Investigating the efficacy and safety of over-the-counter codeine containing combination analgesics for pain and codeine based antitussives

Contributors

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Contents

Executive summary

Combination codeine medicines are widely available over-the-counter and concerns over misuse have risen. Common indications for use include headache, back pain, dental pain and post-surgical pain. The aim of this systematic review was to determine the efficacy and safety of over-the-counter codeine combination analgesics for the treatment of any pain condition or as an anti-tussive. MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CENTRAL, CINAHL and PsycINFO (inception to end December 2015) were searched for randomised controlled trials (RCTs). Two authors independently extracted data and assessed risk of bias. Data were pooled using a random effects model with strength of evidence assessed using GRADE. A total of 14 placebo-controlled RCTs of combination codeine analgesics or codeine based medicines [involving 788 participants] were included in this review. Ten evaluated effects on various pain conditions and four trials evaluated anti-tussive effects. There is high quality evidence that combination codeine medicines provide clinically important pain relief in the immediate term (3 hours post ingestion) mean difference (MD) [95% CI] -11.7 [-16.1, -7.2]. However for single dose trials, the effect declines in the short term (4-6 hours post ingestion) MD -2.8 [95% CI -7.9, 2.18]. Codeine-based medicines have been shown to reduce cough severity, but not frequency, however the evidence for this is very low quality.

It was difficult to evaluate the incremental effectiveness of codeine as some of the studies comparing combination codeine medicines with single ingredient medicines did not use same-drug comparisons e.g. NSAID + codeine vs paracetamol, making it difficult to attribute the findings to codeine alone. Three trials compared combination codeine medicines with appropriate single ingredient comparisons, two of which report no statistically significant difference in analgesia and one reported a marked difference in analgesia attributable to codeine.

Documented harms associated with codeine combination misuse include death, gastric haemorrhage, renal impairment and life-threatening biochemical imbalances. The experience from RCTs shows less serious side effects such as irritated stomach and tiredness are common with these medicines. There were no data on long term outcomes from RCTs making it difficult to extrapolate findings beyond the short term.

1.1 Introduction

Combination opioid products containing codeine are widely available in community pharmacies in Australia and overseas to manage common pain conditions such as migraine, headache, dental pain (Ahlstrom et al., 1985; Giles et al., 1986), musculoskeletal pain and also as adjuvant therapy for post-surgical pain relief (Heidrich et al., 1985; Skoglund et al., 1991) and for management of cold and flu symptoms (including cough). Typically in the over-the-counter (OTC) context, codeine is available in combination with paracetamol or a non-steroidal anti-inflammatory (NSAID) such as ibuprofen or aspirin and / or an antihistamine such as doxylamine or chlorpheniramine and decongestants such as phenylephrine (Codral: Cold and Flu, 2015). The rationale for these combination medicines is to reduce the need for higher doses of the opioid analgesic or anti-tussive as synergistic effects are believed to occur with combination pain medicines.

Codeine-based medicines are also commonly used in cough mixtures for the suppression of cough and other symptoms commonly associated with upper respiratory tract infections and chronic obstructive pulmonary disease (COPD). However there has been no systematic evaluation of the effectiveness of combination codeine medicines or codeine-based cough mixtures that would typically be available in the OTC setting. Furthermore there are concerns over abuse and dependency in line with increased access and availability of these combination opioid analgesic medicines. The aims of this research were therefore:

i) To determine the efficacy and safety of OTC codeine combination analgesics (ibuprofen + codeine or aspirin + codeine or paracetamol + codeine or doxylamine + paracetamol + codeine) for the treatment of any pain condition;

ii) To determine the efficacy and safety of OTC codeine-based products as an antitussive.

1.2 Methods

1.2.1 Data sources and searches

MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CENTRAL, CINAHL and PsycINFO (inception to end December 2015) were searched for randomised controlled trials (RCTs) evaluating combination medicines containing codeine for any pain condition or for use as an antitussive (Search Strategy Summary in Appendix Table 1). Additionally we screened reference lists of included RCTs and relevant systematic reviews to identify additional RCTs (Figure 1).

After screening titles and abstracts of retrieved studies, two reviewers drawn from a pool of three reviewers (CAS, AJM and CGM) independently inspected the full manuscript of potentially eligible RCTs to determine eligibility, with disagreements resolved by consensus.

1.2.2 Study selection

We included English language RCTs evaluating single ingredient or combination OTC medicines containing codeine for pain or for use as an antitussive. This report included studies that investigated a dose of codeine that could be achieved with doses available in OTC products in Australia. Study selection was not restricted by pain duration, comorbid condition(s) or concurrent medication use (e.g. to treat hypertension) provided participants were stabilised on these medications and the pattern of use was unchanged throughout the study. We included the Anatomical Therapeutic Chemical (ATC) codes for drug classes relevant to this review in the search.

Placebo-controlled RCTs and comparative effectiveness RCTs evaluating different doses of the same drug or combination were eligible for inclusion. Trials were included if they reported pain, cough count, or adverse events outcomes.

1.2.3 Data extraction and quality assessment

Two reviewers (CAS, CGM) independently extracted outcomes data from included studies. Missing data were obtained by contacting authors or estimated using the methods described in the Cochrane Handbook (Higgins et al., 2009). Analysis of data from a cross-over trial was performed according to recommendations in the Cochrane Handbook (Higgins et al., 2009). Only three trials provided the standard deviation value (SD) so we used the median SD from these studies for studies where the SD was not reported.

Risk of bias was assessed using the 11-item PEDro scale (de Morton 2009., Macedo et al 2010., Maher et al., 2003) (Table 1), which is a valid and reliable method of rating methodological quality of individual RCTs (de Morton 2009., Macedo et al 2010., Maher et al., 2003). Each item (excluding the item for external validity) is scored as either present (1) or absent (0) to give a total score out of 10. Rating of trials was carried out by two independent raters (CAS + AJM or CGM) with disagreements resolved by an independent third rater. Trials scoring <7/10 on the PEDro scale were defined as *high* risk of bias; those scoring 7 or more were considered at *low* risk of bias (de Morton 2009).

1.2.4 Data synthesis and analysis

Pain outcomes were converted to a common 0-100 scale (0: *no pain* to 100: *worst possible pain*). The pain intensity measures used in the retrieved trials were visual analogue scale (VAS) scores (scale range, 0 to 100) and numerical rating scale (NRS) scores (range, 0 to 10). The NRS was converted to the same 0-100 scale as in the VAS as these two pain measures have been shown to be highly correlated and when transformed, can be used interchangeably (Hjermstad et al., 2011). For one trial a nine point pain rating scale was used and outcomes were similarly converted to a 0-100 scale.

We present results as mean differences (MD) rather than standardised mean differences (SMD) as the benchmarks for clinically important difference in pain are expressed in points on a 0-100 pain scale not proportions of a standard deviation (Dworkin et al., 2008; Ostelo et al., 2008). We considered treatment effects in the range 10-19 points as small; $\geq$ 20 points as moderate and $\geq$ 30 points as large. These values are consistent with the proposed thresholds for *clinically important* changes in pain response from the literature on chronic pain (Dworkin et al., 2008). Effects <10 points were considered as not clinically meaningful (Ostelo et al., 2008).

We considered *immediate term* pain relief as the primary outcome. Outcomes were grouped into three time categories (with respect to follow up): *immediate term* (3 hours after a *single dose*) *short term* (4, 5 or 6 hours after a single dose *or* as part of a continuing course) and *intermediate term* (≥ 7 hours after a single dose *or* as part of a continuing course). Pooling of trial data was conducted for single dose trials. We did not combine data from single dose and multiple dose regimens as this may have led to confounding of results.

Where there were multiple comparisons from a single study, we divided the number of participants in the common arm by the number of comparisons, according to recommendations in the Cochrane Handbook (Higgins et al., 2009). Meta-analysis was carried out using RevMan 5.1 and Comprehensive Meta-Analysis. Pooled effects from those studies where 30 mg or less of codeine were administered in a single dose were calculated using a random effects model. Where possible, we explored possible causes of heterogeneity for I^2 values significantly greater than 40%.

We used the GRADE criteria (Atkins et al., 2004) to evaluate the overall quality of the evidence for an intervention. This method is described elsewhere (Pinto et al., 2012a; Pinto et al., 2012b), but briefly

the quality of evidence was downgraded a level for each of four factors: poor study design (25% or more of trials, weighted by sample size, have a low PEDro score [<7/10]), inconsistency of results (25% or more of the trials, weighted by sample size, have results which are not in the same direction), imprecision (sample size <300) and publication bias (assessed using funnel plot analysis/ Egger's regression test). Where Egger's regression two-tailed p-value was <0·10, the overall quality of evidence was downgraded by one level (Egger et al., 1997). It was not necessary to downgrade for indirectness (when the trial context is not the same as the review question) as this review evaluated administration of specific pain medicine combinations (containing codeine). The quality of evidence was defined as "high quality," "moderate quality," "low quality," and "very low quality" (Atkins et al., 2004).

Where results could not be pooled, a descriptive summary of results is presented. For adverse events we reported the proportion of participants experiencing one or more adverse events and calculated risk ratio based on this information. To evaluate the evidence around incremental effects of codeine, we looked at studies which compared codeine combination medicines with single ingredient NSAIDs and paracetamol, double doses of codeine based medicines compared with single doses and we also report on studies which evaluated two different combinations of codeine combination medicines. A summary of key findings from such studies are presented in Table 4. We also collated qualitative evidence from systematic reviews/ narrative reviews and case report studies which report adverse events outcomes from codeine use. The results are in Table 4 appended to the end of this document.

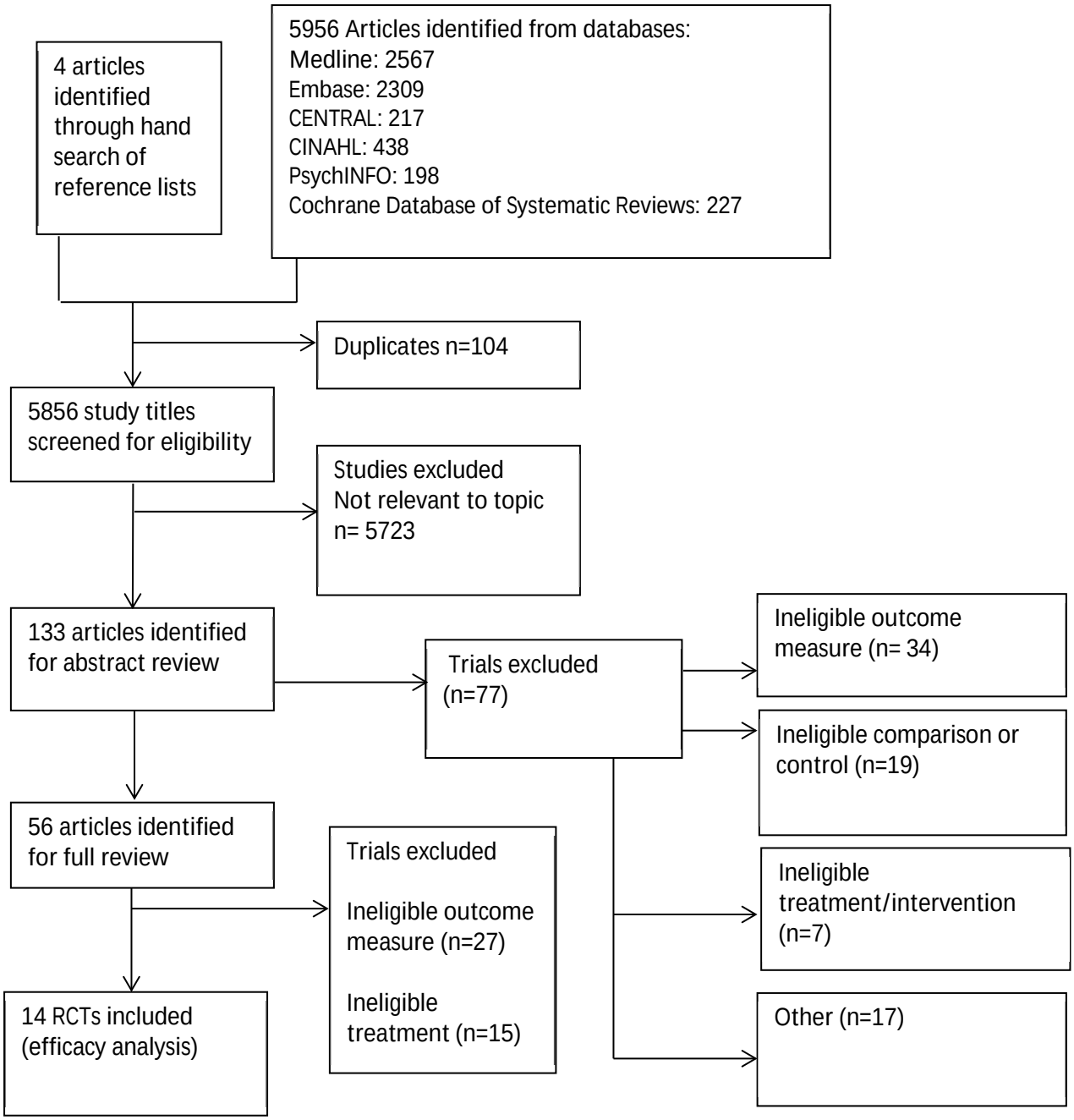

Figure 1: Summary of search strategy and outcome of trial inclusion and exclusion

1.3 Results Part A: Efficacy

A total of 14 placebo controlled trials of codeine containing combination products or codeine-based analgesics [involving 788 participants] were included in this review (see Table 2). Ten of these trials evaluated the effects of combination codeine medicines for pain conditions (e.g. dental pain, joint pain and post-surgical pain) and four of these trials evaluated the effects of codeine on cough. None of the trials evaluated long term use or outcomes, the maximum treatment period was up to 2 weeks and the maximum follow up periods were between 12-32 hours. The medicine products used in these trials included: paracetamol + codeine +/- caffeine, ibuprofen + codeine, aspirin + codeine +/-caffeine and codeine phosphate in tablet, capsule or liquid dose forms.

The Risk of Bias results are shown in Table 1. The trials were typically of high quality with a mean (SD) PEDro score of 8.1 (1.0).

Table 1: PEDro ratings for eligible trials

PEDro criterion	Trials													
	Ahlstrom 1985	Eccles 1992	Frame 1986	Heidrich 1985	Smith 2006	Quiding 1983	Skoglund 1991	Squires 1981	Cater 1985	Gerschman 1984	Giles 1986	Quiding 1992	Freestone 1997	Matthys 1983
1.	0	0	0	0	0	0	0	0	0	1	0	0	1	0
2.	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3.	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4.	1	1	1	1	1	1	1	0	1	0	1	0	1	1
5.	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6.	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7.	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8.	1	1	0	0	1	0	1	0	0	1	1	1	1	1
9.	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10.	1	1	1	1	1	1	1	1	1	1	0	1	1	1
11.	1	1	0	1	1	1	0	0	0	1	0	1	1	1
Total Score	**9**	**9**	**7**	**8**	**9**	**8**	**8**	**6**	**7**	**9**	**7**	**8**	**9**	**9**

Legend: 1= the trial complied with the PEDro item, 0= non-compliance. Operational definitions for each PEDro item are provided below.

PEDro Criteria (de Morton 2009., Macedo et al 2010., Maher et al., 2003).

1. Eligibility criteria were specified.
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects.
6. There was blinding of all therapists who administered the therapy.
7. There was blinding of all assessors who measured at least one key outcome.
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”.
10. The results of between-group statistical comparisons are reported for at least one key outcome.
11. The study provides both point measures and measures of variability for at least one key outcome.

1.3.1 Treatment efficacy: pain outcomes

Of the ten trials that provided data on pain outcomes, seven were single dose trials i.e. no subsequent doses were administered (Ahlstrom et al., 1985; Frame et al., 1986; Heidrich et al., 1985; Quiding et al., 1983; Skogland et al., 1991; Squires et al., 1981; Cater et al., 1985; Giles et al., 1986) and three trials (Ahlstrom et al., 1985; Gerschman et al., 1984; Quiding et al., 1992) used a multiple dose regimen. Two of these trials (Gerschman et al., 1984; Quiding et al., 1992) administered the medicines every 4 hours (total of six doses in 24-hours). Half of the trials evaluated dental pain (Ahlstrom et al., 1985; Frame et al., 1986; Giles et al., 1986; Skogland et al., 1991; Squires et al., 1981). No placebo controlled trials of combination codeine analgesics were identified for headache or back pain. Characteristics of the studies included in this analysis are presented in Table 2.

The pooled results (from studies where 30 mg or less of codeine were administered in a single dose) provide high quality evidence from five studies [involving 383 participants] that combination codeine analgesics provide a clinically important pain relieving effect in the immediate term; MD -11.7 [-16.1, -7.2] (Figure 2). There is high quality evidence from four studies [327 participants] that combination codeine analgesics, delivered as a single dose, provide pain relief which is less than the clinically important threshold in the short term; mean difference (MD -2.8 [95% CI -7.9, 2.2]) (Figure 3), this effect is considerably less than the clinically worthwhile threshold of 10-points.

Results from individual trials suggest that codeine and paracetamol combination medicines provide greater pain relief vs placebo and that these results are generally superior to the pain relief effects obtained from combination of codeine and NSAIDs vs placebo (see Figure 4).

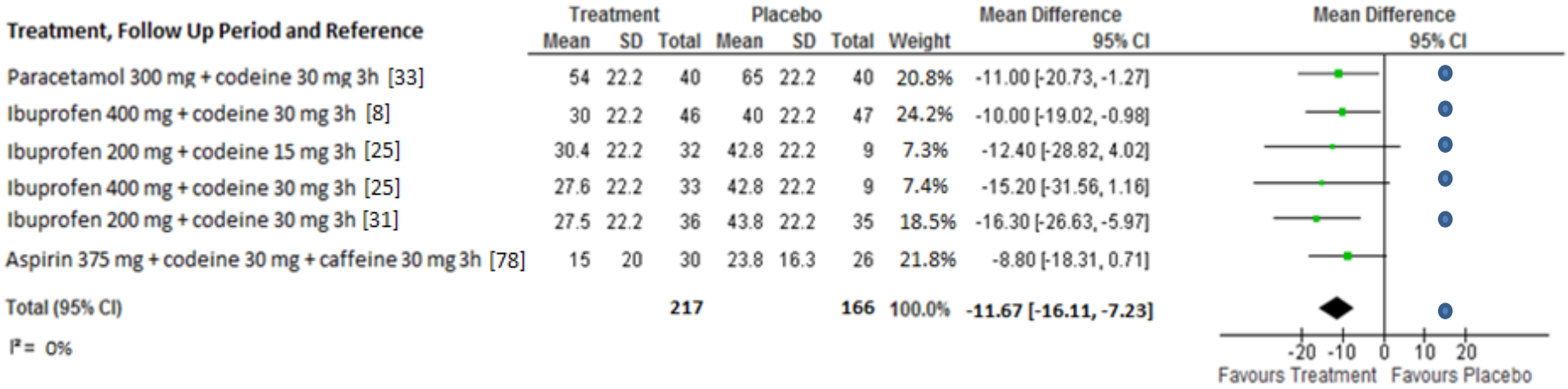

Figure 2: Pooled immediate term effects from OTC combination codeine medicines at 3 hours (3 h)
The pooled effect of -11.67 is considered a clinically important pain relieving effect. All single dose trials. The blue dots signify treatment effects >10 units which are considered clinically worthwhile.

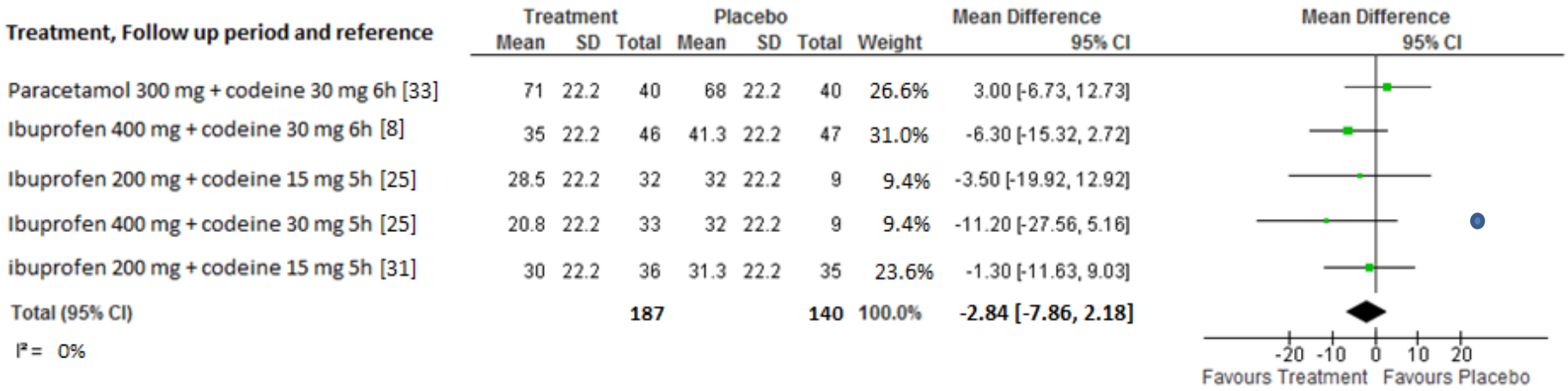

Figure 3: Pooled short term effects of combination OTC medicines containing codeine at time points from 4 hours (4h) to 6hours (6h)
The pooled effect of -2.84 was not considered clinically worthwhile. The blue dots signify treatment effects >10mm which are considered clinically worthwhile.

The trials by Ahlstrom et al., 1985 [1], Quiding et al., 1983 [65] and Quiding et al., 1992 [66] all report the average pain intensity ratings *over* 12 hours, 8 hours and 4 hours respectively (i.e. not the pain intensity rating measured *at* 12 hours, 8 hours and 4 hours respectively). Hence these studies were not included in the pooled analysis but results from each trial are presented separately in Figure 4. The study by Ahlstrom et al., 1985 [1] showed that the combination of paracetamol 1000 mg + codeine 60 mg provided almost double the pain relief that was seen with the combination of paracetamol 500 mg + codeine 30 mg (MD [95% CI] -31.00 [-40.39, -21.61] vs -16.00 [-25.38, -6.62] over a 12 hour period. The study by Gerschman et al., 1984 [30] and Quiding et al., 1992 [66] employed a multiple dose regimen (two tablets every four hours). Both these studies demonstrated pain relief that was considerably higher than the minimum clinically important threshold of 10-points MD [95% CI] -26.00 [-44.54, -7.46] (at 4 hours) and -19.00 [-31.19, -6.81] (mean pain intensity difference over 0-8 hours) respectively. Conversely pain relief from single dose studies appeared to decline over time. For example in the study by Cater et al., 1985 pain relief changed from -10.00 [-19.02, -0.98] at 3 hours to 3.80 [-5.22, 12.82] at 8 hours post ingestion (Figure 4, trial [8]).

1.3.2 Dose Differences

The study by Frame et al., 1986 [25] showed that higher dosages of combination ibuprofen + codeine do not necessarily result in greater pain relief in the short term (following a single dose administration). In fact at 5 hours post ingestion, ibuprofen 400 mg + codeine 30 mg provided more than double the pain relief than the combination of ibuprofen 800 mg + codeine 60 mg MD [95% CI] -11.20 [-27.56, 5.16] vs -4.20 [-21.79, 13.39] respectively. However higher dose combinations of paracetamol and codeine were shown to provide greater pain relief in the short term compared with lower dose regimens (Figure 4).

Treatment, Follow Up Period and Reference	Treatment Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference 95% CI
Paracetamol + Codeine Combination							
Paracetamol 1000 mg + codeine 60 mg 12 h [1] *	15	22.2	44	46	22.2	42	-31.00 [-40.39, -21.61]
Paracetamol 500 mg + codeine 30 mg 12 h [1] *	30	22.2	43	46	22.2	43	-16.00 [-25.38, -6.62]
Paracetamol 450 mg + codeine 9.75 mg 4h [30]**	-45.4	24.8	14	-19.4	27	16	-26.00 [-44.54, -7.46]
Paracetamol 1000 mg + codeine 60 mg 4h [65]*	44	13.6	16	51	24.4	10	-7.00 [-23.53, 9.53]
Paracetamol 300 mg + codeine 30 mg 3h [33]	54	22.2	40	65	22.2	40	-11.00 [-20.73, -1.27]
Paracetamol 300 mg + codeine 30 mg 6h [33]	71	22.2	40	68	22.2	40	3.00 [-6.73, 12.73]
Paracetamol 1000 mg + codeine 60 mg 3h [73]	21	22.2	37	47	22.2	33	-26.00 [-36.42, -15.58]
Paracetamol 1000 mg + codeine 60 mg 6h [73]	27	22.2	37	42	22.2	33	-15.00 [-25.42, -4.58]
NSAID + Codeine +/- Caffeine Combination							
Ibuprofen 400 mg + codeine 30 mg 3h [8]	30	22.2	46	40	22.2	47	-10.00 [-19.02, -0.98]
Ibuprofen 400 mg + codeine 30 mg 6h [8]	35	22.2	46	41.3	22.2	47	-6.30 [-15.32, 2.72]
Ibuprofen 400 mg + codeine 30 mg 8h [8]	43.8	22.2	46	40	22.2	47	3.80 [-5.22, 12.82]
Ibuprofen 200 mg + codeine 15 mg 3h [25]	30.4	22.2	32	42.8	22.2	9	-12.40 [-28.82, 4.02]
Ibuprofen 200 mg + codeine 15 mg 5h [25]	28.5	22.2	32	32	22.2	9	-3.50 [-19.92, 12.92]
Ibuprofen 400 mg + codeine 30 mg 3h [25]	27.6	22.2	33	42.8	22.2	9	-15.20 [-31.56, 1.16]
Ibuprofen 400 mg + codeine 30 mg 5h [25]	20.8	22.2	33	32	22.2	9	-11.20 [-27.56, 5.16]
Ibuprofen 800 mg + codeine 60 mg 3h [25]	24.5	22.2	26	42.8	22.2	8	-18.30 [-35.89, -0.71]
Ibuprofen 800 mg + codeine 60 mg 5h [25]	27.8	22.2	26	32	22.2	8	-4.20 [-21.79, 13.39]
Ibuprofen 200 mg + codeine 15 mg 3h [31]	27.5	22.2	36	43.8	22.2	35	-16.30 [-26.63, -5.97]
Ibuprofen 200 mg + codeine 15 mg 5h [31]	30	22.2	36	31.3	22.2	35	-1.30 [-11.63, 9.03]
Aspirin 375 mg + codeine 30 mg + caffeine 30 mg 3h [78]	15	20	30	23.8	16.3	26	-8.80 [-18.31, 0.71]
Ibuprofen 200 mg + codeine 30 mg 0-8 h [66]**	10	22.2	26	29	22.2	25	-19.00 [-31.19, -6.81]
Ibuprofen 200 mg + codeine 30 mg 1-8 h [66]**	25	22.2	26	26	22.2	26	-1.00 [-13.07, 11.07]

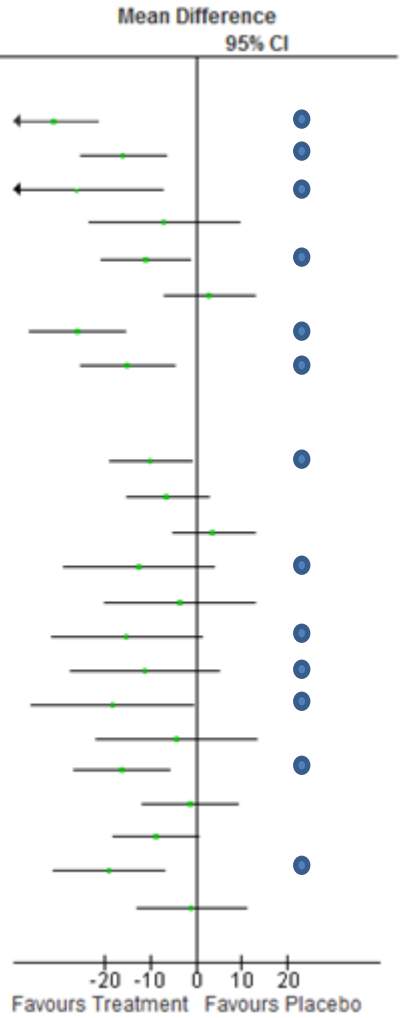

Figure 4: Treatment effects reported in individual studies at time points from 3 hours (3 h) to 12hours (12h)

The blue dots signify treatment effects >10-points which are considered clinically worthwhile. Note Quiding et al., 1992 [53]; results are for average pain over 8 hours following 1st dose and 6th dose. The 6th dose was measured from 24 - 32hours. * Study reported the mean pain intensity difference over the follow up period specified. ** Study used a multiple dose regimen.

Table 2: Characteristics of included studies

Study	**Setting / Country**	**Indication**	**Mean age of participants** [years]	**Participant Characteristics (number entered)**	**Intervention** [Randomised, double blind, parallel group]	**Control**	**Outcome Measure**	**Follow Up period (post ingestion)**
Pain Trials								
Ahlstrom 1985	Stockholm Sweden	Surgical removal of an impacted wisdom tooth.	I (A): 31 I (B): 29 P (C): 27 P (D): 28	I (A): 44 I (B): 43 Placebo: 85 F: 82 M: 90	I (A): paracetamol 1000 mg + codeine 60 mg I (B): paracetamol 500 mg + codeine 30 mg *A second dose could be taken*	Placebo	0-10 VAS	12 h
Cater 1985	Nottingham England	Post episiotomy pain	I: 23.1 P: 22.7	I: 46 P: 47	*single dose study* Ibuprofen 400 mg + codeine 30 mg n=46	Placebo	9 point pain rating scale i.e. 0-8	8 h
Frame 1986	Queensway Birmingham	Removal of an impacted mandibular third molar tooth	I (C): 23.55 I (D):25.09 I (E): 23.70 P (A): 23.55	I (C): 33 I (D):33 I (E): 33 P (A): 33	*single dose study* I (C): 33 ibuprofen 200 mg + codeine 15 mg I (D):33 ibuprofen 400 mg + codeine 30 mg I (E): 33 ibuprofen 800 mg + codeine 60 mg P (A): 33	Placebo	9 point pain rating scale i.e. 0-8	5 h
Gerschman 1984	Copenhagen	Temporomandibular joint pain dysfunction syndrome	I: 34.6 P: 29.7	I: 14 P: 16	Paracetamol 450 mg + codeine 9.75 mg 2 tabs every 4 hours	Placebo	VAS 0-100	2 weeks (cross over study design)

Study	**Setting / Country**	**Indication**	**Mean age of participants** [years]	**Participant Characteristics (number entered)**	**Intervention** [Randomised, double blind, parallel group]	**Control**	**Outcome Measure**	**Follow Up period (post ingestion)**
Giles 1986	Nottingham England	Postoperative dental pain	I: 23.9 P: 25.7	I: 36 P: 35	*Single dose study* Ibuprofen 200 mg + codeine 15 mg	Placebo	9 point pain rating scale i.e. 0-8	5 h
Heidrich 1985	Washington	Post-orthopaedic surgery patients with moderate to severe pain.	31 years across entire cohort	I: 40 P: 40	*Single dose study* Paracetamol 300 mg + codeine 30 mg	Placebo	VAS 0-100	6 h
Quiding 1983	Sweden	Post meniscectomy	I: 33 (9.6) P: 38 (11.3)	I: 16 P:10	*Single dose study* paracetamol 1000 mg + codeine 60 mg	Placebo	Pain intensity Difference 0-10	6 h
Skoglund 1991	Norway	Post-surgery to remove impacted wisdom teeth	I: 25 P: 24.4	I: 37 P 33	*Single dose study* paracetamol 1000 mg + codeine 60 mg	Placebo	VAS 0-100	6 h
Squires 1981	Canada	Dental surgery pain	I: 27.0 P: 28.7	I: 30 P: 26	*Single dose study* ASA-30 (Aspirin 375 mg + codeine 30 mg + caffeine 30 mg)	Placebo	9 point pain rating scale i.e. 0-8	4 h
Quiding 1992	Sweden	Coxarthrosis	53	I: 26 P: 26 M: 4 F: 22	I (A): ibuprofen 200 mg + codeine 30 mg Six doses during 24 hours	Placebo	0-100 VAS	32 h
Cough Trials								
Smith 2006 (cross-over design)	United Kindgdom	Cough in COPD	68.0 (6.86)	21 I: 19 P: 19 14 Male	Codeine phosphate 60 mg capsules and again after 12 hours	Placebo	Cough frequency (coughs/hour) Cough symptom score (0-100 VAS)	12 h (day and night)

Study	**Setting / Country**	**Indication**	**Mean age of participants** [years]	**Participant Characteristics (number entered)**	**Intervention** [Randomised, double blind, parallel group]	**Control**	**Outcome Measure**	**Follow Up period (post ingestion)**
Matthys 1983	Germany	Chronic stable cough due to pulmonary tuberculosis, bronchial carcinoma or obstructive lung disease	55.9 (17.2)	16 M: 11 F: 5	2 doses of codeine phosphate 20 mg for three consecutive nights	Placebo	Cough frequency (per hour)	8 h
Eccles 1992	Wales, Cardiff	Cough associated with acute upper respiratory tract infection	23	91 M: 47 F: 44	Codeine 30 mg / 10 mL four times a day up to 120 mg codeine / day	Placebo	Cough frequency per minute Cough severity (0-100 VAS)	~ 3 h (150 minutes)
Freestone 1997	Cardiff, UK	Cough associated with upper respiratory tract infection	23.5	82 F: 51 M: 31	*Single dose* of codeine 50 mg capsules	Placebo	Cough frequency	90 minutes

I: Intervention; P: Placebo

1.3.3 Cough

There were four eligible trials (total sample size of 208 participants) that evaluated codeine phosphate preparations for cough. Two of these studies (Matthys et al., 1983; Smith et al., 2006) evaluated treatment for chronic cough (COPD and chronic stable cough due to pulmonary tuberculosis, bronchial carcinoma or obstructive lung disease) and two trials evaluated treatment for acute upper respiratory tract infection or acute simple bronchitis (Eccles et al., 1992; Freestone et al., 1997). One study (Freestone et al., 1997) found no significant difference in cough count between treatment and control groups (MD 0.52 p=0.84) however the evidence for this is of very low quality (single trial with small sample size). Two studies (Eccles et al., 1992; Smith et al., 2006) reported the cough severity symptom score (on a 0-100 VAS) and found that there was a reduction in cough severity in both treatment and control groups over time. One of these studies (Smith et al., 2006) showed there was significant reduction in night time cough severity but not cough count with the use of codeine compared with placebo (mean difference of 10-points on 0-100 cough severity scale; mean difference of 0.4 on cough count p=0.86). However the evidence for this is of very low quality as it is a single trial with a small sample size (< 300 participants).

1.3.4 Adverse events

Six trials evaluating pain reported on adverse events outcomes. Adverse events outcomes were generally obtained at the end of the follow up period (4 hours to 2 weeks). Four of these trials were single dose trials (Cater et al., 1985; Giles et al., 1986; Skoglund et al., 1991 and Squires et al., 1981) and two trials were continuing courses (Gerschman et al., 1984 and Quiding et al., 1992) up to 2-weeks (2 weeks and 32 hours respectively). Table 3 below summaries the relative risk for adverse events outcomes. Adverse events such as irritated stomach, tiredness, and nausea were more likely to occur in the treatment groups than in the placebo groups but in general (reflecting the small trial sizes the estimate of the relative risk was imprecise) not statistically significant.

Table 3: Relative risk of adverse events: codeine combination medicines vs placebo

Study	Adverse event	Treatment	Placebo	RR (95% CI)	Statistically significant
Cater 1985	Faintness and dizziness	0/46	1/47	0.34 (0.01, 8.15)	No
Gerschman 1984	Drowsiness	8/14	0/16	19.27 (1.21, 306.35)	Yes
Giles 1986	Tiredness Nausea	1/36 1/36	0/35 0/35	2.92 (0.12, 69.32) 2.92 (0.12, 69.32)	No No
Quiding 1992	AE (general) Nausea Other adverse events included: constipation, flatulence, feeling slightly intoxicated, heartburn, headache, swollen ankle, heavy body and dizziness	11/26 6/26	6/26 2.26	1.83 (0.80, 4.22) 3.00 (0.67, 13.51)	No No
Skoglund 1991	Tiredness Fever	5/37 1/37	1/33 1/33	4.46 (0.55, 36.24) 0.89 (0.06, 13.70)	No No
Squires 1981	Cold sweats and dizziness Irritated stomach	0/26 3/26	3/30 0/30	0.38 (0.04, 3.48) 8.04 (0.43, 148.71)	No No

1.4 Discussion

There is high quality evidence that combination medicines containing codeine and paracetamol or codeine and NSAID (+/- caffeine) provide significantly greater pain relief compared with placebo. For single dose trials, these combination medicines provide clinically significant pain relief for the immediate term however these effects appear to decline in the short term (between 4-6 hours after a single dose). For trials evaluating multiple dose regimens, there continued to be pain improvement over time and the effects were generally higher than the minimum clinically important threshold.

For cough, codeine preparations are effective in reducing cough severity but not frequency and the evidence in this area is of very low quality.

Strengths of this review include a comprehensive search strategy identifying combination codeine medicines for the treatment of any pain condition. The PEDro scale was used to assess risk of bias because it has acceptably high clinimetric properties whereas limitations have been reported for the Cochrane risk of bias scale (Armijo-Olivo et al., 2012; Hartling et al., 2009). Limitations of the efficacy analysis include possible publication bias, as only English-language studies published in peer-reviewed journals were included.

To our knowledge, this is the first systematic review to evaluate evidence for combination codeine medicines that are typically available in the OTC setting. Whilst the majority of the studies included in this review were conducted overseas, the codeine preparations are similar to those available in Australia making the findings relevant to the Australian clinical setting. It was surprising however that there were no eligible placebo controlled trials evaluating codeine combination medicines for headache or back pain despite evidence to suggest these conditions are among the most common reasons for use and misuse of combination codeine medicines (Frei et al., 2010; Sproule et al., 1999).

This review has shown that whilst clinically important pain relief is achieved for the immediate term with combination codeine medicines, none of the studies reported on efficacy outcomes beyond 12 hours making it difficult to extrapolate efficacy outcomes beyond the intermediate term.

Few studies used multiple dose regimens although, where this design was implemented, the pain relief was generally higher than for single dose study designs. This suggests that a continued course of these medicines is effective in relieving pain however the duration of use must be balanced against the risk of adverse events and dependency which is believed to have risen in line with increased availability of these medicines (Nielsen et al., 2010).

1.5 Conclusion

Combination medicines containing codeine provide clinically significant pain relief for the immediate term following a single dose however these effects decline after 3 hours of ingesting the first dose. There were limited data on adverse events outcomes from RCTs, however nausea, tiredness, dizziness and GI upset were notably higher in treatment groups compared to placebo. Evidence on long term outcomes is lacking and it is not possible to determine prevalence of abuse/dependency based on the RCTS included.

1.6 Part B: Incremental effectiveness of codeine

Seventeen reports were identified which evaluated the incremental effectiveness of codeine. Many of these were head to head studies evaluating combination codeine medicines versus single ingredient NSAIDs or paracetamol. Six studies (Bruni et al., 1964; Friday et al., 2009; Gatoulis et al., 2012; Ragg et al., 1997; Skjelbred et al., 1982; Walton et al., 1990) reported no significant difference between the codeine combination medicine and the comparison drug (usually a single ingredient

NSAID or paracetamol). One systematic review (Nautu et al., 2009) evaluating nine trials of combination codeine and paracetamol preparations vs NSAIDs for post abdomen surgery pain found no statistically significant difference in pain relief between the combination medicines and NSAID. However three trials reported a notable difference between the combination codeine medicine and comparison drug (Dahl et al., 1985; Madore et al., 1967; McQuay et al., 1989) and two studies (Cooper et al., 1976; De Craen et al., 1996) reported a "minimal" difference. It is difficult to quantify these differences as the pain scales used vary between the studies making pooling of findings challenging. Additionally in studies comparing combination codeine medicines with single ingredient medicines, the comparison drug was not always the same medicine that was in the combination product e.g. NSAID + Codeine vs paracetamol. This makes it difficult to attribute the findings to the codeine component alone. Three trials compared combination codeine medicines with appropriate single ingredient comparisons, two of which (Skjelbred et al., 1982; Walton et al., 1990) report no statistically significant difference in analgesia and one trial (McQuay et al., 1989) reported a marked difference in analgesia attributable to codeine. A qualitative summary of these findings is presented in supplementary Table 4 below.

Table 4: Incremental effects of codeine

Study	Indication	Outcome measure	Interventions	Key Findings
Bruni et al., 1964.	Post-partum pain	Degree of pain relief – five point verbal rating scale – Complete to None	Codeine 30 mg + Aspirin 600 mg vs Aspirin 600 mg	No significant difference between treatments – but all superior to placebo.
Cooper et al., 1976.	Oral surgery outpatients	Verbal rating scale	Aspirin 650 mg vs codeine 30 mg + aspirin 650 mg	The combination of codeine and aspirin is only slightly more effective than aspirin alone.
Dahl et al., 1985.	Removal of impacted mandibular	10 cm VAS	Aspirin 500 mg + codeine 30 mg vs aspirin 500 mg	Combination tablets provide better pain relief and quantity of tablets used were less and time intervals between repeated doses were longer ($p<0.02$ for all comparisons).
De Craen et al., 1996.	Systematic review – various pain conditions postsurgical pain (21 studies), postpartum pain (1 study), osteo-arthritic pain (1 study)	Sum of Pain Intensity Difference	Paracetamol 400 mg to 1000 mg + codeine 10 mg to 60 mg	The difference in analgesic effect between paracetamol-codeine combinations and paracetamol alone was small but statistically significant.

Study	Indication	Outcome measure	Interventions	Key Findings
Friday et al., 2009.	Extremity injuries	10 cm colour analogue scale	Paracetamol–codeine (1 mg⁄kg as codeine, maximum 60 mg) n=32 or ibuprofen (10 mg⁄kg, maximum 400 mg) n=34	In children presenting to ED with moderate to severely painful extremity injuries, there was adequate and equivalent analgesia with ibuprofen or the paracetamol–codeine combination. Note differences favour ibuprofen in the first 40 minutes and the combination at 1 hour. Results were not statistically significant based on 95% CI.
Gatoulis et al., 2012.	Third molar extraction or tension type headache	Pain Intensity Difference on 5-point verbal rating scale	Aspirin (1000 mg), acetaminophen (300 mg) + codeine (30 mg), or placebo	Treatment with aspirin (1000 mg) provides statistically significant analgesia compared with placebo use and comparable efficacy with acetaminophen (300 mg) + codeine (30 mg) therapy after impacted third molar extraction and in tension- type headache.
Hellman et al., 1992.	Removal of lower third molars	VAS	Two-dose regimen: combination ibuprofen 200 mg + codeine 30 mg was compared with that of acetylsalicylic acid 500 mg + codeine 30 mg and codeine 30mg	The combination ibuprofen-codeine had greater analgesic efficacy compared to the combination acetylsalicylic acid-codeine ($P<0.005$) or codeine alone in patients with pain after removal of the lower third molars.
Madore et al., 1967.	Post-operative pain	Pain Intensity Difference on 4-point rating scale	Fiorinal with codeine	Double dose of Fiorinal was superior to the single dose.
Matts et al., 1966.	Recurring pain	Sequential Analysis Chart	Panadeine Co (paracetamol 1 g plus codeine phosphate 16 mg) vs soluble aspirin 1 g	Panadeine Co was superior to soluble aspirin in obtaining pain relief.

Study	Indication	Outcome measure	Interventions	Key Findings
McQuay et al., 1989.	Bilateral third molar removal	Pain Intensity	A combination of 20 mg codeine base and ibuprofen 400 mg was compared with ibuprofen 400 mg in a randomised double-blind cross-over study of multiple doses in 25 patients after 2-stage bilateral third molar removal.	The combination produced significantly greater pain relief and doubled the hours of minimum pain intensity and maximal relief on the day of surgery.
McQuay et al., 1992.	Third molar surgery	Pain Intensity on 4-point verbal rating scale and pain relief on 5-point rating scale	Study compared ibuprofen + codeine combination (400 mg ibuprofen/25.6 mg codeine phosphate) with a paracetamol + codeine + caffeine combination (I g paracetamol + 16 mg codeine phosphate + 60 mg caffeine) for pain relief over 6 days after two-stage bilateral lower third molar removal. Randomised crossover study (n=30)	The ibuprofen combination produced significantly greater analgesia than the paracetamol combination, both on single-dose analysis of the first and second days and on multiple-dose measures for days I , 2, 3 and 4 (P< 0.02 for all comparisons).
Modaresi et al., 2006.	Root canal therapy	Tooth sensitivity levels	Acetaminophen 300 mg + 20 mg codeine vs ibuprofen 200 mg	Significantly lower tooth sensitivity levels (TSLs) were observed with the acetaminophen-codeine and ibuprofen groups, which was more significant in the ibuprofen group.
Nautu et al., 2009.	Systematic review of nine trials evaluating pain relief in post abdominal surgery pain	VAS	Codeine + paracetamol vs NSAID	None of the studies found the combination of codeine + paracetamol to be superior to NSAIDs in controlling post-laparotomy pain.

Study	Indication	Outcome measure	Interventions	Key Findings
Ragg et al., 1997.	Premedication and analgesia for myringotomy in children	4 point pain face rating scale	Paracetamol vs Painstop (paracetamol 12 mg, codeine 0.5 mg and promethazine 0.65 mg per ml) 30 to 60 minutes prior to surgery	Pain scores were similar in both treatment arms. Little need for additional analgesia p<0.03.
Skjelbred et al., 1982.	Oral surgical procedures	100 mm VAS	Paracetamol + codeine phosphate (400 mg + 30 mg), vs plain paracetamol (400 mg)	No increase in analgesia was demonstrated by the addition of codeine to paracetamol. The majority of participants (n=20) preferred treatment with plain paracetamol over the combination (n-4) p<0.001.
Sniezek et al., 2011.	Postoperative pain relief	VAS	Patients undergoing MMS and reconstruction for head and neck skin cancers received 1 g paracetamol paracetamol plus 400mg ibuprofen, or 325mg paracetamol plus 30mg codeine immediately after surgery and every 4 hours for up to four doses	The group administered the combination of paracetamol + ibuprofen had the lowest pain scores (mean change from baseline/immediately prior to surgery) at each postoperative recorded time interval and a significantly smaller change from baseline pain scores than the paracetamol + codeine group at 4 hours (p = 0.005) and the paracetamol group at 8 hours (p = 0.02).

Study	Indication	Outcome measure	Interventions	Key Findings
Walton et al., 1990	Post-operative oral surgery pain	Five point verbal rating scale	Ibuprofen 300 mg tablets vs ibuprofen 300 mg + codeine 20 mg tablets	There was no statistically significant difference in the effectiveness of either preparation in the control of postoperative pain. Both preparations were reported to provide good pain relief throughout the study.

1.7 Part C: Harms of codeine combination medicines (narrative review and appended table)

Dependency to codeine has been the subject of careful investigation in such countries as Canada, France and Australia (Nielson et al., 2010; Sproule et al., 1999; Roussin et al., 2013). The US Food and Drug Authority (US FDA) and the European Medicines Agency (EMA) have issued recommendations to prevent the use of codeine-based preparations in children under 12 and to carefully consider the use of these medicines in children aged 12-18 years with breathing problems.

Although several case report studies have shown that codeine can produce physical dependence (Himmelsbach et al., 1934, Himmelsbach et al., 1940a, Himmelsbach et al., 1940b), its potential for abuse has previously been the topic for debate. Abuse with codeine or codeine-based products was thought to be low because of reports of lower euphoric effects compared with other opioid drugs such as heroin and morphine and also because codeine is difficult to administer parenterally due to its physical properties (Himmelsbach et al., 1940). Earlier reviews had also concluded that addiction to codeine is rare (Rowden et al., 1989; Weppner et al.,1971). However there are several other reports, including more recent ones, which describe individuals who misuse or regularly use codeine (Busto et al., 1998, Dutch et al., 2008; Kliner et al., 1982, Nielson et al., 2010; Sproule et al., 1994). A study by Sproule et al (1994) conducted in Canada showed that codeine dependence is common among regular users of combination codeine medicines. Overall however there are few studies which have evaluated codeine dependence in great detail (Nielsen et al., 2010).

The synthesis of evidence from case studies conducted as part of this review (and which is appended to the end of the document; Table 5) has identified that adverse events resulting from the misuse of codeine can be life threatening and even fatal, and commonly revolve around renal and biochemical/metabolic impairment. However it is not possible to determine the prevalence of this problem from case studies alone, warranting a more detailed evaluation of codeine dependence.

The majority of evidence around harms from the Australian setting comes from the state of Victoria. Harms relating to OTC combination codeine medicines have included gastric bleeding (Dutch et al., 2008) and potentially fatal metabolic imbalances (Chetty et al. 2003; Dyer et al. 2004; Lambert & Close 2005). Anecdotal evidence suggests that some individuals may not be aware of a drug use problem until there are serious health harms (Nielsen et al., 2010) highlighting the need to educate consumers about the potential for codeine to cause dependency. Case report studies also point to the fact that persistent users of combination codeine medicines often use these medicines for their euphoric or anxiolytic effects.

A number of case studies reported life threatening hypokalaemia with the use of codeine/ibuprofen combinations – this is most likely attributable to the dose of anti-inflammatory (ibuprofen) ingested to gain euphoric effects of codeine when taking this combination. Life threatening effects such as gastric erosion, and gastric haemorrhage are similarly likely to be attributed to the anti-inflammatory component. Over 100 deaths in Australia (3 documented in published case studies and 115 from post-mortem investigations) have been attributed to the misuse of combination codeine medicines (Dobbin et al., 2008; Ferguson et al., 2010; McDonough et al., 2011; Pilgrim et al., 2013). Opioid withdrawal symptoms upon cessation appear to propagate the cycle of misuse and dependency as evidenced in some case studies where opioid withdrawal was of notable concern (Frei et al., 2010; Romach et al., 1999).

A number of studies (Neilson et al., 2010, Frei et al., 2010) report that codeine-based medicines are purchased from multiple pharmacies among people with problematic codeine use behaviours. This adds to the challenges of monitoring codeine misuse in the primary care setting. One study (Frei et al., 2010) reported that the majority of the 27 patients evaluated had purchased the OTC codeine medicines from multiple pharmacies, while another study (Nielsen et al., 2010) reported that just

over one third (37%) of codeine-dependent users had purchased OTC codeine medicines from multiple pharmacies. In the Nielsen study, the majority (58%) had purchased these medicines from a single pharmacy. Another study of harms associated with codeine dependence conducted in Canada (Sproule et al., 1994) showed that most participants indicated obtaining their codeine from one physician (66%) or by purchasing it over the counter (54%).

There is a limitation in data as there were no prospective studies of a representative population sample. Therefore the population at risk is unclear as is the duration of exposure.

Table 5: Summary of harms from combination codeine medicines use

Study	Summary
Frei et al., 2010.	**Study Type:** Prospective case series study carried out by clinicians in a network of specialist addiction treatment services (the Victorian Addiction Inter-hospital Liaison Association) in several Victorian health regions **Study Period:** May 2005 and December 2008 **Country/Setting:** Victoria, Australia **Cases/Studies involved:** 27 cases **Medication initiated to treat:** Pain conditions e.g Back Pain, Dental Pain, Headache in 15 patients overall. Non-medical related use prevalent. **Medication type:** OTC codeine + ibuprofen combination **Total daily codeine dose ingested (range):** 435–602 mg of codeine phosphate. Minimum 34 conventional OTC tablets/day. **Total daily ibuprofen ingested (range):** 6800–9400 mg ibuprofen i.e. 34-47 conventional tablets/ day **Patient Characteristics/ History:** History of intravenous drug use n=10; Reported only using pharmaceutical opioids n=14; Reported no other substance use with OTC codeine n=15; Reported prolonged codeine use n=26; Anaemia n=12. **Key Findings around reported Harms: (based on results from Table 2 of this study and descriptive data)** *Life threatening* · Hospitalisations (n=4, all ICU) · Opioid dependence and withdrawal (attributed to codeine) · Gastrointestinal haemorrhage (n=7) · Perforated duodenal ulcer (n=3) · Gastric erosion (n=2) · Hypokalaemia (n=4) · Acute renal failure (n=1) One patient required dialysis and another required gastrectomy *Other* · Anaemia (documented n=12) · Persistent vomiting (n=2) · Nausea (n=1) · Insomnia (n=1)

Study	Summary
	· Hematemesis (n=2) · Peripheral oedema (n=1) · No Deaths reported **Management Strategies:** Treated with one or combination of the following: · Opioid substitution program e.g. Buprenorphine/naloxone, Methadone substitution, controlled release oxycodone, transferred to codeine phosphate · Proton Pump Inhibitor · Mental Health plan **Considerations:** Most patients had no previous history of substance use disorder (n=15). 26 out of 27 patients reported prolonged use (> 6 months) of supratherapeutic doses of OTC codeine–ibuprofen (mean duration 3.6 years). Most obtained these from multiple pharmacies.
Nielsen et al., 2010.	**Study Type:** Web-based survey using Lime Survey 2008 (800 participants) (cross sectional self-report questionnaire) and qualitative interviews (n=20). **Study Period:** March and July 2009 **Country/Setting:** Victoria, Australia (state and nation wide) **Cases/Studies involved:** 800 participants for the web-based survey and 20 participants for the interviews **Medication initiated to treat:** various pain conditions **Medication type:** Combination codeine analgesics available over-the-counter **Total daily codeine dose ingested (range):** not reported **Patient Characteristics/ History:** Dependent codeine users were more likely to report chronic pain, fair or poor health (rather than good to excellent) and significantly poorer mental health functioning. **Key findings around reported use:** 138 (17%) were classified using the Severity of Dependence Scale (SDS) as likely to meet criteria for codeine dependence. Eighty four percent of participants who were codeine dependent reported one or more opioid withdrawal symptoms on codeine cessation vs 18% of those that were not classified as dependent. **Considerations:** Compared to non-dependent codeine users, dependent codeine users: · were generally younger · had lower levels of education · were less likely to be in full time employment · were more likely to have sought treatment for alcohol or drug problems · were more likely to have a family history of alcohol or drug problems · were more likely to have exceeded the recommended dose on the last use occasion (65% vs 10%) – [14% of

Study	Summary
	those with a codeine dependency took at least 10 times the maximum recommended dose]. · were more likely to use codeine for non-medical purposes (67% vs 25%) · were more likely to use codeine daily (or most days) for > 1 year [87% of codeine dependent users used daily (or most days for > 1 year and 47% for > 3 years.
Dobbin et al., 2008.	**Study Type:** Case Studies **Study Period:** **Country/Setting:** Australia **Cases/Studies involved:** 77 individual case reports of dependence on OTC codeine and ibuprofen combinations were documented **Medication initiated to treat:** **Medication type:** ibuprofen + codeine **Daily codeine dose ingested:** Average of 50 tablets consumer per day for 2.5 years (6 cases reported persistent use for > 5 years) **Daily ibuprofen ingested (range):** 640 mg codeine phosphate and 10 grams of ibuprofen daily. **Patient Characteristics/ History:** Mental health disorders documented in 22 cases. **Reported Harms associated with overuse:** 1 death reported Life threatening or fatal: · Death (n=1) · Gastrointestinal haemorrhage or perforation (n=39) · Renal failure (n=7) · Potentially life threatening hypokalaemia (n=5) Other · Anaemia (n=15) **Management:** "Many" required treatment with methadone as part of an opioid substitution/detoxification program **Considerations:** Drug dependence on codeine, renal tubular acidosis, hypokalaemia also noted. Many patients needed life support in ICU, as well as emergency surgery.
Sproule et al.,1999 and Romach et al., 1999.	**Study Type:** Cross sectional self-report questionnaire of regular codeine users (> 3 times a week for > 6 months). Participants accessed via newspaper recruitment **Study Period:** Not stated, study published in 1999. **Country/Setting:** Canada **Cases/Studies involved:** 339 regular codeine users (using at least 3 days per week for 6 months or more)

Study	Summary
	Medication initiated to treat: Headache (41%), back pain (22%) or other pain e.g muscle or joint pain (25%). 19% reported using codeine to relax or reduce stress. **Medication type:** Paracetamol with 8 mg of codeine (23%), paracetamol with 15 mg of codeine (7%), paracetamol with 30 mg of codeine (37%), and paracetamol with 60 mg of codeine (3%). **Daily codeine dose ingested (range):** Average codeine doses of 179mg per day with 80% reporting using codeine on 5 or more days per week. **Patient Characteristics/ History:** In a sample of 333 of these participants, 64% had sought help for mental health problems, 56% consulted with a psychiatrist or psychologist. Among the 213 participants who sought help, the most common mental health problems were: depression (70%), generalized anxiety (55%) and panic attacks (24%). More subjects in the dependent group compared with those in the nondependent group sought medical help for a substance use disorder (27% vs. 6%, respectively; $p < 0.001$), especially alcohol (15% vs. 3%, respectively; $p < 0.001$) and stimulants (14% vs. 2%, respectively; $p < 0.001$). **Reported Harms:** One hundred twenty-four participants (37%) were codeine-dependent according to DSM-IV criteria, 15 (4%) met criteria for codeine abuse. The most commonly endorsed criteria in dependent users included development of tolerance (86%), withdrawal symptoms (82%), loss of control over use (81%), and difficulties cutting down or stopping (78%). **Considerations:** This study found that participants who were dependent t codeine combination medicines were more likely to report chronic pain and to have used codeine for its pleasurable effects. 54% of participants were using OTC codeine.
Roussin et al., 2013.	**Study Type:** Cross sectional Study. An anonymous survey was administered to patients purchasing combination codeine medicines from community pharmacies in France to illicit information about misuse, abuse and dependence **Study Period:** 15th February to 15th March 209 **Country/Setting:** Community pharmacies in France. "A total of 2,263 community pharmacies were solicited to participate, representing 10% of the pharmacies in each of the 22 administrative areas of the French metropolitan territory." **Cases/Studies/participants involved:** 915 questionnaires were offered in 145 pharmacies (6.4% of the solicited pharmacies). **Medication initiated to treat:** The most common reasons for persistent use included: Headache N=15 (migraine specified in nine cases), Musculoskeletal pain (n=6) six, origin not specified (n=8). **Medication type:** codeine combined with paracetamol **Total daily codeine dose ingested (range):** not clear **Key Findings around reported use:** 118 participants had used codeine combined with paracetamol. Misuse and

Study	Summary
	dependence to codeine analgesics was evident in 6.8% and 17.8% of the patients purchasing combination codeine medicines, respectively, (n = 118). 19.5% had used codeine analgesics daily for more than six months. Eleven of the 30 persistent users of codeine combined with paracetamol were dependent. Seven participants reported exceeding the maximum recommended dose (> 8 tablets/day). One patient reported using codeine daily for three years because of a codeine dependency. Another 2 patients were using concomitant combination codeine medicines. In 118 participants taking codeine combination: 8/118 = misused opioids 1/118 – abused codeine containing medicines 21/118 – were dependent 30 (25.4%) had daily consumption 23 had used codeine combined with paracetamol daily for more than six months, (mostly during a 2 to 5 year period [36.7%]). Among the 21 participants who had a dependency to codeine, adverse effects were described by nine patients. Adverse events were: Physical (n=4) [constipation, nausea, vertigo, and stomach-ache] Psychological (n=6) [depressive mood, anxiety, tiredness, inattention, nervousness, and feeling sleepy]. **Considerations:** A large majority of patients dependent on codeine (18 out of 21 cases) declared that persistence of pain led them to increase the doses. The two items of dependence of DSM-IV the most frequently retrieved were the intake of doses of codeine higher than intended (55.9%), and the persistent desire, or the unsuccessful efforts to control the consumption of codeine analgesics (37.3%). Note: misuse of codeine combined with paracetamol was determined when the drug was used in excessive doses (above maximal recommended doses of 120 mg/day for codeine phosphate), and when the use was regular (more than 10 days during the last month).
Robinson et al., 2010.	**Study Type:** Case Report Study **Study Period:** 2009-2010 (2 years) **Country/Setting:** New Zealand, Kenepuru Hospital Detoxification Unit **Cases/Studies involved:** 7 cases **Medication initiated to treat:** unclear **Medication type:** Nurofen Plus **Total daily codeine dose ingested (range):** Nurofen Plus 60-80/day, 48/day, 20/day, up to 72/day, 80/day, up to 120/day, 48/day. Mean dose: ~65 tablets/day; mean codeine dose = 832 mg/day

Study	Summary
	Daily ibuprofen ingested: Mean dose 13g ibuprofen / day **Patient Characteristics/ History:** 6 patients had prior or current history of alcohol dependence and 4 had mental health conditions (depression or anxiety and or psychosis). Average duration of use of codeine combination medicines was 22 months. **Reported Harms associated with overuse:** Life threatening: · gastric ulcer (4 patients), · gastrointestinal bleeding (3), · hepatotoxicity (1), · inflammatory bowel conditions (2). **Considerations:** Other long term complications possibly attributed to the NSAID included: gastric ulcer and haemorrhage, anaemia, gastrectomy, ileal resection, inflammatory bowel disease with gastric bypass and colectomy.
McAvoy et al., 2011.	**Study Type:** Cross-sectional study of clients presenting to a regional, open-access detoxification clinic covering the Greater Auckland area between 1 January and 31 March 2010. **Study Period:** Over a 12-week period at the beginning of 2010 **Country/Setting:** New Zealand (Greater Auckland Area) **Cases/Studies involved:** 15 cases **Medication initiated to treat:** Unclear **Medication type:** OTC codeine-ibuprofen average 49 per day for average 27 months **Total daily codeine dose ingested:** 627 mg /day **Total daily ibuprofen ingested (range):** 9.8 g **Patient Characteristics/ History:** 53% reported alcohol or other drug use, 93% had mental health conditions. Average use of codeine combination medicines was 27 months. **Reported Harms associated with overuse:** Life threatening: · GI Bleeding/dyspepsia (53%) · Renal Tubular acidosis (7%) · Hospitalisations (66%) **Management Strategies:** detoxification

Study	Summary
Ernest et al., 2010.	**Study Type:** Case Study report **Study Period:** - **Country/Setting:** Australia **Cases/Studies involved:** 2 cases **Medication initiated to treat:** **Medication type:** Nurofen Plus **Total daily codeine dose ingested (range):** 24 tabs/day for 3 days **Total daily ibuprofen ingested (range):** 4800 mg/day **Patient Characteristics/ History:** **Reported Harms associated with overuse:** Life Threatening: · Profound hypokalaemia · rhabdomyolysis presenting as severe quadriparesis. · ICU admission. **Management Strategies:** Admitted for detoxification
Lambert et al., 2005.	**Study Type:** Case Report Study **Study Period:** - **Country/Setting:** Manchester UK **Cases/Studies involved:** 1 case **Medication initiated to treat:** **Medication type:** codeine + ibuprofen **Total daily codeine dose ingested:** 597 mg codeine/day **Total daily ibuprofen ingested (range):** 28 g ibuprofen/day **Patient Characteristics/ History:** previous hospital admissions documented **Reported Harms associated with overuse:** Life-threatening: · Profound hypokalaemia · Renal tubular acidosis
Dyer et al., 2004.	**Study Type:** Case Report Study **Study Period:** - **Country/Setting:** Imperial College London

Study	Summary
	Cases/Studies involved: 1 case **Medication initiated to treat:** unclear **Medication type:** Nurofen Plus (ibuprofen + Codeine) **Total daily codeine dose ingested:** unclear – at least 24 tablets consumed in one day **Total daily ibuprofen ingested:** **Patient Characteristics/ History:** **Reported Harms associated with overuse:** Admitted to hospital initially with 5-day history of epigastric discomfort, vomiting, weakness and lethargy, hypokalaemia, hyperuriceamia. Life threatening: · Metabolic acidosis with respiratory compensation. · Hospital admission, · Psychotic episode, · Decreased level of consciousness that improved with naloxone (opioid antagonist) **Management Strategies:** naloxone to reverse opioid related respiratory depression
Dutch et al., 2008.	**Study Type:** Case Report Study **Study Period:** 6 month period **Country/Setting:** Australia **Cases/Studies involved:** 2 cases **Medication initiated to treat:** abdominal pain **Medication type:** Codeine + ibuprofen (Nurofen Plus) **Total daily dose ingested (range):** pack/day, and 16-24/day (204.8 mg/day to 307.2 mg/day) **Total daily ibuprofen ingested (range):** 3.2 g to 4.8 g/day **Patient Characteristics/ History:** **Reported Harms associated with overuse:** 24-hour history of epigastric pain, 12-hour history of severe progressively worsening epigastric pain Life threatening · Perforated gastric ulcer (n=2) · ICU admission (n=1)
Chetty et al., 2003.	**Study Type:** Case report Study **Study Period:** Not specified **Country/Setting:** Dudley UK

Study	Summary
	Cases/Studies involved: 1 case **Medication initiated to treat:** unclear **Medication type:** Nurofen Plus (codeine + Ibuprofen) 40-60 tablets/day **Total daily codeine dose ingested (range):** 512 mg - 786 mg / day **Total daily ibuprofen ingested (range):** 8 g to 12 g / day **Patient Characteristics/ History:** **Reported Harms associated with overuse:** patient presented to ED with a 2-day history of severe generalised muscle weakness. Life threatening: · Renal tubular acidosis (hypokalaemia, hyperchloremia, low serum bicarbonate and normal anion gap) **Management Strategies: IV serum potassium therapy to normalise potassium levels.** **Considerations:** prior hospital admissions, main complaint GI discomfort, evidence of hypokalaemia corrected with IV potassium.
Evans et al., 2010.	**Study Type:** Case report Study **Study Period:** Not specified **Country/Setting:** Otago, New Zealand **Cases/Studies involved:** 1 case **Medication initiated to treat:** back pain **Medication type:** Nurofen Plus (ibuprofen + codeine) **Total daily codeine dose ingested (range):** > 100 tablets /day (1280 mg /day) **Total daily ibuprofen ingested (range):** 20 g /day **Patient Characteristics/ History:** presented to ED with anaemia, exertional dyspnoea and lower leg oedema. Had a history of epigastric pain for one year that was worse on eating. **Reported Harms associated with overuse:** Life threatening: · Acute pyloric ulcer with oedema and stenosis · Post bulbar duodenitis with erosions **Management Strategies:** Balloon dilatation of pyloric stenosis later required. Counselling and treatment for addiction. Switched to codeine phosphate. **Considerations:** This is one of four cases presenting to the service in 2 years with significant GI pathology as a result of gross overuse of combination ibuprofen/codeine products.

Study	Summary
Ali et al., 2010.	**Study Type:** Case report Study **Study Period:** Not Specified **Country/Setting:** Australia **Cases/Studies involved:** 1 case **Medication initiated to treat:** **Medication type:** 60-80 Nurofen Plus tablets/day for many months **Total daily codeine dose ingested (range):** 768 mg to 1024 mg / day **Total daily ibuprofen ingested (range):** 12 g to 16 g per day **Patient Characteristics/ History:** **Reported Harms associated with overuse:** Life threatening: · Renal tubular acidosis · Hypokalaemic paraparesis
Blackstock et al., 2012.	**Study Type:** Case report Study **Study Period:** Not specified **Country/Setting:** Edinburgh UK **Cases/Studies involved:** 1 case **Medication initiated to treat: unclear** **Medication type:** Nurofen Plus (20-40 tablets /day for the preceding weeks) **Total daily codeine dose ingested (range):** 256 mg to 512 mg /day **Total daily ibuprofen ingested (range):** 4g to 8 g / day **Patient Characteristics/ History:** past medical history included gastric bypass surgery, depression, and previous alcohol abuse. Regular medications were fluoxetine, omeprazole, and cetirizine. **Reported Harms associated with overuse:** presented with ED with tachycardia, confusion, profound hypokalemia **Management Strategies:** IV potassium
Miles et al., 2010.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 1 case **Medication initiated to treat:** unclear **Medication type:** Nurofen Plus (ibuprofen + codeine)

Study	Summary
	Reported Harms associated with overuse: Life threatening: · Acute Tubular Necrosis · Renal Tubular Acidosis
Medani et al.,2010.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Dublin Ireland **Cases/Studies involved:** 1 case **Medication initiated to treat:** Toothache **Medication type:** Nurofen Plus (ibuprofen + codeine) 12 tablets daily for several years and had taken 24 tablets over a 36-h period in hospital prior to the onset of neurological symptoms **Total daily codeine dose ingested (range):** 307 mg of codeine **Total daily ibuprofen ingested (range):** 4800 mg of ibuprofen **Patient Characteristics/ History:** past history included a diagnosis of renal tubular acidosis (RTA), peptic ulcer disease (PUD) and depression. **Reported Harms associated with overuse:** presented with acute kidney failure, cough, anorexia and vomiting. Developed a severe headache with visual hallucinations, confusion and transient visual loss followed by two tonic clonic seizures. Life threatening: Anaemia – required transfusion Admitted unconscious to ICU **Management Strategies**: Short-term haemodialysis with ongoing potassium, calcium and magnesium replacement. Transfusion to correct anaemia.
Ferguson et al., 2010.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 5 **Medication initiated to treat: dental pain, post IUD insertion pain, Termination of pregnancy pain** **Medication type:** Nurofen Plus **Total daily codeine dose ingested (range):** 60, 50, 60, 40-60,75 tablets/day respectively (512 mg to 960 mg /day) **Total daily ibuprofen ingested (range):** 8 g to 15 g / day

Study	Summary
	Patient Characteristics/ History: One patient had a past history of sexual abuse, unplanned pregnancy with termination, commenced Nurofen plus to alleviate right sided abdominal pain. Use escalated to over 60 tablets a day. Had a history of mental health conditions. Medical and surgical interventions failed and patient died of complications associated with perforated ulcer. Another patient also had a previous history of physical abuse, use of Nurofen plus escalated to > 50 tablets/day. One patient had initially started Nurofen Plus for post IUD insertion pain, at recommended doses. However later (after 2 weeks) escalated the dose due to euphoric effects. One patient started Nurofen Plus for dental pain and continued use to treat anxiety. Last patient was admitted to hospital suffering from withdrawal. **Reported Harms associated with overuse:** Life threatening: · Increased muscle weakness (n=1) (unable to walk) · Death (n=1) (resulting from perforated ulcer) · Life threatening hypokalaemia (n=1) · Renal tubular acidosis (n=1) · Perforated ulcer (n=1) · Peritonitis (n=1) · ICU admission (n=1) · Acidotic (n=1) · Hypoalbuminemic (n=1) · Withdrawal (n=1) **Management strategies:** opioid substitution therapy e.g. buprenorphine 8mg daily. Gastroscopy (n=1)
Storor 2011.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 56 cases **Medication initiated to treat:** unclear **Medication type:** combination codeine + ibuprofen or paracetamol **Total daily codeine dose ingested (range): -**

Study	Summary
	Total daily ibuprofen ingested (range): - **Patient Characteristics/ History:** - **Reported Harms associated with overuse:** **Life threatening:** · Opioid dependence · Gastritis, · peptic ulcer, · scarring and strictures, · intestinal obstruction and · renal failure. · Hepatitis from paracetamol. **Management Strategies:** blood transfusions, opioid substitution therapy
Ng et al., 2011.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 2 **Medication initiated to treat:** **Medication type:** codeine-ibuprofen **Total daily codeine dose ingested (range):** up to 20 tabs/day, and 24 tabs/day (codeine-ibuprofen) 256 mg to 307.2 mg /day **Total daily ibuprofen ingested (range):** 4 g to 4.8 g / day **Patient Characteristics/ History:** One had a history including iron deficiency anaemia, chronic constipation, migraines, depression and IV drug use. She was admitted to ED with evolving paralysis and profound hypokalaemia, renal tubular acidosis, oesophageal erosions and gastric ulcer. Another patient had been taking 24 tabs/day of OTC codeine-ibuprofen for several years and presented with progressive muscle weakness and hypokalaemia. **Reported Harms associated with overuse:** **Life threatening:** · Profound hypokalaemia (n=2) · Renal tubular acidosis (n=1) · Oesophageal erosion (n=1) · Gastric ulcer (n=1)

Study	Summary
	· Opioid withdrawal (n=1) Other: · Iron deficiency anaemia (n=1) · Chronic constipation (n=1) · Muscle weakness (n=1)
Page et al., 2011.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** **Medication initiated to treat:** **Medication type:** codeine + ibuprofen 45-90, 25, 40 and unclear but years' duration. **Total daily codeine dose ingested (range):** (320 mg to 1152 mg / day) **Total daily ibuprofen ingested (range):** 5 g to 18 g / day **Patient Characteristics/ History:** - **Reported Harms associated with overuse:** Life threatening: · hypokalaemia (n=4) · renal tubular acidosis (n=4) · ICU admission (n=2). · Opioid addiction common
McDonough et al., 2011.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 32 cases **Medication initiated to treat: -** **Medication type:** codeine + ibuprofen up to 70 tablets / day **Total daily codeine dose ingested (range):** up to 896 mg /day **Total daily ibuprofen ingested (range):** up to 14 g / day **Patient Characteristics/ History:** All patients had a history of chronic pain and combination codeine-analgesic use **Reported Harms associated with overuse:** Life threatening:

Study	Summary
	· Gastric ulceration requiring surgery · Death (n=1) **Management Strategies:** Cases referred to one addiction medicine service. Opioid replacement therapy.
Mallett et al., 2011.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 1 case **Medication initiated to treat:** **Medication type:** OTC codeine-ibuprofen. Tablets /day: 45-90, 25, 40 **Total daily codeine dose ingested (range):** 320 mg to 1152 mg /day **Total daily ibuprofen ingested (range):** 5 g to 8 g /day **Patient Characteristics/ History:** 34-year-old woman in third trimester of pregnancy presented with renal tubular acidosis related to ibuprofen codeine abuse. Early delivery necessary. Renal tubular acidosis and hypokalaemia were mitigated, but some renal damage was sustained. **Reported Harms associated with overuse:** Life threatening: · Renal tubular acidosis · Evolving pre-eclampsia requiring early delivery of baby · Hypokalaemia
Karamatic et al., 2011.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 3 cases **Medication initiated to treat: -** **Medication type:** OTC codeine-ibuprofen. Tablets /day 10, 10-12, and 20 tablets a day, in two cases for 5 years or more. **Total daily codeine dose ingested (range):** 128 mg to 256 mg /day **Total daily ibuprofen ingested (range):** 2 g to 4 g day **Patient Characteristics/ History:** - **Reported Harms associated with overuse:** Life threatening:

Study	Summary
	· small bowel NSAID enteropathy (n=3), including diaphragm disease and small bowel ulceration, Other · iron deficiency anaemia (n=3) · hypoalbuminaemia (n=3)
Lake 2013.	**Study Type:** Case Report Study **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 1 case **Medication initiated to treat:** **Medication type:** codeine-ibuprofen **Total daily codeine dose ingested (range):** up to 90 tablets/day (up to 1152 mg / day) **Total daily ibuprofen ingested (range):** 18 g /day **Patient Characteristics/ History:** - **Reported Harms associated with overuse:** **Life threatening:** · Worsening abdominal pain, · bowel obstruction · Fibrous stricture. Other: · Delirium · multiple code black interventions - aggressive and violent behaviour **Management:** · Small bowel resection.
Pilgrim et al., 2013.	**Study Type:** Case report Study - Coroners' cases **Study Period:** Not specified **Country/Setting:** Australia **Cases/Studies involved:** 115 cases identified **Medication initiated to treat: -** **Medication type:** codeine + ibuprofen **Total daily codeine dose ingested (range):** **Total daily ibuprofen ingested (range):**

Study	Summary
	Patient Characteristics/ History: Dependency / addiction to codeine / ibuprofen **Reported Harms associated with overuse:** · Death (ultimately 115 cases) · Gastric erosion (n=7) · Gastric ulceration (n=3) · Chronic gastritis (n=1) · Renal necrosis and disease (n=2) · Hepatocyte necrosis (n=1). **Considerations:** Codeine and ibuprofen detected in post-mortem toxicology, or where codeine–ibuprofen analgesic misuse was described in coroners' findings.

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Appendix

Appendix Table 1: Search Strategy Summary

Studies	*Systematic review OR Systematic overview OR Systematic adj25 analysis OR Random$ controlled trial$ or RCT OR placebo-controlled adj25 trial*
Medicines	*(Codeine adj25 acetaminophen) OR (Codeine adj25 paracetamol) OR (Codeine adj25 ibuprofen) OR (Codeine adj25 aspirin) OR (Codeine adj25 acetylsalicylic acid) OR (codeine adj25 doxylamine*
Harms	*+ Adverse event OR adverse effect OR side effect OR dependency OR addiction* *+ Efficacy OR effectiveness OR effect*

Limit to: human studies

Appendix Table 2: Data Extraction Table

Study	Treatment Mean (SD)	N	Placebo Mean (SD)	N	Mean Difference	Clinically Significant
Heidrich 1985 – post orthopaedic surgery Paracetamol 300 mg + codeine 30 mg VAS 0-100						
3 h	54 (22.2)	40	65 (22.2)	40	-11.0 (-20.7, -1.3)	Yes
6 h	71 (22.2)	40	68 (22.2)	40	3.0 (-6.7, 12.7)	No
Median SD value used						
Ahlstrom 1985						
Paracetamol 1000 mg + codeine 60 mg (treatment A) PID 12h	15 (22.2)	44	46 (22.2)	85	-31.0 (-39.1, -22.9)	YES
Paracetamol 500 mg + codeine 30 mg (treatment B) PID 12h Median SD used	30 (22.2)	43	46 (22.2)	85	-16.0 (-24.1, -7.9)	YES
Giles 1986 (Median SD used) Ibuprofen 200 mg + codeine 15 mg 0-9 pain rating scale						
3h	2.2	36	3.5	35		
5h	2.4	36	2.5	35		
0-100						
3h	27.5 (22.2)	36	43.8 (22.2)	35	-16.3 (-26.6, -6.0)	Yes
5h	30 (22.2)	36	2.5 (22.2)	35	-1.3 (-11.6, 9.0)	No
Skoglund 1991 Codeine 60 mg paracetamol 1000 mg PI VAS 0-100						
3h	21 (22.2)	37	47 (22.2)	33	-26.0 (-36.4, -15.6)	Yes
6h Median SD value used	27 (22.2)	37	42 (22.2)	33	-15.0 (-25.4, -4.6)	Yes

Study	Treatment Mean (SD)	N	Placebo Mean (SD)	N	Mean Difference	Clinically Significant
Squires 1981 (dental surgery) (ASA 375mg + codeine 30mg + caffeine 30 mg) 9 point rating scale (0-8) PID 3h SD converted and used from baseline	1.2 15 (20)	30	1.9 23.8 (16.3)	26	-8.8 (-18.31, 0.71)	No
Quiding 1983 Single dose of paracetamol 1000 mg codeine 60 mg Mean PI (over 4 h)	44 (13.6)	16	51 (24.4)	10	-7.0 (-23.53, 9.53)	No
Gerschman 1984 Paracetamol 450 mg + codeine 9.75 mg (2 tabs 4 hourly) _end of treatment Mean Difference in Pain VAS 0-100	-45.4 (24.8)	14	-19.4 (27.0)	16	-26.0 (-44.54, -7.46)	Yes
Cater 1985 Ibuprofen 400 mg + codeine 30 mg 3h 0-8 0-100 6h 0-8 0-100 8 h 0-8 0-100 Median SD value used	 2.4 30 (22.2) 2.8 35 (22.2) 3.5 43.8 (22.2)	 46 46 46	 3.2 40 (22.2) 3.3 41.3 (22.2) 3.2 40 (22.2)	 47 47 47	 -10.00 (-19.0, -1.0) -6.3 (-15.3, 2.7) 3.80 (-5.2, 12.8)	 No No No
Frame (1986) Ibuprofen 200 mg + codeine 15 mg 9 point rating scale (Intervention C) 3h 0-8 0-100 (Intervention C) 5h 0-8	 2.43 30.38 (22.2) 2.28	 32	 3.42 42.75 (22.2) 2.56	 26	 -12.4 (-23.9, -0.9) -3.5 (-15.0, 8.0)	 Yes No

Study	Treatment Mean (SD)	N	Placebo Mean (SD)	N	Mean Difference	Clinically Significant
0-100 Frame Ibuprofen 400 mg + codeine 30 mg (Intervention D) 3 h 0-8 0-100 (Intervention D) 5 h 0-8 0-100 Frame – third molar Ibuprofen 800 mg + codeine 60 mg (Intervention E) 3h 0-8 0-100 (Intervention E) 5 h 0-8 0-100 Median SD value used	28.5 (22.2) 2.21 27.6 (22.2) 1.66 20.8 (22.2) 1.96 24.5 (22.2) 2.22 27.8 (22.2)	32 33 33 26 26	32 (22.2) 3.42 42.75 (22.2) 2.56 32 (22.2) 3.42 42.75 (22.2) 2.56 32 (22.2)	26 26 26 26 26	 -15.2 (-26.6, -3.8) -11.2 (-22.6, 0.2) -18.3 (-30.4, -6.2) -4.2 (-16.3, 7.9)	 Yes Yes Yes No
Quiding 1992 Median SD value used Ibuprofen + codeine Mean VAS 1-8 h after first dose 0-8 h after 6th dose	 25 (22.2) 10 (22.2)	 26 26	 26 (22.2) 29 (22.2)	 26 25	 -1.0 (-13.1, 11.1) -19.0 (-31.2, -6.8)	 No Yes