National Institute for Health and Care Excellence

Final

Otitis media with effusion in under 12s

[H] Evidence reviews for non-antimicrobial pharmacological interventions for children with OME

NICE guideline NG233

Evidence reviews underpinning recommendations 1.5.3 to 1.5.4 and recommendations for research in the NICE guideline

August 2023

Final

This evidence review was developed by NICE

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Non-antimicrobial pharmacological interventions for children with OME

Review question

What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Introduction

The aim of this review is to assess the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) in managing OME in children under 12 years.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME). • If a trial includes children aged younger than 6 months and older than 12 years, we will only include the study if the majority of children fit our inclusion criteria or only if the trialists present outcome data by age group. • Include all children regardless of any comorbidity such as Down syndrome or cleft palate Clinical diagnosis of OME will be confirmed by oto(micro)scopy or tympanometry or both
Intervention	**NICE part of the review:** • Antihistamines • Decongestants • Leukotriene receptor antagonists • Mucolytics • PPIs (Proton pump inhibitors) and reflux medicines **Steroids/Cochrane part of the review:** • Topical (intranasal) steroids • Oral steroids
Comparison	**NICE part of the review:** • Head-to-head comparisons between all the above intervention categories* (single or in combination, including combinations with steroids) • Placebo

	• No intervention for treating OME *Please note, we will not include head-to-head comparisons between different interventions within each category (e.g., comparisons between different types of antihistamine), only head to head comparisons of interventions from different categories (e.g., a histamine versus a decongestant) **Steroids/Cochrane part of the review:** • topical (intranasal) steroids versus placebo • topical (intranasal) steroids versus no topical treatment • oral steroids versus placebo • oral steroids versus no oral treatment. If trial participants have received other treatments, for example, antibiotics, mucolytics or decongestants, we will include these studies if both arms of the study received identical treatments.

Outcome	**Critical**
	NICE part of the review:
	• Hearing
	  ○ proportion of children whose hearing has returned to normal;
	  ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis);
	  ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis).
	• Presence/persistence of OME
	• Discontinuation of treatment
	• Adverse events: Systemic corticosteroid side-effects
	
	Steroids/Cochrane part of the review:
	• We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. We will assess all outcomes in the very short term (< 6 weeks for adverse events), short term (≤ 3 months), medium term (> 3 months to ≤ 1 year) and long term (> 1 year).
	• Hearing
	  ○ proportion of children whose hearing has returned to normal;
	  ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis);
	  ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis).

	• Disease-specific quality of life measured using a validated instrument, for example:
	  ○ OM8-30;
	  ○ Otitis Media-6
	• Adverse events: Systemic corticosteroid side-effects
	• Discontinuation of treatment
	
	Important
	NICE
	• Listening skills, for example, listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists.
	• Receptive language skills, measured using a validated scale, for example:
	  ○ Peabody Picture Vocabulary Test – Revised;
	  ○ relevant domains of the Reynell Developmental Language Scales;
	  ○ relevant domains of the Preschool Language Scale (PLS);
	  ○ relevant domains of the Sequenced Inventory of Communication (SCID).
	• Disease-specific quality of life measured using a validated instrument, for example:
	  ○ OM8-30;
	  ○ Otitis Media-6
	
	Steroids/Cochrane part of the review:
	• Presence/persistence of OME.
	• Receptive language skills, measured using a validated scale, for example:
	  ○ Peabody Picture Vocabulary Test – Revised;
	  ○ relevant domains of the Reynell Developmental Language Scales;
	  ○ relevant domains of the Preschool Language Scale (PLS);
	  ○ relevant domains of the Sequenced Inventory of Communication (SCID).
	• Listening skills, for example, listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists

NICE: National Institute of Health and Care Excellence; OM: otitis media; OME: otitis media with effusion; PLS: Preschool Language Scale; PPI: proton pump inhibitor; SCID: Sequenced Inventory of Communication

For further details see the review protocol in appendix A.

Methods and process

Steroids

During the development of this guideline, a registered Cochrane protocol was identified which matched the committee's intended PICO for the steroids part of the review. The

Cochrane protocol differed from the committee's intended population in that the Cochrane protocols excluded studies that did not meet their inclusion criteria for trustworthiness (that is, those identified as being potentially 'high-risk' using a screening tool developed by Cochrane Pregnancy and Childbirth which included specified criteria to identify studies that are considered sufficiently trustworthy), however no studies were identified that were excluded from the review on these grounds alone.

The Cochrane review team completed a review investigating the effectiveness of steroids for OME in children (Mulvaney 2023b) during guideline development and presented their results to the committee, who used them to make recommendations. Cochrane's methods are closely aligned to standard NICE methods; minor deviations (summary of findings tables instead of full GRADE tables, defining primary and secondary outcomes as opposed to critical and important, assessing the risk of bias in primary studies using version 1 (as opposed to version 2) of the Cochrane Risk of Bias tool, how clinically important differences are determined, and including countries from a broader range of income categories than the majority of the other reviews in the guideline) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence. Where results were reported per ear instead of per child, Cochrane used an assumed intra-cluster correlation coefficient of 0.5 to adjust the sample size. Full details of the Cochrane review, including methods, are available in the review of steroids for children with OME, see Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

We thank the Cochrane ENT Group for their assistance in providing the literature searches and data for review questions relating to Otitis media with effusion in under 12s.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

The parts of the evidence review on the effectiveness of antihistamines, leukotriene receptor antagonists, mucolytics and decongestants was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1). Where results were reported per ear instead of per child, an assumed intra-cluster correlation coefficient of 0.5 was used to adjust the sample size.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Steroids

A Cochrane review on the effectiveness of steroids (Mulvaney 2023b) including 26 randomised controlled trials (RCT) (Acharya 2020; Ahmed 2022; Barati 2011; Beigh 2013; Berman 1990; Bhargava 2014; Cengel 2006; Choung 2008; Francis 2008 (OSTRICH); Hemlin 1997; Hussein 2017; Karlidag 2002; Khanam 2022; Lambert 1986; Lildholdt 1982; Macknin 1985; Mandel 2002; Niederman 1984; Podoshin 1990; Puhakka 1985; Rahmati 2017; Saffar 2001; Scadding 2014; Schwartz 1980; Stuart 1995; Williamson 2009) were considered in this review. This review was used for making recommendations by the committee, as it was considered sufficiently relevant, high quality and up to date.

Three studies compared oral steroids with no treatment (Acharya 2020; Choung 2008; Hussein 2017); 11 studies compared oral steroids with placebo (Berman 1990; Francis 2008; Hemlin 1997; Lambert 1986; Macknin 1985; Mandel 2002; Niederman 1984; Podoshin 1990; Puhakka 1985; Saffar 2001; Schwartz 1980); 7 studies compared nasal steroids with no treatment (Acharya 2020; Ahmed 2022; Barati 2011; Beigh 2013; Cengel 2006; Karlidag

2002; Rahmati 2017); and 6 studies compared nasal steroids with placebo (Bhargava 2014; Khanam 2022; Lildholdt 1982; Scadding 2014; Stuart 1995; Williamson 2009).

All studies included children aged over 4 years (Acharya 2020; Ahmed 2022; Barati 2011; Beigh 2013; Berman 1990; Bhargava 2014; Cengel 2006; Choung 2008; Francis 2008; Hemlin 1997; Hussein 2017; Karlidag 2002; Khanam 2022; Lambert 1986; Lildholdt 1982; Macknin 1985; Mandel 2002; Niederman 1984; Podoshin 1990; Puhakka 1985; Rahmati 2017; Saffar 2001; Scadding 2014; Schwartz 1980; Stuart 1995; Williamson 2009). None of the studies reported data on participants' hearing levels at baseline, or whether participants had allergy, cleft palate, or Down's syndrome. The Cochrane review is summarised in Table 2.

See the Cochrane review for the literature search strategy and study selection flow chart, see Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Twenty-four studies, reported in 25 articles, were included for this review; 23 RCTs (Babic 2017, Balatsouras 2005, Cantekin 1983, Choung 2008, Commins 2000, Dusdieker 1985, Edstrom 1977, Fraser 1977, Haugeto 1981, Hayden 1984, Hisamatsu 1994, Hughes 1984, Khan 1981, Kumazawa 1989, Mandel 1987, McGuiness 1977, O'Shea 1980/1982, Rahmati 2017, Ramsden 1977, Roydhouse 1981, Saunte 1978, Schoem 2010, van der Merwe 1987) and data from groups that were not crossed over in 1 cross-over RCT (Stewart 1985).

The included studies are summarised in Table 3.

Two studies compared mucolytic, decongestant and antihistamine with placebo (Hughes 1984; Khan 1981); 2 studies compared mucolytic, decongestant and antihistamine with mucolytic (Hughes 1984; Khan 1981); 1 study compared mucolytic, decongestant and antihistamine with decongestant and antihistamine (Hughes 1984); 8 studies compared mucolytic with placebo (Commins 2000; Edstrom 1977; Hughes 1984; Khan 1981; Kumazawa 1989; Ramsden 1977; Stewart 1985; van der Merwe 1987); 2 studies compared mucolytic with no treatment (Babic 2017; McGuiness 1977); 1 study compared mucolytic and antihistamine with placebo and antihistamine (Roydhouse 1981); 1 study compared mucolytic and antihistamine with placebo (Edstrom 1977); 1 study compared antihistamine with mucolytic (Edstrom 1977); 2 studies compared antihistamine with placebo (Dusdieker 1985; Edstrom 1977); 2 studies compared antihistamine with no treatment (Choung 2008; Hisamatsu 1994); 1 study compared decongestant and antihistamine with decongestant (Haugeto 1981); 1 study compared decongestant and antihistamine with mucolytic (Hughes 1984); 5 studies compared decongestant and antihistamine with placebo (Cantekin 1983; O'Shea 1980/1982; Saunte 1978; Haugeto 1981; Hughes 1984); 2 studies compared decongestant and antihistamine with no treatment (Fraser 1977; Mandel 1987); 1 study compared decongestant with antihistamine (Dusdieker 1985); 3 studies compared decongestant with placebo (Dusdieker 1985; Haugeto 1981; Hayden 1984); 1 study compared decongestant with no treatment (Fraser 1977); 1 study compared leukotrine receptor antagonist with placebo (Schoem 2010); 2 studies compared leukotrine receptor antagonist with no treatment (Balatsouras 2005; Rahmati 2017).Studies were classified as compared against no treatment when any additional treatments received (that were not of interest for the current review) were equivalent across arms.

Children in 5 studies had, on average, mild hearing loss at baseline (Choung 2008; Commins 2000; Fraser 1977; Mandel 1987; Saunte 1978), and another study included children who mostly had hearing loss <15dB (Hisamatsu 1994); 1 study included children with mild, moderate, or worse hearing loss (van der Merwe 1987); 5 studies included children with hearing loss at baseline but did not report the average severity (Edstrom 1977; Haugeto 1981; Khan 1981; O'Shea 1980/1982; Ramsden 1977); 1 study excluded children with sensory-neural or conductive hearing loss at baseline (Dusdieker 1985); and 11 studies did not report hearing thresholds at baseline (Babic 2017; Balatsouras 2005; Cantekin 1983;

Hayden 1984; Hughes 1984; Kumazawa 1989; McGuiness 1977; Rahmati 2017; Roydhouse 1981; Schoem 2010; Stewart 1985).

A minority of children in 6 studies had diagnosed allergy (Cantekin 1983; Mandel 1987), history of allergy (Dusdieker 1985; Fraser 1977), allergic symptoms or positive allergic skin-prick tests (Choung 2008), or atopic heredity to allergic rhinitis to a moderate degree (Saunte 1978) at baseline; 4 studies excluded children with allergic rhinitis (Hisamatsu 1994; Rahmati 2017), proven allergy (Babic 2017) or history of allergy (Schoem 2010) at baseline; and 14 studies did not report whether participants had allergy at baseline (Balatsouras 2005; Commins 2000; Edstrom 1977; Haugeto 1981; Hayden 1984; Hughes 1984; Khan 1981; Kumazawa 1989, McGuiness 1977; O'Shea 1980/1982; Ramsden 1977; Roydhouse 1981; Stewart 1985; van der Merwe 1987).

Two studies included children aged up to 4 years (Babic 2017; Dusdieker 1985); 16 studies included both children aged up to and those aged over 4 years (Cantekin 1983; Choung 2008; Commins 2000; Edstrom 1977; Fraser 1977; Hayden 1984; Haugeto 1981; Hisamatsu 1994; Mandel 1987; O'Shea 1980/1982; Rahmati 2017; Ramsden 1977; Roydhouse 1981; Saunte 1978; Schoem 2010; Stewart 1985);; 4 studies included children aged 4 years and over (Balatsouras 2005; Khan 1981; Kumazawa 1989; McGuiness 1977); 2 studies did not report ages of participants (Hughes 1984; van der Merwe 1987).

Eleven studies excluded children with cleft palate (Choung 2008; Commins 2000; Dusdieker 1985; Stewart 1985), congenital malformations (Babic 2017), congenital craniofacial malformations (Cantekin 1983; Mandel 1987), malformations (Hisamatsu 1994), craniofacial disorders (Schoem 2010), externally obvious ear or nose deformities (O'Shea 1980/1982), or children without normal palatal function (Hughes 1984); and 13 studies did not report whether any participants had cleft palate (Balatsouras 2005; Edstrom 1977; Fraser 1977; Haugeto 1981; Hayden 1984; Khan 1981; Kumazawa 1989; McGuiness 1977; Rahmati 2017; Ramsden 1977; Roydhouse 1981; Saunte 1978; van der Merwe 1987).

Four studies excluded children with Down's syndrome (Cantekin 1983; Commins 2000; Stewart 1985) or developmental difficulties (Choung 2008); and 20 studies did not report whether any participants had Down's syndrome (Babic 2017; Balatsouras 2005; Dusdieker 1985; Edstrom 1977; Fraser 1977; Haugeto 1981; Hayden 1984; Hisamatsu 1994; Hughes 1984; Khan 1981; Kumazawa 1989; Mandel 1987; McGuiness 1977; O'Shea 1980/1982; Rahmati 2017; Ramsden 1977; Roydhouse 1981; Saunte 1978; Schoem 2010; van der Merwe 1987).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included studies

Steroids

A summary of the Cochrane review that was included in this review is presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Comparison	Outcomes
Mulvaney 2023b	Children aged 6 months to 12 years with unilateral or bilateral OME.	**Oral steroids vs no treatment** 3 RCTs, N=542 children with OME (Acharya 2020; Choung 2008; Hussein 2017)	**Primary:** • Hearing as (i) return to normal; and

Study	Population	Comparison	Outcomes
Systematic review	Number of studies: 24 Number of participants: 3248	**Oral steroids vs placebo** 11 RCTs, N=1184 children with OME (Berman 1990; Francis 2008; Hemlin 1997; Lambert 1986; Macknin 1985; Mandel 2002; Niederman 1984; Podoshin 1990; Puhakka 1985; Saffar 2001; Schwartz 1980) **Nasal steroids vs no treatment** 7 RCTs, N=833 children with OME (Acharya 2020; Ahmed 2022; Barati 2011; Beigh 2013; Cengel 2006; Karlidag 2002; Rahmati 2017) **Nasal steroids vs placebo** 6 RCTs, N=693 children with OME (Bhargava 2014; Khanam 2022; Lildholdt 1982; Scadding 2014; Stuart 1995; Williamson 2009)	(ii) mean threshold • Disease-specific quality of life • Systemic corticosteroid side-effects **Secondary:** • Persistence of OME • Adverse events: local nasal • Receptive and expressive language • Cognitive development • Psychosocial development • Listening skills • Generic health-related QoL • Parental stress • Vestibular function • Number of episodes of AOM

AOM: acute otitis media; N: number; OME: otitis media with effusion; QoL: quality of life; RCT: randomised controlled trial

See the Cochrane review for characteristics of studies tables and forest plots, Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Summaries of the studies that were included in this review are presented in Table 3.

Table 3: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Babic 2017 RCT Croatia	N=90 children diagnosed with bilateral chronic OME • Age in months, mean (SD): 49.5 (NR, range: 24-72) • Sex (male/female): 51/39	Mucolytic and antibiotic (n=30): • Acetylcysteine (AC; 100mg 3 times daily, for 3 weeks) and azithromycin (AZ; dosing based on the child's weight, for 3 days)	Antibiotic only (n=30): • AZ; dosing based on the child's weight, for 3 days	• Presence/ Persistence of OME	An additional group received mucolytic only, but data from this group were not extracted for the purposes of this review as it had no direct head-to-head comparison OME diagnosed based on heterohistory data reported by parents, pneumato-oscopy, endoscopic ear examination, and

Study	Population	Intervention	Comparison	Outcomes	Comments
					tympanometry (type B bilaterally)
Balatsouras 2005 RCT Greece	N=50 children aged 6 to 13 years with a diagnosis of bilateral OME and asthma • Age in years, mean (SD): 10.4 (2.1) • Sex (male/female): NR	<u>Leukotriene receptor antagonist and inhalers (n=25):</u> • Montelukast (5mg chewable tablet) taken once a day between meals for 30 days) • Budesonide and terbutaline inhalers. Treatment regimen/ dosages not reported	<u>Inhalers only (n=25):</u> • Budesonide and terbutaline inhalers. Treatment regimen/ dosages not reported	• Presence/ persistence OME	OME was diagnosed using pneumatic otoscopy, tympanometry and pure-tone audiometry.
Cantekin 1983 RCT US	N=553 children aged between 7 months and 12 years who had unilateral or bilateral OME Decongestant & antihistamine group: • Age in years, mean (SD): NR ○ 7-23 months: 79/278 (28%) ○ 2-5 years: 136/278 (49%) ○ 6-12 years: 63/278 (23%) • Sex (male/female)*: NR, percentages (male/female): 59%/41% • Allergy diagnosed*: ○ Yes: 5% ○ No: 94% ○ Not recorded: 1% Placebo group: • Age in years, mean (SD): NR ○ 7-23 months: 81/275 (29%) ○ 2-5 years: 132/275 (48%)	<u>Decongestant & antihistamine (n=278):</u> • Liquid preparation (Novafed A syryup) of pseudoephedrine hydrochloride (dosage 1.0mg/ kg of body weight) and chlorpheniramine maleate (dosage 0.09mg/ kg of body weight) administered 4 times daily for 4 weeks	<u>Placebo (n=275):</u> • 4 weeks of placebo identical in appearance and similar in taste to the active medication, containing the same inert ingredients (Merrell-Dow)	• Presence/ persistence of OME	OME diagnosed based on a decision-tree algorithm which combined independent findings obtained by a "validated" otoscopist with results of tympanometry and middle-ear muscle-reflex testing. Children in both groups received a standardised antimicrobial regimen if they had an episode of acute suppurative otitis media or acute purulent rhinitis during follow-up

Study	Population	Intervention	Comparison	Outcomes	Comments
	○ 6-12 years: 62/275 (23%) • Sex (male/female)*: NR, percentages (male/female): 62%/38% • Allergy diagnosed*: ○ Yes: 5% ○ No: 94% ○ Not recorded: 1% *Numbers of participants not reported				
Choung 2008 RCT Korea	N=84 children with OME • Age in months, mean (SD): 69 (NR, range: 5 months - 12 years) • Sex (male/ female): 57/27 • Hearing thresholds (pure tone average): ○ Mean air conduction threshold (SD): - Right: 26.1 (11.3) dB - Left: 26.4 (11.0) dB ○ Mean air-bone gap (SD): - Right: 22.1 (13.6) dB - Left: 23.8 (12.1) dB • Children with allergic symptoms: 34/84 (41%) • Children with positive allergic skin-prick tests*: 17/40 (48%) *Only performed in children suspected of having allergies	<u>Antihistamine and antibiotic and (n=15):</u> • Ebastine (0.2 cc/kg, Ebastel) • Amoxicillin-clavulanate syrup (1 cc/kg, Augmex Duo syrup) • Treatments taken for 2 weeks. Treatment regimens not reported.	<u>Antibiotic (n=16):</u> • Amoxicillin-clavulanate syrup (1 cc/kg, Augmex Duo syrup) for 2 weeks. • Treatment regimen not reported.	• Presence/ persistence of OME	Three additional groups received the following: antibiotic and steroid; antibiotic, steroid, and antihistamine; mucolytic. Data from the first 2 groups were not of interest for this review; data from the mucolytic group could not be extracted because this group had no direct head-to-head comparison. OME diagnosed using pneumatic otoscopy, tympanography (type B or C tympanograms), and pure tone audiometry (hearing loss >25 dB)

Study	Population	Intervention	Comparison	Outcomes	Comments
Commins 2000 RCT UK	N=163 children aged 2 to 11 years with OME of at least 3 months duration Mucolytic group: • Age in years, mean (SD): 5.1 (NR, range: 2-10) • Sex (male/female): NR, ratio (male/female): 53/28 • Mean hearing loss (SD): 32.1 (NR) dB Placebo group: • Age in years, mean (SD): 5.7 (NR, range: 2-11) • Sex (male/female): NR, ratio (male/female): 52:35 • Mean hearing loss (SD): 33.8 (not reported) dB	<u>Mucolytic (n=78):</u> • Patients <5 years of age: Mucodyne 125mg (Carbocisteine, 2.5ml) three times a day for 6 weeks; patients >5 years of age: Mucodyne 250mg (5ml) three times a day for 6 weeks	<u>Placebo (n=85):</u> • Placebo was matched in colour and taste to the active drug • Patients <5 years of age: placebo (2.5ml) three times a day for 6 weeks; patients >5 years of age: placebo (5ml) three times a day for 6 weeks	• Presence/ persistence of OME	Diagnosis of OME was based on clinical otoscopy, tympanometry (type B) and an average hearing loss >25 dB. 30% of the children had grommet insertion and ≈ 13% had adenoidectomy prior to the study.
Dusdieker, 1985 RCT US	N=66 children aged 6 months to 10 years with OME who had completed a standard course of antibiotics before enrolment Pseudoephedrine group: • Age in years, mean (SD): 3 (2.68) • Sex (male/female): 9/11 • Allergic history*: 2/20 (10%) Chlorpheniramine group: • Age in years, mean (SD): 2.5 (1.34)	<u>Decongestant (n=20):</u> • Pseudoephedrine syrup (4 mg/ kg/day); medication given 3 times a day • Mean dose administered: 4.1 ± 0.98 mg/kg/day <u>Antihistamine (n=22):</u> • Chlorpheniramine syrup (0.35 mg/kg/day); medication given 3 times a day Mean dose administered: 0.35 ± 0.03 mg/kg/day	<u>Placebo (n=24):</u> • Similarly favoured placebo syrup given 3 times a day e	• Presence/ persistence of OME • Discontinuation of treatment (due to hyperactivity and poor sleeping)* *Could only be extracted for hyperactivity and poor sleeping because the rest of the data were not reported separately for each group	OME diagnosed by the principle investigator using pneumatic otoscopy and tympanometry (type B, or C3 if accompanied by physical findings of fluid in the middle ear). .

Study	Population	Intervention	Comparison	Outcomes	Comments
	• Sex (male/female): 7/15 • Allergic history*: 4/22 (18%) Placebo group: • Age in years, mean (SD): 1.9 (1.03) • Sex (male/female): 13/11 • Allergic history*: 5/24 (21%) *Children with any of the following: asthma; eczema; allergic rhinitis				
Edstrom 1977 RCT Sweden	N=178 children with secretory otitis media. • Age in years, mean (SD):: NR ○ 0-2 years: 55/178 (31%) ○ 3-4 years: 38/178 (21%) ○ 5-6 years: 41/178 (23%) ○ 7-8 years: 25/178 (14%) ○ 9-10 years: 6/178 (3%) ○ >10 years: 13/178 (7%) • Sex (male/female): NR	<u>Mucolytic (n=38):</u> • Bromhexine (Bisolvon) administered orally 3 times daily in the following doses until healing (but not longer than 7 weeks): ○ 0-1 year: 2 mg ○ 2-5 years: 3 mg ○ 6—-12 years: 4 mg ○ >12 years: 8 mg <u>Antihistamine (n=43):</u> • Cinnarizin (Rinomar) administered orally twice daily in the following doses until healing (but not longer than 7 weeks): ○ 0-1 year: 2.5 mg ○ 2-5 years: 5 mg ○ 6-12 years: 10 mg ○ >12 years: 20 mg <u>Mucolytic and antihistamine (n=46):</u> • Bromhexine and Cinnarizin administered according to the	<u>Placebo (n=51):</u> • No information reported	• Presence/ persistence of OME	Study reported data separately for the below groups, but results were combined for this review as they did not represent subgroups of interest: • Children who completed a course of antibiotics 3 weeks before the study was started (assumed for AOM): n=102/178 (57%) Children without preceding symptoms of AOM and antibiotic therapy: n=76 (43%) Criteria for a diagnosis of OME included a dull tympanic membrane with impaired mobility in Siegle's funnel (assessed during routine ENT examination)

Study	Population	Intervention	Comparison	Outcomes	Comments
		regimens above until healing (but not longer than 7 weeks)			and, in most cases, impaired hearing.
Fraser 1977 RCT UK	N=85 children aged 3 to 12 years with bilateral secretory otitis media • Age in years, mean (SD): 5.1 (NR, range: 3-12) • Sex (male/female): 47/38 • History of allergy: 9/85 (11%) • Mean pure-tone thresholds* (SD): 26.7 (9.7) dB *Averaged across 0.5, 1, and 2 kHz	<u>Decongestant (n=43):</u> • Ephedrine nose drops (0.5% ephedrine hydrochloride in 0.9% saline): two drops in each nostril given twice a day for 6 weeks. <u>Decongestant + antihistamine (n=43):</u> • Amoxicillin-clavulanate syrup (1 cc/kg, Augmex Duo syrup) for 2 weeks. Treatment regimen not reported.	Participants were split into 8 different groups to receive a combination of any or none of the following: decongestant nose drops; combination of antihistamine and nasal decongestant; autoinflation. Results were only reported according to whether participants received each treatment or not, irrespective of the other treatments received, so data could not exclusively be extracted for groups of interest for the purposes of this review (decongestant alone; combination of decongestant & antihistamine; no treatment. However, rates of people receiving other treatments was equivalent across groups.	• Mean change in hearing from baseline Authors also reported change in middle ear pressure but did not provide thresholds for resolution of OME, so this outcome has not been extracted. Authors do note in the Discussion section the number of participants who experienced resolution of OME, but this is reported as a total number for the whole cohort and per group/ intervention received, so this has not been extracted	Results relating to groups who received and did not receive autoinflation were not extracted as not of interest for this review. Participants were assessed using clinical history, pure-tone audiometry, and all diagnoses of OME were confirmed using tympanometry: a negative middle ear pressure in both ears and compliance less than 0.3cc in one or both ears.
Haugeto 1981 RCT Norway	N=77 children with secretory otitis media • Age in years, mean (SD): NR, range: 1-14 Decongestant group: • Age in years, mean (SD): 7.5 (NR) • Sex (male/female): NR • Hearing: ○ Mean air conduction	<u>Decongestant (n=22):</u> • 4-week course of phenylpropanolamine chloride (Monydrin). Further details about treatment regimen/ dosage not reported <u>Decongestant and antihistamine (n=28):</u> • 4-week course of phenylpropanolamine chloride (Monydrin) and brompheniramine maleate (Lunerin). Further details	<u>Placebo (n=27):</u> • 4-week course of placebo. Further details not reported	• Presence/ persistence of OME • Number of ears with hearing returned to normal	Secretory otitis media diagnosed using pneumatic otoscopy, otomicroscopy, and impedance audiometry. Pure tone audiometry was also performed where possible.

Study	Population	Intervention	Comparison	Outcomes	Comments
	threshold >20dB: 10/36 ears (28%) <u>Decongestant and antihistamine</u> group: • Age in years, mean (SD): 6.6 (NR) • Gender (male/female): NR • Hearing: ○ Mean air conduction threshold >20dB: 9/49 ears (18%) Placebo group: • Age in years, mean (SD): 7 (NR) • Sex (male/female): NR • Hearing: ○ Mean air conduction threshold >20dB: 8/42 (19%)	about treatment regimen/ dosage not reported			
Hayden 1984 RCT US	N=152 children aged 3 months to 10 years with persistent middle ear effusion, who returned for follow-up visits 2 weeks after treatment with a single course of an antimicrobial for an episode of AOM; n=79 completed study (characteristics reported for those who completed study only) • Sex (male/female)*: NR, percentages (male/female): 58%/42% Phenylephrine group:	<u>Decongestant (n=38):</u> • 0.25% phenylephrine hydrochloride nose drops or nasal spray. One-fourth dropperful (nose drops) administered in the following pattern each week: 4 times a day on day 1, 3 times on day 2, 2 times on day 3, once on day 4, then no medication for the final 3 days of the week • Participants repeatedly weekly cycles for 3-4 weeks or until OME resolved	<u>Placebo (n=41):</u> • Placebo nose drops or nasal spray. Unclear if timing patterns matched those for the phenylephrine group	• Presence/ persistence of OME (otoscopy) • Presence/ persistence of OME (tympanometry) • Discontinuation of treatment due to AOM • Discontinuation of treatment due to use of additional medication • Discontinuation of treatment due to inability to tolerate medication	Diagnostic criteria for OME at baseline were the presence of visible middle ear fluid and/ or impaired mobility of the tympanic membrane on pneumatic otoscopy,and a type B, C, or A(s) tympanogram (only type A tympanograms were considered normal). At follow-up, clinical (otoscopic) criteria are the same as at baseline (presence of visible middle ear fluid and/ or impaired mobility of the

Study	Population	Intervention	Comparison	Outcomes	Comments
	• Age in years, mean (SD): 4.1 (NR, range: 9 months to 10 years) Placebo group: • Age in years, mean (SD): 4.0 (NR, range: 7 months to 9 years) *Numbers of participants not reported; not reported separately for each group				tympanic membrane on pneumatic otoscopy). However, for tympanometry, both type A and A(s) tympanograms were considered normal at follow-up and therefore reported as resolution of OME, which was different to the tympanometry diagnostic criteria used at baseline.
Hisamatsu 1994 RCT Japan	N=62 children under the age of 15 years diagnosed with OME Antihistamine and local treatment group: • Age in years, mean (SD): NR ○ 0-5 years: 13 children (23 ears) ○ 6-15 years: 22 children (32 ears) • Sex (male/female): 21 children (32 ears)/14 children (23 ears) Local treatment only group: • Age in years, mean (SD): NR ○ 0-5 years: 13 children (22 ears) ○ 6-15 years: 14 children (26 ears) • Sex (male/female): 9 children (15 ears)/18 children (33 ears)	<u>Antihistamine and local treatment (n=35):</u> • 0.05 mg/kg of Tranilast (Rizaben Granule) administered orally for 6 weeks • Local treatment consisted of nasal spraying (1:5000 epinephrine) and suctioning (Dibekacin and Dexamethason were nebulized prior to ventilation therapy by catheterization or Politzer's method) once a week when patients visited the outpatient clinic	<u>Local treatment only (n=27):</u> • Local treatment consisted of nasal spraying (1:5000 epinephrine) and suctioning (Dibekacin and Dexamethason were nebulized prior to ventilation therapy by catheterization or Politzer's method) once a week when patients visited the outpatient clinic	• Number of ears with hearing returned to normal • Presence/ persistence of OME	OME was diagnosed based on the findings of the eardrum noted through the use of an operating microscope, mobility of the eardrum noted through the Bruning's otoscope, and their subjective symptoms with reference to pure tone audiometry, tympanometry, and more (complete information about diagnostic criteria not reported).

Study	Population	Intervention	Comparison	Outcomes	Comments
	Hearing loss (air conduction level calculated using thresholds at 0.5, 1, and 2 kHz, with additional weight given to the threshold at 1 kHZ in calculations) was measured at baseline but not reported. Authors note that only a small number of patients had hearing loss above 15 dB				
Hughes 1984 RCT Germany	N=83 children with a clinical diagnosis of MEE, no history of previous ENT surgery , and normal palatal function. Patient characteristics not reported.	<u>Mucolytic (n=27):</u> • Mucodyne (carbocisteine) + Actifed placebo. For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily. Further information about dosages not reported <u>Decongestant and antihistamine (n=20):</u> • Mucodyne placebo + Actifed (Pseudoephedrine hydrochloride + triprolidine hydrochloride). For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily. Further information about dosages not reported <u>Mucolytic, decongestant and antihistamine (n=20):</u> • Mucodyne + Actifed. For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily.	<u>Placebo (n=16):</u> • Mucodyne placebo + Actifed placebo. For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily	• Presence/ persistence of OME	OME diagnosis based on patient's symptoms, previous medical history, physical examination, and tympanometry. Most children also had audiograms, though number is not reported.

Study	Population	Intervention	Comparison	Outcomes	Comments
		Further information about dosages not reported			
Khan 1981 RCT UK	N=60 children with bilateral OME • Age in years, mean (SD): 7.3 (NR, range: 5-14) • Sex (male/female): 39/21	Mucolytic, antihistamine and decongestant (n=19): • Bromhexine and brompheniramine, phenylephrine, and phenylpropanolamine were given at the following dosages, according to age: ○ 4 years: 4.5mls 3 times a day ○ 5-9 years: 5mls 3 times a day ○ 10-14 years: 10mls 3 times a day • After 1-28 days all children underwent myringotomies, and children with mucoid MEE had VTs inserted • Not clear when (i.e., pre- or post-operatively) or for how long medications were taken but trial ended 1 month after operation in each case Mucolytic (n=20): • SCMC/ carbocisteine was given at the following dosage, according to age: ○ 4 years: 4.5mls 3 times a day ○ 5-9 years: 5mls 3 times a day ○ 10-14 years: 10mls 3 times a day • After 1-28 days all children underwent myringotomies, and children with mucoid MEE had VTs inserted • Not clear when (i.e., pre- or post-operatively) or for	Placebo (n=19): • Medications were given at the following dosages, according to age: ○ 4 years: 4.5mls 3 times a day ○ 5-9 years: 5mls 3 times a day ○ 10-14 years: 10mls 3 times a day • After 1-28 days all children underwent myringotomies, and children with mucoid MEE had VTs inserted • Not clear when (i.e., pre- or post-operatively) or for how long medications were taken but trial ended 1 month after operation in each case	• Number of children with hearing returned to normal	OME diagnosed based on clinical history, otoscopic examination, and audiology (including tuning fork testing and pure-tone audiometry). OME criteria were bilateral reduced hearing, retracted tympanic membrane with diminished light reflexes, and an air-bone gap.

Study	Population	Intervention	Comparison	Outcomes	Comments
		how long medications were taken but trial ended 1 month after operation in each case			
Kumazawa 1989 RCT Japan	N=214 children with OME who weighed 18 to 33kg and were 5 to 10 years old <u>Mucolytic group (n=104):</u> • Age in years, mean (SD): NR ○ <5 years: 8/104 (8%) ○ 5-6 years: 61/104 (59%) ○ 7-8 years: 24/104 (23%) ○ 9-10 years: 8/104 (8%) ○ >11 years: 3/104 (3%) • Sex (male/female): 61/43 <u>Placebo group:</u> • Age in years, mean (SD): NR ○ <5 years: 12/110 (11%) ○ 5-6 years: 58/110 (53%) ○ 7-8 years: 28/110 (25%) ○ 9-10 years: 11/110 (10%) ○ >11 years: 1/110 (1%) • Sex (male/female): 63/47	<u>Mucolytic (n=104):</u> • 5% SCMC syrup (50mg SCMC per 1ml syrup) administered 3 times daily after meals for 4 consecutive weeks (30 mg/kg/day in 1 dosage each, i.e., 4 ml for patients weighing 18 kg-23 kg, 5 ml for 23 kg-28 kg and 6 ml for 28 kg-33 kg) • Antibiotics (penicillin origin or cefaclor) were allowed for use upon myringotomy prior to administration of the syrup, for a maximum of 3 days	<u>Placebo (n=110):</u> • Placebo syrup indistinguishable from active drug by odour, taste, or appearance, administered orally 3 times daily after meals for 4 consecutive weeks (amount to match active drug) • Antibiotics (penicillin origin or cefaclor) were allowed for use upon myringotomy prior to administration of the syrup, for a maximum of 3 days	• Presence/ persistence of OME • Discontinuation of treatment due to side-effects	OME diagnosed based on observations of MEE, dullness and retraction of the eardum, standard audiometry, and tympanometry.
Mandel 1987 RCT US	N=474 infants and children aged 7 months to 12 years with OME <u>Antibiotic, decongestant and antihistamine group:</u>	<u>Antibiotic, decongestant and antihistamine (n=158):</u> • Antibiotic (amoxicillin): liquid suspension, 40mg/kg/day divided into 3 doses for 2 weeks	<u>Antibiotic only (n=160):</u> • Antibiotic (amoxicillin): liquid suspension, 40mg/kg/day divided into 3 doses for 2 weeks	• Presence/ persistence of OME ○ Mean final hearing threshold	OME diagnosed based on standardised ENT examination (including pneumatic otoscopy).

Study	Population	Intervention	Comparison	Outcomes	Comments
	• Age in years, mean (SD): NR ○ 7-23 months: 37% ○ 2-5 years: 48% ○ 6-12 years: 16% • Sex (male/female): NR, percentages (male/female): 36%/64% • Allergy diagnosed: ○ No: 99% ○ Yes: 1% ○ Unknown: 0% Mean speech awareness thresholds at baseline/ child (SD)*: 23.25 (9.28) dB <u>Antibiotic only group:</u> • Age in years, mean (SD): NR ○ 7-23 months: 33% ○ 2-5 years: 49% ○ 6-12 years: 18% • Sex (male/female): NR, percentages (male/female): 36%/64% • Allergy diagnosed: ○ No: 97% ○ Yes: 3% ○ Unknown: 1% Mean speech awareness thresholds at baseline/ child (SD)**: 23.00 (11.74) dB *Only reported for 57/158 (36%) participants who had data at baseline and 4-week follow-up **Only reported for 50/160 (31%)	• Decongestant-antihistamine: liquid preparation of pseudoephedrine hydrochloride and chlorpheniramine maleate (Novafed A) administered in a dose of 1.0 mg/kg and 0.09mg/kg of each drug respectively 4 times daily for 4 weeks	• Placebo identical in appearance and similar in taste to decongestant-antihistamine, and containing the same inert ingredients, administered for 4 weeks		

Study	Population	Intervention	Comparison	Outcomes	Comments
	participants who had data at baseline and 4-week follow-up				
McGuiness 1977 RCT UK	N=36 children with non-suppurative otitis media and intact tympanic membranes Patient characteristics not reported.	Mucolytic (n=20): • 5ml of SCMC delivered 3 times a day orally for 14 days • No surgery performed during trial	No treatment (n=16): • No surgery performed during trial	• Change in hearing threshold	Diagnosis of OME made based on clinical history, appearance of tympanic membrane, and pure-tone audiometry. Authors do not explicitly report the use of otoscopy or tympanometry, but examination of tympanic membrane presumed to have been done using otoscopy.
O'Shea 1980/1982 RCT US	N=55 children aged 3 to 9 years with the following: first known diagnosis of serous otitis media within 1 month prior to the trial; rectal temperature less than 38.4 C or an oral temperature less than 37.8 C; no externally obvious ear or nose deformities • Age in years, mean (SD): 6 (NR, range: 3-9) • Sex (male/female): 33/22 • Mean hearing loss (air and bone conduction): Not reported. All participants had, in at least 1 ear, hearing loss (air conduction) >15 dB at ≥2 consecutive frequencies, and no hearing loss (bone conduction) >10 dB	Antihistamine and decongestant (n=27): • Combination of diphenhydramine and pseudoephedrine, each taken 5 mg/kg/day orally in 3 divided doses. Duration of treatment not reported	Placebo (n=28): • Similar tasting placebo taken in comparable volume orally in 3 divided doses. Duration of treatment not reported	• Presence/ persistence of OME • Number of children with hearing returned to normal • Change in hearing threshold from baseline	Diagnosis of serous otitis media made based on the following criteria: • Fluid in at least 1 middle ear and no bulging of either tympanic membrane, assessed using pneumatic otoscopy • In at least 1 ear, hearing loss (air conduction) >15 dB at ≥2 consecutive frequencies, and no hearing loss (bone conduction) >10 dB • At least one ear with a flat (type B) tympanogram on impedance tympanometry

Study	Population	Intervention	Comparison	Outcomes	Comments
Rahmati 2017 RCT Iran	N=143 children aged 2 to 6 years with a diagnosis of OME <u>Leukotriene receptor antagonist</u> group: • Age in months, mean (SD): 43.05 (19.08) Sex (male/female): 32/27 No treatment group: • Age in months, mean (SD): 41.27 (15.90) • Sex (male/female): 31/13	<u>Leukotriene receptor antagonist (n=59):</u> • 4ml Montelukast per day for 1 month. Further information regarding dosage not reported	<u>No treatment (n=44):</u> • No further details reported	• Presence/ persistence of OME	One additional group received Mometasone but data for this group were not extracted as not of interest for this review. OME diagnosed based on "symptoms and examination". Further detail not reported; however, OME diagnosis was confirmed by tympanometry at baseline.
Ramsden 1977 RCT UK	N=52 children with OME who had not had previous surgery • Age in years, mean (SD): NR, range: 3-9 • Sex (male/female): NR • Mean duration of hearing loss (range): 14 (2-48) months	<u>Mucolytic (n=18):</u> • SCMC given in the following amounts dependant on participant age: 3-4 years: 5ml twice daily; 5-10 years: 5ml three times daily. Further information about dosage not reported	<u>Placebo (n=19):</u> • Placebo given in the following amounts dependant on participant age: 3-4 years: 5ml twice daily; 5-10 years: 5ml three times daily	• Presence/ persistence of OME	OME was diagnosed based on the following criteria (otoscopic diagnosis and shape of compliance curve considered to be the most important criteria): • Subjective clinical assessment based on a history of fluctuating hearing loss, the otoscopic appearance of the tympanic membrane and a negative Rinne test • Conductive hearing loss on pure tone audiometry • A flat curve on the middle ear compliance instrument
Roydhouse 1981 RCT	N=113 children aged ≤14 years seen at the ENT clinic who had OME which did not resolve after	<u>Mucolytic + antihistamine (n=57):</u> • Bromhexine taken for 1 month with dosage depending on age of the	<u>Placebo + antihistamine (n=58):</u> • Placebo taken for 1 month, plus a refill after 1 month	• Presence/ persistence of OME	OME diagnosed on clinical grounds and confirmed with impedance audiometry (participants had

Study	Population	Intervention	Comparison	Outcomes	Comments
New Zealand	phase 1 of the trial Mucolytic + antihistamine group: • Age in years, mean (SD): 6.7 (2.5) • Sex (male/female): 31/26 Placebo + antihistamine group: • Age in years, mean (SD): 6.5 (1.9) • Sex (male/female): 34/22 ○	participant, plus a refill after 1 month: ≥7 years: 16mg twice daily; ≤6 years: 10ml bromhexine elixir (4mg/ 5ml) three times daily. • Participants also took: ○ ≥7 years: Chlorpheniramine maleate long-acting 8mg twice daily and pseudoephedrine 30 or 60mg twice daily ○ ≤6 years: Chlorpheniramine maleate elixir (2mg/ 5ml) combined with pseudoephedrine elixir (30mg/ 5ml), 5ml three times daily	• Participants also took: ○ ≥7 years: Chlorpheniramine maleate long-acting 8mg twice daily and pseudoephedrine 30 or 60mg twice daily ○ ≤6 years: Chlorpheniramine maleate elixir (2mg/ 5ml) combined with pseudoephedrine elixir (30mg/ 5ml), 5ml three times daily		to have a B- or C-type curve with a peak pressure <-300mm water) In phase 1 of the trial, participants were given specific measures to improve the health of the nose and sinuses (including the use of nasal sprays), and non-specific measures to improve general resistance to infection
Saunte 1978 RCT Norway	N=21 children with secretory otitis media who met the following criteria: reduced hearing ability recognised by the child or their parent for ≥14 days; minimum hearing threshold ≥20 dB measured using audiometry; reduced mobility of the ear drum found on otoscopy; if the child had previously had AOM, it must be cured and the child must be without symptoms for ≥2 weeks; normal hearing ability prior to the OME <u>Antihistamine and decongestant</u> group: • Age in years, mean (SD): 6.3 (NR, range: 3-10)	<u>Antihistamine and decongestant (n=11):</u> • Either Lunerin mixture (0.4mg brompheniramine maleate and 1.7mg phenylpropanolamine hydrochloride per ml) or Lunerin mite (tablet, 6mg brompheniramine maleate and 25mg phenylpropanolamine hydrochloride). The child/ their parents had a free choice whether to use tablet or mixture. • Children taking tablets took 1 in the morning and 1 in the afternoon • Mixture dosages were age dependent: ○ 3-4 years: 7.5ml, 3 times a day ○ 6-10 years: 10 ml, 3 times a day ○ >11 years: 15 ml, 3 times a day	<u>Placebo (n=10):</u> • Same appearance and taste to Lunerin (unclear if children in this group were also offered a choice between tablet or mixture) •	• Change in hearing threshold from baseline	OME diagnosed based on medical history, a reduced mobility of the ear drum on otoscopy, and minimum hearing threshold ≥20 dB measured using audiometry.

Study	Population	Intervention	Comparison	Outcomes	Comments
	• Sex (male/female): NR • Atopic heredity to allergic rhinitis to a moderate degree: 4/11 (36%) • Mean hearing threshold at baseline/ear (SE): ○ 0.5 kHz (14 ears): 27.5 (1.6) dB ○ 1 kHz (14 ears): 27.1 (2.2) dB ○ 2 kHz (7 ears): 29.3 (3.7) dB Placebo group: • Age in years, mean (SD): 5.8 (NR, range: 1-12) • Sex (male/female): NR • Atopic heredity to allergic rhinitis to a moderate degree: 5/10 (50%) • Mean hearing threshold at baseline/ear (SE): ○ 0.5 kHz (10 ears): 36.0 (4.2) dB ○ 1 kHz (12 ears): 35.0 (3.3) dB ○ 2 kHz (10 ears): 33.5 (3.4) dB				
Schoem 2010 RCT US	N=38 children aged 2 to 6 years presenting with persistent MEE in at least one ear for ≥2 months Patient characteristics not reported.	<u>Leukotrine receptor antagonist (n=19):</u> • 4mg of oral montelukast once an evening for 1 month. Further information regarding dosage not reported	<u>Placebo (n=19):</u> • 4mg of placebo once an evening for 1 month	• Presence/ persistence of OME	Diagnosis of OME was confirmed by otoscopy and validated independently via tympanometry.
Stewart 1985	N=95 children aged 3 to 8 years attending the	<u>Mucolytic:</u> • Bromhexine tablets: for	<u>Placebo:</u> • Placebo tablets were not	• Presence/ persistence of OME	OME diagnosed using otomicroscopy

Study	Population	Intervention	Comparison	Outcomes	Comments
Cross-over RCT New Zealand	ENT Clinic of Dunedin Hospital during the study dates, who met the following criteria: proven effusion in at least 1 ear by otomicroscopy and type-B tympanogram; no other significant ear pathology; no previous ear surgery; no antibiotic treatment over the study period; no underlying structural abnormality, e.g., Down's syndrome, cleft palate Bromhexine group*: • Age in months, mean (SD): 67.0 (NR) • Sex (male/female): NR, ratio (male/female): 60/40 Placebo*: • Age in months, mean (SD): 66.0 (NR) • Sex (male/female): NR, ratio (male/female): 58/42 *Numbers of participants in each group at baseline not reported. Authors note patient characteristics for each group reported at baseline overlap to some extent since some children received both placebo and bromhexine	children aged 3-5 years, 8mg (1 tablet) 3 times daily; for children aged 6-8 years, 16mg (2 tablets) 3 times daily • Drugs were issued every 2 weeks in batches which included 6 extra doses • The results from 1 group which took bromhexine for the full 8 weeks of the trail (did not cross-over) is extracted for the purpose of this review	readily distinguishable from the active drug • Drugs were issued every 2 weeks in batches which included 6 extra doses • The results from 1 group which took placebo for the full 8 weeks of the trail (did not cross-over) is extracted for the purpose of this review		and impedance tympanometry.
van der Merwe 1987	N=60 patients with OME seen in	<u>Mucolytic (n=29):</u> • Bromhexine taken for 1 month using	<u>Placebo (n=31):</u> • Placebo taken for 1 month.	• Presence/ persistence of OME	OME diagnosed based on ENT examination,

Study	Population	Intervention	Comparison	Outcomes	Comments
RCT South Africa	routine outpatient clinics • Age in years, mean (SD)*: NR. 91% of participants were <12 years • Sex (male/female)*: 40/20 Mucolytic group: • Hearing thresholds (pure-tone audiometry of free-field audiometry; n=58 ears)/ ear**: ○ Right ear <15dB: 8/29 (27%) ○ Left ear <15dB: 7/29 (23%) ○ Right ear 15-30dB: 13/29 (45%) ○ Left ear 15-30dB: 14/29 (48%) ○ Right ear >30dB: 8/29 (27%) ○ Left ear >30dB: 8/29 (27%) Placebo group: • Hearing thresholds (pure-tone audiometry of free-field audiometry; n=29 ears each side, 58 ears total)**: ○ Right ear <15dB: 8/29 (27%) ○ Left ear <15dB: 6/29 (21%) ○ Right ear 15-30dB: 12/29 (42%) ○ Left ear 15-30dB: 15/29 (51%)	the following dosage regimens depending on age: ○ <1 year: 1.25ml (2.5mg) 3 times a day ○ 1-5 years: 2.5ml (5mg) 3 times a day ○ 6-10 years: 4ml (8mg) 3 times a day ○ >10 years: 8ml (16mg) 3 times a day	Treatment regimen not further described.	• Number of ears with hearing returned to normal	with emphasis on tympanic membrane appearance and movement, pure-tone audiometry and tympanometry

Study	Population	Intervention	Comparison	Outcomes	Comments
	○ Right ear >30dB: 9/29 (31%) ○ Left ear >30dB: 10/29 (35%) *These patient characteristics not reported separately per group **Results reported as percentages and converted to number of events assuming number of ears is the same at each time point; data extracted from figure and numbers do not add up exactly to totals ears reported at baseline for placebo group				

AC: acetylcysteine; AOM: acute otitis media; AZ: azithromycin; dB: decibel; dBHL: decibel hearing level; ENT: ears, nose and throat; MEE: middle ear effusion; N: number; NR: not reported; OME: otitis media with effusion; RCT: randomised controlled trial; SCMC: S-carboxymethylcysteine; SD: standard deviation; SE: standard error; VT: ventilation tube

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Steroids

The Cochrane review of topical and oral steroids for children with OME investigated 4 comparisons, with the following findings:

- Comparison 1: Oral steroid versus no treatment. Oral steroids had an important benefit for persistence of OME in the very short term (very low quality evidence according to GRADE criteria), but no important difference between oral steroids and no treatment for persistence of OME in the short or medium term (both low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol.
- Comparison 2: Oral steroid versus placebo. Oral steroids had an important benefit for persistence of OME in the medium term when persistence was undefined (low quality evidence according to GRADE criteria), and a possible important benefit for persistence of OME in the very short term (90% CI: 0.54 to 0.96; very low quality). There was no important difference or no evidence of an important difference between oral steroids and placebo for any of the remaining outcomes: normal hearing in the very short, short, or medium term; hearing thresholds in the very short term; disease-specific quality of life in the very short or medium term; persistence of OME in the short term, or in the medium term when persistence was defined as effusion in both affected ears; acute otitis media in the very short term; generic health-related quality of life in the very short or medium term (when assessed with PedsQL or HU13). The outcomes normal hearing in the medium term, disease-specific quality of life in the

medium term, persistence of OME in the medium term, and generic health-related quality of life in the medium term were all moderate quality evidence according to GRADE criteria. The rest of the outcomes were all low to very low quality evidence according to GRADE criteria. There was no evidence available for this comparison for any of the other outcomes specified in the protocol.
    - Subgroup analyses assessing the differences between oral steroid versus placebo for children with allergy versus without were done for the following outcomes: normal hearing in the very short term and persistence of OME in the very short term. Oral steroids had an important benefit for persistence of OME in the 'no allergy' group, but there was no important difference for those with allergy for this outcome, and no evidence of an important difference or no important difference between interventions for either group for hearing outcomes (all low or very low quality evidence according to GRADE criteria).
    - Subgroup analyses assessing the differences between oral steroid versus placebo for children aged <4 versus ≥4 years were done for persistence of OME in the very short term. There was no important difference for these comparisons (low or very low quality evidence according to GRADE criteria)
- Comparison 3: Topical (nasal) steroid versus no treatment. Nasal steroids had an important benefit for persistence of OME in the very short and short term (both very low quality evidence according to GRADE criteria). There was no important difference between nasal steroids and no treatment for the other outcome: final hearing threshold in the very short term (low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol
- Comparison 4: Topical (nasal) steroid versus placebo. Nasal steroids had an important benefit for persistence of OME in the medium term when persistence was undefined, final hearing threshold in the short term, and generic health-related quality of life in the medium term (very low to low quality evidence according to GRADE criteria). There was no important difference between nasal steroids and placebo for any of the other outcomes: change in hearing threshold in the short term; persistence of OME in the very short or short term, or in the medium term when persistence was defined as being in both ears; adverse event: nasal bleeding in the medium term; disease specific quality of life in the short or medium term (all low or very low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol.

For all outcomes, time of follow-up was defined as follows: very short term: <6 weeks; short term: ≤3 months; medium term: >3 months to ≤1 year; long term: >1 year.

See the Cochrane review for summary of findings tables and full results, including all primary and secondary outcomes and sub-group analyses, Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

For the purposes of this review and analyses, interventions were considered to be compared to 'no treatment' when there was an additional intervention/s in the intervention arm that was the same as the comparator (provided it was not an intervention of interest). For example, antihistamine plus local treatment versus local treatment alone, and antihistamine plus antibiotic versus antibiotic, were both included under the comparison antihistamine versus no treatment. Outcomes which include comparisons like this are as follows:

- Leukotriene receptor antagonist versus no treatment, presence/ persistence of OME (per child, short term) (relevant study: Balatsouras 2005). See Figure 7
- Antihistamine versus no treatment, presence/ persistence of OME (per child, short term) (relevant study: Choung 2008)

- Antihistamine versus no treatment, presence/ persistence of OME (per ear, short term) (relevant study: Hisamatsu 1994)
- Antihistamine versus no treatment, hearing returned to normal (per ear, short term; air conduction) (relevant study: Hisamatsu 1994)
- Decongestant and antihistamine versus no treatment, presence/ persistence of OME (per child, short term) (relevant studies: Mandel 1987)
- Decongestant and antihistamine versus no treatment, mean final hearing threshold (per child, short term) (relevant studies: Mandel 1987)
- Decongestant and antihistamine versus no treatment, mean final hearing threshold (per ear, short term) (relevant studies: Mandel 1987)
- Mucolytic versus no treatment, presence/ persistence of OME (per ear, short term) (relevant studies: Babic 2017)

Results were pooled where studies reported the same class of medication or treatment received in the intervention and comparator arms for the same outcome. For example, presence/persistence of OME results from a study examining carbocisteine or bromhexine compared with placebo and another study examining bromhexine compared with placebo were pooled in an analysis examining mucolytic compared with placebo. There was no significant heterogeneity for any of the pooled outcomes and so sub-group analyses were not performed; however, in the forest plots results are presented according to the drug used. For all outcomes, time of follow-up was defined as follows: short term: ≤3 months; medium term: >3 months to ≤1 year; long term: >1 year.

Important or possible important benefits or harms

A mucolytic, decongestant and antihistamine (bromhexine and brompheniramine, phenylephrine, and phenylpropanolamine) had the possible important harm of less children having their hearing returned to normal compared with mucolytic alone (S-carboxymethylcysteine (SCMC)/ carbocisteine) in the short term, when assessed using air conduction at 0.25kHz (90% CI: 0.28 to 0.99; very low quality evidence). The same study showed that a mucolytic (SCMC/ carbocisteine) had the important benefit of more children having their hearing returned to normal compared with placebo in the short term, when assessed using air conduction at 0.25kHz (low quality evidence). For these outcomes, the children included were aged 4 years or over, all children had an air-bone gap at baseline, and information on allergy, cleft palate, and Down syndrome was not reported. A mucolytic (SCMC/ carbocisteine) had the important benefit of improving hearing thresholds compared with no treatment in the short term (very low quality evidence). For this outcome, the children included were aged 4 years or over, and information on hearing, allergy, cleft palate, and Down syndrome was not reported. A mucolytic plus an antihistamine (bromhexine and chlorpheniramine maleate) had the important benefit of less ears with presence/ persistence of OME compared with placebo plus an antihistamine (placebo and chlorpheniramine maleate) in the short term (low quality evidence). For this outcome, the children included were aged up to and over 4 years, and information on hearing, allergy, cleft palate, and Down syndrome was not reported. Only single studies reported each of these outcomes.

No important difference or no evidence of an important difference between interventions

For all the rest of the outcomes for all the comparisons, there was no important difference or no evidence of an important difference between the intervention and comparator arms. These outcomes were as follows:

- Mucolytic, decongestant, and antihistamine versus placebo (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Hearing returned to normal in the short term
  - Hearing returned to normal in the short term

- Mucolytic, decongestant, and antihistamine versus mucolytic alone (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Hearing returned to normal in the short term, when assessed using air conduction at 0.5, 1, 2, 4, and 8kHz, and bone conduction
- Mucolytic, decongestant, and antihistamine versus decongestant and antihistamine (very low quality evidence):
  - Presence/ persistence of OME in the short term
- Mucolytic versus placebo:
  - Presence/ persistence of OME in the short term (per child: moderate quality evidence; per ear: very low quality evidence)
  - Hearing returned to normal in the short term, when assessed using air conduction at 0.5, 1, 2, 4, and 8kHz, bone conduction, and pure-tone audiometry or free-field audiometry (all very low to low quality evidence)
  - Discontinuation of treatment due to vomiting in the short term (very low quality evidence)
- Mucolytic versus no treatment (very low quality evidence):
  - Presence/ persistence of OME in the short term
- Mucolytic and antihistamine versus placebo (very low quality evidence):
  - Presence/ persistence of OME in the short term
- Antihistamine versus mucolytic (very low quality evidence):
  - Presence/ persistence of OME in the short term
- Antihistamine versus placebo (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Discontinuation of treatment due to hyperactivity and poor sleeping in the short term
- Antihistamine versus no treatment (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Hearing returned to normal in the short term
- Decongestant and antihistamine versus decongestant (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Hearing returned to normal in the short term
- Decongestant and antihistamine versus mucolytic (very low quality evidence):
  - presence/ persistence of OME in the short term
- Decongestant and antihistamine versus placebo:
  - Presence/ persistence of OME in the short term (per child: moderate quality evidence; per ear or per assessment: very low quality evidence)
  - Hearing returned to normal in the short and medium term (all low to very low quality evidence)
  - Change in hearing threshold from baseline in the short and medium term (all low to very low quality evidence)
- Decongestant and antihistamine versus no treatment:
  - Presence/ persistence of OME in the short term (moderate quality evidence)
  - Mean final hearing threshold in the short term (moderate quality evidence)
  - Change in hearing threshold from baseline in the short term (very low quality evidence)
- Decongestant versus antihistamine (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Discontinuation of treatment due to hyperactivity and poor sleeping in the short term

- Decongestant versus placebo (all very low quality evidence):
  - Presence/ persistence of OME in the short term
  - Hearing returned to normal in the short term
  - Discontinuation of treatment due to hyperactivity and poor sleeping in the short term
  - Discontinuation of treatment due to acute otitis media (AOM) in the short term
  - Discontinuation of treatment due to use of additional medication in the short term
  - Discontinuation of treatment due to inability to tolerate medication in the short term
- Decongestant versus no treatment (very low quality evidence):
  - Change in hearing threshold from baseline in the short term
- Leukotrine receptor antagonist versus placebo (very low quality evidence):
  - Presence/ persistence of OME in the short term
- Leukotrine receptor antagonist versus no treatment (very low quality evidence):
  - Presence/ persistence of OME in the short term.

No evidence available

There was no evidence available for proton pump inhibitors (PPIs) and reflux medicines, and no evidence for any of the important outcomes (listening skills, receptive language skills measured using a validated scale, or disease-specific quality of life measured using a validated scale). There was no evidence for long term follow-up.

See appendix F for full GRADE tables.

Economic evidence

Included studies

Two economic studies were identified which was relevant to this question (Williamson 2009; Francis 2018).

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included economic evidence

See Table 4 for the economic evidence profiles of the included studies.

Table 4: Economic evidence profile of a systematic review of economic evaluations of budesonide for maintenance of remission in Crohn's disease

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectivenss	
Williamson 2009 Mometasone furoate	Minor limitations	Directly applicable[1]	Economic evaluation alongside a randomised controlled trial	£11	-0.0166 QALYs	Intranasal steroids dominated by	Probabilistic sensitivity analysis showed there was a 24%

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectivenss	
50 µg (intranasal steroids)versus placebo nasal spray						placebo	probability of intranasal steroids being cost-effective at a cost-effectiveness threshold of £20,000 per QALY
Francis 2018 Oral prednisolone versus oral placebo	Minor limitations	Directly applicable[1]	Economic evaluation alongside a randomised controlled trial	£145	-0.015 QALYs	Oral steroids dominated by placebo	Probabilistic sensitivity analysis showed a 17% probability of oral steroids being cost-effective at a cost-effectiveness threshold of £20,000 per QALY rising to 22% at a threshold of £30,000 per QALY

[1] HUI3 (Health Utilities Index 3) was used in preference to EQ-5D to generate QALYs as it is a well validated instrument in children and is likely to have greater sensitivity and less ceiling effects in this population

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The primary outcomes in the Cochrane protocol for the review on steroids were hearing, disease-specific quality of life, systemic corticosteroid side-effects, and discontinuation of treatment. The committee agreed these outcomes were critical: hearing is a direct measure of any differential effectiveness associated with the use of medication; disease-specific quality of life is a measure of well-being which may capture long-term health-related outcomes associated with the effectiveness of interventions; discontinuation of treatment would capture both potential benefits and risks of the intervention depending on the reason for discontinuation of treatment (for example, because they no longer need the medication, or because the child could not tolerate the medication); systemic corticosteroid side-effects would capture the risk of adverse events (such as muscle weakness) which can happen as a result of the use of oral steroids. The primary outcomes for the review on antihistamines, leukotriene receptor antagonists, mucolytics and decongestants were similar to those for the Cochrane review on steroids; however, presence/ persistence of OME was chosen as a

primary outcome instead of disease-specific quality of life, which was a secondary outcome for this review. The committee agreed that presence or persistence of OME after the use of medication directly measures the effectiveness of the intervention whereas quality of life is a less direct measure with other influences and arguably a greater subjective element. Therefore, presence of OME was kept as a primary outcome for internal consistency with other reviews conducted for this guideline, however Cochrane kept it as a secondary outcome to be consistent with their previous reviews.

The other outcomes listed in the Cochrane protocol (presence/ persistence of OME; receptive language skills; listening skills) were agreed to be important outcomes by the committee. The committee agreed that OME-related hearing loss can be associated with impairment of receptive language and listening skills, which could impact on the child's development, and therefore the committee agreed these were important outcomes. The review on antihistamines, leukotriene receptor antagonists, mucolytics and decongestants also had receptive language and listening skills as secondary outcomes.

The quality of the evidence

Steroids

The quality of the evidence was assessed using GRADE methodology and was moderate to very low quality, mainly due to risk of bias assessed using version 1 of the Cochrane RoB tool and imprecision in the effect estimate. Where outcomes were downgraded for risk of bias, this was mainly due to selection, performance, attrition, reporting and/ or detection bias. In some cases, there was also bias arising from the randomisation process and/or measurement of the outcomes. For some outcomes, there was additionally inconsistency due to opposite directions of effect and an I-squared value >50% or >80%, and/or indirectness due to the inclusion of an indirect population.

There was no evidence for any of the following outcomes: discontinuation of treatment; listening skills, or receptive language skills measured using a validated scale. There was no evidence for long term follow-up.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

The quality of the evidence was assessed using GRADE methodology and was moderate to very low quality, mainly due to risk of bias assessed using version 2 of the Cochrane RoB tool and imprecision in the effect estimate. Where outcomes were downgraded for risk of bias, this was mainly due to deviations from the intended interventions, missing outcome data, and/or selection of the reported result. In some cases, there was also bias arising from the randomisation process and/or measurement of the outcomes. For some outcomes, there was additionally indirectness due to the inclusion of an indirect population, outcome, or intervention, and/or suspected publication bias due to the majority of studies contributing to the outcome being industry funded.

There was no evidence available for proton pump inhibitors (PPIs) and reflux medicines, and no evidence for any of the secondary outcomes (listening skills, receptive language skills measured using a validated scale, or disease-specific quality of life measured using a validated scale). There was no evidence for long term follow-up.

Benefits and harms

Steroids

The committee discussed the evidence on steroids, in particular the moderate quality evidence comparing oral steroids with placebo for the medium-term outcomes: normal hearing, persistence of OME, disease-specific quality of life, and generic health-related quality of life. Additionally, the committee discussed the fact that oral steroids often have a

stronger effect that nasal steroids. Considering the moderate quality evidence that oral steroids made no difference in terms of the above outcomes when compared to placebo and the limited, low quality evidence when compared to no treatment, the committee agreed that it was unlikely that nasal steroids, which usually have a weaker effect, would have an important hearing-, OME-, or quality of life-related benefit either. They agreed this reasoning outweighed the low to very low quality evidence that nasal steroids had an important benefit when compared to not treatment or placebo with regards to final hearing thresholds in the short term, persistence of OME in the very short, short, and (when persistence was undefined in the evidence) medium term, and generic health-related quality of life in the medium term. There was some limited evidence that oral steroids had an important benefit in terms of persistence of OME in the medium term (when persistence was undefined in the evidence) compared to no treatment, and a possible important benefit in terms of persistence of OME in the very short term. However, where there was evidence of a clinically important effect of oral steroids for any of the outcomes, the evidence was all low or very low quality, or there was uncertainty in the importance of the outcome. The committee agreed the evidence was not strong enough to recommend oral steroids when there was the potential for children to experience systemic corticosteroid side effects, especially in light of the lack of available evidence for this outcome. The committee also discussed the potential harms of using nasal steroids and agreed that, although the risks of side effects was lower than for oral steroids, nasal steroids can be difficult to administer, particularly for very young children or children with learning difficulties or other disabilities. They agreed that using nasal drops or spray could be traumatic for children and ultimately agreed the very low quality evidence showing a potential benefit on hearing or persistence of OME did not outweigh these harms. As a result, the committee recommended that nasal and oral steroids should not be used to treat OME in children.

The committee agreed the evidence base regarding the effectiveness of topical nasal steroids in the management of OME was limited and tended to focus on the outcome persistence of OME. It is therefore not clear if these are effective for improving the hearing of children with OME, and the committee agreed a research recommendation investigating the effectiveness of topical nasal steroids on OME-related hearing loss should be made, as this intervention could be a low-cost, readily accessible management option that might be preferable to other, more invasive interventions such as surgery.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

The committee agreed that the evidence tended to show no important difference in effectiveness of antihistamines, leukotriene receptor antagonists, mucolytics, and decongestants, whether alone or in combination, for most of the outcomes when compared to any of the comparison arms. Where there was evidence of a difference between treatment groups, the evidence was of low or very low quality or there was uncertainty in the importance of the outcome, whereas all the available moderate quality evidence showed no important difference between groups. As a result, the committee agreed that these medications should not be offered to treat OME in children under 12. The committee agreed they could not make recommendations about PPIs or other reflux medicines without any evidence regarding their effectiveness, because PPIs and reflux medicines are not routinely offered to children with OME in current practice, and it is unclear whether they would be effective for treating OME or OME-related hearing loss.

Although the committee agreed antihistamines, leukotriene receptor antagonists, mucolytics, and decongestants should not be offered based on the current evidence, the committee members agreed that further research into the effectiveness of these interventions in children with OME and chronic respiratory conditions is important as there might be benefit for this subgroup, based on the evidence of risk factors and respiratory conditions that are commonly associated with OME, for which these medications might be effective.

Cost effectiveness and resource use

Two included studies (Williamson 2009; Francis 2018) reported on the cost-effectiveness of intranasal and oral steroids respectively. Neither study found steroids to be cost-effective with placebo dominating intervention in the base case utility analyses. Whilst differences in costs and effects were not statistically significant, probabilistic sensitivity analysis suggested that there was only a relatively small probability that giving steroids was cost-effective. Therefore, the committee concluded there was no cost-effectiveness evidence that would support a recommendation to give steroids.

The committee also concluded that it would not be a cost-effective use of NHS resources to recommend other non-antimicrobial pharmacological treatments for OME given the lack of evidence of clinical benefit in the studies reviewed.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.3 and 1.5.4, the research recommendation on the effectiveness of topical nasal steroids on OME and OME-related hearing loss in children under 12 years, and the research recommendation on the effectiveness of antihistamines, leukotriene receptor antagonists, mucolytics, PPIs and decongestants on hearing in children with OME and chronic respiratory conditions.

References – included studies

Effectiveness

Steroids

Mulvaney 2023b

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Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

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Economic

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Appendices

Appendix A Review protocol

Review protocol for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Table 5: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022334031
1.	Review title	Non-antimicrobial pharmacological interventions for children with otitis media with effusion (OME)
2.	Review question	What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?
3.	Objective	To determine the effectiveness of non-antimicrobial pharmacological interventions for managing OME in children under 12 years
4.	Searches	NGA part of the review: The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • International Health Technology Assessment (INAHTA) database • MEDLINE & MEDLINE In-Process • ClinicalTrials.gov, www.clinicaltrials.gov: • search via the Cochrane Register of Studies to date;

ID	Field	Content
		• search via www.clinicaltrials.gov to date; • World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://trialsearch.who.int: • search via the Cochrane Register of Studies to date; • search via https://apps.who.int/trialsearch/ to date. Searches will be restricted by: • Systematic review study filter • RCT study filter • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews • Citation searches of included studies With the agreement of the guideline committee, the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. Steroids/Cochrane part of the review: The Cochrane ENT Information Specialist will conduct systematic searches for published, unpublished, and ongoing randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary. The following databases will be searched from Inception:

ID	Field	Content
		• Cochrane ENT Register (search via the Cochrane Register of Studies to date); • Cochrane Central Register of Controlled Trials (CENTRAL) (search via the Cochrane Register of Studies to date); • Ovid MEDLINI) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDIE(R) Daily and Ovid ILINE(R) (1946 to date); • Ovid EMBASE (1974 to date); • Web of Science, Web of Science (1945 to date); • ClinicalTrials.gov, www.clinicaltrials.gov: • search via the Cochrane Register of Studies to date; • search via www.clinicaltrials.gov to date; • World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://trialsearch.who.int: • search via the Cochrane Register of Studies to date; • search via https://apps.who.int/trialsearch/ to date. The subject strategies for databases will be modelled on the search strategy designed for CENTRAL, Ovid MEDLINE and Ovid Embase. The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for otitis media with effusion. Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the Technical Supplement to Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions version. Limitations: None
5.	Condition or domain being studied	Otits media with effusion
6.	Population	Inclusion: Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME). If a trial includes children aged younger than 6 months and older than 12 years, we will only include the study if the majority of children fit our inclusion criteria or only if the trialists present outcome data by age group.

ID	Field	Content
		Include all children regardless of any comorbidity such as Down syndrome or cleft palate Clinical diagnosis of OME will be confirmed by oto(micro)scopy or tympanometry or both Exclusion: None
7.	Intervention	NGA part of the review: • Antihistamines • Decongestants • Leukotriene receptor antagonists • Mucolytics • PPIs (Proton pump inhibitors) and reflux medicines Steroids/Cochrane part of the review: • Topical (intranasal) steroids • Oral steroids
8.	Comparator	NGA part of the review: • Head-to-head comparisons between all the above intervention categories* (single or in combination, including combinations with steroids) • Placebo • No intervention for treating OME *Please note, we will not include head-to-head comparisons between different interventions within each category (e.g., comparisons between different types of antihistamine), only head to head comparisons of interventions from different categories (e.g., a histamine versus a decongestant) Steroids/Cochrane part of the review: • topical (intranasal) steroids versus placebo • topical (intranasal) steroids versus no topical treatment

ID	Field	Content
		• oral steroids versus placebo • oral steroids versus no oral treatment. If trial participants have received other treatments, for example, antibiotics, mucolytics or decongestants, we will include these studies if both arms of the study received identical treatments.
9.	Types of study to be included	NGA part of the review: Include published full-text papers: • Systematic reviews of RCTs • RCTs with randomisation by participant or by cluster • Quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates, and alphabetical order) • Randomised studies that use a cross-over design (data from the first phase only) Other inclusion criteria: • Language limitations: studies published not in English-language • Conference abstracts will not be considered. Steroids/Cochrane part of the review: • Include published full-text papers: • RCTs with randomisation by participant or by cluster • Quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates, and alphabetical order) • Randomised studies that use a cross-over design (data from the first phase only) There will be no language, publication year or publication status restrictions.
10.	Other exclusion criteria	None

ID	Field	Content
11.	Context	This guidance will fully update the following NICE guideline: Otitis media with effusion in under 12s: surgery (2008; CG60)

12.	Primary outcomes (critical outcomes)	NGA part of the review:
		• Hearing
		  ○ proportion of children whose hearing has returned to normal;
		  ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis);
		  ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis).
		• Presence/persistence of OME
		• Discontinuation of treatment
		• Adverse events: Systemic corticosteroid side-effects
		
		Steroids/Cochrane part of the review:
		We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. We will assess all outcomes in the very short term (< 6 weeks for adverse events), short term (</= 3 months), medium term (> 3 months to </= 1 year) and long term (> 1 year).
		• Hearing
		  ○ proportion of children whose hearing has returned to normal;
		  ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis);
		  ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis).
		• Disease-specific quality of life measured using a validated instrument, for example:
		  ○ OM8-30;
		  ○ Otitis Media-6
		• Adverse events: Systemic corticosteroid side-effects
		• Discontinuation of treatment

ID	Field	Content
13.	Secondary outcomes (important outcomes)	NGA part of the review: Listening skills, for example, listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists. Receptive language skills, measured using a validated scale, for example: o Peabody Picture Vocabulary Test – Revised; o relevant domains of the Reynell Developmental Language Scales; o relevant domains of the Preschool Language Scale (PLS); o relevant domains of the Sequenced Inventory of Communication (SCID). Disease-specific quality of life measured using a validated instrument, for example: o OM8-30; o Otitis Media-6. Steroids/Cochrane part of the review: • Presence/persistence of OME. • Receptive language skills, measured using a validated scale, for example: o Peabody Picture Vocabulary Test – Revised; o relevant domains of the Reynell Developmental Language Scales; o relevant domains of the Preschool Language Scale (PLS); o relevant domains of the Sequenced Inventory of Communication (SCID). • Listening skills, for example, listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists.
14.	Data extraction (selection and coding)	NGA part of the review: All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies

ID	Field	Content
		that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. Steroids/Cochrane part of the review: Two review authors will independently extract outcome data from each study using a standardised data collection form. Where a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors will be checked against the original reports, and differences will be resolved through discussion and consensus, with recourse to a third author where necessary. If required, we will contact the study authors for clarification. We will include key characteristics of the studies, such as the study design, setting, sample size, population and the methods for defining or collecting outcome data in the studies. We will extract data on study findings according to treatment assignment, irrespective of whether study participants complied with treatment or received treatment to which they were randomised. In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract the following summary statistics for each trial and outcome: For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where endpoint data are not available, we will extract the values for change-from-baseline data instead. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. mean difference) from the studies. For binary data: we will extract information on the number of participants experiencing an event, and the number of participants assessed at that time point. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. risk ratio) from the studies.

ID	Field	Content
		For ordinal scale data: we do not anticipate identifying ordinal data which is of relevance for our outcomes. However, if this is identified and if the data appear to be normally distributed, or if the analysis performed by the investigators indicates that parametric tests are appropriate, then we will treat the outcome measure as continuous data. Alternatively, if data are available, we will convert these to binary data for analysis. We have pre-specified time points of interest for the outcomes in this review. Where studies report data at multiple time points, we will take the longest available follow-up point within each of the specific time frames. For example, if a study reports an outcome at 4 months, 8 months and 12 months of follow-up then the 12-month data will be included for the time point > 3 months to </= 1 year. For adverse events, some studies may report frequency data for events, and it may not be possible to determine whether these events occurred in one participant on one occasion or more than one occasion. In such circumstances we will report the data narratively.
15.	Risk of bias (quality) assessment	NGA part of the review: Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool (v.1) for RCTs and quasi-RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer. Steroids/Cochrane part of the review: Two authors will undertake assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011): • sequence generation; • allocation concealment; • blinding of participants and personnel; • blinding of outcome assessment; • incomplete outcome data;

ID	Field	Content
		• selective outcome reporting; • other sources of bias. We will use the Cochrane risk of bias tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of ea'h e'tr': 'l'w', 'high' o' 'unclear' risk of bias.
16.	Strategy for data synthesis	NGA part of the review: Quantitative findings will be formally summarised in the review. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences (MIDs): Validated scales: Published MIDs where available; if not 0.8 and 1.25 for dichotomous outcomes and 0.5 SD of the control group at baseline for continuous outcomes All other outcomes: 0.8 and 1.25 for dichotomous outcomes and 0.5 SD of the control group at baseline for continuous outcomes Steroids/Cochrane part of the review:

ID	Field	Content
		Where two or more studies report the same outcome we will perform a meta-analysis using Review Manager 5 (RevMan 2020). We will report pooled effect measures for dichotomous outcomes as a risk ratio (RR) using the Mantel-Haenszel methods. For continuous outcomes measured using the same scales we will report the mean difference (MD) and if studies have assessed the same outcomes using different scales we will report the standardised mean difference (SMD). We will use a random-effects model. Where it is not possible to pool the findings from studies in a meta-analysis, we will present the results of each study and provide a narrative synthesis of findings. We will use the SWiM guidelines to guide us through this process (Campbell 2020). We will group the studies according to what seem to be appropriate groupings once we have identified included studies that do not provide data suitable for meta-analysis. We will then identify the standardised metric for each outcome and calculate an intervention effect using the appropriate transformation. We will use the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (https://gradepro.org/). This will be done independently by two reviewers. Minimally important differences (MIDs): Validated scales: Published MIDs where available; if not 0.8 and 1.25 for dichotomous outcomes and 0.5 SD of the control group at baseline for continuous outcomes All other outcomes: 0.8 and 1.25 for dichotomous outcomes and 0.5 SD of the control group at baseline for continuous outcomes
17.	Analysis of sub-groups	We propose the following subgroup analyses if sufficient data is available in trial reports: • children with mild hearing loss versus moderate or worse; • children with allergy versus those without (using the'trialists' own definition); • children aged up to four years versus children aged 4 years and over; • children with cleft palate versus children without; • children with Down syndrome versus children without.

ID	Field	Content			
		Unless trials report these subgroups, it will be necessary to carry out the subgroup analysis at the study level, i.e. group the studies according to the characteristics of the majority of their participants.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	29/03/2022			
22.	Anticipated completion date	02/12/2022			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐ ☐	☑ ☑
		Piloting of the study selection process		☐ ☐	☑ ☑
		Formal screening of search results against eligibility criteria		☐ ☐	☑ ☑
		Data extraction		☐ ☐	☑ ☑
		Risk of bias (quality) assessment		☐ ☐	☑ ☑
		Data analysis		☐ ☐	☑ ☑
24.	Named contact	Named contact: National Guideline Alliance			

ID	Field	Content
		Named contact e-mail: otitis@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
25.	Review team members	National Guideline Alliance and Cochrane ENT Group
26.	Funding sources/sponsor	The National Guideline Alliance receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line'with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes t' a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10193
29.	Other registration details	Cochrane Library
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022334031
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline th'ough NICE's newsletter and alerts

ID	Field	Content	
		issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Otitis media with effusion, glue ear, antibiotics, hearing loss	
33.	Details of existing review of same topic by same authors	Not applicable	
34.	Current review status	☒	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

ENT: ears, nose and throat; MID: Minimally important difference; NGA: National Guideline Alliance; NICE: National Institute of Health and Care Excellence; OME: otitis media with effusion; RCT: randomised controlled trial; SD: standard deviation

See also the Cochrane review protocol on steroids, Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Steroids

See Appendix 1 and Appendix 2 of the Cochrane review on steroids, Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Database: MEDLINE – OVID interface

Date last searched: 21/07/2022

?	Searches
1	otitis media with effusion/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	exp Histamine Antagonists/
5	(antihistam* or (anti adj histam*) or H1RA? or H2RA? or ((H1 or H2 or histamin*) adj3 (agent* or agonist* or antagonist* or blocker* or inhibitor*))).ti,ab,kf.
6	(acrivastine* or alimemazine* or azelastine* or bilastine* or brompheniramine* or cetirizine* or chlorphenamine* or chlorpheniramine* or clemastine* or cyclizine* or cyproheptadine* or desloratadine* or dimetindene* or diphenh?dramine* or doxylamine* or ebastine or fexofenadine* or hydroxyzine* or ketotifen* or levocetirizine* or loratadine* or mizolastine* or olopatadine* or oxatomide* or promethazine* or rupatadine* or terfenadrine* or triprolidine*).ti,ab,kf.
7	exp Vasoconstrictor Agents/
8	((vasoconstrictor and agent*) or decongest*).ti,ab,kf.
9	(desoxephedrine* or ephedrine* or fenoxazoline* or metizoline* or methoxamine* or midrodrine* or mephentermine* or naphazoline* or oxymetazoline* or phenylephrine* or phenylpropanolamine* or pseudoephedrine* or propylhexedrine* or saline or sodium chloride or tramazoline* or tetrahydrozoline* or xylometazoline*).ti,ab,kf.
10	Leukotriene Antagonists/
11	(antileu?otriene* or leu?otriene* or montelukast* or pranlukast* or zafirlukast* or zileuton or LTRA?).ti,ab,kf.
12	exp Expectorants/
13	(expectorant? or mucoactive or (mucociliary adj clear*) or mucolytic? or mucokinetic? or mucoregulator? or thiol?).ti,ab,kf.
14	(acetylc?steine* or ambroxol or bromhexine* or carboc?steine* or carboxymethylc?steine* or cineole or dornase alfa or erdosteine* or eucalyptus or gelsolin* or glyceryl guaiacolate or guaifenesin* or human DNase or iodinated glycerol or isobutyrylc?steine* or mannitol or mesna* or methyl?steine* or myrtol or nacetylc?steine* or NAC or neltenexine* or recombinant human deoxyribonuclease or RhDNase or scarboxymethylc?steine* or sobrerol or strepronin*).ti,ab,kf.
15	exp Proton Pump Inhibitors/
16	(proton pump inhibitor* or PPI?).ti,ab,kf.
17	(dexlansoprazole or esomeprazole or lansoprazole or omeprazole or pantoprazole or rabeprazole).ti,ab,kf.
18	or/4-17
19	3 and 18
20	letter/ or editorial/ or news/ or exp historical article/ or Anecdotes as Topic/ or comment/ or case report/ or (letter or comment*).ti.
21	randomized controlled trial/ or random*.ti,ab.
22	20 not 21
23	(animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
24	22 or 23
25	19 not 24
26	limit 25 to english language
27	meta-analysis/ or meta-analysis as topic/ or "systematic review"/
28	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab.
29	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
30	(search strategy or search criteria or systematic search or study selection or data extraction or (search* adj4 literature)).ab.
31	(MEDLINE or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
32	cochrane.jw.

?	Searches
33	or/27-32
34	26 and 33
35	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
36	drug therapy.fs.
37	(groups or placebo or randomi?ed or randomly or trial).ab.
38	Clinical Trials as Topic/
39	trial.ti.
40	or/35-39
41	26 and 40
42	34 or 41

Database: Embase – OVID interface

Date last searched: 21/07/2022

?	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	exp antihistaminic agent/
5	(antihistam* or (anti adj histam*) or H1RA? or H2RA? or ((H1 or H2 or histamin*) adj3 (agent* or agonist* or antagonist* or blocker* or inhibitor*))).ti,ab,kf.
6	(acrivastine* or alimemazine* or azelastine* or bilastine* or brompheniramine* or cetirizine* or chlorphenamine* or chlorpheniramine* or clemastine* or cyclizine* or cyproheptadine* or desloratadine* or dimetindene* or diphenh?dramine* or doxylamine* or ebastine or fexofenadine* or hydroxyzine* or ketotifen* or levocetirizine* or loratadine* or mizolastine* or olopatadine* or oxatomide* or promethazine* or rupatadine* or terfenadrine* or triprolidine*).ti,ab,kf.
7	exp vasoconstrictor agent/
8	((vasoconstrictor and agent*) or decongest*).ti,ab,kf.
9	(desoxephedrine* or ephedrine* or fenoxazoline* or metizoline* or methoxamine* or midrodrine* or mephentermine* or naphazoline* or oxymetazoline* or phenylephrine* or phenylpropanolamine* or pseudoephedrine* or propylhexedrine* or saline or sodium chloride or tramazoline* or tetrahydrozoline* or xylometazoline*).ti,ab,kf.
10	exp leukotriene receptor blocking agent/
11	(antileu?otriene* or leu?otriene* or montelukast* or pranlukast* or zafirlukast* or zileuton or LTRA?).ti,ab,kf.
12	exp expectorant agent/ or exp mucolytic agent/
13	(expectorant? or mucoactive or (mucociliary adj clear*) or mucolytic? or mucokinetic? or mucoregulator? or thiol?).ti,ab,kf.
14	(acetylc?steine* or ambroxol or bromhexine* or carboc?steine* or carboxymethylc?steine* or cineole or dornase alfa or erdosteine* or eucalyptus or gelsolin* or glyceryl guaiacolate or guaifenesin* or human DNase or iodinated glycerol or isobutyrylc?steine* or mannitol or mesna* or methyl?steine* or myrtol or nacetylc?steine* or NAC or neltenexine* or recombinant human deoxyribonuclease or RhDNase or scarboxymethylc?steine* or sobrerol or strepronin*).ti,ab,kf.
15	exp proton pump inhibitor/
16	(proton pump inhibitor* or PPI?).ti,ab,kf.
17	(dexlansoprazole or esomeprazole or lansoprazole or omeprazole or pantoprazole or rabeprazole).ti,ab,kf.
18	or/4-17
19	3 and 18
20	letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.
21	randomized controlled trial/ or random*.ti,ab.
22	20 not 21
23	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
24	22 or 23
25	19 not 24
26	limit 25 to english language
27	systematic review/ or meta-analysis/
28	(meta analy* or metanaly* or metaanaly* or ((evidence or systematic*) adj2 (overview* or review*))).ti,ab.
29	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
30	(search strategy or search criteria or systematic search or study selection or data extraction or (search* adj4 literature)).ab.
31	(MEDLINE or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
32	cochrane.jw.
33	or/27-32
34	26 and 33
35	(random* or factorial* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or assign* or allocat* or volunteer* or placebo*).ti,ab.
36	crossover procedure/ or single blind procedure/ or randomized controlled trial/ or double blind procedure/
37	35 or 36
38	26 and 37
39	34 or 38

Database: Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface

Date last searched: 21/07/2022

ID	Search
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serous) near/2 "otitis media")):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Histamine Antagonists] explode all trees
#5	(antihistam* or (anti near/1 histam*) or H1RA* or H2RA* or ((H1 or H2 or histamin*) near/3 (agent* or agonist* or antagonist* or blocker* or inhibitor*))):ti,ab,kw
#6	(acrivastine* or alimemazine* or azelastine* or bilastine* or brompheniramine* or cetirizine* or chlorphenamine* or chlorpheniramine* or clemastine* or cyclizine* or cyproheptadine* or desloratadine* or dimetindene* or diphenh?dramine* or doxylamine* or ebastine or fexofenadine* or hydroxyzine* or ketotifen* or levocetirizine* or loratadine* or mizolastine* or olopatadine* or oxatomide* or promethazine* or rupatadine* or terfenadrine* or triprolidine*):ti,ab,kw
#7	MeSH descriptor: [Vasoconstrictor Agents] explode all trees
#8	((vasoconstrictor and agent*) or decongest*):ti,ab,kw
#9	(desoxephedrine* or ephedrine* or fenoxazoline* or mephentermine* or metizoline* or methoxamine* or midrodrine* or naphazoline* or oxymetazoline* or phenylephrine* or phenylpropanolamine* or pseudoephedrine* or propylhexedrine* or saline or "sodium chloride" or tramazoline* or tetrahydrozoline* or xylometazoline*):ti,ab,kw
#10	MeSH descriptor: [Leukotriene Antagonists] this term only
#11	(antileu?otriene* or leu?otriene* or montelukast* or pranlukast* or zafirlukast* or zileuton or LTRA?):ti,ab,kw
#12	MeSH descriptor: [Expectorants] explode all trees
#13	(expectorant? or mucoactive or (mucociliary adj clear*) or mucolytic? or mucokinetic? or mucoregulator? or thiol?):ti,ab,kw
#14	(acetylc?steine* or ambroxol or bromhexine* or carboc?steine* or carboxymethylc?steine* or cineole or "dornase alfa" or erdosteine* or eucalyptus or gelsolin* or "glyceryl guaiacolate" or guaifenesin* or "human DNase" or "iodinated glycerol" or isobutyrylc?steine* or mannitol or mesna* or methyl?steine* or myrtol or nacetylc?steine* or NAC or neltenexine* or "recombinant human deoxyribonuclease" or RhDNase or scarboxymethylc?steine* or sobrerol or strepronin*):ti,ab,kw
#15	MeSH descriptor: [Proton Pump Inhibitors] this term only
#16	("proton pump inhibitor*" or PPI?):ti,ab,kw
#17	(dexlansoprazole or esomeprazole or lansoprazole or omeprazole or pantoprazole or rabeprazole):ti,ab,kw
#18	{or #4-#17}
#19	#3 and #18
#20	"conference":pt or (clinicaltrials or trialsearch):so
#21	#19 not #20

Database: Epistemonikos

Date last searched: 20/07/2022

#	Searches
1	(title:(("glue ear" OR (("middle ear" OR "otitis media") AND effusion*) OR ome OR ((secretory OR serous) AND "otitis media"))) OR abstract:(("glue ear" OR (("middle ear" OR "otitis media") AND effusion*) OR ome OR ((secretory OR serous) AND "otitis media")))
2	(title:((antihistamin* OR histamin* OR H1RA* OR H2RA* OR acrivastine* OR alimemazine* OR azelastine* OR bilastine* OR brompheniramine* OR cetirizine* OR chlorphenamine* OR chlorpheniramine* OR clemastine* OR cyclizine* OR cyproheptadine* OR desloratadine* OR dimetindene* OR diphenhydramine* OR diphenhydramine* OR doxylamine* OR ebastine OR fexofenadine* OR H2RA OR hydroxyzine* OR ketotifen* OR levocetirizine* OR loratadine* OR mizolastine* OR olopatadine* OR oxatomide* OR promethazine* OR rupatadine* OR terfenadrine* OR triprolidine*)) OR abstract:((antihistamin* OR histamin* OR acrivastine* OR alimemazine* OR azelastine* OR bilastine* OR brompheniramine* OR cetirizine* OR chlorphenamine* OR chlorpheniramine* OR clemastine* OR cyclizine* OR cyproheptadine* OR desloratadine* OR dimetindene* OR diphenhydramine* OR doxylamine* OR ebastine OR fexofenadine* OR hydroxyzine* OR ketotifen* OR levocetirizine* OR loratadine* OR mizolastine* OR olopatadine* OR oxatomide* OR promethazine* OR rupatadine* OR terfenadrine* OR triprolidine*))
3	(title:(vasoconstrictor OR decongest* OR desoxephedrine* OR ephedrine* OR fenoxazoline* OR mephentermine* OR metizoline* OR methoxamine* OR midrodrine* OR naphazoline* OR oxymetazoline* OR phenylephrine* OR phenylpropanolamine* OR pseudoephedrine* OR propylhexedrine* OR saline OR "sodium chloride" OR tramazoline* OR tetrahydrozoline* OR xylometazoline*) OR abstract:(vasoconstrictor OR decongest* OR desoxephedrine* OR ephedrine* OR fenoxazoline* OR mephentermine* OR metizoline* OR methoxamine* OR midrodrine* OR naphazoline* OR oxymetazoline* OR phenylephrine* OR phenylpropanolamine* OR pseudoephedrine* OR propylhexedrine* OR saline OR "sodium chloride" OR tramazoline* OR tetrahydrozoline* OR xylometazoline*))
4	(title:((antileukotriene* OR antileukotriene* OR leukotriene* OR leukotriene* OR montelukast* OR pranlukast* OR zafirlukast* OR zileuton OR LTRA*) OR abstract:((antileukotriene* OR antileukotriene* OR leukotriene* OR leukotriene* OR montelukast* OR pranlukast* OR zafirlukast* OR zileuton OR LTRA*))
5	(title:((expectorant* OR mucoactive OR (mucociliary AND clear*) OR mucolytic* OR mucokinetic* OR mucoregulator* OR thiol* OR acetylcysteine* OR acetylcysteine* OR ambroxol OR bromhexine* OR carbocysteine* OR carbocisteine* OR carboxymethylcysteine* OR carboxymethylcisteine* OR cineole OR “dornase alfa” OR

#	Searches
	erdosteine OR eucalyptus or gelsolin* OR "glyceryl guaiacolate" OR guaifenesin* OR "human DNase" OR "iodinated glycerol" OR isobutyrylcysteine* OR isobutyrylc?steine* OR mannitol OR mesna* OR methylcysteine* OR myrtol OR nacetylcysteine* OR nacetylcisteine* OR NAC OR neltenexine* OR "recombinant human deoxyribonuclease" OR RhDNase OR scarboxymethylcysteine* OR scarboxymethylcisteine* OR sobrerol OR strepronin*) OR abstract:((expectorant* OR mucoactive OR (mucociliary AND clear*) OR mucolytic* OR mucokinetic* OR mucoregulator* OR thiol* OR acetylcysteine* OR acetylcisteine* OR ambroxol OR bromhexine* OR carbocysteine* OR carbocisteine* OR carboxymethylcysteine* OR carboxymethylcisteine* OR cineole OR “dornase alfa” OR erdosteine* OR eucalyptus or gelsolin* OR "glyceryl guaiacolate" OR guaifenesin* OR "human DNase" OR "iodinated glycerol" OR isobutyrylcysteine* OR isobutyrylcisteine* mannitol OR mesna* OR methylcysteine* OR methylcisteine* OR myrtol OR nacetylcysteine* OR nacetylcisteine* OR NAC OR neltenexine* OR "recombinant human deoxyribonuclease" OR RhDNase OR scarboxymethylcysteine* OR scarboxymethycisteine* OR sobrerol OR strepronin*))
6	(title:(("proton pump inhibitor" OR "proton pump inhibitors" OR PPI* OR dexlansoprazole OR esomeprazole OR lansoprazole OR omeprazole OR pantoprazole OR rabeprazole) OR abstract:(("proton pump inhibitor*" OR "proton pump inhibitors" OR PPI* OR dexlansoprazole OR esomeprazole OR lansoprazole OR omeprazole OR pantoprazole OR rabeprazole))
7	2 OR 3 OR 4 OR 5 OR 6
8	1 AND 7

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

Date last searched: 20/07/2022

#	Searches
1	"Otitis Media with Effusion"[mhe]
2	((“glue ear” or ((“middle ear” or “otitis media”) and effusion*) or ome or ((secretory or serous) and “otitis media”))
3	1 OR 2
15	3 AND (English)[Language]

Economic literature search strategy

A global, population-based search was undertaken to find economic evidence covering all parts of the guideline.

Database: MEDLINE – OVID interface

Date last searched: 09/11/2022

#	Searches
1	otitis media with effusion/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	Economics/
5	Value of life/
6	exp "Costs and Cost Analysis"/
7	exp Economics, Hospital/
8	exp Economics, Medical/
9	Economics, Nursing/
10	Economics, Pharmaceutical/
11	exp "Fees and Charges"/
12	exp Budgets/
13	budget*.ti,ab.
14	cost*.ti.
15	(economic* or pharmaco?economic*).ti.
16	(price* or pricing*).ti,ab.
17	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
18	(financ* or fee or fees).ti,ab.
19	(value adj2 (money or monetary)).ti,ab.
20	or/4-19
21	exp models, economic/
22	*Models, Theoretical/
23	*Models, Organizational/
24	markov chains/
25	monte carlo method/
26	exp Decision Theory/
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.

#	Searches
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/21-29
31	20 or 30
32	3 and 31
33	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Embase – OVID interface

Date last searched: 09/11/2022

#	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	health economics/
5	exp economic evaluation/
6	exp health care cost/
7	exp fee/
8	budget/
9	funding/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/4-16
18	statistical model/
19	exp economic aspect/
20	18 and 19
21	*theoretical model/
22	*nonbiological model/
23	stochastic model/
24	decision theory/
25	decision tree/
26	monte carlo method/
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/20-29
31	17 or 30
32	3 and 31
33	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface

Date last searched: 09/11/2022

ID	Search
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	(("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serious) near/2 "otitis media"))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Economics] this term only
#5	MeSH descriptor: [Value of Life] this term only
#6	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#7	MeSH descriptor: [Economics, Hospital] explode all trees
#8	MeSH descriptor: [Economics, Medical] explode all trees
#9	MeSH descriptor: [Economics, Nursing] this term only
#10	MeSH descriptor: [Economics, Pharmaceutical] this term only
#11	MeSH descriptor: [Fees and Charges] explode all trees

ID	Search
#12	MeSH descriptor: [Budgets] explode all trees
#13	budget*:ti,ab
#14	cost*:ti
#15	(economic* or pharmaco?economic*):ti
#16	(price* or pricing*):ti,ab
#17	(cost* near/2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)):ab
#18	(financ* or fee or fees):ti,ab
#19	(value near/2 (money or monetary)):ti,ab
#20	{or #4-#19}
#21	MeSH descriptor: [Models, Economic] explode all trees
#22	MeSH descriptor: [Models, Theoretical] this term only
#23	MeSH descriptor: [Models, Organizational] this term only
#24	MeSH descriptor: [Markov Chains] this term only
#25	MeSH descriptor: [Monte Carlo Method] this term only
#26	MeSH descriptor: [Decision Theory] explode all trees
#27	(markov* or "monte carlo"):ti,ab
#28	(econom* next model*):ti,ab
#29	(decision* near/2 (tree* or analy* or model*)):ti,ab
#30	{or #21-#29}
#31	#20 or #30
#32	#3 and #31 with Cochrane Library publication date Between Jan 2000 and Apr 2022

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

Date last searched: 09/11/2022

#	Searches
1	((("Otitis Media with Effusion"[mhe]) OR ((("glue ear" or (("middle ear" or "otitis media") and effusion*) or ome or ((secretory or serous) and "otitis media")))
2	1 and FROM 2000 TO 2022 AND (English)[Language]

Database: NHS Economic Evaluation Database (NHS EED) – CRD interface

Date last searched: 09/11/2022

Line	Search for
1	MeSH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL TREES
2	((glue ear or ((middle ear or otitis media) and effusion*) or ome or ((secretory or serous) and otitis media))) IN NHS EED
3	#1 OR #2

Appendix C Effectiveness evidence study selection

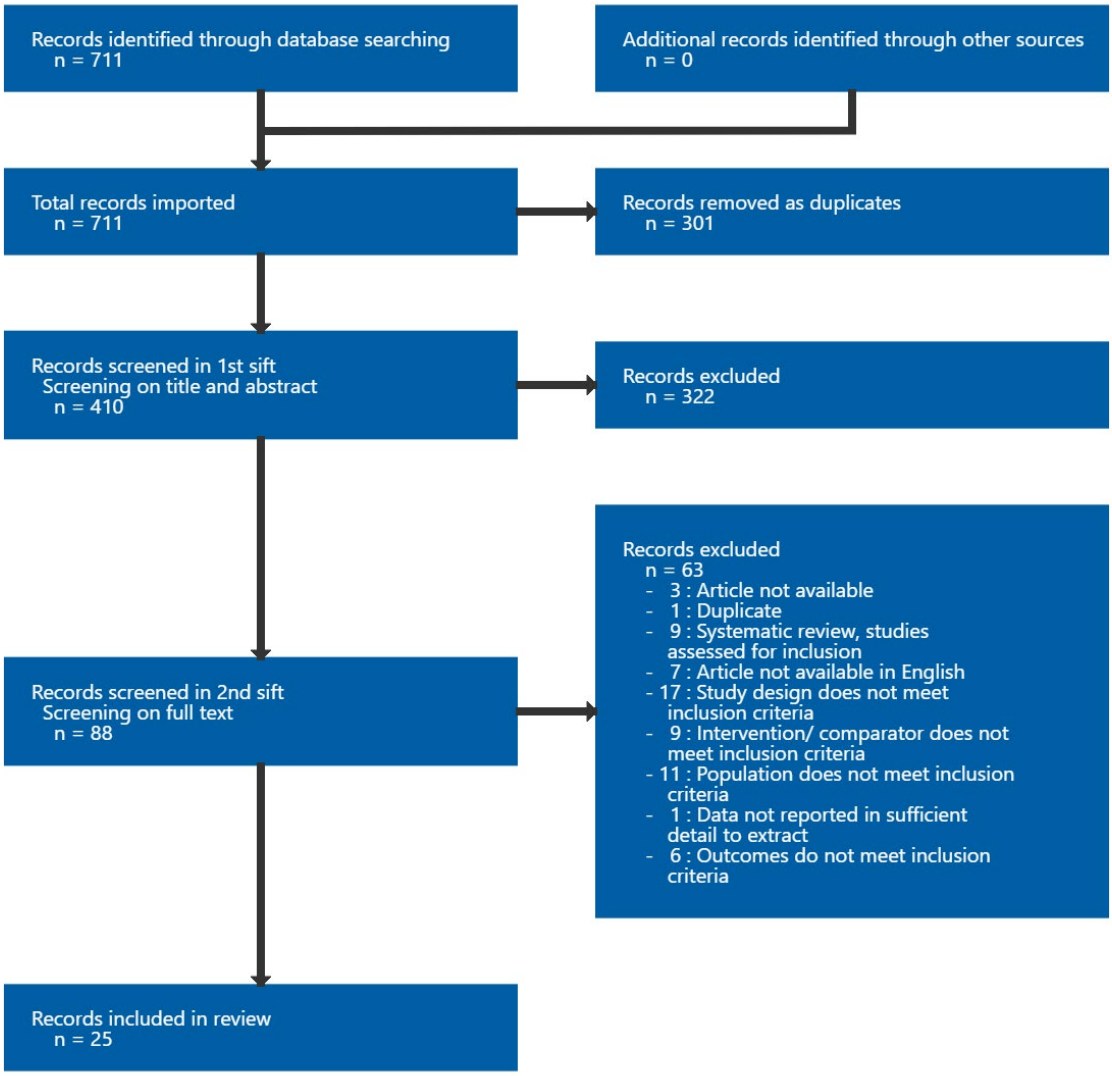
Study selection for: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Steroids

See Results of the search – figure 1 from the Cochrane review on steroids, Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Steroids

See the Characteristics of included studies tables from the Cochrane review on steroids, Mulvaney 2023b at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Table 6: Evidence tables (antihistamines, leukotriene receptor antagonists, mucolytics and decongestants)

Babic, 2017

Bibliographic Reference	Babic, Irena; Baudoin, Tomislav; Trotic, Robert; Bedekovic, Vladimir; Therapeutic efficacy of azithromycin and acetylcysteine in chronic otitis media with effusion.; European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery; 2017; vol. 274 (no. 3); 1351-1356

Study details

Country/ies where study was carried out	Croatia
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children diagnosed with bilateral chronic OME
Exclusion criteria	• Proven allergy • Respiratory infections in the last 3 months • Otitis media in the last 3 months (type of OM not reported) • Congenital malformations

	• History of operative procedure (including tonsillectomy, adenotomy, and VT insertion)
Patient characteristics	N=90 children (N=180 ears): • Mean age (range): 49.5 (24-72) months • Gender (male:female): 51:39 Patient characteristics not reported separately for each group.
Intervention(s)/control	Mucolytic and antibiotic: • Acetylcysteine (AC; 100mg 3 times daily, for 3 weeks) and azithromycin (AZ; dosing based on the child's weight, for 3 days) Antibiotic only: • AZ; dosing based on the child's weight, for 3 days An additional group received mucolytic only, but data from this group were not extracted for the purposes of this review as it had no direct head-to-head comparison.
Duration of follow-up	1 month. No comparative data reported for follow-up at 2 months
Sources of funding	Not reported
Sample size	N=90 children (N=180 ears) AC+AZ group: n=30 children (n=60 ears) AZ only group: n=30 children (n=60 ears)
Other information	OME diagnosed based on heterohistory data reported by parents, pneumatooscopy, endoscopic ear examination, and tympanometry (type B bilaterally)

Study arms

AC + AZ group (N = 60)
n=number of ears. Number of children=30

AZ only group (N = 60)
n=number of ears. Number of children=30

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	AC + AZ group, 1 month, N=60	AZ only group, 1 month, N=60
Presence/Persistence of OME* Reported as number of ears with type B tympanogram No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 23 ; % = 39	n = 28 ; % = 47

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Method of randomisation and allocation concealment not reported. Insufficient reporting of participant characteristics to determine baseline differences)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Not enough information provided to determine deviations from the intended intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Objective measurement used to classify tympanograms-pressure thresholds)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(No specified protocol available to assess selective reporting. Presence/ persistence of OME not reported separately for each group at 2 months follow-up, and reason for this not given)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to selective reporting, and lack of information about the randomisation process, allocation concealment, patient characteristics, blinding, and analysis.*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Balatsouras, 2005

Bibliographic Reference	Balatsouras, D G; Eliopoulos, P; Rallis, E; Sterpi, P; Korres, S; Ferekidis, E; Improvement of otitis media with effusion after treatment of asthma with leukotriene antagonists in children with co-existing disease.; Drugs under experimental and clinical research; 2005; vol. 31suppl; 7-10

Study details

Country/ies where study was carried out	Greece
Study type	Randomised controlled trial (RCT)
Study dates	September 2002 - December 2003
Inclusion criteria	Children aged 6 to 13 years with a diagnosis of bilateral OME and asthma
Exclusion criteria	• Children with previous history of AOM 6 months before examination, or OME that had not resolved for ≥1 year prior to examination • Children aged <6 years

Patient characteristics	N=50: • Mean age (SD): 10.4 (2.1) years • Gender (male:female): not reported Patient characteristics not reported separately for each group.
Intervention(s)/control	Leukotriene receptor antagonist and inhalers: • Montelukast (5mg chewable tablet) taken once a day between meals for 30 days) • Budesonide and terbutaline inhalers. Treatment regimen/ dosages not reported Inhalers only: • Budesonide and terbutaline inhalers. Treatment regimen/ dosages not reported
Duration of follow-up	30 days
Sources of funding	Not reported
Sample size	N= 50: Inhalers and leukotriene receptor antagonist: n=25 children Inhalers only: n=25 children
Other information	OME was diagnosed using pneumatic otoscopy, tympanometry and pure-tone audiometry. Children were considered free of OME when both ears appeared normal on examination with pneumatic otoscopy, mean pure-tone thresholds <20dBHL across all examined frequencies (0.25, 0.2, 1, 2, 3, 4, and 8 kHz) were obtained in pure-tone audiometry, and normal tympanometric findings were observed in both ears.

Study arms

Inhalers and leukotriene receptor antagonist (N = 25)
n=number of children

Inhalers only (N = 25)
n=number of children

Outcomes

Outcomes for children with otitis media with effusion

Outcome	Inhalers and leukotriene receptor antagonist, 30 days, N = 25	Inhalers only, 30 days, N = 25
Presence/ persistence OME Reported per child. Reported as number of children free of OME (see Other information), number of participants remaining extracted here No of events	n = 10 ; % = 60	n = 16 ; % = 36

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information regarding randomisation and allocation concealment. Insufficient information to determine differences in participant characteristics at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Unclear if outcome assessors were blinded to the intervention. Outcome assessed using pure-tone audiometry with standard thresholds.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Protocol was unavailable. No evidence of selective reporting)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding lack of information on randomisation process, allocation concealment, patient characteristics, and blinding)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Cantekin, 1983

Bibliographic Reference	Cantekin, E I; Mandel, E M; Bluestone, C D; Rockette, H E; Paradise, J L; Stool, S E; Fria, T J; Rogers, K D; Lack of efficacy of a decongestant-antihistamine combination for otitis media with effusion ("secretory" otitis media) in children. Results of a double-blind, randomized trial.; The New England journal of medicine; 1983; vol. 308 (no. 6); 297-301

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	July 1978 - June 1981
Inclusion criteria	Children aged between 7 months and 12 years who had unilateral or bilateral OME
Exclusion criteria	• Congenital craniofacial malformations • Down syndrome • Systemic illness such as asthma, cystic fibrosis, or diabetes mellitus • History of tonsillectomy, adenoidectomy, or tympanostomy-tube insertion • Structural middle-ear abnormality such as tympanic-membrane perforation or adhesive otitis media • Sensorineural hearing loss or a conductive loss not attributable to the middle-ear effusion • Severe upper-airway obstruction • Acute suppurative otitis media • Purulent rhinitis • Acute or chronic sinusitis • History of having received sympathomimetic amines or antihistamines during the preceding 30 days

Patient characteristics	N=553 children (611 initially enrolled but 58 children not evaluated at 4 weeks excluded from analysis)
	
	• Laterality of OME:
	  ○ Bilateral: 393/553 (71%)
	  ○ Unilateral: 160/553 (29%)**
	
	Decongestant + antihistamine group (n=278):
	
	• Mean age (SD): Not reported.
	  ○ 7-23 months: 79/278 (28%)
	  ○ 2-5 years: 136/278 (49%)
	  ○ 6-12 years: 63/278 (23%)
	• Sex (male:female)*: 59%:41%
	• Allergy diagnosed*:
	  ○ Yes: 5%
	  ○ No: 94%
	  ○ Not recorded: 1%
	
	Placebo group (n=275):
	
	• Mean age (SD): Not reported.
	  ○ 7-23 months: 81/275 (29%)
	  ○ 2-5 years: 132/275 (48%)
	  ○ 6-12 years: 62/275 (23%)
	• Sex (male:female)*: 62%:38%
	• Allergy diagnosed*:
	  ○ Yes: 5%
	  ○ No: 94%
	  ○ Not recorded: 1%
	
	*Numbers of participants not reported for these characteristics

	**In 10/160 subjects in this group, one ear could not be examined satisfactorily
Intervention(s)/control	Decongestant + antihistamine: • Liquid preparation (Novafed A syrup) of pseudoephedrine hydrochloride (dosage 1.0mg/ kg of body weight) and chlorpheniramine maleate (dosage 0.09mg/ kg of body weight) administered 4 times daily for 4 weeks Placebo: • 4 weeks of placebo identical in appearance and similar in taste to the active medication, containing the same inert ingredients (Merrell-Dow) Children in both groups received a standardised antimicrobial regimen if they had an episode of acute suppurative otitis media or acute purulent rhinitis during follow-up
Duration of follow-up	4 weeks; 8 weeks (for outcome recurrence of OME; for participants without MEE by 4-week follow-up only)
Sources of funding	Not industry funded
Sample size	N=611 children initially included, results only reported for 553 children who were evaluated at 4 weeks
Other information	OME diagnosed based on a decision-tree algorithm which combined independent findings obtained by a "validated" otoscopist with results of tympanometry and middle-ear muscle-reflex testing. A standardised history and findings of an ENT examination (including pneumatic otoscopy) were also recorded for each child 8-week data were not included in the analysis to avoid including data from the same study twice within the short-term outcome period. Data from 4-week follow-up period were selected due to similarity with follow-up periods reported by other studies contributing to the analysis

Study arms

Decongestant + antihistamine (N = 278)
n=number of children

Placebo (N = 275)
n=number of children

Outcomes

Study timepoints

- 4 week
- 8 week

Outcomes

Outcome	Decongestant + antihistamine, 4 week, N = 278	Decongestant + antihistamine, 8 week, N = 47	Placebo, 4 week, N = 275	Placebo, 8 week, N = 47
Presence/ persistence of OME* Reported as status of effusion (none, unilateral, or bilateral) per child, extracted here as total number of children with unilateral or bilateral OME at follow-up. Note at 8 weeks results only reported for 94 of the 134 children who did not have OME at 4 weeks (recurrence of OME) No of events *8-week data not included in the analysis (see Other information)	n = 210	n = 20	n = 209	n = 12

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Some concerns due to lack of information reported about allocation sequence and concealment. No excessive differences between groups; similarities between groups due to stratification according to age, duration of OME, and whether antimicrobial drugs had been administered for OME during the preceding 60 days (24 subgroups). Within each stratification, participants were randomised in blocks of two to active drug or placebo)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended	Low *(Double-blind trial using placebo.)*

Section	Question	Answer
interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some concerns due to missing outcome data: 58/611 participants (9%) initially enrolled but lost to follow-up; it is not reported which groups these participants belonged to but likely to be even between groups as participants were randomised in blocks of 2 and numbers in each group at 4-week follow-up are even. Reasons for loss to follow-up not reported but the number of events is much greater than the number of participants lost to follow-up at 4 weeks, so result not likely to be biased by missing outcome data. For results at 8 weeks, 40 of the 134 children (30%) who did not have OME at 4-week follow-up were not re-examined at 8 weeks. Reasons are not given, and it is unclear how this would affect the outcomes at 8 weeks)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(OME diagnosed using tympanometry. Authors note outcome assessors blinded to intervention received, though further information about blinding not reported)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Minor concerns regarding lack of pre-specified analysis plan)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some minor concerns due to missing outcome data, and a lack of information regarding randomisation process and allocation concealment.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Choung, 2008

Bibliographic Reference	Choung, Yun-Hoon; Shin, You Ree; Choi, Seong Jun; Park, Keehyun; Park, Hun Yi; Lee, Jong Bin; Han, Dong Hee; Kahng, Hison; Management for the children with otitis media with effusion in the tertiary hospital.; Clinical and experimental otorhinolaryngology; 2008; vol. 1 (no. 4); 201-5

Study details

Country/ies where study was carried out	Korea
Study type	Randomised controlled trial (RCT)
Study dates	June 2003 - March 2005
Inclusion criteria	Children with OME in the tertiary Ajou University Hospital (Suwon, Korea) during the study dates
Exclusion criteria	• AOM and fever or otalgia • Cleft palate • Developmental difficulties • Contraindications to study medications

Patient characteristics	N=84 (100 originally enrolled but 16 children lost to follow-up excluded from analysis):
	
	• Mean age (range): 69 months (5 months - 12 years)
	• Sex (male:female): 57:27
	• Hearing thresholds (pure tone average):
	  ○ Mean air conduction threshold (SD):
	  ▪ Right: 26.1 (11.3) dB
	  ▪ Left: 26.4 (11.0) dB
	  ○ Mean air-bone gap (SD):
	  ▪ Right: 22.1 (13.6) dB
	  ▪ Left: 23.8 (12.1) dB
	• Children with allergic symptoms (including itching, sneezing, nasal obstruction, or watery rhinorrhea): 34/84 (41%)
	• Children with positive allergic skin-prick tests*: 17/40 (48%)
	
	Participant characteristics not reported separately for each group.
	
	*40/84 (47.6%) children who were suspected of having allergies underwent allergic skin tests

Intervention(s)/control	Antihistamine and antibiotic: • Ebastine (0.2 cc/kg, Ebastel) • Amoxicillin-clavulanate syrup (1 cc/kg, Augmex Duo syrup)

	• Treatments taken for 2 weeks. Treatment regimens not reported. Antibiotic: • Amoxicillin-clavulanate syrup (1 cc/kg, Augmex Duo syrup) for 2 weeks. • Treatment regimen not reported. Three additional groups received the following: antibiotic and steroid; antibiotic, steroid, and antihistamine; mucolytic. Data from the first 2 groups were not of interest for this review, data from the mucolytic group could not be extracted because this group had no direct head-to-head comparison.
Duration of follow-up	3 months
Sources of funding	Not reported
Sample size	N=84 (100 originally enrolled but 16 children lost to follow-up excluded from analysis) Antibiotic group: n=16 Antibiotic and antihistamine group: n=15
Other information	OME diagnosed using pneumatic otoscopy, tympanography (type B or C tympanograms), and pure tone audiometry (hearing loss >25 dB)

Study arms

Antihistamine and antibiotic (N = 15)
n=number of children

Antibiotic (N = 16)
n=number of children

Outcomes

Study timepoints
- 3 month

Outcomes

Outcome	Antihistamine and antibiotic, 3 month, N = 15	Antibiotic, 3 month, N = 16
Presence/ persistence of OME Reported per child. Reported in study as number of children with unilateral or bilateral OME requiring observation/ VT insertion No of events	n = 9 ; % = 60	n = 8 ; % = 50

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Information about method of randomisation and allocation concealment not reported. Insufficient reporting of participant characteristics to determine baseline differences)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information reported on blinding of either participants or outcome assessors, or on deviations from the intended intervention. Children and their parents/ carers likely to have been aware of intervention assignment as authors do not report the use of placebo in children not receiving 2 medications, and there is no information about concealing medication. However, this is unlikely to have affected outcomes due to use of validated instruments to assess presence/ persistence of OME. No information reported on deviations from intended interventions.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(16/100 participants (16%) initially enrolled lost to follow-up; it is not reported which groups these participants were assigned to. Reasons for loss to follow-up not reported; although the number of events is greater than the number of participants lost to follow-up, it is possible that missingness in the outcome*

		depended on its true outcome due to low number of included participants and relatively high drop-out rate)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(All patients were diagnosed by one experienced otologist, using tympanometry. No information about blinding of outcome assessors, but assessment of outcome unlikely to have been influenced by knowledge of intervention received due to robustness of diagnostic methods using validated instruments (pneumatic otoscopy, tympanography (B or C type), and pure tone audiography (hearing loss >25 dB)))*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Minor concerns regarding lack of pre-specified analysis plan)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to lack of information about blinding suggesting participants likely knew which intervention they were receiving, and high rate of loss to follow-up with no reasons given. Missingness in the outcome therefore potentially dependent on its true value, and participants lost to follow-up excluded from analysis. Some concerns due to lack of information about the randomisation process.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Commins, 2000

Bibliographic Reference	Commins, D J; Koay, B C; Bates, G J; Moore, R A; Sleeman, K; Mitchell, B; Bates, S; The role of Mucodyne in reducing the need for surgery in patients with persistent otitis media with effusion.; Clinical otolaryngology and allied sciences; 2000; vol. 25 (no. 4); 274-9

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)

Study dates	January 1996 - April 1998
Inclusion criteria	Children aged 2 - 11 years with OME of at least 3 months duration
Exclusion criteria	• Cleft Palate • Down's Syndrome
Patient characteristics	N=163 children (168 initially recruited, but n=5 declined to participate) Mucolytic group (n=78): • Mean age (range): 5.1 (2-10) years • Gender ratio (male: female): 53:28 • Mean hearing loss (SD): 32.1 (not reported) dB Placebo group (n=85): • Mean age (range): 5.7 (2-11) • Gender ratio (male: female): 52:35 Mean hearing loss (SD): 33.8 (not reported) dB
Intervention(s)/control	Mucolytic: • Patients <5 years of age: Mucodyne 125mg (Carbocisteine, 2.5ml) three times a day for 6 weeks; patients >5 years of age: Mucodyne 250mg (5ml) three times a day for 6 weeks Placebo: • Placebo was matched in colour and taste to the active drug • Patients <5 years of age: placebo (2.5ml) three times a day for 6 weeks; patients >5 years of age: placebo (5ml) three times a day for 6 weeks
Duration of follow-up	8 weeks
Sources of funding	Not reported
Sample size	N=163 (168 initially recruited, but n=5 declined to participate)
Other information	Diagnosis of OME was based on clinical otoscopy, tympanometry (type B) and an average hearing loss >25 dB.

	30% of the children had grommet insertion and ≈ 13% had adenoidectomy prior to the study. Results were also reported for hearing loss, but insufficient data reported to extract (no measure of deviation or additional statistics).

Study arms

Mucolytic (N = 78)
n=number of children

Placebo (N = 85)
n=number of children

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Mucolytic, 8 weeks, N = 70	Placebo, 8 weeks, N = 79
Presence/ persistence of OME Reported as number of children with bilateral type B tympanograms. Results available for 149/163 children (n=70 in Mucodyne group; n=79 in placebo group) No of events	n = 61 ; % = 87	n = 69 ; % = 87

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Computer generated randomisation and allocation via opaque envelopes. Insufficient patient characteristics to determine differences at baseline)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and parents/ carers were blinded)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 91% of participants for tympanogram and 100% for hearing threshold)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(OME diagnosed based on tympanometry and otoscopy. Outcome assessors were blinded to the intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Pre-specified protocol unavailable. Results were reported for hearing loss, but insufficient data reported to extract (no measure of deviation or additional statistics). However, this was not the main outcome measure of the study (resolution rate of persistent OME))*
Overall bias and Directness	Risk of bias judgement	Low *(Some minor concerns regarding insufficient reporting of hearing outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Dusdieker, 1985

Bibliographic Reference	Dusdieker, L B; Smith, G; Booth, B M; Woodhead, J C; Milavetz, G; The long-term outcome of nonsuppurative otitis media with effusion.; Clinical pediatrics; 1985; vol. 24 (no. 4); 181-6

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)

Study dates	Not reported
Inclusion criteria	Children aged 6 months to 10 years with OME who had completed a standard course of antibiotics before enrolment
Exclusion criteria	• Cleft lip and/or cleft palate regardless of repair status • Chronic debilitating diseases • Cystic fibrosis • Immunodeficiency diseases • A course of corticosteroids within 90 days of study enrolment • Known sensory-neural or conductive hearing loss >25 dB bilaterally or >35 dB unilaterally
Patient characteristics	N=66 (74 initially enrolled but n=8 dropped out of the study and excluded from analyses (see Other information)) Decongestant group (n=20): • Mean age (SD): 3 (2.68) years • Gender (male:female): 9:11 • Allergic history*: 2/20 (10%) Antihistamine group (n=22): • Mean age (SD): 2.5 (1.34) years • Gender (male:female): 7:15 • Allergic history*: 4/22 (18%) Placebo group (n=24): • Mean age (SD): 1.9 (1.03) years • Gender (male:female): 13:11 • Allergic history*: 5/24 (21%) *Children with any of the following: asthma; eczema; allergic rhinitis
Intervention(s)/control	Decongestant:

	• Pseudoephedrine syrup (4 mg/ kg/day); medication given 3 times a day using a pre-marked syringe • Mean dose administered: 4.1 ± 0.98 mg/kg/day Antihistamine: • Chlorpheniramine syrup (0.35 mg/kg/day); medication given 3 times a day using a pre-marked syringe • Mean dose administered: 0.35 ± 0.03 mg/kg/day. Placebo: • Similarly favoured placebo syrup given 3 times a day using a pre-marked syringe
Duration of follow-up	12 weeks
Sources of funding	Not industry funded
Sample size	N=66 (74 initially enrolled but n=8 dropped out because of hospitalisation for gastroenteritis, family strife about participation in the research, or failure to return for appointments, and excluded from analyses)
Other information	OME diagnosed by the principle investigator using pneumatic otoscopy and tympanometry (type B, or C3 if accompanied by physical findings of fluid in the middle ear). 2 children developed severe hearing loss and were withdrawn; 1 child reported hyperactivity and poor sleeping and was withdrawn. It appears that results for these children are still included in analyses as they are not reported with the other 8 children who withdrew from the study and were excluded from analyses because of hospitalisation for gastroenteritis (n=3), family strife about participation in the research (n=1), or failure to return for appointments (n=4). Discontinuation of treatment results could only be extracted for hyperactivity and poor sleeping because the rest of the data were not reported separately for each group.

Study arms

Decongestant group (N = 20)
n=number of children

Antihistamine group (N = 22)
n=number of children

Placebo group (N = 24)
n=number of children

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Decongestant, 12 weeks, N = 20	Antihistamine, 12 weeks, N = 22	Placebo, 12 weeks, N = 24
Presence/ persistence of OME Reported per child. Reported in study as number of children with unresolved OME, i.e. excluding participants who developed AOM. Includes children withdrawn from the study due to severe medication side effects or hearing loss No of events	n = 5 ; % = 25	n = 4 ; % = 18	n = 3 ; % = 13
Discontinuation of treatment (due to hyperactivity and poor sleeping) Reported per child. No of events	n = 1 ; % = 5	n = 0 ; % =	n = 0 ; % =

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Children were randomly assigned to treatments within two age groups (<2 years or ≥2 years). Further information about randomisation process and allocation concealment not reported. However, patient characteristics at baseline are extensively reported and do not indicate problems with randomisation)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Patients and caregivers were blinded and placebo/ similar interventions received by participants. Participants who withdrew because of adverse events (n=3: hospitalisation for gastroenteritis) or because of family strife about participation in the research (n=1) were inappropriately excluded from the*

Section	Question	Answer
		analysis. This number is low (5%), however number of events for the outcome presence/ persistence of OME was also low in each group, meaning exclusion of these participants may have had a substantial impact on the result. Additionally, only 70% of participants who completed the trial were ≥80% compliant with medications. Further information about non-compliance, including between groups, is not reported)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Data are not available for 8/74 (11%) participants. It is unclear if missingness in the outcome is dependent on its true value because the number of participants who dropped out is not reported separately for each group)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome measurement appropriate. Double-blind study, further information about blinding of outcome assessors not provided)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(Prespecified protocol unavailable. Discontinuation of treatment outcomes could largely not be extracted because the number of participants experiencing adverse events or family strife was excluded from analyses and not reported separately for each group, despite the potential for this outcome to be linked to true effect of treatment. Only discontinuation of treatment for hyperactivity and poor sleeping reported; withdrawal from study because of development of severe hearing loss (>35dB) results are not reported separately for each group)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to deviations from the intended intervention, inappropriate analysis, and selection of the reported result. Some concerns regarding missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Edstrom, 1977

Bibliographic Reference	Edstrom, S; Lundin, K; Jeppsson, P H; Secretory otitis media. Aspects on treatment and control.; ORL; journal for oto-rhino-laryngology and its related specialties; 1977; vol. 39 (no. 2); 68-73

Study details

Country/ies where study was carried out	Sweden
Study type	Randomised controlled trial (RCT)
Study dates	1974
Inclusion criteria	Children with secretory otitis media. Two main groups of patients were included: • Children who completed a course of antibiotics 3 weeks before the study was started (assumed for AOM symptoms): n=102/178 (57%) • Children without preceding symptoms of AOM and antibiotic therapy: n=76 (43%) Results were reported separately for these groups according to treatment received, but results were combined because this was not a subgroup/ stratification of interest
Exclusion criteria	Not reported

Patient characteristics	N=178 (228 initially included, n=50 excluded from analysis because they did not return for follow-up, did not follow the prescriptions, got infections in the upper respiratory tract or had aerobic microorganisms in the middle ear by the time of paracentesis/myringotomy):
	
	• Mean age (SD): not reported
	  ○ 0-2 years: 55/178 (31%)
	  ○ 3-4 years: 38/178 (21%)
	  ○ 5-6 years: 41/178 (23%)
	  ○ 7-8 years: 25/178 (14%)
	  ○ 9-10 years: 6/178 (3%)
	  ○ >10 years: 13/178 (7%)
	• Gender (male:female): not reported
	
	Patient characteristics not reported separately for each group.

Intervention(s)/control	Placebo:
	• No information reported
	
	Mucolytic:
	• Bromhexine (Bisolvon) administered orally 3 times daily in the following doses until healing (but not longer than 7 weeks):
	  ○ 0—1 year: 2 mg
	  ○ 2—5 years: 3 mg
	  ○ 6— 12 years: 4 mg
	  ○ >12 years: 8 mg
	
	Antihistamine:
	• Cinnarizin (Rinomar) administered orally twice daily in the following doses until healing (but not longer than 7 weeks):
	  ○ 0—1 year: 2.5 mg
	  ○ 2—5 years: 5 mg
	  ○ 6— 12 years: 10 mg
	  ○ >12 years: 20 mg
	
	Mucolytic + antihistamine:
	• Bromhexine and Cinnarizin administered according to the regimens above until healing (but not longer than 7 weeks)

Duration of follow-up	7 weeks
Sources of funding	Not reported
Sample size	N=178 (228 initially included, n=50 excluded from analysis because they did not return for follow-up, did not follow the prescriptions, got infections in the upper respiratory tract or had aerobic microorganisms in the middle ear by the time of paracentesis/myringotomy) • Placebo group: n=51

	• Mucolytic group: n=38 • Antihistamine group: n=43 • Mucolytic + antihistamine group: n=46
Other information	Criteria for a diagnosis of OME included a dull tympanic membrane with impaired mobility in Siegle's funnel (assessed during a routine ENT examination which included microscopy) and, in most cases, impaired hearing. Secretory otitis media was considered to be healed when anatomic and functional restitution occurred.

Study arms

Placebo (N = 51)
n=number of children

Mucolytic (N = 38)
n=number of children

Antihistamine (N = 43)
n=number of children

Mucolytic + antihistamine (N = 46)
n=number of children

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Placebo, 7 weeks, N = 51	Mucolytic, 7 weeks, N = 38	Antihistamine, 7 weeks, N = 43	Mucolytic + antihistamine, 7 weeks, N = 46
Presence/ persistence of OME Reported as number of cured patients, extracted here as number remaining in each group No of events	n = 20 ; % = 40	n = 15 ; % = 40	n = 15 ; % = 35	n = 19 ; % = 42

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation technique, allocation concealment or baseline differences. Minimal patient characteristics reported overall)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Double-blind study using placebo, though unclear if participants only receiving 1 active drug also received placebo for the intervention not received. If not, participants might have been able to discern which group they were allocated to. Participants who did not follow the prescriptions, got upper respiratory tract infections (URTI) or had aerobic microorganisms in the middle ear by the time of paracentesis were inappropriately excluded from analyses, however difficult to assess if this would have had a substantial impact on the result because numbers lost in each group and for each reason not reported.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(50/228 participants (22%) were lost to follow-up. Number of participants in each group lost to follow-up, and number lost to follow up for each reason not reported, but high drop-out rate and reasons for loss to follow-up (did not return for follow-up, did not take interventions as prescribed, developed URTI, presence of aerobic microorganisms in the middle ear) indicate that missingness depended on the true value)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Resolution of OME described in study as 'anatomic and functional restitution', but this is not further defined. It is not reported whether the same person assessed presence/ persistence of OME for all participants so it is unclear if measurement of this outcome could have differed between groups. Trial was double-blind but further information about blinding of outcome assessors not reported)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Prespecified protocol unavailable. Failure to report number of participants lost to follow-up in each group and for each reason meant discontinuation of treatment outcomes could not be extracted.)*
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
		(High risk of bias due to missingness in the outcome. Some concerns related to appropriateness of the analysis, measurement of the outcome, selection of the reported result, and lack of information regarding randomisation process, allocation concealment, and patient characteristics)
Overall bias and Directness	Overall Directness	Directly applicable *(n=13 participants (7%) were over the age of 10 but unclear if they were >12 years)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Fraser, 1977

Bibliographic Reference	Fraser, J G; Mehta, M; Fraser, P A; The medical treatment of secretory otitis media. A clinical trial of three commonly used regimes.; The Journal of laryngology and otology; 1977; vol. 91 (no. 9); 757-65

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children aged 3 to 12 years with bilateral secretory otitis media.
Exclusion criteria	Not reported
Patient characteristics	N=85 (88 initially included but 3 who did not complete their treatment as planned were excluded from analysis): • Mean age (range): 5.1 (3-12) years • Gender (male:female): 47:38 • History of allergy: 9/85 (11%) • Mean pure-tone thresholds* (SD): 26.7 (9.7) dB Patient characteristics not reported separately for each group.

	*Averaged across 0.5, 1, and 2 kHz
Intervention(s)/control	Participants were split into 8 different groups to receive a combination of any or none of the following: decongestant nose drops; combination of antihistamine and nasal decongestant; autoinflation. Results were only reported according to whether participants received each treatment or not, irrespective of the other treatments received, so data could not exclusively be extracted for groups of interest for the purposes of this review (decongestant alone; combination of decongestant and antihistamine; no treatment). However, rates of people receiving other treatments was equivalent across groups. Decongestant: • Ephedrine nose drops (0.5% ephedrine hydrochloride in 0.9% saline): two drops in each nostril given twice a day for 6 weeks. Parents were given verbal and written instructions for how to deliver the intervention • Groups 1,2,5, and 6 received Ephedrine (n=43 total) Decongestant + antihistamine: • Dimotapp elixir (brompheniramine maleate (4mg/5ml of elixir), phenylephrine hydrochloride (5mg/5ml of elixir), phenylpropanolamine hydrochloride (5mg/5ml of elixir)) given as 5ml, 3 times a day (15ml per day total) for 6 weeks • Groups 1,2,3, and 4 received Dimotapp (n=43 total)
Duration of follow-up	6 weeks
Sources of funding	Industry funded
Sample size	N=85 (88 initially included but 3 who did not complete their treatment as planned were excluded from analysis)
Other information	Participants were assessed using clinical history, pure-tone audiometry, and all diagnoses of OME were confirmed using tympanometry: a negative middle ear pressure in both ears and compliance less than 0.3cc in one or both ears. Although not all ears were fluid-filled, participants were diagnosed with bilateral OME if all participants showed clear evidence of bilateral Eustachian tube disfunction. Results relating to groups who received and did not receive autoinflation were not extracted as not of interest for this review. Authors also reported change in middle ear pressure but did not provide thresholds for resolution of OME, so this outcome has not been extracted. Authors do note in the Discussion section the number of participants who experienced

	resolution of OME, but this is reported as a total number for the whole cohort and not per group/ intervention received, so this has not been extracted

Study arms

Decongestant (N = 43)
n=number of children. This arm includes all groups who received Ephedrine either alone or in combination with Dimotapp and/ or autoinflation (groups 1,2,5, and 6)

No decongestant (N = 42)
n=number of children. This arm includes all groups who did not receive Ephedrine, but received no treatment, or Dimotapp and/ or autoinflation (groups 3,4,7, and 8)

Decongestant + antihistamine (N = 43)
n=number of children. This arm includes all groups who received Dimotapp either alone or in combination with Ephedrine and/ or autoinflation (groups 1,2,3, and 4)

No decongestant + antihistamine (N = 42)
n=number of children. This arm includes all groups who did not receive Dimotapp, but received no treatment, or Ephedrine and/ or autoinflation (groups 5,6,7, and 8)

Outcomes

Study timepoints
- 6 week

Outcomes

Outcome	Decongestant, 6 week, N = 43	No decongestant, 6 week, N = 42	Decongestant + antihistamine , 6 week, N = 43	No decongestant + antihistamine , 6 week, N = 42
Mean change in pure-tone threshold from baseline (dB)	5.69 (8.2509)	2.19 (8.2509)	3.08 (8.2509)	4.93 (8.2509)

Outcome	Decongestant, 6 week, N = 43	No decongestant, 6 week, N = 42	Decongestant + antihistamine , 6 week, N = 43	No decongestant + antihistamine , 6 week, N = 42
Reported per child. It is not noted in the study whether the change is positive or negative Mean (SD*) *SDs calculated using SEs reported in study: Ephedrine vs no ephedrine: SE: 1.76; Dimotapp vs no dimotapp: SE: 1.79				

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported on randomisation process or allocation concealment, and patient characteristics not reported separately according to each group. Authors do note that "no great differences were found between the patients in any of the groups", but further explanation is not given and this cannot be verified due to presentation of characteristics.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information reported on blinding or whether placebo were used for blinding to medications, however based on differences in nature of interventions it is likely that participants and parents/ carers knew which intervention was being received (especially with regards to autoinflation). However, this is unlikely to have affected results due to the use of validated instruments to assess hearing (pure-tone audiometry). No information is reported regarding deviations from intended interventions.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Only 3% of participants did not complete treatment; these participants were split across 3 different treatment groups and therefore missingness in the outcome not likely to be related to its true value)*

Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(OME diagnosed using tympanometry for all participants)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Results were not analysed according to group, but according to whether or not the participant received a particular intervention, although this analysis seems to be appropriate for the purpose of the study.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns relating to lack of blinding, methods of measuring and reporting the outcome, and a lack of information regarding randomisation process and allocation concealment.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Results reported in a way that it is not possible to extract results only for participants who received the interventions of interest; therefore, data extracted are partially from participants who received combinations of treatments including autoinflation.)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Haugeto, 1981

Bibliographic Reference	Haugeto, O.K.; Schroder, K.E.; Mair, I.W.S.; Secretory otitis media, oral decongestant and antihistamine; Journal of Otolaryngology; 1981; vol. 10 (no. 5); 359-362

Study details

Country/ies where study was carried out	Norway
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children with secretory otitis media
Exclusion criteria	Not reported

Patient characteristics	N=77 children (127 ears with SOM; 83 initially included but n=7 excluded from analysis for failure to comply with instructions):
	
	• Mean age (range): Not reported (1-14 years)
	
	Decongestant group (n=22 children, n=36 ears with SOM):
	
	• Mean age (SD): 7.5 years (not reported)
	• Gender (male:female): not reported
	• Hearing:
	  ○ Mean air conduction threshold >20dB: 10/36 ears (28%)
	
	Decongestant + antihistamine group (n=28 children, n=49 ears with SOM):
	
	• Mean age (SD): 6.6 years (not reported)
	• Gender (male:female): not reported
	• Hearing:
	  ○ Mean air conduction threshold >20dB: 9/49 ears (18%)
	
	Placebo group (n=27 children, n=42 ears with SOM):
	
	• Mean age (SD): 7 years (not reported)
	• Gender (male:female): not reported
	• Hearing:
	  ○ Mean air conduction threshold >20dB: 8/42 (19%)

Intervention(s)/control	Decongestant: • 4-week course of phenylpropanolamine chloride (Monydrin). Further details about treatment regimen/ dosage not reported

	Decongestant + antihistamine: • 4-week course of phenylpropanolamine chloride (Monydrin) and brompheniramine maleate (Lunerin). Further details about treatment regimen/ dosage not reported Placebo: • 4-week course of placebo. Further details not reported
Duration of follow-up	4 weeks. Authors note assessments were repeated at 16 weeks but results not reported for this time period.
Sources of funding	Industry funded
Sample size	N=77 children (127 ears; 83 initially included but n=7 excluded from analysis for failure to comply with instructions)
Other information	Secretory otitis media diagnosed using pneumatic otoscopy, otomicroscopy, and impedance audiometry. Pure tone audiometry was also performed where possible.

Study arms

Decongestant (N = 44)
n=number of ears. Number of ears with SOM at baseline=36; number of children=22

Decongestant + antihistamine (N = 56)
n=number of ears. Number of ears with SOM at baseline=49; number of children=28

Placebo (N = 54)
n=number of ears. Number of ears with SOM at baseline=42; number of children=27

Outcomes

Presence/Persistence of OME outcomes

Outcome	Decongestant, 4 weeks, N = 44	Decongestant + antihistamine, 4 weeks, N = 56	Placebo, 4 weeks, N = 54
Presence/Persistence of OME* Reported per ear. Results reported in study for n=127 ears which had SOM at baseline, extracted here for all ears (using narrative data on development of SOM in previously healthy ears) No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 20 ; % = 45	n = 24 ; % = 43	n = 19 ; % = 15

Hearing outcomes

Outcome	Decongestant, 4 weeks, N = 10	Decongestant + antihistamine, 4 weeks, N = 9	Placebo, 4 weeks, N = 8
Number of ears with hearing returned to normal Reported as number of ears with air conduction threshold <20dB. Results only reported for n=27 ears which had a mean air conduction threshold >20dB at baseline No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 7 ; % = 70	n = 6 ; % = 67	n = 6 ; % = 75

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Information on randomisation process and allocation concealment not reported. Insufficient information to determine differences at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Information on blinding not reported but placebo was used and authors mention an assignment code. It is unclear if participants only receiving 1 active drug also received placebo for the intervention not received. If not, participants might have been able to discern which group they were allocated to. Participants who did not did not comply with instructions (6/83 participants (7%), further information not given) were potentially inappropriately excluded from analyses, however difficult to assess if this would have had a substantial impact on the result because numbers lost in each group not reported.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(6/83 participants (7%) did not complete the experimental protocol. Numbers in each group not given, though low number indicate this was unlikely to affect results)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Outcomes measured using appropriate tools (tympanometry; audiometry). Information on blinding of outcome assessors not reported but placebo was used and authors mention an assignment code)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(No prespecified protocol was available. Hearing results only reported for ears which had air conduction thresholds >20dB. Additionally, authors note assessments were repeated at 4 and 16 weeks follow-up, but results are only reported for all outcomes at 4 weeks)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to selective reporting. Some concerns regarding appropriateness of analyses and lack of information on randomisation process, allocation concealment and patient characteristics)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(Children were aged 1-14 years but likely that there were few children above 12 years old included in the study)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Hayden, 1984

Bibliographic Reference	Hayden, G F; Randall, J E; Randall, J C; Hendley, J O; Topical phenylephrine for the treatment of middle ear effusion.; Archives of otolaryngology (Chicago, Ill. : 1960); 1984; vol. 110 (no. 8); 512-4

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	Every October-May between the years 1978-1982
Inclusion criteria	Children aged 3 months to 10 years with persistent middle ear effusion, who returned for follow-up visits 2 weeks after treatment with a single course of an antimicrobial for an episode of AOM
Exclusion criteria	Exclusion criteria prior to randomisation not reported. Participants were excluded post-randomisation if they: • developed AOM • began taking either a systemic antibiotic or an oral decongestant
Patient characteristics	N=152 initially enrolled (73 either excluded post-randomisation (n=27) or lost to follow-up (n=46), unclear if these participants were included in analyses). Of those initially enrolled, n=68 in phenylephrine group; n=84 in placebo group; n=79 completed study (characteristics reported for those who completed study only): • Gender (male:female)*: 58%/42% Decongestant group (n=38):

	• Mean age (range): 4.1 years (9 months to 10 years) Placebo group (n=41): • Mean age (range): 4.0 years (7 months to 9 years) *Numbers of participants not reported; not reported separately for each group
Intervention(s)/control	Decongestant: • 0.25% phenylephrine hydrochloride nose drops or nasal spray. One-fourth dropperful (nose drops) administered in the following pattern each week: 4 times a day on day 1, 3 times on day 2, 2 times on day 3, once on day 4, then no medication for the final 3 days of the week • Participants repeatedly weekly cycles for 3-4 weeks or until OME resolved • During the first part of the study (time not defined), nose drops were used, but due to issues with compliance, nasal spray was used for the remainder of the study Placebo: • Placebo nose drops or nasal spray. Unclear if timing patterns matched those for the phenylephrine group • During the first part of the study (time not defined), nose drops were used, but due to issues with compliance, nasal spray was used for the remainder of the study
Duration of follow-up	1, 2, 3, and 4 weeks
Sources of funding	Not reported
Sample size	N=152 initially enrolled (73 either excluded post-randomisation (n=27) or lost to follow-up (n=46), unclear if these participants were included in analyses). Of those initially enrolled, n=68 in phenylephrine group; n=84 in placebo group. N=79 completed study
Other information	Diagnostic criteria for OME at baseline were the presence of visible middle ear fluid and/ or impaired mobility of the tympanic membrane on pneumatic otoscopy, and a type B, C, or A(s) tympanogram (only type A tympanograms were considered normal). At follow-up, results are split according to whether OME had resolved based on clinical or tympanometry diagnosis. At follow-up, clinical (otoscopic) criteria are the same as at baseline (presence of visible middle ear fluid and/ or impaired mobility of the tympanic membrane on pneumatic otoscopy). However, for tympanometry, both type A and A(s)

	tympanograms were considered normal at follow-up and therefore reported as resolution of OME, which was different to the tympanometry diagnostic criteria used at baseline. It appears as though results are only reported in the study for the participants who satisfied the otoscopic criteria at baseline for the outcome 'cumulative clinical cure rates', and reported for the participants who had a B or C type tympanogram at baseline for the outcome 'cumulative tympanometric cure rates'. Results are presented as percentages only so these have been turned into number of events for the purposes of extraction, based on the 'number of patients' reported in table 2 (assuming this is the 'denominator', or number of patients satisfying the respective criteria at baseline - this is not clear in the article). Results have been rounded to whole integers when necessary

Study arms

Decongestant (N = 68)
n=number of children

Placebo (N = 84)
n=number of children

Outcomes

Study timepoints

- 4 week

Presence/ persistence of OME (otoscopy)

Outcome	Decongestant, 4 week, N = 20	Placebo, 4 week, N = 23
Presence/ persistence of OME (otoscopy) Reported per child. Measured using pneumatic otoscopy alone, total number of participants taken from 'number of patients' column of Table 2 in the study. Percentages extracted as reported; number of events calculated using method outlined in 'other information'. Number of events are cumulative each week No of events	n = 4 ; % = 22	n = 5 ; % = 20

Presence/ persistence of OME (tympanometry)

Outcome	Decongestant, 4 week, N = 30	Placebo, 4 week, N = 37
Presence/ persistence of OME (tympanometry) Reported per child. Measured using tympanometry alone, total number of participants taken from 'number of patients' column of Table 2 in the study. Percentages extracted as reported; number of events calculated using method outlined in 'other information'. Number of events are cumulative each week No of events	n = 17 ; % = 58	n = 21 ; % = 58

Discontinuation of treatment outcomes

Outcome	Decongestant, 4 week, N = 68	Placebo, 4 week, N = 84
Discontinuation of treatment due to AOM Number of participants who were excluded from the study post-randomisation due to development of AOM No of events	n = 6	n = 6
Discontinuation of treatment due to use of additional medication Number of participants who were excluded from the study post-randomisation due to use of antibiotic or oral decongestant No of events	n = 8	n = 6
Discontinuation of treatment due to inability to tolerate medication Number of participants who were excluded from the study post-randomisation due to their inability to tolerate the medication. No of events	n = 4	n = 16

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported about randomisation process or allocation sequence. Minimal baseline participant characteristics reported but of the characteristics reported, baseline differences are not significant enough to suggest a problem with the randomisation process)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Placebo used and parents/ carers administering the intervention not aware of the assignments. Significant deviation from intended interventions: nose drops initially used but changed to nasal spray after an unspecified amount of time due to issues with compliance. The medication and dosage were the same. Authors note participants' inability to tolerate medication was much higher for those using nose drops than nasal spray so it is likely that compliance issues were due to medication intolerance. Participants were excluded from the study post-randomisation if they developed AOM or took antibiotics or oral decongestants. It is not clear if these exclusion criteria were defined prior to randomisation and if therefore the participants excluded post-randomisation were merely found to be ineligible, or if they were excluded from analyses inappropriately. Authors did conduct a sensitivity analysis whereby participants excluded for developing AOM were treated as treatment failures instead, and found no significant difference in outcomes. The same was not done for participants excluded for taking antibiotics or oral decongestants. It is unclear whether participants who were lost to follow-up (due to inability to tolerate medication, missing >1 appointment, or unknown reasons) were included in analysis because the figures in Table 2 do not match the number of participants either initially included or who completed the study. However, authors do note that only participants who met the follow-up diagnostic criteria for OME at baseline in each group were included in analyses, which means multiple included participants were likely excluded from analyses, particularly for the outcome 'tympanometric cure rates'. Therefore, while there are some concerns regarding bias for the discontinuation of treatment outcomes, there is a high risk of bias for the presence/ persistence of OME outcomes.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Not including participants who were excluded from the study post-randomisation, 46/152 participants (30%) were lost to follow-up (15/68 (22%) in the*

		phenylephrine group, 31/86 (37%) in the placebo group). It is unclear if these participants were included in the analyses. Of those lost to follow-up, numbers are balanced between groups with regards to those who missed >1 appointment or who dropped out for unknown reasons, but loss to follow-up due to failure to tolerate the medicine was more common in the placebo group than the phenylephrine group. Sensitivity analyses were conducted, but not to account for those lost to follow-up. Therefore missingness in the outcome might be dependant on its true value, dependent on whether these participants were included in analyses or not. Additionally, it appears as though results are only reported in the study for the participants who satisfied the otoscopic criteria at baseline for the outcome 'cumulative clinical cure rates', and only reported for the participants who had a B or C type tympanogram at baseline for the outcome 'cumulative tympanometric cure rates'. It is not clear how many participants were excluded from analyses as a result of this, but the numbers reported in Table 2 indicate that 71% and 73% of participants from the phenylephrine and the placebo groups, respectively, were excluded from the 'clinical cure' outcome, and 56% each of participants from the phenylephrine and the placebo groups excluded from the 'tympanometric cure' outcome)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Despite tympanometry and/ or otoscopy being used to diagnose OME in the study, there is inconsistency in the methods used to diagnose OME throughout. At baseline, OME was diagnosed based on the presence of visible middle ear fluid and/ or impaired mobility of the tympanic membrane on pneumatic otoscopy, and a type B, C, or A(s) tympanogram (only type A tympanograms were considered normal). However, at follow-up, results are split according to whether OME had resolved based on clinical diagnosis alone or tympanometry diagnosis alone. At follow-up, clinical (otoscopic) criteria are the same as at baseline (presence of visible middle ear fluid and/ or impaired mobility of the tympanic membrane on pneumatic otoscopy). However, for tympanometry, both type A and A(s) tympanograms were considered normal at follow-up and therefore reported as resolution of OME, which was different to the tympanometry diagnostic criteria used at baseline. Authors report their reasoning for this: "effusion has been clearly associated with the flat type B tracing and its variants and with the underpressure type C tracing and its variants", which indicates their inclusion criteria for the study was inappropriate. Participants with a type A(s) tympanogram at baseline were therefore excluded from analyses. Authors also*

		note there was a statistically significant difference in diagnostic results between the clinical and tympanometry criteria, indicating either "inadequate sensitivity of the otoscopic criteria", or "inadequate specificity of the tympanometric criteria". Authors do not explain their reasoning for splitting measurement of the outcome and therefore the results in this manner. It is reported that tympanograms were interpreted without knowledge of the intervention received, but the same is not reported for pneumatic otoscopy.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Authors chose to present clinical and tympanometry results separately despite using combined results as criteria for OME at baseline, with no reason given. Although both are reported, authors do not report the outcome presence/ persistence of OME using their initial diagnostic criteria, and authors use multiple outcome measurements throughout the study.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to deviations from the intended intervention, inappropriate analysis, and bias in the measurement of the outcome. Some additional concerns related to missing outcome data, selection of the reported result, and lack of information about randomisation method and allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable *(Participants with a type A(s) tympanogram are included in the study, which authors later regard as a normal tympanogram. However, these participants are not included in the analyses for the presence/ persistence of OME outcomes.)*
Overall bias and Directness	Risk of bias variation across outcomes	Overall high risk of bias for presence/ persistence of OME outcomes, as above. Overall some concerns for discontinuation of treatment outcomes due to deviations from the intended intervention and lack of information about randomisation process and allocation concealment. The concerns regarding inappropriate analyses, bias in the measurement of the outcome, missing outcome data, and selection of the reported result do not apply to these outcomes. However, this outcome is indirectly applicable because participants with A(s) type tympanograms who were later regarded as having normal tympanograms were included in these results.

Hisamatsu, 1994

Bibliographic Reference	Hisamatsu, K.; Ganbo, T.; Nakazawa, T.; Goto, R.; Ogino, J.; Nozawa, I.; Murakami, Y.; Clinical efficacy of tranilast on otitis media with effusion in children; Auris Nasus Larynx; 1994; vol. 21 (no. 3); 150-157

Study details

Country/ies where study was carried out	Japan
Study type	Randomised controlled trial (RCT)
Inclusion criteria	Patients under the age of 15 years diagnosed with OME, who were examined at the departments of otorhinolaryngology in specific local hospitals and clinics
Exclusion criteria	• Adenoid vegetation • Malformations • Chronic sinusitis • Allergic rhinitis • Tumours

Patient characteristics	N=62 children (103 ears)
	
	• Hearing loss (air conduction level)*: Not reported. Authors note that only a small number of patients had hearing loss above 15 dB
	
	Antihistamine + local treatment group (n=35 children, 55 ears):
	
	• Mean age (SD): not reported
	  ○ 0-5 years: 13 children (23 ears)
	  ○ 6-15 years: 22 children (32 ears)
	• Gender (male:female): 21 children (32 ears):14 children (23 ears)
	
	Local treatment only group (n=27 children, 48 ears):
	
	• Mean age (SD): not reported
	  ○ 0-5 years: 13 children (22 ears)
	  ○ 6-15 years: 14 children (26 ears)

	• Gender (male:female): 9 children (15 ears):18 children (33 ears) Hearing loss (air conduction level calculated using thresholds at 0.5, 1, and 2 kHz, with additional weight given to the threshold at 1 kHZ in calculations) was measured at baseline but not reported. Authors note that only a small number of patients had hearing loss above 15 dB.
Intervention(s)/control	Antihistamine + local treatment: • 0.05 mg/kg of Tranilast (Rizaben Granule) administered orally for 6 weeks • Other medications thought to affect the judgement of this drug such as anti-inflammatory drugs and anti-histamines were prohibited • Local treatment consisted of nasal spraying (1:5000 epinephrine) and suctioning (Dibekacin and Dexamethason were nebulized prior to ventilation therapy by catheterization or Politzer's method) once a week when patients visited the outpatient clinic Local treatment only: • Local treatment consisted of nasal spraying (1:5000 epinephrine) and suctioning (Dibekacin and Dexamethason were nebulized prior to ventilation therapy by catheterization or Politzer's method) once a week when patients visited the outpatient clinic
Duration of follow-up	6 weeks
Sources of funding	Not reported
Sample size	N=62 children (103 ears)
Other information	OME was diagnosed based on the findings of the eardrum noted through the use of an operating microscope, mobility of the eardrum noted through the Bruning's otoscope, and their subjective symptoms with reference to pure tone audiometry, tympanometry, and more (complete information about diagnostic criteria not reported). Results are reported according to how improved the participants' tympanic membrane, audiogram, and tympanometry findings are, separately. For audiograms, 'marked improvement' was defined as improvement of ≥25 dB, 'improvement' defined as improvement of 15-25 dB, and 'unchanged/aggravation' defined as improvement of <15 dB or aggravation. Authors separately report the percentage of ears with 'marked improvement' or 'improvement'; therefore for the purposes of this review, number of ears with 'marked improvement' or 'improvement' are extracted here as number of ears with hearing returned to normal.

	Results for overall improvement were also reported as an overall evaluation of improvement in tympanic membrane, audiogram, and tympanometry findings combined. Levels of improvement as defined by the authors for each assessment method were assigned a number, which were then totaled and given an overall improvement rating dependent on the total number. The full judgment criteria for overall improvement are outlined in table 2 of the study. Authors separately report the percentage of ears with 'moderate improvement' or above; therefore for the purposes of this review, number of ears with 'slight improvement', 'unchanged' or 'aggravated' are extracted here as number of ears with presence/ persistence of OME.

Study arms

Antihistamine + local treatment (N = 55)
n=number of ears. Number of children=35

Local treatment only (N = 48)
n=number of ears. Number of children=27

Outcomes

Study timepoints

- 6 week

Hearing outcomes

Outcome	Antihistamine + local treatment, 6 week, N = 18	Local treatment only, 6 week, N = 18
Hearing returned to normal (air conduction level)* Reported per ear. Reported in study as number of ears with 'marked improvement' or 'improvement' (improvement of ≥15 dB) No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 9	n = 7

Presence/ persistence of OME outcomes

Outcome	Antihistamine + local treatment, 6 week, N = 55	Local treatment only, 6 week, N = 48
Presence/ persistence of OME* Reported per ear. Reported in study as number of ears with overall improvement rate from tympanic membrane, audiogram, and tympanometry findings combined as 'slight improvement', 'unchanged' or 'aggravated' No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 20	n = 25

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(The only information provided is that participants were "blindly divided into the following two groups in a randomized manner using envelopes". There is no information regarding the transparency of the envelopes, etc. Baseline differences between groups suggest a problem with randomisation because the genders of the participants were unbalanced between groups: 60% of participants in the Tranilast and local treatment group were male, versus 33% of participants in the local treatment only group. There was also a slight discrepancy in age between groups, although the difference is not as significant: 37% of participants in the Tranilast and local treatment group were between the ages of 0-5 years, versus 48% of participants in the local treatment only group. It is possible that the between-group difference might have resulted in bias in the intervention effect estimate. Authors note that the distribution of participants with unilateral and bilateral morbidity was not significantly different between groups.)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended	Low *(This was an open study and participants and their parents/ carers were aware of the interventions received. However, this is unlikely to have influenced*

Section	Question	Answer
interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*outcomes because of the robustness of the methods used to assess outcomes and the fact that outcome assessors seem to have been blinded to interventions received by participants (although this is not completely explicit in the article).)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Data were only available for 18/55 ears (33%) in the Tranilast and local treatment group, and 18/48 ears (38%) in the local treatment only group at follow-up. Authors do not explain why audiometric data are not available for all ears at follow-up, and it is therefore unclear whether missingness in the outcome depended on its true value, however a high risk of bias judgment is not given because proportions of missing data are similar across groups.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Method of the measuring the outcome inappropriate despite use of tympanometry and otoscopy to diagnose OME, and use of audiometry to measure air conduction levels, because the criteria for judgement of improvement for each assessment do not appropriately take into account characteristics of each ear at baseline (i.e. tympanometry type, otoscopy findings, and air conduction level at baseline for the outcome presence/ persistence of OME, and air conduction level at baseline for the outcome hearing returned to normal). For example, ears with an improvement in tympanometry from type B to type C were defined as 'moderate improvement', whereas participants with a type A tympanogram at baseline and follow-up were defined as 'unchanged', and ears with a change from type A to a type C tympanogram were defined as 'aggravated'. In this way, ears with the same tympanometry type at follow-up could be treated differently according to their scoring system. Similarly, an improvement of >15 dB on audiometry was defined as 'unchanged/ aggravated', despite the fact that only "a small number of patients" had hearing loss >15 dB at baseline, and most participants would therefore have been unlikely to experience significant improvement in air conduction level. Additionally, the criteria for judgment of improvement meant that regardless of how results were extracted for the purposes of this review, this problem would have persisted. The criteria were applied consistently between groups but consistent application might have affected results depending on number of abnormal findings for each assessment between groups, which is not reported. Outcome assessors seem to have been blinded*

Section	Question	Answer
		to interventions received by participants (although this is not completely explicit in the article).)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(Data were collected for tympanometry, otoscopy, and audiometry findings but only presented according to trial authors' definitions of improvement, which were flawed and is likely to have introduced bias into the reported results.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to bias in the measurement of the outcome and selection of the reported result. Additionally some concerns relating to missing outcome data, lack of blinding of participants and parents/ carers, and lack of information about the randomisation process)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Children over the age of 12 are included, the number of these participants is not reported, and results are not presented separately for these participants. However, the percentage of participants over 12 is likely to be small as 63% of participants in the Tranilast and local treatment group were in the age group 6-15 years, and 52% in the local treatment group were in the age group 6-15 years)*
Overall bias and Directness	Risk of bias variation across outcomes	Risk of bias related to missing outcome data likely to be higher for the hearing outcome because it is only for this assessment that there were missing data, however audiometry results were also used to inform the outcome presence/ persistence of OME.

Hughes, 1984

Bibliographic Reference	Hughes, K B; Management of middle-ear effusions in children.; The Journal of laryngology and otology; 1984; vol. 98 (no. 7); 677-84

Study details

Country/ies where study was carried out	Germany
Study type	Randomised controlled trial (RCT)

Study dates	Not reported
Inclusion criteria	Children with a clinical diagnosis of MEE, no history of previous ENT surgery, and normal palatal function
Exclusion criteria	Not reported
Patient characteristics	N=83 children Patient characteristics not reported.
Intervention(s)/control	Mucolytic: • Mucodyne (carbocisteine) + Actifed placebo. For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily. Further information about dosages not reported Decongestant + antihistamine: • Mucodyne placebo + Actifed (Pseudoephedrine hydrochloride + triprolidine hydrochloride). For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily. Further information about dosages not reported Mucolytic, decongestant + antihistamine: • Mucodyne + Actifed. For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily. Further information about dosages not reported Placebo: • Mucodyne placebo + Actifed placebo. For both, children <5 years were given 5ml twice daily; children >5 years were given 5 ml 3 times daily
Duration of follow-up	3 months (or 6 months only for participants who did not require surgery). Results at 3 and 6 months post-surgery also reported but not extracted for the purposes of this review
Sources of funding	Not industry funded
Sample size	N=83 children

	• Mucolytic: n=27 • Decongestant + antihistamine: n=20 • Mucolytic, decongestant + antihistamine + Actifed: n=20 • Placebo: n=16
Other information	OME diagnosis based on patient's symptoms, previous medical history, physical examination, and tympanometry. Most children also had audiograms, though number is not reported.

Study arms

Mucolytic (N = 27)
n=number of children

Decongestant + antihistamine (N = 20)
n=number of children

Mucolytic, decongestant + antihistamine (N = 20)
n=number of children

Placebo (N = 16)
n=number of children

Outcomes

Presence/ persistence of OME outcomes

Outcome	Mucolytic, 3 months, N = 27	Decongestant + antihistamine, 3 months, N = 20	Mucolytic, decongestant + antihistamine , 3 months, N = 20	Placebo, 3 months, N = 16
Presence/ persistence of OME Reported as number of participants needing surgery. No of events	n = 14 ; % = 52	n = 13 ; % = 65	n = 13 ; % = 65	n = 10 ; % = 63

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on randomisation, allocation concealment or baseline differences)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind trial using placebo. No evidence of deviations from the intended intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all participants at 3 month follow-up)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(OME diagnosed using tympanogram. Double-blind trial, no information on blinding of outcome assessors)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(No prespecified protocol available, but no evidence of selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns due to lack of information on randomisation process, allocation concealment, or patient characteristics)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Ages of participants not reported beyond that they were children; all participants were the children of general practitioners in the British Army of the Rhine)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Khan, 1981

Bibliographic Reference	Khan, J A; Marcus, P; Cummings, S W; S-carboxymethylcysteine in otitis media with effusion. (A double-blind study).; The Journal of laryngology and otology; 1981; vol. 95 (no. 10); 995-1001

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children with bilateral OME
Exclusion criteria	Children with AOM
Patient characteristics	N=60 children (120 ears; 2 children lost to follow-up and excluded from analysis): • Mean age (range): 7.3 (5-14) years • Gender (male:female): 39:21 Patient characteristics not presented separately for each group.

Intervention(s)/control	Mucolytic, antihistamine and decongestant (n=19):
	
	• Bromhexine and brompheniramine, phenylephrine, and phenylpropanolamine were given at the following dosages, according to age:
	  ○ 4 years: 4.5mls 3 times a day
	  ○ 5-9 years: 5mls 3 times a day
	  ○ 10-14 years: 10mls 3 times a day
	• After 1-28 days all children underwent myringotomies, and children with mucoid MEE had VTs inserted
	• Not clear when (i.e. pre- or post-operatively) or for how long medications were taken but trial ended 1 month after operation in each case
	
	Mucolytic) (n=20):
	
	• S-carboxymethylcysteine (SCMC)/ carbocisteine was given at the following dosage, according to age:
	  ○ 4 years: 4.5mls 3 times a day
	  ○ 5-9 years: 5mls 3 times a day
	  ○ 10-14 years: 10mls 3 times a day
	• After 1-28 days all children underwent myringotomies, and children with mucoid MEE had VTs inserted

	• Not clear when (i.e. pre- or post-operatively) or for how long medications were taken but trial ended 1 month after operation in each case
	
	Placebo (n=19):
	
	• Medications were given at the following dosages, according to age:
	  ○ 4 years: 4.5mls 3 times a day
	  ○ 5-9 years: 5mls 3 times a day
	  ○ 10-14 years: 10mls 3 times a day
	• After 1-28 days all children underwent myringotomies, and children with mucoid MEE had VTs inserted
	• Not clear when (i.e. pre- or post-operatively) or for how long medications were taken but trial ended 1 month after operation in each case

Duration of follow-up	28 days post surgery
Sources of funding	Not reported
Sample size	N=58 children (116 ears; 60 initially included and patient characteristics reported for but 2 lost to follow-up not included in analyses) Mucolytic, antihistamine and decongestant: n=19 Mucolytic: n=20 Placebo: n=19
Other information	OME diagnosed based on clinical history, otoscopic examination, and audiology (including tuning fork testing and pure-tone audiometry). OME criteria were bilateral reduced hearing, retracted tympanic membrane with diminished light reflexes, and an air-bone gap. Change in hearing thresholds from baseline (air conduction and bone conduction) results were also reported for both ears but insufficient data reported to extract (no measure of deviation or additional statistics).

Study arms

Mucolytic, antihistamine and decongestantgroup (N = 19)
n=number of children. Number of ears=38

Mucolytic group (N = 20)
n=number of children. Number of ears=40

Placebo group (N = 19)
n=number of children. Number of ears=38

Outcomes

Study timepoints

- 28 day

Outcomes

Outcome	Mucolytic, antihistamine and decongestant group, 28 day, N = 19	Mucolytic group, 28 day, N = 20	Placebo group, 28 day, N = 19
Number of children with hearing returned to normal (air conduction, 0.25 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall of ≥10dB in 1 or both ears No of events	n = 6	n = 12	n = 3
Number of children with hearing returned to normal (air conduction, 0.5 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 8	n = 9	n = 4
Number of children with hearing returned to normal (air conduction, 1 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears	n = 6	n = 9	n = 6

Outcome	Mucolytic, antihistamine and decongestant group, 28 day, N = 19	Mucolytic group, 28 day, N = 20	Placebo group, 28 day, N = 19
No of events			
Number of children with hearing returned to normal (air conduction, 2 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 2	n = 3	n = 0
Number of children with hearing returned to normal (air conduction, 4 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 9	n = 10	n = 8
Number of children with hearing returned to normal (air conduction, 8 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 7	n = 11	n = 8
Number of children with hearing returned to normal (bone conduction, 0.25 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 2	n = 2	n = 0

Outcome	Mucolytic, antihistamine and decongestant group, 28 day, N = 19	Mucolytic group, 28 day, N = 20	Placebo group, 28 day, N = 19
Number of children with hearing returned to normal (bone conduction, 0.5 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 0	n = 1	n = 1
Number of children with hearing returned to normal (bone conduction, 1 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 1	n = 2	n = 1
Number of children with hearing returned to normal (bone conduction, 2 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 2	n = 3	n = 1
Number of children with hearing returned to normal (bone conduction, 4 kHz) Reported in study as incidence of response after treatment and defined as a threshold fall from preoperative levels of ≥10dB in 1 or both ears No of events	n = 2	n = 7	n = 3

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported about randomisation process or allocation concealment. Insufficient information to assess whether there were baseline differences between groups as patient characteristics not reported separately for each group. Authors note there was no significant difference between the 3 groups with respect to age, sex, duration of medical treatment before surgery, or type of MEE found before surgery.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Trial is double blind and placebo is used, though no other information regarding blinding of participants and parents/ carers is reported. However, authors do not report the mean length of treatment in each group, which seems to differ depending on when surgery was performed (between 1 and 28 days after initial assessment, at which participants were assigned their treatment group). It is unclear whether treatment continued post-operatively. Additionally, participants with mucoid MEE had VTs inserted. The number of participants receiving VTs is not reported. Therefore, interventions might have differed between and within groups dependent on when participants received surgery and how many participants in each groups had VTs inserted. It is not reported whether the analyses accounted for differences in treatment/ treatment length.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(2/60 participants (3%) withdrew from the study prior to surgery, for "reasons unrelated to the study".)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Air and bone conduction thresholds assessed using audiometry for all participants. Trial is double blind, though further information about blinding of outcome assessors not reported.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Otoscopy was performed weekly throughout the trial but otoscopic results only reported narratively: "audiometric improvement was seen to correlate well with normalisation of the otoscopic appearance of the tympanic membrane at weekly post-operative assessments". There is no information on whether*

Section	Question	Answer
		otoscopic results were intended to be reported in a pre-specified analysis plan, and not discernible from the text.)
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to analysis not accounting for likely differences in interventions received within and between groups. Some concerns regarding bias in selection of the reported result and a lack of information about randomisation process and allocation concealment. Authors additionally make inappropriate conclusions on the basis of the study findings, i.e. that SCMC should be "considered as an alternative to surgery". All participants underwent myringotomy and, in some cases, VT insertion, so this conclusion is not justified by the data.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Ages of participants are not reported)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Kumazawa, 1989

Bibliographic Reference	Kumazawa, T.; Ushiro, K.; Clinical evaluation of S-CMC syrup applied in the treatment of otitis media with effusion. Double blind comparative test with placebo; Acta Oto-Laryngologica, Supplement; 1989; vol. 107 (no. 458); 56-62

Study details

Country/ies where study was carried out	Japan
Study type	Randomised controlled trial (RCT)
Study dates	August 1986 - April 1987
Inclusion criteria	Children with OME who weighed 18-33kg and were 5-10 years old
Exclusion criteria	• Serious complications found (not defined) • Cases requiring a surgical approach (tympanostomy tube insertion, adenoidectomy) • Cases who had undergone tympanostomy tube insertion, adenoidectomy prior to the start of the trial • Cases who were judged as being improper to receive this trial by the physicians in charge

Patient characteristics	N=214 children (250 initially randomised but n=36 dropped/ excluded from trial and excluded from improvement analysis. N=243 participants included in safety evaluation).
	
	Mucolytic group (n=104):
	
	• Mean age (SD): Not reported
	  ○ <5 years: 8/104 (8%)
	  ○ 5-6 years: 61/104 (59%)
	  ○ 7-8 years: 24/104 (23%)
	  ○ 9-10 years: 8/104 (8%)
	  ○ >11 years: 3/104 (3%)
	• Gender (male:female): 61:43
	
	Placebo group (n=110):
	
	• Mean age (SD): Not reported
	  ○ <5 years: 12/110 (11%)
	  ○ 5-6 years: 58/110 (53%)
	  ○ 7-8 years: 28/110 (25%)
	  ○ 9-10 years: 11/110 (10%)
	  ○ >11 years: 1/110 (1%)
	• Gender (male:female): 63:47

Intervention(s)/control	Mucolytic: • 5% SCMC/ carbocisteine syrup (50mg SCMC per 1ml syrup) administered 3 times daily after meals for 4 consecutive weeks (30 mg/kg/day in 1 dosage each, i.e. 4 ml for patients weighing 18 kg-23 kg, 5 ml for 23 kg-28 kg and 6 ml for 28 kg-33 kg) • Antibiotics (penicillin origin or cefaclor) were allowed for use upon myringotomy prior to administration of the syrup, for a maximum of 3 days Placebo:

	• Placebo syrup indistinguishable from active drug by odour, taste, or appearance, administered orally 3 times daily after meals for 4 consecutive weeks (amount to match active drug) • Antibiotics (penicillin origin or cefaclor) were allowed for use upon myringotomy prior to administration of the syrup, for a maximum of 3 days Drugs for concurrent use including steroids, non-steroid antiinflammatories, enzyme preparations, mucolytics, and herb remedies, which might influence the results of this trial, were avoided in both groups
Duration of follow-up	4 weeks
Sources of funding	Not reported
Sample size	N=214 children (250 initially randomised but n=36 dropped/ excluded from trial and excluded from improvement analysis) • Mucolytic group: n=104 • Placebo group: n=110 N=243 participants included in safety evaluation (250 initially randomised but n=7 excluded from safety evaluation) • Mucolytic group: n=121 • Placebo group: n=122
Other information	OME diagnosed based on observations of MEE, dullness and retraction of the eardum, standard audiometry, and tympanometry Cases who discontinued the trial within 1 week of the administration were usually not included in the improvement analysis, and dropped cases who received the syrup for 2 weeks or more were only included in the safety evaluation. However, 2 cases who discontinued the trial within 1 week due to side-effects were included in the safety and usefulness analyses.

Study arms

Mucolytic group (N = 121)
n=number of children

Placebo group (N = 122)
n=number of children

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Mucolytic group, 4 weeks, N = 104	Placebo group, 4 weeks, N = 110
Presence/ persistence of OME Reported per child. Reported in study as tympanogram unchanged or aggravated No of events	n = 51 ; % = 49	n = 63 ; % = 57
Discontinuation of treatment due to side-effects Reported narratively as number of children who discontinued treatment due to vomiting. Brief discontinuation of treatment (i.e for 3 or 4 days before restarting intervention), dosage reduction, or symptomatic treatment for other side-effects/ participants also reported but not extracted due to treatment continuation No of events	n = 2 ; % = 2	n = 0

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(No information regarding randomisation process or allocation concealment. However, patient characteristics are reported extensively and authors report*

Section	Question	Answer
		that Data analysis revealed no significant difference between the two groups in the following items: sex, age, in- or out-patient, affected ear, severity, presence or absence of complications, remedies previously used, drugs for concomitant use, and duration of the disease.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Double-blind trial using placebo. Participants who discontinued the trial were excluded from analyses, except in the cases of 2 participants who entirely discontinued treatment due to side-effects.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(36/250 participants (14%) dropped or excluded from study post-randomisation, lack of/ unclear reporting on why participants were dropped or excluded. It is therefore difficult to assess whether missingness in the outcome relates to its true value, however dropped/ exclusion rates are roughly even between groups.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Method of outcome measurement was by tympanogram. Double-blind trial, further information regarding blinding of outcome assessors not reported)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(No prespecified protocol available, but no evidence of selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding deviations from the intended interventions and missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Mandel, 1987

Bibliographic Reference	Mandel, E M; Rockette, H E; Bluestone, C D; Paradise, J L; Nozza, R J; Efficacy of amoxicillin with and without decongestant-antihistamine for otitis media with effusion in children. Results of a double-blind, randomized trial.; The New England journal of medicine; 1987; vol. 316 (no. 8); 432-7

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	July 1981 - October 1984
Inclusion criteria	Infants and children aged 7 months to 12 years with OME
Exclusion criteria	• Congenital craniofacial malformation • Systemic illness • History of tonsillectomy • Adenoidectomy • Insertion of a tympanostomy tube • Structural middle-ear abnormality • Hearing loss not attributable to MEE • Severe upper airway obstruction • AOM • Acute or chronic sinusitis • History of treatment with sympathomimetic amines or antihistamines in the past 30 days • History of hypersensitivity to any form of penicillin

Patient characteristics	N=474 children (N=518 initially included but n=44 children not evaluated at 4 weeks follow-up excluded from analysis)
	
	Antibiotic, decongestant + antihistamine group (n=158):
	
	• Mean age (SD): not reported
	  ○ 7-23 months: 37%
	  ○ 2-5 years: 48%
	  ○ 6-12 years: 16%
	• Gender (male:female): 36%:64%
	• Laterality of middle ear infection:
	  ○ Unilateral: 51/158 (32%)
	  ○ Bilateral: 107/158 (68%)
	• Allergy diagnosed:
	  ○ No: 99%
	  ○ Yes: 1%
	  ○ Unknown: 0%

	• Mean speech awareness thresholds at baseline/ child (SD)*: 23.25 (9.28) dB
	• Mean speech reception thresholds at baseline/ right ear (SD)**: 19.02 (12.22) dB
	• Mean speech reception thresholds at baseline/ left ear (SD)***: 18.41 (11.73) dB
	
	Antibiotic only group (n=160):
	
	• Mean age (SD): not reported
	  ○ 7-23 months: 33%
	  ○ 2-5 years: 49%
	  ○ 6-12 years: 18%
	• Gender ratio (male:female): 36:64
	• Laterality of middle ear infection§:
	  ○ Unilateral: 54/160 (34%)
	  ○ Bilateral: 106/160 (66%)
	• Allergy diagnosed:
	  ○ No: 97%
	  ○ Yes: 3%
	  ○ Unknown: 1%
	• Mean speech awareness thresholds at baseline/ child (SD)****: 23.00 (11.74) dB
	• Mean speech reception thresholds at baseline/ right ear (SD)†: 18.42 (10.95) dB
	• Mean speech reception thresholds at baseline/ left ear (SD) ‡: 20.00 (10.10) dB
	
	*Only reported for 57/158 (36%) participants who had data at baseline and 4 week follow-up
	
	**Only reported for 87/158 (55%) right ears which had data at baseline and 4 week follow-up
	
	***Only reported for 85/158 (54%) left ears which had data at baseline and 4 week follow-up
	
	****Only reported for 50/160 (31%) participants who had data at baseline and 4 week follow-up
	
	†Only reported for 98/160 (61%) right ears which had data at baseline and 4 week follow-up
	
	‡Only reported for 97/160 (61%) left ears which had data at baseline and 4 week follow-up

	§Numbers calculated from percentages Only percentages/ ratios and not numbers of participants reported for any patient characteristics
Intervention(s)/control	Antibiotic, decongestant + antihistamine: • Antibiotic (amoxicillin): liquid suspension, 40mg/kg/day divided into 3 doses for 2 weeks • Decongestant-antihistamine: liquid preparation of pseudoephedrine hydrochloride and chlorpheniramine maleate (Novafed A) administered in a dose of 1.0 mg/kg and 0.09mg/kg of each drug respectively 4 times daily for 4 weeks Antibiotic only: • Antibiotic (amoxicillin): liquid suspension, 40mg/kg/day divided into 3 doses for 2 weeks • Placebo identical in appearance and similar in taste to decongestant-antihistamine, and containing the same inert ingredients, administered for 4 weeks An additional group received only placebo but data for this group were not extracted for the purposes of this review.
Duration of follow-up	4 weeks
Sources of funding	Not reported
Sample size	N=474 children (N=518 initially included but n=44 children not evaluated at 4 weeks follow-up excluded from analysis)
Other information	OME diagnosed based on standardised ENT examination (including pneumatic otoscopy). Results for presence/ persistence of OME outcomes were also collected at 8, 12 and 16 weeks follow-up only for participants who did not have effusion at 4 weeks follow-up, but these results are reported narratively and there are insufficient data for extraction.

Study arms

Antibiotic, decongestant + antihistamine (N = 158)
n=number of children

Antibiotic only (N = 160)
n=number of children

Outcomes

Outcomes

Outcome	Antibiotic, decongestant + antihistamine, 4 weeks, N = 158	Antibiotic only, 4 weeks, N = 160
Presence/ persistence of OME Reported as number of participants with unilateral or bilateral effusion regardless of laterality at baseline No of events	n = 108 ; % = 68	n = 114 ; % = 71
Mean final hearing threshold (speech awareness thresholds) (dB) Reported per child. These results were only reported for 57/158 (36%) participants in the amoxicillin and decongestant-antihistamine group, and 50/160 (31%) participants in the amoxicillin only group, who had data at baseline and 4 week follow-up. (A lower hearing threshold represents better hearing) Mean (SD)	17.81 (7.50)	17.00 (7.07)
Mean final hearing threshold (speech reception thresholds, right ears)* (dB) Reported per ear. These results were only reported for 87/158 (55%) right ears in the amoxicillin and decongestant-antihistamine group, and 98/160 (61%) right ears in the amoxicillin only group, which had data at baseline and 4 week follow-up. (A lower hearing threshold represents better hearing)	15.63 (13.03)	15.82 (12.60)

Outcome	Antibiotic, decongestant + antihistamine, 4 weeks, N = 158	Antibiotic only, 4 weeks, N = 160
Mean (SD) *Mean and SDs of right and left ears pooled for each arm to find average for both ears in analysis. Sample size adjusted in analysis to account for lack of independence between ears from the same child		
Mean final hearing threshold (speech reception thresholds, left ears)* (dB) Reported per ear. These results were only reported for 85/158 (54%) left ears in the amoxicillin and decongestant-antihistamine group, and 97/160 (61%) left ears in the amoxicillin only group, which had data at baseline and 4 week follow-up. (A lower hearing threshold represents better hearing) Mean (SD) * Mean and SDs of right and left ears pooled for each arm to find average for both ears in analysis. Sample size adjusted in analysis to account for lack of independence between ears from the same child	13.37 (11.26)	14.95 (10.72)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participants were stratified according to age (7-23 months, 2-5 years, or 6-12 years), duration of OME (<4 weeks, 4-8 weeks, >8 weeks, or unknown), and*

Section	Question	Answer
		whether an antimicrobial agent had been during the preceding 2 months. Within each stratification (24 total), subjects were randomly assigned to groups in blocks of 3. Further information about randomisation process and allocation concealment not reported. Baseline patient characteristics do not indicate problems with randomisation.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Double-blind trial using placebo. Appropriate analyses used)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(44/518 (8%) were lost to follow-up by 4 weeks. Hearing outcome data were only available for a limited number of participants in each group (data not available for 39-69% of participants for all hearing outcomes; amount of missing data particularly high for the outcome mean final speech awareness threshold). However, this is linked to which testing methods were used for each age group: children <2 years had speech awareness thresholds tested due to inability to be tested by other methods; children >2 years had speech reception and pure-tone thresholds tested.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double-blind trial, 92% of observations made by author who was blinded to treatment groups; remaining observations made by validated otoscopists (blinding of these assessors not reported). Use of validated tools and objective outcome measurements mean knowledge or intervention received unlikely to influence measurement of the outcome.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol available. Authors report children aged >2 years had pure-tone thresholds tested, but these results are only reported narratively as being "similar with each of the measures used for analysis". A reason is not given.)*
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
		(Some concerns due to selection of the reported result and lack of information about randomisation process and allocation concealment. Some minor concerns due to missing outcome data for hearing outcomes only.)
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Low risk of bias for missing outcome data for presence/ persistence of OME outcome. Some concerns regarding missing outcome data for hearing outcomes, however all outcomes still have some concerns overall

McGuiness, 1977

Bibliographic Reference	McGuiness, R J; Carboxymethylcysteine in the glue ear syndrome.; The British journal of clinical practice; 1977; vol. 31 (no. 78); 105-6

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children with non-suppurative otitis media and intact tympanic membranes
Exclusion criteria	Children <4 years
Patient characteristics	N=36 children No patient characteristics reported.
Intervention(s)/control	Mucolytic (n= 20): • 5ml of S-Carboxymethylcysteine (SCMC)/ carbocisteine delivered 3 times a day orally for 14 days • No surgery performed during trial No treatment (n=16): • No surgery performed during trial

Duration of follow-up	22 days
Sources of funding	Not reported
Sample size	N=36 children • Mucolytic: n= 20 • No Treatment: n=16
Other information	Diagnosis of OME made based on clinical history, appearance of tympanic membrane, and pure-tone audiometry. Authors do not explicitly report the use of otoscopy or tympanometry, but examination of tympanic membrane presumed to have been done using otoscopy.

Study arms

Mucolytic (N = 20)

No Treatment (N = 16)

Outcomes

Study timepoints

- 22 day

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Mucolytic, 22 day, N = 40	No Treatment, 22 day, N = 32
Change in hearing threshold (pure-tone threshold)* (dB) Reported as 'Average reduction in hearing loss' after 22 days by ear (lowering of hearing threshold represented as negative values here, a lower hearing threshold represents hearing improvement). Mean (SD**)	-8.35 (6.2262)	-2.65 (6.2262)

Outcome	Mucolytic, 22 day, N = 40	No Treatment, 22 day, N = 32
*Sample size adjusted in analysis to account for lack of independence between ears from the same child **SDs calculated from t value reported in study: mucolytic vs no treatment: t=-3.86		

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on randomisation process, allocation concealment or baseline characteristics)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(No information on blinding; participants and parents/ carers were likely to be aware of assignment due to nature of interventions. No information on intervention deviations, or analyses. Unclear how this could have affected results due to lack of information in study)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(No information regarding loss to follow-up or number of participants included in analyses reported. Cannot judge missingness in the outcome or relation to true value)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Hearing outcomes assessed using pure-tone audiometry. Blinding of outcome assessors not reported, but assessment methods objective so unlikely to affect measurement of the outcome)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Prespecified protocol unavailable. Minimal information reported throughout does not make the lack of evidence of selective reporting noteworthy.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to lack of information reported in all domains.)*
Overall bias and Directness	Overall Directness	Directly applicable

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	None

O'Shea, 1980

Bibliographic Reference	O'Shea, J S; Langenbrunner, D J; McCloskey, D E; Pezzullo, J C; Regan, J B; Diagnostic and therapeutic studies in childhood serous otitis media. Results of treatment with an antihistamine-adrenergic combination.; The Annals of otology, rhinology & laryngology. Supplement; 1980; vol. 89 (no. 3pt2); 285-9

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	March - December 1977
Inclusion criteria	Children aged 3 to 9 years with the following: • First known diagnosis of serous otitis media within 1 month prior to the trial • Rectal temperature less than 38.4 C or an oral temperature less than 37.8 C • No externally obvious ear or nose deformities
Exclusion criteria	Not reported
Patient characteristics	N=55 participants (66 initially randomised but n=6 participants who did not complete the study excluded from analyses): • Mean age (range): 6 (3-9) years • Gender (male:female): 33:22 • Mean hearing loss (air and bone conduction): Not reported. All participants had, in at least 1 ear, hearing loss (air conduction) >15 dB at ≥2 consecutive frequencies, and no hearing loss (bone conduction) >10 dB Patient characteristics not reported separately for each group.
Intervention(s)/control	Antihistamine + decongestant:

	• Combination of diphenhydramine and pseudoephedrine, each taken 5 mg/kg/day orally in 3 divided doses. Duration of treatment not reported Placebo: • Similar tasting placebo taken in comparable volume orally in 3 divided doses. Duration of treatment not reported
Duration of follow-up	Follow up appointments every 4 weeks for 3 months
Sources of funding	Not reported
Sample size	N=55 participants (66 initially randomised but n=6 participants who did not complete the study excluded from analyses) • Antihistamine + decongestant: n=27 • Placebo: n=28
Other information	Diagnosis of serous otitis media made based on the following criteria: • Fluid in at least 1 middle ear and no bulging of either tympanic membrane, assessed using pneumatic otoscopy • In at least 1 ear, hearing loss (air conduction) >15 dB at ≥2 consecutive frequencies, and no hearing loss (bone conduction) >10 dB • At least one ear with a flat (type B) tympanogram on impedance tympanometry

Study arms

Antihistamine + decongestant group (N = 27)
n=number of children

Placebo group (N = 28)
n=number of children

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Antihistamine + decongestant group, 3 months, N = 27	Placebo group, 3 months, N = 28
Presence/ persistence of OME* Reported as number of tympanograms performed at return visits that were worse than or the same as the previous visit. Unclear if per child or per ear. Antihistamine-decongestant group: n=151 tympanograms. Placebo group: n=161 tympanograms No of events *Sample size/number of events adjusted in analysis to account for lack of independence between tympanograms from the same child	n = 108 ; % = 72	n = 101 ; % = 63
Proportion of children with hearing returned to normal (air conduction) Reported per child. Reported as children without hearing loss of ≥20dB in at least 1 ear No of events	n = 14 ; % = 52	n = 14 ; % = 50

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on randomisation or allocation concealment, and insufficient patient characteristics reported to determine baseline differences. Authors note girls were no more likely to be assigned the active drug than boys were)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Double-blind trial using placebo but further information regarding blinding not reported. Authors report that on average, only 60% of the prescribed substances (both drug and placebo) were taken during the study period. Potential effect of deviation from intended interventions on results not reported*

Section	Question	Answer
		or analysed by trial authors, but similar deviation between groups indicates this is unlikely to have had a significant effect on results.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data not available for 6/61 (10%) of participants. Information regarding reasons for loss to follow-up or number of participants with missing data in each group not reported, but numbers in each group indicate loss to follow-up was balanced between groups and therefore unlikely to be related to true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Presence/ persistence of OME assessed using tympanometry, hearing outcomes assessed using air conduction audiometry. Trial was double-blind but further information on blinding of outcome assessors not reported.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(Prespecified protocol unavailable. Reporting of the outcome presence/ persistence of OME is done in such a way that it is not possible to discern the number of participants who still had OME at follow-up. Authors report it would have been inappropriate to compare assessments of OME at follow-up because the "comparison might be influenced differently for drug patients than for control patients". This explanation is insufficient and further reasoning for not reporting presence of OME at follow-up per participants or ear is not reported.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to selection of the reported result. Some concerns regarding deviations from the intended interventions and lack of information about randomisation process, allocation concealment, and patient characteristics)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	The presence/ persistence of OME outcome is indirectly applicable because it is reported per assessment rather than per child or ear. Including the number of tympanograms that were the same or worse than the last visit means that some children whose OME had previously cleared were included in the number of events, meaning this outcome also includes recurrence of OME.

Section	Question	Answer
		Hearing outcomes are directly applicable and only have some concerns as there is not a high risk of bias due to selection of the reported result

O'Shea, 1982

Bibliographic Reference	O'Shea, J S; Langenbrunner, D J; McCloskey, D E; Pezzullo, J C; Regan, J B; Childhood serous otitis media: fifteen months' observations of children untreated compared with those receiving an antihistamine-adrenergic combination.; Clinical pediatrics; 1982; vol. 21 (no. 3); 150-3

Study details

Country/ies where study was carried out	See O'Shea 1980
Study type	Randomised controlled trial (RCT)
Study dates	See O'Shea 1980
Inclusion criteria	See O'Shea 1980
Exclusion criteria	See O'Shea 1980
Patient characteristics	See O'Shea 1980
Intervention(s)/control	See O'Shea 1980
Duration of follow-up	1 year
Sources of funding	See O'Shea 1980
Sample size	N= 48 (66 initially randomised in first study but n=16 participants who did not complete the study excluded from analyses) • Antihistamine + decongestant: n=24 • Placebo: n=24
Other information	See O'Shea 1980.

	Methods for measuring hearing loss not reported for 1 year follow-up. Authors defined type C tympanograms as indicating negative middle ear pressure but no fluid; therefore, only type B tympanogram extracted as presence/ persistence of OME (in line with baseline measures)

Study arms

Antihistamine + decongestant group (N = 24)
n=number of children. Number of ears=48

Placebo group (N = 24)
n=number of children. Number of ears=48

Outcomes

Outcomes for Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME)

Outcome	Antihistamine + decongestant group, 1 year, N = 24	Placebo, 1 year, N = 24
Presence/Persistence of OME* Reported as number of ears with type B tympanograms. Number of ears=48 in each group No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 18 ; % = 38	n = 11 ; % = 23
Change in hearing threshold from baseline (air conduction) (dB) Reported as average improvement per child (lowering of hearing threshold represented as negative values here, a lower hearing threshold represents hearing improvement) Mean (SD)	-4.0 (11.1)	-6.6 (13.6)
Number of children with hearing returned to normal (air conduction) Reported as number of children without persistent hearing loss ≥20dB in either ear	N = 18 ; % = 75	N = 15 ; % = 63

Outcome	Antihistamine + decongestant group, 1 year, N = 24	Placebo, 1 year, N = 24
No of events		

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Bias assessed in O'Shea 1980)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Bias assessed in O'Shea 1980)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Bias assessed O'Shea1980)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data not available for 16/61 (26%) of participants (additional 10 participants lost to follow-up between 3 months and 1 year follow-up). Information regarding reasons for loss to follow-up or number of participants with missing data in each group not reported, but numbers in each group indicate loss to follow-up was balanced between groups and therefore unlikely to be related to true value)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Bias assessed O'Shea1980)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(No prespecified protocol was available, but no evidence of selective reporting)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding deviations from the intended interventions and lack of information about randomisation process, allocation concealment, and patient characteristics)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Rahmati, 2017

Bibliographic Reference	Rahmati, Mohammad Bagher; Safdarian, Fatemeh; Shiroui, Babak; Zare, Shahram; Sadeghi, Naser; Montelukast versus inhaled mometasone for treatment of otitis media with effusion in children: A randomized controlled trial.; Electronic physician; 2017; vol. 9 (no. 7); 4890-4894

Study details

Country/ies where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	2014
Inclusion criteria	Children aged 2 to 6 years with a diagnosis of OME
Exclusion criteria	• Currently using corticosteroids or prophylactic montelukast • Chronic pulmonary diseases • Chronic cardiac diseases • Immune deficiency • Allergic rhinitis • Hypersensitivity to montelukast or corticosteroids • Parents did not provide written informed consent
Patient characteristics	N=143 children Leukotriene receptor antagonist group (n=59): • Mean age (SD): 43.05 (19.08) months • Gender (male:female): 32:27 • Laterality of effusions: ○ Unilateral: 35/59 (59%)

	○ Bilateral: 24/59 (41%) No treatment group (n=44): • Mean age (SD): 41.27 (15.90) months • Gender (male:female): 31:13 • Laterality of effusions: ○ Unilateral: 27/44 (61%) ○ Bilateral: 17/44 (39%) One additional group received Mometasone but data for this group were not extracted as not of interest for this review.
Intervention(s)/control	Leukotriene receptor antagonist: • 4ml Montelukast per day for 1 month. Further information regarding dosage not reported No treatment: • No further details reported
Duration of follow-up	1 month
Sources of funding	Not industry funded
Sample size	N=143 children
Other information	OME diagnosed based on “symptoms and examination”. Further detail not reported; however, OME diagnosis was confirmed by tympanometry at baseline. At follow-up, authors note “data were collected using a checklist, which included the child’s general information and tympanometry, and was completed by the parents. All patients were evaluated by a physician for assessment of treatment response after one month, and the data were recorded.”

Study arms

Leukotriene receptor antagonist (N = 59)
n=number of children

No treatment (N = 44)
n=number of children

Outcomes

Outcomes

Outcome	Leukotriene receptor antagonist, 1 month, N = 59	No treatment, 1 month, N = 44
Presence/ persistence of OME Reported as number of children with no response to treatment (i.e. no improvement, complete or relative). Complete and relative improvement not defined in study. No of events	n = 5 ; % = 9	n = 2 ; % = 5

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Method of randomisation is unclear; study only states that the children were randomised. No information on allocation concealment. No baseline differences between groups for patient characteristics reported, but number assigned to each group is not balanced, suggesting problems with randomisation.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Likely that participants and parents/ carers were aware of the intervention the child was assigned to, due to the nature of the interventions. Authors report all participants received their allocated interventions. Minimal information regarding analysis reported)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data collected for all participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(OME diagnosis confirmed using tympanometry at baseline, but information regarding data collection at follow-up imply data for presence/ persistence of*

Section	Question	Answer
		OME were collected via parent checklist. Parents were likely aware of interventions received, so if data were collected in this way there could be significant impact on the measurement of the outcome.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(Audiometry was conducted at baseline and 4 weeks follow-up, but none of these data are presented.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to lack of information about randomisation procedure and allocation concealment plus differences between numbers of participants groups at baseline, measurement of the outcome, and selection of the reported result.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	*None*

Ramsden, 1977

Bibliographic Reference	Ramsden, R T; Moffat, D A; Gibson, W P; Jay, M M; S-carboxymethylcysteine in the treatment of glue ear: a double blind trial.; The Journal of laryngology and otology; 1977; vol. 91 (no. 10); 847-51

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children with OME who had not had previous surgery
Exclusion criteria	• Any previous surgery for glue ear
Patient characteristics	N=52 children (N=37 available at final follow-up and included in analysis; patient characteristics reported for all 52 initially included):

	• Mean age (range): not reported (3-9 years) • Gender (male:female): not reported • Mean duration of hearing loss (range): 14 (2-48) months Patient characteristics not reported separately for each group.
Intervention(s)/control	Mucolytic: • S-Carboxymethylcysteine (SCMC)/ carbocisteine given in the following amounts dependant on participant age: 3-4 years: 5ml twice daily; 5-10 years: 5ml three times daily. Further information about dosage not reported Placebo: • Placebo given in the following amounts dependant on participant age: 3-4 years: 5ml twice daily; 5-10 years: 5ml three times daily
Duration of follow-up	1 and 3 months
Sources of funding	Industry funded
Sample size	N=37 children by final follow-up at 3 months (52 initially included but n=15 either failed to return after initial appointment (n=8) or 'defaulted' out between 1st and 3rd follow up appointment or else due to administrative error were admitted for surgery before the end of the trial (n=7). Participants were included in analyses up until their final appointment attendance (N=44 children at 1 month follow-up)) • Mucolytic group: n=18 • Placebo group: n=19
Other information	OME was diagnosed based on the following criteria (otoscopic diagnosis and shape of compliance curve considered to be the most important criteria): • Subjective clinical assessment based on a history of fluctuating hearing loss, the otoscopic appearance of the tympanic membrane and a negative Rinne test • Conductive hearing loss on pure tone audiometry • A flat curve on the middle ear compliance instrument

	Treatment was discontinued at the 1 month or 3 month mark if full recovery was found to have occurred. Outcomes also reported at 1 month; only latest time point within short term (≤3 months) extracted

Study arms

Mucolytic group (N = 18)
n=number of children at final follow-up (3 months)

Placebo group (N = 19)
n=number of children at final follow-up (3 months)

Outcomes

Outcomes

Outcome	Mucolytic group, 3 months, N = 18	Placebo group, 3 months, N = 19
Presence/ persistence of OME Reported as number of participants with unchanged OME status requiring surgery, reported as 'poor' in Table 1 No of events	n = 13 ; % = 62	n = 17 ; % = 74

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Patients were randomised into 2 groups using allocated numbers in a serial manner, in accordance with a code compiled before the trial. Insufficient information describing participant characteristics to determine differences at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended	Low

Section	Question	Answer
interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*(Description of randomisation procedure and use of placebo indicate a double-blind study. Appropriate analyses were conducted.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(15/52 participants (29%) lost to follow-up by final follow-up at 3 months (n=8 failed to return after initial appointment; n=7'defaulted' out between 1st and 3rd follow up appointment or else due to administrative error were admitted for surgery before the end of the trial). However, authors note the high rate of drop was likely due to the length of the trial and the less than average reliability of the population served by the London hospital. Additionally, numbers of participants lost to follow-up balanced between groups so missingness in outcome unlikely to be linked to true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(OME diagnosed using otoscopy and tympanometry. Description of randomisation procedure and use of placebo indicate a double-blind study)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Prespecified protocol unavailable, but no evidence of selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Low *Some minor concerns regarding missing outcome data and lack of information regarding patient characteristics, but overall low risk of bias in all domains.*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Roydhouse, 1981

Bibliographic Reference	Roydhouse, N; Bromhexine for otitis media with effusion.; The New Zealand medical journal; 1981; vol. 94 (no. 696); 373-5

Study details

Country/ies where study was carried out	New Zealand
Study type	Randomised controlled trial (RCT)

Study dates	August 1978 - September 1979
Inclusion criteria	Patients aged ≤14 years seen at the ENT clinic in Middlemore Hospital, South Auckland, who had OME which did not resolve after phase 1 of the trial (in which participants were given specific measures to improve the health of the nose and sinuses (including the use of nasal sprays and the combination of chlorpheniramine maleate and pseudoephedrine), and non-specific measures to improve general resistance to infection).
Exclusion criteria	Not reported

Patient characteristics	N=113 (195 affected ears; 140 initially included but 27 participants lost to follow up excluded from analyses)
	
	Mucolytic + antihistamine group (n=57):
	
	• Mean age (SD): 6.7 (2.5) years
	• Gender (male:female): 31:26
	• Laterality of OME:
	  ○ Unilateral: 17/57 (30%)
	  ○ Bilateral: 40/57 (70%)
	
	Placebo + antihistamine group (n=58):
	
	• Mean age (SD): 6.5 (1.9) years
	• Gender (male:female): 34:22
	• Laterality of OME:
	  ○ Unilateral: 14/58 (24%)
	  ○ Bilateral: 44/58 (76%)

Intervention(s)/control	Mucolytic + antihistamine: • Bromhexine taken for 1 month with dosage depending on age of the participant, plus a refill after 1 month: ≥7 years: 16mg twice daily; ≤6 years: 10ml bromhexine elixir (4mg/ 5ml) three times daily. • Participants also took: ○ ≥7 years: Chlorpheniramine maleate long-acting 8mg twice daily and pseudoephedrine 30 or 60mg twice daily

	○ ≤6 years: Chlorpheniramine maleate elixir (2mg/ 5ml) combined with pseudoephedrine elixir (30mg/ 5ml), 5ml three times daily Placebo + antihistamine: • Placebo taken for 1 month, plus a refill after 1 month • Participants also took: ○ ≥7 years: Chlorpheniramine maleate long-acting 8mg twice daily and pseudoephedrine 30 or 60mg twice daily ○ ≤6 years: Chlorpheniramine maleate elixir (2mg/ 5ml) combined with pseudoephedrine elixir (30mg/ 5ml), 5ml three times daily
Duration of follow-up	2 months (4 months in full study, 2 months of medication post entry into double blind trial)
Sources of funding	None
Sample size	N=113 (195 affected ears; 140 initially included but 27 participants lost to follow up)
Other information	OME diagnosed on clinical grounds and confirmed with impedance audiometry (participants had to have a B- or C-type curve with a peak pressure <-300mm water)

Study arms

Mucolytic + antihistamine group (N = 97)
n=number of ears. n=57 children

Placebo + antihistamine group (N = 98)
n=number of ears. n=56 children

Outcomes

Study timepoints
- 2 month

Outcomes

Outcome	Mucolytic + antihistamine group, 2 month, N = 97	Placebo + antihistamine group, 2 month, N = 98
Presence/ persistence of OME* Reported as number of ears not cured of OME No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 49	n = 77

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Limited information given about randomisation process and allocation concealment: a number was written on the participants' prescriptions which corresponded to a treatment received, according to a random code. Minimal patient characteristics reported (age, gender), but no differences at baseline)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Double-blind trial using placebo. Minimal information given regarding analysis used. 4 participants failed to comply with taking the medicine but authors do not note which groups they belonged to, or how their results were analysed)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(27/140 participants (19%) were lost to follow-up in the randomised controlled trial. The reasons given for loss to follow-up are given for the entire trial period, including the phase prior to the randomised trial: 42 participants did not attend follow-up and 12 participants were excluded due to incorrect diagnosis. It is unclear which of these participants were lost to follow-up during the randomised trial. Missingness in the outcome might depend on its true value, however the number of participants lost to follow-up is balanced between each*

Section	Question	Answer
		groups (12/57 (21%) in the bromhexine group and 15/56 (27%) in the placebo group))
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Impedance audiometry (including tympanometry) used to diagnose OME. Trial was double-blind but no further information about blinding of outcome assessors given.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Prespecified protocol unavailable, but no evidence of selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns related to missingness in the outcome and minor concerns relating to potential deviations from intended interventions)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Saunte, 1978

Bibliographic Reference	Saunte, C; Clinical trial with Lunerin mixture and Lunerin mite in children with secretory otitis media.; The Journal of international medical research; 1978; vol. 6 (no. 1); 50-5

Study details

Country/ies where study was carried out	Norway
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Children with secretory otitis media who met the following criteria: • reduced hearing ability recognised by the child or their parent for ≥14 days • minimum hearing threshold ≥20 dB measured using audiometry • reduced mobility of the ear drum found on otoscopy • if the child had previously had AOM, it must be cured and the child must be without symptoms for ≥2 weeks

	• normal hearing ability prior to the OME
Exclusion criteria	Patients with adenoids, where an adenoidectomy was decided

Patient characteristics	N=21 (31 initially included but 5 later excluded for adenoidectomy and 5 failed to follow the treatment regimen and were excluded from analysis)
	
	Antihistamine and decongestant group (n=11):
	
	• Mean age (range): 6.3 (3-10) years
	• Gender: not reported
	• Atopic heredity to allergic rhinitis to a moderate degree: 4/11 (36%)
	• Mean hearing threshold at baseline/ear (SE):
	  ○ 0.5 kHz (14 ears): 27.5 (1.6) dB
	  ○ 1 kHz (14 ears): 27.1 (2.2) dB
	  ○ 2 kHz (7 ears): 29.3 (3.7) dB
	
	Placebo group (n=10):
	
	• Mean age (range): 5.8 (1-12) years
	• Gender: not reported
	• Atopic heredity to allergic rhinitis to a moderate degree: 5/10 (50%)
	• Mean hearing threshold at baseline/ear (SE):
	  ○ 0.5 kHz (10 ears): 36.0 (4.2) dB
	  ○ 1 kHz (12 ears): 35.0 (3.3) dB
	  ○ 2 kHz (10 ears): 33.5 (3.4) dB

Intervention(s)/control	Antihistamine and decongestant:
	
	• Either Lunerin mixture (0.4mg brompheniramine maleate and 1.7mg phenylpropanolamine hydrochloride per ml) or Lunerin mite (tablet, 6mg brompheniramine maleate and 25mg phenylpropanolamine hydrochloride). The child/ their parents had a free choice whether to use tablet or mixture.
	• Children taking tablets took 1 in the morning and 1 in the afternoon
	• Mixture dosages were age dependent:
	  ○ 3-4 years: 7.5ml, 3 times a day
	  ○ 6-10 years: 10 ml, 3 times a day

	○ >11 years: 15 ml, 3 times a day Placebo: • Same appearance and taste to Lunerin (unclear if children in this group were also offered a choice between tablet or mixture) • Children were not allowed to use other decongestants, antihistamines, or nose-drops during the trial
Duration of follow-up	All patients were asked to return after 2 weeks. Mean (range) time between the first and second visit to the ENT Department was 17·4 (14-28) days for the Lunerin group and 15·3 (8-29) days for the placebo group
Sources of funding	Not reported
Sample size	N=21 (31 initially included but 5 later excluded for adenoidectomy and 5 failed to follow the treatment regimen and were excluded from analysis)
Other information	OME diagnosed based on medical history, a reduced mobility of the ear drum on otoscopy, and minimum hearing threshold ≥20 dB measured using audiometry. The audiometry type used to measure hearing outcomes was not reported. Authors note that to be included in the audiological material, the participant's hearing threshold had to be ≥20dB. Number of participants who failed to follow the trial regimen not reported separately according to trial group, so not extracted

Study arms

Antihistamine and decongestant (N = 11)
n=number of children

Placebo (N = 10)
n=number of children

Outcomes

Outcomes

Outcomes

Outcome	Antihistamine and decongestant, 2 weeks, N = 11	Placebo, 2 weeks, N = 10
Change in hearing threshold from baseline (0.5 kHz)* (dB) Reported per ear (lowering of hearing threshold represented as negative values here, a lower hearing threshold represents hearing improvement). Number of ears in each group at this frequency: Lunerin: n=14; placebo: n=10) Mean (SD**) **SDs calculated using SEs reported in study: Lunerin at 2 weeks vs baseline: 2; placebo at 2 weeks vs baseline: 5.3	-8.9 (7.4833)	-3 (16.7601)
Change in hearing threshold from baseline (1 kHz)* (dB) Reported per ear (lowering of hearing threshold represented as negative values here, a lower hearing threshold represents hearing improvement). Number of ears in each group at this frequency: Lunerin: n=14; placebo: n=12) Mean (SD**) **SDs calculated using SEs reported in study: Lunerin at 2 weeks vs baseline: 2.2; placebo at 2 weeks vs baseline: 5.4	-9.3 (8.2316)	-1.7 (18.7061)
Change in hearing threshold from baseline (2 kHz)* (dB) Reported per ear (lowering of hearing threshold represented as negative values here, a lower hearing threshold represents hearing improvement). Number of ears in each group at this frequency: Lunerin: n=7; placebo: n=10) Mean (SD**) **SDs calculated using SEs reported in study: Lunerin at 2 weeks vs baseline: 4.9; placebo at 2 weeks vs baseline: 3.2	-12.9 (12.9642)	-6 (10.1193)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(The treatments were allocated at random to a consecutive series of numbers by the manufacturer, then children numbered consecutively as they entered the trial and thus allocated to Lunerin or placebo. However, the child/ their parents were given the choice between using the tablet or the mixture. Differences between the range in ages in each group, and the groups' baseline hearing levels for all frequencies (0.5, 1, and 2 kHz) suggest a potential problem with the randomisation process - children in the placebo group had a wider range of ages in years, and consistently had higher mean hearing thresholds (representing worse hearing) for all frequencies at baseline, with a statistically significant difference at 1 kHz ($p<0.05$).)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Double-blind trial using placebo. However, participants were allowed to choose between the tablet or the mixture in the active drug group, and it is unclear if this also applied to the placebo group. If participants in the placebo group could not choose between a mixture and a tablet, children and their parents/ carers might have been able to discern their assigned intervention. The regimen for taking the tablet versus the mixture also meant that the dosages of the active drug were different (those who received the mixture had different treatment regimens and dosages dependent on age, while all children taking the tablet took 2 a day). Authors report 3/11 children (27%) in the Lunerin group used the tablet; information about the placebo group is not given. The analysis does not account for the differences in treatment received for these 3 children, and authors report it was not possible to analyse only 3 children separately. Additionally, 5 children were excluded from the analysis for failure to follow the trial regimen. It is not reported which groups these children were in.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(10/31 participants (32%) were lost to follow-up, 5 of whom received adenoidectomy and were therefore excluded post-randomisation, and 5 of whom failed to follow the treatment regimen. It is possible that missingness in the outcome depended on its true value, but it is not reported which groups these participants belonged to.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Trial was double-blind, though further information about the blinding of the outcome assessors not reported. Hearing was assessed using audiometry by the same specially trained assistant)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Prespecified protocol unavailable, but no evidence of selective reporting)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to missingness in the outcome, deviations from intended interventions, inappropriate analysis, and baseline differences in hearing thresholds between groups despite randomisation.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(It was not possible to adjust the sample size to account for lack of independence, so precision is likely to be over-estimated for all hearing outcomes)*
Overall bias and Directness	Risk of bias variation across outcomes	None

Schoem, 2010

Bibliographic Reference	Schoem, Scott R; Willard, Alice; Combs, Jerome T; A prospective, randomized, placebo-controlled, double-blind study of montelukast's effect on persistent middle ear effusion.; Ear, nose, & throat journal; 2010; vol. 89 (no. 9); 434-7

Study details

Country/ies where study was carried out	US
Study type	Randomised controlled trial (RCT)
Study dates	September 2005 - February 2007
Inclusion criteria	Children aged 2 to 6 years presenting with persistent MEE in at least one ear for ≥2 months
Exclusion criteria	• History of allergy • Current use of montelukast for asthma or allergic rhinitis • Previous adverse reaction to montelukast

	• Presence of craniofacial disorder • Use of systemic steroid within one month prior to presentation • Presence of acute otitis media at presentation • Parental desire for the child to remain on prophylactic antibiotics as prescribed by a primary care provider
Patient characteristics	N= 38 children. Patient characteristics are not reported.
Intervention(s)/control	Leukotrine receptor antagonist: • 4mg of oral montelukast once an evening for 1 month. Further information regarding dosage not reported Placebo: • 4mg of placebo once an evening for 1 month
Duration of follow-up	1 month
Sources of funding	Industry funded
Sample size	N= 38 children • Leukotrine receptor antagonistgroup: n=19 • Placebo group: n=19
Other information	Diagnosis of OME was confirmed by otoscopy and validated independently via tympanometry. The study aimed to recruit 120 participants but after 38 patients had completed their regimen, an interim analysis was performed. The study was terminated early by funding sponsor due to early trend of ineffectiveness of Montelukast regimen.

Study arms

Leukotrine receptor antagonistGroup (N = 19)
n=number of children

Placebo Group (N = 19)
n=number of children

Outcomes

Outcomes

Outcome	Leukotrine receptor antagonist Group, 1 month, N = 19	Placebo Group, 1 month, N = 19
Presence/ persistence of OME Reported as number of children who did not have OME clearance No of events	n = 16 ; % = 84	n = 15 ; % = 79

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Information on randomisation process, allocation concealment, and patient characteristics not reported.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Double-blind trial using placebo. Information regarding analysis not reported.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for all recruited participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double-blind trial. Further information regarding blinding of outcome assessors not reported, but presence of OME assessed using otoscopy and tympanometry, including independent assessment by 2 different clinicians)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Prespecified protocol was not available, but no evidence of selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns regarding a lack of information on randomisation process, allocation concealment, patient characteristics, analysis methods, and a prespecified protocol.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Stewart, 1985

Bibliographic Reference	Stewart, I A; Guy, A M; Allison, R S; Thomson, N J; Bromhexine in the treatment of otitis media with effusion.; Clinical otolaryngology and allied sciences; 1985; vol. 10 (no. 3); 145-9

Study details

Country/ies where study was carried out	New Zealand
Study type	Cross-over randomised controlled trial
Study dates	June 1983 - May 1984
Inclusion criteria	All children aged 3 to 8 years attending the ENT Clinic of Dunedin Hospital during the study dates, who met the following criteria: • Proven effusion in at least 1 ear by otomicroscopy and type-B tympanogram • No other significant ear pathology • No previous ear surgery • No antibiotic treatment over the study period • Co-operative with examination and tablet taking • No underlying structural abnormality, e.g. Down's syndrome, cleft palate

Exclusion criteria	Children with previous tympanostomy tubes; children with <80% compliance with medication

Patient characteristics	N=95 (190 ears; 114 participants initially entered into the study, 19 withdrawn due to adverse events (n=6) or administrative error (n=3), or excluded for treatment non-compliance through the whole trial (n=6))
	
	Mucolytic group*:
	
	• Mean age (SD): 67.0 months (not reported)
	• Gender (ratio of male:female): 60:40
	• Laterality of OME**:
	  ○ Unilateral: 35%
	  ○ Bilateral: 65%
	
	Placebo*:
	
	• Mean age (SD): 66.0 months (not reported)
	• Gender (ratio of male:female): 58:42
	• Laterality of OME**:
	  ○ Unilateral: 25%
	  ○ Bilateral: 75%
	
	*Numbers of participants in each group not reported, though number of children/ ears for those who took either mucolytic or placebo for the full 8 weeks without crossing over are given in the results (see Study arms below). Authors note patient characteristics for each group reported at baseline overlap to some extent since some children received both placebo and bromhexine
	
	**Only percentages reported for this characteristic, numbers could not be calculated because number of participants in each group not reported

Intervention(s)/control	Mucolytic: • Bromhexine tablets: for children aged 3-5 years, 8mg (1 tablet) 3 times daily; for children aged 6-8 years, 16mg (2 tablets) 3 times daily • Drugs were issued every 2 weeks in batches which included 6 extra doses

	• The results from 1 group which took bromhexine for the full 8 weeks of the trail (did not cross-over) is extracted for the purposes of this review Placebo: • Placebo tablets were not readily distinguishable from the active drug • Drugs were issued every 2 weeks in batches which included 6 extra doses • The results from 1 group which took placebo for the full 8 weeks of the trail (did not cross-over) is extracted for the purposes of this review A letter to the family practitioner requested that other medications be withheld if possible over the trial period, for both groups
Duration of follow-up	8 weeks
Sources of funding	Industry funded
Sample size	N=95 (190 ears; 114 participants initially entered into the study, 19 withdrawn due to adverse events (n=6) or administrative error (n=3), or excluded for treatment non-compliance through the whole trial (n=6)) Note only results for n=44 children (n=88 ears) who took either mucolytic or placebo for the full 8 weeks without crossing over are extracted for the purposes of this review (see Other Information).
Other information	OME diagnosed using otomicroscopy and impedance tympanometry. At entry, authors report participants had a type B tympanogram as inclusion criteria. In the results section, authors note that where participants did not have a type B or C2 tympanogram, otomicroscopic diagnosis of effusion was accepted as a diagnosis of OME. It is unclear if the inclusion criteria changed or if these criteria were inconsistent throughout the trial. Results for the outcome presence/ persistence of OME could not be extracted at 4 weeks follow-up, because the way results are displayed seems to count all participants twice (it is unclear why, but results for a total of 380 ears are given despite N=190 ears in study), and results for participants who exclusively took either bromhexine or placebo and did not cross over do not appear to be reported separately from those who crossed over. Results for hearing outcomes could not be extracted because results for participants who exclusively took either mucolytic or placebo and did not cross over do not appear to be reported separately from those who crossed over. Results for the outcome treatment discontinuation due to adverse events could not be extracted because results for participants who exclusively took either mucolytic or placebo and did not cross over are not reported separately from those who crossed over.

Study arms

Mucolytic (N = 40)
n=number of ears. Number of participants=20

Placebo (N = 48)
n=number of ears. Number of participants=24

Outcomes

Study timepoints
- 8 week

Outcomes

Outcome	Mucolytic, 8 week, N = 40	Placebo, 8 week, N = 48
Presence/ persistence of OME* Reported as number of ears with effusion No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 25	n = 32

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Authors report "To avoid seasonal bias, the subjects were randomized within groups of 4, each group containing 1 subject following each of the 4 above regimes. The randomization code was held by the pharmacy and was broken only when possible side-effects presented." Additional information about the randomisation process and allocation concealment is not reported. Although*

Section	Question	Answer
		limited patient characteristics are reported and there are no significant baseline differences, they are separated according to which participants received bromhexine and which received placebo, and authors report that "These groups overlap to some extent since some children received both placebo and bromhexine." Patient characteristics for all 4 groups who received different regimens over the 8 week duration of the trial are not reported.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High *(Double-blind trial using placebo tablets which were not readily distinguishable from the active drug. Participants who experienced side-effects (diarrhoea, enuresis, rash, or diarrhoea and enuresis; n=5) or who had an administrative error, were withdrawn from the study and not included in analyses. Participants who had <80% compliance with the medication were also excluded post-randomisation. All participants who experienced side-effects were all receiving the active drug.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(19/114 participants (17%) were excluded from the study post-randomisation. Information on which groups these participants belonged to is only reported for 5 of these participants (withdrawn due to side-effects), and all of the participants in this group belonged to the bromhexine group)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Double-blind trial. Criteria for diagnosing OME seemed to change throughout the trial: at entry, authors report a type B tympanogram as criteria for proving effusion. In the results section, authors note that where participants did not have a type B or C2 tympanogram, otomicroscopic diagnosis of effusion was accepted as a diagnosis of OME. It is unclear if the inclusion criteria changed and therefore these participants were included at baseline, or if these criteria were inconsistent throughout the trial, which may have affected results for the outcome presence/ persistence of OME.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High *(Reporting methods meant results for presence/ persistence of OME at 4 weeks follow-up could not be extracted, as well as results for hearing outcomes or for discontinuation of treatment due to adverse events. These results were all reported according to whether the participants received the*

Section	Question	Answer
		drug (bromhexine or placebo) at any point in the trial, rather than which groups the participants were assigned to, meaning there might be duplication/ overlap in the results. It is also unclear whether OME was assessed using different criteria than at baseline)
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to selection of the reported result, inappropriate analysis, and missing outcome data. Some concerns regarding measurement of the outcome and the way patient characteristics were presented.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

van der Merwe, 1987

Bibliographic Reference	van der Merwe, J; Wagenfeld, D J; The negative effects of mucolytics in otitis media with effusion.; South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde; 1987; vol. 72 (no. 9); 625-6

Study details

Country/ies where study was carried out	South Africa
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Patients with OME seen in the routine outpatient clinics of Tygerberg Hospital
Exclusion criteria	Patients with previous ear surgery
Patient characteristics	N=60 (at 12 weeks follow-up, 33 participants had not been lost to follow-up and were still included in the trial. Data for participants who were lost to follow-up are reported until their final appointment) • Mean age (SD)*: Not reported. 91% of participants were <12 years • Gender (male:female)*: 40:20

	Mucolytic group (n=29):
	
	• Hearing thresholds (pure-tone audiometry of free-field audiometry; n=58 ears)/ ear**:
	  ○ Right ear <15dB: 8/29 (27%)
	  ○ Left ear <15dB: 7/29 (23%)
	  ○ Right ear 15-30dB: 13/29 (45%)
	  ○ Left ear 15-30dB: 14/29 (48%)
	  ○ Right ear >30dB: 8/29 (27%)
	  ○ Left ear >30dB: 8/29 (27%)
	
	Placebo group (n=31):
	
	• Hearing thresholds (pure-tone audiometry of free-field audiometry; n=29 ears each side, 58 ears total)**:
	  ○ Right ear <15dB: 8/29 (27%)
	  ○ Left ear <15dB: 6/29 (21%)
	  ○ Right ear 15-30dB: 12/29 (42%)
	  ○ Left ear 15-30dB: 15/29 (51%)
	  ○ Right ear >30dB: 9/29 (31%)
	  ○ Left ear >30dB: 10/29 (35%)
	
	*These patient characteristics not reported separately per group
	
	**Results reported as percentages and converted to number of events assuming number of ears is the same at each time point; data extracted from figure and numbers do not add up exactly to total ears reported at baseline for placebo group

Intervention(s)/control	Mucolytic:
	
	• Bromhexine taken for 1 month using the following dosage regimens depending on age:
	  ○ <1 year: 1.25ml (2.5mg) 3 times a day
	  ○ 1-5 years: 2.5ml (5mg) 3 times a day
	  ○ 6-10 years: 4ml (8mg) 3 times a day
	  ○ >10 years: 8ml (16mg) 3 times a day
	
	Placebo:

	• Placebo taken for 1 month. Treatment regimen not further described.
Duration of follow-up	2, 4, and 12 weeks
Sources of funding	Industry funded
Sample size	N=60 (at 12 weeks follow-up, 33 participants had not been lost to follow-up and were still included in the trial. Data for participants who were lost to follow-up are reported until their final appointment)
Other information	OME diagnosed based on ENT examination, with emphasis on tympanic membrane appearance and movement, pure-tone audiometry and tympanometry Outcomes also reported at 2 and 4 weeks; only latest time point within short term (≤3 months) extracted Results reported as percentages; converted to number of events using WebPlotDigitizer <https://apps.automeris.io/wpd/>

Study arms

Mucolytic (N = 62)
n=number of ears. Number of participants=31

Placebo (N = 58)
n=number of ears. Number of participants=29

Outcomes

Study timepoints
- 12 week

Presence/ persistence of OME outcomes

Outcome	Mucolytic, 12 week, N = 32	Placebo, 12 week, N = 34
Presence/ persistence of OME (per ear)* Number of right and left ears with MEE reported in study separately and combined here. No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 19 ; % = 59	n = 20 ; % = 59

Hearing outcomes

Outcome	Mucolytic, 12 week, N = 32	Placebo, 12 week, N = 34
Number of ears with hearing returned to normal (pure-tone audiometry) (per ear)* Number of right and left ears with MEE reported in study separately and combined here. Reported as the number of ears with hearing thresholds <15dB (assessed using pure-tone audiometry or free-field audiometry) No of events *Sample size/number of events adjusted in analysis to account for lack of independence between ears from the same child	n = 16 ; % = 50	n = 21 ; % = 62

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information reported about the randomisation process or allocation concealment. Age and gender characteristics not reported separately for each group, however hearing at baseline appears to be balanced between groups.)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Double-blind trial using placebo. Participants experiencing prolonged severe (>40-50 dB) bilateral conductive hearing loss were removed from the study. The number of these participants is not reported, and it's unclear if their results are included in the analyses up until their last attended appointment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(By final follow-up at 12 weeks, authors report data remained for only 45% in the bromhexine group, and 41% in the placebo group. Authors note that participants were either lost to follow-up due to not attending appointments, or were excluded because of longstanding severe (>40-50 dB) bilateral hearing loss. The numbers of participants who were excluded for this reason are not reported and it is possible that missingness in the outcome depended on its true value, depending on whether the reasons for missing outcome data differed between groups. However, overall the missingness in the outcome was balanced between groups.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Tympanometry and likely otoscopy used to diagnose OME. Trial was double-blind, however further information about blinding of outcome assessors not reported)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No prespecified protocol was available. No evidence of selective reporting, though reporting methods through the use of graphs do not provide numerical figures and are unclear)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to significant missingness in the outcome at 12 weeks. Some concerns regarding inappropriate analysis, selection of the reported result, and lack of information on randomisation process, allocation concealment, and patient characteristics)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

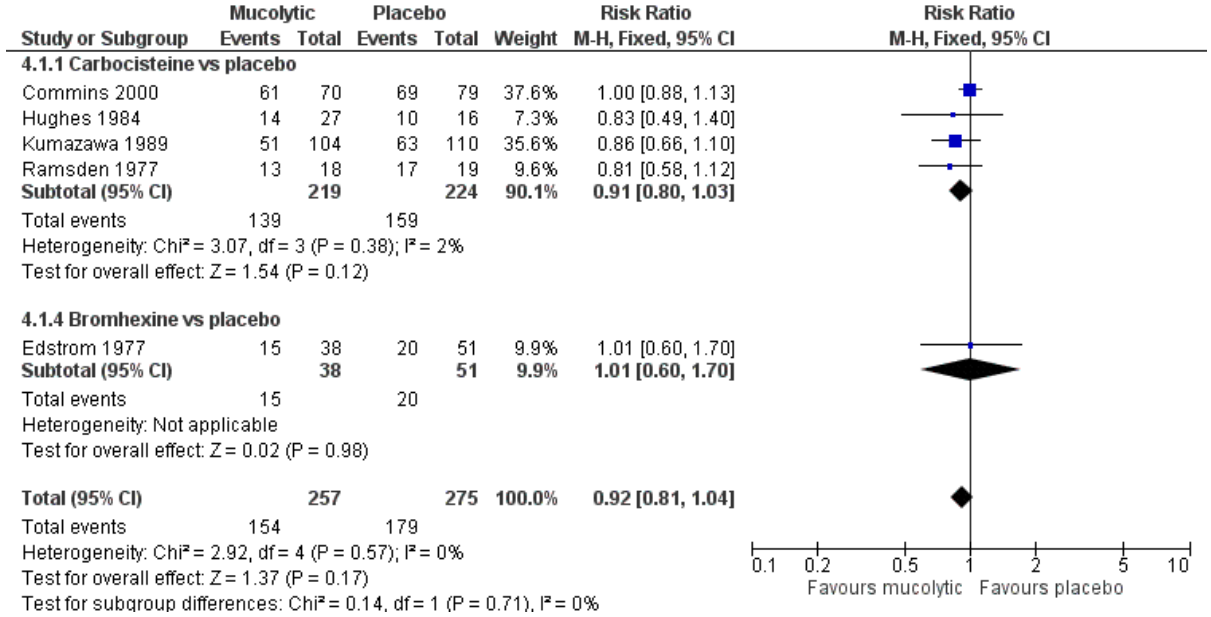
Steroids

See the Data and analyses tables from the Cochrane review on steroids at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

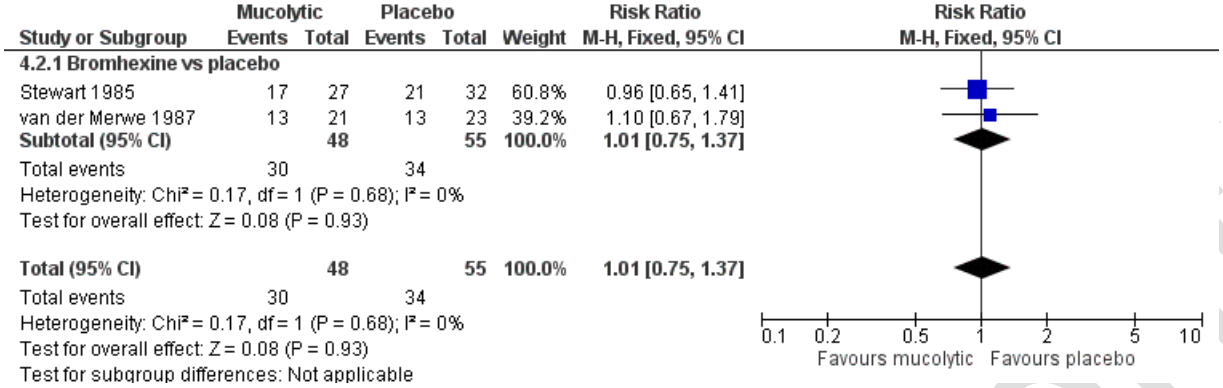
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Mucolytic versus placebo: Presence/ persistence of OME (per child, short term)



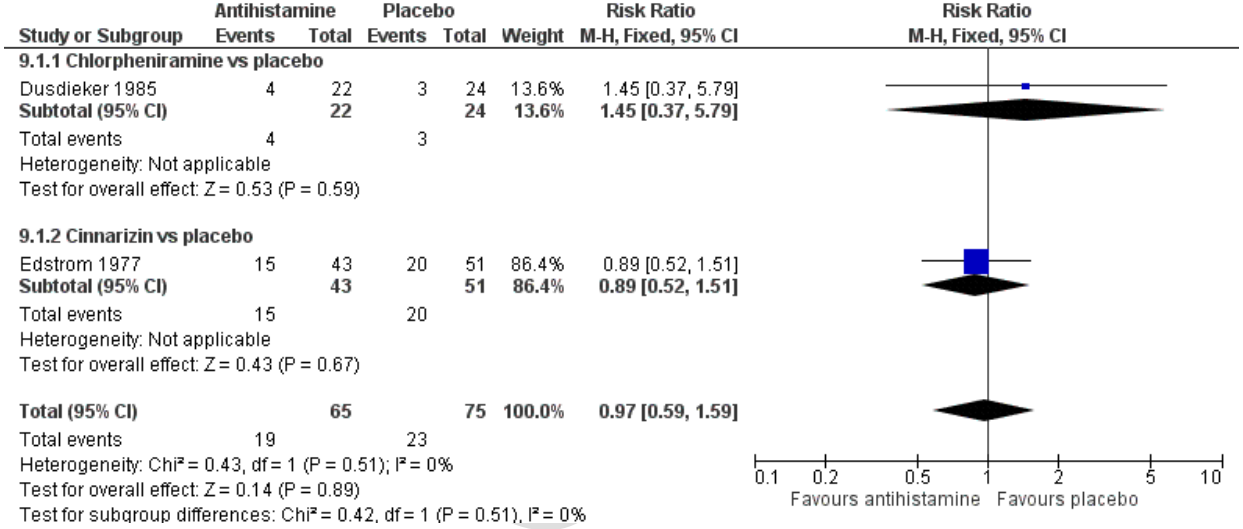
CI: confidence intervals; M-H: Mantel-Haenszel; OME: otitis media with effusion

Figure 3: Mucolytic versus placebo: Presence/ persistence of OME (per ear, short term; assumed ICC=0.5)



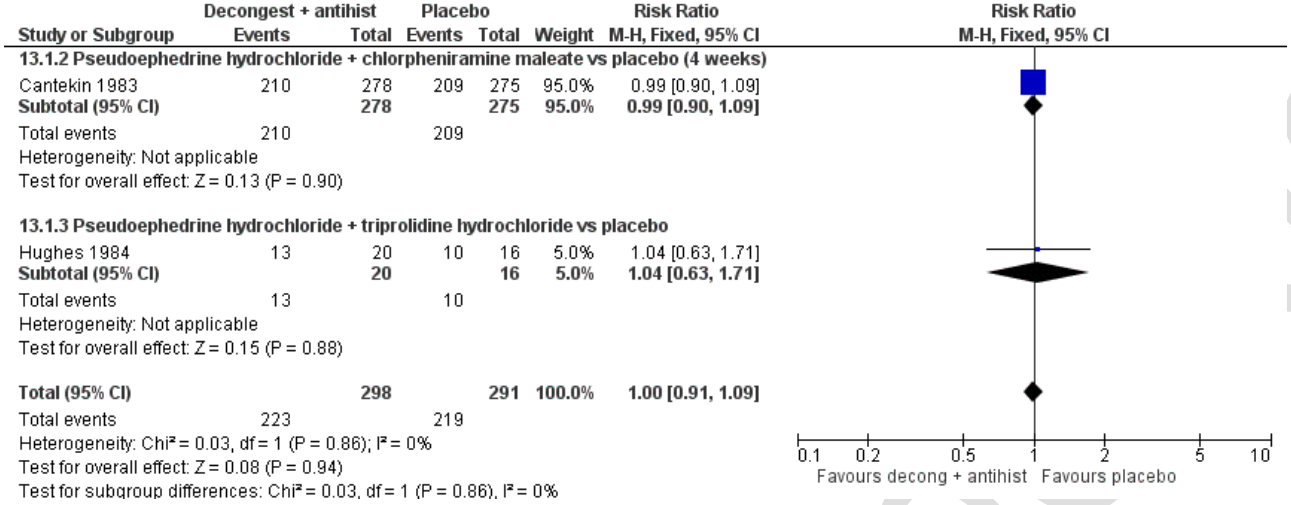
CI: confidence intervals; ICC: intra-cluster correlation coefficient; M-H: Mantel-Haenszel; OME: otitis media with effusion

Figure 4: Antihistamine versus placebo: Presence/ persistence of OME (per child, short term)



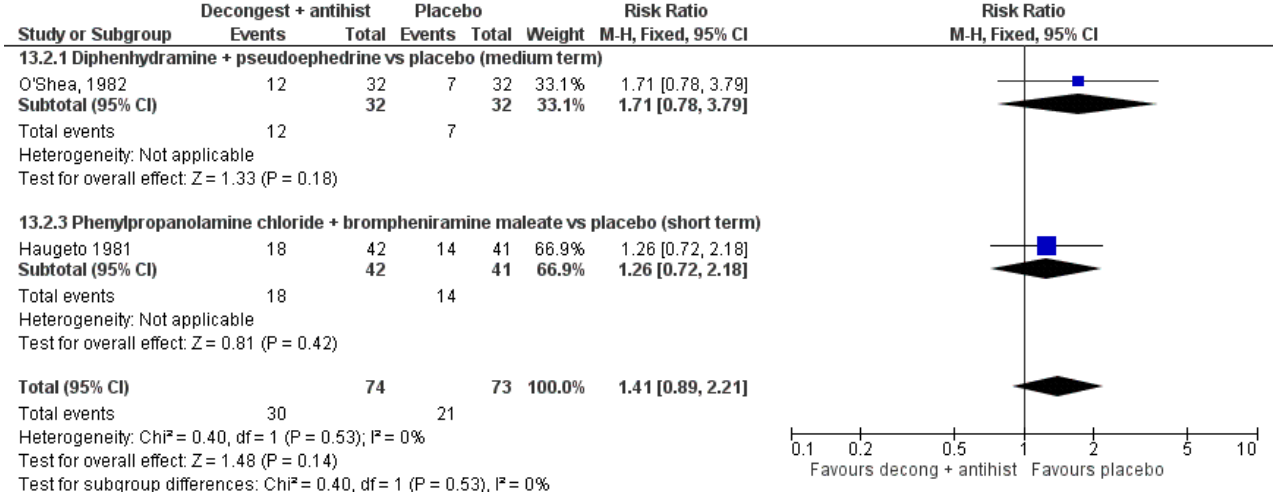
CI: confidence intervals; M-H: Mantel-Haenszel; OME: otitis media with effusion

Figure 5: Decongestant + antihistamine versus placebo: Presence/ persistence of OME (per child, short term)



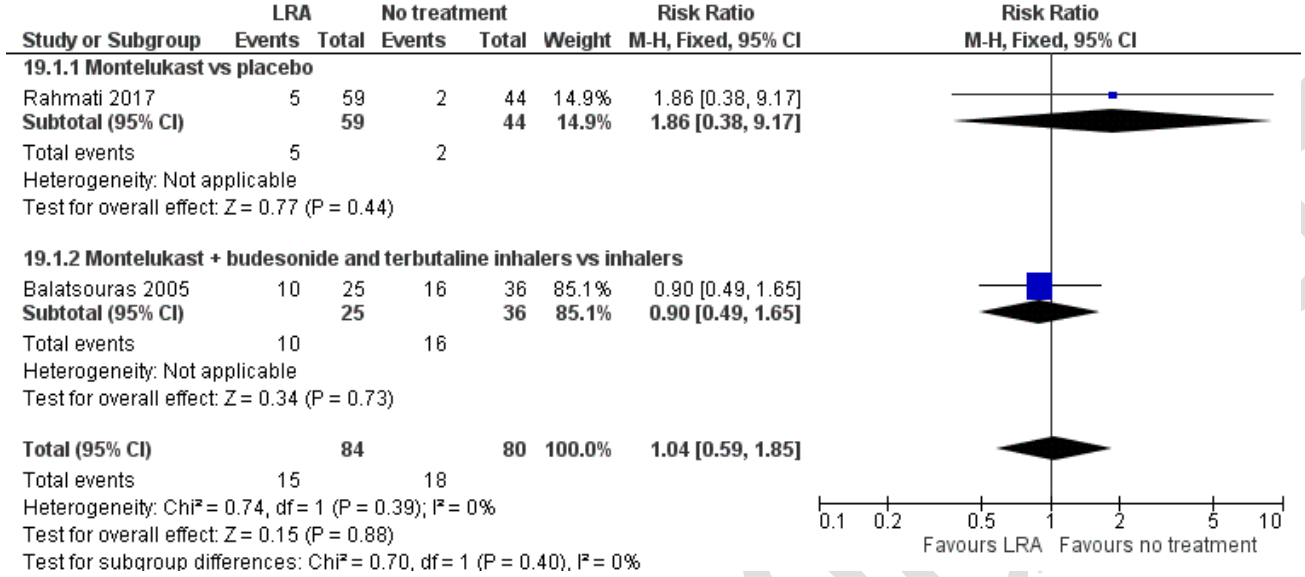
CI: confidence intervals; M-H: Mantel-Haenszel; OME: otitis media with effusion

Figure 6: Decongestant + antihistamine versus placebo: Presence/ persistence of OME (per ear, short/ medium term; assumed ICC=0.5)



CI: confidence intervals; ICC: intra-cluster correlation coefficient; M-H: Mantel-Haenszel; OME: otitis media with effusion

Figure 7: Leukotriene receptor antagonist versus no treatment: Presence/ persistence of OME (per child, short term)



CI: confidence intervals; LRA: leukotrine receptor antagonist; M-H: Mantel-Haenszel; OME: otitis media with effusion

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Steroids

See the Summary of findings tables from the Cochrane review on steroids at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Table 7: Evidence profile for comparison between mucolytic, decongestant + antihistamine (MDA) versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDA	placebo	Relative (95% CI)	Absolute (95% CI)		
Presence/ persistence of OME (per child, short term*)												
1 (Hughes 1984)	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	13/20 (65.0%)	10/16 (62.5%)	**RR 1.04** (0.63 to 1.71)	**25 more per 1,000** (from 231 fewer to 444 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 0.25kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	6/19 (31.6%)	3/19 (15.8%)	**RR 2.00** (0.58 to 6.85)	**158 more per 1,000** (from 66 fewer to 924 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 0.5kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	8/19 (42.1%)	4/19 (21.1%)	**RR 2.00** (0.72 to 5.53)	**211 more per 1,000** (from 59 fewer to 954 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 1kHz)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDA**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	6/19 (31.6%)	6/19 (31.6%)	**RR 1.00** (0.39 to 2.55)	**0 fewer per 1,000** (from 193 fewer to 489 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 2kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	0/19 (0.0%)	**RR 5.00** (0.26 to 97.70)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 4kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	9/19 (47.4%)	8/19 (42.1%)	**RR 1.13** (0.55 to 2.29)	**55 more per 1,000** (from 189 fewer to 543 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 8kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	7/19 (36.8%)	8/19 (42.1%)	**RR 0.88** (0.40 to 1.93)	**51 fewer per 1,000** (from 253 fewer to 392 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 0.25kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	0/19 (0.0%)	**RR 5.00** (0.26 to 97.70)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 0.5kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	0/19 (0.0%)	1/19 (5.3%)	**RR 0.33** (0.01 to 7.70)	**35 fewer per 1,000** (from 52 fewer to 353 more)	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDA**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hearing returned to normal (per child, short term*; bone conduction, 1kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	1/19 (5.3%)	1/19 (5.3%)	**RR 1.00** (0.07 to 14.85)	**0 fewer per 1,000** (from 49 fewer to 729 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 2kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	1/19 (5.3%)	**RR 2.00** (0.20 to 20.24)	**53 more per 1,000** (from 42 fewer to 1,000 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 4kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	3/19 (15.8%)	**RR 0.67** (0.13 to 3.55)	**52 fewer per 1,000** (from 137 fewer to 403 more)	Very low	CRITICAL

CI: confidence interval; MDA: mucolytic, decongestant + antihistamine; OME: otitis media with effusion; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. Population is indirect due to ages of participants not being reported
c. 95% CI crosses 2 MIDs
d. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

Table 8: Evidence profile for comparison between mucolytic, decongestant + antihistamine (MDA) versus mucolytic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDA**	**mucolytic**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDA**	**mucolytic**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Hughes 1984)	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	13/20 (65.0%)	14/27 (51.9%)	**RR 1.25** (0.77 to 2.04)	**130 more per 1,000** (from 119 fewer to 539 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 0.25kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	serious[e]	none	6/19 (31.6%)	12/20 (60.0%)	**RR 0.53** (0.25 to 1.12)	**282 fewer per 1,000** (from 450 fewer to 72 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 0.5kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	8/19 (42.1%)	9/20 (45.0%)	**RR 0.94** (0.46 to 1.91)	**27 fewer per 1,000** (from 243 fewer to 410 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 1kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	6/19 (31.6%)	9/20 (45.0%)	**RR 0.70** (0.31 to 1.59)	**135 fewer per 1,000** (from 311 fewer to 266 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 2kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	3/20 (15.0%)	**RR 0.70** (0.13 to 3.75)	**45 fewer per 1,000** (from 131 fewer to 413 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 4kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	9/19 (47.4%)	10/20 (50.0%)	**RR 0.95** (0.50 to 1.81)	**25 fewer per 1,000** (from 250 fewer to 405 more)	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDA	mucolytic	Relative (95% CI)	Absolute (95% CI)		
Hearing returned to normal (per child, short term*; air conduction, 8kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	7/19 (36.8%)	11/20 (55.0%)	**RR 0.67** (0.33 to 1.36)	**182 fewer per 1,000** (from 369 fewer to 198 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 0.25kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	2/20 (10.0%)	**RR 1.05** (0.16 to 6.74)	**5 more per 1,000** (from 84 fewer to 574 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 0.5kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	0/19 (0.0%)	1/20 (5.0%)	**RR 0.35** (0.02 to 8.10)	**33 fewer per 1,000** (from 49 fewer to 355 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 1kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	1/19 (5.3%)	2/20 (10.0%)	**RR 0.53** (0.05 to 5.34)	**47 fewer per 1,000** (from 95 fewer to 434 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 2kHz)												
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	3/20 (15.0%)	**RR 0.70** (0.13 to 3.75)	**45 fewer per 1,000** (from 131 fewer to 413 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 4kHz)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDA**	**mucolytic**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Khan 1981)	randomised trials	very serious[d]	not serious	not serious	very serious[c]	none	2/19 (10.5%)	7/20 (35.0%)	**RR 0.30** (0.07 to 1.27)	**245 fewer per 1,000** (from 325 fewer to 95 more)	Very low	CRITICAL

CI: confidence interval; MDA: mucolytic, decongestant + antihistamine; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. Population is indirect due to ages of participants not being reported
c. 95% CI crosses 2 MIDs
d. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
e. 95% CI crosses 1 MID

Table 9: Evidence profile for comparison between mucolytic, decongestant + antihistamine (MDA) versus decongestant + antihistamine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDA**	**decongestant + antihistamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Hughes 1984)	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	13/20 (65.0%)	13/20 (65.0%)	**RR 1.00** (0.63 to 1.58)	**0 fewer per 1,000** (from 241 fewer to 377 more)	Very low	CRITICAL

CI: confidence interval; MDA: mucolytic, decongestant + antihistamine; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. Population is indirect due to ages of participants not being reported
c. 95% CI crosses 2 MIDs

Table 10: Evidence profile for comparison between mucolytic versus placebo

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytic**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
5 (Commins 2000, Edstrom 1977, Hughes 1984, Kumazawa 1989, Ramsden 1977)	randomised trials	serious[a]	not serious	not serious	not serious	none	154/257 (59.9%)	179/275 (65.1%)	**RR 0.92** (0.81 to 1.04)	**52 fewer per 1,000** (from 124 fewer to 26 more)	Moderate	CRITICAL
Presence/ persistence of OME (per ear, short term*; assumed ICC=0.5)												
2 (Stewart 1985, van der Merwe 1987)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	publication bias suspected[d]	30/48 ears (62.5%)	34/55 ears (61.8%)	**RR 1.01** (0.75 to 1.37)	**6 more per 1,000** (from 155 fewer to 229 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 0.25kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	not serious	none	12/20 (60.0%)	3/19 (15.8%)	**RR 3.80** (1.27 to 11.40)	**442 more per 1,000** (from 43 more to 1,000 more)	Low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 0.5kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	9/20 (45.0%)	4/19 (21.1%)	**RR 2.14** (0.79 to 5.79)	**240 more per 1,000** (from 44 fewer to 1,000 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 1kHz)												

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytic**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	9/20 (45.0%)	6/19 (31.6%)	**RR 1.43** (0.63 to 3.24)	**136 more per 1,000** (from 117 fewer to 707 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 2kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	3/20 (15.0%)	0/19 (0.0%)	**RR 6.67** (0.37 to 121.07)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 4kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	10/20 (50.0%)	8/19 (42.1%)	**RR 1.19** (0.60 to 2.36)	**80 more per 1,000** (from 168 fewer to 573 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction, 8kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	11/20 (55.0%)	8/19 (42.1%)	**RR 1.31** (0.68 to 2.53)	**131 more per 1,000** (from 135 fewer to 644 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 0.25kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	2/20 (10.0%)	0/19 (0.0%)	**RR 4.76** (0.24 to 93.19)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 0.5kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[b]	none	1/20 (5.0%)	1/19 (5.3%)	**RR 0.95** (0.06 to 14.13)	**3 fewer per 1,000** (from 49 fewer to 691 more)	Very low	CRITICAL

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytic**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Hearing returned to normal (per child, short term*; bone conduction, 1kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	2/20 (10.0%)	1/19 (5.3%)	**RR 1.90** (0.19 to 19.27)	**47 more per 1,000** (from 43 fewer to 962 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 2kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	3/20 (15.0%)	1/19 (5.3%)	**RR 2.85** (0.32 to 25.07)	**97 more per 1,000** (from 36 fewer to 1,000 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; bone conduction, 4kHz)												
1 (Khan 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	7/20 (35.0%)	3/19 (15.8%)	**RR 2.22** (0.67 to 7.34)	**193 more per 1,000** (from 52 fewer to 1,000 more)	Very low	CRITICAL
Hearing returned to normal (per ear, short term*; pure-tone or free-field audiometry; assumed ICC=0.5)												
1 (van der Merwe 1987)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	publication bias suspected[d]	11/21 ears (52.4%)	14/23 ears (60.9%)	**RR 0.86** (0.51 to 1.45)	**85 fewer per 1,000** (from 298 fewer to 274 more)	Very low	CRITICAL
Discontinuation of treatment due to vomiting (per child, short term*)												
1 (Kumazawa 1989)	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	2/104 (1.9%)	0/110 (0.0%)	**RR 5.29** (0.26, 108.81)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

c. 95% CI crosses 2 MIDs
d. Publication bias suspected due to majority of studies being industry funded

Table 11: Evidence profile for comparison between mucolytic versus no treatment[a]

Certainty assessment							№ of ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytic**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per ear, short term*)												
1 (Babic 2017)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	15/40 ears (37.5%)	19/40 ears (47.5%)	**RR 0.79** (0.47 to 1.32)	**100 fewer per 1,000** (from 252 fewer to 152 more)	Very low	CRITICAL
Change in hearing threshold from baseline (per ear, short term*; pure-tone average; assumed ICC=0.5)												
1 (McGuiness 1977)	randomised trials	very serious[b]	not serious	not serious	serious[d]	none	27 ears	21 ears	-	MD **5.7 lower** (9.25 lower to 2.15 lower)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; MD: mean difference; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. studies have been classified as compared against no treatment when any additional treatments received were equivalent across arms
b. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
c. 95% CI crosses 2 MIDs
d. 95% CI crosses 1 MID (0.5x control group SD: for change in hearing threshold from baseline = 3.11)

Table 12: Evidence profile for comparison between mucolytic + antihistamine versus placebo + antihistamine

Certainty assessment							№ of ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytic + antihistamine**	**placebo + antihistamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per ear, short term*; assumed ICC=0.5)												
1 (Roydhouse 1981)	randomised trials	serious[a]	not serious	not serious	serious[b]	none	33/66 ears (50.0%)	52/67 ears (77.6%)	**RR 0.64** (0.49 to 0.85)	**279 fewer per 1,000** (from 396 fewer to 116 fewer)	Low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; RR: risk ratio

**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 1 MID

Table 13: Evidence profile for comparison between mucolytic + antihistamine versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mucolytic + antihistamine**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Edstrom 1977)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	19/46 (41.3%)	20/51 (39.2%)	**RR 1.05** (0.65 to 1.71)	**20 more per 1,000** (from 137 fewer to 278 more)	Very low	CRITICAL

CI: confidence interval; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs

Table 14: Evidence profile for comparison between antihistamine versus mucolytic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antihistamine**	**mucolytic**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Edstrom 1977)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	15/43 (34.9%)	15/40 (37.5%)	**RR 0.93** (0.53 to 1.65)	**26 fewer per 1,000** (from 176 fewer to 244 more)	Very low	CRITICAL

CI: confidence interval; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs

Table 15: Evidence profile for comparison between antihistamine versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antihistamine**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
2 (Dusdieker 1985, Edstrom 1977)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	19/65 (29.2%)	23/75 (30.7%)	**RR 0.97** (0.59 to 1.59)	**9 fewer per 1,000** (from 126 fewer to 181 more)	Very low	CRITICAL
Discontinuation of treatment due to hyperactivity and poor sleeping (per child, short term*)												
1 (Dusdieker 1985)	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	0/22 (0.0%)	0/24 (0.0%)	**RD 0.00** (-0.08 to 0.08)	**0 fewer per 1,000** (from 80 fewer to 80 more)	Very low	CRITICAL

CI: confidence interval; RD: risk difference; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs
c. Sample size <200

Table 16: Evidence profile for comparison between antihistamine versus no treatment[a]

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antihistamine**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Choung 2008)	randomised trials	very serious[b]	not serious	not serious	very serious[c]	none	9/15 (60.0%)	8/16 (50.0%)	**RR 1.20** (0.63 to 2.28)	**100 more per 1,000** (from 185 fewer to 640 more)	Very low	CRITICAL
Presence/ persistence of OME (per ear, short term*; assumed ICC=0.5)												

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antihistamine**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Hisamatsu 1994)	randomised trials	very serious[b]	not serious	not serious	serious[d]	none	15/41 ears (36.6%)	19/36 ears (52.8%)	**RR 0.69** (0.42 to 1.15)	**164 fewer per 1,000** (from 306 fewer to 79 more)	Very low	CRITICAL
Hearing returned to normal (per ear, short term*; air conduction; assumed ICC=0.5)												
1 (Hisamatsu 1994)	randomised trials	very serious[b]	not serious	serious[e]	very serious[c]	none	7/14 ears (50.0%)	5/14 ears (35.7%)	**RR 1.40** (0.58 to 3.36)	**143 more per 1,000** (from 150 fewer to 843 more)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. studies have been classified as compared against no treatment when any additional treatments received were equivalent across arms
b. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
c. 95% CI crosses 2 MIDs
d. 95% CI crosses 1 MID
e. Population is indirect due to children over the age of 12 included, the number of these participants is not reported, and results are not presented separately for these participants. However, the percentage of participants over 12 is likely to be small as 63% of participants in the Tranilast and local treatment group were in the age group 6-15 years, and 52% in the local treatment group were in the age group 6-15 years

Table 17: Evidence profile for comparison between decongestant + antihistamine versus decongestant

Certainty assessment							№ of ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**decongestant**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per ear, short term*; assumed ICC=0.5)												
1 (Haugeto 1981)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	publication bias suspected[c]	18/42 ears (42.9%)	15/33 ears (45.5%)	**RR 0.94** (0.57 to 1.57)	**27 fewer per 1,000** (from 195 fewer to 259 more)	Very low	CRITICAL
Hearing returned to normal (per ear, short term*; air conduction; assumed ICC=0.55)												

Certainty assessment							№ of ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**decongestant**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Haugeto 1981)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	publication bias suspected[c]	5/7 ears (71.4%)	5/8 ears (62.5%)	**RR 1.14** (0.56 to 2.33)	**87 more per 1,000** (from 275 fewer to 831 more)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs
c. Publication bias suspected due to majority of studies being industry funded

Table 18: Evidence profile for comparison between decongestant + antihistamine versus mucolytic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**mucolytic**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Hughes 1984)	randomised trials	serious[a]	not serious	serious[b]	very serious[c]	none	13/20 (65.0%)	14/27 (51.9%)	**RR 1.25** (0.77 to 2.04)	**130 more per 1,000** (from 119 fewer to 539 more)	Very low	CRITICAL

CI: confidence interval; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. Population is indirect due to ages of participants not being reported
c. 95% CI crosses 2 MIDs

Table 19: Evidence profile for comparison between decongestant + antihistamine versus placebo

Certainty assessment							№ of patients/ ears/ assessments		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
2 (Cantekin 1983, Hughes 1984)	randomised trials	serious[a]	not serious	not serious	not serious	none	223/298 (74.8%)	219/291 (75.3%)	**RR 1.00** (0.91 to 1.09)	**0 fewer per 1,000** (from 68 fewer to 68 more)	Moderate	CRITICAL
Presence/ persistence of OME (per ear, short/ medium term*; assumed ICC=0.5)												
2 (O'Shea 1980/1982, Haugeto 1981)	randomised trials	very serious[b]	not serious	not serious	serious[c]	publication bias suspected[h]	30/74 ears (40.5%)	21/73 ears (28.8%)	**RR 1.41** (0.89 to 2.21)	**118 more per 1,000** (from 32 fewer to 348 more)	Very low	CRITICAL
Presence/ persistence of OME (per assessment, short term*; assumed ICC=0.5)												
1 (O'Shea 1980/1982)	randomised trials	very serious[b]	not serious	serious[d]	very serious[e]	none	30/45 assessments (66.7%)	32/48 assessments (66.7%)	**RR 1.00** (0.75 to 1.33)	**0 fewer per 1,000** (from 167 fewer to 220 more)	Very low	CRITICAL
Hearing returned to normal (per child, short term*; air conduction)												
1 (O'Shea 1980/1982)	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	14/27 (51.9%)	14/28 (50.0%)	**RR 1.04** (0.62 to 1.74)	**20 more per 1,000** (from 190 fewer to 370 more)	Very low	CRITICAL
Hearing returned to normal (per child, medium term*; air conduction)												
1 (O'Shea 1980/1982)	randomised trials	serious[a]	not serious	not serious	serious[c]	none	18/24 (75.0%)	15/24 (62.5%)	**RR 1.20** (0.82 to 1.77)	**125 more per 1,000** (from 113 fewer to 481 more)	Low	CRITICAL
Hearing returned to normal (per ear, short term*; air conduction; assumed ICC=0.5)												

Certainty assessment							№ of patients/ ears/ assessments		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Haugeto 1981)	randomised trials	very serious[b]	not serious	not serious	very serious[e]	publication bias suspected[h]	5/7 ears (71.4%)	5/6 ears (83.3%)	**RR 0.86** (0.48 to 1.55)	**117 fewer per 1,000** (from 433 fewer to 458 more)	Very low	CRITICAL
Change in hearing threshold from baseline (per child, medium term*; air conduction)												
1 (O'Shea 1980/1982)	randomised trials	serious[a]	not serious	not serious	serious[f]	none	24	24	-	MD **2.6 higher** (4.42 lower to 9.62 higher)	Low	CRITICAL
Change in hearing threshold from baseline (per ear, short term*; audiometry, 0.5kHz; not adjusted for independence)												
1 (Saunte 1978)	randomised trials	very serious[b]	not serious	no serious	very serious[g]	none	14 ears	10 ears	-	MD **5.9 lower** (17 lower to 5.2 higher)	Very low	CRITICAL
Change in hearing threshold from baseline (per ear, short term*; audiometry, 1kHz; not adjusted for independence)												
1 (Saunte 1978)	randomised trials	very serious[b]	not serious	no serious	very serious[g]	none	14 ears	12 ears	-	MD **7.6 lower** (19.03 lower to 3.83 higher)	Very low	CRITICAL
Change in hearing threshold from baseline (per ear, short term*; audiometry, 2kHz; not adjusted for independence)												
1 (Saunte 1978)	randomised trials	very serious[b]	not serious	no serious	very serious[g]	none	7 ears	10 ears	-	MD **6.9 lower** (18.37 lower to 4.57 higher)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; MD: mean difference; RR: risk ratio
**Short term outcomes defined as ≤ 3 months; medium term outcomes defined as > 3 months to ≤ 1 year*

a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
c. 95% CI crosses 1 MID
d. Outcome is indirect due to being reported per assessment rather than per child or ear. Including the number of tympanograms that were the same or worse than the last visit could have resulted in some children whose OME had previously cleared being included in the number of events, meaning this outcome could include recurrence of OME.
e. 95% CI crosses 2 MIDs
f. 95% CI crosses 1 MID (0.5x control group SD: change in hearing threshold from baseline per child = 6.8)
g. 95% CI crosses 1 MID (0.5x control group SD: change in hearing threshold from baseline per ear, 0.5kHz = 6.64; change in hearing threshold from baseline per ear, 1kHz = 5.72; change in hearing threshold from baseline per ear, 2kHz = 5.38), however it was not possible to adjust the sample size to account for lack of independence, so precision is likely to be over-estimated
h. Publication bias suspected due to majority of studies being industry funded

Table 20: Evidence profile for comparison between decongestant + antihistamine versus no treatment[a]

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Mandel 1987)	randomised trials	serious[b]	not serious	not serious	not serious	none	108/158 (68.4%)	114/160 (71.3%)	**RR 0.96** (0.83 to 1.11)	**29 fewer per 1,000** (from 121 fewer to 78 more)	Moderate	CRITICAL
Mean final hearing threshold (per child, short term*; speech awareness)												
1 (Mandel 1987)	randomised trials	serious[b]	not serious	not serious	not serious	none	57	50	-	MD **0.81 higher** (1.95 lower to 3.57 higher)	Moderate	CRITICAL
Mean final hearing threshold (per ear, short term*; speech reception; assumed ICC=0.5)												
1 (Mandel 1987)	randomised trials	serious[b]	not serious	not serious	not serious	none	159 ears	181 ears	-	MD **0.87 lower** (3.42 lower to 1.67 higher)	Moderate	CRITICAL
Change in hearing threshold from baseline (per child, short term*; pure-tone audiometry)												

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant + antihistamine**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Fraser 1977)	randomised trials	serious[b]	not serious	serious[c]	serious[d]	publication bias suspected[e]	43	42	-	MD **1.85 lower** (5.36 lower to 1.66 higher)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; MD: mean difference; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Studies have been classified as compared against no treatment when any additional treatments received were equivalent across arms
b. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
c. Intervention is indirect due to results being reported in such a way that it is not possible to extract results only for participants who received the interventions of interest; therefore, data extracted are partially from participants who received combinations of treatments including autoinflation
d. 95% CI crosses 1 MID (0.5x control group SD: change in hearing threshold from baseline = 4.13)
e. Publication bias suspected due to majority of studies being industry funded

Table 21: Evidence profile for comparison between decongestant versus antihistamine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant**	**antihistamine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
1 (Dusdieker 1985)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	5/20 (25.0%)	4/18 (22.2%)	**RR 1.13** (0.36 to 3.55)	**29 more per 1,000** (from 142 fewer to 567 more)	Very low	CRITICAL
Discontinuation of treatment due to hyperactivity and poor sleeping (per child, short term*)												
1 (Dusdieker 1985)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/20 (5.0%)	0/22 (0.0%)	**RR 3.29** (0.14 to 76.33)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL

CI: confidence interval; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs

Table 22: Evidence profile for comparison between decongestant versus placebo

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*; otoscopy and tympanometry)												
1 (Dusdieker 1985)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	5/20 (25.0%)	3/24 (12.5%)	**RR 2.00** (0.54 to 7.36)	**125 more per 1,000** (from 57 fewer to 795 more)	Very low	CRITICAL
Presence/ persistence of OME (per child, short term*; otoscopy)												
1 (Hayden 1984)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	4/20 (20.0%)	5/23 (21.7%)	**RR 0.92** (0.29 to 2.97)	**17 fewer per 1,000** (from 154 fewer to 428 more)	Very low	CRITICAL
Presence/ persistence of OME (per child, short term*; tympanometry)												
1 (Hayden 1984)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	17/30 (56.7%)	21/37 (56.8%)	**RR 1.00** (0.66 to 1.52)	**0 fewer per 1,000** (from 193 fewer to 295 more)	Very low	CRITICAL
Presence/ persistence of OME (per ear, short term*; assumed ICC=0.5)												
1 (Haugeto 1981)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	publication bias suspected[f]	15/33 ears (45.5%)	14/41 ears (34.1%)	**RR 1.33** (0.76 to 2.34)	**113 more per 1,000** (from 82 fewer to 458 more)	Very low	CRITICAL
Hearing returned to normal (per ear, short term*; air conduction; assumed ICC=0.5)												
1 (Haugeto 1981)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	publication bias suspected[f]	5/8 ears (62.5%)	5/6 ears (83.3%)	**RR 0.75** (0.39 to 1.43)	**208 fewer per 1,000** (from 508 fewer to 358 more)	Very low	CRITICAL
Discontinuation of treatment due to hyperactivity and poor sleeping (per child, short term*)												

Certainty assessment							№ of patients/ ears		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Decongestant**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Dusdieker 1985)	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	1/20 (5.0%)	0/24 (0.0%)	**RR 3.57** (0.15 to 83.14)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	Very low	CRITICAL
Discontinuation of treatment due to AOM (per child, short term*)												
1 (Hayden 1984)	randomised trials	serious[c]	not serious	serious[d]	very serious[b]	none	6/68 (8.8%)	6/84 (7.1%)	**RR 1.24** (0.42 to 3.66)	**17 more per 1,000** (from 41 fewer to 190 more)	Very low	CRITICAL
Discontinuation of treatment due to use of additional medication (per child, short term*)												
1 (Hayden 1984)	randomised trials	serious[c]	not serious	serious[d]	very serious[b]	none	8/68 (11.8%)	6/84 (7.1%)	**RR 1.65** (0.60 to 4.52)	**46 more per 1,000** (from 29 fewer to 251 more)	Very low	CRITICAL
Discontinuation of treatment due to inability to tolerate medication (per child, short term*)												
1 (Hayden 1984)	randomised trials	serious[c]	not serious	serious[d]	serious[e]	none	4/68 (5.9%)	16/84 (19.0%)	**RR 0.31** (0.11 to 0.88)	**131 fewer per 1,000** (from 170 fewer to 23 fewer)	Very low	CRITICAL

CI: confidence interval; ICC: intracluster correlation coefficient; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs
c. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
d. Population is indirect due to participants with a type A(s) tympanogram being included in these results, which authors later regard as a normal tympanogram (not OME)
e. 95% CI crosses 1 MID
f. Publication bias suspected due to majority of studies being industry funded

Table 23: Evidence profile for comparison between decongestant versus no treatment[a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decongestant	no treatment	Relative (95% CI)	Absolute (95% CI)		
Change in hearing threshold from baseline (per child, short term*; pure-tone threshold)												
1 (Fraser 1977)	randomised trials	serious[b]	not serious	serious[c]	serious[d]	publication bias suspected[e]	43	42	-	MD **3.5 higher** (0.01 lower to 7.01 higher)	Very low	CRITICAL

CI: confidence interval; MD: mean difference
**Short term outcomes defined as ≤ 3 months*
a. Studies have been classified as compared against no treatment when any additional treatments received were equivalent across arms
b. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
c. Intervention is indirect due to results being reported in such a way that it is not possible to extract results only for participants who received the interventions of interest; therefore, data extracted are partially from participants who received combinations of treatments including autoinflation
d. 95% CI crosses 1 MID (0.5x control group SD: decongestant vs no treatment, change in hearing threshold from baseline = 4.13)
e. Publication bias suspected due to majority of studies being industry funded

Table 24: Evidence profile for comparison between leukotrine receptor antagonist (LRA) versus placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LRA	placebo	Relative (95% CI)	Absolute (95% CI)		
Presence/ persistence of OME (per child, short term*)												
1 (Schoem 2010)	randomised trials	serious[a]	not serious	not serious	very serious[b]	publication bias suspected[c]	16/19 (84.2%)	15/19 (78.9%)	**RR 1.07** (0.79 to 1.44)	**55 more per 1,000** (from 166 fewer to 347 more)	Very low	CRITICAL

CI: confidence interval; LRA: leukotrine receptor antagonist; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
b. 95% CI crosses 2 MIDs
c. Publication bias suspected due to majority of studies being industry funded

Table 25: Evidence profile for comparison between leukotrine receptor antagonist (LRA) versus no treatment[a]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LRA**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Presence/ persistence of OME (per child, short term*)												
2 (Balatsouras 2005, Rahmati 2017)	randomised trials	serious[b]	not serious	not serious	very serious[c]	none	15/84 (17.9%)	18/80 (22.5%)	**RR 1.04** (0.59 to 1.85)	**9 more per 1,000** (from 92 fewer to 191 more)	Very low	CRITICAL

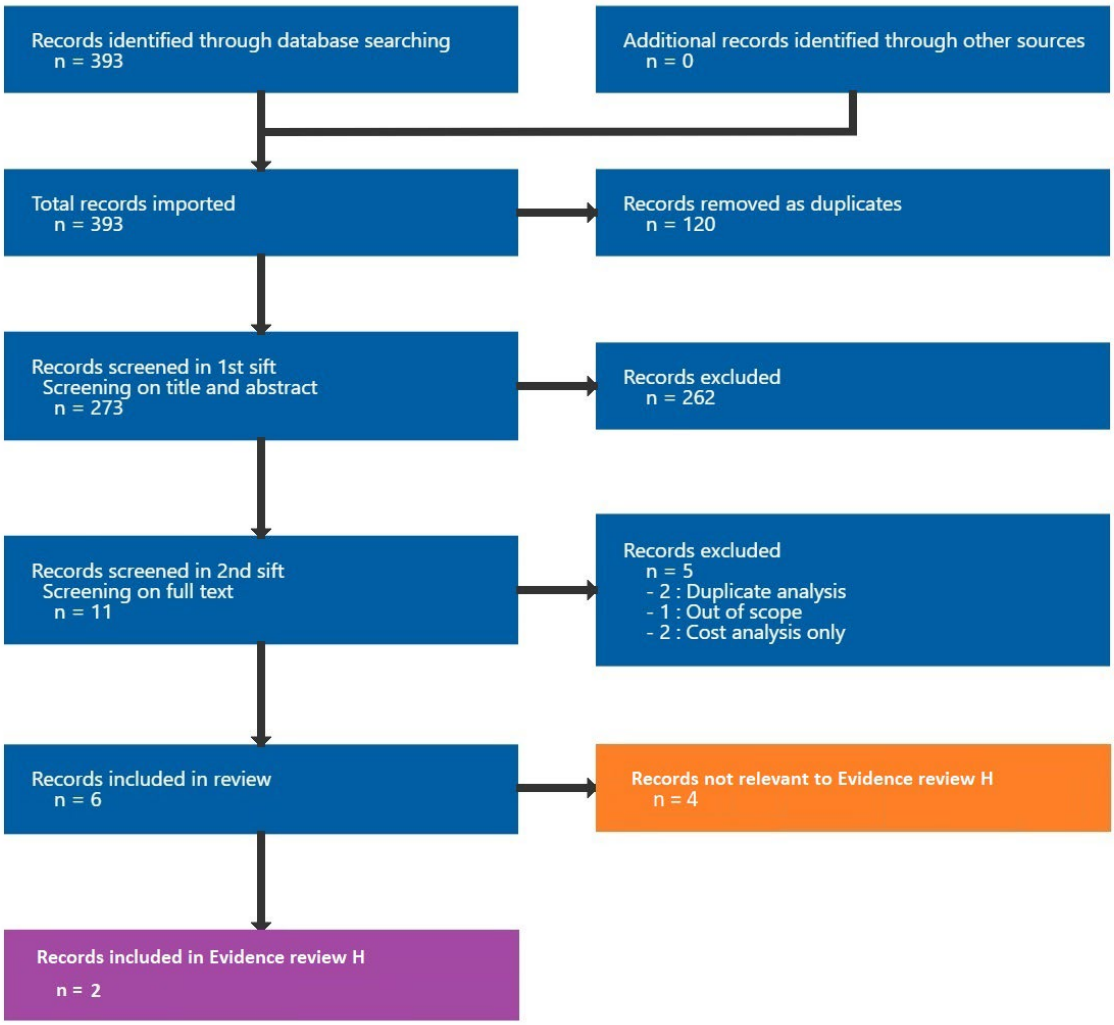
CI: confidence interval; LRA: leukotrine receptor antagonist; RR: risk ratio
**Short term outcomes defined as ≤ 3 months*
a. studies have been classified as compared against no treatment when any additional treatments received were equivalent across arms
b. Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
c. 95% CI crosses 2 MIDs

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

A global search was undertaken to cover all the review questions considered in this guideline, and 2 studies were identified which was applicable to this review question (see Figure 8).

Figure 8: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Table 26: Economic evidence tables for non-antimicrobial pharmacological interventions for managing OME with associated hearing loss in children under 12 years

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Williamson 2009 **Country:** UK **Type of economic analysis:** Cost utility analysis **Source of funding:** Heath Technology Assessment programme of the National Institute for Health Research	**Intervention:** Mometasone furoate 50 µg (intranasal steroids) in each nostril once a day for 3 months **Comparator:** Placebo nasal spray	**Population characteristics:** Children aged 4-11 years with attendance at GP surgery with at least 1 episode of a related hearing problem in the last 12 months who have failed tympanometry **Modelling approach/alongside an RCT:** Economic evaluation alongside an RCT **Source of baseline data:** Placebo arm in RCT **Source of effectiveness data:** Intervention arm in RCT **Source of cost data:**	**Mean cost per participant:** *Intervention:* £454 (95% CI: £283 to £624) *Placebo*: £442 (95% CI: £315 to £570) *Difference:* £11 (95% CI: -£199 to £222) **Primary measure of outcome**: QALYs In the base case analysis utilities were based on HU13 with QALYs estimated from utilities at different time points using linear interpolation **Mean QALY per participant:** *Difference:* -0.0166 QALYs	**ICERs:** Intervention dominated by placebo **Probability of intervention being cost effective:** 24% at a cost-effectiveness threshold of £20,000 per QALY	**Perspective:** NHS perspective **Currency:** GBP **Cost year:** 2006-07 **Time horizon:** 9 months **Discounting:** N/A **Applicability:** Directly applicable **Limitations:** Minor limitations **Other comments:** Time horizon may have been too short to capture differences in outcomes

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Resource use data was collected as part of the trial by study data forms completed by nurses and parents **Source of unit cost data:** BNF; PCA122; PSSRU (2006); NHS Reference Costs (2006)	(SE: 0.0235)		
Author and year: Francis 2018 **Country:** UK **Type of economic analysis:** Cost utility analysis **Source of funding:** Heath Technology Assessment programme of the National Institute for Health Research	**Intervention:** 7-day course or oral steroids (oral prednisolone, as a single daily dose of 20 mg for children aged 2-5 years or 30 mg for 6-8-year-olds) **Comparator:** Oral placebo	**Population characteristics:** Children with persistent OME symptoms and bilateral OME with hearing loss demonstrated by audiometry **Modelling approach/alongside an RCT:** Economic evaluation alongside an RCT **Source of baseline data:** Placebo arm in RCT	**Mean cost per participant:** *Intervention:* £934 *Placebo*: £794 *Difference:* £145 (95% CI: -£136 to £426) **Primary measure of outcome**: QALYs Utilities were based on HUI3 with QALYs estimated from the area under the curve method assuming linear interpolation	**ICERs:** Intervention dominated by placebo **Probability of intervention being cost effective:** 17% at a cost-effectiveness threshold of £20,000 per QALY 22% at a cost-effectiveness threshold of £30,000 per QALY	**Perspective:** NHS and Personal Social Services perspective **Currency:** GBP **Cost year:** 2015-06 **Time horizon:** 12 months **Discounting:** N/A **Applicability:** Directly applicable **Limitations:** Minor limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of effectiveness data: Intervention arm in RCT **Source of cost data:** Resource use data was collected at 5 weeks, 6 months and 12 months after randomisation from parent completed questionnaires **Source of unit cost data:** BNF (2015); PSSRU (2016); NHS Reference Costs (2015-16)	between each time point **Mean QALY per participant:** *Intervention:* 0.051 QALYs *Placebo*: 0.070 QALYs *Difference:* -0.015 QALYs (95% CI: -0.054 to 0.023)		**Other comments:**

BNF = British National Formulary; CI = Confidence interval; GBP = Great British Pound; HUI = Health Utilities Index; ICER = Incremental cost-effectiveness ratio; N/A = Not applicable; OME = Otitis media with effusion; PSSRU = Personal and Social Services Research Unit; QALYs = Quality adjusted life years; RCT = Randomised control trial; SE = Standard error

Appendix I Economic model

Economic model for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

Steroids

See the Characteristics of excluded studies table from the Cochrane review on steroids at https://doi.org/10.1002/14651858.CD015255.pub2.

Antihistamines, leukotriene receptor antagonists, mucolytics and decongestants

Excluded effectiveness studies

Study	Code [Reason]
Balli, R. (1980) Controlled trial on the use of oral acetylcysteine in the treatment of glue-ear following drainage. European Journal of Respiratory Diseases 61(suppl111): 158	- Study design does not meet inclusion criteria *Conference abstract*
Bellussi, L., Ciferri, G., De Seta, E. et al. (1984) Effect of 2-(alpha-thenoylthio)propionylglycine in the treatment of secretory otitis media. Current Therapeutic Research - Clinical and Experimental 36(3): 596-605	- Intervention/ comparator does not meet inclusion criteria *Study compares an acyl glycine (propionylglycine) to placebo and to propionylglycine plus NSAID*
Bellussi, L, Bernocchi, D, Ciferri, G et al. (1989) Sobrerol in the treatment of secretory otitis media in childhood. The Journal of international medical research 17(3): 277-86	- Study design does not meet inclusion criteria *Non-comparative study*
Bonci, M and Bozzi, A (1994) Mucoregulatory therapy in secreting disease of the middle ear. Minerva medica 85(3): 83-87	- Article not available in English
Burton, M.J. and Rosenfeld, R.M. (2007) Extracts from The Cochrane Library: Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Otolaryngology - Head and Neck Surgery 136(1): 11-13	- Systematic review, studies assessed for inclusion
Butler, C C and MacMillan, H (2001) Does early detection of otitis media with effusion prevent delayed language development?. Archives of disease in childhood 85(2): 96-103	- Systematic review, studies assessed for inclusion
Cantekin, E I, Bluestone, C D, Rockette, H E et al. (1980) Effect of decongestant with or without antihistamine on eustachian tube function. The Annals of otology, rhinology & laryngology. Supplement 89(3pt2): 290-5	- Outcomes do not meet inclusion criteria *Study looks at effect of decongestants with or without antihistamines on eustachian tube function*
Carmona, N; Garcia, M; Fuentes Rejon, T (1997) Serous otitis media. Comparative study	- Article not available in English

Study	Code [Reason]
of carbinoxamine-pseudofedrina vs astemizole-pseudoephedrine. Revista alergia Mexico 44: 70-73	
ChiCTR-TRC-12002227 (2012) A randomized, double-blinded and placebo-controlled multicenter clinical trial to evaluate the efficacy and safety of Myrtol Standardized Enteric Coated Soft Capsules (Children) in the treatment of Otitis Media with Effusion (OME) in Children. ChiCTR [www.chictr.org]	- Article not available
Combs, Jerome T (2004) The effect of montelukast sodium on the duration of effusion of otitis media. Clinical pediatrics 43(6): 529-33	- Population does not meet inclusion criteria *Participants had AOM*
de Castro, FJ; Jackson, PL; Reed, KD (2001) Efficacy of oral leukotriene together with inhaled steroid in serous otitis media. Pediatric research 49(4): 14a	- Study design does not meet inclusion criteria *Conference abstract*
Dewan, Karuna and Lieu, Judith (2018) A Clinical Trial of Proton Pump Inhibitors to Treat Children with Chronic Otitis Media with Effusion. The journal of international advanced otology 14(2): 245-249	- Data not reported in sufficient detail to extract *Results were reported for hearing loss, but insufficient data reported to extract (no measure of deviation or additional statistics for each hearing outcome measure).*
Elbeltagy, Reem and Abdelhafeez, Marwa (2022) Outcome of Gastroesophageal Reflux Therapy in Children with Persistent Otitis Media with Effusion. International archives of otorhinolaryngology 26(1): e058-e062	- Study design does not meet inclusion criteria *Non-randomised trial*
Elcock, H W and Lord, I J (1972) Bromhexine hydrochloride in chronic secretory otitis media--a clinical trial. The British journal of clinical practice 26(6): 276-8	- Study design does not meet inclusion criteria *Non-randomised trial*
Eliopoulos, P, Balatsouras, D, Sterpi, P et al. (2004) Improvement of otitis media with effusion after treatment of asthma by leukotriene antagonists in children with co-existing disease. International journal of pediatric otorhinolaryngology 68(5): 651	- Study design does not meet inclusion criteria *Conference abstract*
Ertugay, Cigdem Kalaycik, Cingi, Cemal, Yaz, Aytekin et al. (2013) Effect of combination of montelukast and levocetirizine on otitis media with effusion: a prospective, placebo-controlled trial. Acta oto-laryngologica 133(12): 1266-72	- Outcomes do not meet inclusion criteria *Insufficient presentation of results - authors report the mean difference in otoscopic/ tympanometry scores for each group but do not report the number of participants with improvement to 'normal' category. Tympanometry scores are also insufficiently explained to determine which category would equate to a normal ear*
Eyibilen, Ahmet, Aladag, Ibrahim, Guven, Mehmet et al. (2009) The effectiveness of nasal decongestants, oral decongestants and oral	- Population does not meet inclusion criteria *Participants had AOM*

Study	Code [Reason]
decongestant-antihistamines in the treatment of acute otitis media in children. Kulak burun bogaz ihtisas dergisi : KBB = Journal of ear, nose, and throat 19(6): 289-93	
Garabedian, EN, Ducroz, V, Manach, Y et al. (1999) Effect of loratadine (L) syrup in the treatment of otitis media with effusion (OME): randomized double-blind placebo (P) controlled trial. Journal of allergy and clinical immunology 103(1part2): 255	- Article not available
Griffin, G.H., Flynn, C., Bailey, R.E. et al. (2006) Antihistamines and/or decongestants for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews: cd003423	- Systematic review, studies assessed for inclusion
Griffin, Glenn and Flynn, Cheryl A (2011) Antihistamines and/or decongestants for otitis media with effusion (OME) in children. The Cochrane database of systematic reviews: cd003423	- Systematic review, studies assessed for inclusion
Grundfast, K M (1981) A review of the efficacy of systemically administered decongestants in the prevention and treatment of otitis media. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 89(3pt1): 432-9	- Study design does not meet inclusion criteria *Narrative review*
Guo, Y and Sun, XM (2004) Clinical observation on Biyan Qingdu Granule and ambroxol hydrochloride in treating secretory otitis media. Zhong xi yi jie he xue bao [Journal of Chinese integrative medicine] 2(4): 277291	- Article not available in English
Jiang, Z, Liu, W, Zhao, C et al. (2004) Adjuvant treatment of anisodamine to acute serous otitis media. Lin chuang er bi yan hou ke za zhi [Journal of clinical otorhinolaryngology] 18(7): 406-407	- Article not available in English
Kjellman, N I, Harder, H, Lindwall, L et al. (1978) Longterm treatment with brompheniramine and phenylpropanolamine in recurrent otitis media--a double-blind study. The Journal of otolaryngology 7(3): 257-61	- Population does not meet inclusion criteria *Participants were required to have a history of AOM or secretory otitis media (SOM) but only 8/ 44 (18%) had SOM at entry to trial*
Klein, S W, Olson, A L, Perrin, J et al. (1980) Prevention and treatment of serous otitis media with an oral antihistamine. A double-blind study in pediatric practice. Clinical pediatrics 19(5): 342-7	- Population does not meet inclusion criteria *Participants had to have AOM but serous otitis media (SOM) was not a requirement for entry into the study*
Kripke, Clarissa (2007) Decongestants and antihistamines do not relieve symptoms of otitis	- Study design does not meet inclusion criteria *Conference abstract*

Study	Code [Reason]
media with effusion. American family physician 75(7): 1001	
La Mantia, I and Andaloro, C (2018) Effects of salso-bromo-iodine thermal water in children suffering from otitis media with effusion: a randomized controlled pilot study. La Clinica terapeutica 169(1): e10-e13	- Intervention/ comparator does not meet inclusion criteria *Study compares the efficacy of a natural medicine (seawater) vs iodine*
La Mantia, I, Varricchio, A, Di Girolamo, S et al. (2019) The role of bacteriotherapy in the prevention of adenoidectomy. European review for medical and pharmacological sciences 23(1suppl): 44-47	- Intervention/ comparator does not meet inclusion criteria *Study compared bacteriotherapy (Streptococcus oralis 89a nasal spray) to placebo*
Lesser, T H; Clayton, M I; Skinner, D (1986) Efficacy of medical treatment as an adjunct to surgery in the treatment of secretory otitis media. The Journal of laryngology and otology 100(12): 1347-50	- Population does not meet inclusion criteria *OME was confirmed using pure tone audiometry and microscopy, not tympanometry/ otoscopy*
Malik, Sohail Ahmad, Muhammad, Raza, Yousaf, Muhammad et al. (2014) Effectiveness of conservative treatment in the management of secretory otitis media. Journal of Ayub Medical College, Abbottabad : JAMC 26(3): 337-40	- Study design does not meet inclusion criteria *Non-randomised study*
Malm, L (1985) Oral decongestants in acute rhinitis, acute sinusitis, acute otitis media and secretory otitis media: prognostic implications. Workshop Treatment of Ear, Nose and Throat Infections 1: 99-106	- Article not available
Malm, L and White, P (1992) Beta-agonists and surfactant in eustachian tube function. Acta oto-laryngologica. Supplementum 493: 133-6	- Study design does not meet inclusion criteria *Commentary*
Manrique, MJ, Hern?ndez, J, Huarte, A et al. (1987) Treatment of serous otitis media with ambroxol. Acta pedi? Trica espa? Ola 45(1): 17-20	- Article not available in English
Mel-Hennawi, D and Ahmed, M R (2015) Outcome evaluation of clarithromycin, metronidazole and lansoprazole regimens in Helicobacter pylori positive or negative children with resistant otitis media with effusion. The Journal of laryngology and otology 129(11): 1069-72	- Study design does not meet inclusion criteria *Commentary*
Miller, T, Bauknight, R S, Swanson, G C et al. (1977) Evaluation of oral decongestants in the treatment of serous otitis media. Transactions of the Pacific Coast Oto-Ophthalmological Society annual meeting 58: 243-52	- Population does not meet inclusion criteria *No baseline characteristics provided for participants (e.g. age, setting), and it is unclear from text whether the included participants were children*
Moller, P (1980) Negative middle ear pressure and hearing thresholds in secretory otitis media.	- Outcomes do not meet inclusion criteria

Study	Code [Reason]
A double-blind crossover study with Lunerin. Scandinavian audiology 9(3): 171-6	*Insufficient presentation of results for a crossover RCT*
Moore, R A, Commins, D, Bates, G et al. (2001) S-carboxymethylcysteine in the treatment of glue ear: quantitative systematic review. BMC family practice 2: 3	- Systematic review, studies assessed for inclusion
Moran, D M, Mutchie, K D, Higbee, M D et al. (1982) The use of an antihistamine-decongestant in conjunction with an anti-infective drug in the treatment of acute otitis media. The Journal of pediatrics 101(1): 132-6	- Population does not meet inclusion criteria *Participants have AOM*
Moran, DM, Mutchie, KD, Higbee, MD et al. (1982) Use of an antihistamine decongestant in conjunction with an anti infective drug in the treatment of acute otitis media. Journal of pediatrics 101: 132-136	- Duplicate
Nsouli, S. (2014) The efficacy of a nasal antihistamine azelastine hydrochloride and corticosteroid fluticasone propionate for the treatment of serous otitis media. Annals of Allergy, Asthma and Immunology 113(5suppl1): a110	- Study design does not meet inclusion criteria *Conference abstract*
Nsouli, S. (2010) The efficacy of a nasal antihistamine olopatadine for the treatment of serous otitis media in children. Annals of Allergy, Asthma and Immunology 105(5): a9	- Study design does not meet inclusion criteria *Conference abstract*
Olson, A L, Klein, S W, Charney, E et al. (1978) Prevention and therapy of serous otitis media by oral decongestant: a double-blind study in pediatric practice. Pediatrics 61(5): 679-84	- Population does not meet inclusion criteria *Participants have AOM*
Ortega del Alamo, P; Rivera, RT; Sanz, FR (2005) The effect of AM3 in the resolution of otitis media with effusion (OME) in paediatric patients. Acta otorrinolaringologica espanola 56(1): 1-5	- Article not available in English
Otten, F W and Grote, J J (1990) Otitis media with effusion and chronic upper respiratory tract infection in children: a randomized, placebo-controlled clinical study. The Laryngoscope 100(6): 627-33	- Intervention/ comparator does not meet inclusion criteria *Study compares the following groups: placebo vs decongestant + antibiotic vs maxillary sinus drainage + placebo vs axillary sinus drainage + decongestant + antibiotic. Antibiotics will be investigated in Cochrane systematic review*
Ovesen, T, Felding, J U, Tommerup, B et al. (2000) Effect of N-acetylcysteine on the incidence of recurrence of otitis media with effusion and re-insertion of ventilation tubes. Acta oto-laryngologica. Supplementum 543: 79-81	- Outcomes do not meet inclusion criteria *Recurrence of OME after VT extrusion and treatment with active drug, not presence/ persistence, is reported*

Study	Code [Reason]
Park, K; Choung, YH; Mo, JY (2005) Do we need antibiotics or antihistamines for treatment of otitis media with effusion in the tertiary hospital?. 5th Extraordinary International Symposium on Recent Advances in Otitis Media . Amsterdam, The Netherlands, April 24-27, 2005: 166abstractnop0403	- Study design does not meet inclusion criteria
Renou, G, Ketari, M, Toutée, JP et al. (1989) Medical treatment of seromucous otitis. Revue de laryngologie - otologie - rhinologie 110(3): 327-328	- Article not available in English
Rukholm, G., Wong, J., Lui, B. et al. (2016) Role of empiric anti-reflux therapy in pediatric otitis media with effusion-a pilot study. European Journal of Pediatrics 175(11): 1658	- Study design does not meet inclusion criteria *Conference abstract*
Safak, M A, Kilic, R, Haberal, I et al. (2001) A comparative study of azithromycin and pseudoephedrine hydrochloride for otitis media with effusion in children. Acta oto-laryngologica 121(8): 925-9	- Intervention/ comparator does not meet inclusion criteria *Study compared a decongestant with two different antibiotics regimens*
Samim, E, Kilic, R, Akmansu, H et al. (1998) Secretory otitis media treatment with azitromycine compared to decongestant: a double-blind, randomized controlled trial. 21st Politzer Society Meeting . Antalya, Turkey, 8-11 June, 1998	- Study design does not meet inclusion criteria *Conference poster*
Sorri, M., Sipila, P., Palva, A. et al. (1982) Can secretory otitis media be prevented by oral decongestants?. Acta Oto-Laryngologica 94(suppl386): 115-116	- Population does not meet inclusion criteria *Diagnostic criteria for OME for inclusion to study not reported*
Suzuki, M; Kawauchi, H; Mogi, G (1999) Clinical efficacy of an antiallergic drug on otitis media with effusion in association with allergic rhinitis. Auris, nasus, larynx 26(2): 123-9	- Population does not meet inclusion criteria *Included participants are aged between 5-38 years but it is unclear what percentage of participants are under 12. Based on means and SDs of each group (11.9 +/- 10.8 and 9.0 +/- 7.2), significant number of participants likely to be over 12 years*
Testa, B, Testa, D, Mesolella, M et al. (2001) Management of chronic otitis media with effusion: the role of glutathione. The Laryngoscope 111(8): 1486-9	- Intervention/ comparator does not meet inclusion criteria *Study compares an atioxidant (glutathione) to placebo*
Theoharides, T C, Manolidis, S S, Vliagoftis, H et al. (1994) Treatment of secretory otitis media with local instillation of hydroxyzine. International archives of allergy and immunology 103(1): 95-101	- Outcomes do not meet inclusion criteria *The outcome 'rate of relapse' initially appears to refer to number of participants with recurring MEE requiring repeat grommet insertion, however only the number of grommet rejections appears to be reported for all groups at all time points. Recurrence of MEE is not consistently reported and not extractable for all groups as necessary for comparison*

Study	Code [Reason]
Topazio, D., Passali, F., Cama, A. et al. (2019) Intranasal hyaluronic acid improves the audiological outcomes of children with otitis media with effusion. Indian Journal of Otology 25(3): 155-161	- Intervention/ comparator does not meet inclusion criteria *Study compares a hyaluronic acid nasal spray to saline solution*
Torretta, S, Marchisio, P, Rinaldi, V et al. (2017) Endoscopic and clinical benefits of hyaluronic acid in children with chronic adenoiditis and middle ear disease. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 274(3): 1423-1429	- Intervention/ comparator does not meet inclusion criteria *Study assesses the efficacy of saline vs hyaluronic acid*
van Heerbeek, Niels; Ingels, Koen J A O; Zielhuis, Gerhard A (2002) No effect of a nasal decongestant on eustachian tube function in children with ventilation tubes. The Laryngoscope 112(6): 1115-8	- Outcomes do not meet inclusion criteria *Outcome reported is Eustachian tube function as measured using different tests (forced-response test, pressure equilibration test, and sniff test). Presence of OME/ MEE not reported as an outcome* - Population does not meet inclusion criteria *Diagnostic criteria for OME for inclusion to study not reported*
Varricchio, A, De Lucia, A, Varricchio, A M et al. (2017) Sinuclean Nebules treatment in children suffering from otitis media with effusion. International journal of pediatric otorhinolaryngology 94: 30-35	- Intervention/ comparator does not meet inclusion criteria *Study compares saline to alternative medicine (Sinuclean; water solution containing plant extracts)*
Williamson, I (2011) Otitis media with effusion in children. Clinical evidence 2011(nopagination)	- Systematic review, studies assessed for inclusion
Williamson, I. (2007) Otitis media with effusion in children. BMJ clinical evidence 2007	- Systematic review, studies assessed for inclusion
Wing, L W (1978) Bisolvon and Actifed in the conservative management of glue ear. The Medical journal of Australia 1(5): 289-90	- Study design does not meet inclusion criteria *Conference abstract*
Witmer, A; Wells, A M; Seymour, R J (1998) A comparison of the effectiveness of pharmacologic treatment of otitis media with effusion in children: integrative and meta-analysis. The online journal of knowledge synthesis for nursing 5: 4	- Systematic review, studies assessed for inclusion
Zhou, Xufeng, Jin, Xiulin, Yang, Linhong et al. (2022) Efficacy and safety of ambroxol hydrochloride in the treatment of secretory otitis media: a systematic review and meta-analysis. Annals of translational medicine 10(3): 142	- Systematic review, studies assessed for inclusion

Excluded economic studies

Study	Code [Reason]
Petrou, Stavros, Dakin, Helen, Abangma, Giselle et al. (2010) Cost-utility analysis of topical intranasal steroids for otitis media with effusion based on evidence from the GNOME trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 13(5): 543-51	- Duplicate analysis

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of non-antimicrobial pharmacological interventions (such as steroids, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants) for managing OME in children under 12 years?

K.1.1 Research recommendation

What is the effectiveness of topical nasal steroids on the management of OME and OME-related hearing loss in children under 12 years?

K.1.2 Why this is important

There is little evidence regarding the effectiveness of nasal steroids in the management of OME. Furthermore, whilst the current evidence looks at the persistence of OME, it is not clear if this translates through to a benefit to hearing for children. Nasal steroids, if found to be effective, represent a more readily accessible management option for OME and OME-related hearing loss at an earlier timepoint within the natural history of the disease, potentially reducing the need for secondary care healthcare services.

K.1.3 Rationale for research recommendation

Table 27: Research recommendation rationale

Importance to 'patients' or the population	Topical nasal steroids are potentially a low barrier management option for OME and in particular for OME-related hearing loss. Topical nasal steroid sprays, if found to be beneficial, potentially represent a management option that can be administered at an earlier stage within the disease process before accessing secondary care, potentially reducing the need for hearing aids or surgical management options. There is some very low quality evidence to suggest topical nasal steroids may positively impact generic health-related quality of life in the medium term (>3 months to <=1 year), though this has not shown the same effect in disease-specific quality of life.
Relevance to NICE guidance	This intervention was specifically considered in the current NICE guidance under "Non-antimicrobial pharmacological interventions". The very low quality of the current evidence base meant that topical nasal steroids could not be recommended for treatment of OME in NICE guidance. If topical nasal steroids are shown to be an effective management option in the management of OME and OME-related hearing loss, it could directly impact this recommendation.

	This research is essential to inform future update of this key recommendation in the guidance.
Relevance to the NHS	Given the low cost nature, if found to be an effective management option for OME and OME-related hearing loss in particular, would have significant financial advantages for the NHS as it could be started in primary care, reducing the need for secondary care interventions such as hearing aids and surgical management. Furthermore, it could potentially reduce workload for secondary care by shortening patient pathways to discharge.
National priorities	Core20PLUS5 in paediatrics prioritises reducing health care inequalities and has a focus on one of the core priority areas, which is chronic respiratory diseases such as asthma.
Current evidence base	A Cochrane review on this found very low quality evidence when looking at the effectiveness of nasal steroids. Furthermore, the review found only one RCT (Lindholt 1982), looking at the effect of nasal steroids on hearing thresholds, which was limited to the short-term <3 months.
Equality considerations	No issues identified.
Feasibility	This would be considered a feasible research topic. Given the likely limited adverse effect profile of short-term (<= 3 months) topical nasal steroids, there are unlikely to be significant barriers. Further consideration to systemic absorption may have to be given to longer topical nasal steroid durations.
Other comments	Drug license use would have to be considered as there are restrictions by age.

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OME: otitis media with effusion; RCT: randomised controlled trial

K.1.4 Modified PICO table

Table 28: Research recommendation modified PICO table

Population	Children aged 6 months to 12 years with unilateral or bilateral OME. Include all children regardless of any comorbidity such as Down syndrome or cleft palate.
Intervention	Topical nasal steroid usage
Comparator	Placebo or no intervention
Outcome	Primary outcome: • Hearing ○ proportion of children whose hearing has returned to normal

	○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis) ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis) Secondary outcomes: • Presence of OME • Disease-specific quality of life measured using a validated instrument (for example OM8-30 or Otitis Media-6) • Adverse events • Discontinuation of treatment Outcomes by time • very short term (< 6 weeks for adverse events) • short term (</= 3 months) • medium term (> 3 months to </= 1 year) • long term (> 1 year)
Study design	• RCTs with randomisation by participant or by cluster
Timeframe	1-12 weeks
Additional information	None

OME: otitis media with effusion; RCT: randomised controlled trial

K.1.5 Research recommendation

What is the effect of antihistamines, leukotriene receptor antagonists, mucolytics, PPIs and decongestants on hearing in children with OME and chronic respiratory conditions?

K.1.6 Why this is important

Given the association of respiratory conditions and atopy with OME, antihistamines, leukotriene receptor antagonists, mucolytics and decongestants might have a beneficial effect on treating OME for the large subgroup of children who have both respiratory conditions and OME.

K.1.7 Rationale for research recommendation

Table 29: Research recommendation rationale

Importance to 'patients' or the population	OME is common in children: 80% experience OME at least once before the age of 10 years, and OME can cause hearing loss. Respiratory conditions are commonly associated with OME and therefore research is needed to understand the effectiveness of antihistamines, leukotriene receptor antagonists, mucolytics and decongestants for children with OME and chronic respiratory conditions as these

	interventions might be beneficial to this large subgroup. .
Relevance to NICE guidance	These interventions are currently not recommended for use for the management of OME or OME-related hearing loss in children by the current guideline. However, given the association of OME with respiratory conditions, there may be a role for the use of these pharmacological interventions in the management of OME or OME-related hearing loss in a subgroup of children who have chronic respiratory conditions.
Relevance to the NHS	Simple pharmacological treatments for OME, if effective, can be more readily accessible for patients, expediting patient pathways. Pharmacological alternatives, if effective, also have the potential to reduce a large burden on NHS secondary care services including reducing need for surgical management and hearing aids, thereby and reducinge morbidity in this common condition.
National priorities	Core20PLUS5 in paediatrics prioritises reducing health care inequalities and has a focus on one of the core priority areas, which is chronic respiratory diseases such as asthma.
Current evidence base	A NICE systematic review was conducted by NICE investigating the effectiveness of antihistamines, leukotriene receptor antagonists, mucolytics, PPIs and decongestants for children with OME. This review did not find sufficient evidence regarding the effectiveness of these interventions for children with chronic respiratory conditions to conduct a sub-group analysis for this population.
Equality considerations	A difference between male and female participants is not expected, although sex disaggregated data may be helpful. There are certain populations for whom OME is more prevalent, such as children with Down syndrome.
Feasibility	The interventions are low cost and suitable for children and used safely for conditions other than OME. Research can be carried out within a realistic timescale of around 1 year in total. The sample size needed to resolve the question is likely to be feasible/ achievable. The appropriateness of pharmacological interventions will be guided by consideration of drug licensing for different age groups and consideration to contra-indications.
Other comments	None

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OME: otitis media with effusion

K.1.8 Modified PICO table

Table 30: Research recommendation modified PICO table

Population	Children aged 6 months to 12 years with unilateral or bilateral OME, with and without chronic respiratory conditions. Include all children regardless of any comorbidity such as Down's syndrome or cleft palate.
Intervention	• Decongestants • Leukotriene receptor antagonists • Mucolytics • PPIs (Proton pump inhibitors) and reflux medicines • Antihistamines
Comparator	Head-to-head comparisons between all the above intervention categories (single or in combination, including combinations with steroids) • Placebo • No intervention for treating OME
Outcome	• Hearing ○ proportion of children whose hearing has returned to normal ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis) ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis) • Presence of OME • Disease-specific quality of life measured using a validated instrument (for example OM8-30 or Otitis Media-6) • Adverse events • Discontinuation of treatment Outcomes by time • very short term (< 6 weeks for adverse events) • short term (</= 3 months) - to align with current Guideline recommendations • medium term (> 3 months to </= 1 year) • long term (> 1 year)
Study design	• RCTs with randomisation by participant or by cluster We propose the following subgroup analyses if possible: • children with mild hearing loss versus moderate or worse; • children with allergy versus those without • children aged up to four years versus children aged 4 years and over

Timeframe	1 week to 1 year
Additional information	None

OME: otitis media with effusion; RCT: randomised controlled trial