REVIEW ARTICLE

Systematic review of the limited evidence base for treatments of Eustachian tube dysfunction: a health technology assessment

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Background: The Health Technology Assessment programme commissioned a wide-ranging review of treatments for adult Eustachian tube dysfunction. Treatments range from advice and observation and pharmacological treatments to surgical options.
Objective: (i) To assess the evidence for interventions for adults with a clinical diagnosis of Eustachian tube dysfunction and (ii) to identify priorities for future research.
Type of review: Systematic review (PROSPERO registration CRD42012003035) adhering to PRISMA guidance.
Search: An extensive search of 15 databases including MEDLINE, EMBASE and CENTRAL (up to October 2012).
Evaluation method: Controlled and uncontrolled studies of interventions for adult Eustachian tube dysfunction were included. Because of insufficient data, the protocol was amended to also include controlled studies with mixed adult/child populations. Risk of bias was assessed. Narrative synthesis was employed due to high clinical heterogeneity.
Results: Interventions assessed were pharmacological treatments [two randomised controlled trials (RCTs), one controlled non-randomised trial (CCT), 159 patients]; mechanical pressure equalisation devices (one randomised controlled trial, one CCT, 48 patients); and surgery, including laser tuboplasty (seven case series, 192 patients), balloon dilatation (three case series, 103 patients), myringotomy without grommet insertion (two case series, 121 patients), transtubal steroids (one case series, 11 patients) and laser coagulation (one retrospective controlled study, 40 patients). All studies had high risk of bias except two pharmacological trials; one had low risk and one unclear risk. No evidence was found for many treatments. The single low risk of bias RCT (n = 91; 67% adults) showed no effect of nasal steroids and favoured placebo for improved middle ear function (RR 1.20, 95% CI 0.91–1.58) and symptoms (P = 0.07). Other studies showed improvements in middle ear function for mechanical devices, antihistamine/ephedrine and nasal decongestant, but they had significant methodological weaknesses including insufficient length of follow-up. None of the surgical studies were adequately controlled, and many reported high levels of co-intervention. Therefore, observed benefits for tuboplasty and balloon dilatation in symptoms, middle ear function or hearing could not be reliably attributed to the interventions assessed. There was variability in definitions of the condition.
Conclusion: Eustachian tube dysfunction is a poorly defined condition. Due to the limited and poor-quality evidence, it is inappropriate to make conclusions on the effectiveness of any intervention; the evidence base is insufficient to guide recommendations for a trial of any particular intervention. Consensus on diagnostic criteria for Eustachian tube dysfunction is required to inform inclusion criteria of future trials.

Background and objective

The Health Technology Assessment (HTA) programme commissioned a broad review of interventions for treatment of adults diagnosed with Eustachian tube dysfunction (ETD). The HTA scope did not identify diagnostic criteria for the condition but outlined possible symptoms (muffled hearing, pain, feeling of fullness in the ear, tinnitus and dizziness). Patients may also have impaired hearing, abnormal tympanograms or abnormal physical appearance on otoscopic examination, but the relationship of these to the condition is unclear. The scope stated that pragmatic diagnostic criteria used in published trials should be considered.

Eustachian tube dysfunction-associated symptoms are responsible for substantial numbers of doctor visits.

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Persistence beyond a few weeks may lead to clinical diagnosis of ETD. ETD may be acute or chronic. Chronic ETD that fails to resolve with first-line treatment and continues for months or years has been associated with damage to the middle ear and tympanic membrane.[1] Suggested complications may include otitis media with effusion (OME), middle ear atelectasis and chronic otitis media (COM).[1,2] Treatments range from advice and initial observation, through pharmacological treatments such as steroids and sometimes referral for surgery.

Despite extensive searches, we found very little information on prevalences of acute or chronic ETD in adults. The only prevalence estimate identified was a British national survey conducted more than 20 years ago.[3] This reported an incidence of 0.9% based on otoscopic and audiological assessment in a stratified sample randomly selected from the electoral roll. The survey did not assess symptoms (usually critical to diagnosis). We were unable to identify information on the proportion of patients who have invasive treatment.

The aetiology of ETD is unclear. Several studies have suggested factors that may make ETD more likely (enlarged adenoids, trauma or nasopharyngeal tumour,[2,4,5] cleft palate,[6] or nasal septal deviation[7–10]). ETD most commonly presents following upper respiratory tract infection and in patients with allergic rhinitis or rhinosinusitis,[11,12] or following air travel or scuba diving.

Previous evidence synthesis is restricted to a 2002[13] non-systematic review mostly of paediatric and animal studies for which an update has been recommended.[14] NICE guidance on the technique of balloon dilatation for adult ETD concluded that there was inadequate evidence for the intervention.[15]

This review aimed to assess the evidence base for a range of interventions for adults with a clinical diagnosis of ETD and identify priorities for future research.

Methods

A systematic review of the efficacy and safety of interventions for the treatment of ETD in adults was undertaken. The protocol is available on PROSPERO (CRD42012003035).[16] PRISMA guidance was followed. A full account of the research will be published as an NIHR HTA report (http://www.hta.ac.uk/).

An information specialist searched 15 databases (Table 1) from inception to October 2012 for published and unpublished studies, without language restrictions. The strategy focused on terms for the Eustachian tube and relevant

Table 1. Resources searched

Databases searched
BIOSIS via ISI Web of Knowledge (1969 to 2008)
BIOSOS via Dialog (1993 to Sept week 5 2012)
Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley (Issue 9, Sept 2012)
Cochrane Database of Systematic Reviews (CDSR) via Wiley (Issue 9, Sept 2012)
Conference Proceedings Citation Index: Science via ISI Web of Knowledge (1990 to Oct 2012)
Cumulative Index to Nursing & Allied Health (CINAHL) via EBSCO (Inception to 28th Sept 2012)
Database of Abstracts of Reviews of Effects (DARE) via Wiley (Issue 3, July 2012)
Dissertation Abstracts via Dialog (1861 to Aug 2012)
EMBASE via Ovid (1974 to 5th Oct 2012)
Health Technology Assessment (HTA) database via Wiley (Issue 3, July 2012)
Inside Conferences via Dialog (1993 to Oct week 4 2012)
Latin American and Caribbean Health Sciences (LILACS) via http://lilacs.bvsalud.org/en/ (8th October 2012)
MEDLINE via Ovid (1946 to 4th Oct 2012)
MEDLINE In-Process via Ovid (7th Oct 2012)
PASCAL via Dialog (1973 to Sept week 5)
Science Citation Index via ISI Web of Science (1900 to October 2012)
Other sources searched (trials registers, websites)
ClinicalTrials.gov via http://clinicaltrials.gov/ (15th Oct 2012)
Controlled Clinical Trials via http://www.controlled-trials.com/ (15th Oct 2012)
EU Clinical Trials Register via https://www.clinicaltrialsregister.eu/ (15th Oct 2012)
European Medicines Agency (EMA) via http://www.ema.europa.eu/ema/ (1st Nov 2012)
National Research Register Archive via http://www.nihr.ac.uk/Pages/NRRArchiveSearch.aspx (15th Oct 2012)
UK Medicines and Healthcare products Regulatory Agency (MHRA) via http://www.mhra.gov.uk/ (5th Nov 2012)
US Food and Drug Administration (FDA) via http://www.fda.gov/ (1st Nov 2012)
WHO International Clinical Trials Registry Platform portal via http://www.who.int/ictrp/en/ (15th Oct 2012)

interventions. Full search strategies are available on request (see online Appendix for MEDLINE strategy). Regulatory agency websites, trial registers and references of relevant studies were searched.

Pre-specified inclusion criteria are shown in Table 2. Initially, we included studies of adults only or studies of mixed populations where outcome data were reported separately for adults. Because of a lack of studies in adults, a protocol amendment allowed inclusion of controlled studies with mixed adult/paediatric populations. Although uncontrolled studies have considerable limitations when used to assess the effectiveness of interventions, these were included to allow comprehensive coverage of all relevant interventions, including those such as surgery where RCTs are scarce. The primary outcome, selected for patient relevance, was change in symptom severity or frequency. Uncertainty about diagnostic criteria required a pragmatic approach: authors' statements that patients had ETD or symptom(s) the authors attributed to ETD were accepted. Studies not reported in English were excluded at this stage. This allowed us to quantify the excluded non-English language studies.

Studies were assessed for inclusion and appraised for quality by two independent reviewers; data were extracted by one reviewer and checked by a second. A third researcher was consulted where necessary. Where possible, relative risks or mean differences, with 95% confidence intervals, were extracted or calculated; where this was not possible, *P* values alone were extracted. We used the Cochrane risk of bias tool to assess randomised controlled trials (RCTs).[17] Tools from previous reviews were adapted for assessment of non-randomised controlled studies and case series (see online Appendix).[18,19] In cases of uncertainty, missing or incomplete data, we attempted to contact authors.

We undertook a narrative synthesis because of high levels of clinical heterogeneity and interpreted results in the context of clinical heterogeneity and risk of bias.

Results

Quality and quantity of evidence

The searches identified 3262 records. Nineteen studies (24 records) were included in the review (Fig. 1): three randomised controlled trials (147 patients),[20–22] two controlled non-randomised trials (CCTs) (60 patients),[23,24] one retrospective controlled study (40 patients)[25] and 13 case series (421 patients).[26–38] All five controlled trials related to pharmacological interventions (nasal steroids; antihistamine plus ephedrine; decongestant)[20,21,23] or mechanical devices (an N-300 device to apply mild negative pressure and an automated device for politzeration).[22,24] The case series and retrospective controlled study assessed surgical interventions such as laser tuboplasty, balloon dilatation or myringotomy.[25–38] Three ongoing studies including two randomised controlled trials (assessing balloon dilation and simethicone) were identified; no outcome data were available.[39–41] An excluded studies list is available on request.

Participants in surgical studies were all adults. One non-surgical study included adults only;[24] three included adults

Table 2. Inclusion criteria

Participants	Adults aged ≥ 18 years with a clinical diagnosis of ETD or mixed adult/paediatric population with separate data for adults or mixed diagnoses but separate data on those with ETD Patients with a cleft palate were not excluded Patients with patulous Eustachian tubes, a diagnosis of nasopharyngeal tumours or enlarged adenoids were excluded Following a protocol amendment, controlled studies with mixed/uncertain age populations, and without separate data on adults, were included
Interventions	Active observation, supportive care, auto-inflation, nasal douching, nasal decongestants, antihistamines, oral or nasal corticosteroids, LTRAs, antibiotics, simethicone, any surgery, for example, grommets, balloon dilatation, transtubal fluids, tuboplasty)
Comparators	Any
Primary outcome	Change in severity and/or frequency of symptoms
Secondary outcomes	Quality of life, middle ear function, hearing, clearance of middle ear effusion, need for additional treatment, early tube extrusion, adverse effects, complications of ETD
Study designs	Experimental trials (randomised or non-randomised) and controlled observational studies In the absence of controlled studies, case series with ≥10 patients

LTRA, leukotriene receptor antagonists; ETD, Eustachian tube dysfunction.

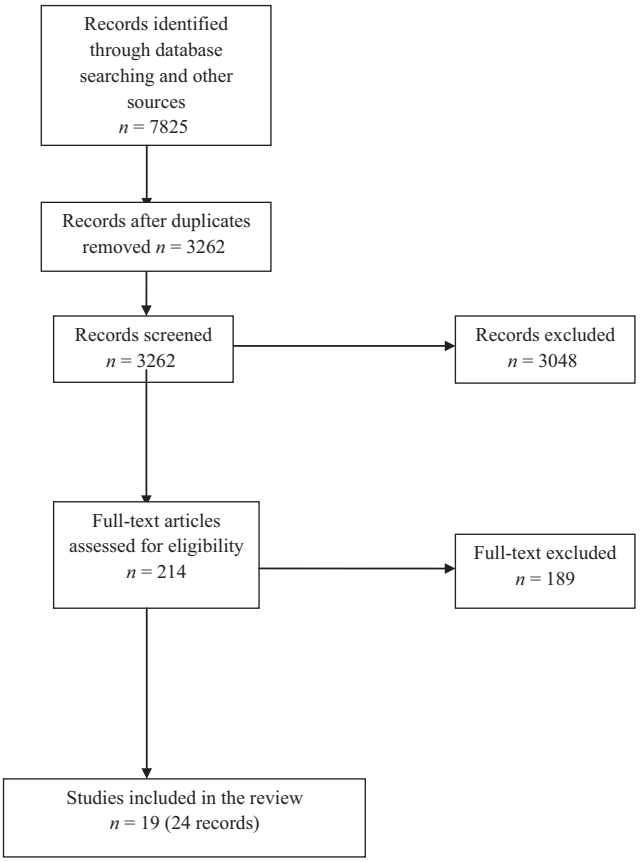

Fig. 1. Flow chart of study selection.

and children and/or adolescents,[20,21,23] and in one, it was unclear whether children were included.[22] The randomised controlled trial of nasal steroids included 34 patients aged between six and 18 years (total $n = 91$).[20] The proportion of adolescents aged 12–17 years in two other studies was unclear.[21,23]

There were a substantial number of treatments for which no studies were found despite our broad inclusion criteria (Table 3). No evidence was identified on most strategies used in primary care, in particular, active observation, supportive care, nasal douching, leukotriene receptor antagonists or antibiotics. Another notable gap was the lack of studies evaluating grommets (pressure equalisation tubes) for ETD.

The quality of the studies was low: all surgical studies and three of five non-surgical studies were at high risk of bias. The lack of control groups in 13 surgical studies made it difficult to reliably attribute benefit to the intervention assessed, particularly in a condition with a variable and uncertain natural course. Sample sizes were small (range 11–108). Reported follow-up was a maximum 10 weeks in non-surgical and 30 months in surgical studies. Very short follow-up durations in two of the three pharmacological

Table 3. Overview of gaps in the evidence identified

Intervention	Total number of studies	Number of RCTs
Active observation	0	0
Supportive care	0	0
Any non-surgical pressure equalisation technique	2	1
Nasal douching	0	0
Decongestants	1	1
Antihistamines	2*	0
Corticosteroids	2*	1
LTRA	0	0
Simethicone	1†	1†
Antibiotics	0	0
Grommets	1*	0
Balloon dilation	4	1‡
Tuboplasty	7	0
Transtubal fluids	1	0
Other surgical intervention§	3	0

LTRA, leukotriene receptor antagonists.
*Ongoing single uncontrolled study assessing nasal steroids + antihistamine and subsequent grommets.
†Ongoing placebo-controlled RCT.
‡Ongoing grommet-controlled RCT (within subject design).
§Myringotomy (two studies) or point laser coagulation of superior and posterior margin of ET nasopharyngeal opening (one study).

trials and high levels of co-intervention in surgical studies, including additional surgeries, were additional limitations.

Where diagnostic criteria were specified, there was substantial variability between studies in how ETD was defined. Common criteria were symptoms of pain, inability to equalise pressure and feeling of aural fullness. Significant numbers of patients reported tinnitus or dulled hearing. Studies often required participants to have abnormal middle ear function identified using a tool such as a tympanogram. Minimum durations of ETD varied from none specified up to 5 years. Many surgical studies specified that patients had failed various previous treatment options (sometimes including surgery). Therefore, patients in surgical studies often had more extensive histories of symptoms and previous failed treatments. Outcome assessments varied widely and were often poorly reported. Key study characteristics are in Table 4, and outcome data are summarised in Table 5.

There was limited use of patient-reported outcome measures (Table 5). Change in symptom severity or frequency was reported in only 10 studies, eight of which evaluated surgical interventions. Symptom assessment was often reported only in general terms; only one study used a validated ETD-specific tool.[34,42] No studies reported data on quality of life.

Table 4. Characteristics of included studies

Study	Design	Age	*n*	Inclusion criteria	Exclusion criteria	Diagnostic methods	Intervention Comparator	Follow-up	Study quality
Pharmacological interventions									
Gluth[22]	RCT	Adults and children aged ≥6 years Mean: 41.7 years	91	OME, or negative ME pressure, or OME+negative ME pressure and intact TM TM/cholesteatoma/ suppurative OM/cleft palate/developmental delay/type 4 retraction of TM	Perforated TM	Otoscopic examination Tympanometry Nasopharyngoscopy	Intervention: nasal steroid spray (triamcinolone 55 ug, 2 sprays/nostril b.i.d[b].for 6 weeks) Comparator: placebo spray	6 weeks	Low risk of bias (high-quality RCT)
Holmquist and Larsson[25]	CCT	Adults and children aged ≥14 years Mean: NR (range 14–66 years)	32	Opening pressure ≥200 mm H_2O(perforated TM patients) or tympanometric ear pressure between -100 and -400 mm H_2O (intact TM) Reduced opening pressure or negative ME		Manometry tympanometry	Intervention: Antihistamine + ephedrine (N-hydroxiaethylpromethazin chloride 15 mg, ephedrine sulphate 10 mg (tablets), single dose) Comparator: placebo (tablet)	≤3 h	Unclear (4 criteria were unclear)
Jensen[23]	RCT	Adults and children aged ≥12 years Mean: NR (median: 42 years)	36	Age ≥12 years No passage on Valsalva manoeuvre and/or incomplete pressure equalisation in aspiration/ deflation test; Dry eardrum perforation; normal ear mucosa; absent or reduced ET patency	Normal ET function/ URTI/adenoids/other lesions in nasopharynx/ ME lesions/ decongestant or antihistamine within 24 h	Valsalva manoeuvre, aspiration/deflation test	Intervention: nasal decongestant, sprayed directly towards pharyngeal opening of the ET (Xylometazoline chloride 0.1%, 0.4 ml, single dose) Comparator: placebo spray (saline)	30 min	Unclear risk of bias (unclear quality RCT)
Mechanical devices									
Alpini[24]	RCT	Adults? Mean: 39.2 years	20	Persistent ear fullness sensation following OM Abnormal tubotympanometry (95%) Normal pure tone audiometry and stapedial reflexes		VAS Tubotympanometry Vestibular evoked myogenic potentials	Intervention: N-300 device applying mild negative pressure to sealed external ear canal (manual device; pressure ≤ 350-400 mmH_2O; 5 min t.i.d[*] for 1 week) Comparator: No treatment	1 week	High risk of bias (low-quality RCT)

Table 4. continued

Study	Design	Age	*n*	Inclusion criteria	Exclusion criteria	Diagnostic methods	Intervention Comparator	Follow-up	Study quality
Silman[26]	CCT	Adults Mean: 35 years	28	Age ≥18 years Middle ear pain, fullness or clogged sensation following airplane travel or descent Tympanometric peak pressure <−100 daPa		Otolaryngologic evaluation Audiologic evaluation Tympanometry	Intervention: politzeration using an automated device (continuous air flow through the nose twice weekly for 6 weeks) Comparator: No treatment	9-10 weeks	Unclear (4 criteria were unclear)
Surgical interventions (tuboplasty)									
Caffier[28]	Case series	Adults Mean: 42 years	31	Therapy refractory chronic ETD (hyperplastic mucosa at the epipharyngeal dorsal ostium of the ET, abnormal tubal function tests) ETD symptoms for ≥ 5 years	History of allergic or reflux disease	Detailed examination: full neurootological diagnostics	Laser Eustachian tuboplasty; LA Comparator: none reported	1 year	Low
Jumah[29]	Case series	Adults Mean: NR Median: 40 years	30	Chronic obstructive ETD with intact TM Otalgia during pressure equalisation while flying/diving, recurrent OME, sensation of fullness in ear. Hyperplasia of at least one of the following: adjacent epipharyngeal soft tissue OR dorsal circumference of the ET ostium OR posterior end of the lower turbinate	History of severe allergic or reflux disease	Impedance in pressure chamber Valsalva manoeuvre/tympanometry Nasopharyngeal endoscopy Ear microscopy	Unilateral minimally invasive laser Eustachian tuboplasty under endoscopic control; GA Comparator: none reported	6 weeks	Low
Metson[30]	Case series	Adults Mean: 49.1 years	20	Chronic rhinosinusitis severe enough for surgery Symptoms of ETD: (persistent sensation of ear blockage with abnormal tympanogram or recurrent episodes of discomfort with altitude change)		Tympanogram Harvard staging and Lund-McKay staging for sinus disease Tissue eosinophil count for sinus disease	Microdebrider Eustachian tuboplasty; GA Comparator: none reported	Postoperative; 13 months	Low

Table 4. continued

Study	Design	Age	*n*	Inclusion criteria	Exclusion criteria	Diagnostic methods	Intervention Comparator	Follow-up	Study quality
Poe[31]	Case series	Adults Mean: 44 years	13	Adults with OME for ≥ 5 years, documented to reoccur immediately after extrusion/obstruction of most recent grommet. OME presumed to result from ETD Disease within cartilaginous portion of ET consistent with obstructive disorder Failure to show improvement of OME after medical management	Cholesteatoma or atalectasis without effusion	Microotoscopy; Transnasal endoscopic slow-motion video Endoscopic examination Audiogram Tympanogram Tubal dysfunction score	Unilateral laser Eustachian tuboplasty; GA and LA Comparator: none reported	2 years	Low
Sedlmaier[34]	Case series	Adults Mean: NR (Median: 44.7)	38	ME ventilation problems Negative Valsalva, no passive tubal opening, or long history of complaints and symptoms (difficult pressure equalisation, otalgia during pressure change)	History of allergic or reflux disease	Passive tubal opening and Valsalva (COM group) Tympanogram and microscopically controlled Valsalva	Laser ablation of epipharyngeal ET; LA Comparator: none reported	8 weeks	Low
Yanez†,[33]	Case series	Adults Mean: NR	25	Obstructive or non-obstructive (patulous) Eustachian tube disorder		NR	Laser tuboplasty; anaesthesia: NR Comparator: none reported	NR (study completion)	Low
Yañez[32]	Case series	Adults Mean: 48 years	25	Obstructive ETD severe enough to warrant ET surgery. ETD defined as persistent sensation of ear blockage with abnormal tympanogram or recurrent episodes of ear discomfort with changes in altitude (flying/diving)		Simple endoscopy or slow-motion video-endoscopic analysis Audiograms Tympanograms Symptom assessment	Laser Eustachian tuboplasty with cross-hatching technique; GA Comparator: none reported	Mean 15 months (range 3–37 months)	Low

Table 4. continued

Study	Design	Age	*n*	Inclusion criteria	Exclusion criteria	Diagnostic methods	Intervention Comparator	Follow-up	Study quality
Surgical interventions (balloon dilatation)									
Catalano[135]	Case series	Adults Mean: 45 years	70	Aged ≥18 years Reported chronic sensation of ear fullness, pressure, pain and otitic barotrauma (developed in adulthood)		Tympanogram clinical examination Symptomatology	Balloon dilation; LA unless concomitant procedure required GA Comparator: none reported	Mean 30.3 (SD 3.6) weeks (up to 34 months)	Low
McCoul[36]	Case series	Adults Mean: 55.1 years	22	Aged ≥ 18 years Abnormal tympanogram – any non A curve Abnormal otoscopic examination Unilateral/bilateral ETD symptoms (aural fullness/ pressure, clogged/muffled sensation in ears, recurrent/ persistent middle ear effusion, inability to rapidly self-equilibrate ME pressure following ambient pressure change)	Any extraneous cause (listed)	ETDQ7 SNOT-22 Physical examination including pneumatic otoscopy Tympanometry Pure tone audiometry CT scan of paranasal sinuses (Lund-McKay score)	Balloon dilation Eustachian tuboplasty; GA Comparator: none reported	12 weeks	Low
Poe[37]	Case series	Adults Mean: 51.8 years	11	Unilateral or bilateral persistent OME for at least 5 years, broken only by tympanostomy tubes or TM perforation (aetiology consistent with ETD)		Valsalva manoeuvre Otomicroscopy Tympanometry Video rigid or fibre-optic endoscopy Mucosal inflammation score CT scans	Unilateral balloon dilation at 8–12 atmospheres, reinsertion/repeat dilation where necessary; GA Comparator: none reported	6–14 (median 7) months	Low
Surgical interventions (Myringotomy)									
Potocki[38]	Case series	Adults Mean: 53 years	13	Patients undergoing hyperbaric oxygen therapy who would otherwise have required grommets for ETD		Otoloaryngologic examination Audiologic testing including tympanogram and pure tone audiometry	Bilateral thermal myringotomy; LA Comparator: None reported	4 months	Low

Table 4. continued

Study	Design	Age	*n*	Inclusion criteria	Exclusion criteria	Diagnostic methods	Intervention Comparator	Follow-up	Study quality
Prokopakis[39]	Case series	Adults Mean: 53 years	108	Adults with serous otitis media, ETD, or acute otitis media		Valsalva-Toynbee and inflation-deflation tests Audiological examination Tympanogram/ audiogram for 8 weeks. Nasal endoscopy Allergy tests	Laser assisted tympanostomy without ventilation tubes; LA Comparator: none reported	2 months	Low
Surgical interventions (others)									
Boboshko[†,27]	Retrospective controlled before-and-after	Adults Mean: NR (Range 21–56 years)	40	Intermittent hearing loss, ear pain, autophony, discomfort in the ears, poor endurance of differences in atmospheric pressure (flying in an airplane, diving, etc.), others (NR). (based on author contact)		Symptomatology, tympanometry (based on author contact)	Intervention: Point laser coagulation (superior and posterior margin of ET nasopharyngeal opening); LA Comparator: catheterisation of ET with insufflation, application of medications (not specified) under rhinoscopic control	2 weeks; 1 year	Low
Silverstein [c,40]	Case series	Adults Mean: 63 years	11	Chronic ETD: Symptoms consistent with ETD (e.g. hearing loss and aural fullness) Previous medical therapy and ≥ 1ME ventilation Tympanometry/clinical examination indicated abnormal ME pressure		Tympanometry Audiometry Clinical examination	Laser tympanostomy or vertical myringotomy; insertion of ventilation tube and microwick; administration of dexamethasone 4 mg/ml through wick t.i.d. for 4 weeks; LA Comparator: none reported	Mean 7.2 or 8 months	Low

ET, Eustachian tube; GA, general anaesthesia; LA, local anaesthesia; NR, not reported; OME, otitis media with effusion; TM, tympanic membrane.

Table 5. Outcome data from included studies

Study	Symptoms	Hearing	ME function	Clearance of effusion	Need for additional treatment	AEs/Complications of ETD
Pharmacological						
Gluth[22]	Symptom score at FU favoured control (P = 0.07)		No between-group difference in% with tympanogram normalisation (RR 1.20, 95% CI 0.91–1.58)		No difference in% requiring antibiotics/ oral decongestants (RR 1.00, 95% CI 0.39–2.57)	Minor events (coughs and nosebleeds in both arms, no discontinuations due to AE
Holmquist[25]			Normalisation of pressure equalisation function favoured treatment (RR 0.47, 95% CI 0.27–0.81			
Jensen[23]			Positive result of ≥1 test[a] favoured intervention (RR 0.63, 95% CI 0.31–1.27)			No adverse events
Pressure equalisation device						
Alpini[24]	Intervention group: decrease in VAS score (P < 0.001) Control group: NS		Normalisation of tubotympanometry favoured intervention (RR 0.13, 95% CI 0.02–0.85)			
Silman[26]		Air-bone gap increased: worse in control group (MD 12.9 dB, 95% CI 2.85 5 22.95)	Mean tympanometric peak pressure favoured intervention at FU: (RR of abnormality 0.36, 95% CI 0.15–0.87)			
Surgery: Tuboplasty						
Caffier[28]	VAS scores of between 5 – 7 for ETD improvement and specific symptoms. Described as 'high'	Air-bone gap reduced by mean 12.3 (SD 14.4) sB from baseline, benefit greater in perforated TM patients	Increase in proportion of patients with normal tympanogram from 13 to 26%			Discomfort in 3 patients relieved by additional anaesthesia; 1 case of an adhesion
Metson[30]	Resolution of ETD symptoms in 70% patients	Mean improvement in pure tone average -6 dB (*P* = 0.013)	65% of 17 patients with undefined baseline tympanogram abnormality demonstrated improvement		10% of patients required grommets	No adverse events

Table 5. continued

Study	Symptoms	Hearing	ME function	Clearance of effusion	Need for additional treatment	AEs/Complications of ETD
Poe[31]		Mean improvement in pure tone average −9.2 (SD 16.6) dB	Conversion to type A tympanogram in 15% patients	Absence of effusion in 38% patients	25% of patients with FU data (n = 8) required grommets	1 case of synechia between inferior turbinate and septum; 1 between posterior cushion and nasopharyngeal mucosa; 2 of granuloma in centre of resected area of mucosa
Jumah[29]			Conversion to type A tympanogram in 40% patients with baseline abnormality (N + 10) ($p < 0.135$)			No acute or long-term complications
Sedlmaier[34]			Increase in proportion of patients with normal tympanogram from 16 to 26%			1 case of synechia between posterior tubal ostium and adjacent epipharynx tissue
Yanez[33]	Symptom free 90% patients (recurrence: partial 5%; full 5%)					
Yañez[32]	Resolution of defined symptoms in 92% patients	Mean improvement in pure tone average −10 dB	96% of patients demonstrated undefined improvement in tympanogram (from non A baseline)		No grommets required	
Surgery: Balloon dilation						
Catalano[35]	Changes in defined symptoms/TM appearance in 71/100 ears		Conversion to type A tympanogram in 89% ears		10% of 71 ears with initial good response required repeat dilation	1 case of pre-auricular emphysema in the ipsilateral parotid region following difficult insertion; resolved within 48 h

Table 5. continued

Study	Symptoms	Hearing	ME function	Clearance of effusion	Need for additional treatment	AEs/Complications of ETD
McCoul[36]	Global improvement (patient response) in 92% ears; ETDQ-7 score improved: mean 1.8 (SD 2.2) points ($P = 0.001$)		Conversion to type A tympanogram in 96% ears		9% of patients required repeat dilation	1 patient had bleeding which resolved after myringotomy
Poe[37]			Conversion to type A tympanogram in 36% patients			Minor mucosal lacerations of ET lumen; 1 contralateral radiculopathy at C6-7 (full recovery)
Surgery: Myringotomy						
Potocki[38]		1 patient experienced unspecified change			1 repeat procedure, 2 myringoplasties for persistent perforation	Persistent bilateral perforations in 2 patients
Prokopakis[39]	Defined ETD symptoms resolved in 79% ears					
Surgery: other intervention						
Silverstein[b,40]	Improvement in aural fullness or pressure in 72% patients	Pure tone average +6 dB Air-bone gap -6 dB. Both changes NS	Conversion to type A tympanogram in 50% patients		3 myringoplasties for persistent perforation	1 patient developed profound sensorineural hearing loss following severe OM
Boboshko[c,27]	Disappearance/ reduction in unpleasant feeling/ noise in ear: 100%; control NR	More ears had an air-bone gap < 10 dB at 1 year in intervention group (RR 0.31, 95% CI 0.15–0.63). Pure tone averages also favoured intervention	97% intervention group had type A tympanogram at follow-up; at baseline most were type B or C; control group NR	Recurrence of OME at 9-11 months: 6% *versus* 40% (favours intervention)		No adverse effects

[a]Valsalva, aspiration or deflation test.
[b]Surgery to permit topical application of steroids.
[c]Laser point coagulation.

Efficacy of non-surgical interventions

The single randomised controlled trial (low risk of bias, $n = 91$) found no evidence that a 6-week course of nasal steroids was effective at improving severity and frequency of ETD symptoms among patients with OME and/or negative ME pressure.[20] The study was underpowered. Only *P* values without supporting data were reported. Data adjusted for baseline severity showed no difference in symptom score on a non-validated disease-specific scale ($P = 0.27$). A plugged sensation in the ear was more frequent and severe in the intervention group ($P \leq 0.03$). There was no evidence that steroids increased the number of patients converting from a type B or C to a type A tympanogram. The relative risk of conversion to a type A was not statistically significant (RR 1.20, 95% CI 0.91–1.58) but favoured the placebo.[20]

The two small trials (68 patients) of other pharmacological interventions (randomised controlled trial of topical decongestants;[21] CCT of antihistamine plus ephedrine[23]) had follow-up durations measured in minutes or hours. They showed improvements in measures of middle ear function but did not assess symptoms. Risk of bias was high or unclear.

Two small studies (48 patients) at high risk of bias assessed different mechanical devices. One randomised controlled trial showed statistically significant rates of improved symptoms in patients using an N-300 device compared with no treatment (measured after 1 week using a visual analogue scale).[22] A CCT found statistically significant improvements in hearing and ME function 9–10 weeks after politzeration twice weekly for 6 weeks compared with no treatment.[24]

Efficacy of surgical interventions

Eustachian tuboplasty using various techniques (seven case series, 182 patients[26–32]) was associated with improvement in symptoms in 36–92% of patients (four studies).[26,28,30,31] Improvements in hearing (four studies) were small with limited clinical significance.[26,28–30] Three studies documented low rates (13–36%) of conversion to type A tympanogram.[26,29,32]

Balloon dilatation studies (three case series, 107 patients[33–35]) showed improvement in symptoms of 92% and 71% of patients/ears (two studies[33,34]). Conversion to type A tympanogram ranged from 36 to 96% of patients (three studies).[33–35] Most patients underwent additional sinonasal or otologic surgical procedures such as partial inferior turbinectomy or submucous resection of the nasal septum. We found no evidence to alter the NICE recommendation that there is insufficient evidence for this procedure.[15]

Myringotomy without insertion of grommets (two case series, 121 patients) was reported to be effective in permitting patients to undergo hyperbaric oxygen therapy[36] and in symptom alleviation in a subgroup of patients with ETD.[37]

Single studies reported positive results for improvement of specific symptoms in most patients following topical application of steroids to the middle ear using a microwick following myringotomy[38] and laser point coagulation of the superior and posterior margin of the ET nasopharyngeal opening.[25] Both studies reported improved middle ear function (50 and 97% of ears).

Safety of treatments

Thirteen studies including 11 surgical series reported some information on safety.[20,21,25–29,32–36,38] No serious adverse effects of treatment were recorded; there were minor complications of surgery and pharmacological treatments. The randomised controlled trial with low risk of bias assessing nasal steroids reported only minor coughs and nosebleeds in both trial arms.[20] Surgical studies reported minor lacerations,[35] discomfort,[26] adhesions[26,29] and granulomas.[29] Single instances of bleeding and radiculopathy were seen after balloon dilatations.[34,35]

Discussion

Limitations of available evidence and gaps in the literature

Despite extensive searches, we identified few studies and multiple gaps in the evidence base for treatment of ETD in adults, including for the relatively common surgical treatment of grommets. The evidence base was sparse (only two controlled studies with wholly adult populations). The studies included after the protocol amendment to include controlled data on mixed adult/paediatric populations increased the available data. Four of five non-surgical interventions were evaluated in populations that included/potentially included children/adolescents; adults appeared to be a majority and most other patients were adolescents. This should be considered when assessing applicability of the findings.

There was no evidence relating to most primary care approaches, including antibiotics and active observation. Studies were mostly small with high risks of bias. They assessed disparate interventions in diverse populations with varying criteria for a diagnosis of ETD and poor reporting of outcome data. Only one underpowered RCT, in adults and children, provided evidence with low risk of bias; this showed no evidence of effectiveness for nasal steroid treatment. Lack of evidence of effectiveness does not equate to evidence of no effectiveness but indicates a need for further evaluation of current approaches.

Uncertainty of diagnostic criteria and assessment methods

The review identified a lack of clear diagnostic criteria for ETD in research studies. We anticipated this and took a pragmatic approach and used a broad definition of ETD when assessing eligibility of studies for inclusion in the review. Included studies rarely used an explicit definition of ETD and seldom reported assessment of baseline symptoms with standardised or validated tools. Although ETD is a symptom-driven diagnosis, there is no established patient-reported measure for either baseline or post-treatment assessment in clinical trials. The ETDQ-7 scale used in one study is a recent development that has been tested for validity in relatively few patients and controls.[42] It is not widely used.[20] Assessment of symptoms following treatment was problematic: most studies reported heterogenous criteria for 'improvement' or 'resolution' of symptoms; only four studies attempted to quantify improvement, and poor reporting was an issue.[20,22,26,34]

The absence of standardised assessment contributed to wide variations in population inclusion criteria and inclusion of heterogeneous populations. Studies varied in whether an abnormal tympanogram was required, how abnormality was defined, and whether patients with a perforated tympanic membrane were included. There were differences in incidences of related conditions (such as rhinosinusitis, reflux and allergy), duration of ETD and previous treatments for ETD. Histories of symptoms and failed prior therapies varied within and between surgical studies. This suggested little consensus on when surgery may be appropriate. Poor reporting frequently contributed to uncertainty around the population diagnosed and treated with ETD.

Strengths and weaknesses of the review

This is the first systematic review to evaluate interventions for adult ETD. Our comprehensive approach included a broad range of eligible interventions and an extensive search for published and unpublished studies. Paucity of the literature required the review to be broadened to include controlled studies with mixed paediatric/adult populations. High levels of clinical heterogeneity in the included studies precluded quantitative synthesis. Small sample sizes in included studies represent an important limitation as these may have been underpowered to detect an effect. The review included only papers reported in English, but the searches had no language restrictions, and we were able to identify that only seven papers in other languages merited full text examination. Brief assessment by readers of these languages indicated that none of the papers related to controlled studies or studies of large numbers of patients, and they were unlikely to alter the review results.

Conclusions

Limitations in the evidence on effectiveness and variability in diagnostic criteria used in the studies precluded firm conclusions on the effectiveness of any treatments.

Recommendations for research

It is not possible to recommend a trial of any particular intervention at this stage. In the first instance, a multidisciplinary consensus meeting including all relevant stakeholders may be helpful to develop explicit diagnostic criteria for ETD that could be used to identify eligible patients for randomised controlled trials. Consensus is required on important clinical outcomes, their assessment and appropriate duration of follow-up.

Keypoints

- This is the first systematic review of interventions for Eustachian tube dysfunction in adults or mixed adult/paediatric populations.
- Despite a comprehensive search, and broad inclusion criteria, there were substantive gaps in the evidence base, including the use of grommets and primary care interventions.
- Evidence identified came from 19 small studies with 659 patients. Fourteen surgical intervention studies included 452 patients (all adults). Five non-surgical studies included 207 patients; 34 were known to be aged 6–17; an unknown proportion of adolescents aged >12 years were also included.
- Only one study at low risk of bias was identified: this showed no evidence of effectiveness of nasal steroids. The evidence was too limited to draw conclusions regarding the effectiveness of any intervention for Eustachian tube dysfunction.
- There is a need for consensus on the definition of Eustachian tube dysfunction in adults and for the development of clear diagnostic and treatment criteria.

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Conflict of interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Results of quality assessment.

Quality assessment of RCTs (non-surgical studies): risk of bias summary.

Quality assessment of non-randomised controlled studies (non-surgical studies and surgical study).

Quality assessment of case series (surgical studies).

Appendix S2. MEDLINE Search strategy.