Queensland University of Technology
Brisbane Australia

This may be the author's version of a work that was submitted/accepted for publication in the following source:

Gardiner, Samantha, Chang, Anne, Marchant, Julie, & Petsky, Helen (2016)
Codeine versus placebo for chronic cough in children.
Cochrane Database of Systematic Reviews, *7*(CD011914), pp. 1-25.

This file was downloaded from: https://eprints.qut.edu.au/222440/

© Consult author(s) regarding copyright matters

This work is covered by copyright. Unless the document is being made available under a Creative Commons Licence, you must assume that re-use is limited to personal use and that permission from the copyright owner must be obtained for all other uses. If the document is available under a Creative Commons License (or other specified license) then refer to the Licence for details of permitted re-use. It is a condition of access that users recognise and abide by the legal requirements associated with these rights. If you believe that this work infringes copyright please provide details by email to qut.copyright@qut.edu.au

Notice: *Please note that this document may not be the Version of Record (i.e. published version) of the work. Author manuscript versions (as Submitted for peer review or as Accepted for publication after peer review) can be identified by an absence of publisher branding and/or typeset appearance. If there is any doubt, please refer to the published source.*

https://doi.org/10.1002/14651858.CD011914.pub2

Cochrane Library

Cochrane Database of Systematic Reviews

Codeine versus placebo for chronic cough in children (Review)

Gardiner SJ, Chang AB, Marchant JM, Petsky HL

Gardiner SJ, Chang AB, Marchant JM, Petsky HL.
Codeine versus placebo for chronic cough in children.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD011914.
DOI: 10.1002/14651858.CD011914.pub2.

www.cochranelibrary.com

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 3
OBJECTIVES . . . 4
METHODS . . . 4
Figure 1. . . . 6
RESULTS . . . 8
DISCUSSION . . . 9
AUTHORS' CONCLUSIONS . . . 10
ACKNOWLEDGEMENTS . . . 11
REFERENCES . . . 11
CHARACTERISTICS OF STUDIES . . . 15
DATA AND ANALYSES . . . 19
APPENDICES . . . 19
CONTRIBUTIONS OF AUTHORS . . . 21
DECLARATIONS OF INTEREST . . . 22
SOURCES OF SUPPORT . . . 22
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 22

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Codeine versus placebo for chronic cough in children

Samantha J Gardiner[1], Anne B Chang[1,2], Julie M Marchant[3], Helen L Petsky[1]

[1]Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia. [2]Child Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, Australia. [3]University of Queensland, Brisbane, Australia

Contact address: Samantha J Gardiner, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia. samantha.gardiner@qut.edu.au. samanthajgardiner@gmail.com.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 7, 2016.
Review content assessed as up-to-date: 8 June 2016.

Citation: Gardiner SJ, Chang AB, Marchant JM, Petsky HL. Codeine versus placebo for chronic cough in children. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD011914. DOI: 10.1002/14651858.CD011914.pub2.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Cough in children is a commonly experienced symptom that is associated with increased health service utilisation and burden to parents. The presence of chronic (equal to or more than four weeks) cough in children may indicate a serious underlying condition such as inhaled foreign body or bronchiectasis. Codeine (and derivative)-based medications are sometimes used to treat cough due to their antitussive properties. However, there are inherent risks associated with the use of these medications such as respiratory drive suppression, anaesthetic-induced anaphylaxis, and addiction. Metabolic response and dosage variability place children at increased risk of experiencing such side effects. A systematic review evaluating the quality of the available literature would be useful to inform management practices.

Objectives

To evaluate the safety and efficacy of codeine (and derivatives) in the treatment of chronic cough in children.

Search methods

We searched the Cochrane Airways Group Register of Trials, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 to 8 June 2016), EMBASE (1974 to 8 June 2016), the online trials registries of the World Health Organization and ClinicalTrials.gov, and the bibliographic references of publications. We imposed no language restrictions.

Selection criteria

We considered studies eligible for analysis when: the participant population included children aged less than 18 years with chronic cough (duration equal to or more than four weeks at the time of intervention); and the study design evaluated codeine or codeine-based derivatives against placebo through a randomised controlled trial.

Data collection and analysis

Two review authors independently screened the search results to determine eligibility against a standardised criteria, and we had a pre-planned method for analysis.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Main results

We identified a total of 556 records, of which 486 records were excluded on the basis of title and abstract. We retrieved the remaining 70 references in full to determine eligibility. No studies fulfilled the inclusion criteria of this review, and thus we found no evidence to support or oppose the use of codeine or derivatives as antitussive agents for chronic cough in children.

While chronic cough is not the same as acute cough, systematic reviews on the use of codeine efficacy for acute cough in children conclude an overall lack of evidence to support or oppose the use of over-the-counter cough and cold medications containing codeine (or derivatives) for treatment of acute cough in children. The lack of sufficient evidence to support the use of these medications has been consistently reaffirmed by medical experts in international chronic cough guidelines and by governing medical and pharmaceutical authorities in the USA, Europe, Canada, New Zealand, and Australia. Due to the lack of sufficient evidence to support efficacy, and the known risks associated with use - in particular the increased risks for children - these medications are now not recommended for children less than 12 years of age and children between 12 to 18 years with respiratory conditions.

Authors' conclusions

This review has highlighted the absence of any randomised controlled trials evaluating codeine-based medications in the treatment of childhood chronic cough. Given the potential adverse events of respiratory suppression and opioid toxicity, national therapeutic regulatory authorities recommend the contraindication of access to codeine in children less than 12 years of age. We suggest that clinical practice adhere to clinical practice guidelines and thus refrain from using codeine or its derivatives to treat cough in children. Aetiological-based management practices continue to be advocated for children with chronic cough.

PLAIN LANGUAGE SUMMARY

Codeine for the treatment of chronic cough in children

Review question

We sought to answer the question of whether codeine (or medications produced from codeine) are safe and effective in the treatment of chronic cough (four weeks or longer) in children.

Background

Cough is a very commonly experienced symptom and is one of the most frequent reasons for visiting doctors and other health service providers. The presence of chronic cough (four weeks or longer) in children may indicate a serious underlying condition. Codeine (or medications produced from codeine) are ingredients in some non-prescription, over-the-counter cough syrups as well as some prescribed by a doctor. These medications are used to reduce the effects of cough, although there are known risks associated with their use, including breathing difficulties, allergic reactions, and addiction. We aimed to look at the safety and benefit of these medications for the treatment of chronic cough in children.

Search date

We searched for any and all trials published and pending as of 8 June 2016.

Study characteristics

We searched for any randomised controlled trial comparing either codeine (or medications produced from codeine) versus placebo in the treatment of chronic cough (4 weeks or longer) in children aged 18 years and younger.

Key results

The search identified 556 records. We reviewed and assessed all of these against predetermined inclusion/exclusion criteria. We found no eligible studies to include in this review. However, our search did find studies that investigated codeine (or medications produced from codeine) in the treatment of acute cough (two weeks or less) in children. Another Cochrane review specifically for children with acute cough evaluated these studies and found no evidence to support or oppose use of codeine (or medications produced from codeine). This overall lack of evidence is consistent with international chronic cough guidelines, which recommend treating the cause of the cough. Due to the known risks associated with use, in particular the increased risks for children, governing bodies in the USA, Europe, Canada, New Zealand, and Australia have stated these medications are now not recommended for children younger than 12 years of age and children between 12 to 18 years with respiratory conditions. Given the lack of supporting trials, the findings from

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

trials of acute cough in children, and the known harmful side effects, we have concluded that codeine-based medications cannot be recommended in children with chronic cough.

Quality of evidence

We found no studies and hence there is no quality of evidence.

BACKGROUND

Description of the condition

Cough is a commonly experienced symptom within the community (Chang 2015), and was identified as the leading reason for acute consultations to general practitioners in Australia between 2009 and 2010 (Britt 2010). Cough in children can be broadly categorised into acute (coughing lasting less than two weeks) or chronic (coughing duration longer than four weeks) (Chang 2006a; de Jongste 2003; Gibson 2010). The latter was the subject of this review.

Unlike acute cough (which often results from a viral infection), the aetiology of chronic cough is diverse and may indicate a serious underlying disease such as an airway abnormality or bronchiectasis. Irrespective of the type of cough or its aetiology, parents and carers often seek relief for their child's cough (Vernacchio 2008). This is not surprising as the burden of cough is multidimensional and can negatively impact individuals and their families (Anderson-James 2014; Marchant 2008).

Description of the intervention

Codeine is derived from the *Papaver somniferum*, or opium poppy plant, and was first extracted in 1830 by a French chemist, Pierre-Jean Robiquet (Kane 2007). Codeine is an alkaloid opiate compound and is predominantly used as an analgesic and antitussive (cough suppressant) agent in health care. Since the discovery of codeine, numerous opiates and semi-synthetic derivatives have been developed and utilised for many reasons, including their antitussive properties (Kane 2007). While preparations may be prescription controlled, many of these drugs are readily available and easily accessible in combination therapies with antihistamines, antipyretics, decongestants, or expectorants as over-the-counter, non-prescription cough syrups or lozenges. The ease of accessibility of such treatments has likely contributed to a perception of their safety and efficacy and has contributed to widespread use within the community (Lokker 2009).

How the intervention might work

Codeine (and derivatives) have been used as an antitussive for centuries. The medication acts primarily through opioid receptors of the central nervous system, although the exact mechanisms of action are unknown (Takahama 2007). An alternative mechanism of action is through sedation (Dickinson 2014). The pharmacodynamic properties of codeine in children are poorly understood, although there are known inherent and undesirable side effects associated with this class of antitussives.

Side effects may include respiratory depression, pruritis, rash, facial swelling, vomiting, and ataxia (Fleming 2014). Codeine is metabolised by several enzymes such as CYP3A4 and CYP2D6. The latter converts codeine to morphine, the active metabolite. There are genetic variants of CYP2D6, and rapid metabolism rates increase the risk of respiratory drive suppression and adverse effects (Committee on Drugs 1997). Individual responsiveness to codeine-based combination therapies is unpredictable, with age, genetic make-up, ethnicity, and disease aetiology influencing the outcome (Fleming 2014; Gadomski 1992).

There is growing international concern regarding the availability and safety of codeine, with the consequences of hyper-metabolism, drug abuse, and the risk of anaesthetic-induced anaphylaxis at the forefront of reform agendas (European Medicines Agency 2015; Florvaag 2012; Mattoo 1997).

Why it is important to do this review

Codeine (and derivatives)-based antitussive agents are widely used in the paediatric population, although the mechanism of action is poorly understood. The safety and efficacy of exposure is highly variable, with children at increased risk of experiencing significant adverse effects (Gadomski 1992). The burden of cough is multifaceted, resulting not only in parental stress and worry, but also on a child's ability to participate fully within society due to school and work time loss (Marchant 2008). Rigorously evaluating the efficacy of various treatment options, including codeine and its derivatives as antitussive agents, will thus assist in clinical management and allow informed burden-reduction treatment strategies in children.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

OBJECTIVES

To evaluate the safety and efficacy of codeine (and derivatives) for the treatment of chronic cough in children.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials (RCTs), quasi-RCTs, and stratified RCTs that compared codeine (or derivatives) versus placebo. We planned to include studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

Due to the differing definitions and aetiology of chronic cough between children and adults, we sought to include studies of children aged 18 years or younger with a diagnosis of chronic cough (cough lasting four or more weeks). We excluded participants with acute cough.

Types of interventions

We sought to include studies comparing medications that contained codeine or codeine derivatives versus placebo.

We included the following derivative agents in the search strategy: dihydrocodeine, nalodeine, azidocodeine, acetylcodeine, dextromethorphan, nicocodine, pholcodine, alpha-codeimethine, 6-succinylcodeine, 6-codeinone, 14-hydroxycodeine, n-methylcodinium iodine, codeine-7,8-oxide, codeine-6-glucronide, and O(6)-codeine methyl ether.

We planned to include the following comparisons.

1. Cough mixture containing codeine or codeine derivative only as the active ingredient versus placebo.
2. Cough mixture containing codeine or codeine derivative plus other active ingredient/s versus cough mixture containing placebo plus the same other active ingredient/s.

Types of outcome measures

Primary outcomes

Primary outcomes were those that reflected objective measures of treatment superiority, non-inferiority, or inferiority, and included:

1. number of children not cured at follow-up;
2. number of children who experienced a reduction in cough severity (clinically defined as a greater than 70% change in severity as per previous RCTs) (Chang 1998; Marchant 2012);
3. serious adverse events (a reaction to the study drug that results in hospital admission or loss of life, or both).

Secondary outcomes

The following secondary outcome measures contribute to the strength of primary outcome analysis:

1. symptoms and burden of cough as reported in cough indices such as cough quality of life scores, diary card, and cough severity index scores;
2. adverse events/side effects (any event that is not considered life-threatening and does not result in a hospital admission and would otherwise not occur without exposure to the study medication).

Reporting one or more of the outcomes listed above in the trial was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We searched the following databases.

- Cochrane Airways Group Register of Trials (via the Cochrane Register of Studies): all years to 8 June 2016
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online: all years to 8 June 2016
- MEDLINE (Ovid): 1946 to June week 1 2016
- EMBASE (Ovid): 1974 to week 23 2016
- Trials registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP))

The MEDLINE strategy is listed in Appendix 1. We adapted this strategy for use in the other databases. We searched all databases from their inception to the 8 June 2016. We searched the trials registries of ClinicalTrials.gov and WHO ICTRP all years to 9 June 2016 (Appendix 2). We placed no restrictions on the language of publication.

Searching other resources

We checked the reference lists of all relevant articles for additional references.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

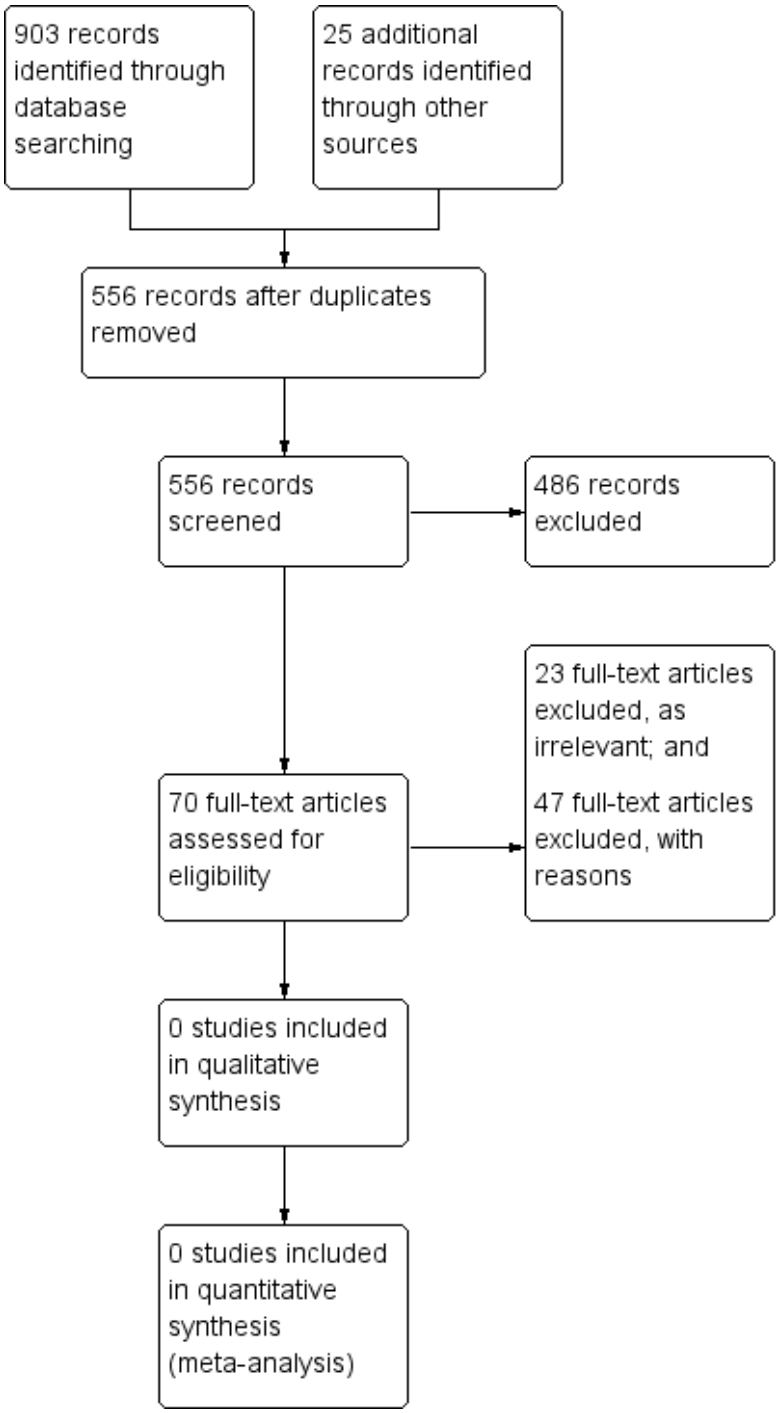
Data collection and analysis

Selection of studies

We uploaded electronic search results to the Covidence software platform (Covidence 2015), and summarised results using the PRISMA flow diagram (Figure 1). We identified and excluded duplicates and collated multiple reports of the same study. Two review authors (SG, HP) independently screened the titles and abstracts of all studies identified for inclusion. We excluded records on the basis of the title and abstract alone when study design was clearly defined with no ambiguity. We retrieved the full-text publications of records that required further clarification, including those published in a language other than English. We sought translation for non-English publications using a standardised inclusion/exclusion criteria sheet. Review authors independently recorded the reason for exclusion. Where there were discrepancies, a third person (AC) adjudicated.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. PRISMA study flow diagram.



Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Data extraction and management

It was planned that two review authors (SG, HP) were to extract the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

However, as no studies fulfilled the inclusion criteria, data extraction was not possible.

Assessment of risk of bias in included studies

It was planned that two review authors (SG, HP) would independently assess risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We would have resolve any disagreements by discussion or by involving another review author (AC). We planned to assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We planned to grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We planned to summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Had we identified sufficient studies, we would have considered blinding separately for different key outcomes where necessary (for example for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we would have noted this in the 'Risk of bias' table.

When considering treatment effects, we planned to take into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in the Differences between protocol and review section of this systematic review.

Measures of treatment effect

We planned to analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We planned to enter data presented as a scale with a consistent direction of effect.

We planned to undertake meta-analyses only where this was meaningful, that is if the treatments, participants, and underlying clinical questions were similar enough for pooling to make sense.

We would have narratively described skewed data reported as medians and interquartile ranges.

If multiple trial arms had been reported in a single trial, we would have included only the relevant arms. Where two comparisons (for example drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we would have halved the control group to avoid double-counting.

Unit of analysis issues

For dichotomous data, we planned to report the proportion of participants contributing to each outcome in comparison with the total number randomised. For rate ratios of common events whereby one participant may have more than one event, we would have used generic inverse variance. We would have taken the rate ratios from the published papers and calculated the standard errors from confidence intervals (CI) or P values published in the papers. For cross-over studies, mean treatment differences would have been calculated from raw data, extracted or imputed and entered as fixed-effect generic inverse variance outcome, to provide summary weighted differences and 95% CIs.

Dealing with missing data

We planned to contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (for example when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we would have explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Assessment of heterogeneity

We planned to describe and test any heterogeneity between the study results to see if it reached statistical significance using a Chi ^{2} test. We would have included the 95% CI estimated using a random-effects model whenever there were concerns about statistical heterogeneity. We would have considered heterogeneity significant when the P value was less than 0.10 (Higgins 2011). We would have used the I^2 statistic to measure heterogeneity among the trials in each analysis. Had we identified substantial heterogeneity, we would have reported this and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

Had we been able to pool more than 10 trials, we would have created and examined a funnel plot to explore possible small-study and publication biases and would have consulted a statistician to ensure appropriate analysis was conducted.

Data synthesis

We planned to use a random-effects model and perform a sensitivity analysis with a fixed-effect model.

'Summary of findings' table

We planned to create a 'Summary of findings' table reporting the following outcomes: number of children not cured at follow-up; number of children who experienced a reduction in cough severity; serious adverse events; and symptoms and burden of cough as reported in cough indices tools. We planned to use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We planned to use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We planned to justify all decisions to down- or up-grade the quality of studies using footnotes and make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Children aged less than seven years and seven years or older.
2. Children with diagnosed respiratory conditions (e.g. cystic fibrosis (CF), non-CF bronchiectasis) versus children with no diagnosed respiratory condition.
3. Active ingredient other than codeine (e.g. expectorants, antihistamines, decongestants, antipyretics, substances that may soften coughing such as honey or syrup).

We planned to use the following outcomes in subgroup analyses.

1. Number of children not cured at follow-up.
2. Number of children who experienced a reduction in cough severity based on objective symptom measures of sputum production, runny nose, fevers, and air entry; as well as subjective measures of cough burden.
3. Serious adverse events.

We planned to use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We planned to carry out the following sensitivity analyses.

1. A comparison based on 'Risk of bias' assessments.
2. A comparison of available-case analyses versus true intention-to-treat (ITT) analyses, when the ITT analyses were imputed with best-case and worse-case outcome data.
3. A comparison of results from fixed-effect models versus results from random-effects models.

RESULTS

Description of studies

We identified 903 records through database searching and an additional 25 records through other sources. After removing duplicates, we screened 556 records and excluded 486 records. We retrieved full-text articles for the remaining 70 records, of which 23 were excluded due to irrelevance and 47 were excluded with reasons. We found no studies that were eligible for inclusion in this review. See Figure 1 for PRISMA diagram and the Characteristics of excluded studies table for specific details on excluded records.

Results of the search

We initially performed the Cochrane Airways Group Register of Trials literature search on 27 March 2015, and subsequently re-ran the search on the 11 September 2015 and then again on the 8 June 2016, which yielded a total of 903 references (Figure 1). A search of ClinicalTrials.gov and the WHO ICTRP yielded an additional 25 results. After de-duplication, we considered 556 abstracts for inclusion against the predetermined criteria.

We excluded a total of 486 studies on the basis of the abstract alone. We retrieved full-text publications for the remaining 70 references in order to further determine inclusion eligibility. Of these, 16 articles were published in a language other than English (German, Italian, Czech, Spanish, and French). Translation was provided against a standardised inclusion/exclusion template. We deemed a total of 23 records irrelevant. The remaining 47 publications did not fulfil the inclusion criteria; reasons for exclusion are provided in the Characteristics of excluded studies table.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Included studies

There were no included studies.

Excluded studies

Reasons for exclusion of the aforementioned full-text articles were either solely, or a combination of, the following: non-RCT publication (n = 15); non-placebo-controlled study design (n = 6); studies evaluating acute cough (n = 6); and studies with an adult-only participant population (n = 20). We excluded NCT02651116 because it did not fit our inclusion criteria (acute cough), however this study is ongoing. We have provided full details of reasons for exclusion in the Characteristics of excluded studies table.

Risk of bias in included studies

No studies met the inclusion criteria.

Effects of interventions

Due to a lack of included studies, we were unable to evaluate the effects of codeine (and derivatives)-based medications for the treatment of chronic cough in children.

DISCUSSION

Summary of main results

We identified no studies eligible for inclusion in this review, and thus found no evidence to support or oppose the use of codeine or derivatives as antitussive agents for chronic cough in children. Our review process identified paediatric studies that evaluated acute cough, in Bhattacharya 2013, Paul 2004, Shadkam 2010, Taylor 1993, and Yoder 2006, and adult-specific chronic cough trials (Barroso 1973; Dierckx 1981; Edwards 1977; Matthys 1983, Matthys 1985; Thackray 1978).

Of the paediatric-specific RCTs that evaluated acute cough (Bhattacharya 2013; Paul 2004; Shadkam 2010; Taylor 1993; Yoder 2006), none reported any statistically significant difference in cough severity between treatment arm and placebo. As the evaluation of safety was an objective of this review, and the authors reported side effects, we have provided a summary of these findings below.

A single-dose, double-blind, placebo-controlled RCT evaluated dextromethorphan, diphenhydramine (an antihistamine) against placebo for the treatment of nocturnal cough due to upper respiratory tract infections in 37 children aged 6 to 18 years (Yoder 2006). The mean cough duration of each treatment arm was 4.17, 3.92, and 4.23 days, respectively. This study found no difference between treatment arms and reported no adverse effects. A similar single-dose RCT of dextromethorphan, diphenhydramine, and placebo on acute (seven days or less) nocturnal cough in children found that neither drug was superior to placebo in regards to reducing the frequency, severity, and bothersome nature of cough (Paul 2004). More notably, however, this study did report an increased adverse reaction of insomnia in the dextromethorphan arm, but this was not significant (P = 0.07). The design of this study was limited by the inclusion of concurrent antibiotic treatments, common analgesics such as acetaminophen and ibuprofen, administration of a single dose, and the possibility of placebo effect. These findings are consistent with an earlier study by Taylor 1993, who conducted an RCT of 49 children with acute cough (duration of less than 12 days) and found that codeine or dextromethorphan compared to placebo was not more efficacious in reducing cough score and symptom score.

Bhattacharya 2013 conducted a double-blind RCT of dextromethorphan, promethazine, and placebo in 120 children with acute cough. The study found that when compared to placebo the treatment arms did not confer any greater benefit with respect to symptom scores. The authors also noted that in the entire cohort there was a propensity for the cough to resolve, irrespective of the intervention type (Bhattacharya 2013). The cohort was evenly divided between groups, with 40 children in each arm. Adverse events were higher in children treated with dextromethorphan (32.5%) compared to the placebo group (5%). Adverse events included abdominal pain, nausea, vomiting, drowsiness, and irritability.

In a non-blind RCT between dextromethorphan, diphenhydramine, honey, and a control group involving 139 children (mean age 37.75 months) with acute cough of 5 days, Shadkam 2010 found honey to be more effective in improving cough frequency, cough severity, and sleep quality when comparing honey with each group separately. However, after each intervention (that is honey, dextromethorphan, and diphenhydramine), the mean difference from baseline was statistically significant. No side effects were reported in the dextromethorphan arm, and in spite of the relative superiority of honey, nervousness was a reported adverse reaction in two children, and the authors further acknowledged the risk associated with honey with regards to botulism in children aged less than 1 year.

The evidence pertaining to acute-cough management practices was previously evaluated by Smith 2014, who conducted a systematic review of evidence evaluating the antitussive efficacy of over-the-counter (OTC) medications in the treatment of acute cough in both adults and children. This review similarly found an overall lack of well-designed studies and no evidence for or against the efficacy of OTC antitussive medications. The lack of evidence to support codeine and OTC medications for cough in children is further reflected in their absence from expert position statements and international cough guidelines (Berlin 1997; Chang 2006b;

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gibson 2010; Gibson 2016; Shields 2008).

An increased awareness of risks associated with codeine has prompted many governmental bodies to review legislation and moderate availability of these drugs, and in recent years there has been an increasing international trend toward greater regulatory framework surrounding the availability and use of codeine in children. Following the American College of Chest Physician's chronic cough guidelines, which recommended against using codeine and OTC medications for cough in children (Chang 2006b), and a citizen petition on the safety and efficacy of OTC cough and cold medications, the US Food and Drug Administration convened an expert advisory committee to evaluate the dispensing practices and accessibility of OTC medications to children (US Food and Drug Administration 2015). More recently, in April 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency conducted an investigation into the use of codeine-based medications as antitussive agents. The investigation concluded that there is a lack of sufficient evidence to support the use of codeine as an effective antitussive agent and that there are continued and varied safety concerns associated with this drug. As a result, the PRAC found codeine to be contraindicated in children less than 12 years of age and recommended it not be used. The report further recommended such medications not be used by children aged 12 to 18 years with breathing difficulties; any person known to be an ultra-rapid metaboliser; or breastfeeding mothers (European Medicines Agency 2015). Principal justification for reform is the unpredictability of codeine to morphine conversion in children and the increased vulnerabilities of children predisposed to airway insufficiency (European Medicines Agency 2015). Similar conclusions pertaining to codeine use were made following investigations by Health Canada (Health Canada 2015), the New Zealand Medicines Adverse Reactions Committee (Medsafe 2015), and the Therapeutic Goods Association of Australia (Therapeutic Goods Administration 2015). Reviews into the continued risks, drug availability, and scheduling classifications are currently under way in the United States, US Food and Drug Administration 2016, and in Australia, where these medications continue to be made available OTC for children aged 6 to 11 years.

Overall completeness and applicability of evidence

This review has highlighted a considerable gap in evidence evaluating codeine (and derivatives) antitussive agents in childhood chronic cough. Identified studies of relevance focused on paediatric populations with acute cough or on adult populations. The pathophysiological differences between adults and children, in addition to the different aetiologies between acute and chronic cough, limit the overall generalisability of these findings.

Quality of the evidence

We found no evidence to support or oppose the use of codeine (or derivatives) for the management of chronic cough in children.

Potential biases in the review process

There were no protocol deviations within this review process, and two review authors independently reviewed the searches using a standardised inclusion/exclusion criteria. We thus believe that there were no potential biases in the determination of studies eligible for inclusion in this review.

Agreements and disagreements with other studies or reviews

Our findings of the absence of any RCTs on the efficacy of codeine and its derivatives for chronic cough, along with its potential serious adverse events including death, are consistent with other prior systematic reviews undertaken in the writing of national and international cough guidelines for children (Chang 2006b; Gibson 2010; Shields 2008). In acute cough, a systematic review found "codeine to be no more effective than placebo" (Smith 2014). This Cochrane review on OTC medications for children and adults concluded that "there is no good evidence for or against the effectiveness of over-the-counter cough medicine" (Smith 2014). In adults with chronic cough, a systematic review found codeine and dextromethorphan more beneficial in reducing cough frequency and severity than placebo but, due to a limited number of studies and study design flaws, the authors concluded that "there were insufficient data to draw conclusions about their relative efficacy" (Yancy 2013).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no published RCT and hence no evidence on the efficacy of codeine (or codeine derivatives)-based medications as antitussives in improving clinical outcomes for chronic cough in children. There are, however, documented risks associated with the use of these medications, and children are particularly at risk. There is a high degree of variability in codeine-morphine metabolism in children, with the potential adverse events of respiratory suppression and opioid-toxicity being particularly concerning. Furthermore, in the management of chronic cough in children, the underlying aetiology should be defined, rather than the cough empirically treated, as recommended in national cough guidelines and systematic reviews (Chang 2006b; Chang 2016;

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gibson 2010; Shields 2008). Thus, as recommended in many national guidelines, it is currently advocated that codeine and its derivatives are not used for cough in children less than 12 years of age.

Implications for research

Childhood chronic cough is a substantial burden for families and the healthcare system alike. This review has highlighted a lack of high-quality RCTs evaluating codeine-based medications in the treatment of childhood chronic cough. However, given the associated risks in children and that aetiological-based management practices are advocated in the management of chronic cough in children (Chang 2006b; Chang 2016), it is highly unlikely that RCTs using currently available preparations of codeine or/and its derivatives will be undertaken in children. If future derivatives that do not have the side effects associated with codeine (and derivatives) become available, such studies should be parallel, double-blinded RCTs using validated cough outcome measures that include patient-relevant and objective outcomes (Boulet 2015),

ACKNOWLEDGEMENTS

We thank the Lung Foundation of Australia and the Australian Satellite of the Cochrane Airways Group for the provision of a scholarship to SG. We thank Liz Stovold, the Information Specialist, in the formulation of the search strategy and undertaking the searches for this review. We are also grateful to the Cochrane Airways Group central group, in particular Dr Chris Cates (editor), for their ongoing support of this review.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

The background and methods sections of this protocol were based on a standard template used by the Cochrane Airways Group.

Dr Chris Cates was the Editor for this review and commented critically on the review.

REFERENCES

References to studies excluded from this review

Aliprandi 2004 *{published data only}*
Aliprandi P, Castelli C, Bernorio S, Dell'Abate E, Carrara M. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. *Drugs Under Experimental and Clinical Research* 2004;**30**(4):133–41. [PUBMED: 15553659]

Arroll 2005 *{published data only}*
Arroll B. Non-antibiotic treatments for upper-respiratory tract infections (common cold). *Respiratory Medicine* 2005; **99**(12):1477–84. [PUBMED: 16291073]

Barroso 1973 *{published data only}*
Barroso FA, Paino JS, Lanagran BA. Double blind study of the clinical cough suppressant action of PB 89 (Oleptan). [Spanish]. *Actualidad Medica* 1973;**59**(585):657–62.

Berlin 1997 *{published data only}*
Berlin CM, McCarver DG, Notterman DA, Ward RM, Weismann DN, Wilson GS, et al. Use of codeine- and dextromethorphan-containing cough remedies in children. American Academy of Pediatrics. Committee on Drugs. *Pediatrics* 1997;**99**(6):918–20. [PUBMED: 9190557]

Bhattacharya 2013 *{published data only}*
Bhattacharya M, Joshi N, Yadav S. To compare the effect of dextromethorphan, promethazine and placebo on nocturnal cough in children aged 1-12 y with upper respiratory infections: A randomized controlled trial. *Indian Journal of Paediatrics* 2013;**80**(11):891–5. [PUBMED: 23592248]

Blanchard 2013 *{published data only}*
Blanchard E, Tunon de Lara M. New insights into the role of pholcodine in the treatment of cough in 2013 [French]. *Therapie* 2013;**68**(2):85–91. [DOI: 10.2515/therapie/2013019; PUBMED: 23773349]

Bolser 2006 *{published data only}*
Bolser DC. Current and future centrally acting antitussives. *Respiratory Physiology and Neurobiology* 2006;**152**(3): 349–55. [PUBMED: 16517221]

Bolser 2006a *{published data only}*
Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**(1 Suppl):238S–49S. [DOI: 10.1378/chest.129.1˙suppl.238S]

Bolser 2007 *{published data only}*
Bolser DC, Davenport PW. Codeine and cough: an ineffective gold standard. *Current Opinion in Allergy and Clinical Immunology* 2007;**7**(1):32–6. [DOI: 10.1097/ACI.0b013e3280115145]

Chang 2006 *{published data only}*
Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**(1 Suppl):260S–83S. [PUBMED: 16428719]

Chang 2014 *{published data only}*
Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD006088.pub3]

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chicouri 1985 *{published data only}*
Chicouri M. Controlled trial of an antitussive (codeine plus ethylmorphine as camsilates). *Comptes Rendus de Thérapeutique et de Pharmacologie Clinique* 1985;**4**(34): 7–11.

Dierckx 1981 *{published data only}*
Dierckx P, Leblanc G, Decoster A, Criscuolo D. Double-blind study of glaucine in chronic cough. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 1981;**19**(9):396–9. [PUBMED: 7028646]

Dobiasova 1984 *{published data only}*
Dobiasova L. A controlled clinical study of intussin [Czech]. *Farmako Terapeutické Zprávy* 1984;**30**(3):241–55.

Dotti 1970 *{published data only}*
Dotti A. Clinical trial of the antitussive action of an association of codeine plus phenyltoloxamine [Italian]. *Giornale Italiano delle Malattie del Torace* 1970;**24**(3): 147–57.

Eddy 1969 *{published data only}*
Eddy NB. Codeine and its alternates for pain and cough relief. *Annals of Internal Medicine* 1969;**71**(6):1209–12. [PUBMED: 2554456]

Edwards 1977 *{published data only}*
Edwards GF, Lewis HE, Stafford D. The effect of pholcodine with and without an antihistamine on cough and expectoration. *British Journal of Diseases of the Chest* 1977;**71**(4):245–52. [PUBMED: 22340]

Gruber 2000 *{published data only}*
Gruber W, Eber E, Zach M. Symptomatic therapy for coughing in colds. An analysis of controlled studies [German]. *Monatsschrift fur Kinderheilkunde* 2000;**148**(2): 156–64.

Kleibel 1980 *{published data only}*
Kleibel F. Clinical trial of an antitussive agent [German]. *Krankenhaus Arzt* 1980;**53**(3):242–4.

Kleibel 1981 *{published data only}*
Kleibel F. Trial of a delayed action formulation of codeine plus carbinoxamine for antitussive activity [German]. *Krankenhaus Arzt* 1981;**54**(1):71–4.

Koster 1970 *{published data only}*
Koster E. Treatment of dry cough with Gujaphenyl cum codeine [German]. *Munchener Medizinische Wochenschrift* 1970;**112**(48):2190–1.

Loos 1973 *{published data only}*
Loos M. Antitussive therapy of chronic unspecific bronchial and lung diseases. Double blind study [German]. *Arzneimittel-Forschung* 1973;**23**(Suppl 2a):331–6.

Lucchesi 1971 *{published data only}*
Lucchesi M. Clinical experiences with pentamethylentetrazole-dihydrocodeine in the therapy of cough in patients with pulmonary [Italian]. *La Clinica Terapeutica* 1971;**58**(6):549–53.

Matera 1977 *{published data only}*
Matera N, Londei M, Guidotti P, Catena R. Drug combination with antitussive activity: a clinical trial [Italian]. *La Clinica Terapeutica* 1977;**80**(2):167–79.

Matthys 1983 *{published data only}*
Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *Journal of International Medical Research* 1983;**11**(2):92–100. [PUBMED: 6852361]

Matthys 1985 *{published data only}*
Matthys H, Erhardt J, Ruhle KH. Objectifying of effect of antitussive agents by tussometry in patients with chronic cough. *Schweizerische Medizinische Wochenschrift* 1985;**115** (9):307–11. [PUBMED: 3885387]

Matts 1977 *{published data only}*
Matts SG. A trial of Lotussin and linctus diphenhydramine in patients with an irritant cough. *Journal of International Medical Research* 1977;**5**(6):470–2.

Maulik 2001 *{published data only}*
Maulik SK, Maulik M. Pharmacological control of cough. *Indian Journal of Paediatrics* 2001;**68 Suppl 2**:S33–8. [PUBMED: 11411376]

Mizoguchi 2007 *{published data only}*
Mizoguchi H, Wilson A, Jerdack GR, Hull JD, Goodale M, Grender JM, et al. Efficacy of a single evening dose of a syrup containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulfate in subjects with multiple common cold symptoms. *International Journal of Clinical Pharmacology and Therapeutics* 2007;**45**(4):230–6. [DOI: 17474541]

NCT02651116 *{published data only}*
NCT02651116. Dextromethorphan pediatric acute cough study (CHPA DXM). https://clinicaltrials.gov/ct2/show/NCT02651116 (accessed 22 June 2016).

Oduwole 2010 *{published data only}*
Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE. Honey for acute cough in children. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD007094.pub3]

Palumbo-Vargas 1971 *{published data only}*
Palumbo-Vargas O. On the therapy of cough in bronchial diseases of children [Italian]. *Minerva Medica* 1971;**62**(17): 833–6.

Paul 2004 *{published data only}*
Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004;**114**(1):e85–90. [PUBMED: 15231978]

Rose 1967 *{published data only}*
Rose JR. Pholcodine plus pseudoephedrine in the treatment of cough. A controlled trial. *Practitioner* 1967;**198**(187): 704–7. [PUBMED: 4860038]

Ruan 1997 *{published data only}*
Ruan J, Li HF, Han FQ, Wei H, Liu SP, Cai ZJ. Clinical evaluation of the effect of codeine platycogenic tablets on cough relieving [Chinese]. *The Chinese Journal of Clinical Pharmacology* 1997;**13**(2):134–8.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Schlesinger 1994 *{published data only}*
Schlesinger FL. Dihydrocodeine in the treatment of children with irritable cough. Better night-sleep results in faster cure. [German]. *Die Therapiewoche* 1994;**44**(9):545–8.

Segal 1978 *{published data only}*
Segal S, Cohen SN, Freeman J, Hill RM, Kagan BM, Kauffman RE, et al. Use of codeine- and dextromethorphan-containing cough syrups in pediatrics. American Academy of Pediatrics. Committee on Drugs. *Pediatrics* 1978;**62**(1): 118–22. [PUBMED: 683771]

Sevelius 1966 *{published data only}*
Sevelius H, Colmore JP. Objective assessment of antitussive agents in patients with chronic cough. *Journal of New Drugs* 1966;**6**(4):216–23. [PUBMED: 5338653]

Sevelius 1971 *{published data only}*
Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. *Clinical Pharmacology and Therapeutics* 1971;**12**(3):449–55. [PUBMED: 4936034]

Shadkam 2010 *{published data only}*
Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. *Journal of Alternative and Complementary Medicine* 2010;**16**(7):787–93. [PUBMED: 20618098]

Skoner 2005 *{published data only}*
Skoner DP. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2005;**115** (2):author reply 512-3.

Smith 2014 *{published data only}*
Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD001831.pub5]

Thackray 1978 *{published data only}*
Thackray P. A double-blind, crossover controlled evaluation of a syrup for the night-time relief of the symptoms of the common cold, containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulphate. *Journal of International Medical Research* 1978;**6** (2):161–5. [PUBMED: 344089]

Vornov 2014 *{published data only}*
Vornov J, Birring SS, Mazhari R, Fraser H, Casper R, Canning BJ, et al. Baseline cough frequency in a randomized, placebo-controlled, phase 2 clinical trial in subjects with upper respiratory tract infection. *Lung* 2014; **192**(1):5. [DOI: 10.1007/s00408-013-9552-7]

Wilhelmi 1977 *{published data only}*
Wilhelmi J. Clinical trial of a new depot codeine cough syrup for children [German]. *Medizinische Monatsschrift* 1977;**31**(6):279–81.

Yoder 2006 *{published data only}*
Yoder KE, Shaffer ML, La Tournous SJ, Paul IM. Child assessment of dextromethorphan, diphenhydramine, and placebo for nocturnal cough due to upper respiratory infection. *Clinical Pediatrics* 2006;**45**(7):633–40. [PUBMED: 16928841]

Zanasi 1993 *{published data only}*
Zanasi A, De Bernardi M, Messina P, Fabiani A. Cough sedation: Effectiveness and safety of the association dextromethorphan-guaiafenesin. *Acta Toxicologica et Therapeutica* 1993;**14**(3):153–62.

Additional references

Anderson-James 2014
Anderson-James S, Newcombe PA, Marchant JM, O'Grady KAF, Acworth JP, Jason P, et al. An acute cough-specific quality-of-life questionnaire for children: development and validation. *Journal of Allergy and Clinical Immunology* 2015; **135**(5):1179–85. [DOI: 10.1016/j.jaci.2014.08.036]

Boulet 2015
Boulet L, Coeytaux RR, McCrory DC, French CT, Chang AB, Birring SS, et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. *Chest* 2015;**147**(3):804–14. [DOI: 10.1378/chest.14-2506]

Britt 2010
Britt H, Miller GC, Charles J, Henderson J, Bayram C, Pan Y, et al. General practice activity in Australia 2009-10. General practice series no. 27. Cat. no. GEP 27. Canberra: AIHW.

Chang 1998
Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Archives of Disease in Childhood* 1998;**79**:6–11.

Chang 2006a
Chang AB, Landau LI, Van Asperen PP, Glasgow NJ, Robertson CF, Marchant JM, et al. Cough in children: definitions and clinical evaluation. *Medical Journal of Australia* 2006;**184**(8):398–403.

Chang 2006b
Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**(Suppl 1):260S–83S.

Chang 2015
Chang AB, Marsh RL, Upham JW, Hoffman LR, Smith-Vaughan H, Holt D, et al. Towards making inroads in reducing the disparity of lung health in Australian indigenous and New Zealand Maori children. *Frontiers in Paediatrics* 2015;**3**:9.

Chang 2016
Chang AB, Oppenheimer JJ, Weinberger M, Weir K, Rubin BK, Irwin RS. Use of management pathways or algorithms in children with chronic cough: systematic reviews. *Chest* 2016;**149**(1):106–19.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Committee on Drugs 1997
Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics* 1997;**99**(6):918–20.

Covidence 2015
Covidence [Computer program]. Covidence (Systematic review software). Veritas Health Innovation 2015.

de Jongste 2003
de Jongste JC, Shields MD. Cough 2: chronic cough in children. *Thorax* 2003;**58**:998–1003.

Dickinson 2014
Dickinson RS, Morjaria JB, Wright CE, Morice AH. Is opiate action in cough due to sedation?. *Therapeutic Advances in Chronic Disease* 2014;**5**(5):200–5.

European Medicines Agency 2015
European Medicines Agency. Codeine not to be used in children below 12 years for cough and cold. EMA 24 April 2015; Vol. 249413.

Fleming 2014
Fleming ML, Wanat MA. To prescribe codeine or not to prescribe codeine?. *Journal of Pain and Palliative Care Pharmacotherapy* 2014;**28**:251–4.

Florvaag 2012
Florvaag E, Johansson SGO. The pholcodine case. Cough medicines, IgE-sensitization, and anaphylaxis: a devious connection. *World Allergy Organization* July 2012;**5**:73–8.

Gadomski 1992
Gadomski A, Horton L. The need for rational therapeutics in the use of cough and cold medicine in infants. *Pediatrics* 1992;**89**:774–6.

Gibson 2010
Gibson PG, Chang AB, Glasgow NJ, Holmes PW, Katelaris P, Kemp AS, et al. CICADA: Cough in children and adults: diagnosis and assessment. Australian cough guidelines summary statement. *Medical Journal of Australia* 2010;**192** (5):265–71.

Gibson 2016
Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS on behalf of the CHEST expert cough panel. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest* 2016;**149**(1): 27–44. [PUBMED: 26426314]

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 7 April 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Health Canada 2015
Health Canada. Summary Safety Review - Codeine prescription products indicated for cough: Further assessing the risk of serious breathing problems in children and adolescents. www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/codeine-eng.php (accessed 9 December 2015).

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kane 2007
Kane BM. *Codeine (Drugs: The Straight Facts)*. 1st Edition. Chelsea House Publishers, 2006.

Lokker 2009
Lokker N, Sanders L, Perrin EM, Kumar D, Finkle J, Franco V, et al. Parental misinterpretations of over-the-counter paediatric cough and cold medication labels. *Pediatrics* 2009;**123**(6):1464–71.

Marchant 2008
Marchant JM, Newcombe PA, Juniper EF, Sheffield JK, Stathis SL, Chang AB. What is the burden of chronic cough for families?. *Chest* 2008;**134**(2):303–9.

Marchant 2012
Marchant J, Masters IB, Champion A, Petsky H, Chang AB. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. *Thorax* 2012;**67**:689–93.

Mattoo 1997
Mattoo SK, Basu D, Sharma A, Balaji M, Malhotra A. Abuse of codeine-containing cough syrups: a report from India. *Addiction* 1997;**92**(12):1783–7.

Medsafe 2015
New Zealand Medicines and Medical Devices Safety Authority. Changes to the use of bromhexine or codeine-containing cough and cold medicines in children. www.medsafe.govt.nz/safety/EWS/2015/BromhexineOrCodeine.asp (accessed 29 April 2015).

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Shields 2008
Shields MD, Everard ML, McKenzie S, Primhak R on behalf of the British Thoracic Society Cough Guidelines Group. British Thoracic Society Guidelines: Recommendations for the assessment and management of cough in children. *Thorax* 2008;**63**:Suppl III. [DOI: 10.1136/thx.2007.077370]

Takahama 2007
Takahama K, Shirasaki T. Central and peripheral mechanisms of narcotic antitussives: codeine-sensitive and -resistant coughs. *Cough* 2007;**3**:8. [DOI: 10.1186/1745-9974-3-8]

Taylor 1993
Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. *Journal of Pediatrics* 1993; **122**:799–802. [PUBMED: 8496765]

Therapeutic Goods Administration 2015
Therapeutic Goods Administration. Codeine use in children and ultra-rapid metabolisers: Pharmacovigilance

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

and special access branch safety review. www.tga.gov.au/sites/default/files/codeine-use-children-and-ultra-rapid-metabolisers.pdf (accessed 15 October 2015).

US Food and Drug Administration 2015
US Food, Drug Administration. FDA briefing document: joint pulmonary-allergy advisory committee and drug safety and risk management advisory committee meeting. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM475975.pdf (accessed 10 December 2015).

US Food and Drug Administration 2016
US Food, Drug Administration. Codeine cough-and-cold medicines in children: Drug safety communication - FDA evaluating potential risk of serious side effects. www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm453379.htm (accessed 7 January 2015).

Vernacchio 2008
Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Cough and cold medication use by US children, 1999-2006: results from the Slone Survey. *Pediatrics* 2008;**122**(2):323–9.

Yancy 2013
Yancy WS, McCrory DC, Coeytaux RR, Schmit KM, Kemper AR, Goode A, et al. Efficacy and tolerability of treatments for chronic cough: A systematic review and meta-analysis. *Chest* 2013;**144**(6):1827–38. [DOI: 10.1378/chest.13-0490]

* *Indicates the major publication for the study*

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aliprandi 2004	Excluded as non-placebo controlled. Study design compared levodropizine, codeine, and DL-cloperastine against levocloperastine without a placebo arm
Arroll 2005	Non-RCT (literature review)
Barroso 1973	Excluded as wrong population (adult). RCT of PB-89, codeine phospate, and placebo in adults with pulmonary tuberculosis
Berlin 1997	Non-RCT. Expert panel evidence review and recommendation
Bhattacharya 2013	Acute cough study. RCT of promethazine, dextromethorphan, and placebo in children
Blanchard 2013	Non-RCT (literature review)
Bolser 2006	Non-RCT (literature review)
Bolser 2006a	Non-RCT (literature review)
Bolser 2007	Non-RCT (literature review)
Chang 2006	Non-RCT. Expert panel evidence review and recommendation
Chang 2014	Excluded as non-RCT (systematic review of acute cough related to pneumonia)
Chicouri 1985	Excluded as study was on acute cough in adults
Dierckx 1981	Excluded as study was in adults. Double-blind RCT of glaucine, codeine, and placebo in adults with chronic cough
Dobiasova 1984	Excluded as study was on acute cough
Dotti 1970	Excluded as study was on adults
Eddy 1969	Non-RCT (literature review)
Edwards 1977	Excluded as study was on an adult population. Double-blind RCT of pholcodine compound versus resinated and unresinated pholcodine versus placebo versus control
Gruber 2000	Non-RCT (literature review)
Kleibel 1980	Excluded as wrong population (adult)

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Kleibel 1981	Excluded as study was on adults
Koster 1970	Excluded as study was on adults
Loos 1973	Excluded as study was on adults
Lucchesi 1971	Excluded as study was on adults
Matera 1977	Excluded as study was on adults
Matthys 1983	Excluded as study was on adults. RCT evaluating dextromethorphan hydrobromide, codeine phospate, and placebo in adults with chronic cough
Matthys 1985	Excluded as study was on adults. RCT evaluating noscapine, dextromethorphan, dihydrocodeine, and placebo for the treatment of chronic cough in adults
Matts 1977	Excluded as study was on adults. Non-placebo-controlled RCT evaluating 2 combination therapies, dextromethorphan/guaifenesin (Lotussin) and linctus diphenhydramine, for the treatment of chronic cough in adults
Maulik 2001	Non-RCT (literature review)
Mizoguchi 2007	Excluded as acute cough in adults
NCT02651116	Excluded as study was on acute cough in children. RCT evaluating dextromethorphan hydrobromide and placebo. Study is ongoing and still in recruitment phase
Oduwole 2010	Non-RCT. Systematic review evaluating honey for acute cough in children
Palumbo-Vargas 1971	Excluded as non-placebo-controlled trial; single-arm study using dihydrocodeine thiocyanate/pentetrazol (Cardiazol-Paracodina)
Paul 2004	Excluded as study was on acute cough in children $\leq$ 7 years. RCT evaluated diphenhydromine, dextromethorphan, and placebo
Rose 1967	Excluded as non-placebo-controlled, adult population-based RCT
Ruan 1997	Excluded as study was on adults
Schlesinger 1994	Excluded as non-placebo-controlled study
Segal 1978	Non-RCT. Expert panel evidence review and recommendation
Sevelius 1966	Excluded as study was on adults
Sevelius 1971	Excluded as study was on adults

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Shadkam 2010	Excluded as study was on acute cough in children. Non-placebo-controlled RCT evaluated honey, diphenhydromine, and dextromethorphan against a control group receiving supportive therapies only. Supportive therapies were offered to all arms and included saline nose drops, water vapor, cleaning a blocked nose, and using acetaminophen if fever was present
Skoner 2005	Non-RCT (commentary)
Smith 2014	Non-RCT (systematic review)
Thackray 1978	Excluded as study was on adults
Vornov 2014	Excluded as study was on adults
Wilhelmi 1977	Excluded as non-placebo-controlled study
Yoder 2006	Excluded as study was on acute cough
Zanasi 1993	Excluded as wrong study design. RCT evaluating dextromethorphan and guaifenesin against a placebo control arm with a participant age range of 40 to 72 years. The study did include a small paediatric treatment group but not a paediatric placebo-controlled cohort as comparator

RCT: randomised controlled trial

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Database search strategies

MEDLINE (Ovid)

1. Cough/
2. exp Bronchitis/
3. (cough$ or bronchit$).tw.
4. or/1-3
5. exp Codeine/
6. codeine$.tw.
7. N-methylcodinium$.tw.
8. nordihydrocodeine$.tw.
9. alpha-codeimethine$.tw.
10. dihydrocodeine$.tw.
11. 6-succinylcodeine$.tw.
12. acetylcodeine$.tw.
13. 14-hydroxycodeine$.tw.
14. 6-codeinone$.tw.
15. pholcodine.tw.
16. nicocodine.tw.
17. dihydrocodeine.tw.
18. nalodeine.tw.
19. azidocodeine.tw.
20. dextromethorphan.tw.
21. or/5-20
22. 4 and 21
23. (controlled clinical trial or randomized controlled trial).pt.
24. (randomized or randomised).ab,ti.
25. placebo.ab,ti.
26. dt.fs.
27. randomly.ab,ti.
28. trial.ab,ti.
29. groups.ab,ti.
30. or/23-29
31. Animals/
32. Humans/
33. 31 not (31 and 32)
34. 30 not 33
35. 22 and 34

EMBASE (Ovid)

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1. exp coughing/
2. exp bronchitis/
3. (cough$ or bronchit$).tw.
4. or/1-3
5. exp codeine/
6. codeine$.tw.
7. N-methylcodinium$.tw.
8. nordihydrocodeine$.tw.
9. alpha-codeimethine$.tw.
10. dihydrocodeine$.tw.
11. 6-succinylcodeine$.tw.
12. acetylcodeine$.tw.
13. 14-hydroxycodeine$.tw.
14. 6-codeinone$.tw.
15. pholcodine.tw.
16. nicocodine.tw.
17. dihydrocodeine.tw.
18. nalodeine.tw.
19. azidocodeine.tw.
20. dextromethorphan.tw.
21. or/5-20
22. 4 and 21
23. Randomized Controlled Trial/
24. randomization/
25. controlled clinical trial/
26. Double Blind Procedure/
27. Single Blind Procedure/
28. Crossover Procedure/
29. (clinica$ adj3 trial$).tw.
30. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.
31. exp Placebo/
32. placebo$.ti,ab.
33. random$.ti,ab.
34. ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.
35. (crossover$ or cross-over$).ti,ab.
36. or/23-35
37. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
38. human/ or normal human/ or human cell/
39. 37 and 38
40. 37 not 39
41. 36 not 40
42. 22 and 41

CENTRAL (CRS Online)

#1 MeSH DESCRIPTOR Cough
#2 MeSH DESCRIPTOR Bronchitis Explode All
#3 cough* or bronchitis*
#4 #1 OR #2 OR #3
#5 MeSH DESCRIPTOR Codeine Explode All
#6 codeine*
#7 N-methylcodinium*
#8 nordihydrocodeine*

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

#9 alpha-codeimethine*
#10 dihydrocodeine*
#11 6-succinylcodeine*
#12 acetylcodeine
#13 14-hydroxycodeine
#14 6-codeinone*
#15 pholcodine
#16 nicocodine
#17 dihydrocodeine
#18 nalodeine
#19 azidocodeine
#20 dextromethorphan
#21 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
#22 #4 and #21
#23 (#22) AND (INREGISTER)

Appendix 2. Search terms for ClinicalTrials.gov and WHO ICTRP

Condition

1. cough

Intervention

1. codeine
2. N-methylcodinium
3. nordihydrocodeine
4. alpha-codeimethine
5. dihydrocodeine
6. 6-succinylcodeine
7. acetylcodeine
8. 14-hydroxycodeine
9. 6-codeinone
10. pholcodine
11. nicocodine
12. dihydrocodeine
13. nalodeine
14. azidocodeine
15. dextromethorphan
16. codeine-7,8-oxide,
17. codeine-6-glucronide
18. O(6)-codeine methyl ether.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CONTRIBUTIONS OF AUTHORS

SG and HP assessed all search results for eligibility, and AC adjudicated on disagreements. SG was the predominant contributor to the abstract, plain language summary, background, results, discussion, authors' conclusions, and 'Characteristics of excluded studies' table. HP was the predominant contributor to the data analysis strategy, and both HP and SG contributed to the body of methodology. AC provided guidance with protocol development. HP, AC, and JM edited the review.

All review authors approved the final draft before submission.

DECLARATIONS OF INTEREST

AC is the recipient of a grant from GlaxoSmithKline to study the effect of a vaccine on the bacteria in bronchoalvoelar lavage of children, a topic unrelated to this review. AC is an author of articles referenced within the background of this protocol.

SG, JM and HP: none known

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- National Health and Medical Research Council (NHMRC), Australia.

AC is supported by a NHMRC Practitioner Fellowship (grant 1058213) and HP is supported through a NHMRC Centre for Research Excellence in Indigenous Lung Health (grant 1040830) post doc fellowship

- Lung Foundation of Australia/Australian Satellite of the Cochrane Airways Group Scholarship to SG, Australia.

Scholarship funds facilitated author attendance at a Cochrane review workshop and contributed towards conference attendance where the review findings were presented.

- Queensland University of Technology, Other.

SG and HP are employees of the Queensland University of Technology. SG is the recipient of an Australian Postgraduate Award and QUT Excellence Top-Up Scholarship awarded by AC.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no protocol deviations, however a co-author, Julie Marchant, was added to the review.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.