work.

Authors' contributions

JB, JE and RAM were involved in searching, obtaining trials, data extraction and quality scoring. JB, JE, RAM and HJM were involved in analysis and writing.

Additional material

Additional File 1

Details of included studies

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Additional File 2

Excluded studies

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