Australian Government
Department of Health
Therapeutic Goods Administration

Update of codeine safety and efficacy review

January 2015 to November 2016

Version 1.0, December 2016

TGA Health Safety Regulation

Contents

Introduction

The aim of this review is to ascertain whether any further evidence has accrued in relation to the safety and efficacy of low-dose codeine containing products for analgesia since the completion of the TGA commissioned review *Investigating the efficacy and safety of over-the-counter codeine containing combination analgesics for pain and codeine-based antitussives*.[1]

The commissioned review included database searches to the end of December 2015 - this update considers papers published in 2016 (up to early November) and any papers published in 2015 that are not mentioned in the commissioned review. The review does not include low-dose codeine containing cough and cold products.

Low-dose codeine containing products are those products which are available over the counter (OTC). In Australia, under the Poisons Standard November 2016, OTC analgesic products may contain 12 mg or less of codeine (as anhydrous codeine) per dosage unit.

This update is presented as a narrative review. It is not a systematic review and the quality of the included studies has not been evaluated.

The databases and search strategies used are provided at Attachment 1.

The report is in two sections addressing issues of incremental effectiveness in Part A and safety (including misuse) in Part B.

A. Incremental effectiveness of low-dose codeine in combination products used for analgesia

Three searches were undertaken (Cochrane Library, Medline and Embase). Three hundred and fourteen (314) articles published in 2015 and 2016 were identified. After removal of duplicates, the abstracts of 245 articles were reviewed. Of these, 237 were considered not relevant. An article was determined to be not relevant if it was: not a systematic review including codeine combination products; not a comparative study; did not include a codeine combination product in the study; did not compare a codeine combination product with the non-opiate medicine in the combination; did not differentiate codeine from other opioids in the study; or was a study protocol only.

Full text was obtained and reviewed for 9 articles (Almossawi and Wilkey 2015; Derry et al 2015, Graudins et al 2015 and 2016; March 2015, Mkontwana and Novikova 2015; Moore et al 2015; Stephens et al 2016; and Wiffen 2016). The assessment of these articles is detailed in Table A1 below, in alphabetical order of the surnames of the first authors. Graudins et al 2015 is a conference abstract which was assessed and included in Table A1 along with the subsequent full report of the study (Graudins et al 2016). The March (2015) paper is a summary of, and commentary on, a 2014 Cochrane Review by da Costa et al and the Wiffen paper is a brief summary of a 2014 Cochrane Review by Straube et al. As neither the da Costa nor the Straube article was included in the commissioned review, they have been assessed and included in Table A1. A previous search had identified one other relevant article (Aminoshariae et al 2016) which has also been included in Table A1.

[1] Shaheed CA, Maher CG, McLachlan A. (2016) Investigating the efficacy and safety of over-the-counter codeine containing combination analgesics for pain and codeine-based antitussives. Therapeutic Goods Administration commissioned report, 21 March 2016. https://www.tga.gov.au/alert/review-efficacy-and-safety-over-counter-codeine-combination-medicines

Any safety information in the articles was also reviewed and included in the table.

An article by Mattia et al (2015) was identified in both the effectiveness and safety searches. It was initially considered not relevant for this section and was reviewed for safety information in Part B. The paper, however, explores the pharmacological basis for increased analgesic efficacy of the codeine-paracetamol combination above the individual drugs and, as it contains only limited safety data, has been included in this section at Table A2. An article by Quiding et al (1982), which was referenced in the Mattia et al paper, has also been reviewed and included in Table A2.

Overall conclusion about evidence for incremental analgesic effectiveness of low-dose codeine in combination products

According to Mattia et al (2015) codeine and paracetamol act synergistically and clinical studies indicate that the analgesic effect of paracetamol and codeine combinations is superior to that obtained by the single components at standard codeine doses (i.e. ≥ 30mg per dose).

There are no new studies specifically examining whether low-dose codeine in combination with non-opiates, such as paracetamol and/or ibuprofen, provides incremental analgesic effectiveness above that provided by the non-opiate(s) alone. One recent systematic review (Moore et al 2015a) has identified that the lack of data on the efficacy of combination products with low doses of codeine represents a major gap in the evidence, which is of concern given their widespread use in the population and the need to balance benefit and possible harms.

This update does not add any significant new information on incremental effectiveness to that contained in the commissioned review.

No new safety issues were identified in this part of the review, however safety issues are further explored in Part B.

Table A1. Incremental effectiveness of low-dose codeine in combination products used for analgesia

Reference	Indication	Outcome measure	Interventions	Key Findings	Comment / Conclusion
Almossawi, O. and O. Wilkey (2015). "To evaluate the management of acute painful crisis, outcomes of safety and efficacy of codeine in children with sickle cell disease." *Archives of Disease in Childhood* **100**: A170.	Painful sickle cell crisis	Pain scores on and after admission	Analgesics administered at home and in hospital were documented as recorded in the case notes	Retrospective audit of case notes of all admissions with sickle cell disease Jan-Dec 2013. 54 patients with 91 admissions. Most patients (93%) received analgesics prior to admission. 20% of these received codeine. 37% received codeine during the admission. Patients receiving codeine had higher initial pain scores than those who did not. Codeine did not greatly improve the pain scores and 10% required step up analgesia. **Authors' conclusion:** clear analgesic benefits could not be demonstrated for codeine use with regards to the outcome of efficacy.	Conference abstract only. Presentation to the Royal College of Paediatrics and Child Health Annual Conference 28-30 April 2015, Birmingham UK. *Doses of codeine are not mentioned in abstract therefore it is not possible to assess whether this study is relevant to low-dose codeine containing products.* *There was no safety information in the abstract.*
Aminoshariae A, Kulid JC, Donaldson M et al. (2016). Evidence-based	Pain of endodontic origin Preoperative and	Various – not well described	Various drugs, doses and methods of	Systematic review of 27 cohort- randomized placebo-controlled trials.	This review did not specifically examine the issue of whether low-dose

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recommendations for analgesic efficacy to treat pain of endodontic origin: A systematic review of randomized controlled trials. *J Am Dent Assoc.* July 28.	postoperative		administration (oral, intramuscular or injection at periapical site)	Moderate evidence to support nonsteroidal anti-inflammatory drugs (NSAIDs) preoperatively or postoperatively to control pain of endodontic origin. When NSAIDs were not effective, a combination of NSAIDs with acetaminophen, tramadol, or an opioid appeared beneficial. **Authors' conclusion:** NSAIDs should be considered as the drugs of choice to alleviate or minimize pain of endodontic origin if there are no contra-indications for the patient to ingest an NSAID. In situations in which NSAIDs alone are not effective, the combination of an NSAID with acetaminophen or a centrally acting drug is recommended. Steroids appear effective in irreversible pulpitis.	codeine combinations are more effective than the non-opiate in the combination alone. The authors' recommendations for adding a centrally acting drug are based on studies that included morphine, tramadol, oxycodone, hydrocodone or high dose codeine (60mg) combinations. *This paper does not provide evidence for the incremental analgesic effectiveness of low-dose codeine combination products over the non-opiate in the combination.* *There was no safety information in the paper.*
da Costa BR, Nüesch E, Kasteler R, et al. (2014) Oral or transdermal opioids for	Osteoarthritis (OA) of knee or hip	Pain, function, adverse events, symptoms of opiod	Oral or transdermal opioids (other than	Cochrane systematic review	Pooling the data from the three codeine trials resulted in an SMD of –0.51 (-1.01, -

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osteoarthritis of the knee or hip. *Cochrane Database of Systematic Reviews* Issue 9. Art No: CD003115 and DOI: 10.1002/14651858.CD003115.pub4		dependence	tramadol) vs placebo or no intervention Opioids used in the included itrials were: · Oral: codeine (3 trials), hydro-morphone (1), morphine (2), oxymorphone (2), oxycodone (10), tapendatol (4) and · Transdermal: buprenorphine (4), fentanyl (1)	22 trials with 8275 participants Opioids were more beneficial in pain reduction than control interventions (SMD -0.28, 95% CI -0.35 to -0.20), which corresponds to a difference in pain scores of 0.7 cm on a 10-cm visual analogue scale (VAS) between opioids and placebo. Note: SMD = standardised mean difference; VAS = visual analogue scale **Authors' conclusions:** The small mean benefits of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI did not include the minimal clinically important difference of 0.37 SMDs, which corresponds to 0.9 cm on a 10-cm VAS.	0.01). Of the three codeine trials: · Peloso (2000) compared oral codeine 100mg, twice daily with placebo, twice daily. · Kjaersgaard-Andersen (1990) compared oral codeine 60mg plus paracetamol 1000mg, three times daily with paracetamol 1000mg, three times daily. The abstract of this study indicates that 83 patients were in the C+PC arm and 75 were in the P only arm. The abstract also states "… when evaluated after 7 days of treatment, the daily addition of codeine 180 mg to paracetamol 3 g significantly reduced the intensity of chronic pain due to osteoarthritis of the hip joint" • Quiding (1992) compared oral codeine 30mg plus ibuprofen 200mg with ibuprofen 200mg and placebo, each given 6 times in 24

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					hours, followed by 5 doses every four hours. The study abstract indicates that it was a double blind randomised crossover investigation of 26 patients with coxarthrosis and persistent pain. The analgesic efficacy of ibuprofen plus codeine was significantly superior to that of ibuprofen which was, in turn, superior to that of placebo. The Peloso study was placebo controlled and did not address the issue of incremental effectiveness. The Kjaersgaard-Andersen study looked at the incremental effectiveness of high dose (60mg) codeine and paracetamol. The Quiding study was included in the commissioned review. *Neither the da Costa Cochrane review, nor the individual studies mentioned above, provides evidence of*

Reference	Indication	Outcome measure	Interventions	Key Findings	Comment / Conclusion
					the incremental analgesic effectiveness of low-dose codeine combinations. *No new adverse events were identified.*
Derry S, Karlin SM, Moore RA. (2015) Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* DOI: 10.1002/14651858.CD010107.pub3	Acute postoperative pain in adults	Area under the pain relief versus time curve. Proportion of patients with at least 50% pain relief over six hours. RR and NNT. Proportion of participants requiring rescue medication and weighted mean of median time to use.	Single dose ibuprofen + codeine vs placebo or the same dose of ibuprofen alone Low (<10mg), medium (10-20mg) and high (>20mg) doses of codeine	Updated Cochrane review (original 2013) - date of search 1 December 2014. No new studies found. Six studies with 1342 participants In four studies (443 participants) using ibuprofen 400 mg plus codeine 25.6 mg to 60 mg (high dose codeine) 64% of participants had at least 50% maximum pain relief with the combination compared to 18% with placebo. The NNT was 2.2 (95% confidence interval 1.8 to 2.6) (high quality evidence). In three studies (204 participants) ibuprofen plus codeine (any dose) was better than the same dose of ibuprofen (69% versus 55%) but the result	The review sought evidence according to the dose of codeine used (low< 10mg, medium 10 to 20mg, and high >20mg). The authors found no data relating to low-dose codeine, limited data for medium dose codeine and most of the data related to high dose codeine (25.6 – 60mg codeine). One study compared ibuprofen 400mg + 20mg codeine with same dose of ibuprofen alone (McQuay 1989) and 2 studies compared ibuprofen 400mg + 60mg codeine with same dose of ibuprofen alone (Cooper 1982 and Sunshine 1987). For these three studies analysed together, ibuprofen plus codeine was better than ibuprofen alone, but the difference only just

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				was barely significant with a relative benefit of 1.3 (1.01 to 1.6) (moderate quality evidence). In two studies (159 participants) ibuprofen plus codeine appeared to be better than the same dose of codeine alone (69% versus 33%), but no analysis was done. There was no difference between the combination and placebo in the reporting of adverse events in these acute studies (moderate quality evidence). Authors' conclusions: The combin-ation of ibuprofen 400 mg plus codeine 25.6 mg to 60 mg demonstrates good analgesic efficacy. Very limited data suggest that the combination is better than the same dose of either drug alone, and that similar numbers of people experience adverse events with the combination as with placebo.	reached statistical significance (relative benefit 1.3 (1.01 to 1.6)) and the McQuay study (medium dose) had insufficient data to analyse on its own. The McQuay study was included in the commissioned review. This paper does not provide additional evidence for the incremental analgesia effectiveness of low-dose codeine in combination products. *The review does not provide detailed safety information.*

Reference	Indication	Outcome measure	Interventions	Key Findings	Comment / Conclusion
Graudins A, Meek R, Egerton-Warburton D, Parkinson J, Meyer A. (2015) A double blind, randomised controlled trial comparing single-dose paracetamol and ibuprofen with or without oxycodone or codeine for initial analgesia in adult emergency department patients with moderate pain from limb injury. *EMA - Emergency Medicine Australasia* 27: 9-10 DOI: 10.1111/17426723.12415	Initial analgesia in adult emergency department patients with moderate pain from limb injury	*Primary outcome:* change in visual analog pain-score rating (VAS) from baseline to 30 minutes (minimum clinically significant difference in pain (MCSD) from baseline expected to be >20mm). *Secondary outcomes:* change in VAS from baseline to 60 and 90 minutes post-analgesia; incidence of adverse events; rescue analgesia requirement; subjective pain assessments; and patient satisfaction	Single-dose of oral paracetamol + ibuprofen + thiamine (placebo-arm) vs paracetamol + ibuprofen + codeine or paracetamol + ibuprofen + oxycodone	DBRCT – three arm 182 adult patients from 18 to 75 years with isolated limb injury and moderate pain (VAS greater than 3 and less than/or equal to 7/10) At the primary outcome of 30 minutes, the reported median VAS reduction for placebo, codeine and oxycodone groups, 8, 13.5 and 14 mm, respectively, were lower than the expected MCSD and not significantly different between groups. Further equivalent reductions in pain severity were reported at 60 minutes for all groups (21, 29, 25 mm, respectively). At 90 minutes, the median reduction in VAS rating (15.5, 31, 30 mm, respectively) and the percentage in whom this exceeded 20 mm increased further for the codeine and oxycodone groups. Significantly more patients in the non-opioid group received rescue analgesia,	Conference abstract only. Abstract submitted to the 31st Annual Scientific Meeting of the Australasian College for Emergency Medicine 7-11 December 2014. *Ingredient doses are not mentioned in abstract therefore it is not possible to assess whether this study is relevant to low-dose codeine containing products.* *There are no details of the adverse events referred to in the abstract.*

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				mostly after the 90 minute assessment. Similar proportions in each group reported satisfaction with the analgesia received. Adverse events were significantly more frequent for those patients receiving oxycodone. **Authors' conclusion:** If moderate pain from limb injury is not expected to persist beyond an hour, then ibuprofen + paracetamol may provide sufficient initial analgesia. If moderate pain is expected to persist beyond an hour, then the combination of ibuprofen + paracetamol with an oral opioid may prolong analgesic effect.	
Graudins, A., et al. (2016). "A randomised controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury." *EMA - Emergency Medicine Australasia* 28: 666–672. DOI:	Adults with moderate pain from limb injury	*Primary outcome:* difference in mean visual analogue scale (VAS) change between groups at 30 minutes, with a limit of inferiority of 13. *Secondary outcomes:* mean change in VAS	All three drug regimens contained 6 tablets taken orally in a single dose 2 x paracetamol 500mg + 2 x ibuprofen 200mg + 2 x thiamine 100mg	DBRC non-inferiority trial – three arm 182 adult patients from 18 to 75 years with acute limb injury and moderate pain (VAS 4 -7 /10). Randomised to non-opioid (61), codeine (62) and	This is the same study reported in the conference abstract above. The dose of codeine used was 60mg. One of the 62 patients in the codeine arm experienced an unspecified adverse event.

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10.1111/1742-6723.12672		rating from baseline to 30 minutes for each group; need for additional analgesia; patient satisfaction; adverse events; pain ratings at 60 and 90 minutes for patients still in the ED.	(non-opioid-arm) vs 2 x paracetamol 500mg + 2 x ibuprofen 200mg + 2 x + codeine 30mg or 2 x paracetamol 500mg + 2 x ibuprofen 200mg + 2 x oxycodone 5mg	oxycodone (59). Differences (95% CI) between groups at 30 min were as follows: non-opioid versus codeine -2.6 (-8.8 to 3.6); non-opioid versus oxycodone -2.7 (-9.3 to 3.9); codeine versus oxycodone 0.1 (-6.6 to 6.4). Mean VAS reductions for non-opioid, codeine and oxycodone were -13.5, -16.1 and -16.2 mm, respectively. Satisfaction with analgesia was reported by 77.6% (64.7-87.5), 81.0% (67.2-89.0) and 73.6% (59.7-84.7) and adverse events by 3.3% (0.4-11.3), 1.6% (0.4-8.7) and 16.9% (8.4-29.0), respectively. Mean VAS reductions at 60 and 90 min were as follows: -23.2 and -18.7 mm for non-opioid; -30.7 and -33.3 mm for codeine; and -26.1 and -31.7 mm for oxycodone. **Authors' conclusions:** For a convenience sample of adult ED patients with moderate pain from limb	The authors noted this was an unexpectedly low rate as previous studies had reported epigastric discomfort, nausea and drowsiness in 16-20% of patients. *This paper does not provide evidence for the incremental analgesic effectiveness of low-dose codeine in combination products.*

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				injury, the present study found that the non-opioid, codeine and oxycodone groups were all non-inferior, at the primary outcome time of 30 min. This supports the initial use of a non-opioid combination for moderate pain from limb injury. Duration of adequate analgesic effect, different non-opioid drug and dosage regimens, and effectiveness in other conditions all warrant further investigation.	
March, L. (2015). "Review: In knee or hip OA, opioids reduce pain and improve function but increase adverse events." *Annals of Internal Medicine* **162**(4): JC8.	Osteoarthritis (OA) of knee or hip	Pain, function, adverse events, symptoms of opiod dependence	Oral or transdermal opioids (other than tramadol) vs placebo or no intervention	The author describes the review and the conclusion that compared with placebo opioids reduce pain and improve function in patients with knee or hip osteoarthritis, but increase adverse events. The author comments that, while this is a well conducted systematic review, and the results seem encouraging, the median duration of the trials (4 weeks) is short while OA is a chronic	This paper is a summary of and commentary on the da Costa et al (2014) Cochrane review, which is included above.

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				disease with fluctuating symptoms. The author advises against using opioids for routine long-term treatment.	
Mkontwana, N. and N. Novikova (2015) Oral analgesia for relieving post-caesarean pain. *Cochrane Database of Systematic Reviews* DOI: 10.1002/14651858.CD010450.pub2	Pain relief following caesarean section	*Primary outcomes:* adequate pain relief (reported) or >50% pain relief (measured); need for additional pain relief. *Secondary outcomes:* adverse events; days in hospital; readmission to hospital.	Opioid analgesics, non-opioid analgesics, combination drugs (all versus placebo/no treatment); opioids vs non opioids, opioids vs combinations and non-opioids vs combinations	Cochrane systematic review of RCTs 13 studies were included of which 8, involving 962 women, contributed data to the analysis. Authors considered only 4 of the 8 trials were of high quality. All trials were small. There was insufficient evidence to establish analgesic effects. There were more side effects, including nausea, vomiting and drowsiness, with the use of an opioid, non-opioid or combination painkillers in comparison with placebo or no treatment. **Authors' conclusion:** Due to limited data available no conclusions can be made regarding the safest and	One of the studies included in the Cochrane review (Bjune at al 1996) was a randomized double blind placebo controlled single oral dose study comparing the maximum single dose of paracetamol 1000mg (50 women) with a combination of submaximal dose of paracetamol 800 mg + codeine 60mg (50 women), and placebo (25 women). The abstract of this study indicates that, in patients with strong baseline pain, statistically highly significant differences were documented in efficacy variables between the active drugs and placebo and between the two active drugs. However, in patients with moderate baseline pain, no differences were found between the study drugs in any of the analgesic

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				most effective forms of oral analgesia for post-caesarean pain.	efficacy variables. *As this study used 60mg of codeine it does not provide evidence of incremental effectiveness of low-dose codeine.*
Moore, R. A., et al. (2015a) Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* DOI: 10.1002/14651858.CD010794.pub2	Acute pain (generally post-operative pain after third molar extraction)	Primary outcome = number of participants with at least 50% pain relief over four to six hours	Over-the-counter (OTC) analgesics vs placebo	Overview of 1 non-Cochrane and 10 Cochrane reviews involving 21 different analgesic products. The authors indicate that they found no data for OTC analgesics combining a low dose of codeine plus aspirin or paracetamol, despite conducting searches of PubMed for any other non-Cochrane reviews or randomised trials with low dose codeine combinations. Within a review of ibuprofen plus codeine (Derry et al 2015 – reviewed above), the authors found information on one trial of an OTC combination product but concluded that the amount of information was too small to make the estimate	The authors considered that "combination products with low doses of codeine represent the major gap in the evidence, but probably represent a large part of OTC analgesic sales. The lack of any information on the efficacy of low dose codeine combination therapies is a major gap in knowledge. While the doses of codeine may be small in individual doses, this possibly represents substantial population consumption, and we need to know that there is some benefit in terms of analgesic efficacy in individuals as a balance to possible harm to the community." *This paper identifies a lack of evidence for the analgesic efficacy of low-dose codeine*

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				of efficacy reliable.	*containing products.*
Stephens, G., et al. (2016) Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults. *Cochrane Database of Systematic Reviews* DOI: 10.1002/14651858.CD011889.pub2	Frequent episodic tension-type headache (TTH)	***Primary:*** Pain free at 2 hours using any standard method of pain assessment and without rescue medication ***Secondary:*** A range of measures	At least one arm paracetamol (various doses) alone or in combination with another active oral treatment vs at least one arm given placebo +/- active control	Cochrane review. 23 studies, 8079 participants For the outcome of being pain free at two hours the NNT for paracetamol 1000 mg compared with placebo was 22 (95% confidence interval (CI) 15 to 40) in eight studies (5890 participants; high quality evidence), with no significant difference from placebo at one hour. The NNT was 10 (7.9 to 14) for pain-free or mild pain at two hours in five studies (5238 participants; high quality evidence). The use of rescue medication was lower with paracetamol 1000 mg than with placebo, with an NNTp to prevent an event of 7.8 (6.0 to 11) in six studies (1856 participants; moderate quality evidence). On limited data, the	The review included two studies which used paracetamol/codeine combinations – one with paracetamol 600mg + codeine 60mg (Friedman 1987) and one with paracetamol 300mg + codeine 30mg (Gatoulis 2012). The reviewers noted that these studies did not provide sufficient data to do any analyses. The Friedman study is for high dose codeine; the Gatoulis study was included in the commissioned review. *This paper does not provide additional evidence for the incremental analgesic effectiveness of low-dose codeine in combination products.*

Reference	Indication	Outcome measure	Interventions	Key Findings	Comment / Conclusion
				efficacy of paracetamol 500 mg to 650 mg was not superior to placebo, and paracetamol 1000 mg was not different from either ketoprofen 25 mg or ibuprofen 400 mg (low quality evidence). Adverse events were not different between paracetamol 1000 mg and placebo (RR 1.1 (0.94 to 1.3); 5605 participants; 11 studies; high quality evidence). Studies reported no serious adverse events.	
Straube C, Derry S, Jackson KC, Wiffen PJ, Bell RF, Strassels S, Straube S. (2014) Codeine, alone and with paracetamol (acetaminophen), for cancer pain. *Cochrane Database of Systematic Reviews* Issue 9. Art. No.: CD006601. DOI:10.1002/14651858.CD006601.pub4.	Cancer pain due to diverse types of malignancy in adults (no studies in children identified)	Various measures of efficacy and adverse events Only two studies reported the preferred responder outcome of "participants with at least 50% reduction in pain" and two reported "participants with no worse than mild pain	Single or multiple doses of codeine with and without paracetamol compared to placebo or alternative actives Any formulation, dosage regimen and route of administration.	Cochrane review of RDBCTs 15 studies with 721 adult participants with cancer pain. Most studies used codeine at doses of 30mg to 120mg The authors noted that • all but one of the studies demonstrated superiority of codeine over placebo in at least one outcome measure	None of the included studies compared codeine containing combinations with the non-opiate in the combination. One included study (Chen 2003) was a three arm crossover study in 18 people with moderate to severe cancer pain. The study compared single dose codeine 30mg (C), placebo (P) and codeine 13mg + ibuprofen 200mg (CI). Partial or complete pain

Reference	Indication	Outcome measure	Interventions	Key Findings	Comment / Conclusion
				• there were insufficient data for any pooled analysis • adverse event reporting was poor • the literature was disappointing - studies were small, of short duration, and most had significant shortcomings in reporting. **Authors' conclusion:** The available evidence indicates that codeine is more effective against cancer pain than placebo, but with increased risk of nausea, vomiting, and constipation.	relief was achieved in 18/18 with C and 17/18 with CI. Time to showing effect was less with CI than with C (48mins vs 60mins) and was main-tained for longer (6.8 hours vs 5.4 hours). While the Chen study gives some limited low quality evidence for analgesic effectiveness of low dose codeine in combination with ibuprofen, it did not include an ibuprofen only arm and the incremental analgesic effectiveness of the codeine in this combination could not be assessed. Reported codeine adverse events across the studies included nausea, vomiting, constipation, diarrhoea, dyspepsia anorexia, somnolence, dizziness, headache, dry mouth, asthenia, sweating, pruritus, hallucinations. *Neither the Straube Cochrane review nor the Chen study provides additional evidence for the incremental effectiveness of low-dose*

Reference	Indication	Outcome measure	Interventions	Key Findings	Comment / Conclusion
					codeine in combination products used for analgesia. No new safety issues were identified.
Wiffen, P. J. (2015). "Systematic reviews published in the October 2014 issue of the Cochrane library." *Journal of Pain and Palliative Care Pharmacotherapy* **29**(1): 72-74.	Cancer pain	Various measures of efficacy and adverse events	Single or multiple doses of codeine with and without paracetamol	Cochrane review of RDBCTs 15 studies with 721 adult participants with cancer pain. Most studies used codeine at doses of 30mg to 120mg. The author largely cites the Straube paper (above).	This is brief summary of a 2014 Cochrane review by Straube et al, which has been reviewed and included above. *The dosages used in the studies included in the review were ≥30mg and therefore this summary article provides no evidence for the incremental effectiveness of low-dose codeine in combination products used for analgesia.*

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Quiding H, Grimstad J, Rusten K, Stubhaug A, Bremnes J, Breivik H. Ibuprofen plus codeine, ibuprofen, and placebo in a single- and multidose cross-over comparison for coxarthrosis pain. *Pain* 1992; 50(3):303-7.

Sunshine A et al. Analgesic efficacy of two ibuprofen-codeine combinations for the treatment of postepisiotomy and postoperative pain. *Clinical Pharmacology and Therapeutics* 1987;42(4):374-80.

Table A2. Additional articles relevant to the incremental effectiveness of low-dose codeine in combination products used for analgesia

Reference	Summary	Evaluator comment / conclusion
Mattia, C. and F. Coluzzi (2015). "A look inside the association codeine-paracetamol: clinical pharmacology supports analgesic efficacy." *European Review for Medical & Pharmacological Sciences* **19**(3): 507-516.	This paper explores the pharmacological basis for analgesic efficacy of the codeine-paracetamol combination. The authors report that recent findings have shown that paracetamol may act through cerebral cyclo-oxygenase, descending opioidergic inhibitory pathways, serotonin pathway, and the endocannabinoid system; while codeine activity seems to be related not only to its conversion to morphine, but also by itself and through its metabolites, such as norcodeine and codeine-6-glucuronide. The authors describe the pharmacological basis for codeine and paracetamol to work synergistically and cite clinical studies to support that the analgesic effect is superior to that obtained by the single components. One cited reference is a 2009 Cochrane review undertaken by Toms et al. All fourteen studies (926 participants) included in the comparison of paracetamol + codeine with the same dose of paracetamol alone used 60mg of codeine in the combination. The review found that addition of codeine increased the proportion of participants achieving at least 50% pain relief over four-to-six hours by 10 to 15%, increased time to use of rescue medication by about one hour, and reduced proportion of participants needing rescue medication by about 15% (NNT to prevent remedication 6.9 (4.2 to 19). Adverse events were mainly mild to moderate in severity and incidence did not differ between groups.	The paper is not a clinical study nor a systematic review of the evidence for effectiveness of the paracetamol-codeine combination. The papers cited in the summary column are listed below. The cited Toms paper was not relevant to the efficacy of low dose codeine combination products. *Although none of the cited references has been included in the commissioned review, this paper provides no information which would change the conclusions of the commissioned review on the efficacy and safety of low-dose codeine combinations.*

Reference	Summary	Evaluator comment / conclusion
	The authors also cited · Quiding et al (1982) as indicating that the optimum single dose of codeine in combination with paracetamol is stated to be 30mg. · Casale R et al (2012) as recommending the the use of 500/30mg paracetamol-codeine combination [for the treatment of osteoarthritis in patients awaiting a total joint replacement] "as this treatment has been shown to be particularly efficacious when compared to paracetamol alone". · the Italian Intersociety Recommendations on Pain Management (Savoia et al 2014), which suggest paracetamol-codeine 500/30mg for moderate pain. The authors conclude: · recent warnings about the risk of its metabolism related to CYP450 and its genetic variability in general population should be mainly considered when the association is used in paediatric patients undergoing tonsillectomy and/or adenoidectomy procedures for obstructive sleep apnoea syndrome (OSAS) · in adults, the association codeine/paracetamol has been shown to be effective and safe in different settings: acute pain, trauma patients, and chronic nociceptive pain.	
Quiding H et al. (1982) "Paracetamol plus supplementary doses of codeine. An analgesic study of repeated doses". *Eur J Clin Pharmacol* 23: 315-319.	**Type of study:** Double blind, randomised multicentre trial of pain management after removal of an impacted wisdom tooth **Number of participants:** 360	This study was not included in the commissioned review. *This study provides some support for the incremental effectiveness of 20mg of codeine added to 500mg of paracetamol in reducing pain after removal of*

Reference	Summary	Evaluator comment / conclusion
	Interventions: paracetamol (500mg) alone vs the same dose of paracetamol plus varying doses of codeine (20mg, 30mg or 40mg). **Outcome measures:** pain intensity assessed by the patient on a visual analogue scale (VAS) hourly on the day of surgery **Analysis:** repeated-dose evaluation **Results:** There was a statistically significant dose-response relationship, with some increased analgesic efficacy (% pain reduction and mean duration of effect) with the addition of 20mg of codeine and increasing efficacy up to the 40mg dose. Higher doses were associated with more side effects, none of which were serious. **Authors' conclusion:** the optimum dosage in clinical practice is 500mg paracetamol with 30mg of codeine taken as a single dose or a double dose, up to four times a day.	*impacted wisdom teeth. The authors concluded, however, that optimum pain relief was achieved with the addition of 30mg of codeine.*

References cited by Mattia et al

Casale R et al. Efficacy of a comprehensive rehabilitation programme combined with pharmacological treatment in reducing pain in a group of OA patients on a waiting list for total joint replacement. *Clin Exp Rheumatol* 2012; 30: 233-239.

Quiding H et al. Paracetamol plus supplementary doses of codeine. An analgesic study of repeated doses. *Eur J Clin Pharmacol* 1982; 23: 315-319.)

Savoia G. Italian Intersociety Recommendations (SIAARTI, SIMEU, SIS 118, AISD, SIARED, SICUT, IRC) on Pain Management in the Emergency Setting. *Minerva Anestesiol* 2014 May 22. [Epub ahead of print]

Toms L, et al. Single dose oral paracetamol (acetaminophen) with codeine for post-operative pain in adults. *Cochrane Database Syst Rev* 2009; (1):CD001547.

B. Harms from low-dose codeine combination medicines

Two searches each were undertaken in the Cochrane Library, Medline and in Embase. The first search in each database included specific terms for addiction or misuse while the second search in each used more general safety terms (see Attachment 1). The results of the searches have been combined for discussion in this section of the update.

The search for articles published in 2015-2016 using specific terms for addiction or misuse identified a total of 61 articles while the searches on general safety terms identified a total of 301 articles. After eliminating duplicates, the total was 242 articles.

After reading the abstracts, 142 articles were excluded from further consideration as they did not include codeine or codeine safety or had already been reviewed in Part A. Full articles were obtained for 93 papers; for 7 articles only abstracts were available for consideration. After review of the articles and abstracts a further 24 were excluded. This resulted in 74 full articles and 2 abstracts being included in this review. They include Cochrane systematic reviews, clinical trials, other studies, guidance, commentaries, and case reports.

No clinical safety studies or systematic reviews of the safety of low-dose codeine combination medicines were identified.

The articles included in this review cover a number of themes and issues. These have been grouped and presented in separate tables below - Tables B1 (uncategorised), B2 (misuse), B3 (case histories and pharmacovigilance), B4 (alternatives to codeine in adults and children), B5 (clinical guidance on pain management), B6 (medication overuse headache) and B7 (pharmacogenomics).

Safety information in uncategorised articles (Table B1)

Thirteen articles are included in this category (Anonymous 2016; Foley et al 2015; Gisev et al 2016; Haynes et al 2015; Ilgen et al 2016; John et al 2016; MacKinnon 2016; Moore et al 2015(b); Roxburgh et al 2015; Steinman et al 2015; Veal et al 2015; Voepel-Lewis et al 2015; Wu et al 2015). The articles cover a number of different aspects of codeine use but do not provide new information about the safety of low-dose codeine-containing combination medicines.

The article by Anonymous (2016) is a literature review which examines the question of whether 'weak' opioids (codeine, dihydrocodeine or tramadol) are more effective than paracetamol or NSAIDS for nociceptive pain and whether they are better tolerated than morphine. The authors do not consider OTC codeine specifically. They note there is some evidence that 60mg of codeine added to paracetamol is more effective for postoperative pain then paracetamol alone, but codeine/paracetamol is not more effective than ibuprofen. Weak opioids, especially at higher doses, share the adverse effects of morphine. The authors consider that, owing to the variability of metabolism and of efficacy and the potential for adverse effects and drug interactions, the weak opioids require at least as much vigilance as morphine.

The Foley et al (2015) article describes the regulation of codeine across each of the 28 EU states and finds that there is considerable variability in the regimes under which codeine is sold. Fifteen countries do not allow codeine containing products to be sold OTC. Where codeine is allowed to be sold OTC, doses per tablet vary from 8mg to 30mg. There are variable levels of pharmacy supervision, pack sizes, limits on advertising, pack warnings, and availability of products for self-selection. The effect of the different regimes in minimising harm from codeine has not been studied.

The Gisev et al (2016) article finds codeine use (prescription and OTC) is common in Australia with clear distinctions in the geographic and sociodemographic characteristics associated with the use of each.

The Haynes et al (2015) article documents a drop in hydrocodone exposures and a large increase in codeine exposures following the rescheduling of hydrocodone to a more restrictive level than codeine in the United States (US). The schedule change requires the use of special prescription pads in some US states. The relevance of the article's findings for the decision on upscheduling low-dose codeine in Australia is uncertain.

The Ilgen et al (2016) paper identifies a greater risk of suicide among veterans receiving higher doses of opioids for chronic pain and recommends that high opioid doses be viewed as a marker of elevated suicide risk.

John et al (2016) report that, of 1827 non-accidental non-fatal poisonings requiring ambulance attendance during a 3 month period in Wales, 266 (15%) included codeine of which half also involved alcohol.

MacKinnon (2016) is a Canadian pharmacist who argues that all codeine products should be prescription except in limited circumstances. He refers to the recent decision by the Manitoba College of Pharmacists (i.e. not a regulator) to make codeine prescription only with some identified exceptions. Pharmacists are able to write prescriptions in Manitoba and the relevance of this decision for Australia is unclear.

The Moore et al (2015b) article is an overview of Cochrane reviews of adverse event (AE) rates associated with single-dose oral analgesics, compared with placebo, for the treatment of acute post-operative pain in adults. Most of the codeine containing products used in studies covered by the overview contained doses of codeine ≥ 30mg. The AE rates were higher for combinations containing codeine than for placebo, but the reviews included in this overview typically did not report on specific AEs.

The Roxburgh (2015) article is a descriptive analysis of trends in codeine related mortality in Australia using data from the National Coronial Information System. It provides evidence of increasing rates of fatal codeine-related overdoses, largely accidental but some intentional, mainly in the context of multiple drug toxicity. Among the cases where data were available OTC products were implicated in a significant minority (40%). The authors speculate that "a potential driver [of the increased rate of codeine-related deaths] may have been the introduction in Australia of OTC products containing larger amounts of codeine, including codeine combined with ibuprofen".

Steinman et al (2015) and Veal et al (2015) examine opioid use among older people in the US and Australia respectively. The authors do not specifically look at the safety of low-dose codeine containing combinations, but report on the harms of opioids in general. The additional potential codeine AEs known to occur in the older adult population include falls and fractures, confusion, and drug interactions.

Voepel-Lewis et al (2015) found that most children receive less than half their prescribed opioid doses after elective hospital procedures and estimate that this leaves a considerable amount of unused opioids in the homes of children. The authors indicate that better alignment of opioid prescriptions with the pain needs of patients and education about safe disposal is warranted to appropriately manage pain while limiting the amounts of unused opioids available for accidental overdose, diversion, and misuse.

The paper by Wu et al (2015) examines analgesic use by patients with chronic kidney disease (CKD). The study found that 10 of the 308 participants in the study (3.2%) reported taking prescription or OTC purchased codeine, of which 2 (0.6% of total participants) reported taking an inappropriate dose for the level of CKD.

Safety information in misuse articles (Table B2)

Five articles are considered in this category (Dada et al 2015; Ellen Tsay et al 2015; James 2016; Miech et al 2015; Van Hout and Norman 2016).

The Van Hout and Norman (2016) article is a policy commentary on the misuse of non-prescription codeine. The authors note that codeine is distinct from other opioids in being readily available and that this can lead to public perception the drug is safe and unawareness of the potential harms. The authors refer to the need to balance access and convenience with patient safety and note that evidence about patient safety needs to be taken into account when making decisions about scheduling. The authors discuss the difficulties for pharmacists in community pharmacies to recognise and manage misuse and make a number of suggestions for supporting an expanded role for pharmacists as "custodians of OTC codeine containing products". The health consequences associated with OTC codeine misuse are discussed.

The article by James (2016) provides guidance to health professionals, especially general practitioners, about recognising and managing dependence and drug-seeking behaviour. James notes that both prescription and OTC opioids can be misused and specifically refers to the potential harms from overusing OTC ibuprofen/ codeine combinations. No new safety information is identified in these articles.

The other three articles examine aspects of misuse in other countries and the relevance of the findings for Australia is uncertain. The Dada et al (2015) study found that codeine was a primary substance of abuse in less than 1% of admissions to drug use treatment centres in South Africa and a secondary drug of misuse in a further 1.5%. Misuse included low-dose codeine analgesic combinations with paracetamol, plus or minus caffeine, and cough syrups. The level of codeine dependency is considered likely to be higher in the community as many people who misuse or a dependent on codeine consult with general practitioners or other health professionals rather than attending a substance abuse centre.

The Ellen Tsay et al (2015) article on a study of promethazine abuse and misuse in the US notes that promethazine is frequently taken with codeine, either in a co-formulation or separately. This combination is used to prevent nausea, to supplement opioid-induced euphoria (so lower dose of opioid can be used) or to self-medicate drug withdrawal. There has been a rise among teenagers and college aged adults in the US in the misuse of promethazine/codeine cough syrups mixed with soft drinks and candy to induce euphoria.

The Miech et al (2015) study found that use of legitimately prescribed opioids (including codeine) by individuals in the 12th grade is associated with a 33% increase in the risk of future opioid misuse after high school.

Safety information in case history and pharmacovigilance articles (Table B3)

Eight articles are included in this category: three are pharmacovigilance papers and five are case reports of adverse events (AEs) associated with codeine.

The pharmacovigilance articles describe: an active collection of adverse drug reactions (ADRs) in elderly patients in Italy (Carnovale et al 2016); a study of epigastric pain and liver dysfunction in cholecystectomised patients (Lenti et al 2015); and a study using disproportionality analysis (DPA) with the proportional reporting ratio (PRR) to identify signals for different psychoactive drugs in a drug abuse and dependence database (Pauly et al 2015).

The study by Caarnovale et al (2016) found, of 1073 case reports of ADRs in patients over age 65 years in Lombardy, 11 were associated with paracetamol-codeine combinations. Reported ADRs include hallucination, urinary incontinence, nightmare and confusion or confusional. The paper

provides insufficient information to determine whether these ADRs are related to the use of low-dose codeine.

The Lenti et al (2015) study identifies a possible increased risk of epigastric pain and liver toxicity with the use of acetaminophen-codeine by patients who have had their gallbladder removed. Abdominal pain is a known association with codeine and morphine (see discussion of Tabner and Johnson 2015 case reports below), but further investigation is needed to confirm that the risk is higher in such patients and to determine whether the increased risk is related to the use of low-dose codeine.

The Pauly et al (2015) study identified a signal of abuse and dependence associated with codeine but the paper provides no further analysis or investigation of the signal and no new information on the safety of low-dose codeine-containing combinations.

Among the case report articles are three which describe skin reactions associated with codeine. One (Ansar et al 2015) is a case report of urticaria, a known AE with codeine. Two articles report rare skin reactions to codeine: a case of acute generalised exanthematous pustulosis (AGEP) (Chaabane et al 2016) and a case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), also known as baboon syndrome (Erfan et al 2015). These need further investigation to determine whether they are safety signals that warrant any action and whether low-dose codeine combinations are implicated.

One case report (Kean et al 2016) describes the successful management of a patient who had developed dependency on OTC and illicit codeine following initial treatment with prescription codeine for acute back pain. No other safety information about codeine is included in this article.

The final case report (Tabner and Johnson 2015) describes 2 cases of acute abdominal pain associated with the use of codeine in standard doses (30mg and 60mg), which recovered after the use of naloxone. Abdominal pain is a known effect of morphine and codeine mediated through spasm of the sphincter of Oddi.

Safety information in articles on alternatives to codeine in children and adults (Table B4)

Ten articles are included in this category. Eight are reports of studies which compare the efficacy and/or adverse effects of a number of different analgesics with codeine combination products for a range of types of pain (Bandieri et al 2016; Chang et al 2015; D'Souza et al 2015; Friedrichsdorf et al 2015; Outhoff et al 2015; Pfaff et al 2016; Polat et al 2015; Stewart 2015). One (Conaghan et al 2016) is a survey of patient satisfaction with a codeine combination compared with other analgesics, while the final article (Poonai et al 2015) provides advice on the management of fracture pain in children and the methodological issues associated with designing high quality analgesic trials in children.

The studies are described in Table B4. Adverse events were not well recorded across the studies and codeine dosages were unspecified, unclear or in the prescription range. The Outhoff study used a low-dose codeine (8mg)/paracetamol (320mg) combination, which was effective in relieving pain after third molar extraction. The combination, however, also included meprobamate, an anxiolytic which is no longer available in Australia and it is not clear how much this contributed to the analgesic effect. Where adverse events to codeine were recorded they were known effects such as nausea, vomiting, constipation, dizziness, somnolence, oversedation, itching, sweating and headache.

Four of the studies in this group examine the issue of pain control associated with tonsillectomy (Friedrichsdorf et al, D'Souza et al, Pfaff et al, Stewart). Three of these studies (D'Souza et al, Pfaff et al, Stewart) specifically examined the issue of post-tonsillectomy haemorrhage (PTH). The D'Souza et al study found a statistically significant increase in PTH in the group taking

ibuprofen/acetaminophen compared with the group taking an opioid (codeine or hydrocodone)/acetaminophen combination. PTH was not found to be statistically significantly higher in the NSAID group than in the codeine group in both the Pfaff and Stewart articles.

None of the studies in this group provides new information about the safety of low-dose codeine.

Safety information in articles on clinical guidance on pain management (Table B5)

Twenty-eight articles are included in this category (Blinderman and Billings 2015; Cohen and Sommer 2016; Cote and Wilson 2016; Ericsson et al 2015; Fawcett and Baldini 2015; Gowan and Roller 2016; Humphries and Kessler 2015; Lundeberg 2015; Koneti and Jones 2016; Malec and Shega 2015; Mallya et al 2016; Marras and Leali 2016; Mifsud and Bonanno 2015; Mishra et al 2015; Naples et al 2016; Pai et al 2015; Palmer 2016; Rodriguez et al 2016; Ruest and Anderson 2016; Schug and Chandrasena 2015; Ternullo and DiAntonio 2015; van Rensburg 2016; Walker 2015; Wehrer 2015; Welker and Mycyk 2016; Wells et al 2016; Witkop et al 2016; Zaidan and Lent 2016).

These articles were reviewed for any references to codeine safety as part of the authors' advice on pain management across different population groups and for different indications. It was found, however, that references to codeine in these articles generally do not have specific information about OTC codeine and no new safety information about low-dose codeine combination medicines was identified.

Issues mentioned among these articles include:

- the WHO analgesic ladder[2], which was originally intended for use in the management of cancer pain, but which has been applied in a range of pain conditions. This is a three-step approach starting with the 'mild' or step 1 analgesics, such as paracetamol, and nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and celecoxib; then moving to the 'moderate' or step 2 analgesics, which are weaker opioids such as codeine; and then using 'strong' or step 3 analgesics, which are strong opioids such as morphine, fentanyl, or oxycodone. Various adjuvant medicines may be added at each step.
- the WHO decision in 2012 to exclude codeine from its recommendations for management of pain in children. The WHO guidelines for managing persistent pain in children are now a 2 step ladder[3], in which, when step 1 analgesics are insufficient, low doses of strong opioids such as morphine are used (with or without adjuvant medicines).
  - some articles suggest a move to a 2-step ladder for all patients
- the variability in the metabolism of codeine to morphine via the CYP2D6 pathway and the risks of either lack of effectiveness in slow metabolisers or increased morphine levels in rapid and ultrarapid metabolisers
- the decisions by the USFDA and other regulators to contraindicate the use of codeine for pain relief in children and in adolescents undergoing adeno-tonsillectomy

Some issues of codeine use for pain management in specific populations include:

- in the elderly – additional safety issues are:

[2] WHO's cancer pain ladder for adults - http://www.who.int/cancer/palliative/painladder/en/
[3] Who guidelines on the pharmacological treatment of persisting pain in children with medical illnesses - http://apps.who.int/iris/bitstream/10665/44540/1/9789241548120_Guidelines.pdf

- drug interactions with drugs that block the CYP2D6 conversion of codeine (eg SSRIs paroxetine and fluoxetine and antihistamine diphenhydramine)
- decreased renal function resulting in decreased excretion of some neurotoxic opioid-related metabolites causing adverse effects such as myoclonus
- increased risk of falls and fractures
- medication errors (because of multiple prescribers or incorrect medicine/dose due to cognitive or eyesight decline)

· in the paediatric population:

- avoid codeine (alone or in combination) and use alternative treatment options

· in palliative care:

- ceiling effect of some weak opioids where increasing the dose does not improve analgesia but increases the risk of side effects

· in pregnancy and lactation:

- potential risks to the foetus from codeine include those for all opioids:
  - § physical dependence and postpartum withdrawal, retardation of growth, and neonatal respiratory depression with high doses
- risks to the neonate during breast feeding include sedation, hypopnea/apnoea and constipation

· in liver failure, cirrhosis, transplantation

- codeine is not recommended due to a lack of clinical studies investigating the metabolism of codeine in patients with liver dysfunction

· haemophilia (acute episodes and chronic arthritis)

- there is little data to guide providers in pain management for people with haemophilia
- opioids can be used, the main safety concern being the potential for addiction and abuse

Safety information in articles on medication overuse headache (MOH) (Table B6)

Five articles referring to the diagnosis or management of medication overuse headache (MOH) are included in this update (Chiang et al 2015; Dong et al, 2015; O'Sullivan et al 2016; Silberstein 2016; and Westergaard et al 2015). The International Headache Society (IHS), in the 3rd edition of the International Classification of Headache Disorders (ICHD-3 Beta)[4] defines MOH as headache occurring on ≥ 15 days/month, developing as a consequence of regular overuse of acute or symptomatic headache medication (on ≥ 10 or ≥ 15 days/month, depending on the medication) for ≥ 3 months. MOH can develop with any analgesic and codeine is a recognised contributor to the condition. Chiang et al (2015) comment that longitudinal studies have suggested that medications containing barbiturates and opioids are associated with the highest risk of developing MOH, while triptans and NSAIDs are associated with lower risk. They also

[4] 8. Headache attributed to a substance or its withdrawal - https://www.ichd-3.org/8-headache-attributed-to-a-substance-or-its-withdrawal/8-2-medication-overuse-headache-moh/

state that patients with opioid overuse tended to have a less favourable outcome with regard to headache frequency, relapse rate, and pain improvement compared to patients overusing other kinds of medications. Apart from the link between codeine and MOH, none of these articles provides safety information specifically for OTC codeine-containing combinations.

Safety information in pharmacogenomics articles (Table B7)

Seven articles are considered in the pharmacogenomics group (Collins et al 2016; Gammal et al 2016; Haufroid and Hantson 2015, Hudak 2016; Nicholson and Formea 2015; Ting and Schug 2016; Turner and Pirmohamed 2015). Pharmacogenomics is the study of inherited genetic traits that result in individual responses to drugs (Ting and Schug). All the articles refer to the variable metabolism of codeine because of CYP2D6 polymorphisms and the risk for ultra-rapid metabolisers of forming higher quantities of morphine, but no paper provides new safety information about OTC codeine containing medicines.

Overall conclusion about the harms of low-dose codeine combination products

This update does not identify significant new information about the safety of low-dose codeine combination products since the earlier commissioned review.

Table B1. Harms from low-dose codeine combination medicines use – uncategorised articles

Reference	Summary	Evaluator comment / conclusion
Anonymous (2016). "Weak" opioid analgesics: Codeine, dihydrocodeine and tramadol: No less risky than morphine. *Prescrire International* **25**(168): 44-51.	**Type of Study:** Literature review undertaken by the Prescrire editorial staff using standard Prescrire methodology **Question:** Are weak opioids any more effective than paracetamol or NSAIDs on nociceptive pain, and are they better tolerated than morphine? **Abstract (partial):** The potency of codeine and tramadol is strongly influenced by the cytochrome P450 isoenzyme CYP2D6 genotype, which varies widely from one person to another. This explains reports of overdosing or underdosing after administration of standard doses of the two drugs. The potency of morphine and that of buprenorphine, an opioid receptor agonist-antagonist, appears to be independent of CYP2D6 activity. All "weak" opioids can have the same dose-dependent adverse effects as morphine. There is no evidence that, at equivalent analgesic efficacy, weak opioids carry a lower risk of addiction than low-dose morphine. Respiratory depression can occur in ultrarapid metabolisers after brief exposure to standard doses of codeine or tramadol. Similar cases have been reported with dihydrocodeine in patients with renal failure. In addition, tramadol can cause a serotonin syndrome, hypoglycaemia, hyponatraemia and seizures. Several trials have compared different weak opioids in patients with postoperative pain. A single dose of a weak opioid, possibly combined with paracetamol, has greater analgesic efficacy than paracetamol alone but is not more effective than an NSAID alone. There is a dearth of evidence on weak opioids in patients with chronic pain. Available trials fail to show that a weak opioid has markedly superior analgesic efficacy to paracetamol or an NSAID. Sublingual buprenorphine at analgesic doses appears less likely to cause respiratory depression, but it seems to have weak analgesic efficacy. In practice, when opioid therapy is needed, there is no evidence that codeine, dihydrocodeine or tramadol is less risky than morphine at its lowest effective dose. Compared to morphine, the efficacy of these	Adverse effects of codeine mentioned in the paper included: constipation, nausea, drowsiness, confusion and addiction; and, in the case of overdose, respiratory depression and coma. The author(s) indicate that · addiction risk "seems to increase with higher 'morphine equivalent' doses" · respiratory depression can occur after brief exposure to standard codeine doses [not defined] in ultrarapid metabolisers · codeine has variable analgesic efficacy with little effect in some patients and others at risk of overdose · codeine is also subject to drug interactions which can increase the risk of overdose or reduce the efficacy of the drug · when used for a long period all opioids can cause a withdrawal syndrome *The paper does not provide new information on the safety of low dose codeine.*

Reference	Summary	Evaluator comment / conclusion
	drugs varies more from one patient to another, and their multiple pharmacokinetic interactions can be difficult to manage. There is also a sometimes unpredictable risk of serious overdose. Tramadol has additional adverse effects unrelated to its opioid effects. **Author(s)' conclusion:** Weak opioids require at least as much vigilance as morphine, despite the major differences in their reputation and regulation.	
Foley, M., et al. (2015). "The availability of over-the-counter codeine medicines across the European Union." *Public Health* **129**(11): 1465-1470.	**Type of study:** Survey **Aim:** To describe the permitted sale of OTC codeine in each of the 28 EU states; and explore the level of regulation imposed and arrangements for the advertisement and self-selection of OTC codeine medicines in each country **Method:** Searches of websites of human medicines regulatory bodies for information about codeine and its regulation; emailed questions to each agency with telephone follow up for 3 of the agencies. Period of data collection: March to August 2014. **Results:** 15 countries did not permit OTC codeine medicines; 1 country permitted general sale outside the pharmacy (packs of fewer than 10 tablets); in 2 countries the only codeine product permitted OTC was a cough linctus. Most OTC medicines were sold as solid dose form oral combination products with paracetamol, ibuprofen or aspirin. Caffeine was a common constituent. Other active drugs may be included in some combinations. Paracetamol strengths in combinations ranged from 250 – 500 mg. Permitted codeine doses per tablet were variable: 8mg (3 countries), 9.6mg (1 country), 10 mg (2 countries); 12.5mg (2 countries), 12.8mg (2 countries), 15mg (1 country), 20mg (1 country), 30mg (1 country). 4 countries permitted OTC codeine cough linctus, all with different codeine doses: 2.5 mg per 5ml (1), 3mg per 5 ml (1), 11mg per 5ml (1), 15mg per 5ml (1). Brands varied across countries. The most common licensed product	The adverse health outcomes of excessive, long term or dependent use of codeine medicines identified by the authors include: · perforated gastric ulcers, · gastrointestinal bleeding · hepatotoxicity · hypokalemia · inflammatory bowel conditions · profound hypokalemia with severe myopathy These often occur in users with no history of substance use disorders and comorbidity, primarily due to the effects of the compounded paracetamol or ibuprofen. There is no new information about the safety of low-dose codeine in this paper. There is considerable variability in the regulatory regimes under which codeine is sold across the 28 EU states.

Reference	Summary	Evaluator comment / conclusion
	was Solpadeine® which is sold in 9 countries. The max dose in Solpadeine was paracetamol 500mg/codeine phosphate 12.8mg. There were variable levels of pharmacy supervision, pack sizes, limits on advertising, pack warnings, and availability of products for self-selection. **Authors' discussion:** The relative merits of the different regimes under which codeine is sold across the EU in terms of minimising harm are unclear. There is little evidence for the efficacy of codeine at low dose (<10mg) and whether this is more effecctive at treating pain than paracetamol, ibuprofen or aspirin alone. Further clinical studies should identify the benefit of low doses of codeine. Measuring the extent of misuse is problematic given its hidden nature, the wide range of misuse behaviours and heterogeneity of misusing populations. The reported adverse health outcomes of excessive, long term or dependent use of codeine medicines are on the increase and include: perforated gastric ulcers, git bleeding, hepatotoxicity, hypokalemia,inflammatory bowel consitions, profound hypokalemis with severe myopathy, often in users with no history of substance use disorders and comorbidity, primarily due to the effects of the compounded paracetamol or ibuprofen. Further research is needed.	
Gisev, N., et al. (2016). "An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia." European *Journal of Clinical Pharmacology* **72**(4): 469-494.	**Type of study:** Ecological **Aim:** To examine the use of prescription and over-the-counter (OTC) codeine in Australia and identify the geographic and socio-demographic characteristics associated with prescription and OTC codeine use. **Methods:** National sales data for prescription and OTC codeine (supplied by IMS Health) were used to estimate codeine utilisation (in pack sales and milligrammes) in Australia during 2013, mapped to Australian Bureau of Statistics (ABS) Statistical Local Areas (SLAs) and Remoteness Areas. Socio-demographic characteristics and total population estimates of SLAs were obtained from the ABS. SLA-level	Safety issues for OTC codeine mentioned in the paper include: · increased access to OTC codeine poses risks to individuals who self-manage their pain conditions on an on-going basis , increasing the potential for inappropriate use, adverse events, misuse and dependence; · burden of pharmaceutical opioid dependence is dispro-portionally higher in regional and remote areas;

Reference	Summary	Evaluator comment / conclusion
	data on sex, age distribution, income, occupations involving physical labour and number of pharmacies were included in linear regression analyses to examine their association with total, prescription and OTC codeine use. **Results:** In total, 27,780,234 packs of codeine were sold in Australia during 2013, equating to 12,376 kg. OTC codeine preparations accounted for 15,490,207 packs (55.8 %) or 4967.30 kg (40.1 %). Nationally, an estimated 1.24 packs (or 554.10 mg) of codeine were sold per person; utilisation was higher in more remote areas. SLAs with a higher percentage of low-income earning households had the highest rates of prescription codeine use (beta 0.16, $p < 0.001$), whereas SLAs with a higher percentage of males had the highest rates of OTC codeine use (beta 0.22, $p < 0.001$). **Author's conclusions:** Codeine use is common in Australia, with clear distinctions in the geographic and socio-demographic characteristics associated with prescription and OTC codeine use.	· lack of efficacy of doses less than 30mg may potentially increase harms without providing any additional clinical benefit; · prolonged use of large quantities of OTC codeine can lead to dependence and may lead to the development of medication overuse headache (MOH); · many of the serious harms associated with OTC codeine products are due to the analgesic in the combination such as liver toxicity (paracetamol), gastrointestinal ulcers and bleeding and renal failure (NSAIDs) especially in the elderly. *The study does not add any new information about the safety of low-dose codeine combinations.*
Haynes, A., et al. (2015). "A comparison of opioid analgesic exposures reported to poison centers before & after hydrocodone reclassification to schedule II." *Clinical Toxicology* **53** (7): 733.	**Type of study:** Case review **Introduction:** The Drug Enforcement Administration (DEA) rescheduled hydrocodone as a class II agent on 10/6/14. The impact of this change on use of other opioids is unclear, especially in states where special prescription pads are required for schedule II agents. This study compares opioid analgesic exposures reported to a large statewide poison center network (PCN) before and after this change in a state that requires special prescription pads for Schedule II agents. **Methods:** Cases were all opioid analgesic exposures reported to a statewide PCN from 5 months before & 5 months after the schedule change, comparing exposures during 5/1/14-9/30/14 with those during 10/1/14-2/28/15. Specific opioids with a large change in reported exposures were further characterized by patient age and	Abstract for the 2015 Annual Meeting of the North American Congress of Clinical Toxicology (NACCT) Documents a drop in hydrocodone exposures (especially intentional misuse) and a large increase codeine exposures (including intentional misuse) following the rescheduling of hydrocodone to a more restrictive level than codeine in the US. The schedule change required the use of special prescription pads in some US states. *Relevance for the decision on upscheduling low-dose codeine in Australia is uncertain.*

Reference	Summary	Evaluator comment / conclusion
	exposure intent. **Results:** Hydrocodone exposures decreased 28% from 1,315 to 951, while codeine exposures increased 186%, from 155 to 443. Together, there were 1,465 hydrocodone and/or codeine exposures before and 1,369 after the change. Oxycodone exposures rose 38% from 110 to 152. Reported heroin exposures increased only 7% from 132 to 141. Tramadol exposures did not change, and 12 other opioids either did not change much or had a very small number of exposures. Hydrocodone exposures decreased by 28% for patients age < 13 years, 9% age 13-19 years, and 31% age 20 + years. Reported intentional misuse decreased 40%, more than the other exposure reasons. Codeine exposures increased 111% among patients age < 13 years, 113% age 13-19 years, and 263% age 20 + years. Intentional misuse of codeine increased 443% and adverse drug events were up 327%. Oxycodone exposures increased 51% among patients age 20 + years, but did not change in the other age groups. **Authors' conclusion:** Due to extra steps required to order class II agents in some states, it was considered that prescribers may turn to the schedule 3-5 agents, such as Tylenol 3 or tramadol, despite concerns over codeine's complicated metabolism or tramadol's serotonergic activity. We found that while tramadol exposures did not change, codeine exposures did increase in all age groups as the hydrocodone exposures decreased in all age groups. The increase in oxycodone exposures may be due to physicians choosing a more potent analgesic than hydrocodone since they had to use the special prescription forms either way.	
Ilgen, M. A., et al. (2016). "Opioid dose and risk of suicide." *Pain* **157**(5): 1079-1084.	**Type of study:** Retrospective analysis of data from Veterans Affairs health care system treatment records and the National Death Index **Aim:** To examine the association between opioid dose and suicide mortality	Codeine use was converted to morphine equivalent doses and was not analysed separately from the other opioids. *There is no new information on the safety of low-dose*

Reference	Summary	Evaluator comment / conclusion
	Method: The records of Veterans Affairs patients with chronic pain receiving opioids in fiscal years 2004 to 2005 (N 123,946) were analyzed. Primary predictors were maximum prescribed morphine-equivalent daily opioid dose and opioid fill type. The main outcome measured was suicide death, by any mechanism, and intentional overdose death during 2004 to 2009. **Results:** Controlling for demographic and clinical characteristics, higher prescribed opioid doses were associated with elevated suicide risk. Compared with those receiving <20 milligrams/day (mg/d), hazard ratios were 1.48 (95% confidence intervals [CI], 1.25-1.75) for 20 to <50 mg/d, 1.69 (95% CI, 1.33-2.14) for 50 to <100 mg/d, and 2.15 (95% CI, 1.64-2.81) for 100+ mg/d. **Authors' conclusion:** Risk of suicide death was greater among those receiving higher doses of opioids . Treatment providers may want to view high opioid dose as a marker of elevated risk for suicide.	*codeine in the paper.*
John, A., et al. (2016). "Non-accidental non-fatal poisonings attended by emergency ambulance crews: An observational study of data sources and epidemiology." *BMJ Open* **6** (8) (no pagination) (011049).	**Type of study:** Observational Study undertaken across Wales, between December 2007 and February 2008 **Methods:** Incidents of non-fatal poisonings (NFP) assessed from electronic ambulance call centre records and paper patient clinical records (PCRs) completed by the attending ambulance crews, **Results (selected):** Of 1827 non-accidental non-fatal poisonings, 266 (15%) included codeine, of which half also included alcohol. The majority of these cases (95.1%) were taken to hospital.	*The paper provided no specific information about the clinical effects of the codeine-related NANFPs.* *Relevance to Australia uncertain.*
MacKinnon, J. I. J. (2016). "Tighter regulations needed for over-the-counter codeine in Canada." *Canadian Pharmacists Journal*	**Type of article:** Commentary The author discusses: · evidence that OTC codeine is being misused in Canada and	In this commentary, a Canadian pharmacist argues that all codeine products should be prescription except in limited circumstances and refers to the recent decision by Manitoba to make codeine prescription only.

Reference	Summary	Evaluator comment / conclusion
149(6): 322-324.	internationally (e.g. France, New Zealand, Australia) and of gastro- intestinal harms secondary to NSAID and codeine combinations · barriers to counselling on OTC codeine in community pharmacy, especially as patients who misuse codeine are unwilling to accept the advice of community pharmacists and may not be telling the truth, and pharmacists don't have access to the patient's medical history or list of current medications · one tool that would help pharmacists to counsel on OTC codeine would be a prescription monitoring program (PMP). A PMP would give pharmacists real-time alerts of potential misuse at the time of purchase · research on PMPs that monitor prescription drugs in Canada and the United States has shown that double-doctoring and polypharmacy use decrease after these programs are implemented, which suggests they can help to reduce inappropriate prescribing and dispensing of opioids and other controlled drugs. Whether this ultimately leads to a reduction in abuse and addiction is not clear, and further research is needed · implementing a PMP is not the ultimate solution and may not be sufficient in curbing OTC codeine misuse as pharmacists in many provinces would still not have access to medical and medication histories and still be left making clinical decisions about these narcotics with an incomplete clinical picture · a convincing argument can be made that all codeine products should be available only by prescription. In the author's practice experience, people purchase OTC codeine for 1) chronic pain, 2) anticipatory acute pain (e.g., to keep on hand in case of migraine), 3) cough and 4) acute pain. Patients with chronic pain requiring narcotics should have their pain assessed by a physician and should be getting these medications with a prescription. In other scenarios, it is debatable whether OTC purchases should be allowed. The risks of keeping codeine available without a prescription need to be weighed against the benefits. Risks include easier public access to a drug associated	*It is noted that this is a decision of the Manitoba College of Pharmacists (not a regulator) and that pharmacists are able to write prescriptions in Manitoba.* *No new safety issues for low-dose codeine are raised by this article.*

Reference	Summary	Evaluator comment / conclusion
	with dependence, addiction, overdose-related deaths and potential collateral toxicity from acetaminophen and aspirin · the Food and Drug Regulations in Canada state that if a drug has abuse or dependence potential, then that factor alone is enough to consider moving a drug to prescription-only status · keeping OTC codeine on hand in home medicine cabinets can be risky, exacerbated by the fact that in many provinces, these products are commonly sold in bottles of 200 pills. In a recent Ontario survey, 1 in 8 youth reported using an opioid pain reliever recreationally in the past year, and the majority got it from home · the benefits seem negligible: OTC analgesics with no codeine (e.g., ibuprofen, naproxen, acetaminophen) are likely just as effective, possibly even more, than OTC products with codeine for acute pain. · for acute cough, there is a paucity of data, but the available evidence shows that codeine is not effective. · it could be argued that Canadians should have access to OTC codeine for acute pain relief or acute cough when no other health facilities (e.g., family physician or dentist) are easily accessible and when the patient has tried all other non-codeine products. This, in the author's opinion, is the only scenario in which pharmacists might be allowed to sell OTC codeine. But this is a rare scenario in community pharmacy and keeping codeine available for this very small group of patients should be questioned. · other less risky options are available · Manitoba [College of Pharmacists] has recently announced that all codeine products will be available only by prescription, with pharmacists being able to prescribe in certain circumstances using a strict protocol.	
Moore, R. A., et al. (2015b) Adverse events associated with single dose	**Type of study:** Overview of Cochrane systematic reviews	Efficacy is dealt with in a separate overview which has

Reference	Summary	Evaluator comment / conclusion
oral analgesics for acute postoperative pain in adults - an overview of *Cochrane reviews. Cochrane Database of Systematic Reviews* DOI: 10.1002/14651858.CD011407.pub2	This is an update of a Cochrane overview published in Issue 9, 2011; only adverse events are covered in this update (efficacy is a separate update). Objectives: To provide an overview of adverse event rates associated with single-dose oral analgesics, compared with placebo, for acute postoperative pain in adults. Results: Information was available from 39 Cochrane reviews for 41 different analgesics or analgesic combinations (51 drug/ dose/ formulations) tested in single oral doses in participants with moderate or severe postoperative pain. This involved around 350 unique studies involving about 35,000 participants. Most studies involved younger participants with pain following removal of molar teeth. For most nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, and combinations not containing opioids, there were few examples where participants experienced significantly more or fewer adverse events than with placebo. For aspirin 1000 mg and diflunisal 1000 mg, opioids, or fixed-dose combination drugs containing opioids, participants typically experienced significantly more adverse events than with placebo. Studies of combinations of ibuprofen and paracetamol reported significantly fewer adverse events. Serious adverse events were rare, occurring a rate of about 1 in 3200 participants. Most reviews did not report specific adverse events. Authors' conclusions: Despite ongoing problems with the measurement, recording, and reporting of adverse events in clinical trials and in systematic reviews, the large amount of information available for single oral doses of analgesics provides evidence that adverse events rates are generally similar with active drug and placebo in these circumstances, except at higher doses of some drugs, and in combinations including opioids.	been included in Table A1. The studies which included codeine alone (12 studies, 798 participants) or in combination with paracetamol (37 studies, 3224 participants) used 30mg or 60mg codeine. In 4 studies (443 participants) combinations of ibuprofen and codeine were used with a range of codeine doses from 26mg to 60mg. However, the authors note that adverse events were frequently reported for a composite of all doses of a drug. The rate of adverse events was higher for combinations containing codeine than for placebo but there is no detail of the AEs as the reviews included in this study typically did not report on specific adverse events. Serious adverse events (unspecified) were reported for 6 patients taking ibuprofen + codeine and 1 taking codeine alone. None led to withdrawal and none was considered related to the study medicine. *There is no new data on the safety of OTC codeine combinations in this Cochrane Review.*
Roxburgh, A., et al. (2015). "Trends	**Type of study:** descriptive analysis of prospectively collected data	This paper is focused on the most severe adverse effect

Reference	Summary	Evaluator comment / conclusion
and characteristics of accidental and intentional codeine overdose deaths in Australia." *Medical Journal of Australia* **203**(7): 299.e291-299.e297.	from the National Coronial Information System **Objectives:** To examine trends in codeine-related mortality rates in Australia, and the clinical and toxicological characteristics of codeine-related deaths. **Design and setting:** Analysis of prospectively collected data from the National Coronial Information System on deaths where codeine toxicity was determined to be an underlying or contributory cause of death. **Study period:** 2000-2013. **Main outcome measures:** Population-adjusted numbers (per million persons) of (1) codeine-related deaths, classified by intent (accidental or intentional); and (2) heroin- and Schedule 8 opioid-related deaths (as a comparator). **Results:** The overall rate of codeine-related deaths increased from 3.5 per million in 2000 to 8.7 per million in 2009. Deaths attributed to accidental overdoses were more common (48.8%) than intentional deaths (34.7%), and their proportion increased during the study period. High rates of prior comorbid mental health (53.6%), substance use (36.1%) and chronic pain (35.8%) problems were recorded for these deaths. For every two Schedule 8 opioid-related deaths in 2009, there was one codeine-related death. Most codeine-related deaths (83.7%) were the result of multiple drug toxicity. **Authors' conclusions:** Codeine-related deaths (with and without other drug toxicity) are increasing as the consumption of codeine-based products increases. Educational messages are needed to better inform the public about the potential harms of chronic codeine use, especially in the context of polypharmacy.	of codeine i.e. death from codeine overdose. The authors mention other adverse effects including: · tolerance, leading to escalating doses and dependence · prolonged use of high-dose codeine-ibuprofen combinations linked with gastrointestinal disease and renal failure · paracetamol-codeine combinations linked to hepatotoxicity · dose escalation increases the risks of side effects associated with ibuprofen and paracetamol The paper documents a significant increase in the rate of codeine-related deaths over the 10 year period 2000-2009, due to an increase in accidental overdoses rather than intentional overdoses. The majority of codeine-related deaths in the period 2000-2013 involved multiple drug toxicity – only 7.8% were due to codeine toxicity alone or to codeine plus carbon monoxide or codeine plus alcohol. The increase in the rate of deaths specifically attributed to codeine was greater than the rate of increase in deaths due to multiple drug toxicity. 48.8% of codeine-related deaths were attributed to accidental overdose, 34.7% were attributed to intentional self-harm and in 16.5% intent was not determined. For the cases where data were available, a significant minority (40%) used OTC codeine products. The authors conclude that a number of approaches are needed to reduce harms from codeine: suicide prevention strategies (e.g. GP education, increased focus on screening for depression and suicide risk); GP

Reference	Summary	Evaluator comment / conclusion
		screening for substance misuse history when prescribing codeine; patient education, which should include information about the risks of chronic use, dangers of taking too much codeine, increased risk of fatal overdose if codeine is taken with other drugs such as benzodiazepines and other opioids, and risks from combination products. As codeine is available over the counter, education at the point of purchase (i.e. pharmacist) is needed as are an increased capacity of primary care to identify high-risk patients and an increase in specialist pain, addiction and mental health treatment services. *This paper provides evidence of increasing rates of fatal codeine-related overdoses, largely accidental but some intentional, mainly in the context of multiple drug toxicity. Among the cases where data were available OTC products were implicated in a significant minority (40%). The authors speculate that "a potential driver [of the increased rate of codeine-related deaths] may have been the introduction in Australia of OTC products containing larger amounts of codeine, including codeine combined with ibuprofen" but have not provided evidence to support this speculation.*
Steinman, M. A., et al. (2015). "Use of Opioids and Other Analgesics by Older Adults in the United States, 1999-2010." *Pain Medicine (United States)* **16**(2): 319-327.	**Type of study:** Observational **Objective:** To evaluate changes in use of opioids and other analgesics in a national sample of clinic visits made by older adults between 1999 to 2010 **Design, Setting, Subjects:** Observational study of adults age 65 and older from the 1999–2010 National Ambulatory and National Hospital Ambulatory Medical Care Surveys, serial cross-sectional surveys of	The authors note that there is uncertainty about the proper use of opioids in older adults, and the balance of these medications' benefits and harms in this population. Pain is common in older adults, and is often undertreated. Potential benefits of opioids for older adults include:

Reference	Summary	Evaluator comment / conclusion
	outpatient visits in the United States. **Methods:** Medication use was assessed at each study visit and included medications in use prior to the visit and medications newly prescribed at the visit. Results were adjusted for survey weights and design factors to provide nationally representative estimates. **Results:** Mean age was 75 +/−7 years, and 45% of visits occurred in primary care settings. Between 1999–2000 and 2009–10, the percent of clinic visits at which an opioid was used rose from 4.1% to 9.0% (P<.001). Although use of all major opioid classes increased, the largest contributor to increased use was hydrocodone-containing combination opioids, which rose from 1.1% to 3.5% of visits over the study period (P<.001). Growth in opioid use was observed across a wide range of patient and clinic characteristics, including in visits for musculoskeletal problems (10.7% of visits in 1999–00 to 17.0% in 2009–10, P<.001) and in visits for other reasons (2.8% to 7.3%, P<.001). **Authors' conclusions:** Opioid use by older adults visiting clinics more than doubled between 1999 and 2010, and occurred across a wide range of patient characteristics and clinic settings.	· reduced pain intensity · improved function · improvements in sleep and physical quality of life. · alternatives e.g. NSAIDs have important adverse effects that disproportionately affect older adults. Pain guidelines released by the American Geriatrics Society in 2009 de-emphasize the use of NSAIDs for control of nociceptive pain in older adults, such that for many patients with inadequate pain control on acetaminophen the next recommended step-up agent is an opioid. Risk of harms from opioids in the elderly include: · constipation · nausea · increased risk of falls and fractures · increased risk of cardiovascular events · risk of dependence and addiction (less well-defined than for younger adults, but remains an important consideration) · physician prescribing errors e.g. starting patients on inappropriately high doses of opioids or starting opioid-naïve patients on long-acting opioids. *Study relates to prescription opioids*
Veal, F. C., et al. (2015). "Use of Opioid Analgesics in Older Australians." *Pain Medicine (United States)* **16**(8): 1519-1527.	**Type of study:** Observational **Objective:** To identify potential medication management issues associated with opioid use in older Australians. **Design:** Retrospective cross-sectional review of the utilization of	Harms of opioids in this population: · constipation · falls · fractures

Reference	Summary	Evaluator comment / conclusion
	analgesics in 19,581 people who underwent a medication review in Australia between 2010 and 2012. **Subjects:** Australian residents living in the community deemed at risk for adverse medication outcomes or any resident living fulltime in an aged care facility. **Methods:** Patient characteristics in those taking regularly dosed opioids and not and those taking opioid doses >120 mg and ≤120 mg MEQ/day were compared. Multivariable binary logistic regression was used to analyze the association between regular opioid and high dose opioid usage and key variables. Additionally, medication management issues associated with opioids were identified. **Results:** Opioids were taken by 31.8% of patients, with 22.1% taking them regularly. Several major medication management issues were identified. There was suboptimal use of multimodal analgesia, particularly a low use of non-opioid analgesics, in patients taking regular opioids. There was extensive use (45%) of concurrent anxiolytics/hypnotics among those taking regular opioid analgesics. Laxative use in those prescribed opioids regularly was low (60%). Additionally, almost 12% of patients were taking doses of opioid that exceeded Australian recommendations. **Authors' conclusions:** A significant evidence to practice gap exists regarding the use of opioids amongst older Australians. These findings highlight the need for a quick reference guide to support prescribers in making appropriate decisions regarding pain management in older patients with persistent pain. This should also be combined with patient and caregiver education about the importance of regular acetaminophen to manage persistent pain.	· respiratory depression · confusion No specific information about low-dose codeine combinations. Recommends, if opioids are prescribed, to use the lowest effective dose in combination with optimised non-opioid analgesics and avoidance of anxiolytics and hypnotics. *The paper does not provide new information on the safety of low dose codeine.*
Voepel-Lewis, T., et al. (2015). "Leftover prescription opioids after minor procedures: An unwitting	**Type of study:** Observational In this study, parents prospectively recorded all analgesics they gave their children (aged 3-17 years) as well as pain scores across 4 days	Letter to the editor. *This study applies to prescription opioids. There is no estimate of the amount of unused low-dose (OTC) codeine*

Reference	Summary	Evaluator comment / conclusion
source for accidental overdose in children." *JAMA Pediatrics* **169**(5): 497-498.	following elective procedures at a tertiary care children's hospital from March 1, 2013 to August 31, 2013. Leftover opioids were estimated by calculating the number of doses and treatment days remaining from the dispensed amount if parents continued giving the opioid at the day 3 dosing frequency. Most children received less than 50% of their prescribed opioid doses because parents gave zero doses (14%), quickly tapered opioids, switched to non-opioids, or discontinued analgesics during the first few post procedure days. This left a considerable amount of unused prescribed opioids in the homes of children who were prescribed these agents for acute pain. **Authors' conclusion:** Better alignment of opioid prescriptions with the pain needs of patients and disposal education is warranted to appropriately manage pain while limiting the amounts of unused opioids available for accidental overdose, diversion, and misuse.	*containing products.*
Wu, J., et al. (2015). "Chronic pain and analgesic use in CKD: Implications for patient safety." *Clinical Journal of the American Society of Nephrology* **10**(3): 435-442.	**Type of study:** Cohort **Background and objectives:** This study examined chronic pain in CKD and its relationship with analgesic usage. **Design, setting, participants, & measurements:** Data include baseline visits from 308 patients with CKD enrolled between 2011 and 2013 in the Safe Kidney Care cohort study in Baltimore, Maryland. The Wong-Baker FACES Pain Rating Scale measured chronic pain severity. Analgesic prescriptions and over-the-counter purchases were recorded up to 30 days before visits, and were classified as a drug-related problem (DRP) based on an analgesic's nephrotoxicity and dose appropriateness at participants' eGFR. Participants were sorted by pain frequency and severity and categorized into ordinal groups. Analgesic use and the rate of analgesics with a DRP were reported across pain groups. Multivariate regression determined the factors associated with chronic pain and assessed the relationship between chronic pain and analgesic usage.	10 of the 308 participants in the study (3.2%) reported taking prescription or OTC purchased codeine, of which 2 (0.6%) reported an inappropriate dose for the level of CKD. *While only a very small proportion of patients were found to be using an inappropriate dose of codeine for their level of renal function, there is a risk that patients taking OTC codeine containing products may not be aware of the need to check with their doctor before taking the product.*

Reference	Summary	Evaluator comment / conclusion
	Results: There were 187 (60.7%) participants who reported chronic pain. Factors associated with pain severity included arthritis, taking ≥12 medications, and lower physical function. Use of nonsteroidal anti-inflammatory drugs was reported by seven participants (5.8%) with no chronic pain. Mild and severe chronic pain were associated with analgesics with a DRP, with odds ratios of 3.04 (95% confidence interval [95% CI], 1.12 to 8.29) and 5.46 (95%CI, 1.85 to 16.10), respectively. The adjusted rate of analgesics with a DRP per participant increased from the group with none to severe chronic pain, with rates of 0.07 (95%CI, 0.04 to 0.13), 0.12 (95% CI, 0.07 to 0.20) and 0.16 (95% CI, 0.09 to 0.27), respectively. **Authors' conclusions:** Chronic pain is common in CKD with a significant relationship between the severity of pain and both proper and improper analgesic usage. Screening for chronic pain may help in understanding the role of DRPs in the delivery of safe CKD care.	

Table B2. Harms from low-dose codeine combination medicines – misuse

Reference	Description	Evaluator comment / conclusion
Dada, S., et al. (2015). "Codeine misuse and dependence in South Africa - learning from substance abuse treatment admissions." S*outh African Medical Journal* **105**(9): 776-779.	**Type of study:** Descriptive study of data collected on patients admitted to centres participating in the South African Community Epidemiology Network on Drug Use. **Objectives:** To investigate the extent of treatment demand related to the misuse of codeine or codeine dependence in South Africa (SA) and the profile of patients seeking treatment, so as to understand the nature and extent of the problem. **Method:** Data were collected from centres participating in the South African Community Epidemiology Network on Drug Use in 2014. A total of 17 260 admissions were recorded. **Results:** There were 435 recorded treatment admissions for codeine misuse or dependence as a primary or secondary substance of abuse (2.5% of all admissions). Of treatment admissions, 137 (0.8%) involved codeine as the primary substance of abuse; 74.9% of patients were males, with an even spread across population groups. Ages ranged from 11 to 70 years, with the highest proportion aged 20 - 29 years; >40% were referred by self, family and/or friends, and 26.7% by health professionals; and 36.8% had received treatment previously. The majority reported misuse of tablets/capsules, with 17.6% reporting misuse of syrups. Oral use comprised 96.6% and daily use 63.1%. **Authors' conclusions:** Data from treatment admissions related to codeine misuse and dependence	The authors found that codeine was a primary substance of abuse in less than 1% of the admissions to treatment centres; but 2.5% when codeine was included as a primary or secondary drug of misuse. Concomitant substances of abuse were alcohol, cannabis, heroin/opiates and methamphetamine. Doses of codeine per tablet or capsule varied from 8-15 mg i.e. low dose. Many of the codeine preparations were combined with paracetamol and some were also combined with caffeine. Some products misused were cough syrups for which no dosages were provided. The authors speculate that the predominance of males in the study reflected barriers to women accessing treatment. They also speculate that many people who misuse or are dependent on codeine do not seek help from specialist substance abuse centres, instead consulting GPs or other healthcare providers. *Relevance to the Australian context is uncertain.*

Reference	Description	Evaluator comment / conclusion
	are informative, but provide an incomplete picture of the nature and extent of codeine-related problems in SA. Other data sources must be considered before further regulatory/ policy changes regarding codeine are implemented.	
Ellen Tsay, M., et al. (2015). "Abuse and intentional misuse of promethazine reported to US poison centers: 2002 to 2012." *Journal of Addiction Medicine* **9**(3): 233-237.	**Type of study:** Retrospective case review Retrospective review of intentional misuse or abuse promethazine exposures in persons ≥ 10 years of age reported to the Amercian Association of Poisons Control Centers National Poisons Data System Jan 2002 – December 2012. **Results (selected):** There were 354 single product abuse or misuse exposures - 95 promethazine alone (PA) and 259 promethazine combination (PC). Over the 11-year timeframe, the annual exposure rate per 100,000 population doubled. Exposures were most prevalent among 10 to 19 years old and young adults (20s), accounting for 69.5% of PA and 57.5% of PC cases. Clinical effects due to PA included drowsiness (43.2%), agitation (13.7%), confusion (13.7%), slurred speech (12.6%), hallucinations (7.4%), dizziness (7.4%), tachycardia (7.4%), vomiting (6.3%), hypertension (5.3%), ataxia (4.2%), dystonia (2.1%), respiratory depression, and hypotension (1%). Drowsiness (53.4%) and tachycardia (20.8%) were more frequent with PC. **Authors' conclusions:** Promethazine-Alone (PA) abuse/misuse most frequently resulted in minor outcomes, and less than 20% required medical admission. Abuse/misuse of PC resulted in a higher frequency of health care facility treatment and a trend	This is a US study of promethazine abuse/misuse. Promethazine is available in the US alone (PA) and in combination with other drugs (PC), including codeine, dextromethorphan and/or other expectorants. Serious clinical effects of PC were rare but included hyperthermia, hypotension, seizures and coma. The 4 cases of seizures all occurred following exposure to promethazine/codeine products. This paper refers to an Australian case series (Page et al 2009) which found similar clinical effects. The authors note that in the US, promethazine is frequently co-formulated or taken with codeine. Users have reported in online forums that promethazine can be combined with opioids to prevent nausea, to supplement the opioid-induced euphoria (so lower dose of opioid can be taken) or to self-medicate drug withdrawal. The authors discuss the rise in abuse/misuse of promethazine/codeine in cough syrups mixed with soft drink and candy among teenagers and college-aged adults, influenced by media, peer pressure or curiosity and continued because of the euphoric effect. The authors mention that codeine is well documented for its abuse potential and that the signs and symptoms of codeine toxicity include somnolence,

Reference	Description	Evaluator comment / conclusion
	toward more moderate outcomes. These differences are most likely attributed to the co-formulate.	respiratory depression, hypotension, bradycardia, cardiac arrest, death. Opioids, including codeine, may aggravate hypoxia induced seizures and promethazine may lower the seizure threshold. *Relevance to Australia is not clear but the OTC availability of promethazine and of low-dose codeine containing products suggests the possibility for similar misuse to occur here.*
James, J. (2016). "Dealing with drug-seeking behaviour." *Australian Prescriber* **39**(3): 96-100.	**Type of article:** Clinical guidance People who misuse prescription drugs most commonly seek prescriptions for opioids and benzodiazepines. Other prescription drugs that are misused include the newer antipsychotics such as quetiapine and olanzapine, and stimulants such as dexamphetamine and methylphenidate. Health professionals should be aware of behaviours that may indicate drug seeking, but dependency on prescription drugs can occur at any age, within any cultural group and across any educational class. Patients with dependencies may not necessarily display obvious drug-seeking behaviours. All general practices should have a practice policy on prescribing drugs of dependence. GPs should register with the Prescription Shopping Information Service. There is strong evidence in Australia of increasing harms from prescription drugs of dependence, including deaths from overdose. Before prescribing any drug of dependence, health professionals require an understanding of the patient's biopsycho-social status, and the evidence-based indications and potential significant harms of these drugs.	Guidance to health professionals The author indicates that both prescription and OTC opioids can be misused. The author notes that complications of overdose with OTC ibuprofen/codeine combinations can be life threatening and include gastrointestinal bleeding, perforation, hypokalaemia, renal failure, anaemia and opioid dependence. This statement is referenced to Frei et al (2010) whose paper was considered in the commissioned review. *There is no new information on the safety of low-dose codeine in this paper.*

Reference	Description	Evaluator comment / conclusion
Miech, R., et al. (2015). "Prescription opioids in adolescence and future opioid misuse." *Pediatrics* **136**(5): e1169-e1177.	**Type of study:** National survey **Methods:** Prospective, panel data come from the Monitoring the Future study. The analysis uses a nationally representative sample of 6220 individuals surveyed in school in 12th grade and then followed up through age 23. Analyses are stratified by predicted future opioid misuse as measured in 12th grade on the basis of known risk factors. The main outcome is nonmedical use of a prescription opioid at ages 19 to 23. Predictors include use of a legitimate prescription by 12th grade, as well as baseline history of drug use and baseline attitudes toward illegal drug use. **Results:** Legitimate opioid use before high school graduation is independently associated with a 33% increase in the risk of future opioid misuse after high school. This association is concentrated among individuals who have little to no history of drug use and, as well, strong disapproval of illegal drug use at baseline. **Authors' conclusions:** Clinic-based education and prevention efforts have substantial potential to reduce future opioid misuse among these individuals, who begin opioid use with strong attitudes against illegal drug use.	Codeine is mentioned but the paper includes no analysis by type of opioid. *Relevance to OTC codeine combinations in Australia is unclear.*
Van Hout, M. C. and I. Norman (2016). "Misuse of non-prescription codeine containing products: Recommendations for detection and reduction of risk in community pharmacies." *International Journal of Drug Policy* **27**: 17-22.	**Type of article:** Policy commentary on OTC codeine Issues discussed in the article include: · Codeine is a weak opioid which is available OTC in low doses for analgesic, antitussive and anti-diarrhoeal purposes.	The authors note that adverse health consequences of excessive or long-term misuse of combination products of codeine and non-opiates such as paracetamol, ibuprofen or aspirin include: · medication overuse headache (MOH) · paracetamol hepatotoxicity

Reference	Description	Evaluator comment / conclusion
	· The availability of OTC medicinal products has contributed to public perceptions of safety and lack of awareness of the potential for misuse, dependence and harm. · Efforts to quantify the extent and nature of misuse of OTC medicines are confounded by the widespread and easy retail availability without prescription, inability of pharmacy to monitor misuse itself and the hidden and heterogeneous nature of therapeutic and non-therapeutic forms of misuse. · Codeine has an identified abuse potential due to its opiate effect and rapid development of tolerance with regular or excessive use. Misuse of codeine-containing combination products is increasing in countries where OTC sales are available. · Misuse of products containing codeine can occur following initial legitimate therapeutic use for the treatment of pain and also from initial non-therapeutic use to produce intoxication. Studies have observed the interplay between self-medication, chronic pain and iatrogenic dependence. · Misuse and dependence occur across a wide range of groups including: parental medication of children; recreational users; university students; older people; psychiatric patients; injecting drug users; non-treatment seeking individuals; and drug treatment patients. · Codeine is distinct from other opioids because of the ease with which codeine containing products can be obtained for therapeutic purposes. This lessens the ability of consumers to recognise that they are opioid dependent and need help.	· gastrointestinal haemorrhage · nephrotoxicity · hypokalaemia · acute haemorrhagic necrotising pancreatitis · opioid dependence Regulatory actions mentioned in the article include: · guidelines for restricted supply · increased visibility of warnings on labels and leaflets about abuse potential and only taking for longer than 3 days on medical advice · restrictions on pack sizes · prevention of public advertising · restrictions on product visibility and customer self-selection · pharmacy record keeping · direct involvement of pharmacists in sales The authors also discuss the extension of real time monitoring systems for prescription products to include OTC medicines to ensure availability for patients with genuine therapeutic need while discouraging misuse through detection of purchases of large quantities and referral to 1o care or pain clinics.

Reference	Description	Evaluator comment / conclusion
	· Global awareness of misuse of OTC codeine containing products is increasing. There are ethical and scientific complications of access and convenience versus patient safety and evidence about patient safety needs to be taken into account when making decisions about scheduling. · Debate about availability of OTC codeine containing products centres on the lack of evidence of a clinically significant analgesic benefit of low dose codeine in combination analgesics and the identified harms. · Codeine containing cough and cold medicines are highly effective for symptomatic relief of self-limiting viral respiratory illnesses, used short term by a generally lower risk patient group · There are unintended consequences of restricting access to codeine containing products, such as – under-treatment of pain – inappropriate prescribing – prescribing of more potent medication – barriers for low income patients to access 1º care – additional cost to taxpayers – reduced pharmacy economic activity – inconvenience related to storage and handling · There are no known validated screening tools for identifying customers who are at risk of codeine misuse and dependence and screening for possible misuse is hampered by the determination of some codeine-seeking individuals to avoid detection. · Recognition of abuse in pharmacies is based on:	

Reference	Description	Evaluator comment / conclusion
	– customer repeated requests for certain codeine containing products by name – refusal to consider single ingredient (non-opiate) products – requesting specific pack sizes – agitation when pharmacists intervene · Community pharmacy actions include: – removal of codeine containing products from display – refusal of sale or restriction of quantity – on-site recording of incidents of suspected misuse – provision of medicines information by pharmacists and assistants – direct pharmacist intervention by additional questioning and customer referral to 1o care professionals · Difficulties exist in incorporating these roles into the business models and public environment of pharmacies with a lack of privacy. · The pharmacist's duty of care is to ensure patients are fully advised of correct use and harms of misuse and directed toward medical advice if misuse occurs. Refusal of sale could result in under-treatment of chronic pain or opiate withdrawal symptoms. · A number of suggestions are made by the authors to support an expanded role for community pharmacists as custodians of OTC codeine containing products, including optimal medicine information communication with consumers, universal screening and brief intervention. The aim is to improve safe public usage of codeine containing products and ensure medicines compliance and referral support.	

Cited references

Page et al. Promethazine overdose: clinical effects predicting delirium and the effect of charcoal. *Q J Med* 2009;102:123–131

Frei et al. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. *Med J Aust* 2010;193:294-296

Table B3. Harms from low-dose codeine combination medicines use - case studies and pharmacovigilance

Reference	Description	Evaluator comment / conclusion
Ansar, A., et al. (2015). "Drug-induced skin reactions: A 2-year study." *Clinical, Cosmetic and Investigational Dermatology* **8**: 53-56.	**Type of study:** Case series of dermatological ADRs. 308 consecutive patients with a diagnosis of an ADR referred to the dermatology service of Sina hospital in Hamadan, Iran. 53% had urticaria, of which 10% were associated with codeine/ paracetamol.	This case series documents cases of urticaria associated with the use of paracetamol with codeine. *Urticaria is a known adverse effect of codeine.*
Carnovale, C., et al. (2016). "The importance of monitoring adverse drug reactions in elderly patients: The results of a long-term pharmacovigilance programme." *Expert Opinion on Drug Safety* **15**(2): 131-139.	**Type of study:** Pharmacovigilance This paper describes the results of a 4-year active pharmacovigilance programme in the elderly in Italy known as Pharmacovigilance in Geriatry (ViGer). ADRs were collected for adults aged over 65 years of age treated in nursing homes, continuing care retirement communities and territorial health services in Lombardy. 1073 case reports corresponding to 2110 ADRs were reported. Vaccines, antibacterials for systemic use and antineoplastic agents were the pharmacotherapeutic subgroups most frequently involved. 18% of ADRs reports were classified as serious.	There were 11 reports of ADRs to paracetamol-codeine combinations. Hallucination, urinary incontinence, nightmare, confusion/confusional state were the most commonly reported previously unknown reactions. *There is insufficient information in this report to determine if this safety information is relevant to the use of low-dose paracetamol-codeine combinations.*

Reference	Description	Evaluator comment / conclusion
Chaabane, A., et al. (2016). "Codeine-induced acute generalized exanthematous pustulosis: An unusual case." Allergy: *European Journal of Allergy and Clinical Immunology* **71**: 422.	**Type of study:** Case report Brief report of a case of acute generalised exanthematous pustulosis (AGEP) associated with the use of paracetamol/codeine (route and dose unspecified). Following resolution of the skin rash, oral challenge with paracetamol alone was tolerated but oral challenge with paracetamol/codeine resulted in the development of an identical rash within a few hours.	*Case report of a rare reaction with good evidence of being causally related to codeine.*
Erfan, G., et al. (2015). "Symmetrical drug-related intertriginous and flexural exanthema due to codeine." *Indian Journal of Dermatology, Venereology and Leprology* **81**(4): 405-406.	**Type of study:** Case report Case of symmetrical drug-related intertriginous and flexurel exanthema (SDRIFE), also known as baboon syndrome, occurring two days after the patient (a 60 year old woman) started on a paracetamol (500mg)/codeine (30mg) combination orally and determined after investigation to be causally associated with codeine. SDRIFE is a systemically induced allergic contact dermatitis, with many drugs reported as being causative agents of this disease. However, the authors were unable to find any previous reports of codeine causing this reaction pattern. The patient was diagnosed based on clinical features, lab investigations including histopathology and drug provocation tests. Two months prior to taking the oral combination, the patient had used a topical diclofenac/codeine gel for three weeks. The authors consider that this may have been responsible for the patient's sensitisation.	Letter to the editor *This appears to be a rare and previously unreported adverse effect of codeine.*

Reference	Description	Evaluator comment / conclusion
Kean, J. (2016). "Illicit and over-the-counter codeine dependence after acute back pain-successful treatment and ongoing recovery after buprenorphine/naloxone taper." *Heroin Addiction and Related Clinical Problems* **18**(2): 21-24.	**Type of study:** Case report This article presents a case report of the successful management of a patient who had developed dependency on OTC and illicit codeine after initial treatment with prescription codeine for acute back pain. After 4 years of escalating use to a daily codeine dose of 1250 mg, the patient attended a substance misuse service. Treatment involved opioid substitution treatment - buprenorphine/naloxone - within a holistic Change Programme that included structured behavioural change psychosocial interventions.	Prescription, OTC and illicit codeine were all used by the patient. *There is no new information on the safety of low-dose codeine in the paper.*
Lenti, M. C., et al. (2015). "Acute epigastric pain and liver toxicity associated with acetaminophen-codeine use in cholecystectomized patients." *Drug Safety* **38** (10): 1036.	**Type of study:** Observational This study collected data on patients admitted to Prado Hospital ED with epigastric pain and increased liver enzymes. The study found an increased risk of pain and raised liver enzymes associated with the use of acetaminophen/codeine in cholecystectomized patients.	Poster presented at the International Society of Pharmacovigilance (ISOP) 2015 meeting. The poster identifies that there may be an increased risk of acute epigastric pain and liver toxicity from the use of acetaminophen-codeine by patients who have had a cholecystectomy. The authors recommend further studies to confirm the finding. *Abdominal pain is a known effect of morphine and codeine. The potential increased risk with the use of codeine in patients who have had a cholecystectomy requires further investigation to confirm the signal (see paper by Tabner et al below).*

Reference	Description	Evaluator comment / conclusion
Pauly, V., et al. (2015). "Detection of signals of abuse and dependence applying disproportionality analysis." *European Journal of Clinical Pharmacology* **71**(2): 229-236.	**Type of study:** Disproportionality analysis This article describes a study which used disproportionality analysis (proportional reporting ratio or PRR) of data in a database specifically constructed for the monitoring of drug abuse and dependence. The aim was to determine the occurrence of signals for different psychoactive drugs. The signals examined were: abuse and dependence; illegal acquisition; diverted route of administration; and concomitant alcohol use. The database provided information on approximately 5000 patients and 8000 consumption modalities for more than 100 distinct psychoactive medications for 2010 and 2011. Among the 100 psychoactive drugs for which a signal could be detected, those presenting the highest signals were the following: flunitrazepam, clonazepam, methylphenidate, ketamine, morphine sulfate, codeine and buprenorphine.	*While the study indicated that codeine was associated with a signal for abuse and dependence, it provides no further analysis or investigation of the signal and no new information on the safety of low-dose codeine.*

Reference	Description	Evaluator comment / conclusion
Tabner, A. and G. Johnson (2015). "Codeine: An under-recognized and easily treated cause of acute abdominal pain." *American Journal of Emergency Medicine* **33**(12): 1847.e1841-1847.e1842.	**Type of study:** Two case histories 2 cases of acute abdominal pain secondary to oral codeine that resolved after the administration of intravenous naloxone. Codeine is a well-recognized but underappreciated cause of acute severe abdominal pain mediated through sphincter of Oddi spasm. It is thought to be of particular significance in patients who have previously undergone cholecystectomy. Administration of naloxone in low doses carries little risk and has the potential to be both diagnostic and therapeutic. Early recognition and management of this treatable condition has the potential to reduce unnecessary investigations and prevent possible progression to pancreatitis.	Case 1 – pain occurred after one dose 1 g paracetamol and 60 mg codeine orally Case 2 – pain occurred after 1 dose of 30mg codeine orally *Known effect of codeine and morphine (see Lenti et al poster above).*

Table B4. Harms from low-dose codeine combination medicines use - alternatives to use of codeine in adults and children

Reference	Description	Evaluator comment / conclusion
Bandieri, E., et al. (2016). "Randomized trial of low-dose morphine versus weak opioids in moderate cancer pain." *Journal of Clinical Oncology* **34**(5): 436-442.	**Type of study:** Multicenter, 28-day, open-label randomized controlled study **Purpose:** The WHO guidelines on cancer pain management recommend a sequential three-step analgesic ladder. However, conclusive data are lacking as to whether moderate pain should be treated with either step II weak opioids or low-dose step III strong opioids. **Patients and Methods:** Adults with moderate cancer pain were assigned to receive either a weak opioid or low-dose morphine. Primary outcome: Number of responder patients, defined as patients with a 20% reduction in pain intensity on the numerical rating scale. **Results:** A total of 240 patients with cancer (118 in the low-dose morphine and 122 in the weak-opioid group) were included in the study. The primary outcome occurred in 88.2% of the low-dose morphine and in 57.7% of the weak-opioid group (odds risk, 6.18; 95% CI, 3.12 to 12.24; P < .001). The percentage of responder patients was higher in the low-dose morphine group, as early as at 1 week. Clinically meaningful (≥30%) and highly meaningful (≥ 50%) pain reduction from baseline was significantly higher in the low-dose morphine group (P > .001). A change in the assigned treatment occurred more frequently in the weak-opioid group, because of inadequate analgesia. The general condition of patients, which was based on the Edmonton Symptom Assessment System overall symptom score, was better in the morphine group. Adverse effects were similar in both groups. **Authors' conclusion:** In patients with cancer and moderate pain, low-dose morphine reduced pain intensity significantly compared with weak opioids, with a similarly good tolerability and an earlier effect.	The authors note: · The study demonstrated that, compared with step II opioids, low-dose morphine provided an earlier and a more adequate level of analgesia for moderate cancer pain, with a fairly good tolerability profile and a positive impact on overall wellbeing. · Oncologists, family physicians, and internists may prefer to prescribe weak opioids in many countries rather than strong ones because of lower regulatory requirements such as not needing special prescription forms. · The data show that this intermediate step may be less effective and more expensive. · The current WHO recommendation has the three-step pain ladder as the basis for treatment of cancer pain. New guidelines, including those by the European Association for Palliative Care (EAPC), describe a two-step approach as an alternative. The weak opioids used in the weak opioid (WO) group included either codeine + paracetamol or tramadol + paracetamol or tramadol alone. Dosages used are unclear. The results within the WO group are not reported separately. There is limited information on adverse events. *The paper does not provide new information on the safety of low dose codeine.*

Reference	Description	Evaluator comment / conclusion
Chang, A. K., et al. (2015). "Comparative Analgesic Efficacy of Oxycodone/ Acetaminophen vs Codeine/Acetaminophen for Short-Term Pain Management Following ED Discharge." *Pain Medicine (United States)* **16**(12): 2397-2404.	**Study type:** Prospective, randomized, double-blind clinical trial **Objectives:** To test the hypothesis that oxycodone/ acetaminophen provides analgesia superior to codeine/ acetaminophen following ED discharge. **Methods:** Adult ED patients with acute extremity pain were randomly allocated upon discharge to oxycodone/ acetaminophen (5 mg/325 mg) or codeine/acetaminophen (30 mg/300 mg). **Primary outcome:** The between group difference in improvement in numerical rating scale (NRS) pain scores over a 2-hour period following the most recent ingestion of study drug obtained during telephone contact one day post-ED discharge. **Secondary outcomes:** Side-effect profiles and patient satisfaction. Results: 120 patients each were randomly allocated to oxycodone/ acetaminophen and codeine/acetaminophen. Mean NRS baseline pain scores immediately prior to the most recent dose of study medication was 7.9 in both groups. Mean decrease in pain scores over 2 hours was 4.5 NRS units in the oxycodone/acetaminophen group vs. 4.2 NRS units in the codeine/acetaminophen group (difference of 0.2 NRS units, 95% CI -0.4 to 0.9 NRS units). No differences were found in side effects or patient satisfaction. **Authors' conclusion:** Both analgesics reduced pain scores by approximately 50% over 2 hours. Oxycodone/acetaminophen failed to provide clinically or statistically superior analgesia compared to oral codeine/ acetaminophen in this post-ED discharge model. Side effects and patient satisfaction were similar in both groups. Pending independent validation, these findings tentatively suggest that codeine/ acetaminophen (30 mg/300 mg), a Schedule III agent, may be a clinically reasonable opioid alternative to oxycodone/acetaminophen (5 mg/325 mg), a more restricted Schedule II agent, for short-term acute extremity pain in adults following ED discharge.	The codeine dose in the combination used in the study was 30mg every 4 hours as needed for pain with no other pain treatment given until after the followup call 24 hours after discharge. The paper notes that hydrocodone / acetominophen combinations are controlled substance that were upscheduled from Schedule III to the more restrictive Schedule II in New York in February 2013 and nationally (US) in October 2014. Codeine / acetominophen is a less restricted Schedule III agent. The authors state this is based on the 'higher potential for abuse and physical dependence of hydrocodone compared with codeine'. The authors indicate that it is "unknown what will happen in terms of abuse or harm should a large scale transition occur from hydrocodone products to codeine products" and refer to an article by Atluri et al (2014) that showed a 39% increase in the abuse of codeine in the US over the period 2004 to 2011. The authors note that the NYC Emergency Department Discharge Opioid Prescribing Guidelines for post-ED management of patients with acute or chronic non-cancer pain include a maximum of 3 days of short-acting oral opioids at the lowest possible effective dose. Adverse events noted in the trial included nausea, vomiting, constipation, diarrhoea, pruritus, rash, dizziness, drowsiness, confusion with no clinically or statistically significant differences in rates of occurrence between the two groups.

Reference	Description	Evaluator comment / conclusion
		The paper does not provide new safety information related to the use of low-dose codeine.
Conaghan, P. G., et al. (2016). "Satisfaction, Adherence and Health-Related Quality of Life with Transdermal Buprenorphine Compared with Oral Opioid Medications in the Usual Care of Osteoarthritis Pain." *Patient* **9**(4): 359-371.	**Type of study:** Observational – patient satisfaction survey. 701 patients treated for knee or hip osteoarthritis (OA) for at least a month with one or more of transdermal buprenorphine (TDB) (releasing 5-30µg/hour), oral codeine (8, 15 or 30mg) with paracetamol (500mg) or tramadol (200-400mg per day). 30% of patients taking one target medicine also took prescribed or OTC paracetamol, 21% in the paracetamol/codeine group were prescribed paracetamol and 18% bought OTC paracetamol. 1 in 12 patients in the paracetamol/codeine group took additional paracetamol both prescribed and OTC. **Outcome:** Patients treated with TDB were more satisfied and more adherent with their medication.	Side effects mentioned in the article include: · constipation (paracetamol/codeine 24% > TDB 9% > tramadol 10%) · dizziness (tramadol 11% > paracetamol/codeine 8% > TDB 6%) · somnolence (tramadol 15% > paracetamol/codeine11% > TDB 1%) · psychiatric disorders (tramadol 11% > paracetamol/codeine 5% > TDB 1%) The study did not report separately on the satisfaction with, or side effects of, the different strengths of codeine. *There is no new information about the safety of low dose codeine in the paper.*
D'Souza, J. N., et al. (2015). "Postoperative nonsteroidal anti-inflammatory drugs and risk of bleeding in pediatric intracapsular tonsillectomy." *International Journal of Pediatric Otorhinolaryngology* **79**(9): 1472-1476.	**Type of study:** Retrospective chart review **Period of study:** 2011 - 2013 **Objective:** To determine the risk of post-tonsillectomy hemorrhage (PTH) in children who received ibuprofen with acetaminophen versus those who received narcotic with acetaminophen for postoperative pain control. **Methods:** Retrospective chart review of patients at a tertiary-care pediatric center. The medical records of 449 children who received acetaminophen and ibuprofen following intracapsular tonsillectomy with or without adenoidectomy were reviewed (NSAID group) and compared with medical records of 1731 children who underwent intracapsular tonsillectomy and received acetaminophen with codeine	This study found the incidence of haemorrhage requiring return to the operating room after tonsillectomy was higher in the NSAID group than in the acetaminophen / codeine group. The only other codeine safety information mentioned is: · variable metabolism via the CYP2D6 enzyme with poor metabolising form resulting in almost no conversion to morphine and the ultrarapid metabolising phenotypes resulting in death from respiratory depression post tonsillectomy in children

Reference	Description	Evaluator comment / conclusion
	or hydrocodone with acetaminophen postoperatively (narcotic group). **Main outcome measure:** Incidence of PTH requiring return to the operating room. **Secondary outcome measures:** Incidence of primary PTH, secondary PTH, and postoperative evaluation in the emergency department or re-admission for pain and/or dehydration. **Results:** Incidence of PTH requiring return to the operating room was higher in the NSAID group (1.6%) compared with the narcotic group (0.5%), P=0.01. Incidence of primary PTH was significantly higher in the NSAID group (2%) versus the narcotic group (0.12%), P<0.0001. Incidence of secondary PTH was 3.8% in the NSAID group and 1.1% in the narcotic group (P<0.0001). **Authors' conclusion:** Use of ibuprofen after intracapsular tonsillectomy in children is associated with statistically significant increase in PTH requiring return to the operating room, as well as an increase in overall rates of both primary and secondary PTH. Ibuprofen provides pain control that is at least equivalent to narcotic and is not associated with respiratory depression. Further study of ibuprofen use in the post-tonsillectomy patient is warranted.	· postoperative nausea, vomiting, urinary retention and constipation The codeine dose is not specified in the article. *The paper does not provide new information on the safety of low dose codeine.*
Friedrichsdorf, S. J., et al. (2015). "Tramadol versus codeine/acetaminophen after pediatric tonsillectomy: A prospective, double-blinded, randomized controlled trial." *Journal of Opioid Management* **11**(4): 283-294.	**Type of study:** Prospective, double-blinded, randomized controlled trial. **Setting:** Large, Midwestern US pediatric hospital. **Objective:** To evaluate efficacy and safety of the single drug tramadol versus codeine/acetaminophen post-tonsillectomy. **Patients:** Eighty-four children aged 4-15 years who underwent a tonsillectomy (with or without adenoidectomy) procedure were randomized and 74 were included in the analysis.	Adverse effects of the codeine / acetominophen combination mentioned include: · nausea · vomiting · fever · itching · sweating · dizziness · headache · constipation

Reference	Description	Evaluator comment / conclusion
	Interventions: Group 1 received liquid codeine/acetaminophen for 10 days post-tonsillectomy (5 days scheduled, followed by 5 days as-needed). Liquid combination 120mg acetominophen + 12mg codeine per 5 mL – dose = 0.3mL/kg up to max of 36mg. Group 2 received liquid tramadol for 10 days post-tonsillectomy (5 days scheduled, followed by 5 days as-needed). **Main outcome measures:** Efficacy and side effects - 10-day take-home diary completed by parents. The study was not powered to detect rare adverse effects such as respiratory depression. **Results:** Children in both study arms reported adequate post-tonsillectomy pain management without significant differences between groups in pain scores. Over sedation was significantly higher on the day of surgery in the codeine/acetaminophen group, and itching was experienced by significantly more children in the tramadol group during the postoperative period. **Authors' conclusions:** As part of multimodal analgesia, scheduled plus as-needed tramadol may be considered for children in the postoperative setting due to its analgesic properties, low potential for side effects, and good safety profile.	· over sedation Itching was more common in the tramadol group than in the codeine groups, while over sedation was more common in the codeine group, but only on day 1 postoperatively. *The paper does not provide new information on the safety of low dose codeine.*
Outhoff, K., et al. (2015). "A randomised clinical trail comparing the analgesic and anxiolytic efficacy and tolerability of Stilpane and Tramacet after third molar extraction: Clinical trail." *Southern African Journal of Anaesthesia and Analgesia* **21**(2): 22-27.	**Type of study:** Prospective randomised parallel group phase IV clinical trial **Aim:** To compare the analgesic and anxiolytic efficacy and tolerability of two widely prescribed combination analgesics, StilpaneR (paracetamol 320mg/codeine 8mg/meprobamate 150mg) and TramacetR (paracetamol 325mg/tramadol 37.5mg) **Methods:** Conducted in 100 patients experiencing moderate to severe pain after third molar extraction at the Oral and Dental Hospital, University of Pretoria. Pain intensity and pain relief were assessed using Likert and visual analogue scales. Medication efficacy, time to	No significant safety concerns were revealed in the study. Vital signs and physical examinations were within normal ranges. The most common treatment emergent events were · nausea (StilpaneR 9.6 %, TramacetR 12.5%) · vomiting (Stilpane 5.8 %, Tramacet 6.3%) · somnolence (Stilpane 15.4%, Tramacet 14.6%) · dizziness (Stilpane 1.9 %, Tramacet 6.3%) · headache (Stilpane 1.9 %, Tramacet 2.1%) · insomnia (Stilpane 1.9%, Tramacet 2.1%) · pruritus (Stilpane 5.8 %, Tramacet 2.1%)

Reference	Description	Evaluator comment / conclusion
	perceptible pain relief and meaningful pain relief were also assessed. Primary variables included the Pain Intensity Difference (PID) between baseline and scheduled visits, and hourly pain relief (PAR). The Summed Pain Intensity Difference (SPID), Sum of hourly PAR, hourly PIDs from baseline (SPRID) and Total Pain Relief (TOTPAR) were calculated according to standard methods. Beck Anxiety Questionnaire assessed anxiety.Tolerability was assessed chiefly by the reporting of adverse events. **Results:** StilpaneR and TramacetR were equally effective at relieving moderate to severe acute pain. No differences in anxiolytic efficacy were found between the two treatment arms and differences in tolerability failed to reach statistical significance. **Authors' conclusions:** Despite their distinctive compositions and mechanisms of action, StilpaneR and TramacetR are equally effective and well-tolerated combination analgesics in patients experiencing moderate to severe acute pain.	· rash (Stilpane 0 %, Tramacet 4.2%). No patients discontinued treatment due to adverse effects and no serious adverse events were reported. The codeine containing product is low-dose but also contains meprobamate. It is not clear that paracetamol/codeine at these doses level would be effective without the meprobamate. Meprobamate is not available in Australia. *The study results are not applicable to the Australian context.*
Pfaff, J. A., et al. (2016). "The use of ibuprofen in posttonsillectomy analgesia and its effect on posttonsillectomy hemorrhage rate." *Otolaryngology - Head and Neck Surgery (United States)* **155**(3): 508-513.	**Type of study:** Case series with chart review. **Objective:** To determine the effect of ibuprofen on post-tonsillectomy bleeding when compared with codeine in post-tonsillectomy analgesia. **Setting:** Tertiary care children's hospital, Philadelphia, Pennsylvania. **Subjects and Methods:** On July 1, 2012, the institution transitioned from acetaminophen with codeine to ibuprofen for post-tonsillectomy analgesia. Pediatric patients (0-18 years old) who underwent surgery from July 1, 2010, to June 30, 2012, were placed in the codeine cohort, and those who underwent surgery from July 1, 2012, to June 30, 2014, were placed in the ibuprofen cohort. **Results:** 6014 patients underwent tonsillectomy between July 1, 2010, and June 30, 2014, and 211 patients presented for post-tonsillectomy hemorrhage during the same period. The incidence of readmission for	Prior to July 1, 2012, patients were prescribed acetaminophen with codeine every 6 hours (120 mg of acetaminophen with 12 mg of codeine) for post-tonsillectomy pain at an acetaminophen dosing of 12 mg/kg or a codeine dosing of 1 mg/kg with a maximum codeine dose of 75 mg/kg/d. After July 1, 2012, patients were prescribed ibuprofen every 6 hours at a dose of 10 mg/kg with a maximum dosage of 400 mg/dose. No other information on the relative safety of the two regimens was provided. *There is no new information about the safety of low dose codeine in the paper.*

Reference	Description	Evaluator comment / conclusion
	post-tonsillectomy hemorrhage was 3.4% and 3.6% (P = .63; odds ratio [OR] = 1.07; 95% confidence interval [95% CI]:0.811-1.410) for the codeine and ibuprofen groups, respectively, and the incidence of second operation for control of post-tonsillectomy bleeding for the codeine and ibuprofen groups was 1.9% and 2.2% (P = .54; OR = 1.117; 95% CI:0.781-1.600), respectively. Patients aged 11 to 18 years demonstrated a higher incidence of post-tonsillectomy bleeding events overall. When age is controlled, multivariate logistic regression demonstrated no statistically significant increase in post-tonsillectomy bleeding events among pediatric patients treated with ibuprofen versus patients treated with codeine (readmission: P = .617; OR = 0.932; 95% CI: 0.707-1.228; reoperation: P = .513; OR = 0.887; 95% CI: 0.618-1.272). **Authors' conclusion:** Age is an independent risk factor for post-tonsillectomy bleeding. When age is controlled, there is no statistically significant increase in the incidence of post-tonsillectomy bleeding events among patients treated with ibuprofen when compared to patients treated with codeine.	
Polat, R., et al. (2015). "Comparison of the postoperative analgesic effects of paracetamol-codeine phosphate and naproxen sodium-codeine phosphate for lumbar disk surgery." *Kaohsiung Journal of Medical Sciences* **31**(9): 468-472.	**Type of study:** Randomised placebo controlled trial **Study aim:** To compare the efficacy of paracetamol-codeine phosphate and naproxen sodium-codeine phosphate on postoperative pain and tramadol consumption during the first 24 hours after a lumbar disk surgery. **Methods:** 64 patients were randomly allocated to receive either: · oral paracetamol-codeine (300 mg + 30 mg; Group P), · naproxen sodium-codeine (550 mg + 30 mg; Group N), · or placebo tablets (Group C) 30 minutes prior to induction of anesthesia. Patient-controlled analgesia was supplied postoperatively using tramadol. Pain intensity, tramadol consumption, and side effects were recorded every 1 hour, 2	The authors note that sedation, nausea and vomiting were similar across all three groups (paracetamol/codeine, naproxen/codeine, placebo). *The paper does not provide new information on the safety of low dose codeine.*

Reference	Description	Evaluator comment / conclusion
	hours, 6 hours, 12 hours, and 24 hours after surgery. **Results:** Whole study period pain intensity (visual analogue scale scores) was lower in Group P ($p = 0.007$) and Group N ($p = 0.001$), compared with Group C, however, there was no statistically significant difference between Group P and Group N regarding pain intensity ($p > 0.05$). Tramadol consumption was lower in Group P and Group N, compared with Group C ($p < 0.001$), and in turn the lowest incidence of tramadol consumption was detected in Group P compared with Group N ($p < 0.001$) and Group C ($p < 0.001$). Side effects were similar between the groups. **Authors' conclusion:** Pre-emptive administration of paracetamol-codeine and naproxen sodium-codeine combinations significantly reduced tramadol consumption and provided more effective analgesia compared with placebo. The paracetamol-codeine combination was superior to naproxen sodium-codeine with regard to tramadol consumption.	
Poonai, N., et al. (2015). "Analgesia for fracture pain in children: methodological issues surrounding clinical trials and effectiveness of therapy." *Pain Management* **5**(6): 435-445.	This article discusses the management of fracture pain in children, including barriers to the provision of analgesia to children, the evidence base for analgesic efficacy in children and barriers to the study of outpatient analgesia in children with fractures. The authors note that · Suboptimal analgesia has been reported in the emergency department and following discharge. · Recent concern about the safety of narcotics such as codeine has sparked a renewed interest in opioids such as morphine for pediatric fracture pain. · Opioids are being increasingly used in the clinical setting. · Clinicians are more willing to offer opioids to adults than children. · The existence of limited evidence supporting their use in children is likely a major contributing factor. Authors' conclusion: A closer look at the limitations of designing high-	*The paper contains no new safety information related to the safety of low-dose codeine.* In relation to comparative efficacy the paper references a study by LeMay et al (2013) – an RCT of 81 children with limb trauma comparing ibuprofen + codeine with ibuprofen alone which showed no significant differences in mean pain scores. This study was not referenced in the commissioned study.

Reference	Description	Evaluator comment / conclusion
	quality analgesic trials in children with fractures is needed.	
Stewart, M. W. (2015). "Postoperative pain control after tonsillectomy." *Journal of perianesthesia nursing : official journal of the American Society of PeriAnesthesia Nurses / American Society of PeriAnesthesia Nurses* **30**(3): 249-251.	This paper provides summaries of two published studies. The relevant study for this update is: Bedwell J et al. Otolaryngology—Head and Neck Surgery. December 2014; 151(6):963-966. **Type of study:** Retrospective chart review **Purpose:** To determine if there was a difference in visits to the emergency department (ED) for postoperative pain or dehydration after tonsillectomy when comparing two groups of patients: (1) acetaminophen with ibuprofen and (2) acetaminophen with codeine. **Method and Analysis:** Authors retrospectively reviewed their own patient charts between January 2011 and June 2013. Patients who had undergone tonsillectomy (with or without adenoidectomy) using monopolar electrocautery were categorized into two groups based on the type of postoperative pain management applied: acetaminophen with ibuprofen or acetaminophen with codeine. Return to the ED for pain control or dehydration (due to pain) served as a surrogate for uncontrolled pain because the caregiver had to seek assistance to make the pain manageable for the patient. In addition to pain, other outcomes evaluated were post-operative bleeding, return to surgery, and tolerating oral food on Postoperative Day 1. Statistical analysis aptly included independent t tests, chi-square assessment, and logistic regression. **Results:** During the time frame of the review, 666 patients met the inclusion criteria: 177 had received acetaminophen and codeine and 489 received acetaminophen and ibuprofen. Differences in the two groups included age and antibiotic use. Those in the ibuprofen group were younger (6.2 vs 8.1 years old), whereas those in the codeine group had received antibiotics more often (50.3% vs 5.9%). The difference in antibiotic use was expected because of the timing of best-practice recommendations to avoid prophylactic antibiotic use in this	No dosages and no safety information are included in this summary. The full paper by Bedwell et al has not been reviewed. *There is no information about the safety of low dose codeine in this summary paper.*

Reference	Description	Evaluator comment / conclusion
	population. Statistically, the researchers controlled for the differences in age and antibiotic use. On the primary outcome of pain control, that is, return visits to the ED, the groups did not differ significantly. Of those who had received codeine, 5.1% returned as opposed to 2.6% of those who had received ibuprofen. Furthermore, the effect of antibiotic use on the number of return visits was also not significant. On the secondary outcomes, the groups were the same. Only three patients (1.7%) from the codeine group had postoperative bleeding compared with seven from the ibuprofen group (1.4%). Data were limited for incidence of vomiting and oral intake during the first 24 hours postoperatively. However, in the subsample of 376 patients, 10 (9.2%) who received codeine and 19 (7.1%) who received ibuprofen reported vomiting. Thirteen (11.9%) patients who had received codeine and 30 (11.2%) who got ibuprofen reported inability to tolerate food intake within 24 hours. These findings were not statistically different. **Authors' conclusions:** At time of publication, this study was the largest to address the use of NSAIDs (ibuprofen) for pain relief in patients after tonsillectomy. Although concern about bleeding with the use of NSAIDs has been posited, these study findings were consistent with others that showed no scientific support for this apprehension. The use of ibuprofen with acetaminophen was shown to control post-tonsillectomy pain, as measured by return visits to the ED as well as ibuprofen with codeine. Because the use of codeine in this population is now restricted, the retrospective approach to data collection was the optimal ethical choice.	

Cited references

Bedwell J, Pierce M, Levy M, Shah R. Ibuprofen With Acetaminophen for Postoperative Pain Control Following Tonsillectomy Does Not Increase Emergency Department Utilization. *Otolaryngology—Head and Neck Surgery*. December 2014; 151(6):963-966.

Le May S, Gouin S, Fortin C, Messier A, Robert MA, Julien M. Efficacy of an ibuprofen/codeine combination for pain management in children presenting to the emergency department with a limb injury: a pilot study. *J. Emerg. Med.* 44(2), 536–542 (2013).

Table B5. Harms from low-dose codeine combination medicines use - guidance on pain management

Reference	Description	Evaluator comment / conclusion
Blinderman, C. D. and J. A. Billings (2015). "Comfort care for patients dying in the hospital." *New England Journal of Medicine* **373**(26): 2549-2561.	Guidance on a set of basic palliative care interventions that provide immediate relief of symptoms in a patient who is very close to death. Recommendations for mild to moderate pain include: · acetaminophen (1000mg orally or rectally 3-4 times per day) - not to exceed 4g per day. Liver disease caution · ibuprofen (800mg orally 3-4 times a day) · codeine 30mg (+/-acetaminophen 325mg) orally every 3-4 hours as needed - not to exceed 360mg per day · oxycodone 5mg (+/-acetaminophen 325mg) orally every 3-4 hours as needed – up to 10mg oxycodone 3-4 hourly Recommendations for moderate to severe pain include morphine or hydromorphone, Recommendations for cough include: · codeine 30mg orally every 4-6 hours as needed · morphine (oral or IV doses)	The analgesic recommendations are in keeping with the WHO three step analgesic ladder approach. Low dose codeine is not included in the recommendations. The paper does not mention specific codeine adverse effects but describes/provides treatment recommendations for opioid AEs: · constipation · sedation · agitation · confusion · nausea · pruritus · myoclonus · urinary retention · respiratory depression Patients with renal failure, including those undergoing dialysis, are susceptible to neurotoxic effects of opioids and dose adjustments may also be required for patients who have liver failure. *There is no new information about the safety of low dose codeine in the paper.*
Cohen, N. and D. D. Sommer (2016). "Post-tonsillectomy pain control: Consensus or controversy?" *Pain Management* **6**(1): 31-37.	This review delineates the clinical and pathophysiological basis for post-tonsillectomy pain, types of analgesics and their risk profiles, as well as special considerations in this clinical population and a review of alternative analgesic treatment options. The article presents a summary of recent literature and discusses evidence-based management options to aid medical and allied health	The review refers to the USFDA warnings against using codeine in the paediatric population. *There is no new information about the safety of low dose codeine in the paper.*

Reference	Description	Evaluator comment / conclusion
	professionals who may encounter these patients.	
Cote, C. J. and S. Wilson (2016). "Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures: Update 2016." *Pediatrics* **138** (1) (no pagination)(e20161212).	**Type of article:** guidance to health professionals **Abstract:** The safe sedation of children for procedures requires a systematic approach that includes the following: no administration of sedating medication without the safety net of medical/dental supervision, careful presedation evaluation for underlying medical or surgical conditions that would place the child at increased risk from sedating medications, appropriate fasting for elective procedures and a balance between the depth of sedation and risk for those who are unable to fast because of the urgent nature of the procedure, a focused airway examination for large (kissing) tonsils or anatomic airway abnormalities that might increase the potential for airway obstruction, a clear understanding of the medication's pharmaco-kinetic and pharmacodynamic effects and drug interactions, appropriate training and skills in airway management to allow rescue of the patient, age- and size-appropriate equipment for airway management and venous access, appropriate medications and reversal agents, sufficient numbers of staff to both carry out the procedure and monitor the patient, appropriate physiologic monitoring during and after the procedure, a properly equipped and staffed recovery area, recovery to the presedation level of consciousness before discharge from medical/dental supervision, and appropriate discharge instructions. This report was developed through a collaborative effort of the American Academy of Pediatrics and the American Academy of Pediatric Dentistry to offer pediatric providers updated information and guidance in delivering safe sedation to children.	The only information about codeine in the article is the mention of the US Food and Drug Administration warning in February 2013 regarding the use of codeine for postoperative pain management in children undergoing tonsillectomy, particularly those with OSA. The authors state that the safety issue is that some children have duplicated cytochromes that allow greater than expected conversion of the prodrug codeine to morphine, thus resulting in potential overdose. The authors indicate that codeine should be avoided for post-procedural analgesia in children. *There is no new information about the safety of low dose codeine in the paper.*
Ericsson, E., et al. (2015). "Swedish guidelines for the treatment of pain in tonsil surgery in pediatric patients up to 18 years." *International Journal of Pediatric Otorhinolaryngology* **79**(4):	**Type of article:** guidance for health professionals This article provides evidenced based pain treatment guidelines for tonsil-surgery in Sweden. The guidelines were developed by an updated literature review and clinical expertise in paediatric pain and review by ENT-doctors and anaesthetists. A multimodal pain treatment approach is advocated, including for premedication, during anaesthesia, post-surgery and after hospital discharge. The need for analgesic treatment after tonsillectomy is usually 5-8 days, after	The paper recommends avoiding codeine alone or in combination because a large proportion (up to 36%) of children 3-12 years of age have very limited metabolism (of codeine to morphine) and therefore no analgesic effect, while others metabolise codeine to a high degree and form morphine at levels which can be dangerous. *There is no new information on the safety of low dose*

Reference	Description	Evaluator comment / conclusion
443-450.	tonsillotomy only 3-5 days	*codeine in the paper.*
Fawcett, W. J. and G. Baldini (2015). "Optimal Analgesia During Major Open and Laparoscopic Abdominal Surgery." *Anesthesiology Clinics* **33**(1): 65-78.	**Type of article:** guidance for health professionals This paper provides guidance on a range of analgesic medications and techniques. Some key points in relation to opioids include: · multi-modal opioid-sparing analgesia is the cornerstone · minimising use of opioids is desirable but they do not have to be avoided · leaving patients in unrelieved pain is not acceptable and opioids should be available as rescue analgesia if other methods fail · because of its constipating effects, many providers avoid the use of oral moderate opioids, such as codeine, although drugs such as tramadol acting via opioid and other mechanisms (such as inhibition of reuptake of serotonin and norepinephrine) are used · in the last 5 years there has been an increasing debate about the relevance of opioid-induced hyperalgesia (OIH), in which there is a paradoxic effect from high-potency opioids (e.g., perioperative remifentanil), and further opioid administration increases rather than reduces pain perception. OIH is a complex area and seems to be multifactorial, including both central and peripheral changes in nociceptive processing, the former involving N-methyl-D-aspartate (NMDA) receptors (discussed later), as well as genetic influences. The magnitude of the problem, including the patient's susceptibility, and potential treatments await further studies · if morphine is used it is often because other methods have failed. It is probably best administered intravenously as patient-controlled analgesia (PCA), permitting good control of pain in the early postoperative period, but with good knowledge of its side effects.	*There is no new information about the safety of low dose codeine in the paper.*
Gowan, J. and L. Roller (2016). "Pain management: Acute and chronic non-cancer pain." *Australian Journal of Pharmacy*	This is an education article aimed at pharmacists on the management of acute and chronic non-cancer pain.	*There is no new information on the safety of low-dose codeine in the paper.*

Reference	Description	Evaluator comment / conclusion
97(1148): 74-83.		
Humphries, T. J. and C. M. Kessler (2015). "Managing chronic pain in adults with haemophilia: Current status and call to action." *Haemophilia* **21**(1): 41-51.	**Type of article:** Guidance for health professionals Haemophilic arthroses are associated with acute pain during bleeding episodes and with chronic pain from arthritic complications of repeated bleeding into joints. There are limited data on pain management in haemophilia. Unique haemorrhagic tendencies, potentially exacerbated by antiplatelet aggregation, drug-drug interactions and pharmacologic effects of some of the most common and efficacious medications for other diseases cannot be ignored. Drug therapy generally follows the WHO analgesic ladder, progressing in 3 steps from non-opioid analgesics such as paracetamol or NSAIDs, to paracetamol plus codeine or a low-dose immediate release opioid, to strong opioids. Adjuvant therapies may be used. NSAIDS are contraindicated during acute bleeding episodes. For children, a 2-step approach has been adopted by the WHO.	Guidance on managing pain in haemophilia Main safety concern among health professionals for opioid use is the potential for addiction and abuse. Many patients discontinue opioids because of minor AEs (nausea, constipation, sedation, respiratory depression) Codeine is mentioned but not dosages or specific AEs *There is no new information about the safety of low dose codeine in the paper.*
Lundeberg, S. (2015). "Pain in children - Are we accomplishing the optimal pain treatment?" *Paediatric Anaesthesia* **25**(1): 83-92.	**Type of article:** Guidance for health professionals This article provides guidance on managing pain in children. Multimodal approach preferred, tailored to the child.	Codeine should no longer be used in children – use other opioids such a morphine or oxycodone. This is because of the variable metabolism of codeine to morphine. Many children under age 6 years have limited metabolism and therefore no analgesic effect, while children who metabolise to a high degree form morphine at levels that can be unsafe. Refers to warnings by the FDA and case reports of deaths in children who have had tonsil surgery. *The paper contains no low dose codeine safety information.*
Koneti, K. K. and M. Jones (2016). "Management of acute pain." *Surgery (United Kingdom)* **34**(2): 84-90.	**Type of article:** Guidance for health professionals This article provides advice on the management of acute pain in the perioperative and post-operative periods, based on the WHO 'analgesic ladder' for treatment of cancer pain adapted for the treatment of acute pain.	The paper refers to codeine as the most commonly used drug in the 'weak opioid' category used in Step 2 of the WHO analgesic ladder. The authors mention that it is widely used in dosages of 30-60mg 4-6 hourly and that its use is now contraindicated in

Reference	Description	Evaluator comment / conclusion
		children below age 18 years undergoing tonsillectomy. Side effects are stated to be typical of any opioid (constipation, nausea). High number needed to treat (NNT) and effect on gastrointestinal motility limit codeine's usefulness in postoperative pain. *There is no new information on the safety of low-dose codeine in the paper.*
Malec, M. and J. W. Shega (2015). "Pain Management in the Elderly." *Medical Clinics of North America* **99**(2): 337-350.	**Type of article:** Guidance for health professionals This article notes that persistent pain in older adults is common, and associated with substantial morbidity. The paper reviews pain assessment/ management for older adults, focusing on commonly used analgesics. Selecting analgesics among patients with non-cancer pain is based on the World Health Organization's 3-step pain ladder.	Codeine issues mentioned include · genetic variations in CYP2D6 dependent metabolism resulting in either reduced efficacy or overmedication in rapid metabolisers · drug interactions with drugs that block the CYP2D6 conversion of codeine (e.g. SSRIs paroxetine and fluoxetine and antihistamine diphenhydramine) and · decreased renal function resulting in decreased excretion of some neurotoxic opioid-related metabolites causing adverse effects such as myoclonus and substantial toxicity even with relatively low doses. *There is no new information on the safety of low-dose codeine in the paper.*
Mallya, L., et al. (2016). "Pharmacology in endodontics: A review article." *Research Journal of Pharmaceutical, Biological and Chemical Sciences* **7**(5):	**Type of article:** Guidance for health professionals Pain and periapical infections are most common complaints with which patients approach a dental surgeon and endodontic therapy is one of the most common dental procedures. Pain control and infection management is the foremost aim while performing the endodontic therapy. Therefore, use of analgesics and antibiotics becomes an integral part of dental procedures for treating dental	Not a systematic review Mentions codeine for management of moderate to severe pain as authors consider it has "low" abuse potential (compared with morphine). Good activity by oral route, single oral dose lasts 4-6 hours. Degree of analgesia comparable to aspirin (60mg codeine ~

Reference	Description	Evaluator comment / conclusion
2481-2485.	infections and providing pain free procedures. Nowadays researches aim on finding medicaments with maximum efficacy and minimal side-effects. The goal of endodontic therapy is elimination of microorganisms by thorough mechanical debridement, cleaning and shaping of the canal and three dimensional obturation. But endodontic therapy is incomplete without pharmacologic management. Since microorganisms are the major cause for pulpal injury, many cases require the need of antibiotics .Certain cases require antibiotic prophylaxis and often pain and anxiety is also associated with endodontic therapy . So , as an endodontist it is essential to know the mechanism of action of drug, side effects, dosage of these drugs. In the light of these findings, the present article describes various antibiotics, analgesics used in endodontics, infection control and antibiotic prophylaxis.	600mg aspirin) but this statement is not referenced. *The paper contains no new low dose codeine safety information.*
Marras, F. and P. T. Leali (2016). "The role of drugs in bone pain." *Clinical Cases in Mineral and Bone Metabolism* **13**(2): 93-96.	**Type of article:** Guidance for health professionals Painful symptomatology in the skeletal system can be found in various pathological conditions and can be either localised or diffused. Bone tenderness is common in those who are of an elderly age. **Treatment strategy:** Patients should be informed of the possible causes of their pain and the different therapies that could alleviate it; furthermore they should be encouraged to have an active role in their therapy. It is necessary to prevent the onset of the pain (by the clock) by considering the biological half-life, the bioavailability and the duration of action of the therapy. According to the World Health Organization (WHO), pain treatment is based on a three-step ladder. Adjuvant therapies: Adjuvant therapies are often associated with the drugs in the WHO three step ladder. This heterogeneous group of non-analgesic drugs is used in the treatment of bone pain by bettering the analgesia or reducing the side effects brought on by analgesics. **Authors' conclusion:** In the daily struggle that doctors face to treat their patients, pain management should not be disregarded. Among the various types of pain, bone pain, must not be underestimated but be fought against by using all means available. Patients need to be treated depending on the severity of their pain, NSAIDs should be the preferred choice of treatment for acute pain	Mentions codeine as one of the drugs at Step II on the WHO analgesia ladder but indicates that there is no general consensus on the efficacy of mild opioids as a treatment for mild to moderate pain. *The paper contains no new low dose codeine safety information.*

Reference	Description	Evaluator comment / conclusion
	but not for that of chronic pain. In the case of chronic pain opioids should be used in their most recent formulations as they can guarantee fewer side effects. Patients should also be prescribed adjuvant drugs as well as being given sychological support in order to ensure successful treatment.	
Mifsud, I. and P. V. Bonanno (2015). "Medicines management in the palliative care of cancer patients." *Journal of the Malta College of Pharmacy Practice* **21**(1): 4-12.	**Type of article:** Guidance for health professionals **Abstract:** Cancer is one of the leading causes of death in Malta. Palliative care is a mainstay in the care of such patients. Commonly encountered symptoms include pain, nausea and vomiting, constipation and oropharyngeal complications. All of these bear an impact on the quality of life of the patient and also of the carers. Drug treatment is an integral part of the management of these symptoms. Patients and their carers may have concerns regarding their medication. The community pharmacist is well positioned and competent to support the needs of these patients as part of their holistic care.	This paper provides guidance on pain management in accordance with the WHO three step analgesic ladder. Codeine and tramadol are 2nd step analgesics when non-opiates are insufficient. The paper mentions a ceiling effect with some weak opioids where increasing the dose beyond the maximum licensed dose will not improve analgesia but will expose the patient to more pronounced adverse effects. Opioid side effects include constipation, nausea (both very common), pruritis (common) and respiratory depression and sedation (uncommon). *There is no new information on the safety of low-dose codeine in the paper.*
Mishra, P., et al. (2015). "Is day surgery failing our children?" *Journal of Paediatrics and Child Health* **51**(10): 960-961.	**Type of paper:** Commentary Issues discussed include: · Advances in paediatric surgery, including less invasive surgical techniques and more refined anaesthetic methods, have resulted in increasing numbers of surgical day cases/short stay procedures. In the United States, an estimated 84% of paediatric surgery is performed as a day stay procedure, facilitating an increasing trend towards early discharge. · While short stay cases curtail costs, reduce disruption to families and minimise risk of nosocomial infection; very often, the responsibility for postoperative pain management rests with parents.	The authors discuss the removal of the 2nd step (codeine) from the WHO analgesic ladder for children, so that once non-opiate analgesics are insufficient, the next step is morphine. *The paper does not provide new information on the safety of low dose codeine.*

Reference	Description	Evaluator comment / conclusion
	· Effective pain management requires a multimodal approach, targeting prescription and administration factors to reduce the burden on parents. · It is vital that barriers to effective pain relief such as parental misconceptions are addressed and medication with appropriate potency made available. · Further research is needed to establish the best combination of interventions to maximise pain control in the home setting. In the interim, surgeons are left with a difficult problem: if pain control cannot be achieved at home ('Primum non nocere'), should these children be discharged?	
Naples, J. G., et al. (2016). "The Role of Opioid Analgesics in Geriatric Pain Management." *Clinics in Geriatric Medicine* **32**(4): 725-735.	**Type of article:** Guidance for health professionals Authors' key points: · Opioids remain a treatment option for moderate to severe chronic noncancer pain when nonopioid analgesics and nonpharmacologic therapies do not provide adequate relief. · Age-related changes in pharmacokinetics (decreases in hepatic and renal function) and pharmacodynamics make older adults more susceptible to adverse consequences associated with opioids, including falls, fractures, and delirium. · To optimize the use of opioids, avoid those that have not been studied in older adults. · Start with the lowest available dose of an immediate-release product, and consult pharmacists or pain experts for challenging cases, including those requiring high doses.	Guidance on management of chronic non-cancer pain (CNCP) Recommends using those opioids (tramadol, oxycodone and morphine) in which PK, PD and efficacy studies have been conducted in older persons. *The paper contains no new low dose codeine safety information.*
Pai, S. L., et al. (2015). "Analgesic considerations for liver transplantation patients." *Current Clinical Pharmacology* **10**(1): 54-65.	The purpose of this review is to summarize the pharmacokinetics and pharmacodynamics of the analgesic medications commonly administered to this patient population. Codeine is metabolized by the liver to codeine-6 glucuronide and norcodeine, and a small fraction is O demethylated to morphine. Its conversion to morphine provides the majority of its clinical analgesic effect. Morphine is then metabolized to the active morphine-6-	The authors note that no clinical studies have investigated the metabolism of codeine in patients with liver dysfunction. *Codeine should not be used for pain management in patients with end stage liver disease.*

Reference	Description	Evaluator comment / conclusion
	glucuronide (M6G) [41, 42]. It is hypothesized that the serum levels are most likely to be decreased due to decreased levels of one of the most important drug-metabolizing enzymes involved in the metabolism of xenobiotics, Cytochrome P450 2D6 (CYP2D6) in the diseased liver [43]. The alteration in metabolism cannot be predicted as the liver disease may affect the activities of specific metabolizing enzymes differently; for example, CYP2C19 is more sensitive than CYP2D6 [44-46]. Nonetheless, clinically significant toxic effects due to opioid excess have been reported in ultra-rapid codeine metabolizers, which suggest that the risk of codeine toxicity depends on genotype [42, 47, 48]. Codeine is also metabolized to produce hydrocodone in quantities of up to 11% of the codeine concentration found in urinalysis [49]. Currently, no clinical studies have investigated the metabolism of codeine in patients with liver dysfunction. Along with the possible genetic and enzymatic variations on liver metabolism, codeine would likely not be the most suitable pain management choice in ESLD patients.	
Palmer, G. M. (2016). "Pain management in the acute care setting: Update and debates." *Journal of Paediatrics and Child Health* **52**(2): 213-220.	This review article focuses on pain management in the paediatric acute care setting, noting that it is underutilised and can be improved. It describes the evolving understanding of relevant pharmacogenomics and safety data of the various analgesic agents with a focus on agents available in Australia and New Zealand. It highlights the concerns with the use of codeine in children and discusses alternative oral opioids. It also addresses the issue of multimodal analgesia where a single agent is insufficient.	The author notes that codeine requires conversion to morphine by the enzyme CYP2D6 which has 4 phenotypes of activity (poor - PM, intermediate - IM, extensive – EM and ultra-rapid - UM - metabolisers). This results in the poor efficacy seen in some trials and in deaths in association with UM in breast-fed neonates, toddlers and older children. This risk has led several regulatory bodies to exclude use under 16-18 years of age, and to the removal of codeine from the WHO analgesic ladder [for children]. The author recommends avoiding codeine and using an alternative opioid. If no alternative available use only under medical supervision. Maximum acute dosing is 30-60mg 6 hourly. *There is no new information on the safety of low-dose codeine in the paper.*

Reference	Description	Evaluator comment / conclusion
Rodriguez, M. C., et al. (2016). "Assessment and management of pain in pediatric otolaryngology." *International Journal of Pediatric Otorhinolaryngology* 90: 138-149.	**Type of study:** Narrative review **Objectives:** to address current definitions of pain, its physiological mechanisms and consequences of inadequate management and to guide clinicians in the management of pain in paediatric ENT. Some key issues: · optimal pharmacological pain management requires and integrated approach of non-pharmacological strategies, non-opioid analgesics, opioid analgesics and adjuvant therapies · use two-step strategy · administer regularly not 'as required' · use appropriate route of administration · dapt treatment to the child	Guidance on in the management of pain in paediatric ENT. Use of codeine is not recommended as its efficacy and safety profile have been questioned due to an evolving understanding of the pharmacogenetics of its metabolism: · CYP2D6 – enzyme responsible for codeine metabolism to morphine · uridine diphosphate-glucuronosyltransferase 2B7 (UGT2B7) – enzyme responsible for codeine metabolism to codeine-6-glucuronide Strong opioids are an essential element in pain management *The paper contains no new low dose codeine safety information.*
Ruest, S. and A. Anderson (2016). "Management of acute pediatric pain in the emergency department." *Current Opinion in Pediatrics* **28**(3): 298-304.	**Purpose of review:** This article provides a summary of recommendations for the multimodal and multidisciplinary approach to acute pediatric pain management and highlights recent research on this topic. **Recent findings:** Recent literature has focused on updating recommendations for the use of various analgesics in the pediatric population. While codeine is no longer recommended due to increasing evidence of adverse effects, the more liberal use of intranasal fentanyl is now encouraged because of the ease of administration and rapid delivery. The evidence base for the use of ultrasound-guided regional nerve blocks by qualified providers in the acute pediatric pain setting continues to grow. **Summary:** The pediatric emergency medicine provider should be able to assess pain and develop individualized pain plans by utilizing a range of nonpharmacologic and pharmacologic strategies. Knowledge of the most recent	The article notes that opioid analgesics may be required for moderate to severe pain in children. Notes that a 2012 review of all published case reports of severe opioid respirator depression in children followed: use of morphine in children with renal impairment, medication dosing or administration errors and codeine use in children who are aultrarapid metabolisers. Mentions CYP 2D6 and the FDA black box contraindication for children < 12 yrs and children <18 years with OSA or post-tonsillectomy. *The paper contains no new low dose codeine safety*

Reference	Description	Evaluator comment / conclusion
	literature and changes in recommendations for various pain medications is essential.	*information.*
Schug, S. A. and C. Chandrasena (2015). "Pain management of the cancer patient." *Expert Opinion on Pharmacotherapy* **16**(1): 5-15.	**Introduction:** Cancer pain is one of the most important symptoms of malignant disease, which has a major impact on the quality of life of cancer patients. Therefore, it needs to be treated appropriately after a careful assessment of the types and causes of pain. **Areas covered:** The mainstay of cancer pain management is systemic pharmacotherapy. This is, in principle, still based on the WHO guidelines initially published in 1986. Although these have been validated, they are not evidence-based. The principles are a stepladder approach using non-opioids, weak and then strong opioids. In addition, adjuvants can be added at any step to address specific situations such as bone or neuropathic pain. Patients, even if they are on long-acting opioids, need to be provided with immediate release opioids for breakthrough pain. In case of inefficacy or severe adverse effects of one opioid, rotation to another opioid is recommended. **Expert opinion:** There is a major need for more and better randomized controlled trials in the setting of cancer pain as the lack of evidence is hampering the improvement of current treatment guidelines.	In the WHO analgesia ladder, step II is a weak opioid such as codeine or dihydrocodeine (DHC) or tramadol administered orally in combinaton with non-opioids for moderate pain. The authors note there is increasing support for omission of this step and moving directly to low-dose strong opioids. The separation of 'weak opioids' from strong opioids is arbitrary and a specific pharmacodynamic differentiation does not exist. In addition, advantages of one weak opioid over another have not been properly evaluated and the question of ceiling effects has also not been addressed. The three trials which addressed the utility of WHO step II opioids all had significant methdoological flaws, insufficient statistical power and selection bias. The authors mention that CYP2D6 polymorphisms result in a range of metabolic patterns from ultra-rapid to ultra-slow metabolisers who experience anything from significant morphine effects (and AEs) to no analgesia at all. Codeine also has a high propensity to induce constipation. Recommends not using codeine if other opiods are available. *The paper contains no new low dose codeine safety information.*

Reference	Description	Evaluator comment / conclusion
Ternullo, S. and A. Diantonio (2015). "Assessment and treatment of pain in children." *U.S Pharmacist* **40**(5): HS11-HS20.	This article provides an overview of the available evidence-based therapeutic options for acute pain management.	Codeine is widely used globally and is available OTC in South Africa. The authors indicate that it has poor analgesic properties and carries a high risk of side effects, especially in children. No information is provided on the side effects. The authors note that the EMA has prohibited its use to treat coughs and colds in children under 12 years and that the FDA is also investigating the risks of codeine cough and cold medicines in children. *The paper contains no new low dose codeine safety information.*
Walker, S. M. (2015). "Pain after surgery in children: Clinical recommendations." *Current Opinion in Anaesthesiology* **28**(5): 570-576.	**Purpose of review:** To summarize recent data related to the safety and efficacy of postoperative analgesia in children that influence clinical practice recommendations. **Recent findings:** Postoperative pain continues to be experienced by hospitalized children and following discharge after short stay or ambulatory surgery. Updated recommendations for post-tonsillectomy analgesia exclude codeine and suggest regular administration of paracetamol and NSAID, but evidence for the most appropriate dose and type of opioid for rescue analgesia is limited. The incidence of opioid-related respiratory depression/over-sedation in hospitalized children ranges from 0.11-0.41%, with recent large series identifying high risk groups and contributory factors that can be targeted to minimize the risk of serious or permanent harm. Data demonstrating feasibility and safety of regional analgesic techniques is increasing, but additional and procedure-specific evidence would improve technique selection and inform discussions of efficacy and safety with patients and families/carers. Persistent postsurgical pain is increasingly recognized following major surgery in adolescents. Evaluation of potential predictive factors in clinical studies, and investigation of underlying mechanisms in laboratory studies, can identify targets for both pharmacological and non-pharmacological interventions.	Guidance on post-operative analgesia in children The paper refers to the regulatory agencies' (USFDA, EMA, UK MHRA, Australian TGA) warnings against using codeine in children and contraindicated use after tonsillectomy. Recommends multimodal analgesia using combination of paracetamol and NSAID. Opioid AEs mentioned include pruritus, post-operative nausea and vomiting, respiratory depression/over sedation, but the most common adverse events were drug administration or prescription errors and pump malfunctions. Important to provide good analgesia to prevent the development of persistent post-surgical pain. *The paper contains no new low dose codeine safety information.*

Reference	Description	Evaluator comment / conclusion
	Summary: Recommendations for postoperative pain in children continue to evolve, with data incorporated from randomized controlled trials, case series and large audits. Management of pain following surgery in children needs to encompass not only efficacy and safety in the immediate perioperative period, but also consider pain following discharge after ambulatory surgery, and the potential risk of persistent postsurgical pain following major surgery.	
Wehrer, M. (2015). "Pain management considerations in cirrhosis." *U.S Pharmacist* **40**(12): HS5-HS11.	**Abstract:** Cirrhosis is a heterogeneous diagnosis that impacts liver function, including the metabolism and clearance of medications, but the exact effect remains unclear. Misconceptions and significant practice vanability exist among healthcare professionals regarding analgesic use in patients with liver dysfunction. Based on limited safety and efficacy data, acetaminophen is the preferred analgesic in patients with liver disease who are not actively drinking, and it may be dosed up to 2 to 3 g a day. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided due to their adverse effects of renal impairment, fluid retention, and increased bleeding risk. Opioids should be used cautiously and initiated with immediate-release products at low doses with extended intervals and close monitoring. All pain medications should be titrated carefully to achieve safe and adequate pain relief in patients with hepatic impairment.	Guidance for managing pain in patient with cirrhosis There is a high prevalence of pain among patients with chronic and end stage liver disease and it is often undertreated. Codeine not recommended in liver dysfunction due to a lack of studies in cirrhotic patients. Codeine's serum levels may be more variable than in healthy patients due to decreased CYP activity causing diminished analgesic effect. *There is no specific safety information for low-dose codeine in this paper.*
Welker, K. L. and M. B. Mycyk (2016). "Pharmacology in the Geriatric Patient." *Emergency Medicine Clinics of North America* **34**(3): 469-481.	Type of article: Guidance for health professionals Authors' key points · A higher proportion of emergency department patients in the future will be elderly. · Elderly patients are often prescribed multiple medications by multiple providers. · Physiological changes with age affect drug metabolism, effect, and elimination. · Drug interactions are more common in elderly patients. · Involving clinical pharmacists can avoid drug interactions and polypharmacy and improve resource utilization.	Guidance on how pharmacology in the geriatric patient affects treatment. Opioid analgesics include fentanyl, hydromorphone, morphine, oxycodone, hydrocodone and codeine. Tramadol has multiple effects at various receptors. Elderly patients are more sensitive to these medications and usually require decreased dosing. Adverse effects of opioids include: · increased risk of falls · sedation

Reference	Description	Evaluator comment / conclusion
		· constipation · respiratory depression · medication errors (due to multiple prescribers or to patient mistakenly taking incorrect medicines or multiple doses due to cognitive and eyesight decline The elderly also have an increased risk of drug interactions (with other drugs, alcohol, food, nutritional supplements and also drug-disease and drug-nutritional status interactions). Causes of drug interactions are either pharmacokinetic or pharmacodynamics. *There is no specific safety information for low-dose codeine in this paper.*
Wells, R. E., et al. (2016). "Managing Migraine During Pregnancy and Lactation." *Current Neurology and Neuroscience Reports* **16**(4) (no pagination)(40).	**Type of article:** Guidance for health professionals This article provides advice on the management of migraine in women during pregnancy, including: differentiating migraine from several dangerous secondary headache disorders; using non-pharmacological migraine treatments; and understanding the safety of medications and dietary supplements in pregnancy and safe treatment options during lactation. The paper notes that new controversy exists over the safety of several historically routine and safe migraine treatment options in pregnancy, such as magnesium, acetaminophen, ondansetron, and butalbital. Opioids have long been considered one of the safer options for treatment of headaches during pregnancy but providers are now advised not to prescribe opioids as first-line treatment of headaches given the risks with long term use (dependence, addiction, medication overuse headache etc.).	The paper provides a table which indicates that potential risks to foetus from codeine include: · ones for all opioids: physical dependence and withdrawal, retardation of growth, and neonatal respiratory depression with high doses; if prolonged use during pregnancy, physical dependence and postpartum withdrawal may occur (infants should be monitored for neonatal opioid withdrawal syndrome) and · ones specific for codeine: 1st trimester use possibly associated with anomalies such as respiratory tract malformation, inguinal hernia, umbilical hernia, pyloric stenosis, cardiac and circulatory system defects, cleft lip and palate, and hydrocephaly. The risks to neonate during breast feeding include

Reference	Description	Evaluator comment / conclusion
		sedation, hypopnoea/apnoea, and constipation. No dosage information is provided. **Note:** No references are provided for the codeine specific 1st trimester risks and they not reflected in either the TGA or the FDA pregnancy categorisations for codeine https://www.drugs.com/pregnancy/codeine.html The paper by Anonymous referenced in Table B1 above, included the information that codeine is the best-evaluated weak opioid during pregnancy with no noteworthy reports of malformations. *Relevance to the safety of low dose codeine combination products is uncertain.*
Witkop, M. L., et al. (2016). "Medical co-morbidities of patients with haemophilia: pain, obesity and hepatitis C." *Haemophilia* **22**: 47-53.	This review article discusses the co-morbidities that patients with hemophilia (PWH) experience now that they have a longer life expectancy, focussing on three common disease states: chronic pain, obesity and hepatitis C. The key points about pain are: · Pain is a significant co-morbidity in PWH · Even with primary prophylaxis many patients, including under age 25, experience significant chronic pain · Acetominophen, non-steroidals and opioids are all commonly used to treat pain in PWH, but have well recognised side effects and complications · In the US, the FDA has recommended abuse-deterrent formulations of opiods to decrease the risk of abuse and misuse · Specific guidelines for pain management in PWH need to be developed.	The authors note there is little data to guide providers in pain treatment of PWH. Acetominophen is effective for some PWH but risks may outweigh benefits in those with history of cirrhosis. NSAIDs may be highly effective for hemarthropathy symptoms but associated bleeding and kidney risks must be considered. Opioids are frequently used, but increased risks of adverse events to codeine in children including severe respiratory depression and death. *There is no specific information about the safety of low-dose codeine in the paper.*

Reference	Description	Evaluator comment / conclusion
Zaidan, I. and A. Lent (2016). "Post-tonsillectomy pain in children: The postcodeine era." *U.S Pharmacist* **41**(5): 31-34.	This article provides advice to pharmacists on the change in post-tonsillectomy pain control recommendations for analgesia after tonsillectomy with or without adenoidectomy, to enable them to assist providers select safe analgesics.	The paper refers to the USFDA Drug Safety Communication advising practitioners that codeine use in certain children after tonsillectomy may lead to rare but life-threatening respiratory failure and death. *There is no specific information about the safety of low-dose codeine in the paper.*

Table B6. Harms from low-dose codeine combination medicines use - medication overuse headache (MOH)

Reference	Description	Evaluator comment / conclusion
Chiang, C. C., et al. (2015). "Treatment of medication-overuse headache: A systematic review." *Cephalalgia* **36**(4): 371-386.	This review is a discussion of different treatment strategies for medication-overuse headache (MOH) based on a systematic review of PubMed articles discussing the treatment and prognosis of MOH published between 2004 and August 2014. Based on current available evidence and the systemic toxicity of overusing acute headache medication, the authors recommend discontinuation of the overused medication with the addition of preventive medication.	The authors comment that longitudinal studies have suggested that medications containing barbiturates and opioids are associated with the highest risk of developing MOH, while triptans and NSAIDs are associated with lower risk. Less than 10% of MOH patients overused opioids in the studies reviewed. The actual rate of opioid overuse in the general population is likely to be higher since some studies intentionally excluded patients with opioid overuse. Among studies that included opioid overusers, patients with opioid overuse tended to have a less favorable outcome with regard to headache frequency, relapse rate, and pain improvement compared to patients overusing other kinds of medications. *The paper contains no specific safety information for low dose codeine.*
Dong, Z., et al. (2015). "Medication-overuse headache in China: Clinical profile, and an evaluation of the ICHD-3 beta diagnostic criteria." *Cephalalgia* **35**(8): 644-651.	**Type of study:** Clinical case series **Purpose:** To validate the ICHD-3 beta diagnostic criteria for medication overuse headache (MOH). **Methods:** Retrospective review of the clinical features of 240 consecutive patients with MOH (55 males, 185 females), against the criteria of the several versions of ICHD (II, IIR and 3-beta). **Results:** Compared with those with other headaches, patients with MOH were more likely to be less well educated (64.6% vs 42.0% for secondary school or lower, $p < 0.0001$), and on lower annual incomes (72.3% vs 56.0% for an income of Chinese yuan (CNY) 30,000 or less, $p < 0.0001$). Combination analgesics were	Codeine was overused in 3 of 217 patients (1.4%). The authors comment that “Overuse of opioids is uncommon in China because the use of these drugs is severely restricted.” *The relevance of the paper to the Australian context is unclear.*

Reference	Description	Evaluator comment / conclusion
	the most commonly overused medications, and, caffeine (89.9%), aminopyrine (70.0%), phenacetin (53.9%) and phenobarbital (48.8%) were the most commonly used specific components of these. Only two patients (0.8%) had previously been given the diagnosis of MOH and mean time to diagnosis after the estimated onset of the disorder was 4.0 years. The majority of patients (83.7%) improved with treatment. All 240 patients fulfilled the diagnostic criteria for MOH according to ICHD-3 beta; only 134 (55.8%) satisfied the diagnostic criteria for definite MOH according to ICHD-II, while 195 (81.2%) met those of ICHD-IIR. **Authors' conclusions:** MOH in China is associated with lower educational level and annual income. MOH has rarely been diagnosed and correctly treated in China. ICHD-3 beta appears to be more appropriate for the diagnosis of MOH than previous versions.	
O'Sullivan, E. M., et al. (2016). "Headache management in community pharmacies." *Irish Medical Journal* **109**(3): 373.	**Type of study:** Survey This article describes the results of a questionnaire administered to 1023 patients requesting headache treatment at community pharmacies in the Munster region of Ireland. 53.3% had not been previously diagnosed by a GP and 49.6% had never sought advice from a pharmacist. Likely diagnoses were definite or probable episodic migraine (47.2%), tension-type headache (30.3%) and medication overuse headache (MOH) (11.8%).	The paper notes that codeine-based products carry risks of habituation, tolerance, dependence, and development of MOH. *The paper does not provide new information about the safety of low dose codeine.*
Silberstein, S. D. (2016). "Considerations for management of migraine symptoms in the primary care setting." *Postgraduate Medicine* **128**(5): 523-537.	**Type of article:** Guidance to primary care physicians (PCPs) on managing migraine. Migraine is a common disabling brain disorder that affects one in seven US citizens annually and is predominantly managed in a primary care setting. This review provides an overview of the prevalence, symptoms, burden, and diagnosis of migraine with a focus on adults. Important aspects of migraine management, such as medication overuse and chronic migraine, are highlighted and insight is provided into factors for consideration when prescribing acute/abortive treatment for migraine to ensure that individual patients receive optimal pharmaceutical management. The effects of associated symptoms, e.g.	This paper refers to the publication of the 3rd edition of the International Classification of Headache Disorders (ICHD-III) (beta version) which has identified six categories of migraine, including chronic migraine. This is defined as a headache occurring on ≥ 15 days/month for ≥ 3 months. A confounder for the diagnosis of migraine is medication-overuse headache (MOH) which is commonly associated with chronic migraine. It is defined as a headache occurring on ≥ 15 days/month, developing as a consequence of regular overuse of

Reference	Description	Evaluator comment / conclusion
	nausea/vomiting, on treatment efficacy are pertinent in migraine; however, many therapy options, including alternative delivery systems, are available, thus facilitating the selection of optimal treatment for an individual patient.	acute or symptomatic headache medication (on ≥ 10 or ≥ 15 days/month, depending on the medication) for ≥ 3 months. Patients can have both chronic migraine and MOH. Refers to the American Headache Society's evidence-based recommendations for the acute pharmacologic treatment of migraine. Codeine 30mg is mentioned as a "possibly effective" medication for acute migraine, codeine 25mg/acetominophen 400mg is "probably effective". *There is no safety information for low-dose codeine in this review.*
Westergaard, M. L., et al. (2015). "Prescription pain medications and chronic headache in Denmark: Implications for preventing medication overuse." European *Journal of Clinical Pharmacology* **71**(7): 851-860.	**Type of study:** cross-sectional population based study This paper describes the results of a study of prescription pain medications most commonly dispensed to people with chronic headache (CH), particularly those with medication-overuse headache (MOH). It was a cross-sectional population based study based on data from the Danish National Health Survey linked at the individual level to the Danish National Prescription Registry. Analysis was of prescription pain medications dispensed within 1 year to 68,518 respondents of a national health survey. Participants with headache >15 days per month for 3 months were classified as having CH. Those with CH and over-the-counter analgesic use >15 days per month or purchase of >20 or >30 defined daily doses (DDDs) of prescription pain medication per month (depending on the drug) were classified as having MOH. Among those with CH (adjusted prevalence 3.3% CI 3.2-3.5%), pain medications most commonly dispensed were paracetamol, tramadol, ibuprofen and codeine.	The authors found that the prevalence of MOH among the respondents was 1.8% (1.7-1.9). Use of codeine was 8 times higher in terms of DDDs among persons with MOH compared with those with CH. Among all MOH cases, 96.2% reported overuse of OTC analgesics. 10% purchased plain codeine but this was used in combination with other medications. The authors note that opioids are not recommended for CH because few improve in terms of function or sustained pain reduction and the risk of dependence outweighs benefits. The authors also note that longitudinal studies have demonstrated a link between opoid use and headache chronification. MOH can arise in susceptible individuals even if the main indication for pain treatment is not headache. Opioid use among people with CH may represent inappropriate opioid use for headache, or the development of MOH in people treated with opioids

Reference	Description	Evaluator comment / conclusion
		for other pain. *The study analyses prescription analgesic use. Apart from information on the relationship between codeine and MOH, there is no other information about the safety of low-dose codeine in the paper.*

Table B7. Harms from low-dose codeine combination medicines use – pharmacogenomics

Reference	Description	Evaluator comment / conclusion
Collins, S. L., et al. (2016). "Advances in the Pharmacogenomics of Adverse Drug Reactions." Drug Safety 39(1): 15-27.	This article discusses the rapid development in pharmacogenomics which has improved understanding of adverse drug reactions. This improved knowledge has largely been the result of improved sequencing technologies and falling costs in this area, as well as improved statistical techniques to analyse the data derived from studies. While the genetic reasons behind adverse drug reactions are becoming better understood, translation of this knowledge, particularly in terms of biomarkers that might be clinically applicable at the bedside, has been more difficult. Understanding of the technologies and their application is limited among practising clinicians. The cost of some of the technologies available may also be prohibitive in stretched healthcare economies. As education about the potential for applying pharmacogenomics improves and costs fall, understanding of adverse drug reactions and application of this knowledge in a clinical setting should improve.	The paper refers to the known issue of CYP2D6 ultra-rapid metabolisers forming higher quantities of morphine, predisposing to respiratory depression, especially in infants and young children. The paper provides no other information about the safety of low dose codeine.
Gammal RS, Crews KR, Haider CE, et al. (2016) Pharmacogenetics for safe codeine use in sickle cell disease. *Pediatrics* **138**(1):e20153497	**Abstract:** After postoperative deaths in children who were prescribed codeine, several pediatric hospitals have removed it from their formularies. These deaths were attributed to atypical cytochrome P450 2D6 (CYP2D6) pharmacogenetics, which is also implicated in poor analgesic response. Because codeine is often prescribed to patients with sickle cell disease and is now the only Schedule III opioid analgesic in the United States, we implemented a precision medicine approach to safely maintain codeine as an option for pain control. Here we describe the implementation of pharmacogenetics-based codeine prescribing that accounts for CYP2D6 metabolizer status. Clinical decision support was implemented within the electronic health record to guide prescribing of codeine with the goal of preventing its use after tonsillectomy or adenoidectomy and in CYP2D6 ultra-rapid and poor metabolizer (high-risk) genotypes. As of June 2015, CYP2D6 genotype results had been reported for 2468 unique patients. Of the 830 patients with sickle cell disease, 621 (75%) had a CYP2D6 genotype result; 7.1% were ultra-rapid or possible ultra-rapid metabolizers, and 1.4% were poor metabolizers. Interruptive alerts recommended against	This paper describes the implementation of pharmacogenetics testing to enable codeine to be used safely in children with sickle cell disease at St Jude Children's Research Hospital. The process involves undertaking pharmacogenetics testing and incorporating the test results into the electronic health record with clinical decision support to guide individualised pharmacy prescription by using clinical support tools. *There is no new safety information about low-dose codeine in this paper.*

Reference	Description	Evaluator comment / conclusion
	codeine for patients with high-risk CYP2D6 status. None of the patients with an ultra-rapid or poor metabolizer genotype were prescribed codeine. Using genetics to tailor analgesic prescribing retained an important therapeutic option by limiting codeine use to patients who could safely receive and benefit from it. Our efforts represent an evidence-based, innovative medication safety strategy to prevent adverse drug events, which is a model for the use of pharmacogenetics to optimize drug therapy in specialized pediatric populations.	
Haufroid, V. and P. Hantson (2015). "CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants." *Clinical Toxicology* **53**(6): 501-510.	This review of PubMed literature up to August 2013 focuses on CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants in humans. For opioid analagesics, CYP2D6 ultra-rapid metabolisers are more likely to experience the adverse effects of codeine and tramadol. Opioid analgesics that do not rely on CYP2D6 for therapeutic activity, such as morphine and hydromorphone, may therefore be a better alternative to codeine and tramadol, with the limitation that these drugs have their own set of adverse reactions.	*There is no new information on the safety of low-dose codeine in the paper.*
Hudak, M. L. (2016). "Codeine pharmacogenetics as a proof of concept for pediatric precision medicine." *Pediatrics* **138**(1) (no pagination) (e20161359).	This article is an editorial related to the paper by Gammal RS, et al. reviewed above. The editorial indicates that the significance of the Gammal study is the successful demonstration of a proof of concept implementation of pharmacogenetics principles in children.	*There is no new information on the safety of low-dose codeine in the editorial or referenced paper, which is reviewed above.*
Nicholson, W. T. and C. M. Formea (2015). "Clinical perspective on the clinical pharmacogenetics implementation consortium updated 2014 guidelines for CYP2D6 and codeine."	The paper discusses the need to be aware of the complex interplay between clinical care and the proper application of pharmacogenomics in the context of the updated (2014) Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. The CPIC guidelines recommend avoidance of codeine in CYP2D6 poor and ultrarapid metabolisers and indicate that tramadol, hydrocodone and oxycodone are not good analgesic alternatives when	*There is no new information on the safety of low-dose codeine in the paper.*

Reference	Description	Evaluator comment / conclusion
Clinical Chemistry **61**(2): 319-321.	metabolic concerns exist with CYP2D6.	
Ting, S. and S. Schug (2016). "The pharmacogenomics of pain management: Prospects for personalized medicine." *Journal of Pain Research* **9**: 49-56.	**Type of study:** Narrative review Pain is a common symptom that can be complex to treat. Analgesic medications are the mainstay treatment, but there is wide inter-individual variability in analgesic response and adverse effects. Pharmacogenomics is the study of inherited genetic traits that result in these individual responses to drugs. This narrative review covers the current under-standing of the pharmacogenomics of pain, examining common genes affecting metabolism of analgesic medications, their distribution throughout the body, and end organ effects.	The author's note that CYP2D6 involved in the metabolism of around a quarter of all currently marketed drugs, including common analgesics such as codeine, dihydrocodeine and tramadol. Depending on their CYP2D6 function, patients can be categorised as poor, intermediate, extensive, or ultrarapid metabolisers. Knowledge of a patient's CYP2D6 phenotype can guide appropriate analgesic dose and reduce the number of adverse reactions. *This paper does not provide information on the safety of low-dose codeine.*
Turner, R. M. and M. Pirmohamed (2015). "Pharmacogenetics of adverse drug reactions." *Advances in Predictive, Preventive and Personalised Medicine* **9**: 109-156.	This paper discusses advances in pharmacogenetics and its potential role for understanding and preventing ADRs. The paper highlights challenges for translating knowledge about a pharmacogenetic association into a clinical test that benefits patient safety. The authors note that the development of international consortia alongside the potential of next generation sequencing technologies and other innovations offer prospects for future advances in pharmacogenetics to reduce the burden of ADRs.	The paper includes a discussion of the principal pharmacokinetic pathways for codeine and the effect of CYP2D6 polymorphism on its metabolism. The authors note a growing series of case reports documenting severe ADRs after "standard codeine use" [undefined] in ultrarapid metabolisers (UM) in neonates, children and adults. The opioidergic ADRs include: · severe epigastric pain · euphoria · dizziness · CNS/respiratory depression · death, including death in a neonate breast fed by an UM mother. The authors note, however, that documented case

Reference	Description	Evaluator comment / conclusion
		reports of severe ADRs are rare when compared to the prevalence of UM in the population, suggesting there are additional genetic and non-genetic susceptibility factors. Other risk factors may include renal dysfunction, drug inhibitors of CYP3A4 (which metabolises codeine to the inactive norcodeine), ontogeny (development) and repeated episodes of hypoxia. CYP2D6 is involved in the metabolism of other opioids including oxycodone, hydrocodone and tramadol. *There is no new information on the safety of low-dose codeine in the paper.*

Attachment 1: Search strategies

Incremental effectiveness of codeine combination products		
Database: Cochrane Library **Date Run: 18/11/16** **Search strategy:** ---------- **#1** "codeine":ti,ab,kw (Word variations have been searched) 1271 **#2** paracetamol:ti,ab,kw (Word variations have been searched) 4454 **#3** ibuprofen:ti,ab,kw (Word variations have been searched) 2896 **#4** Aspirin or acetylsalicylic acid:ti,ab,kw (Word variations have been searched) 11578 **#5** #1 and #2 350 **#6** #1 and #3 184 **#7** #1 and #4 153 **#8** treatment outcome:ti,ab,kw (Word variations have been searched) 192970 **#9** drug effectiveness or drug efficacy:ti,ab,kw (Word variations have been searched) 105018 **#10** pain:ti,ab,kw (Word variations have been searched) 92884 **#11** analgesia:ti,ab,kw (Word variations have been searched) 22487 **#12** #8 or #9 or #10 or #11 312425 **#13** #5 and #12 326 **#14** #6 and #12 173 **#15** #7 and #12 132 **#16** #13 or #14 or #15 Publication Year from 2015 to 2016 46	**Database: Ovid MEDLINE(R) without Revisions <1996 to November Week 2 2016>** **Search Strategy:** ---------- **1.** codeine/ (1475) **2.** paracetamol/ (9835) **3.** ibuprofen/ (4920) **4.** (Aspirin or acetylsalicylic acid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (34063) **5.** 1 and 2 (309) **6.** 1 and 3 (90) **7.** 1 and 4 (35) **8.** treatment outcome/ (720516) **9.** drug effectiveness.mp. or drug efficacy/ (329) **10.** pain/ (73945) **11.** analgesia/ (6925) **12.** 8 or 9 or 10 or 11 (790289) **13.** 5 and 12 (106) **14.** 6 and 12 (36) **15.** 7 and 12 (9) **16.** 13 or 14 or 15 (116) **17.** limit 16 to (english language and humans and yr="2015 -Current") (8)	**Database: Embase <1980 to 2016 November 16>** **Search Strategy:** ---------- **1.** codeine/ (18345) **2.** paracetamol/ (75246) **3.** ibuprofen/ (42242) **4.** (Aspirin or acetylsalicylic acid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (192384) **5.** 1 and 2 (6647) **6.** 1 and 3 (2521) **7.** 1 and 4 (3394) **8.** drug effectiveness.mp. or drug efficacy/ (720405) **9.** pain/ (371236) **10.** analgesia/ (115041) **11.** 8 or 9 or 10 (1120851) **12.** 5 and 11 (3720) **13.** 6 and 11 (1531) **14.** 7 and 11 (1666) **15.** 12 or 13 or 14 (4174) **16.** limit 15 to (human and english language and yr="2015 -Current") (260)

Codeine combination products misuse		
Database: Cochrane Library **Date Run: 21/11/16** **Search Strategy:** --- **#1** codeine:ti,ab,kw (Word variations have been searched) 1271 **#2** paracetamol:ti,ab,kw (Word variations have been searched) 4454 **#3** ibuprofen:ti,ab,kw (Word variations have been searched) **2896** **#4** Aspirin or acetylsalicylic acid:ti,ab,kw (Word variations have been searched) 11578 **#5** #1 and #2 350 **#6** #1 and #3 184 **#7** #1 and #4 153 **#8** Behavior Addictive:ti,ab,kw (Word variations have been searched) 507 **#9** Substance-Related Disorders:ti,ab,kw (Word variations have been searched)2877 **#10** overuse:ti,ab,kw (Word variations have been searched) 400 **#11** misuse:ti,ab,kw (Word variations have been searched) 836 **#12** dependence:ti,ab,kw (Word variations have been searched) 7223 **#13** Prescription Drug Misuse:ti,ab,kw (Word variations have been searched)104	**Database: Ovid MEDLINE(R)** **<1946 to November Week 2 2016>** **Search Strategy:** --- **1.** Codeine/ (4332) **2.** paracetamol.mp. or Acetaminophen/ (19355) **3.** ibuprofen/ (7868) **4.** Aspirin.mp. or acetylsalicylic acid/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (59480) **5.** 1 and 2 (599) **6.** 1 and 3 (144) **7.** 1 and 4 (361) **8.** Behavior, Addictive/ (8704) **9.** Substance-Related Disorders/ (95221) **10.** overuse.mp. (7159) **11.** misuse.mp. (17333) **12.** dependence.mp. (182404) **13.** Prescription Drug Misuse/ (1046) **14.** Nonprescription Drugs/ (5858) **15.** 8 or 9 or 10 or 11 or 12 or 13 or 14 (296512) **16.** 5 and 15 (24) **17.** 6 and 15 (17) **18.** 7 and 15 (39) **19.** 16 or 17 or 18 (76) **20.** limit 19 to (english language and humans and yr="2015 -Current") (4)	**Database: Embase** **<1980 to 2016 November 18>** **Search Strategy:** --- **1.** codeine/ (18345) **2.** paracetamol/ (75236) **3.** ibuprofen/ (42250) **4.** (Aspirin or acetylsalicylic acid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (192419) **5.** 1 and 2 (6648) **6.** 1 and 3 (2522) **7.** 1 and 4 (3395) **8.** Behavior, Addictive/ (34559) **9.** Substance-Related Disorders/ (23633) **10.** overuse.mp. (10532) **11.** misuse.mp. (20827) **12.** dependence.mp. (289528) **13.** Prescription Drug Misuse/ (4088) **14.** non prescription drug/ (11853) **15.** 8 or 9 or 10 or 11 or 12 or 13 or 14 (356278) **16.** 5 and 15 (638) **17.** 6 and 15 (280) **18.** 7 and 15 (388) **19.** 16 or 17 or 18 (778) **20.** limit 19 to (human and english language and yr="2015 -Current") (52)

#14 non-prescription or OTC:ti,ab,kw (Word variations have been searched)337 **#15** #8 or #9 or #10 or #11 or #12 or #13 or #14 11241 **#16** #5 and #15 6 **#17** #6 and #15 4 **#18** #7 and #15 2 **#19** #16 or #17 or #18 Pub. Year 2015 to 2016 5		
Incremental effectiveness codeine combination products		
Database: Cochrane Library **Date Run: 18/11/16** **Search strategy:** --- **#1** "codeine":ti,ab,kw (Word variations have been searched) 1271 **#2** paracetamol:ti,ab,kw (Word variations have been searched) 4454 **#3** ibuprofen:ti,ab,kw (Word variations have been searched) 2896 **#4** Aspirin or acetylsalicylic acid:ti,ab,kw (Word variations have been searched) 11578 **#5** #1 and #2 350 **#6** #1 and #3 184 **#7** #1 and #4 153 **#8** treatment outcome:ti,ab,kw (Word variations have been searched) 192970 **#9** drug effectiveness or drug	**Database: Ovid MEDLINE(R) without Revisions <1996 to November Week 2 2016>** **Search Strategy:** --- **18.** codeine/ (1475) **19.** paracetamol/ (9835) **20.** ibuprofen/ (4920) **21.** (Aspirin or acetylsalicylic acid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (34063) **22.** 1 and 2 (309) **23.** 1 and 3 (90) **24.** 1 and 4 (35) **25.** treatment outcome/ (720516) **26.** drug effectiveness.mp. or drug efficacy/ (329) **27.** pain/ (73945) **28.** analgesia/ (6925) **29.** 8 or 9 or 10 or 11 (790289) **30.** 5 and 12 (106)	**Database: Embase <1980 to 2016 November 16>** **Search Strategy:** --- **17.** codeine/ (18345) **18.** paracetamol/ (75246) **19.** ibuprofen/ (42242) **20.** (Aspirin or acetylsalicylic acid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (192384) **21.** 1 and 2 (6647) **22.** 1 and 3 (2521) **23.** 1 and 4 (3394) **24.** drug effectiveness.mp. or drug efficacy/ (720405) **25.** pain/ (371236) **26.** analgesia/ (115041) **27.** 8 or 9 or 10 (1120851) **28.** 5 and 11 (3720) **29.** 6 and 11 (1531) **30.** 7 and 11 (1666) **31.** 12 or 13 or 14 (4174) **32.** limit 15 to (human and english language and

efficacy:ti,ab,kw (Word variations have been searched)105018 **#10** pain:ti,ab,kw (Word variations have been searched) 92884 **#11** analgesia:ti,ab,kw (Word variations have been searched) 22487 **#12** #8 or #9 or #10 or #11 312425 **#13** #5 and #12 326 **#14** #6 and #12 173 **#15** #7 and #12 132 **#16** #13 or #14 or #15 Publication Year from 2015 to 2016 46	**31.** 6 and 12 (36) **32.** 7 and 12 (9) **33.** 13 or 14 or 15 (116) **34.** limit 16 to (english language and humans and yr="2015 -Current") (8)	yr="2015 -Current") (260)
Codeine combination products safety		
Database: Cochrane Library **Date Run: 21/11/16** **Search Strategy:** --- **#1** codeine:ti,ab,kw (Word variations have been searched) 1271 **#2** paracetamol:ti,ab,kw (Word variations have been searched) 4454 **#3** ibuprofen:ti,ab,kw (Word variations have been searched) 2896 **#4** Aspirin or acetylsalicylic acid:ti,ab,kw (Word variations have been searched) 11578 **#5** #1 and #2 350 **#6** #1 and #3 184 **#7** #1 and #4 153	**Database: Ovid MEDLINE(R)** **<1946 to November Week 2 2016>** **Search Strategy:** --- **1.** codeine/ (4332) **2.** paracetamol.mp. or Acetaminophen/ (19355) **3.** ibuprofen/ (7868) **4.** Aspirin.mp. or acetylsalicylic acid/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (59480) **5.** 1 and 2 (599) **6.** 1 and 3 (144) **7.** 1 and 4 (361) **8.** "Drug-Related Side Effects and Adverse	**Database: Embase** **<1980 to 2016 November 18>** **Search Strategy:** --- **1.** codeine/ (18345) **2.** paracetamol/ (75236) **3.** ibuprofen/ (42250) **4.** (Aspirin or acetylsalicylic acid).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (192419) **5.** 1 and 2 (6648) **6.** 1 and 3 (2522) **7.** 1 and 4 (3395) **8.** "Drug-Related Side Effects and Adverse Reactions"/ or drug safety/ (443555) **9.** risk.mp. or Risk/ (2899572) **10.** side effect*.mp. (1011661)

#8 "Drug-Related Side Effects and Adverse Reactions":ti,ab,kw (Word variations have been searched) 1048 **#9** drug safety:ti,ab,kw (Word variations have been searched) 53708 **#10** risk*:ti,ab,kw (Word variations have been searched) 129634 **#11** side effect*:ti,ab,kw (Word variations have been searched) 85869 **#12** Drug-Related Side Effects and Adverse Reaction*:ti,ab,kw (Word variations have been searched) 1763 **#13** adverse effect*:ti,ab,kw (Word variations have been searched) 92721 **#14** drug overdos* or overdos*:ti,ab,kw (Word variations have been searched)626 **#15** Poison*:ti,ab,kw (Word variations have been searched) 877 **#16** #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 255269 **#17** #5 and #16 199 **#18** #6 and #16 104 **#19** #7 and #16 67 **#20** #17 or #18 or #19 Publication Year from 2015 to 2016 35	Reactions"/ or drug safety/ (29543) **9.** risk.mp. or Risk/ (1938421) **10.** side effect*.mp. (224909) **11.** "Drug-Related Side Effects and Adverse Reactions"/ or drug adverse effect/ (28081) **12.** adverse effect*.mp. (118477) **13.** Drug overdose/ or overdose*/ (9282) **14.** Poisoning/ or poison*/ (22107) **15.** drug safety/ (1546) **16.** 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (2239308) **17.** 5 and 16 (166) **18.** 6 and 16 (58) **19.** 7 and 16 (44) **20.** 17 or 18 or 19 (215) **21.** limit 20 to (english language and humans and yr="2015 -Current") (13)	**11.** "Drug-Related Side Effects and Adverse Reactions"/ or drug adverse effect/ (239754) **12.** adverse effect*.mp. (184009) **13.** Drug overdose/ or overdose*/ (19348) **14.** Poisoning/ or poison*/ (173882) **15.** drug safety/ (289653) **16.** 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (4089530) **17.** 5 and 16 (3742) **18.** 6 and 16 (1478) **19.** 7 and 16 (1865) **20.** 17 or 18 or 19 (4382) **21.** limit 20 to (human and english language and yr="2015 -Current") (253)

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Reference/Publication #