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Validation of Biomarkers and Patient-Reported Outcome Measures to Improve the Diagnosis and Treatment of Eustachian Tube Dysfunction

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Abstract

Patients who suffer from Eustachian tube dysfunction (ETD) experience a significant decline in quality of life. To enhance patient outcomes, it is crucial to establish an accurate diagnosis, assess treatment effectiveness, and evaluate the severity of the condition. Substantial progress has recently been made in identifying biomarkers (BMs) and developing ETD clinical outcome assessments (COAs). This study examines the current state of BMs and COAs in ETD, including the methods evaluated historically and their potential clinical applications. The research in this area emphasizes the importance of using objective measures, such as middle ear pressure (MEP) and patient-reported outcome measures (PROMs), for diagnosing and evaluating ETD. Further, I discuss how electronic PROMs (ePROMs) and other digital health technologies can guide the development of innovative PROMs that ETD. Despite significant advances in COAs for ETD, much work remains to validate and improve them before their implementation in clinical practice. There has been less focus on vertigo as a symptom in recent assessments of ETD, suggesting that further examination of this aspect is needed. By validating BMs and COAs for ETD, we could enhance long-term patient outcomes and quality of life through improved diagnostic accuracy and evaluation of treatment efficacy.

Introduction

In recent years, Eustachian tube dysfunction (ETD), which can cause ear fullness, pain, hearing loss, tinnitus, and vertigo, has become an increasingly prevalent syndrome (Bluestone, 2018; Hamrang-Yousefi et al., 2022; Llewellyn et al., 2014). ETD is characterized by symptoms and signs that indicate impaired Eustachian tube (ET) function (Schilder et al., 2015). ETD has multiple causes, including gastroesophageal reflux disease, laryngopharyngeal reflux (LPR), nasopharyngeal reflux, allergies, infections, and anatomical problems (Hamrang-Yousefi et al., 2022; Llewellyn et al., 2014; Schilder et al., 2015; Yan et al., 2020; Zhen et al., 2022). There are three types of ETD: baro-challenge-induced, patulous, and dilatory (Hamrang-Yousefi et al., 2022; Schilder et al., 2015).

Effective treatment of ETD necessitates an accurate diagnosis and evaluation. Traditional diagnostic procedures, such as pressure equalization tests and Eustachian tube catheterization (ETC), are invasive and require specialized training, rendering them challenging to use in clinical settings (Bluestone, 2018; Kim, 2016; Kim, 2019; Kim, 2021; Kim, 2023a; Kim, 2023b; Merica, 1942; Teixeira, 2020). Objective measures are needed to determine the type of ETD in a patient and estimate the efficacy of treatment (Teixeira, 2020; Teixeira et al., 2018).

Biomarkers (BMs), patient-reported outcome measures (PROMs), and electronic PROMs (ePROMs) are essential tools for evaluating the diagnosis and treatment of ETD. The development of ePROMs has been facilitated by the advent of digital health technology, allowing the electronic collection and monitoring of patient-reported symptoms and treatment efficacy. Surrogate endpoint BMs can be used to assess disease progression or treatment efficacy (Aronson, 2005). Middle ear pressure (MEP) is a potential BM for ETD and can be measured by tympanometry or acoustic reflectometry (Shanks & Shelton, 1991; Teele & Teele, 1984) but requires additional research to establish its reliability and validity in ETD (Bluestone et al., 2012). PROMs and ePROMs are evaluation

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tools that measure patient-reported outcomes, such as symptoms, quality of life, and functional status (Fitzpatrick et al., 1998). The Eustachian Tube Dysfunction Questionnaire-7 (ETDQ-7) is the most frequently used PROM and can be adapted to assess ETD-related symptoms electronically. However, its limitations must be addressed, such as the absence of vertigo as a symptom and the need for more objective tests, including digital tools, to confirm the diagnosis and monitor treatment efficacy (McCoul et al., 2012; Kim, 2020; Kim, 2021; Kim, 2023b).

A precise ETD diagnosis is necessary to select the appropriate treatment. Clinicians should use reliable BMs, validated PROMs, and ePROMs to treat this condition, exploiting digital health technology when applicable. This comprehensive review discusses the validation of BMs and PROMs in ETD, focusing on MEP as a BM and the ETDQ-7 as a PROM. These measures have limitations and difficulties, necessitating new clinical outcome assessments (COAs) for ETD, including digital tools, to address these issues. Clinicians can improve the diagnosis and treatment of ETD and, thus, patient outcomes by advancing research and developing reliable, validated BMs, PROMs, and ePROMs.

Biomarkers for ETD

Definition of biomarkers

BMs are objective indicators that can be used to understand various aspects of a disease or condition (FDA-NIH Biomarker Working Group, 2017c; Food and Drug Administration [FDA], 2018). They can be based on molecular, histological, biochemical, physiological, or imaging measures, providing information on disease behavior, progression, and response to treatment (FDA-NIH Biomarker Working Group, 2017c). Surrogate endpoint BMs refer to any measure that is not an actual outcome; however, not all BMs are useful surrogate endpoints (Aronson, 2005; FDA-NIH Biomarker Working Group, 2017b). BMs must undergo analytical and clinical validation—i.e., the test must measure what was designed to assess and predict or evaluate the relevant clinical concept (FDA-NIH Biomarker Working Group, 2017a).

Explanation of MEP as a potential biomarker for ETD

MEP is the pressure in the middle ear (ME) space. Because MEP is linked to the Eustachian tube (ET) function, it has been implicated as a BM for ETD (Bluestone et al., 2012) (Figure 1). In persons who do not have ETD, the ET typically regulates MEP. MEP ranges from -150 to +50 daPa (decaPascals), averaging 0 daPa; normal MEP is typically approximately 0 daPa (Bluestone, 2018). The ET connects the ME to the back of the nose and throat, and a change in MEP from baseline can be a sign of ETD. ETD can be diagnosed by measuring MEP using a tympanometer, which generates a tympanogram graph. A normal tympanogram shows a peak in MEP at roughly 0 daPa, indicating that the MEP is equal to atmospheric pressure (Kramer, 2022). An abnormal tympanogram might lack a peak (type B) or trough (type C), reflecting fluid or negative pressure in the ME. MEP can be aberrant in persons with ETD, with values that are significantly positive or negative. Positive MEP values indicate that the pressure in the ME is greater than atmospheric pressure, perhaps due to a patulous or blocked ET that cannot escape from the ME (Bluestone, 2018). Negative MEP values suggest that the pressure in the ME is less than atmospheric pressure, signifying a blocked ET (Bluestone, 2018).

In ETD, BMs can measure inflammation, MEP, or mucosal thickening. Reliable BMs for ETD would improve its diagnosis and treatment monitoring and increase our understanding of disease mechanisms. However, searching for such BMs remains in its infancy, necessitating further research to determine their clinical value. A promising BM for ETD is MEP, which can be measured by tympanometry and acoustic reflectometry (Shanks & Shelton, 1991; Teele & Teele, 1984). MEP has been proposed as a surrogate endpoint BM of ET function and can be used to measure the efficacy of treatments for ETD (Aronson, 2005; Bluestone et al., 2012; Schilder et al., 2015). However, more research is needed to establish its reliability and validity as a BM for ETD (Bluestone et al., 2012). A combination of objective measures, including MEP and other diagnostic tests, must be applied to diagnose and monitor ETD accurately. Various diagnostic tools can enhance our understanding of the underlying mechanisms of ETD and improve treatment outcomes (Bluestone, 2018; Bluestone et al., 2012).

Review of "Persistent Alternobaric Vertigo at Ground Level"

The article "Persistent Alternobaric Vertigo at Ground Level" by Bluestone et al. (2012) provides essential insights into the relationship between ETD and alternobaric vertigo (ABV). Its case report of a patient who experienced recurrent episodes of vertigo at ground level due to uneven pressure in the ME underscores the importance of the proper diagnosis and management of ETD to avoid the development of related conditions. How many patients world-

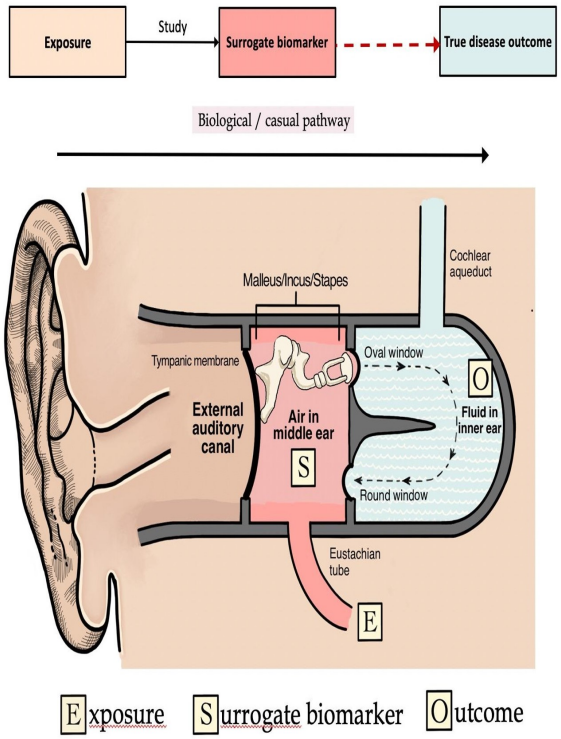

Figure 1: *Diagram of the outer, middle, inner ear and Eustachian tube.*

wide suffer from ground-level ABV (GLABV) due to uneven pressure in their ME at ground level (Kim, 2023b)? Bluestone's clear and concise explanation of the Toynbee phenomenon, which can result in abnormal negative or positive pressure in the ME when a patient swallows with a blocked nose, is appreciated. This article also emphasizes the significance of considering all potential causes of vertigo, including ETD and using objective measures to confirm the diagnosis and evaluate treatment efficacy, such as pressure equalization tests and MEP measurements.

Vertigo can be treated by restoring vestibular function by balancing pressure in both MEs, according to Bluestone et al. (2012). ET function must be assessed before vestibular function because impairments in the former cause the latter. Failure to do so might yield inaccurate results and lead to the conclusion that the vestibular organ is ailing when ETD is, in fact, the cause of the vertigo. Park et al. (2012) have reported that people with inner ear issues have had ETD. One must remember that a unilateral loss of peripheral vestibular function can result in acute true vertigo (Roland, 2004). Although asymmetrical MEPs are likely to cause ABV, distinguishing unilateral from bilateral ETD can be challenging (Kim, 2017; Kim, 2021; Kim, 2023b).

Bluestone et al. (2012) discovered a link between chronic GLABV and abnormal vestibular function test results. Although they could not demonstrate a direct causal association between abnormal MEP and vestibular organ dysfunction, they suggest that abnormal MEP, which can result from ETD, can be a cause of vestibular dysfunction. MEP as a BM for ETD can aid in making an accurate diagnosis and providing the appropriate treatment. Overall, Bluestone's article is helpful for clinicians and researchers who want to learn more about the relationship between ETD and ABV. Using the term "GLABV" to describe this specific type of vertigo might also help promote clarity and consistency in communication (Kim, 2023b).

Limitations and challenges of using MEP as a biomarker for ETD

To diagnose and treat ETD, one must be able to measure ET function directly and objectively. Tympanometry is a standard and straightforward method of assessing MEP and ET function (Smith et al., 2019; Smith et al., 2018b). MEP has been proposed as a BM for ETD, but its implications can be challenging to determine. A type C tympanogram that shows a negative MEP at rest and tympanic insufflation that reveals active negative pressure (Hamrang-Yousefi et al., 2022) do not necessarily indicate ETD (Bluestone, 2018; Smith et al., 2019). Even if there is a clear tympanic membrane and no signs of an ME infection, it is important to check the function of the ET (Bluestone, 2018), primarily due to the emergence of symptoms that might be attributed to ETD. For example, an MEP above -50 daPa does not always reflect a normally functioning ET. Due to asymmetric MEP, such a case could still result in balance problems (Kim, 2021; Kim, 2023b). Suppose MEPs are considered normal values because they are not below -50 daPa. In that case, bias has clearly been introduced—a systematic error that leads to an incorrect measurement of a dependent variable and, as a result, an incorrect conclusion (Fregni & Illigens, 2018). ETD is usually treated by inserting a ventilation tube to bypass the ET, restoring ambient MEP, preventing inflammation of the ME, draining effusions, and improving hearing (Bluestone, 2018; Kim, 2023a; Kim, 2023b; Teixeira, 2020). Asymmetrical MEPs are a potential cause of ABV, and it can be challenging to distinguish between unilateral and bilateral ETD (Bluestone, 2018; Kim, 2017; Kim, 2021; Kim, 2023b). Thus, combining tympanometry, acoustic reflex testing, and MEP measurements can help one diagnose ETD more accurately (Teixeira, 2020).

Testing the ET function is the first step toward understanding that ETD is more than just being "too closed" or "too open" and comprises a spectrum of disorders with varying causes and effects (Teixeira,

2020). The testing criteria, concepts, and understanding of ET function are being expanded through ongoing research using objective measures (Alper et al., 2019; Smith et al., 2018b). The state in which vestibular functions are perfectly equalized is called balance. This status requires the pressure in the ME to be equal bilaterally. Only tympanometry results of 0 daPa for MEP on both sides should be considered normal, and ranges in MEP should be classified as mild, moderate, or severe. By learning how ETD symptoms behave, we have realized that the normal range and commonly used types of tympanometry are ineffective. Only by changing the normal criteria for tympanometry can a new method be developed for validating MEP as a surrogate BM for ETD and the results after ETC. This new tympanometric approach uses normal criteria with an MEP of only 0 daPa.

Our testing criteria for and understanding ET function constantly expand through objective measures research (Alper et al., 2019; Smith et al., 2018b). To this end, we must use multiple tests and conduct ongoing research to develop more accurate and reliable methods of measuring ET function to improve the diagnosis and treatment of ETD-related conditions, such as ABV. PROMs are useful in validating BMs, particularly for conditions like ETD, in which subjective symptoms carry significant weight alongside objective measurements. Whereas BMs provide objective data, the human experience of a disease is multifaceted. PROMs consider the patient's perspective, ensuring that validated BMs are scientifically valid and clinically relevant. By combining these aspects, we can comprehensively understand ETD and the value of BMs, such as MEP. It might be more advantageous first to recognize the patient's viewpoint through PROMs to improve patient care.

Patient-Reported Outcome Measures for ETD

Definition of PROMs

PROMs are questionnaires or surveys that patients complete to report their health status, feelings, and functions in specific areas of their health (Black, 2013). Disease-specific PROMs can be helpful when there is no standard objective test for a disease (Fitzpatrick et al., 1998). PROMs are a type of COA used increasingly in healthcare to evaluate patient experiences and outcomes and inform clinical decision-making (FDA, 2009). PROMs and COAs are typically administered before and after treatment and can measure patient-reported outcomes over time, making them more objective than a clinical history (Smith et al., 2018a).

COAs, including PROMs, are suitable if their measurement properties are appropriate for the situation and population under study (FDA-NIH Biomarker Working Group, 2017a; Streiner et al., 2008). The performance of a COA is validated through evidence that it meets several predetermined criteria, such as whether all of the important elements of the construct (such as disease-related symptoms and physical function) are reflected in the test, tool, or instrument; whether the COA's measurements are sufficiently sensitive to demonstrate changes in the concept; and whether these changes can be interpreted to reflect clinically meaningful changes (FDA-NIH Biomarker Working Group, 2017a). PROMs are part of a broader category of COAs, including clinician-reported outcome measures, observer-reported outcome measures, and performance outcome measures (FDA, 2009). Combining COAs can provide a more comprehensive profile of a patient's health status and treatment outcomes.

Overview of ETDQ-7 as a common PROM for ETD

The ETDQ-7 is a widely accepted instrument that assesses patient-reported outcomes. Its purpose is to identify the severity of ETD on a 7-item Likert scale, from 1 to 7 (McCoul et al., 2012). This validated COA measures symptoms with values that range from 7 to 49; higher scores indicate more severe ETD (a total score of 14.5 is considered normal). Its reliability, which includes internal consistency and test-retest reliability, and validity, comprising face, content, and construct validity, have been researched extensively (McCoul et al., 2012; Middleton, 2023; Fitzpatrick et al., 1998). The following lists the actual questions that constitute the ETDQ-7:

1. Pressure in the ears?
2. Pain in the ears?
3. A feeling that your ears are clogged or "underwater"?
4. Ear symptoms when you have a cold or sinusitis?
5. Crackling or popping sounds in the ears?
6. Ringing in the ears?
7. A feeling that your hearing is muffled? (McCoul et al., 2012)

Vertigo, a typical symptom of ETD, is not included in this list (McCoul et al., 2012). However, it is important to note that the ETDQ-7 has a high level of reliability. The ETDQ-7 has high psychometric qualities, allowing it to be used frequently (McCoul, 2020). The ETDQ-7 is commonly used to assess patient symptoms associated with obstructive ETD and assess the efficacy of balloon dilation of the ET (Froehlich et al., 2020). However, new PROMs

are needed to evaluate therapies for ETD, such as Eustachian tube catheterization, and accurately diagnose ETD.

Analysis of ETDQ-7

The ETDQ-7 is a validated PROM that assesses the severity and frequency of ETD-associated symptoms. However, this questionnaire has several limitations. Vertigo is not measured by the ETDQ-7, limiting its ability to capture the entire range of ETD symptoms (Bluestone, 2018; Bluestone et al., 2012; Mallen & Roberts, 2019). Further, voice disturbance, a sign of LPR that can develop from ETD, should be considered a possible symptom in the ETDQ-7 (Brown & Shermetaro, 2022; Kim, 2015). Also, the ETDQ-7 is not an objective measure of ET function (Andresen et al., 2021). This drawback is particularly significant, given the varied and complex nature of ETD symptoms and their potential impact on quality of life (Teixeira, 2020).

Limitations and challenges of the ETDQ-7 as a PROM for ETD

A normal baseline MEP is generally considered to be approximately 0 daPa (Bluestone, 2018). Any significant deviation in MEP from this baseline suggests the presence of ETD. Thus, the criteria for defining normal and abnormal impedance audiometry results must be specified, and the addition of pure-tone audiometry to the list of objective measures for diagnosing ETD should be considered (Hamrang-Yousefi et al., 2022). Pure-tone audiometry provides important information on low-frequency hearing loss and air-bone gaps, constituting the stiffness effect of ETD, which can help in its diagnosis (Hamrang-Yousefi et al., 2022; Kim, 2021). Even within normal limits, asymmetric tympanometry results can indicate ABV, a significant factor to consider in diagnosing ETD (Kim, 2021). Further, using the ETDQ-7 to diagnose ETD or as an objective measure of ET function is limited, and additional research is needed to improve its validity and reliability (Andresen et al., 2021).

Thus, all potential symptoms that originate from ETD must be considered, and objective measures, such as pressure equalization tests and MEP measurements, should be used to confirm the diagnosis and evaluate treatment efficacy. In conclusion, the ETDQ-7 is a useful PROM for measuring ETD-related symptoms. However, its limitations and challenges need to be addressed, including the exclusion of vertigo as a possible symptom, the need to include voice changes as a potential symptom, the lack of clear criteria for normal and abnormal impedance audiometry results, and the limited use of the ETDQ-7 as an objective measure of ET function.

Developing new COAs for ETD

The need for new ETD COAs that address the limitations and challenges of biomarkers and PROMs

Although current BMs and PROMs for ETD provide valuable information, they have several limitations and challenges. Further, current BMs for ETD, such as ME effusion, tympanometry, and acoustic reflectometry, have limitations concerning their diagnostic accuracy and might only sometimes correlate with symptom severity (Bluestone, 2018; Schilder et al., 2015). For example, a patient could have MEP within the normal limits but still experience symptoms of ETD. Developing new COAs for ETD is crucial for improving its diagnosis and management. By establishing COAs that incorporate a broad range of symptoms and objective measures, clinicians can better diagnose ETD, assess its severity, and evaluate the effectiveness of treatment options. Thus, novel COAs should accurately measure the various symptoms of ETD, including vertigo, and provide objective measures of ET function to manage this condition better.

Finally, developing new COAs for ETD should consider input from patients and clinicians to ensure they are relevant, reliable, valid, and objective measures of ETD-related symptoms (Hamrang-Yousefi et al., 2022). Such a practice can help ensure that new COAs improve the diagnosis and management of ETD and meet the needs of patients and clinicians. In conclusion, new, comprehensive COAs for ETD must be developed, for which strategies such as incorporating vertigo as a symptom, objective measures of ET function, digital health technologies, and input from patients and clinicians can help.

Review of recent research on the development of new COAs for ETD

Lu et al. (2022) developed and validated the Eustachian Tube Function Scoring System (T-ETDQ), a questionnaire that comprises nine items that assess the symptoms and impacts of ETD. These items cover a range of symptoms, including pressure or stuffiness in the ears, pain or discomfort, hearing difficulties, ear ringing, and noises or popping sounds when blowing the nose or swallowing. The questionnaire also evaluates the impact of ETD on daily activities, concentration, mental stress, and sleep. Each item is rated on a scale from 1 (no problem) to 7 (severe problem), with a score of 4

indicating a moderate problem. The T-ETDQ score is calculated by totaling the scores for each item, with a cutoff of 26 indicating the presence of ETD. This study has demonstrated the clinical value of the T-ETDQ as a diagnostic tool for ETD, offering a useful and reliable COA for clinicians to monitor treatment efficacy and improve patient outcomes. However, like the ETDQ-7, the T-ETDQ does not include vertigo as a symptom, either.

A step-by-step guide to creating PROMs for vertigo in ETD

When managing ETD, PROMs can be valuable tools for evaluating how it affects quality of life and guiding treatment decisions. PROMs can complement objective measures by capturing patients' personal experiences and functional limitations, helping healthcare professionals comprehensively understand the illness and its impacts. PROMs refer to validated tools or questionnaires that gather insights into patients' health and quality of life from their perspectives. These tools serve various purposes, such as aiding in selecting treatment options, enhancing communication between patients and healthcare providers, assessing the quality of healthcare services, and supporting research (Johnston et al., 2022; Agarwal et al., 2021). The following section outlines the steps for incorporating vertigo-related questions into a PROM. Depending on the circumstances and goals, these steps might require adjustments or adaptations. Several references are available for consultation, guidance, and examples (Johnston et al., 2022; Agarwal et al., 2021). Developing a PROM entails the following stages:

1. Create an initial version of the PROM
To develop a set of questions for a new PROM for ETD, I will gather information from the relevant literature, draw on my clinical experience, and seek input from experts and patients. It is crucial to determine the appropriate format and response options for the PROM, such as Likert scales, visual analog scales, and yes/no questions. Also, I will consider the length and readability of the PROM to ensure that it is clear and concise. I propose using "21 Proposed Questions for a New Patient-Reported Outcome Measure (PROM) for Eustachian Tube Dysfunction (ETD)" as the basis for the initial version of my PROM and ePROM.

2. Test and validate my PROM
My PROM will be tested and validated to ensure its effectiveness by evaluating its reliability, validity, and responsiveness using a sample of ETD patients who experience vertigo. Reliability refers to how consistent and stable a PROM is over time and between evaluators. Validity assesses how well the PROM measures what it intends to determine and reflects the intended construct. Responsiveness examines whether the PROM can detect changes in the construct over time or after an intervention. Various statistical techniques can be used to assess these psychometric properties, such as Cronbach's alpha, test-retest correlation, factor analysis, correlation with other measures, determination of effect size, and analysis of receiver operating characteristic curves.

3. Revise and finalize my PROM accordingly
Based on the results, I will then make the necessary revisions and finalize my PROM. I might modify or remove certain items, adjust response options, or provide additional instructions or explanations in my PROM if needed. My PROM's development process and psychometric properties must be documented in a report or publication.

Digital health technologies: Developing ePROMs for ETD

Managing ETD is challenging due to the absence of a universally accepted diagnostic standard or an assessment method to determine its severity. Various approaches have been used, including pneumatic otoscopy, impedance audiometry, nasal endoscopy, and evaluation of patient-reported symptoms. However, these methods have limitations and inconsistencies (McCoul, 2020). In contrast, ePROMs are a more standardized and dependable means of gauging a patient's experience and overall outcomes in ETD.

ePROMs are digital versions of PROMs that can be accessed and completed using electronic devices, including personal smartphones, tablets, and laptops (Rosenberg et al., 2023). An ePROM system is software or a platform that allows patients to complete PROMs electronically, such as through a web-based or mobile application. An ePROM system can also provide data storage, analysis, visualization, and feedback features. Several types of ePROM systems are available for various purposes and settings.

We can develop a web-based application that allows individuals with ETD to complete the ETDQ-7 and other PROMs conveniently online. This app also teaches users about the causes and symptoms of ETD and its diagnosis and treatment options. The collection and analysis of PROMs are the main goals of this application in improving ETD patient care and outcomes. It also encourages patient self-management and joint healthcare provider-patient

decision-making. Unlike other, more general ePROM systems, our application can be customized to different domains and measures. For instance, it can incorporate the Patient Reported Outcomes Measurement Information System (PROMIS), a comprehensive range of standardized PROMs encompassing physical, mental, and social health aspects (HealthMeasures, 2023). ePROM systems can benefit patients and providers. They can boost patient engagement, empowerment, satisfaction, and self-management and improve communication, decision-making, quality, and provider research. However, there are obstacles to implementing and using an ePROM system, such as technical issues, privacy concerns, cost considerations, and user acceptance. Thus, their feasibility, usability, and effectiveness must be evaluated before being adopted in practice (Rosenberg et al., 2023).

New COAs should consider the use of digital health technologies, such as smartphone applications and wearable devices, to monitor ETD-related symptoms and objective measures, provide real-time data on symptom severity and treatment effectiveness, and improve patient engagement (Almario, 2017; Mitchell & Kan, 2019; Mosshammer, 2021; Park et al., 2015; Tong, 2018). To this end, an ePROM could be a smartphone app that collects patient-reported health status, symptoms, and quality of life data. ePROMs can facilitate the creation of PROMs for ETD. ePROMs allow researchers to gather patient-reported data efficiently and accurately, improving existing PROMs or guiding the development of new ones. These advances, in turn, can increase our understanding of the experience and ultimately enhance the quality of care provided to patients with ETD or other medical conditions. Before being implemented, ePROMs must undergo content validity and a rigorous psychometric evaluation, including an evidence-based and statistical assessment of their validity and reliability. Further, their usability should be tested to examine the platform and user interface (Rosenberg et al., 2023).

I suggest developing a smartphone application that allows patients to self-monitor their ETD-related symptoms and provides real-time feedback on treatment efficacy. The application should include a symptom diary, quality-of-life questionnaire, and educational module on ETD. Recent research has shown promising results in the development of new COAs for ETD, including the incorporation of objective measures; the consideration of comorbidities, such as LPR and vegetative symptoms; and the use of digital health technologies (Kim, 2015; Roland, 2004; Rosenberg et al., 2023; Sánchez-Manso et al., 2022; Thompson & Amedee, 2009) (Table 1).

Specifically, to validate the direct relationship between ETD and cardiovascular symptoms, I intend to develop new PROMs and ePROMs that incorporate these symptoms, such as bradycardia and hypertension (Sánchez-Manso et al., 2022; Thompson & Amedee, 2009). Capturing patient-reported experiences can provide novel insights, especially into underexamined areas. These developments can potentially improve the accuracy of the diagnosis of ETD and the assessment of treatment responses, ultimately enhancing patient outcomes and quality of life. However, further research is needed to validate and refine these new COAs and ensure their effectiveness in clinical practice.

Conclusion

ETD is a common condition that can significantly affect patients' quality of life. The development of BMs and COAs can increase the accuracy of the diagnosis and assessment of the severity of ETD and treatment efficacy. However, less focus has been placed on incorporating vertigo as a symptom in recent COAs for ETD, necessitating further research in this area. Some studies have added vertigo as an outcome measure, rendering it a potential symptom for inclusion in future COAs for ETD. Based on recent research, new COAs for ETD can be improved by adding objective measures, considering such comorbidities as LPR and vegetative symptoms, and using digital health technologies.

Future research should focus on validating and refining new COAs, determining the potential of BMs, and developing more effective treatments for ETD. Also, efforts should be directed toward establishing user-friendly digital health technologies to improve patient self-monitoring and feedback regarding treatment efficacy. Further, these new COAs can complement clinical trials and aid in developing novel treatments for ETD. By advancing our understanding of ETD and building more effective tools for its diagnosis and treatment, we can ultimately improve the lives of the millions of individuals affected by this condition.

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Category	Brief Symptom Description	Question Number	Question	Severity (0 to 7)	Frequency
Primary symptoms	Ear fullness or pressure	1	Do you often feel a sense of fullness or pressure in your ears?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Tinnitus	2	Do you frequently hear a ringing, buzzing, or other noise in your ears that isn't coming from an external source?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Hearing difficulties	3	Do you often experience difficulties in hearing, such as muffled sounds or temporary mild to moderate hearing loss?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Ear pain or headache	4	Do you feel pain or discomfort in your ears or have a headache? Can you describe the nature of the pain (dull ache, sharp ache, stabbing)?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Popping or clicking sensation	5	Do you regularly experience popping or clicking sensations in your ears, especially when swallowing, yawning, or chewing?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Dizziness or balance problems	6	Do you often have problems with balance or experience dizziness?	0 (None)- 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Ear itching sensation	7	Do you frequently experience an itching sensation in your ears?	0 (None)- 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
Secondary symptoms	Sleep quality	8	Have you noticed any changes in your sleep patterns or quality that aren't related to external factors, such as caffeine or medication?	0 (None)- 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Appetite changes	9	Have you experienced changes in your appetite since experiencing ETD symptoms? Are you eating more or less than usual?	0 (None)- 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Hoarseness	10	Have you noticed changes in your voice quality or experienced a hoarse voice?	0 (None)- 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Energy levels	11	Do you frequently feel fatigued or experience decreased energy levels unrelated to your sleep or activity?	0 (None)- 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Stress or anxiety	12	Does dealing with ETD often make you feel stressed or anxious?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Nausea or vomiting	13	Do you frequently experience nausea, vomiting, or other gastrointestinal symptoms, especially in relation to dizziness or vertigo?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Globus sensation	14	Do you often feel like there is a lump or something stuck in your throat?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never

Table 1: *Proposed questions for a new patient-reported outcome measure (PROM) for Eustachian tube dysfunction (ETD).*

Tertiary symptoms	Reflux symptoms	15	Do you often feel bitterness in your mouth, sputum, or cough, especially upon waking up?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Facial pain and pressure	16	Do you frequently experience pain or a feeling of pressure around your face, especially near the ears and sinuses?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Bradycardia	17	Have you felt your heartbeat unusually slow, especially after dizziness or ear discomfort?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Breathing difficulties	18	Have you felt short of breath without any strenuous activity recently?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Sweating episodes	19	Have you had sudden sweating episodes, possibly related to your symptoms?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Blood pressure change	20	Have you noticed any abrupt changes in your blood pressure, possibly tied to your ear issues?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never
	Other vegetative/autonomic symptoms	21	Have you experienced unexpected physical reactions that you think may be related to your symptoms?	0 (None) - 7 (Extreme)	Always, Often, Sometimes, Rarely, Never

Table 1: *(Continued) Proposed questions for a new patient-reported outcome measure (PROM) for Eustachian tube dysfunction (ETD).*

Conflicts of Interest

The authors declare no conflict of interest.

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