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[Intervention Protocol]

Codeine versus placebo for chronic cough in children

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

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

BACKGROUND

Description of the condition

Cough is a commonly-experienced symptom within the community (Chang 2015) and was identified as the leading reason for encounters between patients and 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 2006; de Jongste 2003; Gibson 2010). The latter will be 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 their antitussive properties (Kane 2007). Preparations may be prescription controlled, but many of these drugs are readily available and easily accessible in combination therapies with antihistamines, antipyretics, decongestants or expectorants as over-the-counter (OTC) 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) has been used as an antitussive for centuries. The medication primarily acts through opioid receptors of the central nervous system, though 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 derivative-) based antitussive agents are widely used in the paediatric population, though 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 and not only impacts on the relationship between children and their parents/caregivers, but also their ability to participate fully within society due to school and work time loss (Marchant 2008). Thus rigorously evaluating the efficacy of various treatment methodologies including codeine and its derivatives as antitussive agents will assist in clinical management and guide burden-reduction strategies.

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 will include randomised controlled trials (RCTs), quasi-RCTs and stratified RCTs that compare codeine (or derivatives) versus placebo. We will 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 will only include studies with children aged 18 years or younger with a diagnosis of chronic cough (cough lasting ≥ 4 weeks). We will exclude participants with acute cough.

Types of interventions

We will include studies comparing medications that contain codeine or codeine derivatives versus placebo.

We will include the following derivative agents: 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 will 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 are those that reflect objective measures of treatment superiority, non-inferiority, or inferiority, and include:

1. Number of children not cured at follow-up;
2. Number of children who experience a reduction in cough severity (clinically defined as a > 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 and or loss of life).

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 of more of the outcomes listed above in the trial is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will search the following databases:

- The Cochrane Airways Group Register of Trials (via the Cochrane Register of Studies), all years
- Cochrane Central Register of Controlled Trials (CENTRAL), latest issue (*Cochrane Library*)
- MEDLINE (Ovid), 1950 to date
- EMBASE (Ovid), 1974 to date
- Trials registries (ClinicalTrials.gov and the WHO trials portal)

The proposed MEDLINE strategy is listed in Appendix 1. This will be adapted for use in the other databases. All databases will be searched from their inception to the present, and there will be no restriction on language of publication. Handsearched conference abstracts and grey literature will be sought through the CENTRAL database.

Searching other resources

We will check reference lists of all relevant primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report in the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (SG, HP) will independently screen for inclusion the titles and abstracts of all the studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (SG, HP) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (AC). We will identify and exclude duplicates and collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (SG, HP) will 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.

Two review authors (SG, HP) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (AC). One review author (SG) will transfer data into the Review Manager 5 (RevMan 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (HP) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SG, HP) will 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 will resolve any disagreements by discussion or by involving another author (AC). We will 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 will 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 judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. 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 relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

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

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

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

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and underlying clinical question are similar enough for pooling to make sense.

We will narratively describe skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

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

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

Any heterogeneity between the study results will be described and tested to see if it reaches statistical significance using a Chi^2 test. The 95% CI estimated using a random-effects model will be included whenever there are concerns about statistical heterogeneity. Heterogeneity is considered significant when the P value is < 0.10 (Higgins 2011). We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases and plan to consult a statistician to ensure appropriate analysis is conducted.

Data synthesis

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

'Summary of findings' table

We will 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 will 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 which contribute data to the meta-analyses for the prespecified outcomes. We will 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). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan 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 which may soften coughing such as honey or syrup).

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

Sensitivity analysis

We plan 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 are imputed with best-case and worse-case outcome data.
3. A comparison of results from fixed-effect models versus results from random-effects models.

ACKNOWLEDGEMENTS

We thank the Lung Foundation of Australia and the Australian Satellite of the Cochrane Airways Group for the provision of a scholarship supporting the development of this review. We further acknowledge the Cochrane Airways Group for allowing us to conduct this systematic review. We also acknowledge the assistance of Trials search Coordinator Liz Stovold in the formulation of the search strategy for this review and thank her for her ongoing support.

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

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

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APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

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

CONTRIBUTIONS OF AUTHORS

SG predominantly described the background and was responsible for formatting. HP predominantly described the data analysis strategy and both HP and SG contributed to the body of methodology. AC provided guidance with protocol development and edited the review. All authors approved the final draft before submission.

DECLARATIONS OF INTEREST

AC is the recipient of a grant from GlaxoSmithKline to study microbia in bronchoalvoelar lavage (BAL), a topic unrelated to this review. AC has been the recipient of multiple Australian Government grants (National Health and Medical Research Council Australia (NHMRC)). AC is an author of articles referenced within the background of this protocol.

HP has been the recipient of a NHMRC Centre of Research Excellence (CRE) Post Doctoral Fellowship (ID.104083) and is an employee of the Queensland University of Technology.

SG is an employee of the Queensland University of Technology.

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Internal sources

- No sources of support supplied

External sources

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

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

  Scholarship funds facilitate author attendance at a Cochrane review workshop and will contribute towards conference attendance where the review findings will be presented upon completion.

INDEX TERMS

Medical Subject Headings (MeSH)

Antitussive Agents [adverse effects] [*therapeutic use]; Chronic Disease; Codeine [adverse effects] [*therapeutic use]; Cough [*drug therapy]; Placebos [therapeutic use]

MeSH check words

Child; Humans