

COMBINATION ANALGESICS

Introduction

Combination analgesics combine two analgesics with different modes of action in a single tablet or capsule. Because they are in the same capsule, they are referred to as fixed-dose combinations, to distinguish them from a different way of combining analgesics, namely to give the drugs separately in variable dose combinations. A variety of combination analgesics are available.

The most popular combinations are of paracetamol (acetaminophen in the USA and some other parts of the world) with codeine, dihydrocodeine, or dextropropoxyphene (the so called weak opioids), or tramadol (which also has weak opioid properties). Other combinations are available, like ibuprofen with codeine, or caffeine.

This review is not going to try to be completely comprehensive, but will limit itself to combinations of paracetamol with weak opioids. There are two reasons. First, that these are the most frequently used combination analgesics, and second, because these are the combinations for which there is most evidence.

Combinations of simple analgesics with opioids are controversial. At a practical clinical level they are considered effective, and are often used as one rung in the ladder of analgesic treatments for cancer. There remain, though, several general arguments used against them.

The first is that a combination of A plus B is no better than A alone. The second is that the combination may be better, but that increased toxicity results from using the combination. The third argument is that they are better, but cost considerations make them too expensive and that the individual drugs should be used in a complicated process of titration. It is not unusual to see several of these arguments used together to argue against the use of combination analgesics.

Most of the evidence, in the form of systematic reviews of randomised, double blind trials, comes from systematic reviews of trials of combination analgesics in acute pain. These show that combination analgesics can be very effective. There is less evidence from trials in chronic pain and cancer, mainly because there are fewer trials of effectiveness, though we do have reviews of adverse events.

Combination analgesics in acute pain

This section examines systematic reviews of combination analgesics in acute pain settings. These will typically have studied patients with established pain of moderate or severe intensity following surgery - often third molar extraction, but also in other surgical settings where an oral analgesic was appropriate.

Patients typically take the tablets, or matching placebo, or an active comparator. Measures of pain and pain relief would then be made over the next four to eight hours, with the proviso that patients who had no appreciable pain relief by (say) 90 minutes, would be able to receive additional analgesia (also called rescue analgesia).

The results for these systematic reviews have been converted to a dichotomous outcome, the number of patients who had at least 50% pain relief. This is not an easy outcome to achieve, and represents a relatively high hurdle of effectiveness.

Paracetamol (acetaminophen) with codeine

Clinical bottom line: Paracetamol with codeine is an effective analgesic. The NNT for at least 50% pain relief over four to six hours with a single dose of paracetamol 1000 mg plus codeine 60 mg was 2.2 (1.7 to 3.9) based on information on 197 patients. Paracetamol 600/650 mg plus codeine 60 mg had an NNT of 4.2 (3.4 to 5.3) for at least 50% pain relief over 4-6 hours in patients with moderate to severe pain compared with placebo based on information from 1136 patients. Paracetamol plus codeine produced significantly more pain relief than paracetamol alone.

SYSTEMATIC REVIEWS

- RA Moore, S Collins, D Carroll, HJ McQuay. Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* 1997 70:193-201.
- RA Moore, SL Collins, D Carroll, HJ McQuay, J Edwards. Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. The Cochrane Library, Update Software, Oxford 2000.
- LA Smith, RA Moore, HJ McQuay, D Gavaghan. Using evidence from different sources: an example using paracetamol 1000 mg plus codeine 60 mg. *BMC Medical*

Research Methodology 2001, 1:1 (<http://www.biomed-central.com/1471-2288/1/1>).

- J Barden, JE Edwards, RA Moore, SL Collins, HJ McQuay. Single dose paracetamol (acetaminophen) plus codeine for postoperative pain. The Cochrane Library, Update Software, Oxford 2002.

Date review completed: 2002

Number of trials included: 25 paracetamol plus codeine vs. placebo / 13 paracetamol plus codeine vs. paracetamol

Number of patients: 1385 paracetamol+codeine vs. placebo / 794 paracetamol+codeine vs. paracetamol

Control groups: placebo and paracetamol

Main outcomes: 4-6 hr TOTPAR (total pain relief); number-needed-to-treat (NNT) for 50% pain relief (with 95% confidence intervals); relative benefit (with 95% confidence intervals).

Inclusion criteria were full journal publication of trials of paracetamol and paracetamol plus codeine in acute postoperative pain; single oral dose; randomised; placebo-controlled; double-blind; moderate to severe baseline pain; adult populations; group sizes at least 10; sufficient data to calculate the area under the curve for pain relief (TOTPAR).

For each trial the mean TOTPAR values for paracetamol and placebo groups were converted to the percent of maximum total pain relief based on the categorical pain scales (%max-TOTPAR). These values were converted to dichotomous information for the proportion, and then the number, of patients who achieved at least 50%maxTOTPAR. A number-needed-to-treat for at least 50% pain relief and the relative benefit of the treatment were then calculated.

Findings

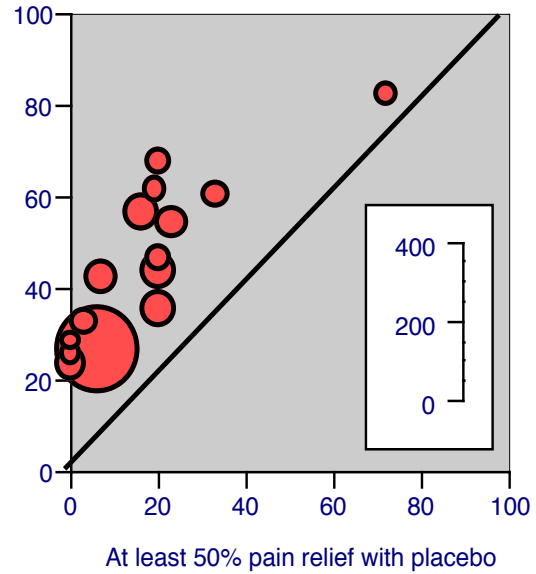
A single oral dose of paracetamol 600/650 mg plus codeine 60 mg generated an NNT of 4.2 (3.4-4.3) for at least 50% pain relief over 4-6 hours in patients with moderate to severe pain compared with placebo (Figure 1; Table 1). Paracetamol 1000 mg plus codeine 60 mg (Figure 1; Table 1) had an NNT of 2.2 (1.7 to 3.9) compared with placebo.

Table 1: NNTs for at least 50% pain relief over 4-6 hours for paracetamol plus codeine at different doses compared with placebo

Paracetamol + codeine dose (mg)	Number of trials	At least 50% pain relief number/total (%)		Relative benefit (95% CI)	NNT (95% CI)
		Paracetamol+ codeine	Placebo		
300 + 30	4	56/215 (26)	14/164 (8)	3.0 (1.8 to 5.3)	5.7 (4.0 to 9.8)
500 + 30	1	13/49 (27)	7/45 (16)	0.7 (0.7 to 3.9)	not calculated
600/650 + 60	17	261/636 (42)	83/487 (18)	2.4 (1.9 to 2.9)	4.2 (3.4 to 5.3)
800 + 60	1	16/44 (36)	0/21 (0)	15.6 (1.0 to 249)	not calculated
1000 + 60	3	65/114 (57)	8/83 (9)	4.8 (2.6 to 8.8)	2.2 (1.7 to 2.9)

Figure 1: Randomised comparisons of paracetamol 600/650 mg plus codeine 60 mg versus placebo

At least 50% pain relief - paracetamol 650 mg + codeine 60 mg



Higher doses of both paracetamol and codeine led to increased efficacy and lower NNTs (Figure 2). With paracetamol 600/650 mg plus codeine 60 mg 42% of patients with initial pain of moderate or severe intensity had at least 50% pain relief over 4-6 hours, as did 57% with paracetamol 1000 mg plus codeine 60 mg.

Addition of 60 mg of codeine was associated with significant extra analgesic effect when compared directly with paracetamol alone. An additional 13%-22% of patients had at least 50% pain relief when codeine 60 mg was added to paracetamol (Figure 3; Table 2).

Figure 2: 95% confidence intervals of NNTs with paracetamol/codeine combinations

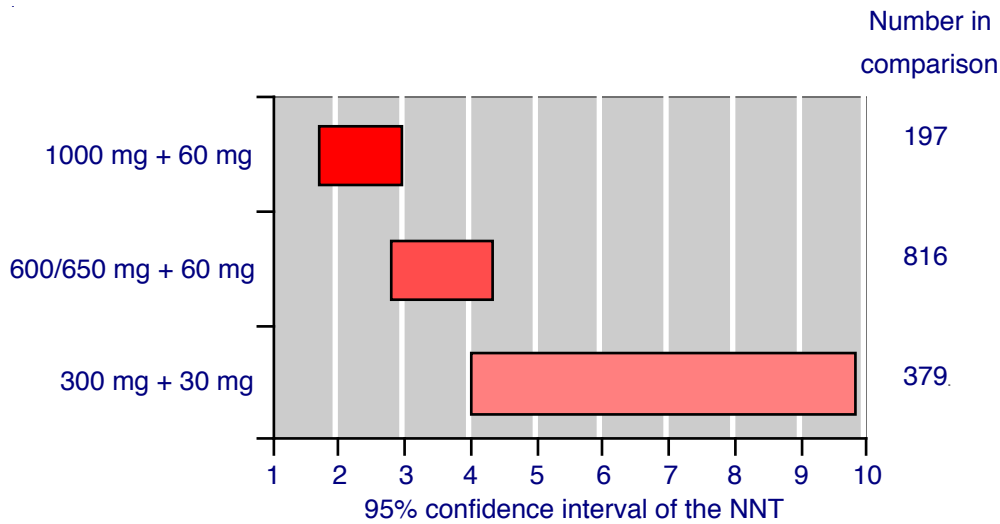
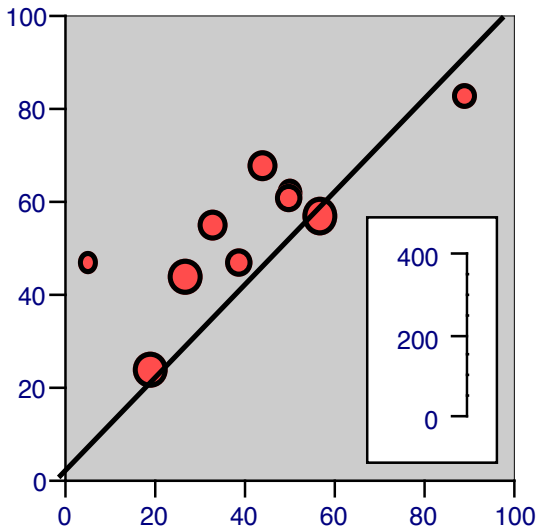


Figure 3: Randomised comparisons of paracetamol 600/650 mg plus codeine 60 mg versus paracetamol 650 mg

At least 50% pain relief - paracetamol 650 mg + codeine 60 mg



At least 50% pain relief with paracetamol 650 mg

Adverse effects

There were no serious adverse effects that necessitated withdrawal from any study. For paracetamol 600/650 mg there were significantly higher levels of drowsiness (NNH 11 (7-18)) and dizziness (NNH 19 (11-50)) with paracetamol plus codeine compared with placebo.

Comment

Paracetamol plus codeine is an effective analgesic combination, with low NNTs for at least half pain relief over 4-6 hours at doses of paracetamol 600/650 mg plus codeine 60 mg and paracetamol 1000 mg plus 60 mg. Though there was limited information for the combination of paracetamol 1000 mg plus codeine 60 mg, there was considerable supporting evidence from other combinations.

In addition, three trials which were not included because they did not have a placebo control had similar event rates for paracetamol 1000 mg plus codeine 60 mg as did those with a placebo. Six other trials with some design issues (such as use of non-standard pain measures which meant that they could not be combined in the analysis) showed the combination to be better than placebo or comparators.

Table 2: NNTs for at least 50% pain relief over 4-6 hours for paracetamol plus codeine at different doses compared with paracetamol

Paracetamol + codeine dose (mg)	Number of trials	At least 50% pain relief number/total (%)		Relative benefit (95% CI)	NNT (95% CI)
		Paracetamol + codeine	Paracetamol		
600/650 + 60	10	165/309 (54)	129/313 (41)	1.3 (1.1 to 1.5)	8.2 (5.0 to 22.7)
1000 + 60	3	74/109 (68)	52/108 (46)	1.4 (1.1 to 1.8)	5.1 (3.1 to 14.5)

FURTHER READING

These are two good reviews addressing similar questions about the effectiveness of paracetamol with and without codeine, but in slightly different ways, and without NNTs:

de Craen AJM, Di Giulio G, Lampe-Schoenmaeckers AJE, Kessels AGH, Kleijnen J. Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: A systematic review. *BMJ* 1996 313:321-325.

Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain - A meta-analysis. *Journal of Clinical Pharmacy and Therapeutics* 1996 21:261-282.

Paracetamol with dextropropoxyphene

Clinical bottom line: Paracetamol 650 mg plus dextropropoxyphene 65 mg is an effective analgesic in postoperative pain. A single oral dose had an NNT of 4.4 (3.5 to 5.6) for at least 50% pain relief over 4-6 hours compared with placebo in pain of moderate to severe intensity. This is equivalent to 1000 mg of paracetamol alone. Adverse effects were transient and of mild to moderate severity, mainly dizziness and drowsiness.

SYSTEMATIC REVIEW

- SL Collins, JE Edwards, RA Moore, HJ McQuay. Single dose dextropropoxyphene in postoperative pain: a quantitative systematic review. *European Journal of Clinical Pharmacology* 1998 54:107-112.

Date review completed: November 1996

Number of trials included: 4 plus 1 meta-analysis of 18 trials

Number of patients: 963 (478 paracetamol plus dextropropoxyphene / 485 placebo)

Control group: oral placebo

Main outcomes: pain relief at 4-6 hrs (TOTPAR / SPID), Number-needed-to-treat (NNT) (with 95% confidence intervals), relative benefit and relative risk (with 95% confidence intervals).

Inclusion criteria were full journal publication of trials of dextropropoxyphene and paracetamol plus dextropropoxyphene in acute postoperative pain; single oral dose; randomised; placebo-controlled; double-blind; moderate to severe baseline pain; adult populations; group sizes at least 10; sufficient data to calculate the area under the curve for pain relief (TOTPAR).

For each trial the mean TOTPAR values for paracetamol and placebo groups were converted to the percent of maximum total pain relief based on the categorical pain scales (%max-TOTPAR). These values were converted to dichotomous information for the proportion, and then the number, of patients who achieved at least 50%maxTOTPAR. A number-needed-to-treat for at least 50% pain relief and the relative benefit of the treatment were then calculated.

Trials using dextropropoxyphene hydrochloride 65 mg and napsylate 100 mg with paracetamol were analysed together because they contain the same amount of dextropropoxyphene.

Findings

Four reports compared dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg with placebo, and one used dextropropoxyphene hydrochloride 65 mg plus paracetamol 650 mg, with a total of about 950 patients. Paracetamol 650 mg plus dextropropoxyphene had an NNT of 4.4 (3.5-5.6) for at least 50% pain relief over 4-6 hours compared with placebo for pain of moderate to severe intensity. The analgesic response was significantly more effective than placebo.

Adverse events

All reported adverse events were transient and of mild to moderate severity. Dizziness and drowsiness were the most commonly reported adverse effects (Table 3). Both were significantly higher in comparison to placebo. No patient withdrew as a result of adverse effects.

Comment

The information we have, from relatively few patients, indicates that dextropropoxyphene alone is not effective

Table 3: Adverse effects with dextropropoxyphene 65 mg plus paracetamol 650 mg compared with placebo.

Number of trials	Adverse effect	Paracetamol + dextropropoxyphene	Placebo	Relative risk (95%CI)	NNH (95%CI)
3	Nausea	12 / 405	33 / 799	0.7 (0.4 to 1.4)	not calculated
1	Vomiting	2 / 323	6 / 714	1.4 (0.3 to 6.7)	not calculated
4	Dizziness	17 / 435	16 / 829	2.2 (1.1 to 4.3)	43 (22 to 607)
3	Drowsiness/ somnolence	57 / 405	55 / 799	2.2 (2.0 to 2.4)	14 (9.1 to 30)
4	Headache	14 / 435	51 / 829	0.5 (0.4 to 0.6)	-33 (-170 to -19)

Negative NNTs indicate that fewer headaches occur with dextropropoxyphene plus paracetamol than with placebo

in single doses, but that in combination with paracetamol it is better. Six reports compared dextropropoxyphene hydrochloride 65 mg with placebo, and one trial also compared a dose of 130 mg with placebo. A single oral dose of dextropropoxyphene 65 mg was no better than placebo for pain of moderate to severe intensity.

Paracetamol plus tramadol

Clinical bottom line: Based on limited patient numbers but on an individual patient analysis, a combination of paracetamol plus tramadol is an effective analgesic in acute postoperative pain. The NNT compared with placebo over six hours was about 2.7.

SYSTEMATIC REVIEW

- JE Edwards et al. Combination analgesic efficacy: Individual patient data meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Journal of Pain and Symptom Management* 2002 23:121-130.

Date review completed: 2001

Number of trials included: 7

Number of patients: various, because different combination strengths

Control group: oral placebo

Main outcomes: pain relief at 6 hours (TOTPAR), Number-needed-to-treat (NNT) (with 95% confidence intervals) and relative benefit (with 95% confidence intervals). Duration of analgesia through time to remedication.

Inclusion criteria were full journal publication of trials of paracetamol plus tramadol in acute postoperative pain; single oral dose; randomised; placebo-controlled; double-blind; moderate to severe baseline pain; adult populations; group sizes at least 10; sufficient data to calculate the area under the curve for pain relief (TOTPAR).

For each trial the mean TOTPAR values for paracetamol and placebo groups were converted to the percent of maximum total pain relief based on the categorical pain scales (%max-TOTPAR). These values were converted to dichotomous information for the proportion, and then the number, of patients who achieved at least 50%maxTOTPAR. A number-needed-to-treat for at least 50% pain relief and the relative benefit of the treatment were then calculated.

Findings

Paracetamol plus tramadol was an effective analgesic in dental and postsurgical pain, based on limited information (Table 4), with NNTs between 2 and 3. NNTs over eight hours were similar to those over six hours.

More dental pain patients reported adverse events with paracetamol plus tramadol. There were more patients experiencing any adverse effect (NNH 5.4), and dizziness (NNH 23), nausea (NNH 7) and vomiting (NNH 6) with paracetamol plus tramadol.

Comment

The paper calculates results based on pain intensity, pain relief and patient global evaluation of treatment, from individual patient data. All produced very similar NNTs, confirming findings from other studies, and underpinning the methods used in meta-analysis of combination analgesics in acute pain.

Summarising combination analgesics in acute pain

We have good information on paracetamol in combination with codeine and with tramadol. In randomised, double blind, and valid trials, these combinations have NNTs between 2 and 3, which is indicative of effective therapy.

It is useful to extend the observation in Figure 2 of the dose-response relationship demonstrated in placebo-controlled trials for increasing doses of paracetamol and codeine, to include active controlled trials. This is shown in Table 5, for percentage of patients with adequate pain relief, in absolute terms rather than the relative comparison to placebo used in the calculation of the number needed to treat.

Using information on doses other than those most frequently used confirms a significant dose-response relationship, with better efficacy at higher doses. This type of evidence supports the finding of good efficacy of paracetamol 1000 mg and codeine 60 mg, even though the numbers of patients in placebo controlled studies at that dose combination was relatively small, at 197.

Table 4: NNTs for paracetamol plus tramadol for half pain relief over six hours compared with placebo

Pain model/dosage	At least half pain relief, number/total (%)		NNT (95% CI)
	Paracetamol plus tramadol	Placebo	
Dental pain: Paracetamol 650 mg + tramadol 75 mg	145/340 (43)	14/339 (4)	2.6 (2.3 to 3.0)
Postsurgical pain: Paracetamol 975 mg + tramadol 112.5 mg	61/101 (60)	25/100 (25)	2.8 (2.1 to 4.4)

Table 5: Summary results for paracetamol/codeine combinations in randomised, double-blind, active- and placebo-controlled trials in acute pain

Drug/dose	Number of		Percentage with pain relief (95%CI)
	Trials	Patients	
Paracetamol 300 mg + codeine 30 mg	3	272	25 (20 to 30)
Paracetamol 600 mg + codeine 60 mg	13	398	48 (43 to 53)
Paracetamol 1000 mg + codeine 60 mg	6	229	66 (59 to 72)

Figure 4: Mean pain relief scores over time in dental pain, for paracetamol 650 mg/tramadol 75 mg, versus components alone, and placebo

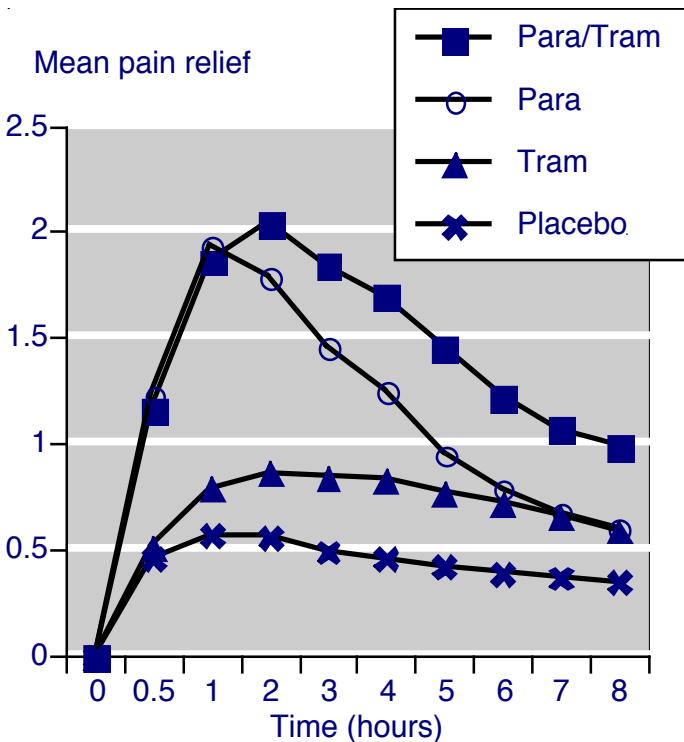
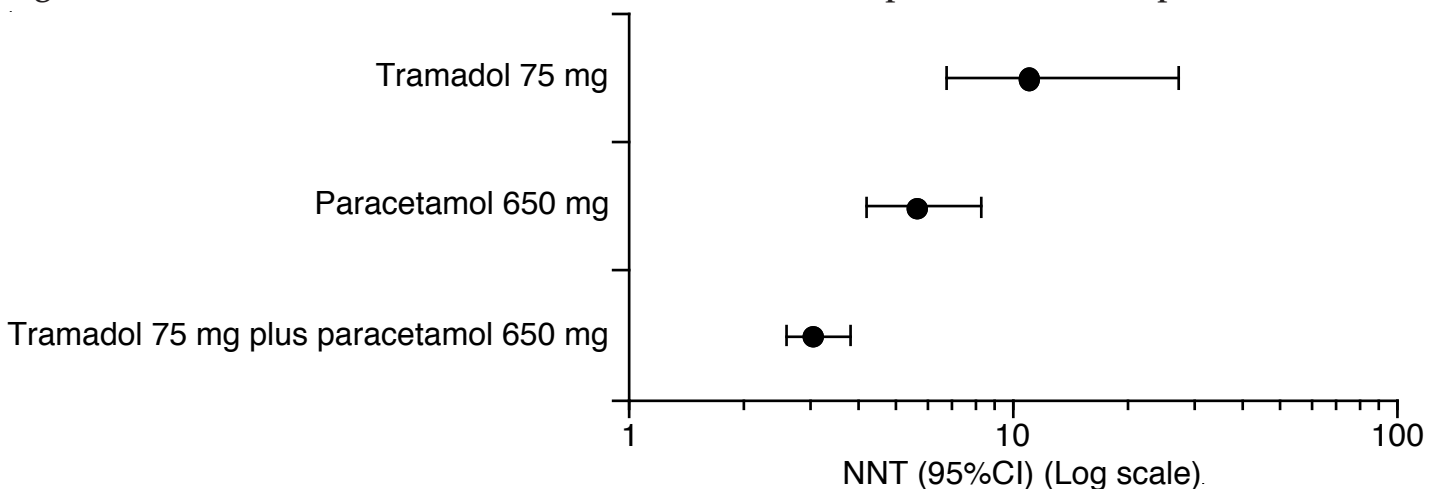


Figure 5: Numbers needed to treat for combination, and components, in dental pain



So why do combinations work so well in acute pain? Figure 4 shows that paracetamol alone produces rapid pain relief within the first few hours, while tramadol has a more lasting effect. The two are additive, so that over eight hours of observation a reasonable level of pain relief is maintained. When we use this information to calculate NNTs, relatively poor NNTs for paracetamol 650 mg and tramadol 75 mg individually translate into a much better NNT of below 3 for the combination (Figure 5).

It is worth noting that for dental pain (top section of Figure 5), where we have a reasonable number of patients, there was no overlap between the confidence interval of the combination, and that of the constituents alone, indicating that the combination was statistically better. Clearly, the combination was better than the individual components alone, and the first argument against combination analgesics, that a combination of A plus B is no better than A alone, is rebutted for this combination.

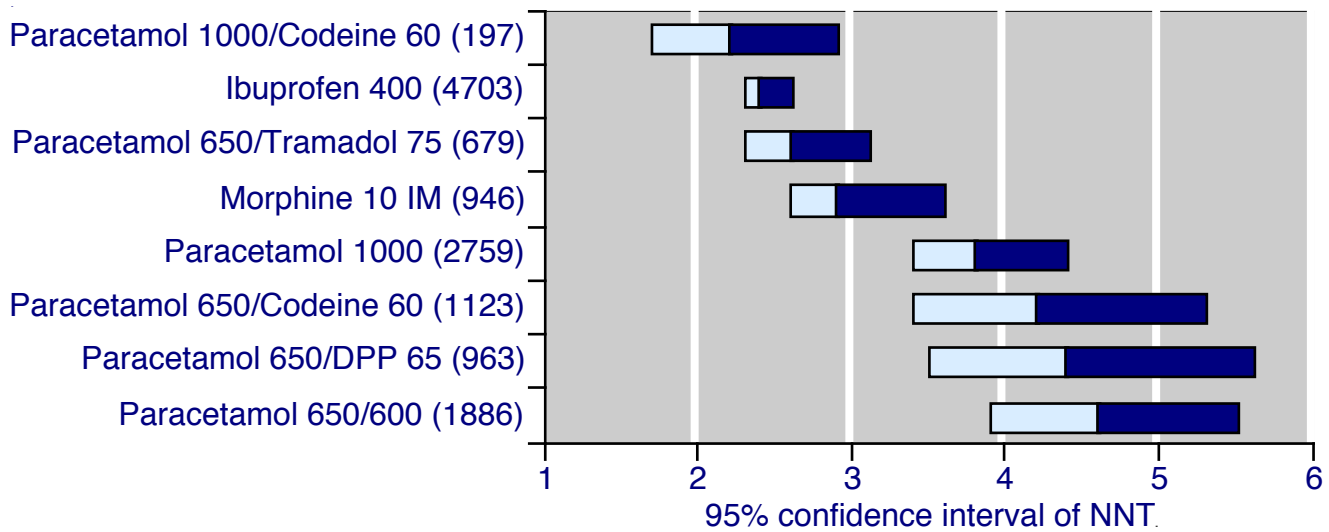
The second argument, that the combination may be better, but that increased toxicity results, is also rebutted. In dental pain, both tramadol 75 mg alone and the combination produced significantly more adverse effects than placebo; the NNH for a patient to report any adverse effect was about 5.0 for both. The results for adverse effects in acute pain studies showed that toxicity of the opioid component was the same whether given alone or in combination. There was no increased toxicity from combination with another analgesic.

Comparisons with other analgesics

Figure 6 shows NNTs for combinations and other selected analgesics in acute pain studies. All the trials were comparable, with similar outcomes measured in the same way over the same period of time. The outcome of at least half pain relief in active treatment and placebo is used to derive the NNT.

It is clear that combination analgesics are comparable with other analgesics we consider to be effective in acute pain. Few are much better. Only higher doses of NSAIDs, or of coxibs, are better, and they would either not normally be used or are not licensed, or otherwise unavailable. Further information is available on the Bandolier Internet site.

Figure 6: Numbers needed to treat for combination analgesics and other oral analgesics and intramuscular morphine, in comparable patients, in comparable trials. Bars represent the 95% confidence interval for the NNT compared with placebo for at least 50% pain relief over 4-6 hours, with the change in shading being the point estimate (numbers of patients in brackets)



Combination analgesics in chronic pain

Randomised trials of paracetamol opioid combinations in chronic pain are shown in Table 6 (overpage). There are few for paracetamol and codeine, though more for paracetamol and tramadol. On one level it is surprising that there is so little information.

The historical perspective explains it. In past years if an analgesic showed efficacy in acute pain, efficacy in chronic conditions was assumed. For instance, information on NSAIDs in chronic pain was sparse before the advent of coxibs, with small trials of short duration comparing different doses of different drugs, and using different outcomes. For coxibs we have information on almost 150,000 patients with chronic pain in randomised trials lasting a few weeks to a year.

For combination analgesics we see a similar picture: little information on the older combinations, more on the newest combination of paracetamol plus tramadol.

Paracetamol plus codeine

Four trials are highlighted that lasted at least one week in musculoskeletal conditions, including osteoarthritis. The most influential was that of Kjaersgaard-Andersen in 1990, comparing paracetamol 1000 mg plus codeine 60 mg with paracetamol alone, because it was stopped early with a high early discontinuation rate. Adverse events were the main cause, and this led to a recognition that titration of dose to effect was important with paracetamol/codeine combinations.

Starting treatment with high doses leads to high levels of adverse events, particularly nausea, vomiting, and dizziness, and these can lead to discontinuation. Titrating up from small initial doses is less problematical, especially because

some of the adverse events, and their severity and impact, can be transient. Starting with lower doses and increasing the dose over several weeks is now the norm for using paracetamol/opioid combinations in chronic pain.

Paracetamol plus tramadol

All of the randomised trials of paracetamol plus tramadol in Table 5 titrated the dose over the first four weeks. There were over 2,000 patients in these trials, conducted over 10 days to three months, in a variety of chronic pain conditions including arthritis, back pain, and fibromyalgia. They all used the combination of paracetamol 325 mg plus tramadol 37.5 mg per tablet, and the average maintenance dose after the first four weeks was four or five tablets daily.

No formal meta-analysis has been published. All the trials with placebo showed superiority for the combination by means of lower pain scores and higher pain relief scores, and some additionally showed quality of life benefits. Benefit was also shown compared to placebo when tested in patients already established on a coxib. The addition of paracetamol plus tramadol to coxib improved pain relief compared with coxib plus placebo.

One large study in 462 patients compared paracetamol 325 mg plus tramadol 37.5 mg per tablet with paracetamol 300 mg plus codeine 30 mg per tablet over four weeks. The combinations were equally efficacious. Somnolence and constipation occurred more frequently with the codeine combination, and headache with the tramadol combination.

Adverse event rates with combination analgesics

Because of the small numbers of randomised trials for combination analgesics in chronic pain we have little to guide us other than clinical experience. That experience tells us that with titrated dose adverse events tend to be transient and more tolerable than with initial use of high

Table 6: Randomised trials of paracetamol plus codeine or paracetamol plus tramadol in chronic pain, with duration of one week or longer

Reference	Study	Results	Adverse events
Paracetamol and codeine			
Palangio et al. Clin Ther 2000 22: 879-892	Randomised, double blind comparison of hydrocodeine 7.5 mg plus ibuprofen 200 mg (or twice this dose), or paracetamol 600 mg plus codeine 60 mg, three to four times daily for 4 weeks. 469 patients with mainly musculoskeletal pain	Paracetamol plus codeine no different to ibuprofen plus hydrocodone over longer period	81% experienced some adverse event with any treatment. Adverse event discontinuation higher with larger dose of ibuprofen plus hydrocodone. Discontinuations for lack of efficacy 7.5% for paracetamol plus codeine, compared with 1% for higher dose ibuprofen plus hydrocodone
Boissier et al. J Clin Pharmacol 1992 32: 990-995	Randomised, double blind comparison of paracetamol with dextropropoxyphene or codeine in 141 outpatients with osteoarthritis, over one week	Overall acceptability less with paracetamol plus codeine (53%) versus paracetamol plus dextropropoxyphene (29%)	No results
Kjaersgaard-Andersen et al. Pain 1990 43: 309-318.	Randomised, double blind comparison of paracetamol 1000 mg plus codeine 60 mg three times daily versus paracetamol alone over four weeks in patients 158 patients with osteoarthritis of the hip	High discontinuation rate with paracetamol plus codeine (36% in first week) led to premature ending of the trial	High rate of adverse events (87%) with paracetamol plus codeine in first week, compared with 38% with paracetamol alone
Muller et al. Arzneimittelforschung 1998 48: 675-679	Randomised, double blind, crossover of paracetamol 1000 plus codeine 60 mg with tramadol 100 mg three times daily in chronic back pain over one week in 55 patients	80% of patients had good or satisfactory pain relief, on both	80% of patients given combination tolerated it well
Paracetamol and tramadol			
Peloso et al. J Rheumatol 2004 31: 2454:2463.	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and placebo in chronic low back pain. 336 patients for 91 days	Severe pain at baseline. Paracetamol/tramadol significantly better than placebo. Good or very good with combination was 64% compared with 25% with placebo.	Lack of efficacy discontinuations 25% compared with 55% with placebo. Nausea, dizziness, constipation (about 10% each) were main adverse events
Rosenthal et al. J Am Geriatr Soc 2004 52: 374-380	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and placebo in painful osteoarthritis flare, added to NSAID 113 patients for 10 days (Probably a sub group of older patients from Silverfield et al)	Combination significantly better than placebo for pain intensity and pain relief, and on global measures	Most common adverse events were nausea, vomiting, and dizziness (10-18%).
Emkey et al. J Rheumatol 2004 31: 150-156	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and placebo in add-on therapy to coxib in osteoarthritis 307 patients for 91 days	Significantly lower pain scores for combination plus coxib than coxib alone, and pain relief significantly higher	Most common adverse events were somnolence, nausea, and constipation (3-7%)
Ruoff et al. Clin Ther 2003 25: 1123-1141	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and placebo in chronic back pain 318 patients for 91 days	Combination significantly reduced pain and improved pain relief compared with placebo	Lack of efficacy discontinuation 22% for combination and 41% for placebo. Adverse events were nausea, somnolence and constipation (11-13%)
Bennett et al. Am J Med 2003 114: 537-545	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and placebo in fibromyalgia 315 patients for 91 days	Combination reduced pain and improved pain relief compared with placebo. All-cause discontinuations 48% with combination compared with 62% for placebo	Adverse event discontinuations 19% with combination compared with 12% with placebo
Silverfield et al. Clin Ther 2002 24: 282-297	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and placebo in painful osteoarthritis flare, added to NSAID 308 patients for 10 days	Combination significantly reduced pain and improved pain relief compared with placebo	No serious adverse events
Mullican et al, Clin Ther 2001 23: 1429-1445	Randomised, double blind comparison of paracetamol 325 mg plus tramadol 37.5 mg (1 or 2 four times daily) and paracetamol 300 mg plus codeine 30 mg in chronic back pain or osteoarthritis flare 462 patients for 4 weeks	Two treatments were equivalent	Higher somnolence and constipation with paracetamol plus codeine, and more headache with paracetamol plus tramadol

doses of opioids, alone or in combination with paracetamol.

We have a guide about how bad adverse events might be, a form of worst case scenario, from a systematic review of oral opioids in chronic non-malignant pain [1] that combined information from any opioid. Information was available from 35 randomised trials with 5,500 patients, mostly in musculoskeletal conditions, and predominantly of four weeks or longer. Overall 4,200 patients contributed data on opioid adverse events, about 1,500 on combinations of paracetamol and opioid, with the majority of the remainder on tramadol, morphine, or dextropropoxyphene alone. Few of the studies used initial dose titration to minimise adverse events.

Adverse event rates with oral opioid were clearly higher than with placebo (Figure 7), and rates of adverse events with placebo were not unlike those found in healthy young individuals [2,3]. Adverse event rates in different musculoskeletal conditions were not dissimilar (Figure 8). The constipation rate of about 15% was comparable to that found in healthy Americans [4].

Conclusions

For combination analgesics the evidence we have from randomised trials in acute and chronic pain confirms clinical experience. In acute pain they are effective, even good, analgesics. In chronic pain, they are also effective analgesics, though they need to be used sensitively to achieve the best results and minimise adverse events with the opioid component.

We know that fixed dose combinations tend to increase adherence to medication [5]. We also know that female sex, older age, and increasing numbers of pills increase the risk of serious adverse drug events. We know that these are common, affecting many thousands of older people.

Sensible and sensitive use of combination analgesics makes sense for some patients with acute or chronic pain.

References

- 1 RA Moore, HJ McQuay. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Research & Therapy* 2005 7: R1046-R1051

Figure 7: Comparison of adverse event rate of oral opioid and placebo in chronic non-malignant pain

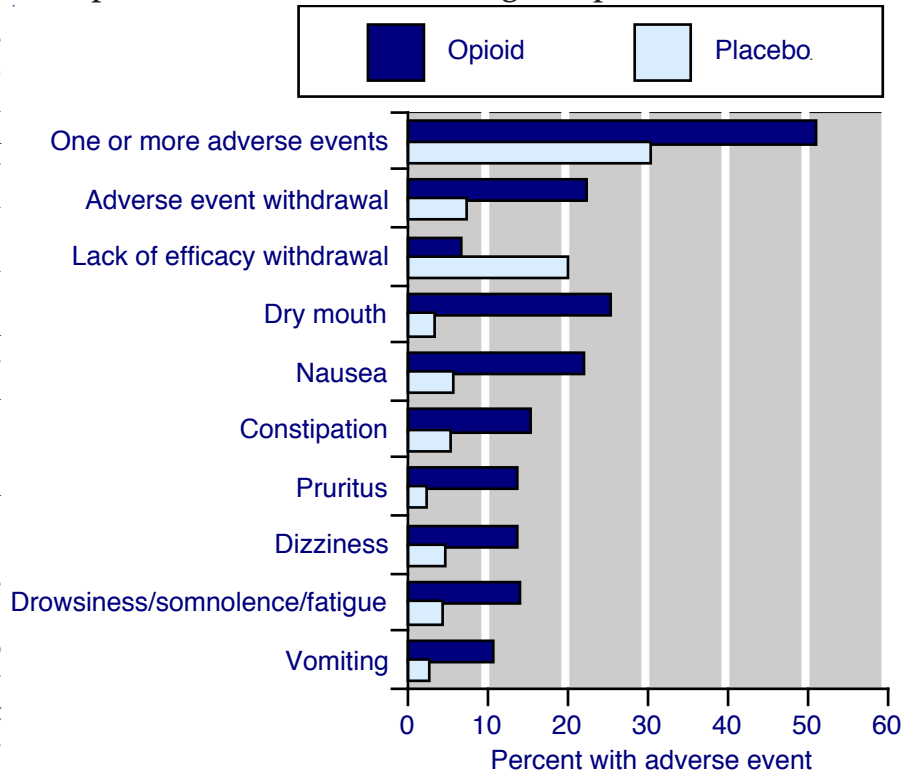
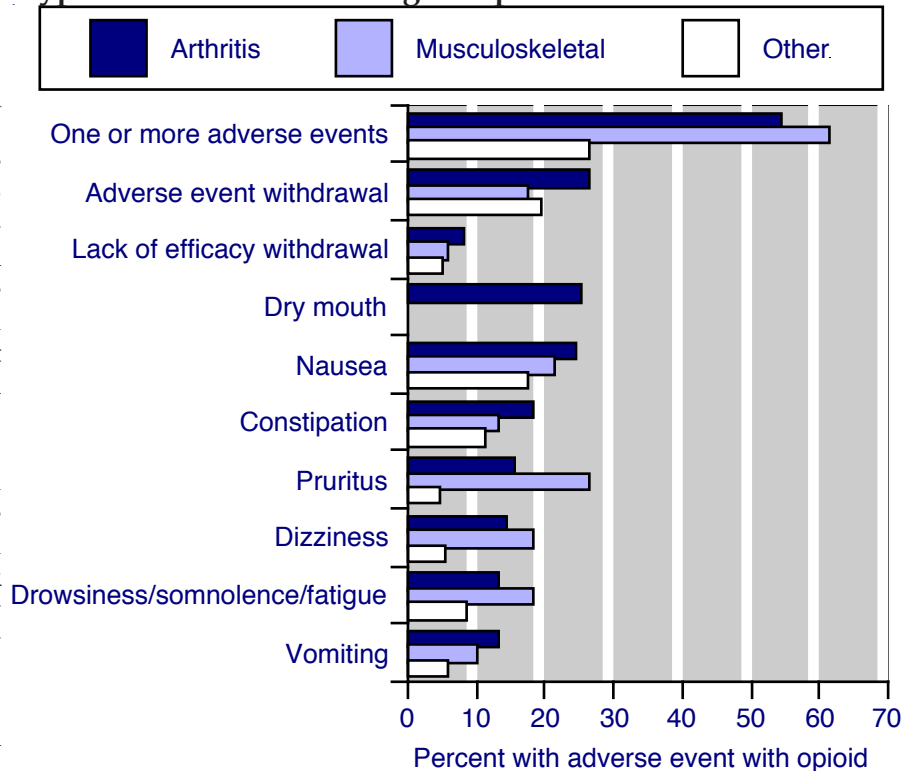


Figure 8: Adverse event rates for oral opioid in different types of chronic non-malignant pain



- 2 MM Reidenberg, DT Lowenthal. Adverse nondrug reactions. *NEJM* 1968 279: 678-679.
- 3 FP Meyer et al. Adverse nondrug reactions: an update. *Clinical Pharmacology and Therapeutics* 1996 60: 347-352.
- 4 PD Higgins, JF Johanson. Epidemiology of constipation in North America: a systematic review. *American Journal of Gastroenterology* 2004 99: 750-759.
- 5 J Connor et al. Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review. *Bulletin of the World Health Organisation* 2004 82: 935-939.