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Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews (Review)

Moore RA, Derry S, Aldington D, Wiffen PJ

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[Overview of Reviews]

Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews

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ABSTRACT

Background

This is an update of a Cochrane overview published in Issue 9, 2011; that overview considered both efficacy and adverse events. This overview considers adverse events, with efficacy dealt with in a separate overview.

Thirty-nine Cochrane reviews of randomised trials have examined the adverse events associated with individual drug interventions in acute postoperative pain. This overview brings together the results of those individual reviews.

Objectives

To provide an overview of adverse event rates associated with single-dose oral analgesics, compared with placebo, for acute postoperative pain in adults.

Methods

We identified systematic reviews in *The Cochrane Database of Systematic Reviews* on *The Cochrane Library* through a simple search strategy. All reviews were overseen by a single review group. We extracted information related to participants experiencing any adverse event, and reports of serious adverse events, and deaths from the individual reviews.

Main results

Information was available from 39 Cochrane reviews for 41 different analgesics or analgesic combinations (51 drug/dose/formulations) tested in single oral doses in participants with moderate or severe postoperative pain. This involved around 350 unique studies involving about 35,000 participants. Most studies involved younger participants with pain following removal of molar teeth.

For most nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, and combinations not containing opioids, there were few examples where participants experienced significantly more or fewer adverse events than with placebo. For aspirin 1000 mg and diflunisal 1000 mg, opioids, or fixed-dose combination drugs containing opioids, participants typically experienced significantly more adverse events than with placebo. Studies of combinations of ibuprofen and paracetamol reported significantly fewer adverse events.

Serious adverse events were rare, occurring a rate of about 1 in 3200 participants.

Most reviews did not report specific adverse events.

Authors' conclusions

Despite ongoing problems with the measurement, recording, and reporting of adverse events in clinical trials and in systematic reviews, the large amount of information available for single oral doses of analgesics provides evidence that adverse events rates are generally similar with active drug and placebo in these circumstances, except at higher doses of some drugs, and in combinations including opioids.

PLAIN LANGUAGE SUMMARY

Adverse events after single doses of oral analgesics for acute pain after operation in adults

Acute pain is often felt soon after injury. Most people who have surgery have moderate or severe pain afterwards. Painkillers (analgesics) are tested in people with pain, often following the removal of wisdom teeth. In all these studies, the participants have to have at least moderate pain in order for there to be a sensitive measure of pain-relieving properties. The pain is usually treated with painkillers taken by mouth. Results can be applied to other forms of acute pain.

In May 2015, we performed searches to update an overview review originally published in 2011. *The Cochrane Library* now has 39 reviews of oral analgesic interventions for pain immediately after operations, with 41 different painkillers at various doses. How well the drugs work is reported in a different overview.

In this overview, we used information from about 35,000 participants in about 350 studies to look specifically at the adverse events (unwanted effects) experienced with painkillers, and compared the results with those for placebo (dummy pill). Measuring adverse events is complicated because the particular method used to collect information influences how many adverse events are reported. Most people in the studies had wisdom teeth removed, were relatively young and fit, and were likely to take occasional painkillers. Adverse events may be different in people who are less well, older, or who take painkillers for several days or longer.

The results we have showed that for most nonsteroidal anti-inflammatory drugs (painkillers like aspirin, ibuprofen, or diclofenac), paracetamol, and combinations of different painkillers that do not contain opioids (drugs like codeine), adverse events happened to the same proportion of people with painkillers and placebo. With aspirin 1000 mg, opioids, or fixed dose combinations containing opioids, people typically experienced significantly more adverse events than with placebo. A combination of ibuprofen and paracetamol resulted in significantly fewer adverse events than placebo.

Serious adverse events were rare, occurring a rate of about 1 in 3200 people.

The results are not unexpected for single dose studies, which are likely to be different from the situation when analgesics are taken over the medium or longer term.

BACKGROUND

This overview is an update of the adverse event section of a previous overview 'Single dose oral analgesics for acute postoperative pain in adults', originally published in issue 9, 2011 (Moore 2011). We decided to split the original overview into two linked overviews, one concentrating on efficacy (Moore 2015) and this one considering only adverse events, for several reasons.

- The original overview was large, included 35 separate Cochrane Reviews with 38 analyses of single-dose oral analgesics tested in acute postoperative pain models, and reported results from about 45,000 participants studied in approximately 350 individual studies.
- Additional reviews have been published and have to be added in an update of the overview.
- Most of the overview necessarily concentrated on efficacy and with sensitivity analyses in different pain conditions; these data tended to overwhelm the evidence about possible harm; there was more information about efficacy than adverse events.
- The original overview did not include information on serious adverse events or death (now part of the core outcome measures that were subsequently agreed (Williamson 2012)).
- There have been many calls for more detailed analyses of adverse events in both individual clinical trials (Edwards 1999; Ioannidis 2001; Loke 2001) and systematic reviews (Golder 2006; Hopewell 2008; Zorzela 2014), and generally (Cornelius 2013).

This new overview of adverse events associated with single-dose oral analgesics for acute postoperative pain in adults complements an updated version of the overview of efficacy (Moore 2015).

Description of the condition

Acute pain occurs as a result of tissue damage, either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of the care of individuals undergoing surgery, and is important for the cost-effective use of healthcare resources. Good postoperative pain management helps to achieve a satisfied patient, in hospital or at home, who can return to normal activities in the minimum amount of time.

It was estimated in 2008 that around 235 million major surgical procedures were being undertaken every year worldwide (Weiser 2008). Postoperative pain is experienced by 80% to 94% of people who undergo surgery (Apfelbaum 2003; McQuay 1982). While there are some differences between procedures, moderate or severe pain is a common experience soon after surgery (Apfelbaum 2003; Bruster 1994; Gebershagen 2013). This may differ between institutions and countries (Chapman 2013), especially when stringent procedures are taken to prevent it (Aldington 2011).

Pain is measured using standard scales, usually a visual analogue scale (0 to 100), a numeric rating scale (0 to 10), or a verbal rating scale (none, mild, moderate, severe). People whose postoperative pain is below 30/100 (or 3/10, or none or mild) tend to rate their experience as very good or excellent, whereas people with higher levels of postoperative pain tend to be more dissatisfied (Mhuircheartaigh 2009). This accords with people's attitudes more generally (Moore 2013). Adverse events associated with analgesics in the postoperative period are common, contribute to the overall patient experience and willingness to continue treatment, can be expensive (Rainer 2000), and are not often systematically explored, particularly in some at-risk populations (eg older adults).

Description of the interventions

Analgesics used for relief of postoperative pain include so-called 'mild' or step 1 analgesics, such as paracetamol, and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and celecoxib; 'moderate' or step 2 analgesics, which are weaker opioids such as codeine; and 'strong' or step 3 analgesics, which are strong opioids such as morphine, fentanyl, or oxycodone (WHO 2010). This review looks at drugs given orally.

Paracetamol has become one of the most popular antipyretic and analgesic drugs worldwide, and is often used in combination with stronger analgesics. NSAIDs as a class are the most commonly prescribed analgesic medications worldwide; their efficacy for treating acute pain has been well demonstrated (Moore 2015). Opioids as a class have long been used to treat pain during and immediately after surgery, because they can be given parenterally, and because the dose can be titrated to effect for immediate pain relief. Oral strong opioids are less often used alone, but are used in fixed-dose combination with drugs such as paracetamol or ibuprofen (McQuay 1997).

This overview will consider only adverse events associated with the oral administration of analgesics. Parenteral administration by intravenous, intramuscular, or subcutaneous injections is useful for some drugs in the immediate aftermath of surgery, particularly for people who are unable to swallow (McQuay 1997). However, people are able to swallow relatively soon after most surgery, and oral administration is clearly the least technically demanding and cheapest way of drug delivery, especially when the benefits of injection over oral administration have not been demonstrated, as has been reported with NSAIDs (Tramèr 1998).

Trials of single dose oral analgesics in acute pain

Postoperative pain relief is part of a package of care that covers the preoperative, perioperative, and postoperative periods, and should use the best evidence at all times (Kehlet 1998). This overview involves only one aspect of one part of the patient journey, namely the tolerability of different oral drug interventions used to relieve pain in the postoperative period. The choice of a particular oral drug intervention depends on the clinical and operational circumstances, and how any choice fits in with local care pathways. The original overview primarily examined the efficacy of oral drug choices; how to use them effectively in the relief of postoperative pain is not addressed here.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. To show that an analgesic is working, it is necessary to use a placebo control (McQuay 2005). There are clear ethical considerations in doing this. These ethical considerations are answered by using acute pain situations in which the pain is expected to go away with time, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about one hour. This is reasonable, because not all participants in a trial who are given an analgesic will have significant pain relief; indeed, up to 50% may have inadequate analgesia with active medicines. In contrast, approximately 18% of people receiving placebo will report significant pain relief (Moore

2006). The use of additional or rescue analgesia is therefore important for all participants in a trial.

Trials have to be randomised and double blind. Typically, in the first few hours or days after an operation, people who develop pain that is moderate to severe in intensity will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following four to six hours for shorter-acting drugs, and for up to 12 or 24 hours for longer-acting drugs. This standardised methodology has, with minor changes, been in use for over 50 years and has stood the test of time (McQuay 2012).

Adverse events in trials of single dose oral analgesics in acute pain

A previous examination of adverse events in trials of single dose oral analgesics in acute pain found that the standards of reporting were very varied, but that there had been some improvement in reporting standards over time (Edwards 1999). It examined 52 clinical trials with around 4500 participants in trials of paracetamol and ibuprofen, and noted differences in the methods of assessing adverse events, particularly spontaneous reporting by participants, direct questioning about adverse events, and the use of diaries that may or may not have had prompts about adverse events or specific adverse events. The study also noted that a substantial minority of trials did not report the method used. With limited numbers of participants and events for each type of reporting method it was difficult to judge whether this might have affected results, but differences between active drug and placebo were little affected. Use of diaries for the assessment of adverse events appeared to produce somewhat higher overall response rates than other methods for both active and placebo treatment groups.

Adverse events generally

Perfectly well young people, not taking any medicines, who are asked to report adverse events over three days, as might be done in a clinical trial, report high levels of events such as fatigue and headache. This was the case in the USA in 1968 (Reidenberg 1968) and Germany in 1996 (Meyer 1996). A blind challenge with placebo elicits adverse-event symptoms in 27% of people (Liccardi 2004). People receiving placebo in trials of statins, or older people without medical complaints, also report high levels of adverse events (Reif 2006).

When questioned, people who are undergoing drug treatment indicate overwhelmingly (76%) that they want to be told about all possible adverse events associated with their therapy, however rare (Ziegler 2001). The irony is that reporting of adverse events in clinical trials is poor, and that any accurate estimation of whether events occur, how frequently, and how serious (harmful) or severe (intense) they may be, is difficult or impossible to assess with any accuracy (Edwards 1999; Ioannidis 2001; Loke 2001). Moreover, assessing adverse effects is not generally (if ever) a primary outcome of randomised controlled trial (RCT)-based analgesic studies, and so studies are neither designed nor powered to detect (rare) adverse events. Recent years have seen considerable attention paid in systematic reviews to the reporting of adverse events, with calls for greater attention to be paid to adverse events in trials (Golder 2006; Hopewell 2008; Zorzela 2014).

It is usual to collect information about all adverse events occurring during a clinical trial. Later there may be a judgement as to whether the test treatment has caused the event, or whether something else might have done so.

How the intervention might work

Nonsteroidal anti-inflammatory drugs

NSAIDs reversibly inhibit the enzyme cyclooxygenase (prostaglandin endoperoxide synthase or COX, now recognised to consist of two isoforms, COX-1 and COX-2), mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive (pain) processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). NSAIDs are known to be associated with bleeding in the upper and lower gastrointestinal tract (Hernández-Díaz 2000; Sostres 2013). Some degree of increased cardiovascular risk has also been seen in chronic pain clinical trials (CNT 2013). There do not appear to be increased cardiovascular risks with ibuprofen or diclofenac used at non-prescription (low) doses (Moore 2014).

Paracetamol

Paracetamol lacks significant anti-inflammatory activity, implying a mode of action distinct from that of NSAIDs. Despite years of use and research, however, the mechanisms of action of paracetamol are not fully understood. Paracetamol was previously shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but was later considered 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 2013). Paracetamol has long been thought to be safer than NSAIDs, but one randomised trial over three months comparing paracetamol with ibuprofen found no differences in adverse event rates (Doherty 2011). However, one large observational study in people with liver failure found that non-overdose paracetamol-exposed liver failure was twice as common as NSAID-exposed liver failure (Gulmez 2013).

Opioids

Opioids bind to specific receptors in the central nervous system (CNS), causing reduced pain perception and reaction to pain, and increased pain tolerance. In addition to these desirable analgesic effects, binding to receptors in the CNS may cause adverse events such as drowsiness and respiratory depression, and binding to receptors elsewhere in the body (primarily the gastrointestinal tract) commonly causes nausea, vomiting, and constipation. In an effort to reduce the amount of opioid required for pain relief, and so reduce problematic adverse events, opioids are commonly combined with non-opioid analgesics, such as paracetamol. Major concerns have been raised over the implications of greatly increased opioid prescribing in chronic pain (Stannard 2012), and over the likelihood that opioids carry much greater risks of all

types than NSAIDs in older people (Solomon 2010). For short-term exposure in acute pain, these concerns are less important, and opioids remain the mainstay of systemic analgesia for the treatment of moderate to severe acute pain (Macintyre 2010).

Why it is important to do this overview

An overview review of adverse events is required to facilitate comparisons between individual analgesics, and help to inform treatment choices for acute pain when analgesics are being prescribed, and also to some extent when analgesics are available without prescription (over-the-counter) for occasional use.

Large numbers of Cochrane reviews of individual oral analgesics versus placebo in acute postoperative pain have been completed, with generally identical methods used in the original trials and in the reviews for the measurement of efficacy. Although adverse events were also recorded in trials, and reported in the Cochrane reviews, the adverse event reporting in a previously published overview of Cochrane reviews assessing analgesic efficacy was limited and did not consider serious adverse events or death (Moore 2011).

OBJECTIVES

To provide an overview of adverse event rates associated with single dose oral analgesics, compared with placebo, for acute postoperative pain in adults.

METHODS

Criteria for considering reviews for inclusion

All Cochrane reviews of RCTs of single dose oral analgesics for acute postoperative pain in adults (aged 15 years and over).

Search methods for identification of reviews

We searched the*Cochrane Database of Systematic Reviews* (Issue 5 of 12, 2015) for relevant reviews. See Appendix 1 for the search strategy. A series of Cochrane reviews has been conducted by the same team, covering analgesics identified in the *British National Formulary*.

Data collection and analysis

Two review authors (RAM, SD) independently carried out searches, selected reviews for inclusion, carried out assessment of methodological quality, and extracted data. We resolved any disagreements by discussion, involving a third review author if necessary.

Selection of reviews

Included reviews assessed RCTs evaluating the effects of a single oral dose of analgesic given for relief of moderate to severe postoperative pain in adults, compared with placebo, and reported:

- a clearly defined clinical question;
- details of inclusion and exclusion criteria;
- details of databases searched and relevant search strategies;
- participant-reported pain relief;
- summary results for at least one desired outcome.

Data extraction and management

We extracted data from the included reviews using a standard data extraction form. We used original study reports only if specific data were missing.

We collected information on the following.

- Number of included studies and participants.
- Drug, dose, and formulation (if formulation is an issue).
- Pain model (dental, other surgical).
- Adverse events experienced over the course of the study (typically 4 to 12 hours).

We report risk ratios (RRs) and numbers needed to treat to prevent an event (NNTp) or numbers needed to treat for an additional harmful outcome (NNH) compared with placebo for the following outcomes.

- Number of participants experiencing at least one adverse event.
- Number of participants experiencing at least one serious adverse event.
- Number of participants who died.

We did not calculate NNTp and NNH when the 95% confidence intervals (CI) of the RR included 1.

Assessment of methodological quality of included reviews

Quality of included reviews

We assessed the methodological quality of included reviews using the following criteria (adapted from AMSTAR (Assessing the Methodological Quality of Systematic Reviews); Shea 2007).

- Was an a priori design provided?
- Was there duplicate study selection and data extraction?
- Was a comprehensive literature search performed?
- Were published and unpublished studies included irrespective of language of publication?
- Was a list of studies (included and excluded) provided?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?
- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was a conflict of interest stated?

The question on likelihood of publication bias assessment was not included because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton 2000).

Data synthesis

We used information on the selected efficacy outcomes to draw up comparisons of harms of drug(s) compared with placebo, to allow indirect comparison of different drugs from almost identical clinical trial conditions, using placebo as a common comparator (Glenny 2005; Song 2003).

We anticipated that the trials included in the reviews identified would demonstrate a high level of clinical homogeneity: for more than 50 years, such trials have used consistent validated methods for measuring pain in people who experience at least moderate pain for a period of at least four to six hours after surgery, with placebo as a common comparator. Some of these data have been used to demonstrate the superiority of indirect over direct comparison in circumstances where there are large amounts of indirect data and small amounts of direct data (Song 2003).

We expressed comparative results as the percentage of participants experiencing an adverse event with drug and placebo, and statistical differences using RRs, with NNTp or NNH when appropriate.

In this overview, we have not attempted to use any GRADE descriptions. The uncertainties over adverse event information methodology and the effect that probably has over absolute adverse event reporting rates makes a GRADE judgement difficult or impossible.

RESULTS

The overview included 39 separate Cochrane reviews investigating 41 analgesics or analgesic combinations given as single oral doses in acute postoperative pain conditions (Aceclofenac 2009; Acemetacin 2009; Aspirin 2012; Celecoxib 2013; Codeine 2010; Dexibuprofen 2009; Diclofenac 2015; Diflunisal 2010; Dihydrocodeine 2000; Dipyrone 2010; Etodolac 2009; Etoricoxib 2014; Fenbufen 2009; Fenoprofen 2011; Flurbiprofen 2009; Gabapentin 2010; Ibuprofen + caffeine 2015; Ibuprofen + codeine 2015; Ibuprofen + oxycodone 2013; Ibuprofen + paracetamol 2013; Ibuprofen 2009; Indometacin 2004; Ketoprofen and dexketoprofen 2009; Lornoxicam 2009; Lumiracoxib 2010; Mefenamic acid 2011; Meloxicam 2009; Nabumetone 2009; Naproxen 2009; Nefopam 2009; Paracetamol + codeine 2009; Paracetamol 2008; Paracetamol ± dextropropoxyphene 1999; Paracetamol ± oxycodone 2009; Piroxicam 2000; Rofecoxib 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009).

The maximum numbers used in analyses amounted to 39,000 participants in 399 studies. However, many studies had both placebo and active comparators, and some active drugs may have been included in comparisons with placebo in other reviews. In addition, some studies may have included participants with different doses of an active drug, resulting in potential double counting of placebo. In these circumstances, the number of unique studies is likely to have been around 350, and the number of unique participants of the order of 35,000.

Description of included reviews

Included reviews each had the same structure and organisation, and used identical methods based on criteria established by extensive analysis and validation, using individual participant data. They all used the same criteria and typically these were as follows.

- Adults with established pain of at least moderate intensity (Collins 1997).
- Single dose oral administration of analgesic or placebo (with additional analgesia available, typically after 60 to 120 minutes).
- Randomised, double-blind studies.
- Pain assessed by participants using standard pain intensity and pain relief scales.
- Study duration of four hours or more.
- Searching included electronic searches, plus databases created by handsearching the older literature, now part of the Cochrane Central Register of Controlled Trials(CENTRAL). Searching also included different retail names for drugs.
- No language restriction on included papers.
- Assessment of study quality according to established criteria and minimum criteria for inclusion.

None of the reviews was able to report adverse event rates according to the method of ascertainment, which can influence reporting rates (Edwards 1999). Neither did any of the reviews specifically comment on the time period over which adverse events might have been recorded.

In all reviews, the majority of the studies (typically more than 80%) involved third molar extraction.

Methodological quality of included reviews

All the reviews:

- had a priori design;
- performed duplicate study selection and data extraction;
- had a comprehensive literature search;
- used published and any unpublished studies included irrespective of language of publication, though not all reviews contacted companies or researchers for unpublished trial data;
- provided a list of included and excluded studies;
- provided characteristics of included studies;
- assessed and documented the scientific quality of the included studies;
- used the scientific quality of the included studies appropriately in formulating conclusions, because only studies with minimal risk of bias were included (a particular issue was trial size, but conclusions were not drawn from inadequate data sets, based on previously established criteria (Moore 1998));
- used appropriate methods to combine findings of studies and importantly provided analyses according to drug dose; and
- provided a conflict of interest statement.

Effect of interventions

No clinical trial information of any sort was available for seven drugs (Acemetacin 2009; Meloxicam 2009; Nabumetone 2009; Nefopam 2009; Sulindac 2009; Tenoxicam 2009; Tiaprofenic acid 2009). No useful adverse event results were available for Dipyrone 2010.

At least one adverse event

Most reviews with data provided information on the number of participants experiencing at least one adverse event with active drug and placebo. Some reviews provided information by drug and dose, while other reviews combined all doses in a single analysis, usually where there were limited amounts of information. We identified relevant information in 51 analyses of different drugs, doses, and formulations tested in single oral doses in participants with moderate or severe postoperative pain.

Nonsteroidal anti-inflammatory drugs

Summary table A gives results for at least one adverse event for NSAIDs. The proportion of participants reporting an adverse event with NSAID ranged between 3% and 44%, and with placebo between 4% and 46%. For most comparisons, there was no statistically significant difference between NSAID and placebo.

For aspirin 1000 mg and diflunisal 1000 mg, the adverse event rate with NSAID was significantly higher than with placebo, with NNH values of 7.5 (95% CI 4.8 to 17) for aspirin 1000 mg, and 7.7 (4.8 to 20) for diflunisal 1000 mg.

Summary table A: participants with at least one adverse event with NSAID or placebo

Drug	Dose (mg)	Number of		Per cent with outcome		Risk ratio (95% CI)
		Studies	Partici-pants	Active	Placebo	
Aspirin	600/650	46	3633	11	9.5	1.2 (1.0 to 1.4)
Aspirin	9200/1000	4	404	26	12	**1.6 (1.1 to 2.3)**
Celecoxib	200	4	669	16	17	0.9 (0.6 to 1.3)
Celecoxib	400	6	725	34	46	1.0 (0.8 to 1.2)
Dexketoprofen	10/12.5	3	258	9	46	0.6 (0.3 to 1.3)
Dexketoprofen	20/25	5	413	20	46	1.3 (0.8 to 2.1)
Diclofenac fast acting	All doses	5	636	8	46	1.0 (0.6 to 1.8
Diclofenac potassium	All doses	7	1090	8	46	1.0 (0.7 to 1.6)
Diflunisal	250	3	195	3	6	0.5 (0.2 to 1.8)
Diflunisal	500	7	462	18	15	1.3 (0.8 to 1.9)
Diflunisal	1000	6	417	29	16	**1.8 (1.2 to 2.6)**
Etodolac	50	4	320	8	6	1.4 (0.6 to 3.2)
Etodolac	100	5	459	11	7	1.6 (0.9 to 2.8)
Etodolac	200	7	633	22	17	1.2 (0.9 to 1.7)
Etodolac	400	4	310	28	34	0.8 (0.5 to 1.2)
Etoricoxib	120/180/240	5	1029	32	38	0.9 (0.7 to 1.1)
Fenoprofen	200	4	287	6	6	0.9 (0.4 to 2.1)
Flurbiprofen	25	3	221	14	16	0.9 (0.5 to 1.7)
Flurbiprofen	50	8	564	13	17	0.8 (0.5 to 1.1)
Flurbiprofen	100	5	342	12	12	1.0 (0.6 to 1.8)
Ibuprofen	50	2	225	10	7	1.3 (0.6 to 3.0)
Ibuprofen	100	3	310	14	13	1.2 (0.7 to 2.1)
Ibuprofen	200	14	1808	19	19	0.9 (0.7 to 1.02)

Ibuprofen	400	40	4867	17	16	0.9 (0.8 to 1.04)
Ketoprofen	12.5	3	274	6	4	1.3 (0.5 to 3.6)
Ketoprofen	25	7	490	10	10	1.2 (0.7 to 2.0)
Ketoprofen	50	4	278	21	14	1.6 (0.9 to 2.6)
Ketoprofen	100	3	175	22	18	1.2 (0.7 to 2.2)
Lornoxicam	8	3	273	44	23	1.4 (0.9 to 2.2)
Lumiracoxib	400	3	460	13	18	0.7 (0.4 to 1.3)
Mefenamic acid	500	2	104	13	6	2.2 (0.7 to 7.2)
Naproxen	400/440	3	334	22	17	1.3 (0.8 to 2.2)
Naproxen	500/550	9	784	27	29	1.0 (0.7 to 1.2)
Rofecoxib	all doses	25	3688	34	35	1.0 (0.9 to 1.1)

Note that statistically significant results in risk ratio are in **BOLD**

Nonsteroidal anti-inflammatory drugs in combination with non-opioid drugs

Summary table B gives results for participants experiencing at least one adverse event for NSAIDs in combination with non-opioid drugs (caffeine and paracetamol) and for placebo. The proportion reporting an adverse event with NSAID in combination with non-opioid drug ranged between 11% and 30%, and with placebo between 6% and 48%. For most comparisons, there was a statistically significant difference between NSAID in combination with non-opioid drugs and placebo.

For ibuprofen 200 mg plus caffeine 100 mg, the adverse event rate with the combination was statistically higher than with placebo, but just so, and the NNH value was 19 (8.9 to -220); this very wide CI reflected the bare statistical significance.

For ibuprofen 200 mg plus paracetamol 500 mg and for ibuprofen 400 mg plus paracetamol 1000 mg, the adverse event rate with the combination was lower than with placebo. This produced NNTp values of 5.4 (3.6 to 11) for ibuprofen 200 mg plus paracetamol 500 mg and 5.1 (3.5 to 9.5) for ibuprofen 400 mg plus paracetamol 1000 mg. The studies in this review did have the highest adverse event rate with placebo of any review.

Summary table B: participants with at least one adverse event with NSAID in combination with non-opioid drug or placebo

Drug	Dose (mg)	Number of		Per cent with outcome		Risk ratio (95% CI)
		Studies	Partici-pants	Active	Placebo	
Ibuprofen + caffeine	100+100	2	201	14	8	1.9 (0.8 to 4.1)
Ibuprofen + caffeine	200+100	4	336	11	6	**2.2 (1.03 to 4.9)**
Ibuprofen + paraceta-mol	200+500	3	508	30	48	**0.7 (0.6 to 0.9)**
Ibuprofen + paraceta-mol	400+1000	3	543	29	48	**0.6 (0.5 to 0.8)**

Note that statistically significant results in risk ratio are in **BOLD**

Paracetamol

Summary table C gives results for at least one adverse event for paracetamol. The proportion of participants reporting an adverse event with paracetamol ranged between 7% and 18%, and with placebo between 6% and 16%. There was no statistically significant difference between paracetamol and placebo for any comparison.

Summary table C: participants with at least one adverse event with paracetamol or placebo

Drug	Dose (mg)	Number of		Per cent with outcome		Risk ratio (95% CI)
		Studies	Participants	Active	Placebo	
Paracetamol	500	3	319	7	6	0.9 (0.4 to 1.9)
Paracetamol	600/650	13	1522	16	14	1.2 (0.9 to 1.5)
Paracetamol	975/1000	19	2342	18	16	1.1 (0.9 to 1.3)
Note that statistically significant results in risk ratio are in **BOLD**						

Opioids, including opioid combination products

Summary table D gives results for at least one adverse event for opioids, including opioid combination products. The proportion of participants reporting an adverse event with opioids alone or in combination ranged between 19% and 68%, and with placebo between 6% and 43%.

For several opioids and opioid combinations, the event rate with active drug was significantly higher than with placebo. These included:

- dihydrocodeine 30 mg; NNH 7.4 (4.1 to 38), though based on only 166 participants;
- paracetamol 600/650 mg plus codeine 60 mg; NNH 6.0 (4.6 to 8.3);
- paracetamol plus codeine where the codeine dose was 30 mg or 60 mg; NNH 8.6 (6.4 to 13);
- paracetamol 325 mg plus oxycodone 5 mg; NNH 4.5 (3.2 to 7.9);
- paracetamol 650 mg plus oxycodone 10 mg; NNH 3.5 (2.7 to 4.8)
- paracetamol 1000 mg plus oxycodone 10 mg; NNH 4.0 (2.8 to 7.3).

Summary table D: participants with at least one adverse event with opioids, including opioid combination products, or placebo

Drug	Dose (mg)	Number of		Per cent with outcome		Risk ratio (95% CI)
		Studies	Partici-pants	Active	Placebo	
Codeine	60	12	798	20	16	1.3 (0.9 to 1.7)
Dihydrocodeine	30	2	166	19	6	**3.4 (1.2 to 9.8)**
Oxycodone	5	3	317	31	29	1.1 (0.8 to 1.6)
Ibuprofen + codeine	400 + 26 to 60	4	443	28	19	1.2 (0.8 to 1.7)
Ibuprofen + oxycodone	100 + 5	3	603	25	25	0.9 (0.7 to 1.2)
Paracetamol + codeine	600/650 + 60	17	1413	34	17	**1.6 (1.3 to 1.9)**
Paracetamol + codeine	All doses including codeine 30 and 60	20	1811	31	19	**1.4 (1.2 to 1.6)**

Paracetamol + oxycodone	325 + 5	3	388	48	26	**1.6 (1.2 to 2.1)**
Paracetamol + oxycodone	650 + 10	10	1043	58	29	**1.8 (1.4 to 2.3)**
Paracetamol + oxycodone	1000 + 10	2	289	68	43	**1.6 (1.3 to 2.0)**

Note that statistically significant results in risk ratio are in **BOLD**

Other drugs

The only information on other drug classes was for gabapentin (Summary table E). There was no difference between gabapentin and placebo.

Summary table E: participants with at least one adverse event with gabapentin or placebo

Drug	Dose (mg)	Number of		Per cent with outcome		Risk ratio (95% CI)
		Studies	Participants	Active	Placebo	
Gabapentin	250	3	327	28	32	0.9 (0.7 to 1.3)

Note that statistically significant results in risk ratio are in **BOLD**

Serious adverse events

All reviews with data made a specific report about the presence or absence of serious adverse events, with the exception of that on aspirin (Aspirin 2012), which commented only in the discussion that no serious adverse events were reported. Serious adverse events were typically reported as being absent, and there were too few of them for any statistical evaluation.

Nonsteroidal anti-inflammatory drugs

Serious adverse events in studies involving NSAIDs were reported for 10 participants:

- three taking ibuprofen;
- three taking placebo;
- two taking rofecoxib;
- one taking etodolac;
- one taking naproxen.

Nonsteroidal anti-inflammatory drugs in combination with non-opioid drugs

No serious adverse events were reported in these studies.

Paracetamol

No serious adverse events were reported in these studies.

Opioids, including opioid combination products

Serious adverse events in studies involving opioids alone and in combination were reported for 12 participants (11 in a single study, in which none led to withdrawal, and none were considered related to study medication):

- six taking ibuprofen + codeine;
- three taking oxycodone;
- one taking codeine;
- one taking ibuprofen;
- one taking placebo.

It is not entirely clear that the 11 serious events should actually be classified as serious adverse events. They may have been severe events misreported as serious, but they are mentioned here for completeness.

Other drugs

No serious adverse events were reported in these studies.

Death

No review mentioned death, although serious adverse events (which would include death) were reported.

Specific adverse events

Reviews typically did not report on specific adverse events, such as headache or nausea. One study reported only on specific adverse events (Paracetamol ± dextropropoxyphene 1999). For paracetamol 650 mg plus dextropropoxyphene 65 mg the incidence of drowsiness (or somnolence) and dizziness were significantly higher than with placebo, nausea was no different, while headache had a significantly lower incidence than with placebo.

DISCUSSION

Summary of main results

Information was available from 51 analyses of different drugs, doses, and formulations tested in single oral doses in participants with moderate or severe postoperative pain in 41 drugs in 39 Cochrane reviews. This involved around 350 unique studies involving about 35,000 participants.

For most NSAIDs, paracetamol, and combinations not containing opioids, there were few examples where participants experienced significantly more or fewer adverse events than with placebo. For opioids, or fixed dose combination drugs containing opioids, participants typically experienced significantly more adverse events than with placebo.

There are two reasons to be cautious about these results. First, we know that adverse event reporting rates are heavily influenced by the method used to capture them (Edwards 1999), and second, with sometimes limited numbers of participants and events, results can be influenced by the random play of chance (Moore 1998).

The results are not unexpected for single dose studies, which are likely to be different from the situation when analgesics are taken over the medium or longer term. Acute liver failure leading to registration for transplantation after exposure to an NSAID was rare, but non-overdose paracetamol exposure resulting in liver failure was twice as common as NSAID-exposed liver failure (Gulmez 2013). Upper and lower gastrointestinal harm, and cardiovascular problems have traditionally been associated with NSAIDs when taken over prolonged periods at typically higher daily doses than seen in these single dose studies; while more recent longitudinal studies did not indicate large increases in harm (Laharie 2010), these adverse events are still of potential concern. Moreover, the randomised PAIN study (Paracetamol, Aspirin and Ibuprofen New tolerability study), with over 8500 adults taking analgesics for short term pain (musculoskeletal or back pain, sore throat, colds) reported relatively low adverse event rates, similar with paracetamol and ibuprofen but lower for both than with aspirin (Moore 1999).

Serious adverse events were rare, and reported as occurring in 22 participants, including four in participants taking placebo. This is a maximum rate of about 1 in 1600 participants in the studies. Not all of these serious adverse events were clearly related to treatment, or were even serious adverse events at all. Eleven from a single study were described as not leading to withdrawal, and not considered related to study medication. Eliminating these, the rate of serious adverse events halved, to 1 in 3200, with 3 of 11 occurring with placebo.

Overall completeness and applicability of evidence

Adverse events were not primary outcomes for these single dose studies, and details of ascertainment and recording are noticeable by their absence. Not all studies reporting on efficacy reported on adverse events. The two overviews of Cochrane reviews for the same interventions reported on more participants for efficacy (about 50,000) than adverse events (about 35,000). Moreover, while efficacy was universally reported for particular drugs and doses, adverse events were frequently reported for a composite of all doses of a drug. This is unlikely to have had any major impact, though there were increased adverse event rates (compared with placebo) reported for higher doses, for instance for aspirin 1000 mg and diflunisal 1000 mg, but not at lower doses. Most analgesics were tested only within narrow dose ranges.

Fast-acting formulations have been shown to have better analgesic effect. A future update of the reviews of ibuprofen, for example, should have adverse event rates reported according to both ibuprofen dose and formulation. There remains no Cochrane review of tramadol, but it was reported in a non-Cochrane review to have higher adverse event rates than placebo for vomiting, nausea, dizziness, and somnolence, but not headache (Moore 1997).

As previously mentioned, the evidence in this review comes from single dose studies, and while the authors believe that the results are applicable to short-term use of these analgesics (up to about seven days), they cannot necessarily be extrapolated to longer term use. Moreover, as most studies involved younger participants with pain following removal of molar teeth, the results may not be applicable to older people undergoing more serious surgery, and where treatment continues over several days.

Quality of the evidence

A major issue concerning the quality of the evidence is that the method used to collect adverse event information influences adverse event reporting rates; patient diaries yielded significantly more adverse effects than other forms of assessment (Edwards 1999). The need for improvements to collecting and reporting adverse events has been highlighted frequently (Edwards 1999; Golder 2006; Smith 2013; Zorzela 2014). Meta-analyses of adverse event rates in randomised trials and observational studies tend not to be very different (Golder 2011).

It is probable that there is no 'correct' way of collecting adverse event information, but the method clearly influences the actual rates recorded and reported. Differences between individual studies or pooled data analyses are not necessarily informative, but meta-analysis should provide good information on relative increases or decreases in adverse events compared with placebo.

Potential biases in the overview process

No obvious biases in the overview process exist, for the reasons given above.

Small data sets are clearly more variable than larger, as would be expected (Moore 1998). However, with few exceptions, placebo response rates were within expected ranges, typically between 5% and 20%.

Most studies in the individual reviews will have been sponsored or conducted by manufacturers. This is not likely to be a source of any bias, since specific analyses have been conducted on some of the larger data sets to demonstrate that no industry bias exists in like-for-like comparisons of efficacy outcomes (Barden 2006).

Agreements and disagreements with other studies or reviews

The only other overview of this type known to exist for acute pain studies is the previous overview (Moore 2011). The methods used were similar and there are no major differences between this and the previous overview.

AUTHORS' CONCLUSIONS

Implications for practice

For people with acute pain

The major implication for people with acute pain is the knowledge that there is a body of reliable evidence about the efficacy of 51 drug and dose combinations in acute pain. In most cases, there was no difference in terms of participants reporting adverse events taking single oral doses of the analgesics, and those taking placebo. The exceptions were high doses of aspirin and diflunisal, and combinations that included opioids. Serious adverse events were very rare.

For clinicians

Adverse events with single dose analgesics for acute pain are not generally more frequent than with placebo, with the exception of opioid combinations. Serious adverse events were very rare.

For policy makers

Adverse events with single dose oral analgesics occur no more frequently than with placebo, except for opioid combinations.

For funders

Opioid combination analgesics tend to have more frequent adverse events, and that is likely to come with greater costs. Other analgesics have the same or better analgesic efficacy and are without raised adverse event rates.

Implications for research

General

Studies in this overview were designed to measure efficacy, not adverse events. In this case that is unlikely to be a problem, since there is a great deal of evidence for the most relevant drugs.

The major implication for research is the different results likely using different methods of adverse event ascertainment. This is not currently a topic of much active research, despite numerous literature surveys commenting on the poor reporting of adverse events and the difference in absolute rates reported with different methods. There is an argument that we actually do not understand this area of importance to patients and to policy making well.

Design

If adverse events were to become a principal topic of research, then study designs would have to change. In particular, considerable effort would be needed to determine which method of ascertainment provided results relevant to patient attitudes.

Measurement (endpoints)

The measurement of adverse events was varied, and they provided different rates. We do not know which is best.

Other

There is probably a need for short-term multiple dose studies over periods of one or two weeks, for adverse events as well as for efficacy.

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APPENDICES

Appendix 1. Search strategy for Cochrane reviews

1. (postoperative or (post NEXT operative)):it,ab,kw
2. (pain or painful or analgesi*):it,ab,kw
3. (1 AND 2) in Cochrane Database of Systematic Reviews

WHAT'S NEW

Date	Event	Description
19 February 2020	Amended	Clarification added to Declarations of interest.
11 October 2017	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 11, 2014
Review first published: Issue 10, 2015

Date	Event	Description
28 May 2019	Amended	Contact details updated.
14 October 2015	Review declared as stable	This review will be assessed for updating in 2018.

CONTRIBUTIONS OF AUTHORS

RAM developed the protocol for the overview, based on a previous overview review (Moore 2011). SD and PJW checked and revised the protocol where necessary. All authors agreed the final version.

For the full review, SD and RAM carried out searches, selected reviews for inclusion, assessed methodological quality, and extracted data. PJW acted as arbitrator if necessary. All authors were involved in writing the review.

RAM will be responsible for updates.

DECLARATIONS OF INTEREST

SD has no declarations of interest relevant to this review.

PJW has no declarations of interest relevant to this review.

RAM has no declarations of interest relevant to this review.

DA has no declarations of interest relevant to this review.

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This review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

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- Oxford Pain Relief Trust, UK.

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External sources

- No sources of support supplied

NOTES

No updates of the included reviews are expected in the next 5 years, and no new data are likely to be available that change the conclusions for at least 10 years. This overview has now been stabilised, and will be reassessed for updating in 2027. If appropriate, we will update the overview earlier 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)

*Review Literature as Topic; Acute Pain [*drug therapy] [etiology]; Administration, Oral; Analgesics [administration & dosage] [*adverse effects]; Analgesics, Opioid [administration & dosage] [adverse effects]; Anti-Inflammatory Agents, Non-Steroidal [administration & dosage] [adverse effects]; Drug Therapy, Combination [adverse effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans