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Inhaled cromones for prolonged non-specific cough in children (Review)

Chang AB, Marchant JM, McKean MC, Morris PS

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[Intervention Review]

Inhaled cromones for prolonged non-specific cough in children

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ABSTRACT

Background

Non-specific cough is defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology. It is commonly seen in paediatric practice. These children are treated with a variety of therapies including inhaled cromones.

Objectives

To determine the efficacy of inhaled cromones in the management of prolonged non-specific cough in children.

Search methods

Trials were identified from CENTRAL, MEDLINE and EMBASE database searches. The Australian representative of the relevant pharmaceutical company was contacted. The latest searches were performed in July 2010.

Selection criteria

All randomised controlled trials comparing inhaled cromones with a placebo medication.

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. No eligible trials were identified and thus no data were available for analysis. One single arm open trial in children and one small randomised controlled trial in adults were reported.

Main results

No randomised-controlled trials that examined the efficacy of inhaled cromones in the management of prolonged non-specific cough in children were found. In the non randomised trials above, a significant effect was seen within two weeks of therapy.

Authors' conclusions

There is currently an absence of evidence to support the routine use of inhaled cromones for symptomatic control of non-specific cough in children. Further research examining the effects of this intervention is needed.

PLAIN LANGUAGE SUMMARY

Inhaled cromones for prolonged non-specific cough in children

Children with non-specific cough (coughing not due to a diagnosed respiratory disease), are commonly treated with a variety of medications to treat the symptoms of cough. This review examined whether there was any evidence for children with non-specific cough to inhale cromoglycate and nedocromil (commonly called 'cromones'). There were no randomised controlled trials identified that assessed inhalation of cromones for prolonged non-specific cough in children. In two non-randomised studies, the researchers found that improvements were seen within two weeks of taking cromones. Because cromones have few adverse effects, they are an attractive treatment for children. However, there is no evidence to support their routine use for the symptoms of non-specific cough in children. Further research examining the effects of this treatment is needed.

BACKGROUND

Cough is a very common symptom of respiratory disease . Non-specific cough has been defined as non-productive cough in the absence of identifiable respiratory disease or known aetiology (Chang 2001). Children with a history of non-specific cough are commonly seen in paediatric practice. The majority have no signs of other current disease processes. In the absence of research to guide clinical practice, these children are treated with a variety of therapies: antibiotics, cough suppressants, anti-histamines, decongestants, bronchodilators, sodium cromoglycate, inhaled corticosteroids and oral corticosteroids, sometimes resulting in significant side effects (Thomson 2002).

These children present a major management problem and cause considerable anxiety to parents. The desire by patients and medical practitioners to treat cough is reflected in the wide use of over-the-counter (OTC) medications for coughs and colds and the frequent prescription of antibiotics for upper respiratory tract infection (McManus 1997). Many children with non-specific cough are treated with asthma type medications (corticosteroids and/or bronchodilators). However, any beneficial effects of these interventions have not been clearly described.

Cromoglycate and nedocromil (commonly grouped together as cromones) are attractive medications as these medications are much less likely to cause significant side effects than inhaled corticosteroids and are alternative first line 'preventative' treatment in some asthma clinical guidelines (National Asthma Guid). Nedocromil and cromoglycate increase cough threshold (Fontana 2002) and reduces neurogenic inflammation which is the most important peripheral inflammation process involved in human cough (Konig 1996; Chang 1999).

OBJECTIVES

To determine the efficacy of inhaled cromones (cromoglycate and nedocromil) in treating children with non-specific cough.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing inhaled cromones with a placebo medication.

Types of participants

All trials which included children under 18 years of age with prolonged (three or more weeks) non-specific cough (dry and non-productive cough without any other respiratory symptom, sign or systemic illness). An a priori subgroup analysis was planned for children < seven years of age.

Exclusion criteria: cough related to mycoplasma, pertussis and chlamydia, presence of underlying cardio-respiratory condition, current or recurrent wheeze (>2 episodes), presence of other respiratory symptoms (productive cough, haemoptysis, dyspnoea), presence of other respiratory signs (clubbing, chest wall deformity, respiratory noises such as wheeze on auscultation and other adventitious sounds), presence of any sign of systemic illness (failure to thrive, aspiration, neurological or developmental abnormality) or presence of lung function abnormality.

Types of interventions

All randomised controlled comparisons of cromones versus placebo medication in the management of non-specific cough. Trials only comparing two or more asthma medications without a placebo comparison group were not included. Two separate treatment regimes were evaluated:
i) Inhaled cromoglycate by metered dose inhaler (with or without spacer device) or by nebulisation,
ii) Inhaled nedocromil by metered dose inhaler (with or without spacer device).
Trials that included the use of other medications or interventions were included if all participants had equal access to such medications or interventions.

Types of outcome measures

Attempts were made to obtain data on at least one of the following outcome measures:

Primary outcomes

Proportions of participants who were not cured or not substantially improved at follow up (clinical failure).

Secondary outcomes

1. Proportions of participants who were not cured at follow up,
2. Proportions of participants who were not substantially improved at follow up,
3. Mean difference in cough indices (cough diary, cough frequency, cough scores),
4. Proportions experiencing adverse effects, e.g. behavioral changes, nausea, paradoxical bronchospasm, hypersensitivity (side effects),
5. Proportions experiencing complications e.g. requirement for medication change.

The proportions of participants who failed to improve on treatment and the mean clinical improvement were determined using the following hierarchy of assessment measures (i.e. where two or more assessment measures are reported in the same study, the outcome measure that was listed first in the hierarchy was used).

i) Objective measurements of cough indices (cough frequency, cough receptor sensitivity, cough amplitude).
ii) Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the child.
iii) Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by the parents/carers.
iv) Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary) - assessed by clinicians.
v) Airway markers consistent with infection or inflammation.

Search methods for identification of studies

The following topic search strategy was used to identify relevant randomised controlled trials (RCTs):

(cough [MeSH] OR cough [text word] OR bronchitis [MeSH] OR bronchitis [text word]) AND (Cromolyn Sodium [MeSH] OR Cromolyn Sodium [text word] OR cromoglycate [MeSH] OR cromoglycate [text word] or Disodium Cromoglycate [MeSH] OR Disodium Cromoglycate [text word] OR Intal [text word] OR

nedocromil [MeSH] OR nedocromil [text word] OR Tilade [text word]).

Trials were identified from the following sources:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (which includes the Cochrane Airways Group Trials Register).
2. MEDLINE 1966-current. Topic search strategy combined with an RCT search filter as outlined in the Airways Group module.
3. OLDMEDLINE 1950-1965. Topic search strategy combined with combined with an RCT search filter as outlined in the Airways Group module.
4. EMBASE 1980-current. Topic search strategy combined with an RCT search filter as outlined in the Airways Group module.
5. The list of references in relevant publications.
6. Written communication with the authors of trials included in the review.
7. Written communication with Aventis Pharma Pty Ltd, the Australian representative of the manufacturer nedocromil and cromoglycate.

For specific search strategies used in each database, please see Appendix 1. Searches are current as of July 2010.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, two reviewers (ABC, JM) independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, the same two reviewers independently selected trials for inclusion. It was planned that agreement be measured using kappa statistics, and disagreement resolved by consensus or third party adjudication (PM). ABC wrote to Aventis Pharma Pty Ltd, the Australian representative for nedocromil and cromoglycate. In all subsequent searches to date, no new studies were fulfilled inclusion criteria. A further study (Koskela 2005) was added to the excluded studies table.

Data extraction and management

Trials that satisfied the inclusion criteria would have been reviewed and the following information recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible children), inclusion and exclusion criteria, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of anti-cholinergic therapy, duration of therapy, co-interventions, numbers of patients not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. Data would have been extracted on the outcomes described previously. Further information would have been requested from the authors where required.

Assessment of risk of bias in included studies

Studies included in the review would have undergone quality assessment performed independently by all reviewers. Risk of bias in included studies would have been assessed as either high, low or unclear risk of bias using the Cochrane Collaboration's risk of bias tool (Higgins 2008), and the following headings 1) sequence generation; 2) allocation concealment; 3) blinding; 4) incomplete outcome data; 5) selective outcome reporting; 6) other bias. Inter-reviewer reliability for the identification of high quality studies for each component would have been measured by the Kappa statistic.

Data synthesis

For the dichotomous outcome variables of each individual study, relative and absolute risk reductions would have been calculated using a modified intention-to-treat analysis. This analysis assumes that children not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies would have examined whether pooling of results (meta-analysis) was reasonable. This would take into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

The results from studies that met the inclusion criteria and reported any of the outcomes of interest would have been included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed effects model) were to be calculated using the inverse of the variance of each study result for weighting (Cochrane statistical package, RevMan Analyses 1.0.1). The number needed to treat was to be calculated using the summary odds ratio and the average control event rate described in the relevant studies. The cough indices were to be assumed to be normally distributed continuous variables so the mean difference in outcomes can be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, the standardised mean difference was to be estimated. Any heterogeneity between the study results was to be described and tested to see if it reached statistical significance using a chi-squared test (where $p < 0.1$ is considered significant) (Higgins 2008). The 95% confidence interval estimated using a random effects model was to be included whenever there are concerns about statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity

An *a priori* subgroup analysis was planned for children less than seven years of age.

Sensitivity analysis

Sensitivity analyses were planned to assess the impact of the potentially important factors on the overall outcomes: a) study quality; b) study size; c) variation in the inclusion criteria; d) differences in the medications used in the intervention and comparison groups; e) differences in outcome measures; f) analysis by standard intention-to-treat (children not available for outcome assessment not included) rather than modified intention-to-treat, and g) analysis by "treatment received (children not available for outcome assessment and children who did not receive intervention in accordance with protocol not included) rather than modified "

RESULTS

Description of studies

Results of the search

The Airways Group specialised register/search identified 500 potentially relevant titles (original search). After assessing the abstracts, 33 studies were considered for inclusion into review

including two articles in German and one in Italian that were translated. No study fulfilled the study eligibility criteria. The main reason for non-eligibility of study criteria was presence of lung function abnormality consistent with unequivocal asthma or asthma-like conditions (at least 15% reversibility demonstrated on forced expiratory flow) in the subjects studied. Update searches have identified studies which we have excluded on the basis of age (Pashkova 2000; adult participants), and lack of clarity regarding study design and entry criteria (authors from Keseloglu 2000 were contacted but we did not receive a response from them). Seven other studies were excluded for reasons listed in Characteristics of excluded studies. The pharmaceutical company did not have any additional or unpublished data (20th Nov 2003). A new search was run in July 2010 and returned 65 references, but no new studies that met the eligibility criteria of this review were identified.

Risk of bias in included studies

Not applicable.

Effects of interventions

There were no RCTs.

DISCUSSION

No randomised controlled trials of inhaled cromones for the treatment of persistent non-specific cough in children were identified. A single arm open trial in children with chronic cough (>four weeks), some of whom also had asthma (undefined) reported clinical response measured by cough severity diary (undefined whether it was parent or child-completed diary) within two weeks of therapy with inhaled nedocromil (4 mg, four times a day via metered dose inhaler and spacer) (Chan 2001). A small study on 10 adults reported significant improvement in cough sensitivity to capsaicin and subjective cough severity when taking inhaled sodium cromoglycate using metered dose inhaler with spacer (10 mg four times a day for two weeks) (Hargreaves 1995).

AUTHORS' CONCLUSIONS

Implications for practice

With the absence of evidence (as opposed to evidence of no effect) use of inhaled cromones in children with prolonged non-specific cough cannot be routinely recommended. If cromones were to be trialed in these children, current data suggest a clinical response (subjective cough severity) within two weeks of therapy. The advantage of using inhaled cromones over other commonly therapy (inhaled or oral corticosteroids, beta-2-agonists, over the counter cough suppressants etc) include the lack of adverse events but the disadvantage is its frequent dosing (four times a day).

Implications for research

Randomised controlled studies using objective and subjective outcome measures to determine the effectiveness of inhaled cromones for symptomatic control of prolonged cough in children with non specific cough are needed.

ACKNOWLEDGEMENTS

We are grateful to Karen Blackhall and Elizabeth Arnold for performing the relevant searches and the Cochrane Airways Group for their supportive role. Thanks also to Claire Allen for providing consumer feedback on the review.

REFERENCES

References to studies excluded from this review

Chan 2001 *{published data only}*

Chan PW, Debruyne JA. Inhaled nedocromil sodium for persistent cough in children. *Medical Journal of Malaysia* 2001;**56**(4):408-13.

Chan-Yeung 1971 *{published data only}*

Chan-Yeung M, Morton J, Grzybowski S. A double-blind trial of disodium cromoglycate (Intal) in the treatment of bronchial asthma. *Canadian Medical Association Journal* 1971;**105**(8):827-31.

De Kock 1971 *{published data only}*

De Kock MA, Rosenstrauch WJ. The role of disodium cromoglycate in its treatment. *South African Medical Journal* 1971;**45**(38):1055-9.

Dungemann 1980 *{published data only}*

Dungemann H, Borelli S, Schiess W. Treatment of seasonal asthmatic symptoms. A multicentre trial to compare the effects of ketotifen and disodium cromoglycate [Behandlung saisonaler asthmatischer Beschwerden]. *Münchener Medizinische Wochenschrift* 1980;**122**(9):313-7.

Hargreaves 1995 *{published data only}*

Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995;**345**(1):13-6.

Keseloglu 2000 *{published data only}*

Keseloglu A, Dayican B, Ardic S, Altinors M, Ozsahin SL. The effect of nedocromil sodium in prolonged cough. *European Respiratory Journal* 2000;**16**(Suppl 31):277s.

Koskela 2005 *{published data only}*

Koskela HO, Martens R, Brannan JD, Anderson SD, Leuppi J, Chan HK. Dissociation in the effect of nedocromil on mannitol-induced cough or bronchoconstriction in asthmatic subjects. *Respirology* 2005;**10**(4):442-8.

Pacor 1994 *{published data only}*

Pacor ML, Biasi D, Lunardi C. The efficacy of nedocromil sodium in light or moderate allergic bronchial asthma. *Clinica Terapeutica* 1994;**145**(9):219-22.

Pashkova 2000 *{unpublished data only}*

* Pashkova T, Averianov A, Chuchalin A. Comparison effects of nedocromil sodium and inhaled salbutamol in patients with asthma cough variant. *European Respiratory Journal* 2000;**16**(Suppl 31):96s.

von Thoma 1984 *{published data only}*

Thoma von R. Mutlicentre, double-blind, randomised, interindividual comparison study in 164 patients between Reproterol and a combination of disodium cromoglycate and Reproterol [Mutlizentrische, doppelblinde, randomisierte, interindividuelle Vergleichsstudie an 164 patienten zwischen Reproterol allein und a einer kombination aus dinatrium cromoglicium (DNCG) und Reproterol]. *Pharmakopie* 1984;**1**(1):40-9.

Additional references

Chang 1999

Chang AB. State of the Art: Cough, cough receptors, and asthma in children. *Pediatric Pulmonology* 1999;**28**:59-70.

Chang 2001

Chang AB, Asher MI. A review of cough in children. *Journal of Asthma* 2001;**38**(4):299-309.

Fontana 2002

Fontana GA, Lavorini F, Pistolesi M. Water aerosols and cough. *Pulmonary Pharmacology & Therapeutics* 2002;**15**(3):205-11.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. Available from: www.cochrane-handbook.org. The Cochrane Collaboration, 2008.

Konig 1996

Konig P. Clinical effects of nedocromil sodium on challenges invoking neuronal mechanisms and on virally induced symptoms. *Journal of Allergy & Clinical Immunology* 1996;**98**:S135-S142.

McManus 1997

McManus P, Hammond ML, Whicker SD, Primrose JG, Mant A, Fairall SR. Antibiotic use in the Australian community, 1990-1995. *Medical Journal of Australia* 1997;**167**:124-7. [MEDLINE: 723]

National Asthma Guid

National Asthma Council Australia. Asthma Management Handbook 2002 [available at: www.NationalAsthma.org.au]. Melbourne: National Asthma Council Australia Ltd, 2002:32.

Thomson 2002

Thomson F, Masters IB, Chang AB. Persistent cough in children – overuse of medications. *Journal of Paediatrics and Child Health* 2002;**38**:578-81.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Chan 2001	No control group. Study using nedocromil was single arm and open trial involving 22 children with persistent cough.
Chan-Yeung 1971	2 children in study, both with spirometry abnormality consistent with obstructive lung disease.
De Kock 1971	No control group. 28 children treated with sodium cromoglycate and no data on cough given.
Dungemann 1980	No placebo group. Study possibly includes some children with non specific cough as asthma was not defined and cough was used as an outcome measure.
Hargreaves 1995	Randomised controlled trial (double blind cross over) using inhaled cromoglycate (40mg/day) in adults with cough associated with use of angiotensin-converting enzyme
Keseloglu 2000	Entry criteria and age of participants unclear from abstract. No additional information received from correspondence with trialists.
Koskela 2005	RCT examining effect of nedocromil on bronchoconstriction and cough. Not a clinical intervention trial.
Pacor 1994	Age of participants not given. No control group. Single arm study using nedocromil.
Pashkova 2000	Recruited only adult participants.
von Thoma 1984	No placebo group and study includes adults. No placebo group. Study possibly includes some children with non specific cough as asthma was not well defined and cough was used as an outcome measure. Asthma was defined as reversibility to beta-2-agonist but reversibility was undefined.

APPENDICES

Appendix 1. Search strategies

CENTRAL	MEDLINE	EMBASE
#1 COUGH #2 cough* #3 BRONCHITIS CHRONIC #4 bronchiti* #5 (#1 or #2 or #3 or #4) #6 CHROMONES #7 NEDOCROMIL #8 (chromone* or cromone* or (cromolyn next sodium) or (disodium next cromoglycate*) or (sodium next cromoglycate*) or chromoglycate* or (chromoglycate next disodium) or (disodium next chromoglycate*) or (disodium next cromoglucate*) or dscg	1.exp COUGH/ 2. cough$.mp. 3. exp Bronchitis, Chronic/ 4. (chronic adj3 bronchiti$).mp. 5. 1 or 2 or 3 or 4 6. exp CHROMONES/ 7. exp NEDOCROMIL/ 8. (Chromone$ or cromone$ or Cromolyn Sodium or disodium cromoglycate$ or sodium cromoglycate$ or Chromoglycate or Chromoglycate Disodium or Disodium Chromoglycate or Disodium Cromoglucate or Dscg or aarane or Allergocrom or Bi-	1. exp COUGHING/ 2. cough$.mp. 3. exp CHRONIC BRONCHITIS/ 4. (chronic adj3 bronchiti$).mp. 5. 1 or 2 or 3 or 4 6. exp Chromone Derivative/ 7. exp Cromoglycate Disodium/ 8. exp Nedocromil Sodium/ 9. (Nedocromil or Alocril or Disodium or Dicarboxylate or Ethyl or Quinoline or Dicarboxylate Disodium or Kovinal or Tilade or Tilarin or Tilavist).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]

(Continued)

or aarane or allergocrom or bicromat or (cromoglicic next acid) or cromoglycate* or (cromoglycic next acid) or (cromoglicate next disodium) or (cromoglicate next sodium next cromoglicin) or crolom or cromolyn or crolom or cromol or cromolon or colimune or cromohexal or cromoral or duracroman or intal or lomudal or nalcrom or nasalcrom or opticrom or vicrom or fivent or (fpl next 670) or frenal or flavone* or anthocyanidin or anthocyanidin* or anthocyanin* or leucoanthocyanidin* or anthocyanin* or benzoflavone* or beta-naphthoflavone* or bioflavonoid* or barosmin or (buchu next resin) or daflon or venosmine or diosmin or (flavoxate next hydrochloride) or urispas or flavoxate or hesperetin-7-rutinoside or hesperidin or isoflavone* or genestein or genistein or gastrocrom or pterocarpan* or quercetin* or rutin* or 0-beta-hydroxyethylrutoside* or beta-hydroxyethylrutoside* or hydroxyethylrutoside* or carsil or karsil or legalon or silimarin or silymarin or intal or introl or irtan or lomudal or lomuforte or lomupren or lomusol or nalcrom or nalcron or nasalcrom or novacrom or opticrom or opticron or rynacrom or (sodium next chromoglycate) or (sodium next cromoglycate) or (sodium next cromolyn) or vicrom or vistacrom or vividrin or nedocromil or alocril or disodium or dicarboxylate or ethyl or quinoline or (dicarboxylate next disodium) or kovinal or tilade or tilarin or tilavist)
#9 (#6 or #7 or #8)
#10 (#5 and #9)

cromat or cromoglicic acid or cromoglycate$ or cromoglycic acid or Cromoglicate Disodium or Cromoglicate Sodium Cromoglicin or Crolom or cromolyn or Crolom or Cromol or Cromolon or Colimune or Cromohexal or Cromoral or Duracroman or intal or lomudal or nalcrom or Nasalcrom or opticrom or vicrom or Fivent or Fpl 670 or Frenal or Flavone$ or anthocyanidin or Anthocyanidin$ or anthocyanin$ or leucoanthocyanidin$ or Anthocyanin$ or Benzoflavone$ or beta-Naphthoflavone$ or Bioflavonoid$ or barosmin or buchu resin or daflon or venosmine or Diosmin or flavoxate hydrochloride or urispas or Flavoxate or hesperetin-7-rutinoside or Hesperidin or Isoflavone$ or genestein or Genistein or Gastrocrom or Pterocarpan$ or Quercetin$ or Rutin$ or 0-beta-hydroxyethylrutoside$ or beta-hydroxyethylrutoside$ or Hydroxyethylrutoside$ or carsil or karsil or legalon or silimarin or Silymarin or intal or Introl or Irtan or Lomudal or Lomuforte or Lomupren or Lomusol or Nalcrom or Nalcron or Nasalcrom or Novacrom or Opticrom or Opticron or Rynacrom or Sodium Chromoglycate or Sodium Cromoglycate or Sodium Cromolyn or Vicrom or Vistacrom or Vividrin or Nedocromil or Alocril or Disodium or Dicarboxylate or Ethyl or Quinoline or Dicarboxylate Disodium or Kovinal or Tilade or Tilarin or Tilavist).mp.
9. 6 or 7 or 8
10. 5 and 9

(Combined with RCT filter as described in the 'About the Airways Group' on the Cochrane Library)

10. (Chromone$ or cromone$ or Cromolyn Sodium or disodium cromoglycate$ or sodium cromoglycate$ or Chromoglycate or Chromoglycate Disodium or Disodium Chromoglycate or Disodium Cromoglucate or Dscg or aarane or Allergocrom or Bicromat or cromoglicic acid or cromoglycate$ or cromoglycic acid or Cromoglicate Disodium or Cromoglicate Sodium Cromoglicin or Crolom or cromolyn or Crolom or Cromol or Cromolon or Colimune or Cromohexal or Cromoral or Duracroman or intal or lomudal or nalcrom or Nasalcrom or opticrom or vicrom or Fivent or Fpl 670 or Frenal or Flavone$ or anthocyanidin or Anthocyanidin$ or anthocyanin$ or leucoanthocyanidin$ or Anthocyanin$ or Benzoflavone$ or beta-Naphthoflavone$ or Bioflavonoid$ or barosmin or buchu resin or daflon or venosmine or Diosmin or flavoxate hydrochloride or urispas or Flavoxate or hesperetin-7-rutinoside or Hesperidin or Isoflavone$ or genestein or Genistein or Gastrocrom or Pterocarpan$ or Quercetin$ or Rutin $ or 0-beta-hydroxyethylrutoside$ or beta-hydroxyethylrutoside$ or Hydroxyethylrutoside$ or carsil or karsil or legalon or silimarin or Silymarin or intal or Introl or Irtan or Lomudal or Lomuforte or Lomupren or Lomusol or Nalcrom or Nalcron or Nasalcrom or Novacrom or Opticrom or Opticron or Rynacrom or Sodium Chromoglycate or Sodium Cromoglycate or Sodium Cromolyn or Vicrom or Vistacrom or Vividrin or Nedocromil or Alocril or Disodium or Dicarboxylate or Ethyl or Quinoline or Dicarboxylate Disodium or Kovinal or Tilade or Tilarin or Tilavist).mp.
11. 6 or 7 or 8 or 9 or 10
12. 5 and 11

(Combined with RCT filter as described in the 'About the Airways Group' on the Cochrane Library)

WHAT'S NEW

Date	Event	Description
16 July 2010	New search has been performed	New search run, no new studies. Proposed risk of bias tool updated.

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 2, 2004

Date	Event	Description
24 March 2009	Amended	Change of contact details
31 July 2008	New search has been performed	Search re-run in July 2008; no new studies found.
12 July 2008	Amended	Converted to new review format.
22 November 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

ABC and PM wrote the protocol. MM edited protocol.
ABC and JMM reviewed abstracts and extracted potentially relevant papers independently. PM would have been the adjudicator if discrepancies occurred. ABC wrote the initial draft of the review and all reviewers contributed to the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.

External sources

- National Health and Medical Research Council, Australia.

  Supports AC through a practitioner fellowship (grant 525216)

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Antitussive Agents [*therapeutic use]; Cough [*drug therapy] [etiology]; Cromolyn Sodium [*therapeutic use]; Nedocromil [*therapeutic use]

MeSH check words

Child; Humans