

Medicines Adverse Reactions Committee

Meeting date:	8 March 2018	Agenda item:	3.2.2
Title:	Codeine – safety concerns when used in children		
Submitted by:	Medsafe Pharmacovigilance Team	Paper type:	For advice
<i>Active constituent</i>	<i>Medicine</i>	<i>Sponsor</i>	
Codeine	Codeine Phosphate Tablet 15 mg, 30 mg and 60 mg (Class C2 Controlled Drug)	PSM Healthcare Ltd trading as API Consumer Brands	
Codeine, paracetamol	Panadeine Tablets or Caplets 500mg/8mg (Restricted)	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	
	Panadeine Extra (or Panadeine Plus) Tablet 500mg/15mg (Restricted)	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	
	Paracetamol + Codeine Tablet, Relieve (Prescription)	Mylan New Zealand Ltd	
Codeine, ibuprofen	Ibucode Plus Film coated tablet, 200 mg/12.8 mg (Restricted)	Teva Pharma (New Zealand) Limited	
	Nurofen Plus Film coated tablet (monolayer) (Restricted)	Reckitt Benckiser (New Zealand) Limited	
	Panafen Plus Film coated tablet, 200mg/12.8mg (Restricted)	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	
Codeine, paracetamol, doxylamine	Mersyndol Tablet (Restricted)	Sanofi-Aventis New Zealand Limited	
Codeine, paracetamol, phenylephrine	Codral Cold & Flu Tablet (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	
Codeine, paracetamol, phenylephrine, chlorphenamine	Codral Day & Night Cold & Flu New Formula Tablet (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	
	Codral Multi Action Cold & Flu Tablet, New Formula (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	
Funding	Codeine phosphate 15 mg, 30 mg and 60 mg tabs (PSM) Paracetamol + Codeine (Relieve) 500 mg/8 mg tabs		
Previous MARC meetings	<p>Paediatric use of codeine has been discussed previously at the following meetings:</p> <ul style="list-style-type: none"> – 152nd Meeting — 6 December 2012 Use of codeine in children post-surgery and implications with ultra-rapid metabolisers <p>Recommendation: contraindicate use of codeine in children under one year.</p> <ul style="list-style-type: none"> – 160th Meeting — 4 December 2014 Codeine-containing cough and cold medicines for use in children 		

	Recommendation: use of codeine containing medicines for cough and cold in children should be restricted to those aged 12 years and over.
International action	<p>US FDA</p> <ul style="list-style-type: none"> – 9 May 2013: boxed warning cautioning against use of codeine to treat pain after surgery to remove tonsils or adenoids in children and adolescents aged < 18 years. – 20 April 2017: all codeine-containing medicines contraindicated in children aged < 12 years. – 11 January 2018: cough & cold medicines containing codeine contraindicated in children and adolescents aged < 18 years. <p>EMA</p> <ul style="list-style-type: none"> – 28 June 2013: codeine-containing pain medicines contraindicated in children < 12 years, and in adolescents < 18 years for treatment of pain after surgery to remove tonsils or adenoids. – 24 April 2015: codeine-containing cough & cold medicines contraindicated in children < 12 years, and not recommended for children and adolescents aged 12-18 years with compromised respiratory function. <p>Health Canada</p> <ul style="list-style-type: none"> – 6 June 2013: all codeine-containing products contraindicated in children < 12 years – 28 July 2016: codeine contraindicated in patients < 18 years of age to treat pain after surgery to remove tonsils or adenoids. <p>Australia</p> <ul style="list-style-type: none"> – 2015: Codeine-containing medicines contraindicated in children < 12 years, and in adolescents 12-18 years after surgery to remove tonsils or adenoids. – 1 February 2018: all codeine-containing medicines scheduled as Prescription Only
Prescriber Update	<p>Reminder: Using Cough and Cold Medicines in Children is Inappropriate Prescriber Update 37(2), June 2016</p> <p>Codeine and Ultra-Rapid Metabolisers Prescriber Update 34(1), March 2013</p> <p>Codeine and Breastfeeding Prescriber Update 31(4), December 2010</p>
Schedule	<p>Pharmacy-only medicine</p> <p>Pharmacist-only medicine</p> <p>Prescription medicine</p>
Usage data	For the six-year period 1-Jan-2012 to 31-Dec-2017, the total number of community dispensings of PHARMAC funded codeine prescriptions for children aged 0-17 years was 80,792 .
Advice sought	<p>The Committee is asked to advise whether:</p> <ul style="list-style-type: none"> – The use of codeine-containing medicines should be contraindicated in children aged < 12 years for all indications.

- The use of codeine-containing medicines should be contraindicated in adolescents < 18 years for pain following surgery to remove tonsils and adenoids.
- The use of codeine-containing medicines should be contraindicated in adolescents < 18 years in whom respiratory function might be compromised.
- The use of codeine-containing medicines should be contraindicated in adolescents aged < 18 years for cough and cold.
- The warning to avoid use using codeine in breastfeeding mothers should be strengthened to a contraindication.
- The outcome of this review requires further communication other than MARC's Remarks in *Prescriber Update*.
- Any other regulatory actions are required.

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1.0 PURPOSE

The purpose of this paper is to review the safety of codeine-containing products in children and adolescents aged < 18 years, and to consider whether there is sufficient evidence to support continued use of these products in this age-group.

This review follows regulatory action in January this year by the United States Federal Drug Authority (FDA) to further limit the use of cough and cold medicines containing codeine to adults 18 years and older (Annex 1). The FDA had previously contraindicated use of codeine-containing medicines for any indication in children < 12 years of age (April 2016), and for post-tonsillectomy pain in children and adolescents < 18 years of age (May 2013).

Similar action has been taken by the European Medicines Agency (EMA). In June 2013, the EMA restricted the use of codeine-containing medicines in the paediatric age-group to children 12 years of age and older for pain management, and contraindicated codeine-containing medicines in all children and adolescents aged < 18 years who undergo surgery for the removal of the tonsils or adenoids. In April 2015, the EMA restricted the use of codeine-containing cough and cold medicines to use in children 12 years and older.

The Australian Therapeutic Goods Administration (TGA) has also contraindicated codeine for any indication in children under the age of 12 years, and in children aged 12-18 years for pain after surgery to remove the tonsils or adenoids.

The age recommendations for codeine-containing pain and cough medicines in New Zealand are inconsistent and out of step with major medicines regulators in Europe, North America and Australia. Currently in New Zealand, codeine phosphate as a single ingredient product is contraindicated in children aged < 1 year. Products containing codeine in combination with paracetamol or ibuprofen, have age restrictions ranging from > 6 years to > 18 years. Package labelling on over-the-counter cough and cold preparations containing codeine indicate that these medicines are not recommended for use in children aged < 12 years.

2.0 BACKGROUND

2.1 Codeine

The analgesic effects of codeine are attributed to its metabolism in the liver to the active compounds morphine and morphine-6-glucuronide [1]. Codeine has a 200-fold weaker affinity for μ -opioid receptors than morphine. Codeine also has antitussive properties, and is used in some cough and cold medicines to control non-productive cough.

2.1.1 Codeine metabolism

Codeine is metabolised in the liver to codeine-6-glucuronide, norcodeine and morphine. Metabolism to morphine predominantly involves the Cytochrome P450 enzyme CYP2D6. The metabolic pathways for codeine are shown in Figure 1.

Genetic polymorphism in the *CYP2D6* gene results in significant variation between individuals in the efficiency of codeine metabolism via this pathway. People can be classified as poor metabolisers, intermediate metabolisers, extensive metabolisers or ultra-rapid metabolisers depending on their CYP2D6 activity score, which in turn is determined by the combination of alleles coding for the CYP2D6 enzyme.

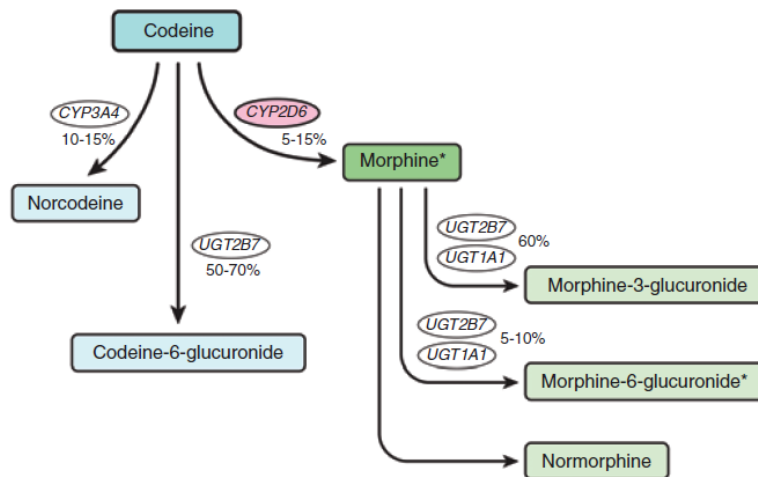


Figure 1: Codeine metabolism pathway. Percentages shown are for extensive metabolisers. Asterisks (*) denote active metabolites [1].

Poor metabolisers are unable to convert codeine to morphine efficiently, resulting in suboptimal pain relief (as the conversion of codeine to morphine is required for analgesia), while ultra-rapid metabolisers may metabolise codeine too efficiently resulting in morphine toxicity and an increased risk of adverse effects.

More than 100 *CYP2D6* alleles have been defined. The particular combination of alleles determines a patient's diplotype. *CYP2D6* alleles are characterized as wild-type (normal function), reduced-function, or non-functional alleles based on the expected activity of the enzyme that they encode. Each allele is assigned an activity value: 0 for non-functional, 0.5 for reduced-function, or 1.0 for fully functional forms. If multiple copies of the *CYP2D6* gene are detected, the activity score is multiplied by the number of copies of each allele present. The total *CYP2D6* activity score is the sum of the values assigned to each allele, which typically ranges from 0 to 3.0 but may exceed 3.0 in rare cases. The *CYP2D6* activity score relates to the phenotype classification as shown in Table 1.

Table 1: Likely codeine metabolism phenotypes based on *CYP2D6* diplotypes

Likely phenotype ^a	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN
Extensive metabolizer (~77–92% of patients)	1.0–2.0 ^b	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10
Intermediate metabolizer (~2–11% of patients)	0.5 ^b	An individual carrying one reduced-function and one nonfunctional allele	*4/*10, *5/*41
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6

^aThe frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See **Supplementary Data** online for estimates of phenotype frequencies among different ethnic/geographic groups. ^bNote that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and those with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.¹²

The extensive metaboliser phenotype represents normal (wild-type) enzyme activity. The frequency of *CYP2D6* poor metabolisers may be up to 10 % in some populations [1]. The frequency of ultra-rapid metabolisers may be as high as 29 % in some populations [2]. Table 2

Table 2: Prevalence of CYP2D6 ultra-rapid metabolic activity in various populations [2]

Population	UM Genotypes/Phenotypes (↑ Activity)	Prevalence % (UM/Total n)
African/Ethiopian	UM (active duplicate genes)	29 (35/122)
African American	UM (3 active duplicate genes)	3.4 (3/87) to 6.5 (60/919)
Asian	UM (active duplicate genes)	1.2 (5/400) to 2
Caucasian	UM (3 active duplicate genes)	3.6 (33/919) to 6.5 (18/275)
Greek	CYP2D6*2 × N/UM	6 (17/283)
Hungarian	UM (active duplicate genes)	1.9
Northern European	UM (active duplicate genes)	1-2

CYP2D6, cytochrome P-450 isoenzyme 2D6; UM, ultra-rapid metabolizer

The codeine metabolic pathway illustrated in Figure 1 shows the percentage of drug that is metabolised via each route by extensive metabolisers. Extensive metabolisers convert 5-15 % of codeine to morphine via the enzyme CYP2D6; accordingly, a 30 mg dose of codeine phosphate would yield 1.5 mg to 4.5 mg of morphine in these patients.

By contrast, pharmacokinetic studies have shown increased conversion of codeine to morphine in CYP2D6 ultra-rapid metabolisers compared to extensive metabolisers, which can result in toxic systemic concentrations of morphine even with low doses of codeine. There is also a large amount of variability within the group classed as extensive metabolisers, and it is possible that some of these patients may also develop symptoms of morphine toxicity.

Common adverse reactions to codeine include nausea, vomiting, drowsiness, light-headedness, dizziness, sedation, shortness of breath, constipation, and itching. Serious adverse reactions include respiratory depression and, rarely, circulatory depression, respiratory arrest, shock, and cardiac arrest.

Therapeutic recommendations for codeine have been developed based on CYP2D6 phenotype (Table 3). For patients identified as CYP2D6 ultra-rapid metaboliser, an alternative analgesic should be used to avoid the risk of severe toxicity with normal doses of codeine. If clinical genotyping identifies a patient as a CYP2D6 poor metaboliser, current evidence supports the avoidance of codeine and the use of an alternative analgesic (one that is not a CYP2D6 substrate) due to the possibility of lack of effect. There is insufficient evidence in the literature to recommend a higher dose of codeine in poor metabolisers, particularly as some adverse effects are not determined by metaboliser category.

There are also significant developmental changes in CYP2D6 activity, which increases with age during childhood. In the fetus, CYP2D6 activity is absent or less than 1% of adult values. CYP2D6 activity increases after birth, but it is estimated to be no higher than 25% of adult values in children below five years of age. As a consequence, the analgesic effect is (very) low or absent in neonates and young children [3].

Both codeine and morphine are excreted into breast milk. Breastfeeding mothers who are ultra-rapid metabolisers will convert a larger proportion of codeine to morphine, resulting in higher levels of morphine in their breast milk. Exposure of the infant to breast milk containing morphine may lead to opioid toxicity in the infant, with the potential for respiratory depression and death. Furthermore, opioid toxicity in the mother may potentially render her unable to identify signs of opioid toxicity in her infant.

Table 3: Codeine therapy recommendations based on CYP2D6 phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy ^a	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity. ^{b,c}
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided. ^{b,c}

^aRating scheme is described in **Supplementary Data** online. ^bThere is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable.^{18,20,21} ^cSome other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.

Comment:

The codeine therapy recommendations shown in Table 3 are somewhat academic at the present time, as pharmacogenomic testing for drug metabolising enzyme variants is not widely available. The field of pharmacogenomics is rapidly developing and the use of high-throughput DNA sequencing is enabling genetic variants that predispose to ADRs to be identified [4]. It is anticipated that pharmacogenomic testing will eventually be incorporated into paediatric treatment guidelines [5]. However, in the meantime, it is not currently feasible to identify in advance the subgroup of children who are at increased risk of toxicity through being an ultrarapid metaboliser, and so the risks should be considered to apply to all children.

The recommendations in Table 3 suggest that codeine is not a suitable analgesic in a significant proportion of the population.

2.1.2 Place of codeine in pain management for children and adolescence

In 1986, WHO developed a step-wise approach to chronic pain management, known as the WHO Analgesic Ladder (Figure 2). The approach considered in parallel the severity of the pain and the presumed efficacy of the analgesic medicines. The first step utilised non-opioid analgesics such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs). If analgesia was inadequate, the patient could be stepped up to 'weak' opioids such as hydrocodone, codeine, or tramadol. The third step introduced 'strong' opioids such as morphine, hydromorphone, oxycodone, fentanyl, or methadone. Additional drugs (adjuvants) could be used at any stage to decrease anxiety.

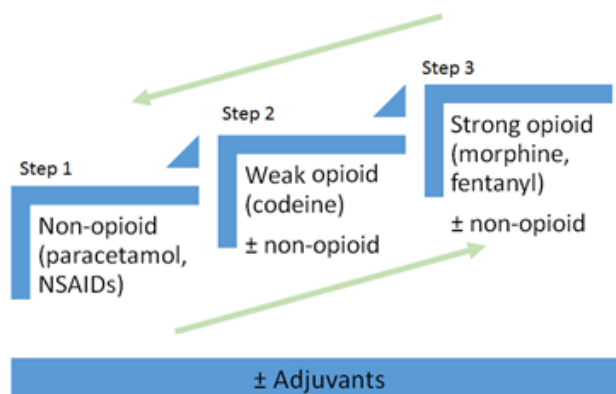


Figure 2: WHO Analgesic Ladder for Chronic Pain Management

In 2012, WHO revised the management of persistent pain in children with a medical illness. The three-step ladder was replaced with a simple two step regimen, without the use of codeine or other weak opioids. Low doses of strong opioid analgesics at step 2 are now preferred for the treatment of moderate pain in children [3]. The benefits of using an effective strong opioid analgesic are considered to outweigh the benefits of intermediate potency opioids in the paediatric population. The known risks associated with strong opioids are acceptable when compared with the uncertainty associated with the response to codeine and tramadol in children.

2.2 International regulatory action to limit use of codeine in children and adolescents

A time-line of changes to the age recommendations for codeine-containing pain and cough medicines in the United States, Europe and Canada are shown in Table 4.

2.2.1 United States (FDA)

The FDA reviewed several decades of adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) from January 1969 to May 2015.

www.fda.gov/Drugs/DrugSafety/ucm549679.htm

The review identified 64 worldwide cases of respiratory depression, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Fifty cases were reported in children younger than 12 years. Respiratory depression occurred after the children received a range of one to 18 doses, with a median of five doses. The most frequently reported codeine-containing medicines in the cases were acetaminophen with codeine used for pain, and promethazine with codeine (with or without phenylephrine) used for cough and cold.

Of the 24 cases reporting death, 21 occurred in children younger than 12 years. The reasons for codeine-containing medicine use in these cases included post-tonsillectomy and/or adenoidectomy pain management, other post-operative pain, general pain, sore or strep throat pain, and cough and cold.

Ten of the 64 cases mentioned the status of cytochrome P450 isoenzyme 2D6 (CYP2D6) genotype. Seven of these patients were ultra-rapid metabolizers, five of whom died. Ultra-rapid metabolizers of substrates of CYP2D6 convert codeine in their bodies too quickly into potentially dangerously high levels of morphine, the active form of codeine, contributing to life-threatening or fatal respiratory depression. The three other patients were extensive metabolizers, with one death.

Fifteen of the 64 cases reported codeine or morphine blood levels; the remaining 49 cases did not. In 13 cases, the blood levels were above the therapeutic range, and in two cases the blood levels were within the therapeutic range. One patient who had blood levels in the therapeutic range died following pain management post-tonsillectomy and adenoidectomy.

Table 4: Time line of changes to age recommendations for pain and cough/cold products by the United States Federal Drug Authority (FDA) and the European Medicines Agency (EMA).

Date	Authority	Use	Age restrictions	Description of regulatory action
9-May-2013	FDA	post-tonsillectomy pain	< 18 y	<p>The US FDA added a Boxed Warning and contraindication to codeine-containing pain medicines cautioning against prescribing codeine to children of any age to treat pain after surgery to remove tonsils or adenoids:</p> <p><i>WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism</i></p> <p>www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf</p> <p>www.fda.gov/Drugs/DrugSafety/ucm549679.htm</p>
6-Jun-2013	Health Canada	any use	< 12 y	<p>Health Canada reviewed the safety of prescription pain and cough medicines containing codeine, and no longer recommended their use in children less than 12 years of age. This recommendation was based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk.</p> <p>Non-prescription products containing codeine were already contraindicated in children.</p>
28-Jun-2013	EMA	pain post-tonsillectomy pain	< 12 y < 18 y	<p>The EMA introduced risk-minimisation measures to address safety concerns with codeine-containing medicines when used for the management of pain in children</p> <p>The PRAC recommended the following risk-minimisation measures to ensure that only children for whom the benefits are greater than the risks are given codeine-containing medicines for pain relief:</p> <ul style="list-style-type: none"> Codeine-containing medicines should only be used to treat acute moderate pain in children 12 years of age and older, and only if it cannot be relieved by other

				<p>painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.</p> <ul style="list-style-type: none"> • Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems. • Codeine should not be used in breastfeeding mothers because codeine can pass to the baby through breast milk. • The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine. • The product information for these medicines should include information on how to recognise morphine-related side effects (e.g. reduced levels of consciousness; somnolence; respiratory depression; 'pin-point' pupils; lack of appetite; constipation; or nausea and vomiting). <p>This action followed a review of codeine-containing medicines by the Pharmacovigilance Risk Assessment Committee (PRAC), which investigated reports of serious and fatal respiratory depression in children after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea. Some of the children who had suffered severe side effects were ultra-rapid metabolisers of codeine.</p> <p>www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Codeine_containing_medicinal_products/Position_provided_by_CMDh/WC500144850.pdf</p>
24-Apr-2015	EMA	cough	<p>< 12 y</p> <p>< 18 y with compromised respiratory function</p>	<p>The EMA introduced the following risk minimisation measures to reduce the risk of serious side effects, including breathing problems, with codeine-containing medicines when used for cough and cold in children:</p> <ul style="list-style-type: none"> • Use of codeine for cough and cold is now contraindicated in children below 12 years of age. • Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years with compromised respiratory function.

				<ul style="list-style-type: none"> Codeine is contraindicated in women during breastfeeding and patients known to be CYP2D6 ultra-rapid metabolisers. <p>Following the previous review of codeine for pain relief in children, the PRAC undertook a second EU-wide review of codeine for relief of cough and cold in children. The PRAC considered that, although morphine-induced side effects may occur in patients of all ages, the way codeine is converted into morphine in children below 12 years is more variable and unpredictable, making this population at special risk of such side effects. In addition, children who already have problems with their breathing may be more susceptible to respiratory problems due to codeine. The PRAC noted that coughs and colds are generally self-limiting conditions and the evidence that codeine is effective at treating cough in children is limited.</p> <p>www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Codeine_cough_or_cold_in_children/Position_provided_by_CMDh/WC500186159.pdf</p>
28-Jul-2016	Health Canada	post-tonsillectomy pain	< 18 y	<p>Codeine contraindicated in patients under 18 years of age to treat pain after surgery to remove tonsils or adenoids, as these patients are more susceptible to the risk of serious breathing problems.</p> <p><i>Also, hydrocodone no longer recommended in patients under six years of age due to rare cases of serious breathing problems including deaths in children in this age group, usually involving higher-than-recommended doses.</i></p> <p>www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-codeine-prescription-products-cough-further-assessing-risk-serious.html</p> <p>healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/59584a-eng.php</p>
20-Apr-2017	FDA	pain, cough	< 12 y	<p>The US FDA restricted the use of codeine pain and cough medicines in children less than 12 years of age: <i>'codeine should not be used to treat pain or cough in children younger than 12 years.'</i></p> <p>Strengthened Warning that codeine is not recommended in mothers who are breastfeeding due to the risk of serious adverse reactions in breastfed infants (including</p>

		pain	< 18 y	<p>excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death).</p> <p>A new Warning to the drug labels of codeine was added to recommend against use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnoea or severe lung disease, which may increase the risk of serious breathing problems.</p> <p>These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children.</p> <p>The FDA reviewed several decades of adverse event reports submitted to the FDA from January 1969 to May 2015, and identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years.</p> <p>www.fda.gov/Drugs/DrugSafety/ucm549679.htm</p>
11-Jan-2018	FDA	cough	<18 y	<p>The U.S. FDA announced safety labelling changes to prescription cough and cold medicines containing codeine or hydrocodone to limit their use to adults 18 years and older.</p> <p>The FDA considers that the risk of harm with these medicines outweighs their benefit in children younger than 18 years.</p> <p>Additional safety information in the form of a Boxed Warning has been added to the US label for each of these products, concerning the risks of misuse, abuse, addiction, overdose, death and slowed or difficult breathing.</p> <p>Healthcare professionals are advised to reassure parents that cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated.</p> <p>Note that some cough medicines are available without prescription in a few states, and the FDA is also considering regulatory action for these products.</p> <p>www.fda.gov/Drugs/DrugSafety/ucm590435.htm</p>

2.2.2 Australia (TGA)

In 2012, the Australian Therapeutic Goods Administration (TGA) published a review of the safety and efficacy of OTC cough and cold medicines in children aged 2-12 years [6]. Codeine-containing cough and cold medicines were considered as part of this review. The TGA concluded that there was a lack of evidence to support the efficacy of OTC cough and cold medicines in children under 12 years of age, and that the potential risks of adverse reactions in children less than 12 years of age were high relative to the limited benefits. The review showed that the risks associated with OTC cough and cold medicines are greater in children aged less than 6 years compared to children between 6 and 11 years. As a result of this review, the TGA recommended that these medicines should not be used to treat children less than 6 years of age, and should only be administered to children aged 6-11 years on the advice of a doctor or pharmacist.

In 2015, the TGA undertook a further safety review of codeine use in children and ultra-rapid metabolisers [7]. This review concluded that codeine should not be used in children under the age of 12 for any reason, or in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea. Additionally, existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products. The TGA therefore recommended:

1. Use of codeine in children younger than 12 years of age for any indication should be contraindicated.
2. Use of codeine in children aged 12-18 years should be contraindicated post adenotonsillectomy for obstructive sleep apnoea.
3. Existing warnings contraindicating codeine use by breastfeeding mothers should be made consistent across all codeine-containing products, and warnings should be added to advise against using codeine if known to be an ultra-rapid metaboliser.
4. Health professionals, patients and caregivers should be educated regarding the variability of codeine efficacy, the possibility of ultra-rapid metabolism-related morphine overdose and the signs of such, including respiratory depression.

Following this review, the Product Information documents for all prescription codeine products were updated to include the following recommendations:

- Codeine products should no longer be used in children under 12 years of age, or in children aged 12-18 years who have recently undergone surgery to remove their tonsils or adenoids.
- Codeine should also not be used by breastfeeding mothers or in patients known to be ultra-rapid metabolisers.

In July 2015, the TGA's Advisory Committee on the Safety of Medicines (ACSOM) proposed changes to the scheduling of codeine, to make all codeine-containing products Prescription Only. Following a public consultation process, the TGA decided in December 2016 to up-schedule all Schedule 2 (Pharmacy Medicine) and Schedule 3 (Pharmacist Only Medicine) codeine-containing products to Schedule 4 (Prescription Only Medicine), effective from 1 February 2018 [8-10].

2.2.3 Summary of current age restrictions for codeine-containing medicines by the FDA, EMA, TGA and Health Canada

In summary, codeine is contraindicated in the following age groups for each region as follows:

United States:

- children and adolescents < 18 years for pain following tonsillectomy/adenoidectomy
- children < 12 years of age for pain not associated with tonsillectomy/adenoidectomy
- children and adolescents < 18 years of age for cough

Europe:

- children and adolescents < 18 years for pain following tonsillectomy/adenoidectomy
- children < 12 years of age for pain not associated with tonsillectomy/adenoidectomy
- children < 12 years of age for cough (< 18 years of age with compromised respiratory function)
- breastfeeding mothers

Canada:

- children and adolescents < 18 years for pain following tonsillectomy/adenoidectomy
- children < 12 years of age for pain not associated with tonsillectomy/adenoidectomy
- children < 12 years of age for cough
- breastfeeding mothers

Australia:

- children and adolescents < 18 years for pain following tonsillectomy/adenoidectomy
- children < 12 years of age for any indication
- breastfeeding mothers

2.3 New Zealand regulatory action

The MARC evaluated the use of codeine in children for pain relief in December 2012 (152nd MARC Meeting) and recommended that the use of codeine in children under one year of age be contraindicated in New Zealand due to the lack of evidence to support safe use in this age group. The data sheet warnings and precautions were strengthened to include the frequency of ultra-rapid metabolisers in the population (up to 10% of the Caucasian population; prevalence in Maori and Pacific people not known), and information on signs of morphine toxicity and what to do should this occur was also added to the data sheet. (www.medsafe.govt.nz/profs/adverse/Minutes152.htm#3.1)

Medsafe published an article in Prescriber Update in March 2013 reminding prescribers that patients may respond variably to codeine due to genetic differences in the expression of the CYP2D6 enzyme. Patients who metabolise codeine very rapidly (ultra-rapid metabolisers) are at increased risk of developing adverse effects of opioid toxicity, while patients who are poor metabolisers may experience lack of analgesic effect with codeine.

(www.medsafe.govt.nz/profs/PUArticles/Mar2013Codeine.htm)

In December 2014, the MARC evaluated the use of codeine-containing cough and cold medicines in children. Use of these medicines was already restricted to children and adolescents aged 12 years and over for over-the-counter preparations; however, the age restriction varied for codeine-containing prescription-only medicines. The Committee recommended that the use of codeine-containing medicines for cough and cold should be restricted to children and adolescents aged 12 years and over. The committee also recommended that Medsafe issue an alert communication to this effect. (www.medsafe.govt.nz/profs/adverse/Minutes160.htm#3.2.4)

Medsafe issued the alert communication in April 2015, noting the MARC's recommendation that the use of codeine-containing cough and cold medicines should be restricted to adults and children 12 years of age and over. (www.medsafe.govt.nz/safety/EWS/2015/BromhexineOrCodeine.asp)

Medsafe published an article in Prescriber Update in June 2016 reminding healthcare professionals that the use of cough and cold medicines in children is inappropriate, and that codeine containing products are contraindicated in children less than 12 years of age.

www.medsafe.govt.nz/profs/PUArticles/June2016/CoughAndColdMedicinesInChildrenInappropriate.htm

Medsafe had previously published an article in Prescriber Update reminding healthcare professionals that codeine use by breastfeeding mothers has been associated with fatal cases of infant morphine toxicity, and that the risks and benefits should be carefully considered before recommending its use to breastfeeding mothers. (www.medsafe.govt.nz/profs/PUArticles/CodeineAndBreastfeeding.htm)

Reclassification of codeine was discussed at the 59th meeting of the Medicines Classification Committee (MCC), held on 7 November 2017. The Committee recommended that from 31 January 2020:

- All codeine in combination medicines, both analgesics and those used for cough and colds, should be reclassified to prescription medicines.
- Medicines containing codeine as the only active ingredient should be reclassified from prescription to restricted medicine; for oral use in adults and children over 12 years of age in medicines containing not more than 15 mg per solid dosage unit with a maximum daily dose not exceeding 90 mg of codeine for use as an analgesic and when sold in a pack of not more than three days' supply.

The Minutes of the 59th MCC meeting are available on the Medsafe website:

(www.medsafe.govt.nz/profs/class/Minutes/2016-2020/mccMin7Nov2017.htm)

Comments:

The distinction between codeine-containing pain medicines and codeine-containing cough and cold medicines is imprecise. Combination medicines containing analgesics such as paracetamol or ibuprofen may be used to treat symptoms of cold and flu, yet they are considered to be analgesic medicines rather than cough and cold medicines. These medicines are therefore not required to carry the age restriction imposed for codeine-containing cough and cold medicines. Although most of the currently available combination products carry a label statement that they should not be used by children under 12 years of age, use of the PHARMAC funded product Paracetamol + Codeine (Relieve) is restricted to children aged 7 years and older.

2.4 Data sheets

2.4.1 New Zealand

Table 5 shows the current paediatric use recommendations for codeine-containing products.

Currently, age restrictions on the use of codeine-containing products are inconsistent:

- Codeine phosphate as a single ingredient product is contraindicated in children aged < 1 year.
- When combined with paracetamol, two products state that they should not be used in children < 18 years (Panadeine and Panadeine Extra, GSK), while one product states that it is not suitable for children < 7 years (Paracetamol + Codeine Relieve, Mylan).
- When combined with ibuprofen, one product states that it should not be used in children < 18 years (Panafen Plus, GSK), while two products state that they should not be used in children < 12 years.
- When combined with the antihistamine doxylamine (Mersyndol), which is indicated for pain relief, use is not recommended for children < 12 years.
- When combined with paracetamol and an antihistamine in cough and cold preparations, use is not recommended for children < 12 years.

There are currently no codeine-containing products available in liquid form. For children, Codeine Linctus Paediatric (3 mg per 5 ml) can be extemporaneously compounded by the dispensing pharmacy. A stronger formulation, Codeine Linctus Diabetic (15 mg per 5 ml), can be extemporaneously compounded for adults. Both preparations are fully funded by PHARMAC, (www.pharmac.govt.nz/2018/02/01/Schedule.pdf).

2.4.1.1 Codeine phosphate data sheet

The data sheet for codeine phosphate contains the following wording in section 4.2 *Dose and method of administration*, under the sub-heading 'Paediatric':

The usual paediatric dose for infants and children is 0.5mg per kg of body weight or 15mg per square metre of body surface, every 4 to 6 hours as needed. The maximum recommended dose is 240 mg in 24 hours. The duration of treatment should not normally exceed 3 days.

Do not give to children aged less than 1 year.

Do not give to children aged less than 6 years with acute diarrhoea.

Section 4.4 *Special warnings and precautions for use*, contains the following wording:

The following patients may be more susceptible to the effects of codeine. The lowest effective dose for the shortest period of time should be prescribed. Signs of toxicity or overdose may include nausea, vomiting, constipation, lack of appetite, somnolence, extreme sleepiness, confusion, shallow breathing and even coma. If symptoms of toxicity are present, codeine should be stopped immediately and medical advice sought.

- **recent tonsillectomy, adenoidectomy or throat surgery**
- *hypothyroidism*
- *adrenocortical insufficiency e.g. Addison's disease*
- *impaired kidney or liver function*
- *prostatic hypertrophy*
- *shock/hypotension*
- *myasthenia gravis*
- *convulsions / convulsive disorders*
- *gall bladder disease or gall stones*
- *recent gastro-intestinal surgery*
- *urinary tract surgery*
- *reduced respiratory function or history of asthma*
- *obstructive bowel disorders – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure*
- *Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment*

The data sheet for codeine contains the following information in section 4.6 *Fertility, pregnancy and lactation* under the subheading 'Breast-feeding':

Codeine is excreted into breast milk. However with usual analgesic doses, concentrations are generally low.

However, infants of nursing mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. When codeine enters the body and is metabolized, it changes to morphine. Nursing mothers taking codeine, who are ultra-rapid metabolisers of codeine, may have higher morphine levels in their breast milk. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies.

When prescribing codeine for a nursing mother, the lowest dose for the shortest amount of time to relieve pain should be prescribed. Nursing patients should be told how to recognize signs of high morphine levels in themselves and their babies.

Signs of high morphine levels in a mother are extreme sleepiness and trouble caring for the baby.

Breastfed babies usually nurse every two to three hours and should not sleep more than four hours at a time. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, the mother should immediately seek medical advice.

Comment:

The paediatric maximum dose recommendation in the data sheet should be revised as it does not take into account weight-based dosing for children. At a dose of 0.5 mg per kg of body weight every 4 to 6 hours, the recommended maximum dose of 240 mg in 24 hours would be an appropriate maximum dose for an adult weighing 80 kg. The maximum paediatric dose should be defined in mg/kg/day.

Use of codeine following tonsillectomy/adenoidectomy is listed as a precaution, but is not currently contraindicated in New Zealand.

Use of codeine by breastfeeding mothers is not currently contraindicated in New Zealand. The data sheet recommends use of the lowest effective dose and advising mothers to watch for signs of extreme sleepiness in their infant.

The data sheet recommendation does not allow for the possibility that the mother's ability to detect opioid toxicity in her baby may be impaired due to her own opioid toxicity as a result of CYP2D6 ultra-rapid metaboliser activity. As it is not possible to determine in advance which mothers or infants may be ultra-rapid metabolisers, a contraindication to the use of codeine in breast-feeding mothers would provide greater protection for the infant.

2.4.2 Australia

From 1 February 2018, all Schedule 2 (Pharmacy Medicine) and Schedule 3 (Pharmacist Only Medicine) codeine-containing products have been rescheduled to Schedule 4 (Prescription Only Medicine).

All codeine-containing medicines are now contraindicated for use in children:

- Younger than 12 years
- Aged between 12 - 18 years in whom respiratory function might be compromised, including post-tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. Respiratory depression and death have occurred in some children who received codeine following tonsillectomy and/ or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism.

Codeine-containing medicines are also contraindicated during breastfeeding and in patients who are known to be ultra-rapid metabolisers.

Table 5: Current paediatric use recommendations for codeine-containing products in New Zealand, as described in the New Zealand data sheet (or package label where no data sheet exists) for each product

Product name and Formulation	Ingredients	Sponsor	Paediatric use
Codeine phosphate, tablet (TT50-1861,a,b)	codeine phosphate 15 mg, 30 mg, 60 mg	PSM	The usual paediatric dose for infants and children is 0.5mg per kg of body weight or 15mg per square metre of body surface, every 4 to 6 hours as needed. The maximum recommended dose is 240 mg in 24 hours. The duration of treatment should not normally exceed 3 days. Do not give to children aged less than 1 year. Do not give to children aged less than 6 years with acute diarrhoea
Panadeine, tablet & caplet (TT50- 0567 &/6)	paracetamol 500 mg codeine phosphate 8 mg	GSK	Must not be used in children under 18 years
Paracetamol + Codeine (Relieve), tablet (TT50-8161)	paracetamol 500 mg codeine phosphate 8 mg	Mylan	Children over 12 years: 1 to 2 tablets every 4 - 6 hours as required. Maximum of 8 tablets in 24 hours. Children 7 - 12 years: 1/2 to 1 tablet every 4 - 6 hours as required. Maximum of 4 tablets in 24 hours. Children < 7 years of age: Not suitable.
Panadeine Extra, tablet (TT50-0567/5)	paracetamol 500 mg codeine phosphate 15 mg	GSK	Must not be used in children under 18 years
Ibucode Plus, Film coated tablet (TT50-8530)	ibuprofen 200 mg codeine 12.8 mg	Teva	Children 12 years and over: Initial dose two tablets taken with fluid, then one or two tablets every 4 to 6 hours as necessary. Maximum 6 tablets in a 24-hour period. Children: Ibucode Plus is not indicated for use in children under 12 years of age.
Nurofen Plus, Film coated tablet (TT50-6123/1)	ibuprofen 200 mg codeine 12.8 mg	Reckitt	Children over 12 years: Initial dose, two tablets taken with fluid, then one to two tablets every 4 to 6 hours as necessary. Maximum 6 tablets in a 24 hour period Children aged less than 12 years: Ibuprofen + Codeine combination solid dose strength products should not be used in children below the age of 12 years

			because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine
Panafen Plus, Film coated tablet (TT50-4601/3)	ibuprofen 200 mg codeine 12.8 mg	GSK	Children (under 18 years): Must not be used in patients under 18 years.
Mersyndol, Tablet (TT50-2228)	codeine phosphate 9.75 mg doxylamine 5 mg paracetamol 450 mg	sanofi-aventis	Children 12 years and older: 1 or 2 tablets every four to six hours as needed for relief. Do not exceed 8 tablets in a 24 hour period. Not recommended for children under 12 years.
Codral Cold & Flu, Tablet (TT50-7370)	codeine paracetamol phenylephrine	J&J	<i>No data sheet</i> Carton states: Do not use for children under 12 years
Codral Day & Night Cold & Flu New Formula, Tablets (TT50-7370/1)	Night: chlorphenamine 2 mg paracetamol 500 mg phenylephrine 5 mg	J&J	<i>No data sheet</i> Carton states: Do not use for children under 12 years
	Day: codeine 9.5 mg paracetamol 500 mg phenylephrine 5 mg		
Codral Multi Action Cold & Flu New Formula, Tablet (TT50-6356/1)	codeine 9.5 mg paracetamol 500 mg phenylephrine 5 mg chlorphenamine 2 mg	J&J	<i>No data sheet</i> Carton states: Do not use for children under 12 years

Colour key:

Restricted < 1 year	Restricted < 7 years	Restricted < 12 years	Restricted < 18 years
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2.5 New Zealand usage data

New Zealand community pharmacy dispensing data for PHARMAC funded codeine phosphate indicates that the number of codeine prescriptions for children has dropped from 14,962 in 2012 to 10,576 in 2017. The greatest reduction in use during this period has been in children aged < 12 years, and is seen from 2015. Use in adolescents aged 12-15 years has also trended downwards, but to a lesser extent, while use in 16 and 17 year olds has been trending upwards. Figure 3

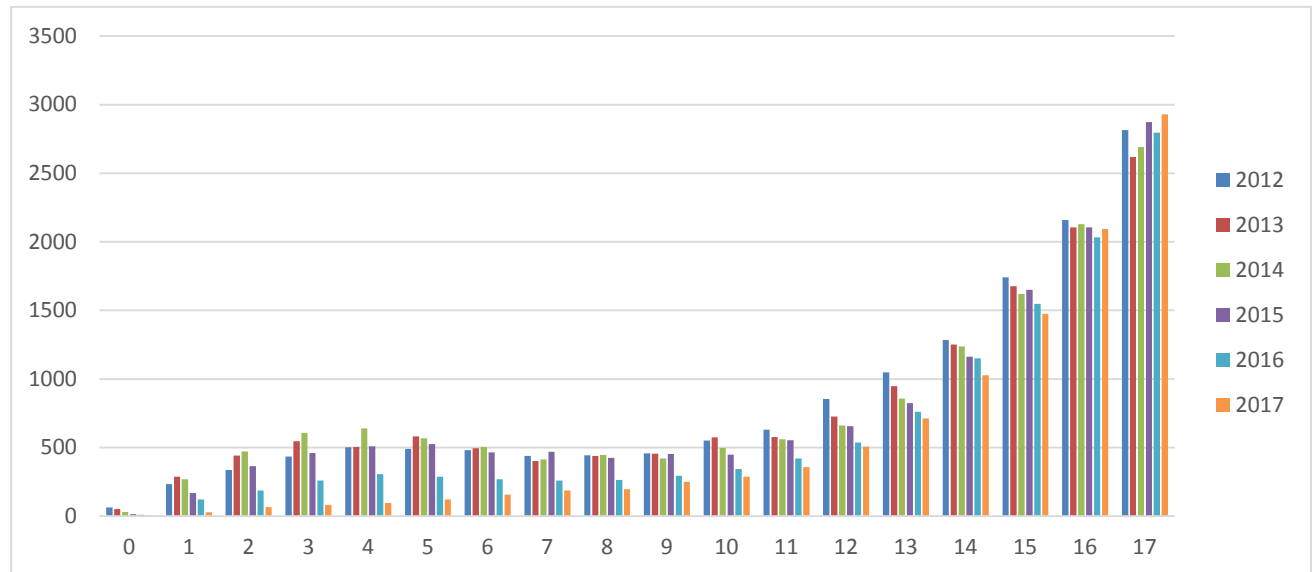


Figure 3: Community dispensed prescriptions of codeine phosphate for period 1 January 2012 to 31 December 2017 for children and adolescents aged 0 to 17 years

Comment:

The drop-off in use of codeine over the past 2-3 years in children aged < 12 years is consistent with the changes recommended by major overseas regulators such as the FDA and EMA in 2013-2014, and also advice on pain management in children issued by the WHO in 2012.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Efficacy of codeine for pain management in children and adolescents aged < 18 years.

3.1.1.1 ANZCA, 2015 [11]

Acute Pain Management: Scientific Evidence. Fourth Edition, 2015

The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine published an updated review of the scientific evidence for acute pain management in 2015. This review updates previous editions published in 1999, 2005, and 2010, and covers acute pain management in adults and children.

A **key message** regarding the use of codeine in children, which has been strengthened since the previous edition, states:

'The efficacy of oral codeine in children is unpredictable due to genetic differences in the ability to generate the active metabolite morphine (Level II), as are adverse effects and serious toxicity (Level IV).'

Note: Level II evidence – obtained from at least one properly designed randomised-controlled trial; Level IV evidence – obtained from case series.

New **recommended best practice** regarding the use of codeine in children, based on this evidence, states:

‘Because of its unpredictable effect, codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death’.

Note: Opioid-induced ventilatory impairment is considered a more appropriate term to describe the effects of opioids on ventilation as it encompasses the central respiratory depression caused by opioids and also the depressed consciousness and the subsequent upper airway obstruction resulting from excessive opioid use.

Information on the paediatric use of codeine is copied below from the review. Note the following abbreviations identify the type of data referred to in the text: CR – case report, GL – clinical practice guidelines, PK – pharmacokinetic studies, NR – narrative review. The Jadad Score (JS) was used to grade the quality of RCTs, ranging from 5 – highest quality down to 0 – lowest quality (Jadad 1996). Levels of evidence refer to the National Health and Medical Research Council grading: Level I – systematic review, Level II – well designed RCT, Level III (1-3) – other types of well-designed comparative studies, IV – case series (NHMRC 1999).

Pharmacogenomics of codeine metabolism

Codeine has been used for decades in paediatric acute pain. Recent publications of deaths and increased understanding of relevant pharmacogenomics are influencing prescribing of this opioid prodrug.

Relevant to codeine as a prodrug, the CYP2D6 enzyme has numerous polymorphisms (Zhou 2009a NR; Zhou 2009b NR) resulting in four phenotypes, which demonstrate a spectrum of activity with overlap (Vuilleumier 2012 NR).

The phenotypes are variably represented in populations depending on ethnicity. The most common (> 70 % of Caucasians to 92% of Asians) ‘normal’ phenotype, termed extensive metabolisers, has 100–200 % CYP2D6 activity and thus analgesic effect with codeine.

Intermediate and poor metabolisers have reduced (intermediate: 50% CYP2D6 activity) to no effect (poor: 0% CYP2D6 activity) from codeine (46% of children undergoing tonsillectomy in a UK population) (Williams 2002 Level II PK, n=96, JS 4) and 49% (intermediate 44% and poor 5.3%) of children with sickle-cell disease (Yee 2013 Level IV). Ultra metabolisers (>200% activity) attain high peak morphine levels and are at risk of sedation and respiratory depression (Kelly 2012 Level IV; Yee 2013 Level IV; Racoosin 2013 Level IV; Niesters 2013 Level IV). Several paediatric deaths associated with codeine administration have been reported, some with confirmed ultra and extensive metaboliser phenotype. Subgroups at particular risk included breastfeeding neonates (whose ultra/extensive metaboliser mothers were taking codeine in the puerperium) (Madadi 2007 CR) and toddlers (Kelly 2012 Level IV, Racoosin 2013 Level IV) and obese older children (Friedrichsdorf 2013 Level IV) following adenotonsillectomy.

In response to the reported deaths, the FDA has relabelled codeine with black-box warnings applied to maternal postpartum use and children (<18 y) undergoing adenotonsillectomy with instruction “to prescribe an alternative analgesic for postoperative pain control” (FDA 2012, FDA 2013). The European Medicines Agency has responded similarly (EMA 2013), as has the WHO in removing codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO 2012 GL). Several paediatric hospitals have removed codeine from their drug formularies (Tremlett 2013 NR).

Codeine Efficacy

In the majority of studies with a codeine treatment arm, CYP2D6 activity is not accounted for and is a significant confounder contributing to conflicting reports of efficacy for postoperative pain.

Perceived advantages of codeine include less respiratory depression in neonates and reduced nausea and vomiting compared with morphine (in one of four time points) (Williams 2002 Level II, n=96, JS 4). These conclusions are probably compromised by low levels of active metabolites and resultant reduced efficacy (Williams 2001 NR). Comparison of codeine and morphine for tonsillectomy has shown either no difference (Semple 1999 Level II, n=40, JS 4) vs an increased requirement for rescue analgesia following codeine (Williams 2002 Level II, n=96, JS 4). Codeine was less effective than ibuprofen for acute musculoskeletal pain in children (Clark 2007 Level II, n=336, JS 5). Addition of codeine to paracetamol has been reported to improve analgesia (Pappas 2003 Level II, n=120, JS 5) or have no effect (Moir 2000 Level II, n=79, JS 5) and was as effective as ibuprofen for fracture pain but ibuprofen-treated patients had fewer adverse effects and better functional outcomes (Drendel 2009 Level II, n=336, JS 5). Codeine is still prescribed due to the influence of efficacy data when combined with non-opioids in adults, familiarity and lower pharmaceutical scheduling with over-the-counter availability (Tremlett 2013 NR). Following paediatric neurosurgery, some centres still use codeine routinely for postoperative pain management (Bronco 2014 Level IV), others less so (Teo 2011 Level IV).

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Comment:

This 2015 ANZCA publication is an authoritative and internationally recognised review of the scientific evidence relating to acute pain management in adults and children. The evidence presented for the safety and efficacy of codeine for acute pain management in children is consistent with the age restrictions for codeine introduced in the US, Europe, Canada and Australia, and the WHO recommendations for pain management in children.

3.1.1.2 Shaheed, 2016 [12]

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

This report was commissioned by the Australian TGA. The research aimed to determine:

- The efficacy and safety of OTC codeine combination analgesics (ibuprofen + codeine or aspirin + codeine or paracetamol + codeine or doxylamine + paracetamol + codeine) for the treatment of any pain condition.
- The efficacy of OTC codeine-based products as an antitussive.

Data sources included MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CENTRAL, CINAHL and PsychoINFO (from inception to end 2015). The search included RCTs evaluating combination medicines containing codeine for any pain condition or for use as an antitussive. Reference lists of included RCTs and relevant systematic reviews were also screened to identify additional RCTs.

The review included English language RCTs evaluating single ingredient or combination OTC medicines containing codeine (at a dose that could be achieved with OTC products available in Australia at the time) for pain or for use as an antitussive. Placebo-controlled RCTs and comparative effectiveness RCTs evaluating different doses of the same drug or combination were eligible for inclusion. Trials were included if they reported pain, cough count, or adverse events outcomes.

Pain outcomes were converted to a common 0-100 scale (0 – no pain to 100 – worst possible pain). Results were presented as mean differences (MD). Treatment effects in the range 10-19 points were considered small; > 20 points moderate and > 30 points large. These values are consistent with the proposed thresholds for *clinically important* changes in pain response from the literature on chronic pain. Effects <10 points were considered as not clinically meaningful.

The GRADE criteria was used to evaluate the overall quality of the evidence for an intervention [13].

For adverse events the proportion of participants experiencing one or more adverse events was reported and the risk ratio calculated based on this information.

The authors concluded there is high quality evidence that combination medicines containing codeine and paracetamol or codeine and NSAID (+/- caffeine) provide significantly greater pain relief compared with placebo. For single dose trials, these combination medicines provide clinically significant pain relief for the immediate term, but these effects appear to decline in the short term

(between 4-6 hours after a single dose). For trials evaluating multiple dose regimens, there continued to be pain improvement over time and the effects were generally higher than the minimum clinically important threshold.

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

Two paediatric papers were included in this review (Table 6).

Table 6: Paediatric studies included in initial TGA review of codeine safety and efficacy (to end of 2015) [12]

Reference	Description
Friday <i>et al</i> (2009) [14]	<p>Type of study: Randomised double-blind equivalence trial.</p> <p>Objective: Compared analgesic effectiveness of acetaminophen + codeine with that of ibuprofen for children with acute traumatic extremity pain, with the hypothesis that the two medications would demonstrate equivalent reduction in pain scores in an emergency department (ED) setting.</p> <p>Methods: Paediatric ED patients 5 to 17 years of age with acute traumatic extremity pain received acetaminophen + codeine (1 mg/kg as codeine, maximum 60 mg) or ibuprofen (10 mg/kg, maximum 400 mg). The patients provided Colour Analog Scale (CAS) pain scores at baseline and at 20, 40, and 60 minutes after medication administration. The primary outcome measured was the difference in changes in pain score at 40 minutes, compared to a previously described minimal clinically significant change in pain score of 2 cm. The difference was defined as (change in ibuprofen CAS score from baseline) – (change in acetaminophen + codeine CAS score from baseline); negative values thus favour the ibuprofen group. Additional outcomes included need for rescue medication and adverse effects.</p> <p>Results: The 32 acetaminophen + codeine and the 34 ibuprofen recipients in our convenience sample had indistinguishable pain scores at baseline. The intergroup differences in pain score change at 20 minutes (-0.6, 95% confidence interval [CI] = -1.5 to 0.3), 40 minutes (-0.4, 95% CI = -1.4 to 0.6), and 60 minutes (0.2, 95% CI = -0.8 to 1.2) were all less than 2 cm. Adverse effects were minimal: vomiting (one patient after acetaminophen + codeine), nausea (one patient after ibuprofen), and pruritus (one after acetaminophen + codeine). The three patients in each group who received rescue medications all had radiographically demonstrated fractures or dislocations.</p> <p>Conclusions: The study found similar performance of acetaminophen + codeine and ibuprofen in analgesic effectiveness among ED patients aged 5–17 years with acute traumatic extremity pain. Both drugs provided measurable analgesia. Patients tolerated them well, with few treatment failures and minimal adverse effects.</p>
Ragg <i>et al</i> (1997) [15]	<p>Type of study: Randomised, prospective, double-blind study</p> <p>Objective: Compared the analgesic effectiveness and incidence of complications of a combination product Painstop (Paedpharm Pty Ltd) containing paracetamol 12 mg, codeine 0.5 mg and promethazine 0.65 mg per 1.0 ml, dosage 1.0 ml/kg, with paracetamol 20 mg/kg.</p> <p>Methods: Ninety-five children aged 1 to 12 years, ASA 1-2, scheduled for myringotomy and drain tube insertion as a day procedure were randomized to</p>

	<p>receive Painstop or paracetamol 30 to 60 minutes prior to surgery. Preoperative drowsiness and complications on induction and postoperative sedation, pain and times to achieve goals were recorded.</p> <p>Results: The groups were comparable for age, gender, weight, anaesthetic technique and duration of surgery. Times to eye opening ($P = 0.05$) and first oral intake ($P = 0.006$) were significantly longer in the Painstop group. There was, however, no difference in times to discharge. Late sedation was more common in the Painstop group ($P = 0.03$).</p> <p>Conclusions: Pain scores were low and similar in both groups and the need for additional analgesia was uncommon.</p>
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Comment:

Neither of the paediatric studies included in this review by the TGA demonstrated superior efficacy of the codeine-containing combination preparation, compared to the single agent analgesic comparator (ibuprofen [14] or paracetamol [15]). One study only included children 5 years and above and therefore does not support use in children younger than this age. Both studies were very small and did not appear to show additional pain relief in the codeine exposed group.

3.1.1.3 TGA, 2016 [16]**Update of codeine safety and efficacy review. January 2015 to November 2016.**

The aim of this review by the TGA was to ascertain whether any further evidence had 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* [12]. The previous review included data base searches to the end of December 2015. This update considers papers published in 2016 (to early November) and any papers published in 2015 that were not mentioned in the previous review. The update does not include low-dose codeine-containing cough and cold products. The update was presented as a narrative review; it was not a systematic review and the quality of the included studies was not evaluated. The report addresses issues of incremental effectiveness in Part A and safety (including misuse) in Part B.

The review identified four paediatric studies in which codeine had been used as one of the comparator drugs. The studies are summarised in Table 7.

Table 7: Paediatric studies included in updated TGA review of codeine safety and efficacy (2015-2016) [16]

Reference	Description
D'Souza <i>et al</i> (2015) [17]	<p>Type of study: Retrospective chart review</p> <p>Period of study: 2011 - 2013</p> <p>Objective: To determine the risk of post-tonsillectomy haemorrhage (PTH) in children who received ibuprofen with acetaminophen vs. those who received narcotic with acetaminophen for postoperative pain control.</p> <p>Methods: Retrospective chart review of patients at a tertiary-care paediatric centre. 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</p>

	<p>with codeine or hydrocodone with acetaminophen postoperatively (narcotic group).</p> <p>Main outcome measure: Incidence of PTH requiring return to the operating room.</p> <p>Secondary outcome measures: Incidence of primary PTH, secondary PTH, and postoperative evaluation in the emergency department or re-admission for pain and/or dehydration.</p> <p>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 ($P<0.0001$).</p> <p>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.</p>
<p>Friedrichsdorf et al, (2015) [18]</p>	<p>Type of study: Prospective, double-blinded, randomized controlled trial.</p> <p>Setting: Large, Midwestern US paediatric hospital.</p> <p>Objective: To evaluate efficacy and safety of the single drug tramadol versus codeine/acetaminophen post-tonsillectomy.</p> <p>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.</p> <p>Interventions: Group 1 received liquid codeine/acetaminophen for 10 days post-tonsillectomy (5 days scheduled, followed by 5 days as-needed). Liquid combination 120mg acetaminophen + 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).</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>Pfaff et al, 2016 [19]</p>	<p>Type of study: Case series with chart review.</p> <p>Objective: To determine the effect of ibuprofen on post-tonsillectomy bleeding when compared with codeine in post-tonsillectomy analgesia.</p>

	<p>Setting: Tertiary care children’s hospital, Philadelphia, Pennsylvania.</p> <p>Subjects and Methods: On July 1, 2012, the institution transitioned from acetaminophen with codeine to ibuprofen for post-tonsillectomy analgesia. Paediatric 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.</p> <p>Results: 6014 patients underwent tonsillectomy between July 1, 2010, and June 30, 2014, and 211 patients presented for post-tonsillectomy haemorrhage during the same period. The incidence of readmission for post-tonsillectomy haemorrhage 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 paediatric 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).</p> <p>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.</p>
<p>Poonai <i>et al</i>, (2015) [20]</p>	<p>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</p> <ul style="list-style-type: none"> • 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 paediatric 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. <p>Authors’ conclusion: A closer look at the limitations of designing high-quality analgesic trials in children with fractures is needed.</p>
<p>Stewart (2015) [21]</p>	<p>This paper provides summaries of two published studies. The relevant study for this update is: Bedwell J <i>et al</i>. Otolaryngology—Head and Neck Surgery. December 2014; 151(6):963-966.</p> <p>Type of study: Retrospective chart review</p>

	<p>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.</p> <p>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.</p> <p>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 population.</p> <p>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.</p> <p>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.</p> <p>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.</p>
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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.

Comment:

This updated review by the TGA of the safety and efficacy of codeine identified five new paediatric publications since the previous review. As noted in the review, no new information on the safety of low dose codeine was provided in these studies.

3.1.1.4 Le May, et al, 2013 [22]

Efficacy of an ibuprofen/codeine combination for pain management in children presenting to the emergency department with a limb injury: a pilot study

This randomised, double-blind, placebo-controlled trial compared the efficacy of codeine plus ibuprofen to ibuprofen alone on the intensity of pain experienced by children aged 6 to 18 years presenting to the Emergency Department with a musculoskeletal trauma to a limb.

Patients were randomised to receive either ibuprofen (10 mg/kg, max 600 mg) plus codeine (1 mg/kg, max 60 mg) orally, or ibuprofen (10 mg/kg, max 600 mg) plus placebo. Pain was assessed with the visual analog scale (0-10) at triage, and at 60, 90 and 120 minutes after administration of the study drug.

A total of 81 patients were recruited: 40 patients received ibuprofen plus codeine, and 41 patients received ibuprofen plus placebo. No significant differences were observed between mean pain scores between the two groups at any time point. At 90 minutes the pain scores were in the moderate range: the mean scores were 4.0 ± 2.4 for the ibuprofen plus codeine group vs. 4.1 ± 2.0 for the ibuprofen plus placebo group.

The authors concluded that, not only was pain inadequately controlled in both groups, the addition of codeine to ibuprofen did not significantly improve pain management in children with musculoskeletal trauma to the limb.

Comment:

Full paper could not be accessed, therefore only the abstract was reviewed. This was a small study in which only 40 patients received codeine-containing study drug. From the information available, the ethnic make-up of each group is not clear. It is also not clear what proportion of each group would be expected to be ultra-rapid metabolisers or poor metabolisers of codeine, and how this may have affected the results.

3.1.2 Efficacy of codeine-containing medicines for treatment of cough in children and adolescents

3.1.2.1 Smith, et al; 2014 [23]

Over-the-counter (OTC) medications for acute cough in children and adults in community settings

Acute cough due to upper respiratory tract infection (URTI) is a common symptom. Non-prescription, over-the-counter (OTC) medicines are frequently used as first-line treatment, but there is little evidence as to whether these drugs are effective.

The objective of this Cochrane Review was to assess the effects of oral OTC cough preparations for acute cough in children and adults in community settings.

Search methods

The authors searched CENTRAL (2014, Issue 1), MEDLINE (January 1966 to March week 3 2014), EMBASE (January 1974 to March 2014), CINAHL (January 2010 to March 2014), LILACS (January 2010 to March 2014), Web of Science (January 2010 to March 2014) and the UK Department of Health National Research Register (March 2010).

Selection criteria

Randomised controlled trials (RCTs) comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in community settings. All cough outcomes (such as frequency, severity, amount of sputum, improvement in cough symptoms) were considered. Secondary outcomes of interest were adverse effects.

Data collection and analysis

Two review authors independently screened potentially relevant citations, extracted data and assessed study quality. Quantitative analysis was performed where appropriate.

Main results

Due to the small numbers of trials in each category, the limited quantitative data available and the marked differences between trials in terms of participants, interventions and outcome measurement, pooling of the results was considered inappropriate.

A total of 29 trials (19 in adults, **10 in children**) were included, involving 4835 people (3799 adults and **1036 children**). All studies were placebo-controlled randomised controlled trials. Assessment of the risk of bias of the included studies was limited by poor reporting, particularly for the earlier studies.

Most adult trials were in young adults with mean ages ranging from 23 to 48 years. **Ages in studies in children ranged from six months to 18 years.** Six trials were more than 20 years old. Nearly half of the studies (13 out of 29) were carried out in the US, with the remaining trials located in the UK (5), Finland (3), Germany (2), India (2), and Italy, South Africa, Thailand and Israel (1 each). The ages of participants ranged from six months to over 70 years. The studies differed in their definition of illness, the content of the drug preparation, drug dosage and frequency, and treatment duration (ranging from a single dose to 18 days), making comparison of trials and quantitative analysis difficult.

In the child studies, antitussives (data from three studies), antihistamines (data from three studies), antihistamine-decongestants (two studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo.

Twenty-one studies reported adverse effects. There was a wide range across studies, with higher numbers of adverse effects in participants taking preparations containing antihistamines and dextromethorphan.

An overview of the paediatric studies of antitussives that were included in the review is shown in Table 8 (adapted from Table 1 in the published article).

Authors' conclusions

The results of this review have to be interpreted with caution because the number of studies in each category of cough preparations was small. Availability, dosing and duration of use of over-the-counter cough medicines vary significantly in different countries. Many studies were poorly reported making assessment of risk of bias difficult and studies were also very different from each other, making evaluation of overall efficacy difficult. **There is no good evidence for or against the effectiveness of OTC medicines in acute cough. This should be taken into account when considering**

prescribing antihistamines and centrally active antitussive agents in children; drugs that are known to have the potential to cause serious harm.

Table 8: Overview of paediatric studies of antitussives included in the review (adapted from Smith *et al*)

Group	Study ID	Number participants	Treatment and duration	Outcome and result	Notes
1. Antitussives					
Antitussives Children	Bhattacharya	120	Dextromethorphan 3 days	Composite 5-item symptom score MD 0.4	NS
	Korppi	50	Dextromethorphan 3 days	4-item cough symptoms score day 3 MD 0.04	NS
	Paul	100	Dextromethorphan Single dose	Composite 5-item symptom score MD 0.79	NS
	Taylor	57	Dextromethorphan or codeine (3 arms) 3 nights	4-item symptom score	NS

Comment:

This Cochrane review is the 2014 update of previous reviews done in 2001, 2004, 2007, 2010, and 2012.

A total of four paediatric studies of antitussives were included in the review, and only one of these (Taylor 1993) included codeine. The study by Taylor was a RCT of 57 children with night cough due to URTI, and was carried out in private practices in the US. Children ranged in age from 18 months to 12 years (mean 4.7 years); 82 % of participants were Caucasian. Patients were randomised to receive dextromethorphan, codeine or placebo as a single bedtime dose for 3 nights. Both active treatments also contained guaifenesin. Cough was measure by parent questionnaire. There was no statistical difference between the groups in cough score. Adverse effects were mainly drowsiness (note dose was given at bedtime), diarrhoea and hyperactivity, and were reported in 54% of placebo group, 32% of the dextromethorphan group and 29% of the codeine group.

The results of this Cochrane Review add little to the discussion about the safety or efficacy of codeine as an antitussive for children and adolescents. Use of codeine-containing cough medicines in children goes against current recommendations for the management of cough in children so it is not surprising that there have not been any new studies in recent years for inclusion in this review.

Overall, the review found 'no good evidence for effectiveness of OTC medicines in acute cough'.

3.2 CARM data

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of respiratory depression associated with the use of codeine in children under the age of 18 years (Table 9). All three cases were reported in the 1970s, concerned infants aged 2-7 months, [REDACTED]

Table 9: CARM Cases of respiratory depression associated with codeine-containing products to 31-12-2017

REPORT	DATE	REACTIONS	DRUGS	AGE	SEX	
002876	AUG1971	HYPOVENTILATION APNOEA MIOSIS HYPOTONIA RESTLESS	* PHOLCODINE + CODEINE (Syrup 15mg/5ml) ACETYLSALICYLIC ACID ERYTHROMYCIN ESTOLATE	7m	M	
002877	AUG1971	CYANOSIS APNOEA	* CODEINE (Syrup) * DIPHENHYDRAMINE (Benadryl elixir) TETRACYCLINE (Syrup)	2m	F	
009056	DEC1979	APNOEA BRADYCARDIA HYPOTENSION	* TRIMEPRAZINE * CODEINE (Linctus) * AMOXICILLIN	4m	M	

Comment:

Respiratory depression is a well-known adverse effect associated with the use of codeine. Well-known adverse effects are often under-reported because there is 'nothing new' or 'interesting'. It is possible that the low level of reporting of this relatively common adverse effect reflects this commonly held view.

4.0 DISCUSSION AND CONCLUSIONS

Codeine is metabolised to morphine via the Cytochrome P450 enzyme CYP2D6. Genetic variability in the expression and activity of this enzyme results in considerable variation between individuals in the proportion of codeine that is converted to morphine. Although most people fall into the category of extensive metabolisers with 'normal' CYP2D6 activity, an unknown proportion of the population are ultra-rapid metabolisers with increased CYP2D6 activity. These people convert a greater proportion of codeine to morphine with the potential for opioid toxicity, which in some cases may be fatal. Additionally, a proportion of the population are poor metabolisers with low or absent CYP2D6 activity. These people are unable to convert codeine to morphine in sufficient quantities to obtain an adequate therapeutic effect.

Although it is technically possible to test for CYP2D6 ultra-rapid metaboliser status, testing is not widely available. It is not currently feasible to test individuals before prescribing codeine to determine their CYP2D6 activity. It is therefore not possible to predict which individuals are likely to be more susceptible to opioid toxicity associated with codeine, or who will experience no analgesic effect. The proportion of the population who are ultra rapid metabolisers or unable to metabolise codeine is likely to be significant.

In the United States, Europe, Canada and Australia, codeine-containing medicines are contraindicated in children aged < 12 years for pain, and in adolescents aged < 18 years for pain following tonsillectomy and/or adenoidectomy.

In Europe, Canada and Australia, codeine-containing medicines are contraindicated in children < 12 years for cough, while in the United States the age restriction for codeine-containing cough & cold medicines was increased to 18 years in January this year.

In Europe, Canada and Australia, codeine is contraindicated in breastfeeding mothers.

The age restrictions for codeine-containing pain and cough & cold medicines in New Zealand are out of step with the United States, Canada, Europe, and Australia. Additionally, there are inconsistencies in the age recommendations between products with the same combinations of ingredients. For example, Paracetamol + Codeine Relieve tablets (Mylan) are labelled as not suitable for children < 7 years of age, while Panadeine tablets (GSK) must not be used in children < 18 years; both products contain paracetamol 500 mg and codeine 8 mg.

From 31 January 2020, codeine-containing combination medicines, both analgesics and those used for cough and colds, will be reclassified to prescription medicines. The Medicines Classification Committee also recommended that medicines containing codeine as the only active ingredient (not more than 15 mg per solid dosage unit) should be reclassified as restricted medicines for use in adults and children over 12 years of age.

Community pharmacy dispensing data for PHARMAC funded codeine shows a drop-off in the number of prescriptions for children aged < 15 years since 2014-2015. This apparent reduction in use may reflect clinical awareness of the changes in codeine use internationally during this time, and of the lack of scientific evidence to support the safety and efficacy of codeine for acute pain management in children (such as the ANZCA Scientific Review of Acute Pain Management [11]).

Literature reviews of codeine safety and efficacy undertaken by the TGA did not find any evidence to support the use of codeine in children for the treatment of pain [12, 16]. Similarly, a 2014 Cochrane review that updated previous reviews (most recently in 2010) of the efficacy of codeine-containing medicines for the treatment of cough and cold identified only one study that had included codeine as a study drug in children. The study showed no difference in efficacy between codeine, dextromethorphan or placebo.

Given the lack of evidence to support the efficacy and safety of codeine-containing medicines in children and adolescents, and international regulatory action to contraindicate the use of codeine-containing medicines in this age-group, the MARC is asked to consider whether similar regulatory action should be taken in New Zealand.

5.0 ADVICE SOUGHT

Specifically, the Committee is asked to advise whether:

- The use of codeine-containing medicines should be contraindicated in children aged < 12 years for all indications.
- The use of codeine-containing medicines should be contraindicated in adolescents < 18 years for pain following surgery to remove tonsils and adenoids.
- The use of codeine-containing medicines should be contraindicated in adolescents < 18 years in whom respiratory function might be compromised.
- The use of codeine-containing medicines should be contraindicated in adolescents aged < 18 years for cough and cold.
- The warning to avoid use using codeine in breastfeeding mothers should be strengthened to a contraindication.
- The outcome of this review requires further communication other than MARC's Remarks in *Prescriber Update*.
- Any other regulatory actions are required.

6.0 ANNEXES

1. Codeine use in children and ultra-rapid metabolisers. Pharmacovigilance and Special Access Branch Safety Review (TGA).
2. FDA Drug Safety Communication (2018-01-11): *FDA requires labelling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older*

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