

Topical review

Evidence for analgesic effect in acute pain – 50 years on

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1. Introduction

The basic design of studies to measure the analgesic effect of drugs in acute pain was worked out in the 1950s and 1960s, was rigorously tested at the time, and established randomisation and double blinding as essential standards for objective assessment of analgesic efficacy [7]. The design became the conventional way to establish analgesic efficacy, typically performed early in the development of new pain-relieving drugs. Several individual patient analyses have confirmed the validity of methods for evaluating efficacy [2,3,16,18,19], but not adverse events [6].

A recent change has been the way in which outcomes are handled. While the original use of average summed pain intensity difference or total pain relief over 4–6 hours has statistical value, emphasis is now placed on the individual patient's response, particularly the proportion of patients achieving the outcome of at least 50% of the maximum possible pain relief. Unsurprisingly, patient satisfaction is highly correlated with good pain relief [13], and the 50% cut point is regarded as acceptable [10].

Even the earliest studies emphasised large variability between individuals and between treatment groups where numbers are small [8]. Imprecision of estimates of effect obtained with small numbers is a key reason for valuing research synthesis and meta-analysis over individual trial results [17].

Perhaps appropriately, given that these methods have been used extensively for over 50 years, the Cochrane Collaboration (www.thecochranelibrary.com) has now published an overview of systematic reviews of single-dose oral analgesics in acute pain [15]. The overview included 35 separate Cochrane reviews of single-dose oral analgesics tested at different doses in acute postoperative pain models; the reviews included about 350 individual studies with about 45,000 patients. It updates and extends the Oxford league table of analgesics in acute pain (www.medicines.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/leagtab.html). A useful time, then, for a good look at what we have.

2. The evidence

To the Cochrane overview [15] we have added results from non-Cochrane reviews on tramadol [18], tramadol plus paracetamol [5], and ibuprofen plus paracetamol [19], all using identical methods. Collectively they provide a wealth of information:

- Seven drugs had no useful trials, including meloxicam, nabumetone, nefopam, and sulindac.
- There was good evidence of no analgesic benefit for aspirin 500 mg, oxycodone 5 mg, and aceclofenac 150 mg.
- Twenty-five drug and dose combinations either had very limited data (fewer than 2 trials and 200 patients), or had more extensive data, but where small numbers of patients and/or small effect size combined to make the results susceptible to potential publication bias. This was defined as needing fewer than 400 additional patients in studies with zero effect to increase the number needed to treat (NNT) for at least 50% maximum pain relief to the arbitrary NNT of 10 [14]. Susceptible results were largely confined to comparisons with 2–6 trials, except codeine 60 mg, where even with 18 trials and 1265 patients, there was a significant potential for publication bias.
- Forty-six drug and dose combinations had reliable data without susceptibility to publication bias. Information for these is provided both as the proportion of patients attaining at least 50% of maximum pain relief over 4–6 hours and as NNTs compared with placebo; Fig. 1 shows NNTs for some commonly used analgesics. Information on re-medication was also provided, and Fig. 2 shows the median time to re-medication for commonly used drugs.
- Some formulations, notably diclofenac potassium and soluble ibuprofen, had better efficacy than standard formulations in pain after third molar extraction.
- The number of patients reporting at least one adverse event in these short trials was largely the same for active drugs and placebo. Adverse event rates were significantly increased above placebo only for some opioids (oxycodone, codeine plus paracetamol), aspirin, and diflunisal.

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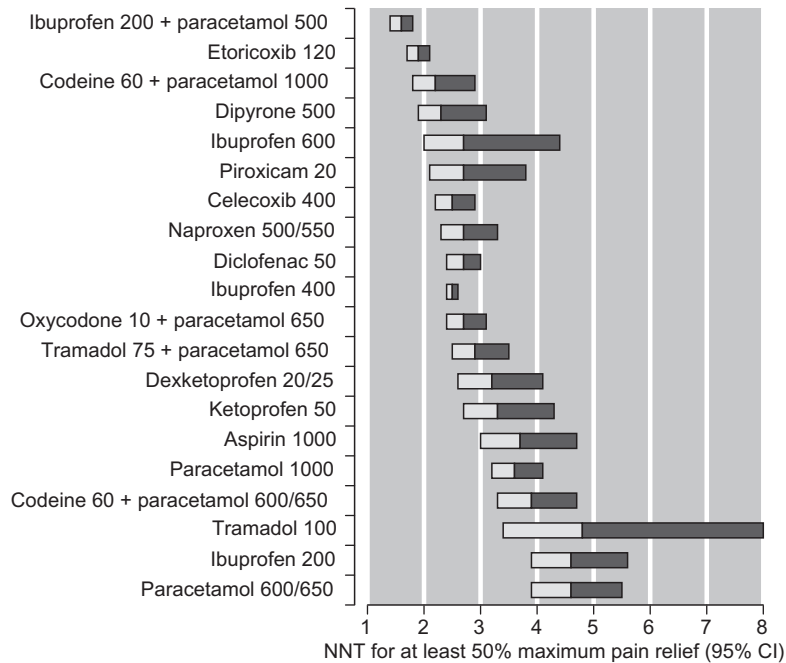


Fig. 1. Numbers need to treat (NNTs) for at least 50% maximum pain relief over 4–6 hours compared with placebo in all acute postoperative trials. CI, confidence interval.

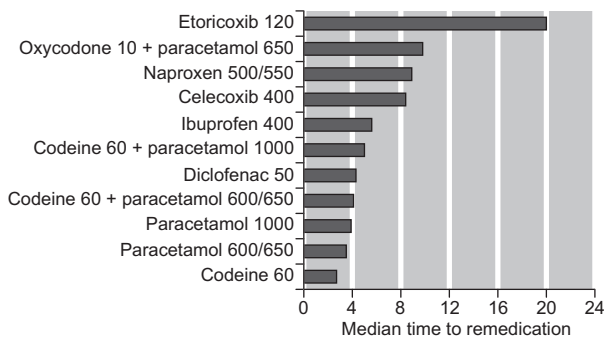


Fig. 2. Median time to remediation in all acute postoperative trials.

3. Methodological points

This large amount of evidence allows examination of a number of methodological points.

3.1. Type of surgery

An important question is whether different types of surgery provide equivalent tests of analgesic efficacy. This is usually seen as a comparison of third molar (dental) pain vs pain following other surgery like orthopaedic, abdominal, or gynaecological surgery, or episiotomy. Previous analyses of large data sets found no consistent difference [3]. That analysis was limited to paracetamol, aspirin, and ibuprofen, and did not address whether the same was true for opioids.

In the overview, 14 comparisons of NNTs in dental and other postoperative pain were available; numerical supremacy (lower NNTs) occurred in half using the dental pain model and half using other postoperative pain. The 2 comparisons with opioids (dextropropoxyphene plus paracetamol and oxycodone plus paracetamol) were similarly split. Bunionectomy, however, may be distinctly different, though with too few data providing evidence on which to speculate how different it may be.

3.2. Dose response

Previous examination of direct, head-to-head comparisons of different doses of the same analgesic drug showed clear dose response, with more effect at higher doses with aspirin, ibuprofen, and paracetamol [12].

In the Cochrane overview, indirect comparisons against placebo tend to support this conclusion. Paracetamol (acetaminophen), however, was a particular exception: dose increase from 500 mg to 600/650 mg to 1000 mg showed progressively higher (less effective) NNTs in the range 1.9–2.7. Despite an adequate number of patients and trials, this emphasises the difficulty of making inferences without very large amounts of comparable information.

3.3. Response with placebo

The proportion of patients attaining at least 50% maximum pain relief with placebo varied widely between about 5% and 35% where the number of patients was small. With large numbers, placebo response rates tended to be consistent, around 15% in dental studies, and around 20–25% in other postoperative conditions. While placebo groups are an essential part of good assay design, consistent response to placebo opens a debate about whether placebo treatment is always required [11].

3.4. Analgesic failure

If analgesic failure is defined as failing to achieve at least 50% of maximum pain relief, analgesic failure is common: most drugs and doses tested did not provide good levels of pain relief in the majority of patients treated. For example, paracetamol 1000 mg, used commonly to treat acute pain, failed in more than half of patients to whom it was given. Ibuprofen 400 mg and diclofenac 50 mg each failed over 40%, and even the most efficacious drug and dose combinations failed about a quarter of patients.

The concept of analgesic failure is difficult; it is argued, plausibly, that analgesic failure in acute pain results in remediation with the same or another analgesic until adequate pain relief is achieved.

While that may be the ideal, in the real world the ideal is notable only by its absence. An Italian survey, for instance, noted the inverse relationship between the prevalence of severe pain on wards and the extent of analgesic prescribing [22], a matter of real concern when more than half the wards reported severe pain in over 50% of patients. Yet severe pain can be almost banished from postoperative wards by appropriate action [1].

Perhaps we have been too fixated on average efficacy in analgesic trials and statistical differences from placebo (does the drug work overall?) rather than thinking about efficacy at the individual patient level (is the level of pain relief adequate, and are any adverse effects at least tolerable so that patients can continue with therapy?). An argument could be made that time to remedication and the percentage of analgesic failures are more relevant outcomes in clinical practice, and that NNTs compared with placebo might conveniently be forgotten.

4. Unanswered questions

Single-dose analgesic studies considered for the individual reviews and the overview have inevitable limitations. They tell us how many people in a particular group of patients obtain good pain relief over a relatively short time. They do not say how to deliver an acute pain service in which all patients have good pain relief all the time: that requires large additional doses of wisdom and experience to find the best use for the knowledge provided.

There are also intriguing questions about the clinical pharmacology of individual drugs where the available evidence in these trials is largely silent. For example, we suspect that, with opioids, patients who can tolerate a first dose do well on second and subsequent doses.

We also believe that higher nonsteroidal antiinflammatory drug doses give longer duration of action rather than greater pain relief in the short term. Some support for this comes from the exponential relationship between remedication time and NNT for at least 50% maximum pain relief over 6 hours and, where short duration analgesics had higher (worse) NNTs and longer duration analgesics had lower (better) NNTs. Median time to remedication was 5 hours or longer where NNTs were about 2 or below. This might, of course, be reflecting an underlying clinical truth in that “early” good pain relief goes on to be reflected in longer duration of effect. It may alternatively simply reflect doses of drugs chosen for use in the particular trials reviewed, or how pharmacokinetic factors like drug half-life influence pharmacodynamic factors like pain relief. To fully understand the relationship would probably require information all along the dose-response curve.

5. What the future holds

For new analgesics, acute pain trial data will be publicly available in some form or other [14]. Some otherwise unavailable trials of older analgesics have been brought to light, as with tramadol [18], but others may never be available, like the many unpublished trials relating to caffeine as an analgesic adjuvant [9]. One excuse given to us when seeking unpublished trial data was that trial results were stored in a salt mine and therefore unobtainable. The overview identified analgesics in quite widespread use, like meloxicam and nefopam, for which no acute pain trials were available.

It is probably a vain hope that the fact of the overview will stimulate pharmaceutical companies to empty their vaults and make available previously unpublished and unavailable trial data [14]. Data availability at the level of the individual patient is especially important in understanding and improving methods and outcomes. It is worth recording that some pharmaceutical companies have been

willing to make individual patient data available from acute pain trials and have contributed to our better understanding: Grünenthal (Aachen, Germany) for tramadol [18], MSD (Whitehouse Station, NJ, USA) for rofecoxib and etoricoxib [16,19], and Reckitt Benckiser (Hull, UK) for ibuprofen-plus-paracetamol combinations [19].

The overview provided data that allowed indirect comparison only, in which each active drug was tested against placebo, and the analgesic efficacy measured against placebo. Indirect comparisons have been shown to be reliable where sufficient high-quality data exist [21]. One further methodological step would be to use network meta-analysis to confirm the assessment of relative efficacy in the overview, and to further explore methodological issues in this highly standardised and homogeneous data set [4,20].

Most trials have tended to employ an “active and placebo control” design, with a range of different active controls, so a network meta-analysis should be possible. Good agreement between indirect comparisons and the result of the networked analysis could provide the background to new trial designs. These would probably have no placebo (reducing ethical objections), large group sizes, a noninferiority statistical test, and a well-understood active comparator; the obvious candidate would be ibuprofen 400 mg tested in 61 trials with 6475 patients in comparisons with placebo.

5.1. Conclusion

The most important outcome of these 50 years of research in acute pain is hopefully a pragmatic one. The analgesic drugs included in formularies can vary widely, and choices are infrequently based on a considered account of evidence, perhaps because the evidence has been too fragmentary. The availability of the extensive evidence collected together in the Cochrane overview offers the important opportunity to look more closely at drug use in acute pain.

Conflict of interest statement

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