EUnetHTA WP5 Joint Action 2 (2012-2015) Strand B, Rapid assessment of other health technologies such as medical devices, surgical interventions or diagnostics

Pilot rapid assessment of other health technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

Balloon Eustachian tuboplasty for the treatment of Eustachian tube dysfunction

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Final Version

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Disclaimer

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Conflict of interest

All authors and reviewers involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA conflicts of interest (COI) statement form or, respectively, the Declaration of Interest and Confidentiality Undertaking (DOICU) form.

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LIST OF ABBREVIATIONS

AOM	Acute otitis media
BET	Balloon Eustachian tuboplasty
CRD	Centre for Reviews and Dissemination (University of York, UK)
COM	Chronic otitis media
CSOM	Chronic suppurative otitis media
CT	Computed tomography
DARE	Database of Abstracts of Reviews of Effects, CDR.
EAM	External auditory meatus
ENT	Ear, nose and throat
ETD	Eustachian tube dysfunction
ETDQ-7	7-item Eustachian Tube Dysfunction Questionnaire
GBI	Glasgow Benefit Inventory
GRADE	Grading for Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
ICD	International Classification of Diseases
IHE	Institute of Health Economics (Alberta Canada)
ICTRP	WHO International Clinical Trials Registry Platform
LETP	Laser Eustachian tuboplasty
MeSH	Medical Subject Headings
OME	Otitis media with effusion
RCT	Randomised controlled trial
REA	Relative Effectiveness Assessment
ROBIS	Risk of Bias in Systematic Reviews
SD	Standard deviation
SNOT-22	22-item Sinonasal Outcome Test
TM	Tympanic membrane
VAS	Visual analogue scale

SUMMARY OF RELATIVE EFFECTIVENESS OF BALLOON EUSTACHIAN TUBOPLASTY

Scope

The aim of this rapid assessment is to summarise the information on the relative effectiveness and safety of balloon Eustachian tuboplasty (BET) for the treatment of Eustachian tube dysfunction (ETD) in a population aged over 12 years. Specific indications are listed in the Scope on page 13.

The comparators included tympanostomy tubes (grommets) and medication (such as nasal decongestants, simethicone, oral or nasal corticosteroids, antibiotics, antihistamines, leukotriene receptor antagonists).

For effectiveness, the primary outcome was normalisation of tympanometry measures indicating normal ear and other measures related to functioning of the middle ear (Valsalva manoeuvre, tube score, otoscopic findings, audiometric evaluation of hearing function). In addition, quality of life, need for additional treatments, and long-term effectiveness were studied.

Adverse effects (e.g. early complications, serious adverse events) were also studied.

Introduction

Health problem

The Eustachian tube consists of bone, cartilage, and fibrous tissue. Under normal circumstances, there is a roughly 8- to 12-mm segment in the middle of the cartilaginous Eustachian tube that is closed at rest, with mucosal surfaces in apposition, and therefore functioning as a valve. The cartilaginous Eustachian tube dilates to the open position on demand, particularly with swallows and yawns [1]. Other functions of the Eustachian tube include clearance of middle-ear fluid and preventing nasopharyngeal secretions refluxing into the middle-ear space [2].

ETD has been defined as the failure of the Eustachian tube to ventilate the middle ear [3]. It has been suggested that ETD is the cornerstone of the pathogenesis of otitis media, an umbrella term for a group of complex infective and inflammatory conditions (including otitis media with effusion (OME) or “glue ear”) affecting the middle ear [4]. Otitis media is mainly an infectious disease, resulting from interplay between microbial load (viral and bacterial) and immune response. Eustachian tube function is believed to play an integral role in the causation of otitis media because the other identified causes either adversely affect Eustachian tube function or reflect functional insufficiencies [5] (A0002, A0003).

ETD results in the development of negative pressures within the middle ear, leading to transudation of fluid and a pro-inflammatory response [6]. ETD may be acute or chronic. Chronic ETD that fails to resolve with treatment and continues for months or years has been associated with damage to the middle ear and tympanic membrane [7]. It is argued that active Eustachian tube opening is the homeostatic process which maintains a semi-stable middle-ear ambient pressure balance and, as a result, middle-ear health and “normal hearing”. ETD has thus been associated with pathology within the middle ear, with the development of complications along the otitis media spectrum, including acute otitis media (AOM), OME/“glue ear“, middle-ear atelectasis, chronic suppurative otitis media (CSOM) and cholesteatoma (A0004).

According to 1 study on middle-ear disease in the adult British population, ETD has a prevalence of 0.9% [8] (A0023).

A number of factors have been identified that are thought to contribute to ETD [2] (A0003):

- Viral upper respiratory tract infection
- Chronic sinusitis
- Allergic rhinitis
- Adenoid hypertrophy
- Tobacco smoke
- Reflux
- Cleft palate
- Radiation
- Reduced mastoid air system
- Nitrous oxide.

AOM typically affects children under 2 years of age, and presents with acute onset symptoms and signs of otalgia and fever, in a child that is systemically unwell. It is an acute inflammation, and may be caused by bacteria or viruses [9]. OME has a lower prevalence in adults, and the incidence of prolonged OME in adults is not known [10]. Its development in adults is frequently associated with other underlying diagnoses. Paranasal sinus disease has been described as the dominant factor in 66% of adults with OME, with other causes including smoking-induced nasopharyngeal lymphoid hyperplasia and adult-onset adenoidal hypertrophy in 19% of cases, and head and neck tumours (mainly nasopharyngeal carcinomas) in 4.8%. In 1.8% of patients no underlying diagnosis was identified [9, 11] (A0004).

OME or “glue ear” is a chronic inflammatory condition; it may occur de novo or as a sequel to AOM [12]. It is most prevalent in children between 8 months and 2 years, thereafter diminishing gradually in children between 3 and 7 years. It is characterised by the presence of a glue-like fluid behind an intact tympanic membrane in the absence of signs and symptoms of acute inflammation (A0004).

Two additional inflammatory conditions of the middle ear are CSOM and cholesteatoma. CSOM is characterised by the presence of long-standing suppurative (pus producing) middle-ear inflammation, usually with a persistently perforated tympanic membrane. Cholesteatoma occurs when keratinising squamous epithelium (skin) is present in the middle ear (normal middle ear is lined by modified respiratory epithelium). It typically presents with chronic smelly ear discharge, and can be diagnosed when squamous epithelium and keratin are seen in the middle ear. Surgical removal is the only curative treatment for cholesteatoma [9] (A0004).

Antibiotic therapy has significantly reduced the burden of intratemporal and intracranial complications of otitis media (A0004).

A number of subjective and objective tests have been proposed for assessing Eustachian tube function. Despite the availability of these tests, however, there persists a lack of clear diagnostic criteria for ETD. Subjective tests include the Valsalva manoeuvre, forcible sniffing and the Toynbee test. Tympanometry, meanwhile, involves measuring tympanic membrane compliance while the pressure in the external auditory meatus (EAM) is automatically varied between +200 and -400 mm H_2O. The resulting graphical output may be categorised into 1 of 3 groups, associated with normal, low or excessive pressure within the middle-ear system, with this pressure reflected in the relative compliance of the tympanic membrane. Sonotubometry involves the application of a sound source to the nostril, with a microphone placed in the external auditory canal to record the transmitted sound. Sound levels are then measured as the Eustachian tube opens and closes. This diagnostic test has the advantage that it allows evaluation of the Eustachian tube with or without an intact membrane under physiological conditions [2]. Other methods of assessing Eustachian tube function in ears with an intact tympanic membrane include modifications of tympanometry, sonotubometry, nasal endoscopy, and the inflation and deflation tests [5] (A0024).

Description of technology

BET is used to address ETD. As of July 2014, there are 2 CE-marked products on the market for BET: the "Bielefelder Ballonkatheter"/ TubaVent® by Spiggle and Theis, and AERA™ by Acclarent Inc. (Johnson and Johnson). Both companies have just one version of their product on the market. BET involves passing a catheter into the Eustachian tube through the pharynx. This catheter is then temporarily inflated before being deflated and withdrawn. The procedure is based upon the idea that this temporary dilatation of the Eustachian tube can improve symptoms for patients with ETD. It has been postulated that while the balloon may shear or crush portions of the epithelium within the Eustachian tube, it appears to spare the basal layer in most cases, and may thus result in relatively rapid healing after the procedure [13] (B0001, B0002).

BET has been done under both local and general anaesthetic. While the earliest published work on BET reported inflation of both the cartilaginous and bony portions of the Eustachian tube, this approach has since fallen out of favour, with inflation of the cartilaginous portion only reported in more recent studies (B0001).

A number of alternative surgical procedures have previously been used in attempting to address ETD. Historically, these involved invasive attempts to widen the osseous portion of the Eustachian tube, and were based on the belief that the bony isthmus is the narrowest portion of the tubal lumen, and hence is most likely to be the site causing dysfunction. None of these techniques were reported to demonstrate long-term success [14, 15] (B0001).

The traditional surgical management of ETD leading to OME involved using ventilation tubes ("grommets") which are placed in the tympanic membrane with the aim of facilitating ventilation of the middle ear. This can result, however, in persistent otorrhoea. In addition, they fail to treat the underlying dysfunction and there is a subset of patients in whom OME repeatedly recurs after extrusion of the tubes [1]. While patients may be offered long-term ventilation tubes with good success, 1 study reported that 79 of 412 patients (19%) were found to have a persisting tympanic membrane perforation at a median follow-up of 3.4 years after insertion of Goode ventilation tubes [16]. Patients diagnosed with ETD have been treated with a range of medical therapies, including antihistamines, topical and systemic decongestants, intranasal corticosteroids, antibiotics, mucolytics, and proton pump inhibitors. The efficacy of all of these remains unproven (B0001).

BET has been promoted as a potential management option for adults with ETD leading to OME. Although ETD usually refers to chronic blockage of the Eustachian tube, it also includes the opposite condition where the Eustachian tube is occasionally or permanently left unclosed, resulting in a condition called patulous eustachian tube (tuba aperta). A health technology assessment (HTA) published on ETD in 2014 did not refer to any one specific diagnosis or set of diagnoses, but rather focused on interventions that have been suggested to improve ETD where it is considered the cause of some, or all, of the following symptoms: muffled hearing, pain, feeling of fullness in the ear, tinnitus and dizziness. The report noted that patients may also have impaired hearing, abnormal tympanograms or abnormal physical appearance on otoscopic examination, but that the relationship of these signs and symptoms to ETD is unclear [7] (B0002).

As noted above, there are a number of alternatives to BET, but none has a solid evidence base (B0003).

BET was first described in 2010 [3]. In 2011, a National Institute for Health and Clinical Excellence review of balloon dilatation of the Eustachian tube concluded that due to inadequate evidence, the procedure should be used in a research-only capacity [17] (B0003).

Methods

Clinical effectiveness and Safety domains

This rapid assessment was based on the assessment elements from the HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals and 1 element from the HTA Core Model® for Diagnostic Technologies (D0023). A systematic literature review was undertaken using the following sources: Medline via OVID, EMBASE, Cochrane database, DARE and HTA databases via the Cochrane Library and CDR. WHO International Clinical trials Registry Platform (ICTRP) and ClinicalTrials.gov were used to identify registered clinical trials. Additional information was also obtained from the manufacturers.

Accepted study designs for "Clinical effectiveness" and "Safety" domains included randomised controlled trials (RCTs), non-randomised trials, controlled observational studies and case series with at least 10 patients in an adult or adolescent population aged more than 12 years. Further, a systematic review [7] was used in the planning stage of the assessment and to compare results and conclusions.

Quality assessment for systematic reviews was based on the ROBIS (Risk of Bias in Systematic Reviews) tool [18] and for case series an 18-criteria checklist by IHE (Institute of Health Economics, Alberta, Canada) was used [19]. The Cochrane risk of bias tables for outcomes were also used. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used for qualitatively summarising the results for the domains: "Safety" and "Clinical effectiveness".

Results

Available evidence

A systematic review and nine case series were included in the assessment of clinical effectiveness and safety. Two studies were based on the same data set [20, 21], and two further studies [22, 23] may also relate to the same data. The age range in one study [21] was from 8 to 84 years. Since this was a large case series (n=351), it was decided to include the study, as there were most likely only a few patients less than 12 years of age.

Clinical effectiveness

Data on the effectiveness of BET is based on non-comparative studies only. Improvement was seen in all the outcome measures (tympanometry, Valsalva manoeuvre, tube score, mucosal inflammation, overall symptom improvement, quality of life) evaluated in all the included studies (D0005).

Postoperative tympanogram results were classified as type A (normal) in the majority of cases. The proportion of patients classified as having type A ears at postoperative follow-up varied from 90-97% in 2 studies [23, 24] to only 28-36% in 2 studies [22, 25]. The duration of follow-up ranged from 2 months [22] to 4.2 years [23] (D0005).

The otoscopy findings were reported in 2 studies [22, 24]. In the first, the tympanic membranes were normal in 45% of patients (5/11) on otomicroscopy examination postoperatively [22]. While in the second study, the 100% of ears with tympanic membrane retractions preoperatively were all free of retraction postoperatively [24] (D0005).

Assessments of the ability to do the Valsalva manoeuvre postoperatively were positive in in 66-100% of studies [20, 22, 23, 25, 26]. Results were always positive in 64-67% [20, 22], and when the ability to do Valsalva "sometimes" or "occasionally" was added, the overall ability to do Valsalva manoeuvre was 81% [20], 90% [26] and 100% [22]. In preoperative records, the majority of Valsalva assessments were abnormal (D0005).

A composite (Eustachian) tube score was used in studies from a German group [20, 21] to assess improvement of symptoms (score range: 0 [poor Eustachian tube function] to 10 [normal Eustachian tube function, score above 5 indicating functional Eustachian tubes). The preoperative tube score was 2.71 (SD 2.2). Postoperative scores at 2, 12 and 24 months were 5.46 (SD 2.6), 6.07 (SD 2.6) and 6.14 (SD 3.2), respectively. However, there was substantial loss to follow-up over the 2 year period (only 22/351 ears assessed at 24 months) [21]. In 2 reports [20, 21], 78% of treated patients showed improvement in tube score at 2 months.

In 1 study using mucosal inflammatory score (unvalidated scale from 1 to 4: 1=normal, 4=severe) the mean score was 2.8 (SD 1.2) preoperatively and 1.4 (SD 0.8) postoperatively ($p<0.001$); 12% (5/41) of patients still had moderate or severe inflammation postoperatively [23].

Some studies used combined measures of subjective and objective responses [24, 25]. In one such study [24] the global response to treatment was 79% (23/29) in week 6, and 92% (24/26) in week 12 following the procedure (D0005).

Long-term results were available for 3 studies. In one [27], 87% showed persistent improvement at 34 months follow-up (8/71 patients left for analysis). In another [21], 86% of operated ears showed improvement (22/351 ears available) at 2 years. In the third [23], 90% (37/41) of ears were considered normal postoperatively (mean follow-up 2.5 years, range 1.5-4.2 years). (D0005)

The need for additional repeated dilatation during follow-up was similar in all studies, in the range 8-10% [22, 24, 27].

The effect of BET on patients' body function (e.g. hearing) was also assessed (D0011). Audiometric evaluation of hearing function was reported only in 1 study [25] and no hearing losses were reported before or after treatment. In the same study the visual analogue scale (VAS) scores (0= never, 100=always) were, for aural fullness, 68.6 (SD 26.9) preoperatively and 42.0 (SD 31.8) postoperatively ($p<0.05$), while for earache, the corresponding scores were 29.8 (SD 25.8) and 14.5 (SD18.3), respectively (D0011).

The issue of how BET affects progression of ETD could not be addressed (D0006).

The quality of life improved according to general and disease-specific measures (D0012, D0013). In the study using the Glasgow Benefit Inventory (GBI) questionnaire [28], statistically significant improvement was seen in the total score ($p=0.001$), "general health" subscore ($p=0.001$) and in the "physical health" subscore ($p=0.039$) (D0012). In a study using the patient-reported ETDQ-7 (7-item Eustachian Tube Dysfunction Questionnaire) score [24], the score was statistically significantly improved from a preoperative value (mean 4.5, SD 1.2) for all postoperative values from 3 weeks to 6 months. The improvement was seen by week 3 (mean 2.7, SD 1.5) and remained steady during the 6 month follow-up (mean 2.8, SD 1.3). The mean overall change in score was 1.9 points, which was considered to be a clinically important improvement (D0013). Mean SNOT-22 (22-Item Sinonasal Outcome Test) scores also significantly improved at all follow-up timepoints. The score was 51.4 (SD 21.1) at baseline and 30.0 (SD 23.9) at 6 months [24] (D0013).

More patients would have recommended the procedure to a friend with equivalent symptoms than would have not recommended the procedure (average score 35, scale 0-100, with 0 indicating that they would recommend the procedure) [25] (D0017).

Safety

Data on the safety of BET is based on non-comparative studies. Overall, adverse effects reported in association with BET seem to be mild and self-limiting. The safety and tolerability of BET in adults, based on the available studies, seem to be good with only minor adverse effects. These effects have been self-limiting or have been treated with local decongestants. The most common adverse effect reported is mild bleeding in the nasopharyngeal area. Other adverse effects include otitis media and emphysema in the facial area. One case with emphysema extending down to the mediastinum has been reported (C0001).

Safety issues are confounded by the fact that in some studies other concomitant procedures were performed.

Upcoming evidence

Three ongoing studies were identified of which one is an RCT (see Appendix 1, Table 5). According to the Acclarent Inc. a study called ELLIOTT (A Randomized Clinical Study Of Safety And Efficacy For The Eustachian Tube Balloon Catheter) is currently enrolling patients to satisfy requests of the US Food and Drug Administration [29]. It includes people with ETD aged 22 and older who are not responding to medical therapy. A randomised trial is also planned, but the study protocol has not yet been posted on the clinical trials register [30] (B0003).

Reimbursement

The current reimbursement status of BET across Europe is as follows: BET is currently not reimbursed in Austria, Belgium, the Czech Republic, France, Hungary, Ireland, Latvia, Malta, Poland and Slovenia. It is formally reimbursed in Lithuania and Switzerland, with limited reimbursement in Finland, Germany, Italy and Spain (A0021).

Summary table of relative effectiveness of balloon Eustachian tuboplasty

Table 1: Summary of relative effectiveness of balloon Eustachian tuboplasty (BET)

	Health benefit				**Harm**	
	Tympanometry	**Valsalva manoeuvre**	**Symptom improvement**	**Quality of life**	**Serious AEs**	**Other AEs**
BET	*Type A ears (normal) postoperatively 28-97% [20, 22-27]*	*66-100% [20, 22, 23, 25, 26]*	*2 months 67-75% [20, 25]* *6-14 months: 60-100% [20-22, 24]* *24 months+: 87-90% [23, 27]*	*Significant improvement at week 6 measured by ETDQ-7, SNOT-22 [24]* *and at 6-18 months by GBI [28]*	*Mediastinal emphysema* *A single case in a series of 210 patients [26]*	*Bleeding in the nasopharyngeal area (2.5 – 46) [22, 26, 27]* *Otitis media (8%) [25]* *Subcutaneous emphysema in the facial area (0.5%) [21, 27]*
Comparator	*lacking*	*lacking*	*lacking*	*lacking*	*lacking*	*lacking*
Assessment elements	D0005	D0005	D005	D0013	C0001 C0008	C0001 C0008
Quality of body of evidence[*]	**Very low**	**Very low**	**Very low**	**Very low**	**Very low**	**Very low**

Abbreviations: AE=adverse event, ETDQ-7= 7-item Eustachian Tube Dysfunction Questionnaire, SNOT-22= 22-item Sinonasal Outcome Test, GBI= Glasgow Benefit Inventory

[*] *Quality of body of evidence was evaluated using GRADE approach; very low = any estimate of effect is very uncertain. (see Appendix, Table 6, Table 8, Table 9)*

Discussion

This rapid assessment included nine studies, 5 more in addition to the studies included in an earlier systematic review by Norman (shorter article version)/LLewellyn (full report of the systematic review) [7, 31]. All the included studies were case series. The quality of the studies was considered to be acceptable for 3 studies (Table 6), but the the risk of bias on outcome level was assessed as being high (Table 8). The quality of the body of evidence was considered very low (Table 9).

All studies showed improvement from the treatment of ETD with BET. The postoperative improvement was observed with objective measures, such as tympanometry, tube score and otoscopy findings. The disease-specific quality of life measures were in line with objective results and showed improvement in the general and physical health and sinonasal quality of life. There was some evidence that improvement is durable for up to 2-3 years, but the numbers of patients assessed after long-term follow up were low. The adverse effects reported seem to be mild and self-limiting.

The use of concomitant surgical procedures makes the assessment difficult. In particular, tympanostomy tubes, which had been planned as a comparative treatment for BET, were used by many patients. The contribution of concomitant surgical procedures and other treatments to outcomes should be evaluated in comparative research designs.

The reporting was incomplete in the majority of the studies. For example, the descriptions of eligibility criteria for selected patients varied and the medical histories of patients before the BET procedure was not described in all studies. It is likely that there were variations in the patient populations between studies. The lack of consensus on the diagnostic criteria for ETD makes the selection of patients challenging. Furthermore, the natural course of ETD is poorly documented and is known to have favourable outcomes without intervention.

Children aged less than 12 years were excluded from the evaluation so the results cannot be generalised to them.

Conclusion

Despite promising results, due to a lack of high quality data no definite conclusions can be drawn as to whether BET is effective in the treatment of ETD. Some studies included concurrent procedures, which most likely lead to an overestimation of the effectiveness of BET as well as increased loss to follow-up. Since the technology is still at an early stage of development, further evidence is needed to determine whether it is more effective and/or safe than the comparators. Further research, including controlled trials, is needed to verify how long the treatment effects remain and to determine the outcomes of repeated treatments. The diagnostic criteria for ETD should be clearly defined. One randomised trial is anticipated to finish data collection in January 2015. A further RCT is planned. After the results of these RCTs are available, the effectiveness of BET should be re-evaluated.

1 SCOPE

Description	Project scope
Population	ICD-10: H65.3 Chronic mucoid otitis media, H65.2 Chronic serous otitis media/otitis media with effusion (OME) (H65.2), H68.1 Obstruction of Eustachian tube, H65.4 Other chronic nonsuppurative otitis media, H65.9 Nonsuppurative otitis media, unspecified, H69.9 Eustachian tube disorder, unspecified. MeSH terms: Ear diseases, Eustachian tube Target population: adolescents over 12 years and adults with OME, middle-ear atelectasis or chronic Eustachian tube dysfunction (ETD) (muffled hearing, pain, feeling of fullness in the ear, tinnitus and dizziness) and other indications mentioned above. The target population covers obstructive (non-patulous) or dilatory dysfunction of the Eustachian tube. ETD needs to be confirmed by objective measure (nasal endoscopy, audiology examinations or radiographic imaging). MeSH terms: Humans, Adult, Adolescent, Ear, Middle ear, Ear diseases
Intervention	In balloon Eustachian Tuboplasty (BET) a balloon catheter is introduced in to the Eustachian tube via the nose under general anaesthesia. Once the balloon is positioned in the cartilaginous part of the Eustachian tube, a saline solution is injected at a pressure of up to 10 bars. Pressure is maintained for approximately 2 minutes and then the liquid is aspirated and the catheter removed (TubaVent®, formerly Bielefeld Bollonkatheter, Spiggle & Theis). In Acclarent's (Johnson & Johnson) catheter AERA™, the cartilaginous position of the Eustachian tube is dilated with a balloon catheter; endoscopic markers are placed along the subject device to aid its positioning under direct endoscopic visualisation. MeSH term: Eustachian tuboplasty, Dilatation, Balloon dilatation, Ventilation
Comparison	– Tympanostomy (ventilation tube, grommet) – Medication (to decrease oedema of the nasopharynx; nasal decongestants, antihistamines, leukotriene receptor antagonists, simethicone, oral or nasal corticosteroids, antibiotics, nasal douching, transtubal fluids) MeSH terms: Middle ear ventilation
Outcomes	Primary outcomes: Normalisation of tympanometry measures (type A) Secondary outcomes: – Middle-ear function measured by Valsalva manoeuvre, tube score (tubomanometry), Toynbee test, clearance of middle-ear effusion – Audiometric evaluation of hearing function – Need for additional treatment – Quality of life – Long-term effectiveness – Adverse effects: early complications, late adverse effects, treatment related adverse effects, serious adverse events

2 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

2.1 Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

Element ID	Research question	Importance 3=critical 2=important 1=optional
A0002	What is the definition of Eustachian tube dysfunction (ETD), glue ear according to ICD-10?	3
A0003	What factors cause ETD or glue ear?	3
A0004	What is the natural course of ETD and glue ear?	3
A0005	What is burden of ETD and glue ear for the patient? How does ETD and glue ear affect the daily life of the patient?	3
A0006	What is the burden of ETD and glue ear for society?	3
A0007	What is the target population in this assessment?	3
A0023	What is the prevalence of ETD and glue ear?	3
A0001	For which indications or symptoms is BET used and in which patient groups?	3
A0011	How widely is BET being used in Europe?	1
A0024	How are ETD and glue ear diagnosed according to clinical practice guidelines and in practice?	3
A0025	How are ETD and glue ear managed according to clinical practice guidelines and in practice?	3

Sources

To answer the research questions in the domain “Description and technical characteristics of the technology”, the results from a systematic literature search (Appendix 1) in Medline via OVID, EMBASE and the following sources were used:

- Cochrane database, DARE (Database of Abstracts of Reviews of Effects) and HTA (Health Technology Assessment) databases via the Cochrane Library and the Centre for Reviews and Dissemination (CRD)
- WHO International Clinical trials Registry Platform (ICTRP) and ClinicalTrials.gov for the identification of registered clinical trials
- Information from the manufacturers.

2.2 Results

Overview of the disease or health condition

A0002: *What is the definition of Eustachian tube dysfunction (ETD)/ glue ear according to ICD-10?*

The Eustachian tube is made up of bone, cartilage, and fibrous tissue. The bony component is approximately 12 mm in length, whereas the cartilaginous component is about 24 mm in length [2]. Under normal circumstances, there is a roughly 8- to 12-mm segment in the middle of the cartilaginous Eustachian tube that is closed at rest, with mucosal surfaces in apposition, and therefore functioning as a valve. The cartilaginous Eustachian tube dilates to the open position on demand to equalise pressure, particularly with swallows and yawns, as a result of sequential activation of the levator veli palatini and tensor veli palatini muscles [1].

The Eustachian tube is the point of entry for middle-ear pathogens from the nasopharynx but it also plays an important part in clearing middle-ear secretions. For many years, physical obstruction of the Eustachian tube was thought to produce an effusion in the middle ear as a result of negative middle-ear pressure and fluid transudation (ex vacuo theory).

A more complex role for this structure has since been suggested where it is responsible for:

- equilibration of pressure between the middle ear and ambient air (ventilatory function)
- protection against nasopharyngeal pressure variations and ascending secretions or pathogens (protective function)
- clearance of secretions and debris towards the nasopharynx (clearance function) [12].

Miller and Elhasan defined ETD as the failure of the Eustachian tube to ventilate the middle ear. These same authors noted, however, that consensus has yet to be reached on diagnostic criteria for ETD, and consequently, on eligibility criteria for undergoing BET [3].

Bailey [4] suggested that ETD is an important factor in the pathogenesis of otitis media, an umbrella term for a group of complex infective and inflammatory conditions (including otitis media with effusion (OME)/"glue ear") affecting the middle ear.

The following ICD-10 codes were considered to classify ETD:

- H65.3 (Chronic mucoid otitis media)
- H65.2 (Chronic serous otitis media/otitis media with effusion [OME])
- H68.1 (Obstruction of Eustachian tube)
- H65.4 (Other chronic nonsuppurative otitis media)
- H65.9 (Nonsuppurative otitis media, unspecified), and
- H69.9 (Eustachian tube disorder), unspecified.

A0003: ***What factors cause Eustachian tube dysfunction or glue ear?***

Seibert and colleagues identified a number of factors that are thought to contribute to ETD [2]:

- Viral upper respiratory tract infection
- Chronic sinusitis
- Allergic rhinitis
- Adenoid hypertrophy
- Tobacco smoke
- Reflux
- Cleft palate
- Radiation
- Reduced mastoid air system
- Nitrous oxide.

Otitis media is an umbrella term for a group of complex infective and inflammatory conditions (including OME/"glue ear") affecting the middle ear. There are a variety of subtypes, which differ in presentation, associated complications, and treatment. The pathogenesis of otitis media is multifactorial, involving the adaptive and native immune system, ETD, viral and bacterial load, and genetic and environmental factors [12]. Otitis media is mainly an infectious disease, resulting from interplay between microbial load (viral and bacterial) and immune response. Swarts et al. noted that Eustachian tube function plays an integral role in the causation of otitis media because the other identified causes either adversely affect Eustachian tube function or reflect functional insufficiencies [5].

A0004: ***What is the natural course of Eustachian tube dysfunction and glue ear?***

ETD results in the development of negative pressures within the middle ear, leading to transudation of fluid and a pro-inflammatory response [6]. ETD may be acute or chronic. Chronic ETD that fails to resolve with treatment and continues for months or years has been associated with damage to the middle ear and tympanic membrane [7]. It is argued that active Eustachian tube opening is the homeostatic process which maintains a semi-stable middle-ear ambient pressure balance and, as a result, middle-ear health and "normal hearing" [5]. ETD has hence been associated with pathology within the middle ear, with the development of complications along the otitis media spectrum, including acute otitis media (AOM), OME/"glue ear", middle-ear atelectasis, chronic suppurative otitis media (CSOM) and cholesteatoma.

AOM typically affects children under 2 years of age, and presents with acute onset symptoms and signs of otalgia and fever in a child that is systemically unwell. It is an acute inflammation, and may be caused by bacteria or viruses [9]. Almost all children experience at least 1 episode, and a third have 2 or more episodes in the first 3 years of life [32]. AOM may be complicated by the development of acute mastoiditis, which occurs when AOM infection spreads from the middle ear itself into the mastoid air cells and their covering periosteum. The incidence of acute mastoiditis is 1.2–6.0 in 100,000 and, as noted, usually occurs in children under 2 years of age [9].

OME or "glue ear" is a chronic inflammatory condition, which may occur de novo or as a sequel to AOM [12]. It is most prevalent in children between 8 months and 2 years old thereafter diminishing gradually in children between 3 and 7 years old. It is characterised by the presence of a glue-like fluid behind an intact tympanic membrane in the absence of signs and symptoms of acute inflammation. For this reason, the commonest reported symptom is hearing loss, which may lead to speech delay or educational problems [9].

OME has a lower prevalence in adults, and the incidence of prolonged OME in adults is not known [10]. Its development in adults is frequently associated with other underlying diagnoses. Paranasal sinus disease has been described as the dominant factor in 66% of adults with OME; other causes include smoking-induced nasopharyngeal lymphoid hyperplasia and adult-onset adenoidal hypertrophy in 19% of cases, and head and neck tumours (mainly nasopharyngeal carcinomas) in 4.8% of cases. In 1.8% of patients no underlying diagnosis was identified [9, 11].

Two additional inflammatory conditions of the middle ear are CSOM and cholesteatoma. CSOM is characterised by the presence of long-standing suppurative middle-ear inflammation, usually with a persistently perforated tympanic membrane. Cholesteatoma occurs when keratinising squamous epithelium (skin) is present in the middle ear (normal middle ear is lined by modified respiratory epithelium). It typically presents with chronic smelly ear discharge, and can be diagnosed when squamous epithelium and keratin are seen in the middle ear. Surgical removal is the only curative treatment for cholesteatoma [9].

Antibiotic therapy has significantly reduced the burden of intratemporal and intracranial complications of otitis media. In a case series of 50 adult patients treated for acute complications over a 15 year period (1990-2004) in Finland, the annual age-adjusted incidence of acute intratemporal and intracranial complications was 0.32/100 000 population. The ear disease behind the acute complication was AOM in 80% (40/50), chronic otitis media (COM) in 12% (6/50) and COM with cholesteatoma in 8% (4/50). Acute mastoiditis (77%) was the most frequently found single intratemporal complication followed by facial paralysis (26%), latent mastoiditis (22%) and labyrinthitis (12%) [33].

Effects of the disease or health condition on the individual and society

A0005: ***What is burden of Eustachian tube dysfunction and glue ear for the patient? How does Eustachian tube dysfunction, glue ear affect the daily life of the patient?***

ETD can result in symptoms of aural fullness, otalgia, tinnitus and hearing loss, often precipitated or made worse by changes in atmospheric pressure. It has been implicated in the pathogenesis of middle-ear disease, specifically OME [3].

When persisting as a chronic condition, OME secondary to ETD is a primary cause of hearing loss in the population. It is also associated with other complications such as balance disturbances and speech and language delays in children [34].

A0006: ***What is the burden of the disease for society?***

There is a lack of evidence on the prevalence of acute or chronic ETD in adults. This conclusion was supported by a 2014 report [7] which identified a British national survey conducted in the early 1990s that reported a prevalence of 0.9% based on otoscopic and audiological assessment in a stratified sample randomly selected from the electoral roll. Symptoms were not assessed as part of this survey [8].

AOM is primarily a diagnosis of childhood, with incidence peaking between the ages of 6 and 11 months [35]. Of more than 22 million office visits to US doctors for AOM in 1989, 83.4% were by patients aged 15 years or younger [36]. Data from the USA have suggested a decline in office visits by children with AOM as the primary diagnosis; from a baseline rate of 344.7 per 1000 children in 1997 to a rate of 213.5 per 1000 children in 2004. Introduction of the pneumococcal conjugate vaccine, introduced in 2000, may partially explain this decline [37]. The pathogenesis of AOM in childhood is multifactorial.

Target population

A0007: ***What is the target population in this assessment?***

The target population in this assessment is adults and adolescents over 12 years of age with ETD. The lack of consensus on the diagnostic criteria for ETD has led to a lack of consensus on the eligibility criteria for BET, resulting in study cohorts with considerable differences in baseline pathology [3].

The following inclusion criteria have been suggested:

1. Persistent OME or non-adherent atelectasis
2. Type B or C tympanogram (see A0024)
3. Symptoms of ETD (pain, blockage, conductive hearing loss)
4. Symptoms improved with tympanostomy tubes [38].

One 2014 study included adult patients with at least 6 months of ETD symptoms [25]. In addition, the authors added those with significant symptoms of ETD during flying, diving and/or secretory otitis media several times a year during even mild upper respiratory tract infections as diagnosed by an ear, nose and throat (ENT) doctor.

A0023: ***What is the prevalence of the condition?***

The target population is adults with ETD. However, the lack of consensus on the diagnostic criteria for ETD has probably contributed to the lack of evidence on the prevalence of acute or chronic ETD in adults [7].

A 2014 HTA report [7] identified a British national survey conducted in the early 1990s. This survey reported a prevalence of 0.9% for ETD based on otoscopic and audiological assessment in a stratified sample randomly selected from the electoral roll; symptoms were not assessed as part of this survey [8]. Of more than 22 million office visits to US doctors for AOM in 1989, only 16.6% were by patients aged 15 years or older [36].

A0001: ***For which indications or symptoms is balloon Eustachian tuboplasty used and in which patient groups?***

BET is used to address ETD. This may be defined as the failure of the Eustachian tube to ventilate the middle ear. ETD has an estimated prevalence of 0.9% [3].

BET has been promoted as a potential management option for adults with ETD leading to OME. An HTA published on ETD in 2014 did not refer to any specific diagnosis or set of diagnoses, but rather focused on interventions that have been suggested to improve ETD where it is considered the cause of some or all of the following symptoms: muffled hearing, pain, feeling of fullness in the ear, tinnitus and dizziness. The report noted that patients may also have impaired hearing, abnormal tympanograms or abnormal physical appearance on otoscopic examination, but that the relationship of these signs and symptoms to ETD is unclear [7].

Just 1 published case study describing the use of BET in children was retrieved [39]. This assessment however will consider its use in the adult population only.

A0011: ***How widely is balloon Eustachian tuboplasty being used in Europe?***

BET is a relatively new technology and was first described in 2010 [3]. A survey of EUnetHTA members revealed that it has been used in 3 member states. Three European groups reported its use in the academic setting; the groups are based in: Bielefeld, Germany; Odense, Denmark; and Tampere, Finland. These groups reported the use of BET in: 320 adult patients and 1 child (Bielefeld group) [26], 34 patients (Odense group) [25] and 41 patients (the Päijät-Hämee hospital [University of Tampere]), respectively [23].

Spiggle and Theis have 1 CE-marked balloon catheter on the market for BET, the TubaVent® (formerly “Bielefelder Ballonkatheter”). Acclarent (Johnson and Johnson) also has CE marking for its balloon catheter, AERA™. As of July 2014, both products have just 1 version on the market.

Current clinical management of the disease or health condition

A0024: ***How are Eustachian tube dysfunction and glue ear diagnosed according to clinical practice guidelines and in practice?***

A number of subjective and objective tests have been proposed for the assessment of ETD. Despite the availability of these tests, however, there persists a lack of clear diagnostic criteria for ETD. This has been identified as a factor limiting the potential relevance of research studies intended to assess the efficacy of interventions aimed at resolving ETD [7].

Norman et al. noted that although ETD is a symptom-driven diagnosis, there is no established patient-reported measure for either baseline or post-treatment assessment in clinical trials [7].

Subjective tests include the Valsalva manoeuvre and the Toynbee test. In the Valsalva manoeuvre patients hold their nose and then blow out with a closed mouth; in the Toynbee test patients swallow. As the patient does this, the examiner performs otoscopy and evaluates the movement of the tympanic membrane [2].

Tympanometry involves measuring tympanic membrane compliance while the pressure in the external auditory meatus (EAM) is automatically varied between +200 and -400 mm H_2O. This results in a graphical output which may be categorised into 1 of 3 groups:

- Type A. Maximal compliance occurs when the pressure in the EAM is between +50 and -100 mm H_20.
- Type B. A low-value flat or horizontal compliance trace occurs, implying persistently low compliance. This is usually taken to indicate fluid in the middle-ear cavity and, in young children (under 7 years) with glue ear, can be correlated with audiometric hearing loss.
- Type C. This group gives a peak compliance when the pressure in the EAM is <-100 mm H_20. This indicates a significant low pressure in the middle-ear system and is a sign of ETD. The C curve can be divided into C1, when the peak is between -100 and -199 mm H_20, and C2, when the peak occurs at less than -200 mm H_20 [40].

Sonotubometry involves the application of a sound source to the nostril, with a microphone placed in the external auditory canal to record the transmitted sound. Sound levels are then measured as the Eustachian tube opens and closes. The advantage of this diagnostic test is its ability to evaluate the Eustachian tube with or without an intact membrane under physiological conditions [2]. Other methods of assessing Eustachian tube function in ears with an intact tympanic membrane (TM) include modifications of tympanometry, sonotubometry, forcible sniffing, the Valsalva manoeuvre, nasal endoscopy, and the inflation and deflation tests [5]. A 2013 review of case series of BET evaluated results across 4 commonly used indicators of Eustachian tube function: tympanometry, otoscopy, subjective reporting of symptoms, and the Valsalva manoeuvre [3].

A0025: ***How are Eustachian tube dysfunction and glue ear managed according to clinical practice guidelines and in practice?***

The effectiveness of medical therapies for ETD remains uncertain [41]. Several factors contributing to physiological obstruction of the Eustachian tube have been proposed, including allergic rhinitis, sinusitis, adenoiditis, and extra-oesophageal reflux. Accordingly, patients diagnosed with ETD have been treated with antihistamines, topical and systemic decongestants, intranasal corticosteroids, antibiotics, mucolytics, and proton pump inhibitors. Despite anecdotal successes, however, high quality data for these measures is lacking [41].

A 2014 HTA examined management options for adults with ETD [7]. Interventions assessed included pharmacological treatments, mechanical pressure equalisation devices, and surgery (including laser tuboplasty, balloon dilatation, myringotomy with grommet insertion, transtubal steroids and laser coagulation). There was no evidence relating to most primary care approaches, including antibiotics and active observation. With the exception of 1 pharmacological study, all studies had significant methodological weaknesses, and none of the surgical trials were adequately controlled. The single placebo-controlled study assessed as having a low risk of bias showed no effect of steroids in improving middle-ear function. The authors concluded that there was not enough evidence to guide recommendations for a trial of any particular intervention.

Clinical guidelines on the management of ETD or OME focus on children. No published guidelines were identified that focused on the management of either condition in adults or that limited the pediatric population to those over 12 years of age.

2.3 Discussion

A number of factors have been implicated in the development of ETD, although the evidence for each is relatively limited. It is clear that ETD can act as a precursor to a spectrum of disease in the middle ear, including AOM, OME, middle-ear atelectasis, CSOM and cholesteatoma. The extent of its role in each of these individual clinical entities, however, remains to be fully elucidated.

The target population in this report is adults and adolescents over 12 years of age with ETD. There is, however, a lack of evidence about the prevalence of acute or chronic ETD in adults. Similarly, while AOM is a relatively common diagnosis in childhood, its burden in the adult population has not been well studied.

A key issue with ETD is that consensus has not been reached on the diagnostic criteria that should be used in its assessment. This, in turn, has resulted in a lack of consensus about the eligibility criteria for BET, which remain to be fully elucidated.

BET seeks to improve on the existing medical therapies which, while they have been widely used, lack a solid evidence base. BET is a relatively new technology, first described in 2010; as of July 2014, there are just 2 product options on the market.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

3.1 Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

Element ID	Research question	Importance 3= critical 2= important 1=optional
B0001	What is balloon Eustachian tuboplasty (BET) and what are the treatment alternatives?	3
B0002	What are the approved indications and claimed benefits of BET and the treatment alternatives?	3
B0003	What is the phase of development and implementation of BET and the treatment alternatives?	2
B0004	Who performs or administers BET and the treatment alternatives?	3
B0005	In what context and level of care are BET and the treatment alternatives used?	2
B0008	What kind of special premises are needed to use BET and the treatment alternatives?	2
B0009	What supplies are needed to use BET and the treatment alternatives?	3
B0010	What kind of data and records are needed to monitor the use of BET and the treatment alternatives?	3
B0011	What kind of registry is needed to monitor the use of BET and the treatment alternatives?	2
A0020	What is the marketing authorisation status of BET catheters in Europe?	2
A0021	What is the reimbursement status of BET catheters in Europe?	2

Sources

To answer the research questions in the domain “Description and technical characteristics of the technology”, the results from a systematic literature search (Appendix 1) in Medline via OVID, EMBASE and the following sources were used:

- Cochrane database, DARE and HTA databases via the Cochrane Library and CDR
- WHO International Clinical trials Registry Platform (ICTRP) and ClinicalTrials.gov for the identification of registered clinical trials
- Information from the manufacturers
- Survey of EUnetHTA members on the reimbursement status in their countries.

3.2 Results

Features of the technology and the comparators

B0001: ***What is balloon Eustachian tuboplasty (BET) and what are the treatment alternatives?***

BET involves passing a catheter into the Eustachian tube through either the nasopharynx (more common) or the oropharynx. This catheter is then temporarily inflated before being deflated and withdrawn. The procedure is based upon the idea that this temporary dilatation of the Eustachian tube can produce symptomatic improvement for patients suffering from ETD [1].

A cadaver study used the following protocol and equipment [41]: the dilation was performed using the Relieva Solo Pro Balloon Catheter (7–16 mm), Relieva Flex Guide Catheter (F-70C), and Acclarent Inflation Device (all from Acclarent, Inc., Menlo Park, CA). After adequate visualisation, the introducer catheter was positioned immediately proximal to the Eustachian tube orifice. The deflated balloon was then passed through the catheter into the Eustachian tube lumen. This was done with minimal pressure and may have required redirection for smooth passage. If the balloon did not pass easily, a guide wire was placed into the Eustachian tube, and the balloon was passed over the guide wire. The balloon was inflated with normal saline to a pressure of 10 atmospheres for 2 minutes using the inflation device under endoscopic visualisation. The balloon was then deflated, and the entire system was gently removed. Currently, Acclarent Inc. (Johnson and Johnson) has received CE marking for its balloon catheter AERA™

The Spiggle and Theis device (TubaVent®, formerly the “Bielefeld Ballonkatheter”) is a single-use balloon dilation catheter with an inflatable balloon near the distal tip. It has an overall length of 400 mm with a working length of 355 mm (from the Luer lock connection to the distal tip). The device has 2 X-ray visible markers to indicate the cylindrical part of the balloon during radiography. The flexible distal part of the catheter has a coaxial structure, with the outer lumen used for inflating the balloon. The proximal part of the catheter is a single-lumen hypotube made of stainless steel, reducing the flexibility in this section, and ensuring ease of introduction into the Eustachian tube lumen. It is designed to be used in conjunction with an inflation pump and a combined insertion instrument also manufactured by the company. The balloon offers controlled compliance that limits its expansion to its defined dimensions (6 bar=3.00 mm, 10 bar=3.28 mm balloon diameter). The catheter is introduced into the Eustachian tube using the insertion instrument. The balloon is then inflated to a pressure of 10 bar for approximately 2 minutes using the inflation device, before being deflated and the entire system removed [42].

A 2013 literature review identified a number of variations on the surgical approach described above [3]. BET has been performed under both local and general anaesthetic, although local anaesthetic was used in isolation in just 1 published report. The authors noted that while the earliest published work on BET had inflated both the cartilaginous and bony portions of the Eustachian tube, this approach has since fallen out of favour, with later reports inflating the cartilaginous portion only. Finally, the authors also noted that 1 study reported advancement of a guide wire with fibreoptic light through the introducer catheter, with visualisation of a red glow through the EAM ensuring correct placement of the catheter [24].

A number of alternative surgical procedures have previously been used in attempting to address ETD. Historically, these involved invasive attempts to widen the osseous portion of the Eustachian tube, and were based on the belief that the bony isthmus is the narrowest portion of the tubal lumen, and hence is most likely to be the site causing dysfunction. None of these techniques were reported to demonstrate long-term success [15, 43].

A 2003 preliminary report considered the potential efficacy of laser Eustachian tuboplasty (LETP) [15]. These authors focused on the cartilaginous portion of the Eustachian tube as the potential site of pathophysiological dysfunction requiring remediation. Using either a 980-nm contact-tip diode laser or an argon ion laser, the authors aimed to ablate the cartilaginous lumen of the Eustachian tube. In addition to the tuboplasty, all patients received a myringotomy intra-operatively. All patients received ongoing medical management postoperatively. Two year results were presented for 13 adult patients (12 male) who had at least 6 months of follow-up postoperatively. Outcome measures presented were presence or absence of middle-ear effusion and impedance tympanometry. LETP eliminated OME in 36% (4 of 11) of patients at 6 months, 40% (4 of 10) at 1 year, and 38% (3 of 8) at 2 years [44].

The traditional surgical management of ETD leading to OME involved using ventilation tubes ("grommets"), which are placed in the tympanic membrane with the aim of facilitating ventilation of the middle ear. These can result, however, in persistent otorrhoea. In addition, they fail to treat the underlying dysfunction and there is a subset of patients in whom OME recurs repeatedly after extrusion of the tubes [1]. While patients may be offered long-term ventilation tubes with good success, 1 study reported that 79 of 412 patients (19%) were found to have a persisting tympanic membrane perforation at a median follow-up of 3.4 years after insertion of Goode ventilation tubes [16].

Patients diagnosed with ETD have been treated with a range of medical therapies, including antihistamines, topical and systemic decongestants, intranasal corticosteroids, antibiotics, mucolytics, and proton pump inhibitors. The efficacy of all of these remains unproven.

B0002: *What are the approved indications and claimed benefits of BET and the treatment alternatives?*

BET is used to address ETD. This may be defined as the failure of the Eustachian tube to ventilate the middle ear. ETD has an estimated prevalence of 0.9% [3].BET has been promoted as a potential management option for adults with ETD leading to OME. An HTA published on ETD in 2014 did not refer to any one specific diagnosis or set of diagnoses, but rather focused on interventions that have been suggested to improve ETD where it is considered the cause of some or all of the following symptoms: muffled hearing, pain, feeling of fullness in the ear, tinnitus and dizziness. The report noted that patients may also have impaired hearing, abnormal tympanograms or abnormal physical appearance on otoscopic examination, but that the relationship of these signs and symptoms to ETD is unclear [7].

It has been suggested that the novel aspect of BET is that it combines controlled catheterisation with the principles of focal expansion of a stenotic lumen, principles which have previously been used in other parts of the body. The authors suggested that BET produces a radial force (as opposed to the shearing forces produced by traditional bougie dilation) that is distributed evenly and simultaneously, and hence may provide a safe alternative treatment for ETD [41]. It has been postulated that while the balloon may shear or crush portions of the epithelium within the Eustachian tube, it appears to spare the basal layer in most cases, and may thus result in relatively rapid healing after the procedure [13].

Different treatment approaches to ETD have included systemic antihistamines and corticosteroids, intranasal corticosteroids and decongestants, non-invasive autoinflation manoeuvres, Eustachian tube catheterisation, bougie dilatation, and drilling of the bone. All have been used to address ETD, without demonstrating evidence of success [25].

A 2013 study noted that nasal steroid sprays appear to be no more effective than placebo for the management of ETD. The authors suggested that ventilation tubes extrude, can result in persistent otorrhoea, and fail to treat underlying dysfunction, with recurrence of atelectasis and OME in 30% and 50% of cases. The authors further noted that long-term ventilation tubes carry the risk of permanent tympanic membrane perforation, in up to 19% of cases [3].

B0003: *What is the phase of development and implementation of BET and the treatment alternatives?*

As noted above, there are a number of alternatives to BET, but they all lack a solid evidence base and as such are not dicussed further.

BET was first described in 2010 [3]. In 2011, a National Institute for Health and Care Excellence (NICE) review of balloon dilatation of the Eustachian tube concluded that, due to inadequate evidence, the procedure should be used in a research-only capacity [17]. As of July 2014, there are 2 CE-marked products on the market for BET; 1 from Spiggle and Theis, TubaVent® (formerly the "Bielefelder Ballonkatheter"), and 1 from Acclarent (Johnson and Johnson), AERA™. Both products have just 1 version on the market. Acclarent is currently enrolling patients in the ELLIOTT (A Randomized Clinical Study of Safety and Efficacy for the Eustachian Tube Balloon Catheter) study to include subjects aged 22 and older with ETD and who are not responding to medical therapy. This study is being performed across centres in the USA to secure approval from the Food and Drug Administration.

The reimbursement status of BET across Europe is listed in Table 2.

Administration, investments, personnel and tools required to use the technology and the comparator(s)

B0004: ***Who performs or administers BET and the treatment alternatives?***

ENT surgeons perform BET in the general operating theatre setting.

B0005: ***In what context and level of care are BET and the treatment alternatives used?***

BET can be performed under local or general anaesthetic or using a combination of both. ENT surgeons perform BET in the general theatre setting.

B0008: ***What kind of special premises are needed to use BET and the treatment alternatives?***

Facilities for pre-interventional CT (computed tomography) angiography of the carotid arteries may be required before proceeding with BET to rule out aberrant carotid anatomy.

B0009: ***What supplies are needed to use BET and the alternative treatments?***

A variety of nasal endoscopes (for example, 0, 30 and 45 degrees) are required to adequately examine the Eustachian tube oriface before proceeding with BET. The instruments specific to the product (Acclarent's AERA™ versus Spiggle and Theis's TubaVent®) being used are then employed. These include both guide catheters and balloon catheters, and the solution that the balloon is dilated with once in the correct position.

B0010: ***What kind of data and records are needed to monitor the use of BET and the treatment alternatives?***

No literature was retrieved that identified specific data or monitoring records for ETD treatment outcomes.

B0011: ***What kind of registry is needed to monitor the use of BET and the treatment alternatives?***

The literature search did not reveal published data on the need, or otherwise, for a registry for those performing BET. As with any surgical procedure, however, mechanisms should be in place that permit audit so that both short and longer term treatment outcomes can be assessed.

Regulatory and reimbursement status

A0020: ***What is the marketing authorisation status of balloon Eustachian tuboplasty catheters in Europe?***

As of July 2014, Spiggle and Theis have 1 CE-marked balloon catheter on the market for BET, TubaVent® (formerly the "Bielefelder Ballonkatheter"). Acclarent Inc. (Johnson and Johnson) also has CE marking for its balloon catheter AERA™. Both products have just 1 version on the market.

A0021: ***What is the reimbursement status of balloon Eustachian tuboplasty catheters in Europe?***

Table 2: Reimbursement status of balloon Eustachian tuboplasty (BET) in Europe

Country	Reimbursement status	Other relevant information
Austria	N	-
Belgium	N	-
Czech Republic	N	-
Finland	(Y)	Available only in hospitals, belongs to the hospital budget.
France	N	-
Germany	(Y)	In Germany, BET is reimbursed as “operation of the Eustachian tube” as no particular diagnosis-related groups exist (yet).
Hungary	N	-
Ireland	N	BET is not currently being done. It may be reimbursed at a local level, but there is no formal national policy on reimbursement.
Italy	(Y)	BET is not reimbursed at a national level, but is not excluded, and so may be reimbursed at a regional level if considered appropriate.
Latvia	N	-
Lithuania	Y	All devices are reimbursed on a national level.
Malta	N	-
Poland	N	-
Slovenia	N	-
Spain	(Y)	BET is not reimbursed at a national level, but is not excluded, and so may be reimbursed at a regional level if considered appropriate.
Switzerland	Y	Medical procedures (including new ones) are by default reimbursed as long as efficacy, safety or cost-effectiveness is not contested by payers or other parties. Only then, a procedure is evaluated and possibly excluded from reimbursement.

Abbreviations: Y – yes, N – no, (Y) – yes but with certain restrictions or only under certain circumstances (e.g. only locally or regionally)

Source: Information on reimbursement status was kindly provided by WP5 Strand B members.

3.3 Discussion

The principle underlying BET is that temporary dilatation of the Eustachian tube can produce symptomatic improvement for patients suffering from ETD, a condition defined as failure of the Eustachian tube to adequately ventilate the middle ear.

While BET has been promoted as a potential management option for ETD, the lack of consistent criteria for the diagnosis of ETD may have implications for research which seeks to evaluate postoperative outcomes in this setting. Of equal importance in the evaluation of the potential applicability of BET is the fact that traditional management alternatives exist in the absence of a solid evidence base, and hence the relevance of comparison between them is questionable.

No literature was identified on the need, or otherwise, to monitor records for ETD treatment outcomes, and no evidence was identified in relation to the need, or otherwise, for a registry for those performing BET.

4 CLINICAL EFFECTIVENESS

4.1 Methods

Domain framing

The project protocol was followed and no deviations were made except for the use of concomitant treatments and the age group in 1 study [21]. According to the protocol, combined interventions should be excluded. This rule was followed when reading the abstracts. However, on closer examination of the selected studies it was found that some patients had ventilation tubes at the time of the procedure or some had otologic or sinonasal procedures performed concomitantly (see Table 3). These studies were included and it was noted that these studies were also included in other (systematic) reviews of the literature [3, 7, 31]. In the study by Sudhoff [21] the age range was from 8 to 84 years. No details were given of how many participants were aged less than 12 years; however, we assume that this number was low. Since this study had the largest number of participants (n=351) it was found necessary to include it.

In addition, in the absence of clear guidance on how to assess the quality of the body of evidence the GRADE approach was ultimately used for qualitatively summarising the results for the domain.

Research questions selected for assessing the clinical effectiveness of BET are listed in the table below. Mortality endpoints are usually the most important endpoints in the assessment of clinical effectiveness. Since ETD is not a life-threatening disease, mortality was not relevant in this assessment.

Research questions

Element ID	Research question	Importance 3=critical 2=important 1=optional
D0001	What is the expected beneficial effect of BET on overall mortality? BET does not have an effect on mortality.	not included
D0002	What is the expected beneficial effect on the disease-specific mortality? BET does not have an effect on the disease-specific mortality.	not included
D0005	How does BET affect symptoms and findings?	3
D0006	How does BET affect progression of Eustachian tube dysfunction?	2
D0011	What is the effect of BET on patients' body functions (e.g. hearing)?	2
D0016	How does the use of BET affect activities of daily living?	1
D0012	What is the effect of BET on generic health-related quality of life?	2
D0013	What is the effect of BET on disease-specific quality of life?	2
D0017	Were patients satisfied with the BET outcomes?	2
D0023	How does BET modify the need for other technologies and the use of resources?	2

Sources

The assessment of the research questions was based on a systematic literature search from the following sources:

- Medline via OVID, Cochrane database, DARE and HTA databases via the Cochrane Library and CDR
- EMBASE
- WHO International Clinical trials Registry Platform (ICTRP) and ClinicalTrials.gov for the identification of registered clinical trials.

Details of the search strategy can be found in Appendix 1. In addition, literature lists provided by the manufacturers during consultation on the project plan were checked for eligible studies that were not found in the basic literature search.

The selection of included studies was done in the first phase by 2 researchers independently and then compared. Consensus was found in all cases about the inclusion and exclusion of individual studies. The accepted study designs for "Clinical effectiveness" included: meta-analysis, systematic reviews, randomised controlled trials (RCTs), non-randomised trials, controlled observational studies and case series with 10 or more patients.

Analysis

Quality assessment of systematic reviews was based on the ROBIS (Risk of Bias in Systematic Reviews) Tool [18]. For the appraisal of case series an 18-criteria checklist by IHE was used [19]. The risk of bias at outcome level was assessed using the Cochrane risk of bias tables. The GRADE approach was used for qualitatively summarising the results for the domain.

Synthesis

The analysis is qualitative and presented mainly in text. A summary of the outcomes is presented also in Table 3. No quantitative analysis (meta-analysis) could be conducted due to a lack of comparison groups and heterogeneity of the data.

4.2 Results

Included studies

In the evaluation of clinical effectiveness one systematic review and 9 case series were included. The authors of the included systematic review [7] published a longer report of the same review in July 2014 [31]. These reports are considered as one, and both are referred to. They cover studies published up to October 2012. The systematic review also covered other interventions in addition to BET that can be used to treat adult ETD. For the assessment of BET, 3 studies were included [22, 24, 27]. The quality assessment of the review based on the ROBIS tool considered this as a high quality review (see Appendix 1).

Another literature review [3] was found, covering studies up to February 2013. This review was not included in this assessment since the search was performed only in Medline, and it was not considered a systematic review. The review had 4 studies included in this assessement [20, 22, 24, 27] and one which was not included due to having less than 10 patients [43].

Nine case series were included [20-28]. Two studies [20, 21] are based on the same follow-up data from a clinic in Bielefeld. One study [43] was excluded since there were only 8 patients, as were two other studies with 3 patients [45], and with 4 patients [46]. No comparative studies were found. According to the quality assessment checklist, 3 of the case series studies were of acceptable quality [22-24] (Appendix 1, Table 6). In the smallest included study, there were 11 patients [22], whereas the follow-up data from the Bielefeld clinic [21] had 351 patients. The follow-up times varied from 2 months [27] to 2.5–3 years [23, 27]. The smallest study [22] was a pilot for a larger 2014 study [23], and it is possible that they included the same patients from a pool of BET patients (n=80).

The procedure was usually done in a similar way, that is, the cartilaginous portion was dilated for 2 minutes; however, the size of the catheter varied. In the majority of studies general anaesthesia was used, but local anaesthesia was used in cases that were limited to unilateral BET operations with no concomitant procedure [24, 25, 27]. The concomitant procedures performed before, or at the time of, the balloon Eustachian tuboplasty varied (Appendix 1, Table 4).

Details of the included publications are shown in the evidence tables (Appendix 1, Table 4).

Mortality

Not assessed.

Morbidity

The outcomes were selected based on the literature and consultation of the clinical experts. Tympanometry was selected as the primary outcome since it is a commonly used objective measure to test the functioning of the middle ear and mobility of the eardrum. Other measures in the assessment of middle-ear function were otoscopy (otomicroscope), tube score, ETD classification and Valsalva manoeuvre. Other outcomes included Toynbee's test, quality of life measures (Glasgow Benefit Inventory [GBI]) and an overall disease-specific score to evaluate effects of treatment (Eustachian Tube Dysfunction Questionnaire, ETDQ-7, Sinonasal Outcome Test, SNOT-22). Improvement was seen in the study measures for all included studies.

It can be questioned whether objective outcomes such as tympanometry results actually predict the effect of treatment or work more like surrogate outcomes. According to the EUnetHTA Guideline on Surrogate endpoints, patient-relevant clinical endpoints should be included in the assessment whenever possible [47]. Patient-relevant outcomes such as quality of life were available in only two studies. "Change in severity/or frequency of symptoms" has been used in an earlier systematic review as the primary outcome" [31]. This is patient-relevant, but a vague outcome. "Tube score" includes 3 relevant outcomes describing functioning of the Eustachian tube, but it is not yet commonly used.

Outcome measures used

Tympanometry provides information about the relationship between air pressure in the external ear canal and impedance (resistance to movement) of the ear drum and middle-ear system. Tympanogram tracings are classified as type A (normal), type B (flat, clearly abnormal), and type C (indicating a significantly negative pressure in the middle ear, possibly indicative of pathology). Results are usually given in a graphical representation (tympanogram).

The Valsalva manoeuvre (maneuver) assesses one's ability to inflate the middle ears via the Eustachian tubes by attempting to forcibly exhale while keeping the mouth and nose closed.

Otoscopy, an examination done with an instrument called an otoscope, is used to assess the external auditory canal as well as the ear drum, i.e. tympanic membrane. Inspection of the tympanic membrane can reveal abnormalities such as signs of otitis media and a hole in the eardrum. In the assessment of the eardrum, the visual inspection is supplemented with the examination of the movements of the tympanum in response to air, puffed though the otoscope into the external auditory canal. Movements of the tympanum reflect how the middle ear is pressurised, and thus, the function of the Eustachian tube.

The (Eustachian) tube score is a composite score that includes symptoms (ear popping during swallowing and blowing the ears), ability to do the Valsalva manoeuvre, and tubomanometry results [20, 21]. In the score range 0–10, 0 indicates poor Eustachian tube function and 10 normal Eustachian tube function. A score above 5 indicates functional Eustachian tubes. It has been proposed [20] that an increase of more than 2 points in the tubescore indicates significant improvement, and an increase of 1 to 2 points, a minor improvement in the Eustachian tube function.

The Eustachian Tube Dysfunction Questionnaire (ETDQ-7) is a 7-item disease-specific instrument of patient-reported severity of ETD symptoms. Patients are asked to indicate the severity of their symptoms on a 7-point scale. The overall score ranges from 1.0 to 7.0, 1 indicating no problem and 7 a severe problem. The Sinonasal Outcome Test (SNOT-22) is a 22-item patient-reported validated measure for sinonasal specific symptoms and quality of life [24]. The GBI consists of 18 questions relevant for surgical and conservative treatments after ear-, nose- and throat procedures [28].

D0005: *How does Eustachian tuboplasty affect symptoms and findings?*

Tympanometry

In the studies that had measured tympanometry data preoperatively, tympanograms were usually abnormal (type B or C). In the majority of the abnormal cases the situation had resolved in the postoperative results and the ears were reclassified to type A (normal). The proportion of patients classified as having type A ears at follow-up were: 70% (148/210) [26], 97% (34/35) [24], 89% (25/28) [27] and 90% (37/41) [23]. In 2 studies the results were worse and only 28% [25] and 36% (4/11) [22] had type A ears or in one study only 40% showed improvement [20] at follow-up. In this last small study [22] the low rates may be partly due to the fact that all patients had a diagnosis of COM with effusion (see Table 3).

Concomitant surgical treatments may have led to overestimation of the positive influence of treatment. For example, in one study [24], partial inferior turbinectomy was performed for all participants and endoscopic sinus surgery for the majority (submucous resection of nasal septum in 15 patients, sphenoethmoidectomy with maxillary sinusotomy in 12, revision of ethmoidotomy in 2, and revision sphenoidotomy in 3). In another study [27] the results were somewhat better for those patients who had BET only (73%, 30/41 ears symptoms improved), compared with 67% (36/54) when concomitant sinonasal procedures were performed, and 60% (3/5) when concomitant otologic procedures were performed.

Otoscopy/Otomicroscopy

The otoscopy findings were reported in 2 studies [22, 24]. In the smallest study [22], 45% (5/11) of the tympanic membranes were normal on otomicroscopy examination postoperatively. In the other study [24], preoperative otoscopy demonstrated tympanic membrane retraction in 33 ears (94%); in the postoperative examination, all the operated ears were free of retraction.

Valsalva manoeuvre

In the preoperative records Valsalva assessments were abnormal (negative) in the majority of cases [20, 22, 23, 25, 26]. The ability to do the Valsalva manoeuvre postoperatively ranged from 66% [22] to 100% of patients [26]. In one study [20], 67% of patients could always do the Valsalva manoeuvre 2 months after the procedure decreasing to 45% at the 12 month follow-up. The proportion of patients who could not do the Valsalva manoeuvre at all after 2 months was 19% decreasing to 10% at 12 months. In another study [23] none of the patients could perform the Valsalva manoeuvre preoperatively whereas 80% could after the procedure. In this study 7 of the 8 patients with negative Valsalva results had a short cartilaginous Eustachian tube (less than 26 mm), which made the procedure more difficult. One study [25] used the visual analogue scale to measure easiness of performing the Valsalva test. The score improved from 85.5 (24.2 SD) to 43.6 (38.6 SD) ($p< 0.05$, 0=no problems, 100=impossible) and 66% indicated a positive effect on doing the Valsalva test (see Table 3).

Other measures of middle-ear function

The German research group [20, 21] used a summary measure called the “tube score” to show improvement of symptoms (range from 0 to 10, 10 indicating normal condition). In the 2 year follow-up, the median preoperative tube score for patients included at 2 months was 2.71 (SD 2.2), with postoperative scores of 5.46 (SD 2.6) at 2 months, 6.07 (SD 2.6) at 12 months and 6.14 (SD 3.2) at 24 months. There was significant loss to follow-up with symptom scores available for only 22 of 351 ears at 24 months.

A mucosal inflammatory score (unvalidated scale from 1 indicating normal to 4 indicating severe inflammation) was used in one study [23] where all the patients had OME or atelectasis. The mean score was 2.8 (SD 1.2) preoperatively and 1.4 (0.8) postoperatively (p<0.001); 12% (5/41) of patients still had moderate (3) or severe (4) inflammation postoperatively.

Some studies reported subjective symptoms improvement [24-27] or combined measures of subjective and objective measurements [24, 25]. One of these [27] reported improvement in ear fullness and pressure in 71% of patients. In another study [26] 70% reported a positive subjective effect. In a further study [24] the global response to treatment was 79% (23/29) in week 6 after the procedure, and 92% (24/26) in week 12. In the fourth study [25], 75% of the treated patients showed improvement at 2 months when subjective and objective measures were combined.

Long-term results

In one study [27], although 87% showed persistent improvement at 34 months follow-up, data were available for only 8 out of 71 participants at that time. In the 2- year follow-up of Bielefeld data, 86% of operated ears showed improvement, but follow-up data were available for only 22 of 351 ears [21]. In the study [23] with the longest follow-up (mean 2.5 years, range 1.5–4.2 years) long-term results were not reported separately; 90% (37/41) of ears were considered normal postoperatively (37/41) and the overall success rate was 80% (33/41).

Need for additional treatment/adjunctive procedures

The need for additional repeat dilatation during follow-up was very similar in all studies, within the range 8-10% (Table 3).

Concomitant treatments were common. In one study [24] concurrent treatments included turbinectomy for all patients, submucous resection of the nasal septum for 15 (43%), sphenoethmoidectomy with maxillary sinusotomy for 12 (34%), revision ethmoidotomy for 2 (5.7%), and revision sphenoidotomy for 3 (8.6%). In addition, myringoplasty was performed in 1 patient (2.9%) [24]. In another study [27] concurrent sinonasal procedures were done in 39 patients (56%) and otologic procedures in 5 (7%) patients. In some studies tympanostomy tubes were either placed or removed from the patients at the time of the BET procedure [22-24] (see Table 4 in Appendix 1).

D0006: ***How does BET affect progression of Eustachian tube dysfunction (ETD)?***

The issue of how BET affects progression of ETD cannot be addressed. While diseases relating to ETD may progress if ETD is not treated, there is no conclusive evidence suggesting that the ETD itself progresses. Only the maintenance of treatment outcomes can be studied, but the follow-up times of current data are too short (see “Long-term results”).

Function

D0011: ***What is the effect of BET on patients’ body functions (e.g. hearing)?***

Audiometric evaluation of hearing function was performed as a part of the diagnosis and pre-examination in many studies [23, 25, 28] but not all reported results.

No hearing losses before or after treatment were found in one study [25].The air-bone gap was seen in 82% of the ears preoperatively, among which 42% had either no air-bone gap or a smaller air-bone gap postoperatively. The air-bone gap changed from 28 dB to 18 dB on average without changes in bone conduction.

In the same study, ear function was assessed using visual analogue scale (VAS) scores: 55% of patients indicated a positive effect on earache, and 48% a positive effect on aural fullness [25]. The overall mean VAS scores for aural fullness were 68.6 (SD 26.9) preoperatively and 42.0 (SD 31.8) postoperatively (p<0.05; where 0 indicates no problem and 100 indicates impossible). Earache scores were 29.9 (SD 25.8) preoperatively and 14.5 (SD 18.3) postoperatively (p<0.05, 0 indicating never, 100 indicating always).

D0016: ***How does the use of BET affect activities of daily living?***

The impact of BET on daily living was not reported separately in any of the studies but it is included as 1 dimension of the GBI instrument (see quality of life, D0012, D0013).

Health-related quality of life

D0012: ***What is the effect of BET on generic health-related quality of life?***

D0013: ***What is the effect of BET on disease-specific quality of life?***

D0017: ***Were patients satisfied with the BET outcomes?***

In one study [24] the patient-reported ETDQ-7 score was statistically significantly improved from a preoperative value (mean 4.5, SD 1.2) in all measured postoperative values. The improvement was seen by week 3 (mean 2.7, SD 1.5) and remained steady during the 6 month follow-up (mean 2.8, SD 1.3). The mean overall change in score was 1.9 points which was considered to be a clinically important improvement. Sensitivity to clinical change was determined separately by calculating the standardised response mean for the ETDQ-7 at the week 6 postoperative visit was 1.1. The authors found this to have high sensitivity to change (values > 0.8 considered significant). Mean SNOT-22 scores were also significantly improved at all follow-up timepoints. The score was 51.4 (SD 21.1) at baseline and 30.0 (SD 23.9) at 6 months (see Table 3).

The patient experience of improvement in symptoms was assessed in some studies [25, 26]. In one [26] 70% of patients felt that their symptoms had improved postoperatively. The other study [25] used a questionnaire 2 months after the procedure to assess patient experiences. The overall reported discomfort score was 11 on a scale from 0 (no discomfort) to 100. Furthermore, a score of 35 was obtained when using a scale to assess whether patients would recommend the procedure to a friend with equivalent symptoms (0 to 100, 0 indicating that they would recommend the procedure). In a study using the GBI questionnaire [28] a significant improvement was seen in the total score (p=0.001), in the “general health” subscore (p=0.001) and in the “physical health” subscore (p=0.039). Patients answered the survey 6-18 months after the BET procedure.

D0023: ***How does balloon Eustachian tuboplasty modify need for other technologies and use of resources?***

BET does not create a demand for new equipment, since nasal endoscopes and camera systems are already used in many, if not the majority of, Ear, Nose and Throat departments. The direct use of resources is based on the use of single-use balloon catheters.

There are currently 2 providers of BET catheters available. Spiggle and Theis provides the TubaVent® (formerly Bielefeld Ballonkatheter) single-use catheter. According to the latest price information the list price for the Spiggle and Theis catheter is €410 (personal communication 18 August 2014). Acclarent has not moved forward with a full market launch and thus has not yet set a list price for the AERA™ (personal communication 14 August 2014). In a review [3], the price of the Bielefeld catheter (Spiggle and Theis) was reported as GBP £450-500 and the Relieva Solo/Balloon Sinuplasty system catheter with delivery system (Acclarent) as GBP £700-950.

Preoperative CT scanning has been used to determine the expected length of the cartilaginous Eustachian tube and to rule out aberrancies or bony dehiscence of the internal carotid artery in order to avoid serious injury. The need for this procedure has been questioned [48]. If the CT scan is deemed unnecessary, that would cut the need for other technologies and reduce the use of additional resources.

Table 3: Clinical effectiveness of balloon Eustachian tuboplasty (BET)

Study **n patients, ears at baseline** **Age: mean (SD or range)** **Follow-up**	**Intervention anaesthesia**	**Tympanometry preoperative**	**Tympanometry postoperative**	**Results of other outcomes**	**Additional treatments***	**Funding**
Poe 2011 [22] n=11, 11 ears age: 51.8 (33-76) follow-up: 7 median (6-14) months	Unilateral BET at 8-12 atmospheres for 1 minute, 7 mm catheter general anaesthesia	type A 0/11 type B/C 4/11 5 tympanostomy tubes, 2 perforated TM	type A 4/11 (36%), type C 1/11, 6/11 open 4 tympanostomy tubes, 2 perforated TM	Valsalva: baseline 0/11, follow-up 7/11 always +ve (64%), 4/11 (36%) inconsistently +ve, in total 100%. Mucosal inflammation score: baseline 2.91 (0.83 SD), follow-up 1.73 (0.79), p=0.003 Otoscopy: baseline 0/11, follow-up 5/11 (45%) symptoms: 11/11 improved	1 repeat BET at 4 months (9%) 2 (18%) myringoplasty for 2 perforated TM	Yes (the lead author received a speaker honorarium from the manufacturer; balloon catheters from manufacturer)
Catalano 2012 [27] n=70, 100 ears age: 45 (18-73) follow-up: 34 months (n=8)	Uni- or bilateral BET 8 atm for 10 second (20 ears), 30 seconds (75 ears), 5 mm catheter local anaesthesia unless concomitant interventions	type A 72/100 type B+C 28/100	type A 25/28 (89%)	Symptoms (fullness, pressure) improved: 71% (71/100 ears), -> 34 patients/41 (73%) ears BET alone, * 36/54 (67%) with sinonasal procedures, * 3/5 (60%) with otologic procedures 34 months: 7/8 (87%) showed persistent improvement	Repeat dilatation 7/71(10%) 39 sinonasal procedures (56%) 5 otologic procedures (7%)	Not reported
McCoul 2012 [24] n=22, 35 procedures age: 55 (SD 8.7) follow-up: 6 months (22 ears)	BET 10 atm for 2 minutes, 5-7 mm catheter, several concomitant interventions general or local anaesthesia	type A 10/35 type B 5/35 type C 20/35	type A 34/35 (97%) 1 pre-existing perforation	ETDQ-7: baseline 4.5 (1.2 SD), 3 weeks 2.7 (1.5), 6 weeks 2.6 (1.1), 12 weeks 2.8 (1.7), 6 months 2.8 (1.3), change p < 0.001 from baseline SNOT-22: baseline 51.4 (21.1 SD), 6 weeks 34.2 (25.3), 12 weeks 34.2 (21.5), 6 months 30.0 (23.9), change p <0.01 Otoscopy: baseline 6/35 normal, 6 months 35/35 normal (100%). 23/25 (92%) symptoms improved	2/22 (9%) revision of BET 22/22 turbinectomy, 15/35 (43%) submucous resection of nasal septum,12/35 (34%) shenoethmoidectomy with maxillatory sinusotomy, 2/35 (6%) revision ethmoidectomy, 3 (9%) revision sphenoidectomy, 1 (3%) myringoplasty	Not reported
Bast 2013 [28] n=30, age: 49.7 (24-73) follow-up: survey after 6-18 months	BET with (Bielefelder) general anaesthesia	Pre-examination with tympanometry, result not given	Not reported	Quality of life and satisfaction, GBI: significant improvement p=0.001	Not reported	No

Study **n patients, ears at baseline** **Age: mean (SD or range)** **Follow-up**	**Intervention anaesthesia**	**Tympanometry preoperative**	**Tympanometry postoperative**	**Results of other outcomes**	**Additional treatments***	**Funding**
Tisch 2013 [26] n=210, 320 procedures age: 46 (SD 27.5) follow-up: not reported	Unilateral (n=100) and bilateral (n=110) BET 10 atm for 2 minutes general anaesthesia	Not reported	Normal 148/210 (70.4%)	Valsalva: preoperative 92.8% -ve, postoperative 10% -ve pressure symptoms improved in 70% subjective improvement 71%	Not reported	Yes
Schröder 2013 [20] n=120, 209 ears age: 54 (18-86) follow-up: 24 months	BET 10 atm for 2 minutes, 3 mm catherer general anaesthesia	normal 0/15	better 6/15 (40%) at 12 months	Valsalva: baseline 14/115 always ve+, 21/115 sometimes ve+, postoperative: 77/115 (67%) alwaysve+, 16/115 (14%) sometimes ve+, in total 81% Tube score: preoperative 2.0 median (SD 2.0), postoperative 2 months: 5.3 (SD 2.6); 24 ears (21%) did not show improvement, 231/295 (78)% showed improved Subjective symptoms improved: 44/66 (67%) at 2 months, 12/20 (60%) at 12 months	Not reported	Yes
Sudhoff 2013 [21] n=350, 616 procedures age: 8-84 follow-up: 12 months (n=53), 24 months (n=not reported, 22 ears)	BET 10 atm for 2 minutes general anaesthesia	Not reported	Not reported	Tube score: preoperative 2.71 (SD 2.2), postoperative 2 months 5.46 (SD 2.6) (n=167, 295 procedures), at 12 months 6.1 (SD 2.6) (n=53, 89 procedures), at 24 months 6.14 (SD 3.2) (n=not reported, 22 procedures) 87% subjective symptoms improved at 12 months	Not reported	Yes
Silvola 2014 [23] n=37, 42 procedures age: 48 (15-38) follow-up: 2.5 (1.5-4.2 range) years	BET < 12 atm for 1 minute (n=15), reinflation for 1 more minute (n=26) type of anaesthesia not stated	type A 1/41 type B 6/41 type C 10/41 type B/open 24/41 (TM perforation or tubes)	type A 37/41 (90%) type B 0/41 type C 6/41 type B/open 12/41	Valsalva: preoperative 0/41, postoperative 33/41 (80%) Mucosal inflammatory rating: baseline 23/41, postoperative 5/41 Clinical findings normal: 0% preoperatively, 90% postoperatively Overall success: 90%	3 (8%) repeated BET	Yes (One author served as a consultant for the manufacturer. Compensation was paid as a donation to the department and as a direct payment to the author)

Study **n patients, ears at baseline** **Age: mean (SD or range)** **Follow-up**	**Intervention anaesthesia**	**Tympanometry preoperative**	**Tympanometry postoperative**	**Results of other outcomes**	**Additional treatments***	**Funding**
Wanscher 2014 [25] n=34, 50 procedures age: 45 (20-74) follow-up:2 months	Unilateral (n=18) or bilateral (n=16) BET with 10 atm for 2 minute (Bielefelder) general or local anaesthesia	type A 0% type c1 11% type c2 31% type B without tubes 42% type B with tubes 17%	type A 28% type c1 17% type c2 19% type B without tubes 19%, 22/38 ears(58%) type B with tubes 17%	Toynbee's test: + preoperative 7%, postoperative 77% ETD classification: class 1 (able to perform normal Valsalva) 0 preoperative%, 45% postoperative, class 4 (not able to equalise pressure by any means) 89% preoperative, 27% postoperative Valsalva: VAS score preoperative 85.8, postoperative 43.6 (0= no problems, 100 impossible); 66% subjective improvement in Valsalva test (VAS score) 75% (some) positive improvement		No

BET= balloon Eustachian tuboplasty, ETD= Eustachian tube dysfunction, TM= tympanic membrane, SD= standard deviation, +ve= can do Valsalva manoeuvre, -ve = cannot do Valsalva manoeuvre

** removal of tympanostomy tubes not included, see Table 4 in Appendix 1*

4.3 Discussion

One systematic review on methods for treatment of ETD was retrieved [7] and a longer report of the same review was published in July 2014 [31]. This current assessment includes 6 additional reports [20, 21, 23, 25, 26, 28] published subsequent to the completion of the literature search by Norman et al. [7]. All the included studies were case series. The quality of the studies was poor for the majority of studies and was considered to be acceptable for only 3 [22-24]. The risk of bias on outcome level was considered high.

All studies showed improvements in outcomes following the treatment of ETD with BET. Postoperative improvements were observed both in objective and subjective measures. Tympanometry, tube score, and otoscopic findings were considered objective measures. The Valsalva manoeuvre is based on performance and reported outcomes of the patient. It is an imprecise measure, but is widely used in clinical settings. The composite tube score also includes the results of the Valsalva test and subjective symptoms and tubomanometry results. For the assessment, tube score would probably be the most relevant outcome measure; however, in current studies it is only used by the German group [20, 21].

In 3 of the included studies [23, 24, 27] the proportion of patients achieving a normal objective tympanostomy result was very high and 89-97% were classified as having normal (type A) ears in the postoperative measurement. In one study improvement was seen in 70% [26]. In contrast, in the other 3 included studies [20, 22, 25] only 28–40% were classified as having normal ears at postoperative follow-up. The reasons for such heterogeneity are not clear.

In the project plan it was stated that studies using concomitant treatments would be excluded. We decided, however, to deviate from this plan since the use of adjunct treatments, especially tympanostomy tubes, was common. These concomitant treatments complicated the assessment of the effectiveness of BET. In the case of the McCoul study [24] all patients also underwent partial inferior turbinectomy with a number undergoing concomitant endoscopic sinus surgery. The authors compared cases undergoing BET only vs. those undergoing BET with sinus surgery. They stated that there were no significant differences between the groups, but actual results were not given. The contribution of turbinectomy and other concomitant procedures to the positive improvements should be evaluated in comparative research designs. Of note, in the study by Catalano [27], subgroups of patients with concomitant sinonasal or otologic procedures had worse results than patients who underwent BET alone, although this difference was not significant. Only 28 out of 100 patients were available for postoperative analysis and 7 for the long-term analysis. Reasons for the high rates of drop out were not given.

In the project plan tympanostomy tubes (grommets) were considered as a comparison treatment. Data from the studies that reported previous use of tympanostomy tubes showed that patients had previous tympanostomy tubes several times or they were inserted in some patients at the time that the BET procedure was performed. For example, in 1 study [25] a patient had undergone tympanostomy tube insertion on 22 previous occasions. In some studies many patients had experienced chronic symptoms for years whereas in other studies the histories of the patients were not given in detail. Presumably, there was variation in the patient populations between studies. There is a lack of consensus on the diagnostic criteria for ETD, which makes the selection of the patients challenging.

The disease-specific quality of life measures (GBI, ETDQ-7, SNOT-22) were consistent with objective results and showed improvements in the general and physical health and sinonasal quality of life [24, 28].

The pathogenesis of OME in children differs from that in adults. Children were excluded from the trials except for the Bielefeld data where the age range was from 8 to 84 years [21]. The actual number of children in the study is unknown.

Despite the shortcomings outlined above, overall study results showed improvement. The general conclusion, however, remains the same as in the earlier systematic review [31]; while studies suggested that there may be some benefits, the current evidence is too limited to draw conclusions. In future studies there is a need for larger controlled trials with longer follow-up. Because the natural course of ETD is poorly documented and known to produce favourable outcomes without interventions, a control group is essential [31]. There was some evidence that the improvements are durable for up to 2–3 years, but the number of patients available for long-term follow-up was low

[23, 27]. Specific attention should be paid to the design of the study, starting from strict definition as to which kind of patients have “ETD”. Several other research questions remain: for example, how long the treatment effects remain, results of repeated treatments, results with different concomitant treatments, and efficacy in children [25]. According to trials registers, there is 1 randomised trial ongoing and the anticipated end date for data collection for this trial is January 2015. At least one other multicentre RCT, led by Dr Dennis Poe (informal information from Dr Jussi Jero), has been planned, but this study is not yet listed in the trial registers. Despite promising results, there is currently insufficient evidence to determine the effectiveness of BET in the management of ETD.

5 SAFETY

5.1 Methods

Domain framing

The general scope of the project, as described in the final project plan, was followed except for qualitatively summarising the results for the domain. In the absence of clear guidance on how to assess the quality of the body of evidence the GRADE approach was ultimately used.

Research questions

Element ID	Research question	Importance 3=critical 2=important 1=optional
C0001	What kind of harms can the use of the BET cause to the patient?	3
C0002	What is the dose relationship of the harms?	2
C0004	How does the frequency or severity of harms change over time or in different settings?	2
C0005	What are the susceptible patient groups that are more likely to be harmed?	2
C0007	What are the user-dependent harms?	1
C0008	How safe is the technology in comparison to the comparator?	3

Sources

The basic search for the project was used. Details of the search strategy can be found in Appendix 1. For the assessment of comparative technologies from the safety perspective, an additional systematic review was used [49].

Analysis

For the appraisal of case series an 18-criteria checklist by IHE was used [19]. The risk of bias at outcome level was assessed using the Cochrane risk of bias tables. The GRADE approach was used for qualitatively summarising the results for the domain.

Synthesis

Most of the research questions are answered in plain text format. In addition, a table is used for an overview of adverse events.

5.2 Results

Included studies

Studies included in this domain were the same as those used in the Clinical Effectiveness domain. Additionally, 1 Cochrane review was used for the assessment of the safety of comparative technologies [49].

Patient safety

C0001: ***What kind of harms can the use of the technology cause to the patient?***

The study with the largest series of BET to date [21], which included 351 patients and 616 operations (the patient population probably includes those previously reported in reference [20]), reported that no patients experienced pain or other discomforts postoperatively. In contrast, all the patients treated with BET in another study [22] had mild sore throat after surgery. A further study [25] reported that their patients indicated mild postoperative discomfort.

The only potentially serious complication reported is one case with mediastinal emphysema, which resolved with conservative treatment [26]. Bleeding in the nasopharyngeal area has been reported to occur in some studies. One study [22] observed mucosal laceration within the lumen of the Eustachian tube with very limited bleeding of brief duration in 5 of their 11 patients (46%). Disruption of the Eustachian tube mucosa, as evidenced by the presence of blood, was identified in 1 patient (2.5%) in another study [27]. In a study with 210 patients and 320 BET operations, 10 cases (5%) with mild nasal bleeding were observed, which were treated with application of a congestant xylometazoline [26]. In a further study [21] minimal bleeding occurred in the nasal and upper pharyngeal areas in some patients (numbers are not given). The bleeding did not, however, require any specific treatment. In a series of 22 patients with 35 BET procedures [24], 1 patient (4.5%), who was concomitantly treated with turbinectomy, had a postoperative bilateral hemotympanum that necessitated myringectomy.

Other adverse events reported in the BET studies include 4 cases of otitis media (in 42 procedures, 8%) [25], a transient increase in the severity of tinnitus, present already before BET, in 2 of 351 patients [21], 2 cases of subcutaneous emphysema in the facial area [21, 27], 1 of which needed antimicrobial therapy [21], and a single case of postoperative contralateral radiculopathy, presumably due to neck extension for intubation, and with full recovery [22].

C0002: ***What is the dose relationship of the harms?***

Studies that have reported results with BET have used equipment manufactured by 2 companies: Spiggle & Theis, Germany [20, 21, 25, 26] and Acclarent, Inc., USA [22, 24, 27]. In most of the studies the balloon, inserted into the Eustachian tube, was pressurised up to 10 bars for 2 minutes [20, 21, 24-26]. One study [22] used a target pressure of up to 12 bars for 1 minute. The authors concluded that there was a tendency for mucosal laceration with the 12 bar pressure: in 4 of the 5 cases with mucosal laceration this pressure was used. Otherwise, the relative safety of BET depending on the pressure and inflation time used cannot be assessed.

C0004: ***How does the frequency or severity of harms change over time or in different settings?***

One study [25] reported a diagnosis of AOM in 3 of their first 20 patients. The authors subsequently introduced a 5 day course of oral antibiotic therapy for postoperative patients. In these cases (30 procedures), only 1 case of otitis media was diagnosed.

Otherwise, no evidence was found to answer the research question.

C0005: ***What are the susceptible patient groups that are more likely to be harmed?***

Most of the reported studies recruited only adult patients [22, 24, 25, 27, 28]. One study [21] included children: patients were aged from 8 to 84 years old. The studies have not tried to identify subgroups that would be especially at risk of harms.

One study [21] noted that patients who are on acetylsalicylic acid, clopidogrel or warfarin anticoagulant treatment, may have mucosal bleeding but they did not give any data on the magnitude of this risk.

C0007: ***What are the user-dependent harms?***

No evidence was found to answer the research question.

C0008: ***How safe is the technology in comparison to the comparator?***

No published studies were identified that included direct comparison between BET and another treatment modality available for ETD. Medical treatment, i.e. nasal decongestants or local steroid application, have been associated with only minor adverse effects (cough, nasal bleeding) in short-term studies [31]. Not all included studies reported data on adverse events. The safety of tympanostomy has been assessed mainly in children. According to a Cochrane review, none of the evaluated studies reported any significant side effects from treatment [49].

5.3 Discussion

Reporting of harms in the published studies has been variable and the adverse events seem to vary qualitatively between studies. Safety issues are also confounded by the fact that, in many studies, other procedures have been performed concomitantly. Some studies failed to comment on safety issues [23, 28].

The most common adverse effect associated with BET has been bleeding in the nasopharyngeal area [22, 26, 27]. This bleeding was mild and self-limiting. The probable cause for bleeding is the mucosal laceration of the Eustachian tube due to BET as reported by Poe et al. [22]. In the follow-up, Poe et al. could not see any long-term complications, such as narrowing of the Eustachian tube or scarring, due to mucosal damage. It is probable that the bleeding may be due to other nasopharyngeal procedures performed concomitantly with BET. One patient in the McCoul and Anand [24] study had postoperative bilateral bleeding into the middle ear (hemotympanum) that necessitated myringectomy. This case was concomitantly treated with turbinectomy. BET may be associated with leakage of air into surrounding subcutaneous tissues. In the reported series two patients had subcutaneous facial emphysema. Additionally, 1 patient showed mediastinal emphysema. All of the emphysema cases recovered fully.

Overall, adverse effects reported in association with BET seem to be mild and self-limiting. The safety and tolerability of BET in adults, based on the available studies, seems to be good with only minor adverse effects. Available studies are, however, mostly small and no randomised comparative trials were idenfied. Thus, there is insufficient evidence to determine whether the safety of BET is comparable with that of other treatments for ETD, such as medical treatment. With the exception of the study by Sudhoff et al. [21] only adult patients have been included in the BET studies. Sudhoff et al. [21] included children over 8 years of age, but neither the number of children nor the number of adverse events occurring in children are reported. Thus, the safety of BET in children cannot be assessed.

6 POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

In the project planning phase it was concluded that BET does not raise serious ethical, social or legal issues and does not require organisational changes (see APPENDIX 2).

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

METHODS

Overall description of methods

This rapid assessment is based on the assessment elements from the HTA Core Model® for rapid REA of pharmaceuticals and on a systematic literature review from the following sources:

- Medline via OVID, EMBASE
- Cochrane database, DARE and HTA databases via the Cochrane Library and CDR
- WHO International Clinical trials Registry Platform (ICTRP) and ClinicalTrials.gov for the identification of registered clinical trials.
- Information from the manufacturers.

Researchers at each of the two authoring agencies (FinoHTA/THL, HIQA) identified the studies and relevant data sources necessary to answer the research questions for their selected domains.

Inclusion and exclusion of the studies were based on the PICO protocol.

The accepted study design for “Clinical effectiveness” included:

- Meta-analysis, systematic reviews, randomised controlled trials, non-randomised trials, controlled observational studies, case series with $\geq$ 10 patients.

- Studies including adults and/or adolescents over 12 years. Studies having mixed population by age were accepted.

For the “Safety” domain, single case reports could be accepted but were not included.

Exclusion by indication/population: children < 12 years, patients with patulous dysfunction of the Eustachian tube.

Exclusion by intervention: laser Eustachian tuboplasty, combined interventions.

No restrictions were made according to the language in the abstract phase.

For the “Health problem and current use of the technology” and “Description and technical characteristics” domains, no restrictions in terms of study design were applied. Additional searches and database information, such as databases for clinical guidelines and register data were used for the “Health problem and current use of the technology” and “Description and technical characteristics” domains.

Two researchers independently extracted (SS and TK) and rated (SS and MS) the studies included.

One systematic review [31] and nine case series were accepted to the assessment of clinical effectiveness and safety. Two studies were based on the same database [20, 21] and possibly two others [22, 23] also were.

Quality assessment for systematic reviews was based on ROBIS (Risk of Bias in Systematic Reviews) [18]. For the case series appraisal an 18-criteria checklist by IHE was used [19]. The Cochrane Risk of bias table for outcomes was also used in the assessment. From the selected studies, study characteristics, results concerning efficacy/effectiveness and safety were extracted into a data extraction table (Table 4). Effectiveness and safety were assessed by using the GRADE-methodology as this methodology allows for a transparent summary of the evidence in a qualitative manner (Table 9).

Distribution of work between author (FinoHTA/THL) and co-author (HIQA):

FinoHTA/THL tasks were:

- responsibility for the coordination of the work
- to develop the first draft of the project plan
- to develop the scientific process plan with specific tasks to be carried out, time frames and deadlines of milestones and deliverables
- to perform the basic literature search
- to involve clinical expert(s)
- to carry out the assessment on the domains: " Clinical effectiveness" and "Safety"
- to perform the assessment of ethical and organizational aspects if needed
- to review assessments of the co-author
- to send the 2nd draft version to reviewers
- to compile the feedback from reviewers and stakeholders and make changes according to reviewers' and stakeholders' comments
- to compile all domains in to a final report and write the final summary of the assessment.

HIQA tasks were to:

- review the draft project plan
- carry out the assessment on the domains: "Health problem and Current use of the technology" and "Description and technical characteristics of technology"
- carry out a search on EMBASE, based on a given literature search protocol by FinoHTA/THL
- review other domain assessments made by FinoHTA/THL
- review the final version of the assessment.

The assessment elements are from the HTA Core Model® for rapid REA of pharmaceuticals and one element from the HTA Core Model® for Diagnostic Technologies (D0023).

Documentation of the search strategies

Balloon dilatation of the Eustachian tube - Literature search strategies 9th May 2014

Centre for Reviews and Dissemination
(HTA, DARE, NHS EED)

Line	Search	Hits
1	MeSH DESCRIPTOR ear diseases EXPLODE ALL TREES	414
2	MeSH DESCRIPTOR eustachian tube	2
3	((middle ear* NEAR3 (inflamm* OR infect* OR disease* OR effus* OR atelectas*)))	25
4	#1 OR #2 OR #3	421
5	MeSH DESCRIPTOR dilatation	32
6	MeSH DESCRIPTOR dilatation, pathologic	6

7	MeSH DESCRIPTOR angioplasty, balloon EXPLODE ALL TREES	593
8	((balloon* NEAR3 (dilat* OR cathet*)))	120
9	#5 OR #6 OR #7 OR #8	709
10	#4 AND #9	0
11	(eustachian NEAR2 tuboplast*)	0
12	#9 AND #11	0
13	#10 OR #12	0

Cochrane Database of Systematic Reviews <2005 to March 2014>

---

1 (ear adj2 disease*).ti,ab,kw. (5)

2 eustachian tube*.ti,ab,kw. (1)

3 (middle ear* adj3 (inflamm* or infect* or disease* or effus* or atelectas*)).ti,ab,kw. (14)

4 or/1-3 (19)

5 (balloon* adj3 (dilat* or cathet*)).ti,ab,kw. (15)

6 4 and 5 (0)

7 eustachian tuboplast*.ti,ab,kw. (0)

8 5 and 7 (0)

9 6 or 8 (0)

Cochrane Central Register of Controlled Trials <April 2014>

---

1 exp Ear Diseases/ (2681)

2 Eustachian Tube/ (43)

3 (middle ear adj3 (inflamm* or infect* or disease* or effus* or atelectas*)).ti,ab,hw. (255)

4 or/1-3 (2767)

5 Dilatation/ (302)

6 Dilatation, Pathologic/ (114)

7 angioplasty, balloon/ (456)

8 (balloon* adj3 (dilat* or cathet*)).ti,ab,hw. (622)

9 or/5-8 (1440)

10 4 and 9 (1)

11 (eustachian adj2 tuboplast*).ti,ab,hw. (0)

12 9 and 11 (0)

13 10 or 12 (1)

Ovid MEDLINE(R) <1946 to April Week 5 2014>, Ovid MEDLINE(R) Daily Update <May 08, 2014>

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1 exp Ear Diseases/ (126871)

2 Eustachian Tube/ (2791)

3 (middle ear* adj3 (inflamm* or infect* or disease* or effus* or atelectas*)).ti,ab. (3864)

4 or/1-3 (128353)

5 Dilatation/ (8281)

6 Dilatation, Pathologic/ (8672)

7 angioplasty, balloon/ (15117)

8 (balloon* adj3 (dilat* or cathet*)).ti,ab. (12778)

9 or/5-8 (42725)

10 4 and 9 (108)

11 (eustachian adj2 tuboplast*).ti,ab. (23)

12 9 and 11 (7)

13 10 or 12 (108)

14 animals/ not (animals/ and humans/) (3844986)

15 13 not 14 (101)

16 limit 15 to yr="2000 -Current" (52)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 08, 2014>

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1 (ear adj2 disease*).ti,ab,kw. (139)

2 eustachian tube*.ti,ab,kw. (132)

3 (middle ear* adj3 (inflamm* or infect* or disease* or effus* or atelectas*)).ti,ab,kw. (168)

4 or/1-3 (373)

5 (balloon* adj3 (dilat* or cathet*)).ti,ab,kw. (649)

6 4 and 5 (4)

7 eustachian tuboplast*.ti,ab,kw. (3)

8 5 and 7 (2)

9 6 or 8 (4)

NLM PubMed

Epubs ahead of print

Search	Query	Items found
#6	Search **(#3 AND #5)**	2
#5	Search **publisher[sb]**	451444
#3	Search **(#1 AND #2)**	73
#2	Search **(balloon OR dilati* OR dilatat*[Title/Abstract])**	150286
#1	Search **eustachian tube[Title/Abstract]**	2833

ISI Web of Science

Set	Results	
# 1	**31**	**TOPIC:** (eustachian tube AND balloon) *OR* **TITLE:** (eustachian tube AND balloon) *Timespan=2000-2014* *Search language=English*

Euroscan

no references

"eustachian tuboplasty"	no references
(ear OR eustachian) AND (dilation OR dilatation)	19 references, not relevant
(ear OR eustachian) AND (balloon OR tuboplasty)	34 references, not relevant

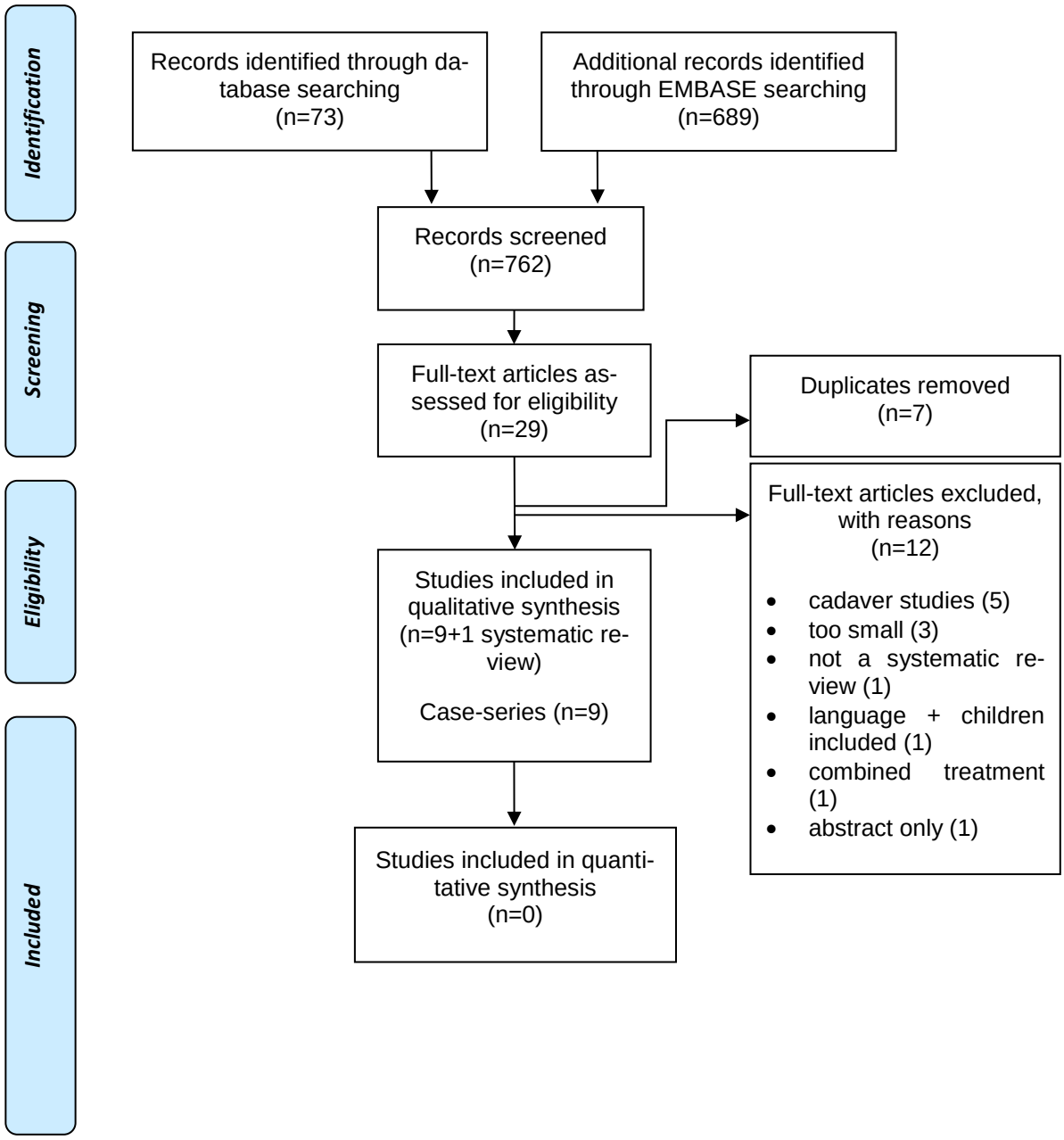
EUnetHTA POP Database

balloon dilat* AND eustachian	1 reference

Embase search:

Search No.	**EMBASE Search Terms**	**EMBASE Results**	**MEDLINE Results**
#1	ear diseases'/exp OR 'ear diseases'	119000	126871
#2	eustachian tube'/exp OR 'eustachian tube'	4537	2791
#3	middle:ab,ti AND (ear* NEAR/3 (inflamm* OR infect* OR disease* OR effus* OR atelecta*)):ab,ti	5252	3864
#4	#1 OR #2 OR #3	121916	128353
#5	dilatation'/exp OR 'dilatation'	93201	8281
#6	dilatation pathologic'/exp OR 'dilatation pathologic'	85062	8672
#7	angioplasty balloon'/exp OR 'angioplasty balloon'	22953	15117
#8	(balloon* NEAR/3 (dilat* OR cathet*)):ab,ti	18275	12778
#9	#5 OR #6 OR #7 OR #8	206084	42725
#10	#4 AND #9	999	108
#11	(eustachian NEAR/2 tuboplast*):ab,ti	27	23
#12	#9 AND #11	9	7
#13	#10 OR #12	999	108
#14	#10 OR #12 AND [humans]/lim AND [2000-2014]/py	689	52

Flow chart of study selection



DESCRIPTION OF THE EVIDENCE USED

Evidence tables of individual studies included for clinical effectiveness and safety

Table 4: Characteristics of relevant studies

Primary reference source	Study type	Number of patients	Inclusion criteria	Intervention(s)	Endpoints	Duplicate publications from the same study
Poe, 2011 [22] Finland	Case serie	n=11 (11 ears)	Unilateral or bilateral persistent OME for ≥ 5 years, broken only by tympanostomy tubes or tympanic membrane perforation	Balloon dilation, reinsertion/repeat dilatation where necessary 2 patients had tympanostomy tubes inserted, 3 patients had tubes removed at the time of BETsurgery	Ability to perform Valsalva Rating of ET mucosal inflammation, tympanogram, and otomicroscopy findings	
McCoul 2012 [24] USA	Case serie	n=22 (35 ears)	Abnormal tympanogram (any non-A curve), unilateral or bilateral symptoms of ETD (aural fullness or pressure, clogged or muffled sensation in the ears, inability to rapidly self-equilibrate middle ear pressure.)	Balloon dilation of the Eustachian tube and partial inferior turbinectomy performed for all patients Submucous resection of nasal septum 15 patients (43%), sphenoethmoidectomy with maxillary sinusotomy 12 patients (34%), revised ethmoidectomy 2 patients (6%), revised sphenoidotomy 3 patients (8,6%), removal of tympanostomy tube 1 patient (3%), myringoplasty 1 patient (3%)	Tympanometry and otoscope findings, scores for ETDQ-7 and SNOT-22	
Catalano 2012 [27] USA	Case serie	n=70 (100 ears)	Reported chronic sensation of ear fullness, pressure, pain and otitic barotrauma. ETD developed during adult years.	Balloon dilatation Sinonasal procedure 39 patients (56%), otologic procedures 5 patients (7%)	Sensation of ear fullness, pressure, pain, and tolerance to air travel Any visible alteration in the appearance of the tympanic membrane Tympanometry findings	
Bast 2013 [28] UK	Case serie	n=30	Diagnosed as having chronic tube ventilation dysfunction	Balloon dilatation	General quality of life	

Silvola 2014 [23] Finland	Case serie	n=37 (41 ears)	Unilateral or bilateral persistent OME or significant nonadherent tympanic membrane atelectasis ≥ 5 years	Balloon dilation Tympanostomy tubes inserted if not placed preoperatively	Ability to perform a Valsalva maneveur Audiometry, tympanometry, videoendoscopy and otomicroscopy findings	Includes Poe 2011 data
Wanscher 2014 [25] Danmark	Case serie	n=34 (50 ears)	At least 6 months of ETD symptoms or significant symptoms during flying, diving and/or secretory otitis media several times a years.	Balloon dilatation 12 ears had ventilation tubes	Findings of otomicroscopy, rhinoscopy, audiometry, tympanometry and (computed tomography of the ET) Symptoms reported by the patient	
Tisch 2013 [26] Germany	Case serie	n=210 (320 ears)	Ventilatory dysfunction of ET which did not respond to other treatment.	Balloon dilatation	Ability to perform a Valsalva and a Toynbee manoeuvre Discomfort reported by the patient Findings of otomicroscopy and tympanometry	
Schröder 2013 [20] Germany	Case serie	n=120 (209 ears)	Chronic ETD	Balloon dilatation In 6 patients, the dilatation was combined operating on the sinus, the septum and/or the lower auricles. In 8 patientsa tympanoplasty revision was also conducted.Cortisone containing nasal spray for 2 months, Xylometazolin/Dexpanthenol nasal spray for 7 days and 2x500g antibiotics for 5 days post-operatively.	Tube score (popping of ears when swallowing, Valsalva-test and tubomanometry findings) Complications	
Sudhoff 2013 [21] Germany	Case serie	n=351 (616 ears)	Not given	Balloon dilatation	Tube score (patient satisfaction, Valsalva-test and tubomanometry findings) Complications	Includes Schröder 2013 data

ET= Eustachian tube, ETD= Eustachian tube dysfunction, OME=Otitis media with effusion, BET balloon Eustachian tuboplasty, ETDQ-7= 7-item Eustachian Tube Dysfunction Questionnaire,

SNOT-22= 22-item Sinonasal Outcome Test

List of ongoing and planned studies

The **WHO International Clinical Trials Registry Platform**
Eustachian tube AND balloon 3 records for 3 trials found

PROSPERO International prospective register of systematic reviews
Eustachian tube AND balloon 2 records

Table 5: List of ongoing relevant studies with balloon Eustachian tuboplasty (BET)

Study Identifier	Time	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
ISRCTNO2147658	1/2012	RCT	200	BET	tympanos-tomy tube	-	tube score, at 24 months
NCT02114762	started 4/2014	safe-ty/efficacy, open label	80	BET	-	18-50 year old patients with ETD	BET function testing at 1 month
NCT0212377	started 5/2014	safe-ty/efficacy, open label	30	BET	-	20-80 year old, tube score < 5	tube score at 24 months

Risk of bias tables

Risk of bias – study level

Table 6: Quality assessment of the case series studies using IHE 18-tem checklist [19]

	McCoul 2012	Bast 2013	Poe 2011	Catalano 2012	Silvola 2014	Wanscher 2014	Tisch 2013	Schröder 2013 Sudhoff 2013
1. Is the hypothe-sis/aim/objective of the study clearly stated in the abstract, introduction or methods section?	Y	Unclear	Y	Unclear	Y	N	N	N
2. Are the characteristics of the participants included in the study described?	Y	Y	Y	Y	Y	Y	N	N
3. Were the cases collect-ed in more than one cen-tre?	N	N	N	N	N	N	N	N
4. Are the eligibility criteria (inclusion and exclusion	Y	Y	Y	N	Y	Y	N	Y

criteria) to entry the study explicit and appropriate?								
5. Were participants recruited consecutively?	Y	Y	Y	Unclear	Y	Unclear	N	Y
6. Did participants enter the study at a similar point in the disease?	Unclear	N	Y	Unclear	Y	N	N	N
7. Was the intervention clearly described in the study?	Y	Y	Y	Y	Y	Y	Y	Y
8. Were additional interventions (co-interventions) clearly reported in the study?	Y	N	Y	N	Y	N	N	Y
9. Are the outcome measures clearly defined in the introduction or methodology section?	Y	N	Y	N	Y	Y	N	Y
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Y	Y	Y	N	Y	Y	N	Y
11. Were outcomes measured before and after intervention?	Y	N	Y	N	Y	Y	Y	Y
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Unclear	Y	N	Y	Y	N	Y
13. Was the length of follow-up reported?	Y	Y	Y	Y	Y	Y	N	Y
14. Was the loss to follow-up reported?	Y	NA	Y	N	Y	N	N	N
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Y	N	Y	N	N	Y	N	Y
16. Are adverse events reported?	Y	N	Y	Y	N	Y	Y	Y
17. Are the conclusions of the study supported by results?	Y	Partially	Y	Y	Y	Y	Y	Y
18. Are both competing interest and source of support for the study reported?	N	Y	Y	N	Y	N	N	Y

Y = Yes; N = No; NA = Not applicable. If the studies had ≥ 14 “Yes” answers, the quality is acceptable.

Table 7: Quality of included systematic review [18]

Review [7, 31]	Phase 2				Phase 3
	1.STUDY ELIGIBILITY CRITERIA	2. IDENTIFICATION AND SELECTION OF STUDIES	3. DATA COLLECTION AND STUDY APPRAISAL	4. SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
	☺	☺	☺	☺	☺

☺ = low risk; ☹ = high risk; ? = unclear risk

Risk of bias – outcome level

Table 8: Risk of bias on outcome level

Outcomes	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Tympanometry						
Poe et al. 2011 [22]	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Catalano et a. 2011 [27]	high[1)]	high[1)]	high[1)]	high[1)]	high[2)]	high[1)]
McCoul and Anand 2012 [24]	high[1)]	high[1)]	high[1)]	low	high[3)]	high[1)]
Schröder et al. 2013 & Sudhoff et al. 2013 [20, 21]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]
Tisch et al. 2013 [26]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]
Silvola et al. 2014 [23]	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Wanscher and Svane-Knudsen 2014 [25]	high[1)]	high[1)]	high[1)]	low	high[2)]	high[1)]
Valsalva manouvre						
Poe et al. 2011 [22]	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Schröder et al. 2013 & Sudhoff et al. 2013 [20, 21]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]
Silvola et al. 2014 [23]	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Tisch et al. 2013 [26]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]

Wanscher and Svane-Knudsen 2014 [25]	high[1)]	high[1)]	high[1)]	low	high[2)]	high[1)]
Symptom improvement						
Poe et al. 2011	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Catalano et a. 2011 [27]	high[1)]	high[1)]	high[1)]	high[1)]	high[2)]	high[1)]
Schröder et al. 2013 & Sudhoff et al. 2013 [20, 21]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]
Silvola et al. 2014 [23]	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Wanscher and Svane-Knudsen 2014 [25]	high[1)]	high[1)]	high[1)]	low	high[2)]	high[1)]
McCoul and Anand 2012 [24]	high[1)]	high[1)]	high[1)]	low	high[3)]	high[1)]
Adverse Events						
Poe et al. 2011	high[1)]	high[1)]	high[1)]	low	low	high[1)]
Catalano et a. 2011 [27]	high[1)]	high[1)]	high[1)]	high[1)]	high[2)]	high[1)]
McCoul and Anand 2012 [24]	high[1)]	high[1)]	high[1)]	low	high[3)]	high[1)]
Schröder et al. 2013 & Sudhoff et al. 2013 [20, 21]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]
Tisch et al. 2013 [26]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]
Wanscher and Svane-Knudsen 2014 [25]	high[1)]	high[1)]	high[1)]	low	high[2)]	high[1)]
HrQoL						
McCoul and Anand 2012 [24]	high[1)]	high[1)]	high[1)]	low	high[3)]	high[1)]
Bast 2013 [28]	high[1)]	high[1)]	high[1)]	high[2)]	high[2)]	high[1)]

[1)] not an RCT, [2)] several methodological problems or problems in reporting (see Table 6), [3)] concomitant treatments.

GRADE profiles

The classification and definitions of the quality of the evidence include: high (i.e. “We are very confident that the true effect lies close to that of the estimate of effect”), moderate (i.e. “We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different”), low (i.e. “Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect”) and very low (i.e. “We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect”).

Table 9: GRADE profiles for the different outcomes

No of studies/ patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors[1]	Quality of evidence
Efficacy							
Outcome: Tympanometry (in % of Type A ears postoperatively)							
7/504	case series	serious limitations (-1)[2]	important inconsistency (-1)	indirect[3]	28 – 97	none	very low
Outcome: Valsalva manouvre (in % of patients able to perform the manouvre postoperatively)							
5/412	case series	serious limitations (-1)[2]	no important inconsistency	indirect[3]	66 – 100	none	very low
Outcome: Symptom improvement (in % of patients at follow-up 2 – 24+ months)							
7/645	case series	serious limitations (-1)[2]	no important inconsistency	indirect[3]	60 - 100	none	very low
Outcome: Quality of life (follow-up 6 weeks to 18 months)							
2/52	case series	serious limitations (-1)[2]	no important inconsistency	indirect[3]	mean change score ETDQ-7, SNOT-22: p<0.05; GBI: p=0.001 for total score	sparse data	very low
Safety							
Outcome: Serious AEs (in % of patients)							
1/210	case serie	serious limitations (-1)[2]	only 1 study	indirect[3]	<1	sparse data	very low
Outcome: Other AEs (including bleeding, otitis media, subcutaneous emphysema in % of patients)							
5/676	case series	serious limitations (-1)[2]	important inconsistency[4] (-1)	indirect[3]	2.5 - 46	imprecise data	very low

ETDQ-7= 7-item Eustachian Tube Dysfunction Questionnaire, SNOT-22= 22-item Sinonasal Outcome Test, GBI= Glasgow Benefit Inventory

Applicability tables

Table 10: Summary table characterising the applicability of the body of evidence

Domain	Description of applicability of evidence
Population	The majority of the available studies included male and female patients over 18 years of age. A few studies included elderly patients and one also included children. Patients had a history of chronic Eustachian tube dysfunction (ETD), and most reported multiple prior treatments using different approaches. Most of the studies do not report any exclusion criteria for the selection of patients. A minority of reports state that disorders such as nasopharyngeal malignancies, radiation therapy and anatomical abnormalities (cleft palate etc.) were reasons for exclusion. The inclusion criteria of the studies seem to be in accordance with the intended patient population for the technology.
Intervention	Balloon dilatation of the Eustachian tube (BET) was performed using commercially available devices. The balloon dilatation catheter was passed into the cartilaginous

1 low incidence, lack of precise data, sparse data, lack of strong or very strong association, high risk of publication bias, residual confounding plausible
2 for further details, see Table 6
3 due to lack of a comparator, estimation of a relative treatment effect is not possible
4 selective and imprecise reporting

	part of the ET under endoscopic guidance. The balloon was then inflated to 10 bars for up to two minutes. The procedure can be done uni- or bilaterally, depending on the patient requirements. In most cases, general anaesthesia was used, especially when concomitant procedures were performed. In some cases, other surgical procedures such as endoscopic sinus surgery or turbinectomy, were performed concomitantly.
Comparators	To date, there are no published studies in which BET has been compared with other treatments.
Outcomes	A range of clinically relevant outcome criteria were applied in the studies and they showed both objective and subjective benefits from the treatment. Concomitant treatments prevent assessment of the value of BET. Due to limited data, especially lack of comparative data, it is not possible to evaluate the effectiveness of BET. For the assessment of safety, clinical symptoms were recorded.
Setting	With one exception, the studies were carried out in Europe, in Denmark, Finland, United Kingdom and Germany. One study was carried out in the United States. Patients were recruited from, and the operations were performed at, secondary or tertiary otolaryngolocical centers. Study centers had experience in the technology used as well as in clinical research in general. The setting of the studies probably reflects accurately the clinical setting in which the technology is intended to be used.

APPENDIX 2: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant?	No
3. **Social**	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. **Legal**	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No

