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Review article

Meniere's disease: Pathogenesis, treatments, and emerging approaches for an idiopathic bioenvironmental disorder

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ABSTRACT

Meniere's disease (MD) is a severe inner ear condition known by debilitating symptoms, including spontaneous vertigo, fluctuating and progressive hearing loss, tinnitus, and aural fullness or pressure within the affected ear. Prosper Meniere first described the origins of MD in the 1860s, but its underlying mechanisms remain largely elusive today. Nevertheless, researchers have identified a key histopathological feature called Endolymphatic Hydrops (ELH), which refers to the excessive buildup of endolymph fluid in the membranous labyrinth of the inner ear. The exact root of ELH is not fully understood. Still, it is believed to involve several biological and bioenvironmental etiological factors such as genetics, autoimmunity, infection, trauma, allergy, and new theories, such as saccular otoconia blocking the endolymphatic duct and sac. Regarding treatment, there are no reliable and definitive cures for MD. Most therapies focus on managing symptoms and improving the overall quality of patients' life. To make significant advancements in addressing MD, it is crucial to gain a fundamental understanding of the disease process, laying the groundwork for more effective therapeutic approaches. This paper provides a comprehensive review of the pathophysiology of MD with a focus on old and recent theories. Current treatment strategies and future translational approaches (with low-level evidence but promising results) related to MD are also discussed, including patents, drug delivery, and nanotechnology, that may provide future benefits to patients suffering from MD.

1. Introduction

Meniere's Disease (MD) is a debilitating hearing and balance disorder, characterized by episodic vertigo, fluctuating, progressive hearing loss, tinnitus, and aural pressure in the diseased ear (Harcourt et al., 2014). Despite being first documented over 150 years ago by French Physician Prosper Meniere, the cause of MD remains unknown. The prevalence of MD has been shown to deviate between 17 and 200 per 100,000 across various countries (Nakashima et al., 2016). This variation can be attributed to methodological and diagnostic differences across regions. A Finnish study of over 1000 patients demonstrated that the average age of onset for MD symptoms was 44 years old (Pyykkö et al., 2013). Hence, on average, MD is a disorder that affects those in their later stages of life, and with an ageing global population, the prevalence of MD is projected to largely increase.

MD poses a significant socio-economic burden due to several direct and indirect costs (Becker-Bense et al., 2019b). Most of these costs fail to be adequately characterized and addressed, exacerbating the challenges associated with MD as a progressive and chronic condition (Basura et al., 2020a; Becker-Bense et al., 2019a; Millennie et al., 2021). MD can place a burden on healthcare systems as patients often require multiple consultations, tests, medications, and treatments leading to increased direct costs. Besides, indirect costs relate to loss of productivity and work absenteeism (Tyrrell et al., 2016). MD can severely impact patients'

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quality of life (Millennie et al., 2021; Talewar et al., 2020) due to the unpredictable nature of the disease, leading to physical discomfort, emotional distress, and reduced social interactions (Arroll et al., 2012; Tyrrell et al., 2017; Yardley et al., 2003). Research costs are also needed to be addressed. Pursuing more efficient management and therapeutic strategies for MD involves ongoing research, clinical trials, and the development of new treatment options. These research endeavors incur costs that contribute to the overall economic impact of the disease. Further research is required in this field to better evaluate the costs and socio-economic burden of MD.

In terms of classification, MD is often characterized as 1) Meniere's syndrome, in which a known or established cause leads to symptoms, such as head trauma or infection such as neurotropic viruses; or 2) Meniere's disease, where there is an idiopathic (unknown) cause leading to symptoms (Committee on and Equilibrium, 1995; Lopez-Escamez et al., 2015). In this review, both conditions will be referred to as the more common Meniere's disease (MD) to avoid ambiguity. Further, based on its symptoms which can either be biased towards hearing or balance dysfunction, MD is often categorized into: (a) cochlear or (b) vestibular MD (Committee on and Equilibrium, 1995). With regards to clinical symptoms, according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) classification, which was updated by the Barany Society's Classification Committee, there are two types of MD: definite MD and probable MD (Fig. 1). This classification is currently used for the diagnosis of MD in clinical practice.

It is worth noting that most cases of MD are sporadic, meaning they occur in patients with no family history of the disorder. (Frejo et al., 2016, 2017). By contrast, approximately 10% of cases are classified as familial MD, meaning there is documented family history of MD. (Perez-Carpena and Lopez-Escamez, 2020; Requena et al., 2014). Some of the candidate genes found in sporadic MD subjects include *SLC26A4, CLDN14, GJB2, ESRRB*, and *USH1G* (Gallego-Martinez et al., 2019, 2020). Moreover, several genes have been identified to play a role in several unrelated families, namely *DTNA, FAM136A, PRKCB, DPT, SEMA3D* (Martín-Sierra et al., 2016, 2017; Requena et al., 2015), *TECTA* (encoding Tectorin Alpha; autosomal dominant) (Roman-Naranjo et al., 2022), *OTOG* (encoding Otogelin; recessive) (Roman-Naranjo et al., 2020), and *MYO7A* (encoding Myosin VIIA; digenic inheritance) (Roman-Naranjo et al., 2021). Because of this, genetic testing (such as exome and genome sequencing) is likely to be valuable for sporadic and familial diagnosis in the future (Gallego-Martinez and Lopez-Escamez, 2020). In addition, gene therapy has potential as a future therapeutic for vestibular disorders and MD (Lopez-Escamez et al., 2018; Mei et al., 2021).

Besides genetic variables, there are several environmental factors associated with MD, such as exposure to loud noise. Prolonged exposure to loud noise, whether from recreational or occupational activities, can damage the delicate structures of the inner ear, leading to hearing loss, tinnitus, and other symptoms associated with MD (Young, 2013). In fact, some studies have suggested that exposure to loud noise may be a significant risk factor for developing MD, particularly in people who are already genetically predisposed to the condition. Other environmental factors that have been linked to MD include pathogens (viral or bacterial infections), allergens, head trauma, changes in air pressure, and ambient particulate matter exposure (Han et al., 2017; Simo et al., 2015; Williams et al., 1987). For example, some people with MD report that changes in altitude or air pressure can trigger their symptoms, and there is some evidence to suggest that exposure to certain viruses, such as human cytomegalovirus (CMV) (Dean et al., 2019), may increase the risk of developing the condition. One potential mechanism by which environmental factors may contribute to the development of MD is damage to the sensory receptors of the inner ear (Dulon et al., 1987).

Researchers are still working to understand the complex interplay between genetic and environmental factors (and epigenetics) in the development of MD. Despite the lack of a definitive understanding of the causes of MD, there are several strategies that can help manage the symptoms of the condition. One of the most effective approaches is to reduce exposure to environmental triggers such as loud noise and changes in air pressure. This may involve using hearing protection when working in noisy environments and other recreational activities that may expose the ears to loud noise. In the current review paper, we will discuss MD pathology, and current and potential therapeutic approaches using novel technologies. This paper consists of Section 1: introduction; Section 2: discussing the etiology and pathophysiology of MD, focusing on previously- and recently-mentioned theories on the disease pathology; Section 3: reviewing currently-available therapeutic options and discussing novel strategies for MD treatment. Drug delivery and nanotechnology in MD research are also reviewed; Section 4: proposing some potential approaches to treating MD, with low-level evidence though. Section 5: Gaps, challenges, and opportunities in MD research are noticed; Section 6: conclusion.

2. Etiology and pathophysiology of acute attacks

Aetiologically, MD is considered a multifactorial disorder, with the involvement of several genetic and/or bioenvironmental factors (Lopez-Escamez et al., 2015; Millennie et al., 2021). Despite being first

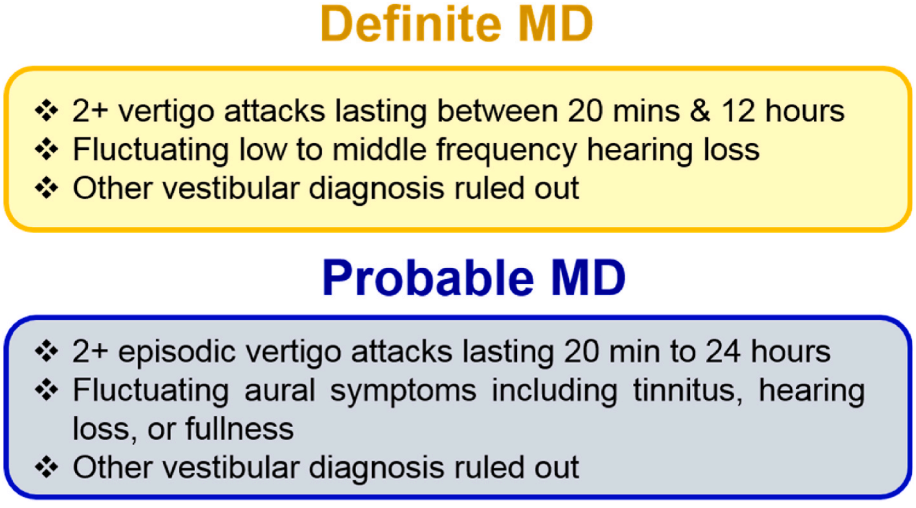

Fig. 1. Current classification of Meniere's disease based on clinical symptoms. Classified by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), updated by the Barany Society's Classification Committee.

described by Prosper Meniere in 1861, the cause of MD remains unknown (Mirza and Gokhale, 2017). Researchers have established the histopathological hallmark of MD in endolymphatic hydrops (ELH), which is an increase of the inner ear fluid, endolymph, within the membranous labyrinth of the inner ear (Fig. 2). This was discovered independently by two research groups in 1938, Hallpike and Cairns in the United Kingdom and Yamakawa in Japan, providing histologic evidence of ELH in cadaveric temporal bone specimens (Hallpike and Cairns, 1938; Yamakawa, 1938). Although ELH is believed to play a central role in the pathogenesis of MD, it is not yet known how this arises. ELH is believed to result from altered endolymph homeostasis, which may occur due to increased endolymph production, endolymph malabsorption, or a combination of both. A popular theory put forward by William Gibson and Kaufman Arenberg is the "drainage theory" (Gibson Md and Kaufman Arenberg, 1997). Although normal cochlear endolymph regulation involves local radial flow regulated by the stria vascularis, excessive volumes in the case of ELH result in longitudinal endolymph flow from the cochlea to the endolymphatic sac to achieve endolymph homeostasis. When the endolymphatic sac (ES) and duct (ED) is functional it can clear away the excess endolymph with no problems, but in the case of a Meniere's patient who may have a dysfunctional ES and ED, endolymph may build up in the sinus of the ED, resulting in significant overflow. This overflow might push open the valve of Bast, a biological membrane separating the utricle and the saccule, causing a hydrodynamic pressure shunt in the pars superior, producing a mechanical stimulus to the utricle, and displacing the cupula of the horizontal canal in a given direction. When the excess endolymph volume is cleared, the stretched crista is reduced in size, and the direction of nystagmus reverses (Gibson, 2010). Several factors may lead to ELH in the first place (Fig. 3a), including the anatomical variation of the ES and ED or vestibular aqueduct, genetic abnormality of endolymph control, and exogenous factors as mentioned above, such as infection (viral or bacterial) and associated inflammation, allergic reaction, and trauma (Mirza and Gokhale, 2017; Paparella and Djalilian, 2002). A more recent theory of interest parallels Benign Paroxysmal Positional Vertigo (BPPV), which is where otoconia become trapped in the semicircular canal and cause vertiginous symptoms. Although it is undisputed that BPPV arises from utricular otoconia, few have inquired as to what happens when saccular otoconia becomes dislodged. In this theory proposed by Jeremy Hornibrook, ELH in MD may be caused by saccular otoconia (ear stones) being detached, blocking the ductus reuniens within the labyrinth, causing pathological endolymph build-up and overflow (Hornibrook and Bird, 2017).

Several theories have been proposed to explain cochleovestibular dysfunction and acute attacks related to ELH. However, several of these contradict clinical and experimental findings, as discussed below. The main theories include a membranous labyrinth rupture, hydraulic pressure fluctuations, an ischemic attack, and acute inflammation or resultant temperature changes (Fig. 3b). These theories are discussed in more detail below.

2.1. The membrane rupture theory

The oldest pathophysiological theory of cochleovestibular dysfunction in MD is a membranous labyrinth rupture (Schuknecht, 1976). Here, an excessive build-up of endolymph causes membranous labyrinth bloating, distention, and subsequent rupture. Since the membranous labyrinth separates endolymph from perilymph, its tear results in the mixing of sodium and potassium fluids and ionic disturbance of inner ear hair cells and afferent neurons. This grossly disrupts their resting membrane potential, which governs neural spontaneous and dynamic electrical activity. The rupture theory emerged after discovering membrane tears in post-mortem temporal bones within the inner ears of MD patients, as well as Reissner's membrane ruptures in the labyrinth of guinea pigs after acute artificial endolymph injections. However, there was some conjecture as membrane ruptures did not occur in all cadaveric ears, and previous guinea pig experiments involving endolymph injections occurred at non-physiological rates (e.g., 3000 nl/min) (Valk et al., 2006). By contrast, slower injection rates in guinea pigs did not find any obvious tears in Reissner's membrane (Brown et al., 2013a). Additionally, it is possible for these post-mortem membrane ruptures to be an artifact of the histological process. Moreover, nystagmus in MD patients did not match with those of guinea pigs in the membrane rupture model. MD patients had nystagmus that transitioned from the paralytic (away from the affected ear) to irritative (toward the affected ear) direction during vertigo onset, whereas guinea pigs displayed the opposite result - nystagmus shifting from the irritative (toward) to the paralytic (away) direction (Brown et al., 1988; McClure, 1982). Another important piece of evidence was the finding that experimental ruptures of the membranous labyrinth typically resulted in a non-recoverable loss of cochlear function, which does not align with quantitative findings in MD patients. Here, clinical electrophysiological and audiological results reveal little to no changes in cochlear function during vertigo attacks, which is in stark contrast to experimental findings. Further evidence against the membrane rupture theory was gained through vestibular reflex testing. In 2010, Manzari et al. measured the ocular Vestibular Evoked Myogenic Response (oVEMP) in MD patients during both acute vertigo attacks and in the quiescent (attack-free) stage (Manzari et al., 2010). The oVEMP is a myogenic response from the Inferior Oblique (IO) driven by the vestibular ocular reflex (VOR) – one of the fastest reflexes in the nervous system, with a latency of ~5ms spanning a 3-neuron arc. Importantly, the oVEMP provides a robust, non-invasive measure of dynamic vestibular function. Results indicated enhanced oVEMP potentials during an acute attack, compared to the symptom-free 'Quiescent' stage, which suggests elevated vestibular sensitivity during vertigo attacks. These results have been reproduced by several other research groups and do not align with the experimental data of the rupture model, which showed vestibular nerve function losses in guinea pigs following KCl perfusion (Kingma and Wit, 2010). Further research is needed to probe the relationship between membrane ruptures and inner ear dysfunction related to MD, but recent experimental and clinical evidence taken together suggest membrane ruptures are unlikely the cause of symptoms in MD.

2.2. Endolymphatic hydraulic pressure theory

Another theory, which has gained acceptance recently, is the idea that cochleovestibular dysfunction is caused by endolymphatic pressure changes or hydraulic pressure modulations within the membranous labyrinth of the inner ear. This is likely triggered by an abrupt increase in endolymph volume and pressure due to altered endolymph homeostasis, such as increased production or reduced absorption of endolymph. The theory suggests that the accumulation of endolymph bloats the membranous labyrinth and displaces the sensory structures within the labyrinth, leading to altered auditory and vestibular sensitivity and function. Recent experimental findings have found support for the hydrostatic pressure theory. Brown et al. demonstrated reversible modulations of cochlear compound action potential (CAP[2]) measures within the guinea pig's inner ear during controlled microinjections of artificial endolymph into the membranous labyrinth (Brown et al., 2013a, 2013b). When the injection volume was increased by 100–150 per cent, a progressive decrease in CAP function was observed, followed by a rapid recovery of cochlear function and simultaneous modulation in utricular nerve function with recovery. Moreover, multiple recovery events were seen in some cases within the same experiment, and importantly morphological analyses revealed no sign of a membrane rupture. Furthermore, injections of fluorescein isothiocyanate-dextran (FITC-dex) in artificial endolymph into the scala media of the guinea

[2] The collective electrical response generated by a group of nerve fibers or neurons when stimulated simultaneously.

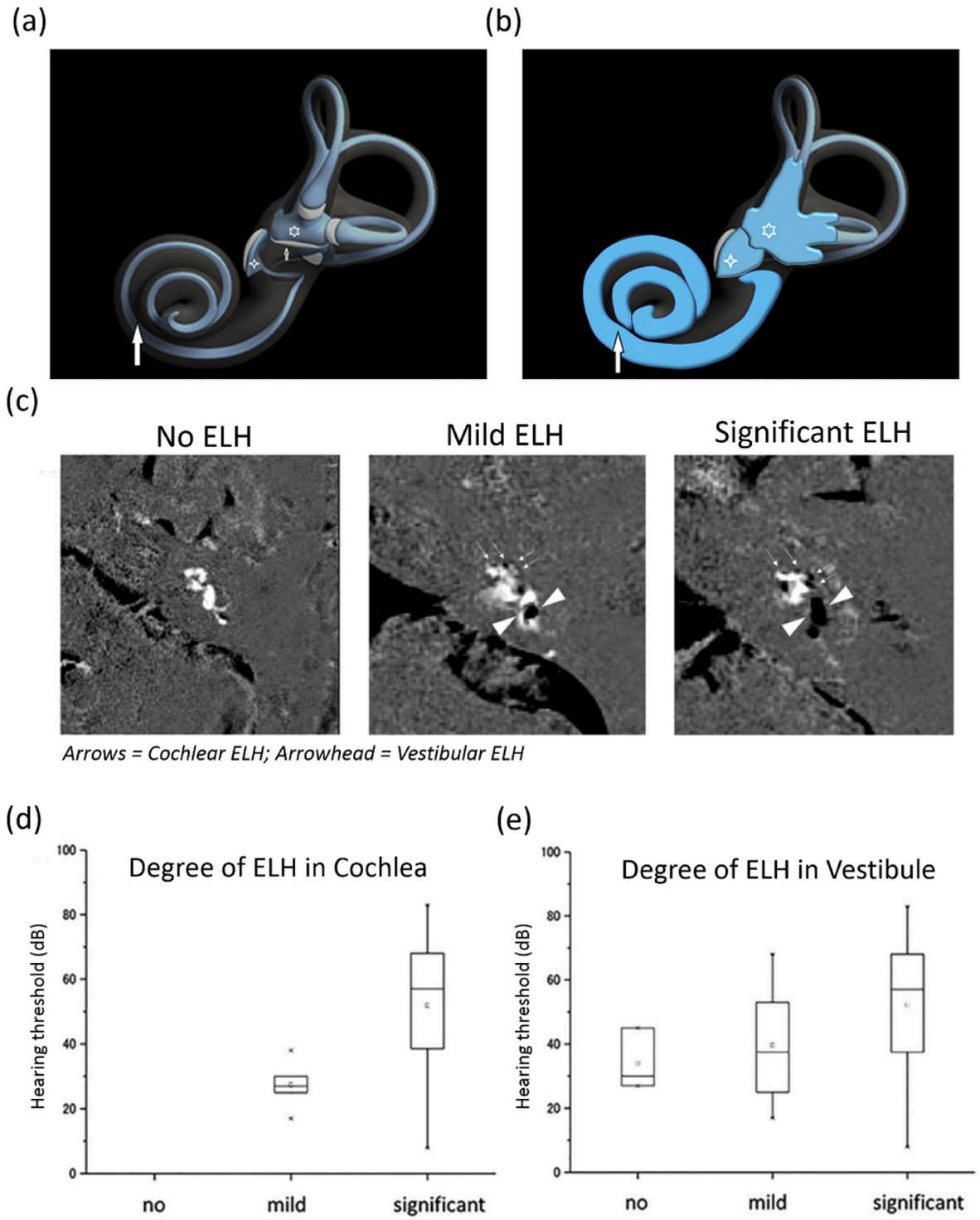

Fig. 2. Representation of Endolymphatic Hydrops (ELH) in the inner ear and functional hearing status (thresholds). **(a)** Normal endolymphatic structures including the utricle ( ), saccule ( ), cochlear duct ( ), and the macula of the utricle ( ). **(b)** Hydropic endolymphatic structures with the distension of the utricle, saccule, ampullae of the semicircular ducts, and the cochlear duct. Reproduced with permission (Connor and Pai, 2021). **(c)** Structural images of the inner ear showing no, mild, and significant ELH, after intravenous injection of an ordinary dose of gadolinium (Gd) contrast agents, using 3 T (3 T) magnetic resonance imaging (MRI). Arrows and arrowheads indicate ELH in the cochlea and in the vestibule, respectively. **(d)** The degree of ELH in the cochlea and **(e)** in the vestibule against hearing thresholds for combined pure-tones of 500 Hz, 1000 Hz, and 2000 Hz, presented as the mean ± SE. Reproduced with permission (Morimoto et al., 2017).

pig cochlea modulated vestibular sensitivity, with subsequent Light Sheet Fluorescence Microscopy (LSFM) revealing endolymph movement into the utricle, semicircular canals, and endolymphatic duct and sac following micropump volumes of >2.5 μL, with no fluid movement into the perilymphatic compartments, suggesting no membrane rupture had occurred in these experiments (Brown et al., 2016). These results provide important first-order support for a non-membrane rupture theory of acute attacks in MD, such as sudden functional changes via the opening of a morphological valve, separating the utricle and saccule (the "utriculosaccular duct"), which efficiently relieves hydraulic pressure

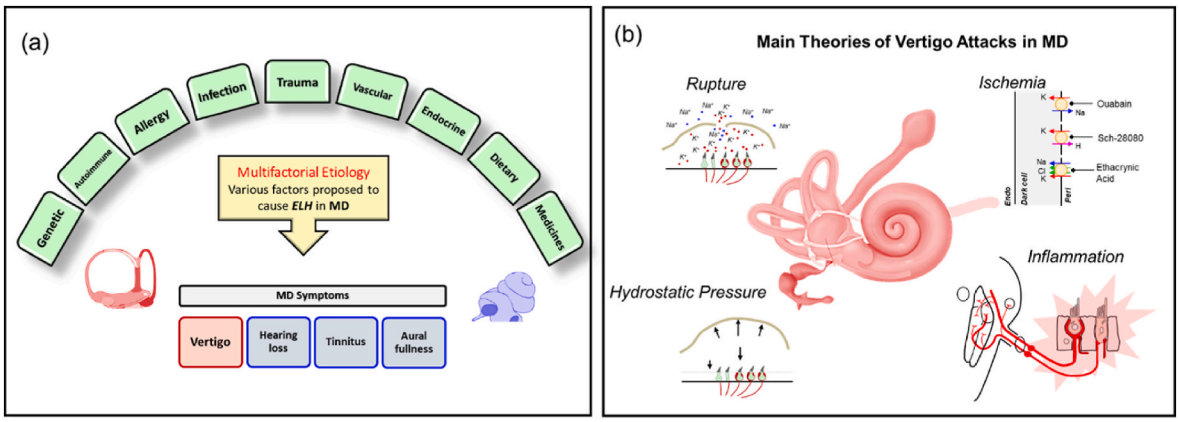

Fig. 3. MD etiologies, symptoms, and pathophysiological mechanisms. (a) Various biological and bioenvironmental factors are proposed to be involved in ELH and MD etiology, leading to the cardinal symptoms of MD – vertigo, hearing loss, tinnitus, and aural fullness. (b) Schematic hydropic labyrinth with four main proposed theories to explain the pathophysiology of acute attacks related to ELH, including membrane rupture, ischemia, hydrostatic pressure, and inflammation.

(whether hydrostatic or hydrodynamic) in the pars inferior (the cochlea and saccule) while increasing pressure in the utricle and canals (Brown et al., 2016; Li et al., 2021a). More recently, low-frequency biasing of the vestibular system resulted in a modulation of vestibular mechanosensory hair cell output and enhancements in vestibular nerve function (Ahmadi et al., 2021; Pastras et al., 2020b), which align with elevated vestibular ocular reflex responses or Vestibular Evoked Myogenic Potentials (VEMPs[3]) reported in the clinic around the time of acute attacks. These results are also supportive of the pressure theory of acute attacks documented by Brown et al. and others.

2.3. Ischemic theory

Ischemia has also been suggested as a possible cause of MD-like symptoms, and its reversible nature is a candidate for MD pathogenesis and acute attack (Foster and Breeze, 2013). The inner ear, with its terminal-type vascular supply and stable metabolic requirements, is a potential target for hemodynamic instability, leading to modulations in inner ear sensitivity following local labyrinthine ischemia, which may then result in vertigo attack (Pirodda et al., 2010). Although the underlying mechanism is unclear, several channels and pumps may be involved. These include the Na^+-K^+-2 C l-cotransporter, Na^+-K^+-ATPase, K^+ (KCNQ/KCNE) channels, and gastric type H^+-K^+-ATPase pump in the inner ear, which are responsible for potassium ion buffering and homeostasis (Pirodda et al., 2011).

The effect of altered K^+ homeostasis on inner ear function has been tested experimentally in animal models using loop diuretics and hypoxia; however, results are mixed. For example, in one case, I.V. injection of 20–100 mg/kg ethacrynic acid (EA) (inhibiting the Na^+-K^+-2Cl-cotransporter) led to a dramatic reduction in the vestibular-ocular reflex (VOR[4]) (Kusakari et al., 1979; Levinson et al., 1974) and caloric response (Mathog, 1977), followed by a 20-30-min recovery. On the contrary, other studies found that long-term exposure to EA had no effect on the VOR nor caused morphological changes in the vestibule [24]. In other studies, the systemic administration of the loop diuretic ethacrynic acid (20–100 mg/kg) suppressed auditory evoked potentials in under 20 min; however, only small changes were observed in the vestibular short-latency evoked potentials (VsEP[5]) after several hours of monitoring (Elidan et al., 1986; Lee and Jones, 2018). Overall, it remains to be seen whether an ischemic-like phenomenon might cause spontaneous vertigo in MD, although this mechanism could explain the rapid alterations in inner ear function with recovery, as seen in MD.

2.4. Inflammatory theory

Another theory used to explain the cause of acute attacks and inner ear dysfunction in MD is an acute inflammatory response which results in changes to the labyrinthine blood supply. This may be caused by an infection, such as viral labyrinthitis. Here, an inflammatory event may be associated with abrupt changes in labyrinthine blood flow, resulting in small fluctuations in inner ear temperature, affecting hair cell and nerve function, leading to a spontaneous vertigo attack. Recent results have demonstrated that the sensitivity of vestibular hair cells and afferents can be modulated via heat pulsed infrared stimulation, by as little as one-degree Celsius changes in temperature (Rabbitt et al., 2016). Furthermore, similar ultraviolet stimulation of otolithic vestibular hair cells resulted in the mechanical activation of hair bundles and the initiation of graded receptor potentials in vitro. This mechanism has been linked to the generation of heat following light absorption by intracellular chromophores, which relax gating springs and open mechanosensitive gating channels. Although it is unknown how much the temperature of the inner ear changes as a result of acute inflammatory activity, -inflammation certainly causes changes in blood flow rate and vascular permeability, which is likely to alter the temperature of the inner ear (Hirose et al., 2014; Zhang et al., 2015). The sensitivity of the vestibular system to temperature fluctuations suggests that sudden vertigo attacks may be induced directly by labyrinthine temperature changes. Further experimental investigations are needed to examine the veracity of this theory using in vivo animal models.

3. Current and future therapies

Since the pathophysiology of MD remains unknown (Basura et al., 2020c), current treatments focus on the reduction and management of symptoms in the acute or intermittent phase (Fig. 4) of the disease rather than targeting the root cause of inner ear dysfunction (Alrowythy et al., 2020; Hoskin, 2022; Swain, 2023). In the acute stage, anti-vertigo drugs

[3] A type of neurophysiological test used to assess the function of the otolithic organs in the inner ear and the vestibulospinal reflex pathways.

[4] A fundamental neurophysiological mechanism that enables humans and many other animals to maintain stable vision and visual focus during head movements.

[5] A neurophysiological test used to evaluate the function of the vestibular system. This test evaluates the early neural processing of vestibular signals from both the semicircular canals and otolithic organs.

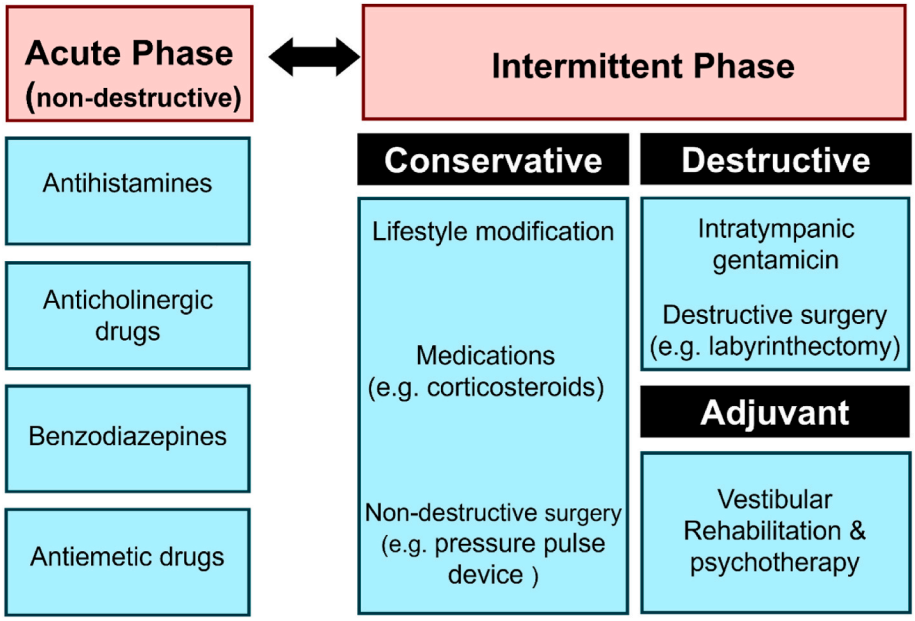

Fig. 4. Treatment options available for the acute and intermittent phases of MD.

or vestibular suppressants are typically used, while in the intermittent phase, clinicians prescribe various types of medical and surgical treatments based on disease progression and severity (Swain, 2022), classed as conservative and destructive, respectively (Table 1).

3.1. Acute phase treatment

It is essential to manage MD symptoms in the acute phase, which are characterized by spontaneous vertigo of sudden onset, often lasting 20 min up to 24 h (Yilmaz et al., 2019). Standard pharmacological treatments are anti-vertigo drugs or vestibular suppressants, which include antihistamines, anticholinergics, and benzodiazepines.

Antihistamines are of interest since the central and peripheral vestibular systems contain histamine receptors which have been shown to modulate vestibular afferent output and sensitivity. The vestibular nuclei contain H_1, H_2, and H_3 histamine receptors, which come from the tuberomammillary nucleus from the posterior hypothalamus, whereas the peripheral vestibular system contains pre-synaptic H_1 on the type-II hair cell and H_3 receptors on the post-synaptic calyx and bouton afferent (Soto and Vega, 2010). A common antihistamine drug to treat vertigo in Meniere's patients throughout Europe, the United Kingdom, Canada, and Latin America is Betahistine. For example, a prospective study in the UK demonstrated that ~92% of doctors prescribe Betahistine to treat Meniere's disease (Smith et al., 2005). By contrast, Betahistine is less commonly used in the United States and was once approved for use in vertigo treatment but was subsequently withdrawn due to a lack of evidence of its activity (Dyhrfjeld-Johnsen and Attali, 2019). More common antihistamines for vertigo control in the US include dimenhydrinate (Alrowythy et al., 2020), diphenhydramine, promethazine (Bahmad Jr, 2020), meclizine, and its derivate cyclizine (Soto and Vega, 2010). The mechanism of action of antihistamines on vertigo control and vestibular suppression in Meniere's disease is not fully

Table 1
Comparison of common guidelines for the treatment of MD. The order of treatment options is from mild to aggressive stages.

Guidelines	International consensus (ICON) on treatment of Ménière's disease (Nevoux et al., 2018)	The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) (Basura et al., 2020c)	European Position Statement on Diagnosis, and Treatment of Meniere's Disease (Magnan et al., 2018)	Guidelines of the French Otorhinolaryngology-Head and Neck Surgery Society (SFORL) (Nevoux et al., 2017)	Japanese Clinical Practice Guideline of Meniere's disease and delayed endolymphatic hydrops 2nd ed. Tokyo: Kanehara Shuppan, 2020 edited by the Japan Society for Equilibrium Research (Iwasaki et al., 2021)
Conservative	• Lifestyle modifications and medical treatments (lifestyle counselling, low salt diet, betahistine, diuretics, vestibular rehabilitation, psychotherapy, and pressure pulse treatment) •Intratympanic corticosteroids •Endolymphatic sac surgery	•Diet restrictions (salt, alcohol, and caffeine) •Medications (diuretics, anti-vertigo, anti-histamines, and betahistine) •Vestibular rehabilitation and hearing aids •Intratympanic steroids •Endolymphatic sac decompression	•Lifestyle modifications and medical treatments (diet change, betahistine, and diuretics) •Intratympanic steroids •Endolymphatic sac surgery	•Lifestyle modifications and medical treatments (lifestyle counselling, betahistine, diuretics, oral corticotherapy, intratympanic corticosteroids) •Surgical treatments (intratympanic ventilator tube, semicircular canal obliteration, and endolymphatic sac surgery) •Vestibular rehabilitation and psychotherapy	•Lifestyle modifications and medical treatments (avoiding (stress, excessive fatigue, and sleeplessness), diuretics, anti-vertigo drugs, vitamin B12, Chinese herbs, etc.) •Middle ear positive pressure treatment •Endolymphatic sac surgery •Intratympanic steroids •Betahistine (inconclusive results)
Destructive	•Intratympanic gentamicin in the case of hearing impairment •Vestibular neurectomy and labyrinthectomy with/without cochlear implantation	•Vestibular neurectomy and labyrinthectomy	•Intratympanic gentamicin •Vestibular neurectomy and labyrinthectomy	•Intratympanic gentamicin •Vestibular neurotomy and labyrinthectomy	•Intratympanic gentamicin therapy •Vestibular neurectomy

understood but is believed to involve inhibition of peripheral and central vestibular afferent activity, which are possibly hyper-excited during an acute attack. Antihistamines also act as vasodilators and increase labyrinthine blood flood and microcirculation, given their powerful antagonistic effect on the H_3 on inner ear blood vessels (Cass et al., 2019). The ability to dilate blood vessels may be associated with increased inner ear permeability and improvements in endolymphatic hydrops and functional inner ear health (Soto and Vega, 2010).

The next anti-vertigo treatment of interest is the anticholinergic drug (Iwasaki et al., 2021). This treatment has a neurobiological basis, as Nicotinic Acetylcholine receptors (nACh-R) and Muscarinic Acetylcholine receptors (mACh-R) are highly expressed in the peripheral and central vestibular system, such as via the vestibular efferent system, which make contacts on type II hair cells, and calyx and bouton afferents. Moreover, electrophysiological studies have revealed that the activation of nACh-R and mACh-R increases the firing rate and sensitivity of the peripheral vestibular system in a complex manner. Specifically, activation of ionotropic nACh-R modulates the sensitivity of the vestibular afferents on a fast time scale on the order of several milliseconds, whereas slower metabotropic mACh-R activation results in modulation of vestibular output on the order of tens to hundreds of milliseconds. Additionally, cholinergic input has been identified on all vestibular nuclei in the Central Nervous System (CNS), and animal model experiments have demonstrated that acetylcholine delivered to the mammalian vestibular nuclei results in its activation. Furthermore, the introduction of the mACh-R antagonist, Scopolamine, resulted in reduced activation of vestibular nuclei following acetylcholine (Soto and Vega, 2010). Hence, it is not surprising that mACh-R antagonists such as Scopolamine and Atropine are commonly used as drugs to treat vestibular dysfunction, such as dizziness, vertigo, and motion sickness in Meniere's disease, where it is hypothesized that the peripheral and central vestibular systems are hyper-excited. These agents may turn down their activity. Although the direct mechanism of action of drugs such as Scopolamine is not clear, it is likely to involve antagonism of mACh-Rs at the level of the vestibular nuclei and/or vestibular efferents, which reduce excitation of primary and secondary vestibular neurons.

The final class of drugs used to treat vertigo is benzodiazepines, which act on the gamma amino butyric acid (GABA)-A receptor pathway in the central vestibular system. GABA is the most abundant inhibitory neurotransmitter in the CNS, which modulates and reduces the excitability of neurons likely responsible for vestibular symptoms such as vertigo and dizziness, hence their classification as vestibular suppressants. Specifically, benzodiazepines, like Diazepam, directly bind to the α and γ subunits of the GABA-A receptor and act as a positive allosteric modulator (Griffin et al., 2013) by inducing a conformational change in the chloride channel that hyperpolarizes the cell and causes inhibitory action throughout the CNS. The inhibitory action of benzodiazepines also makes them advantageous in treating mood disorders associated with Meniere's disease, such as depression and anxiety, with dual-action treatment potential.

Several types of drugs are used to reduce symptoms associated with acute attacks, such as nausea and vomiting. These include antiemetic drugs, such as metoclopramide, which antagonizes dopamine D_2 receptors in the chemoreceptor trigger zone of the medulla oblongata, thereby suppressing nausea and vomiting at the level of the central nervous system (ALBIBI and McCALLUM, 1983).

Anyone following the Meniere's disease literature will know steroids are a common treatment to help the management of symptoms such as hearing loss and vertigo attacks. However, despite their widespread use, there is limited data to support the use of systemic steroids, and no published clinical trial examining the effectiveness of prednisone for vertigo management. The more common treatment method of intratympanic steroid application is also controversial, as study comparisons have important differences such as drug duration, dose, patient cohort, follow-up, and delivery (Cope and Bova, 2008). Despite this, there have been several studies (Okada et al., 2017; Wei, 2013).

3.2. Intermittent phase treatment

Various types of medical and surgical treatments are available to reduce or prevent symptoms in MD. A suitable therapeutic option should be selected by clinicians based on disease progression and severity. Moreover, if specific remedies are unsuccessful, more aggressive strategies can be recommended. Therapeutics are categorized into conservative or destructive approaches. Examples of conservative approaches include lifestyle changes, non-destructive pharmacological interventions such as corticosteroid use, and non-ablative surgery, such as ventilation tubes. Destructive techniques can be pharmacological or surgical and include administering ototoxic agents such as gentamicin, or ablative surgery such as a labyrinthectomy. In addition, there are some adjuvant treatments, such as vestibular rehabilitation and psychotherapy, which are not yet included as main therapeutic methods but are often welcome as a supplement to existing treatment regimes.

Vestibular rehabilitation (a kind of exercise to manage dizziness and balance issues) is beneficial to remedy chronic balance disorders (Ahmadi et al., 2021; Basura et al., 2020b; Rezaeian et al., 2023) and would be more effective in patients with stable conditions, not with episodic vertigo and acute attacks (Yilmaz et al., 2019). Behavioral therapies and vestibular rehabilitation programs have been recommended in recently published guidelines (Yilmaz et al., 2019). They can be customized for different patients, as the ones with additional sensory deficiency, visual issues, or neurologic problems indicate delayed recovery (Yilmaz et al., 2020). Mental conditions even affect treatment outcomes, both non-surgical and surgical, and it is shown that psychological support is also required for better results (Yokota et al., 2016). Thus, the as-mentioned therapeutic approaches are suggested to be highly considered in new guidelines. To reach this aim, more controlled-trial studies are required to provide more compelling evidence.

3.2.1. Conservative treatment

3.2.1.1. Changes in lifestyle. To reduce the disease-related symptoms, multiple lifestyle changes are suggested. Due to the potential association between stress and MD attacks, it is recommended that the sufferer engage in moderate exercise, avoid overworking, and reduce strenuous activities (Onuki et al., 2005). Additionally, having a low-sodium diet (1500–2300 mg/day: recommendation based on the American Heart Association (Basura et al., 2020c)) and suitable water intake can assist in stable vasopressin levels and inner ear/endolymph homeostasis. However, the research regarding salt restriction in the diet is inconclusive, and further research is needed (Shim et al., 2020). The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) recommends imposing restrictions on caffeine, alcohol, and tobacco, due to their vasoconstrictive and diuretic properties which may exacerbate hydrops (Basura et al., 2020b; Magnan et al., 2018). Another parameter that has been given less attention is glucose intake. Gioacchini et al. showed that there might be a direct association between chronic hyperglycemia/hyperinsulinemia and the dysfunction of the peripheral vestibular organ (Gioacchini et al., 2018). It has also been shown that the saccule, as the major labyrinthine structure influenced by endolymphatic hydrops, possesses a high number of insulin receptors (De Luca et al., 2020b). Therefore, the role of glucose intake cannot be discounted in MD pathophysiology. Further research is required to find the link between glucose and insulin biomarkers, hydrops, and MD symptoms.

3.2.1.2. Medications. A range of non-ablative drugs can be used to relieve MD symptoms, including anti-vertigo drugs, such as Betahistine, as discussed above, vitamins such as B-complex Vitamins, Vitamin C & D, and other non-traditional medicines such as Chinese herbs. In addition, diuretics, such as isosorbide, furosemide, amiloride, and

hydrochlorothiazide have been used to lower the intra-labyrinthine pressure associated with endolymphatic hydrops (Bahmad Jr, 2020; Iwasaki et al., 2021).

3.2.1.3. Anti-vertigo drugs. Despite standardized use, anti-vertigo drugs, like Betahistine, have shown controversial results. Studies reveal these drugs might be effective in short-term treatment (less than three months), but are likely inefficient for long-term therapy (more than three months) (Iwasaki et al., 2021). Nonetheless, Betahistine is frequently used throughout Europe and many other countries, and the standard dose in the clinical setting is 48 mg during 3–6 months (Magnan et al., 2018). As mentioned above, Betahistine has a dual action, based on its action as both an H_1 agonist and H_3 antagonist, acting on sensory neurons and blood vessels as both a neuromodulator and a vasodilator, respectively. A recent study indicated the effectiveness of Betahistine in decreasing the falling risk for the sufferers (Liu et al., 2020a). Although there is limited evidence to consider Betahistine a sufficient treatment (Devantier et al., 2020), European (Magnan et al., 2018) and American (Basura et al., 2020b) (latest version) clinical guidelines have recommended it to prevent vertigo attacks and disease aggravation. Considering the need for long-term Betahistine administration for better therapeutic outcomes, new formulations may be required (Parfenov et al., 2020). Modified-release Betahistine (48 mg once a day) could be the new, safe, and convenient option, which provides an initial rapid and sustained release profile, as opposed to Betaserc® (24 mg twice a day) (Parfenov et al., 2020). Another related drug of promise is diphenidol. Despite its unknown mechanism of action, diphenidol has shown vestibular suppression, with effects such as reduced vertigo (short-term therapy), likely via its interactions with mACh-R; however, its efficacy has not been proved (Iwasaki et al., 2021; Soto and Vega, 2010).

3.2.1.4. Diuretics. Another commonly used first-line therapy for Meniere's disease is the use of diuretics. At its simplest, diuretics block specific ion transporters along the kidney nephron to increase the excretion of various salt ions, such as Na^+, K^+, Cl^-, Ca^{2+}, and Mg^{2+}. This is followed by the excretion of water, which follows the movement of salts. This, in turn, decreases plasma volume and reduces blood pressure, which is believed to help to stabilize endolymph pressure and volume within the hydropic ear, thereby minimizing the frequency and severity of acute attacks and inner ear dysfunction. Thiazides are the most common class of diuretic drugs used in the treatment of Meniere's disease, for example, hydrochlorothiazide (often abbreviated as HCTZ). Thiazides exert their action on the distal convoluted tubule of the nephron, by specifically competing for the chloride site on the Na–Cl-cotransporter. This impairs Na^+ transport and reabsorption in the kidney lumen and results in Na+ excretion, as well as Cl-, K+, and H_2O. Long-term effects of thiazides include reduced Ca^{2+}, but increased Mg^{2+} secretion, as well as increased reabsorption of urea in the proximal convoluted tubule, resulting in increased plasma uric acid levels and the potential for gout or arthritis. Hence, this medication must be well monitored to avoid this side effect. Thiazides, such as HCTZ, are often prescribed in conjunction with potassium-sparing diuretics, such as Triamterene (Foster, 2015). This combination is advantageous as it often avoids the requirement for K+ supplementation, which may be necessary with Thiazides alone. K+ supplementation may theoretically exacerbate hydrops, which is the overproduction of K^+-rich endolymph. Potassium-sparing diuretics work in the distal convoluting tubule and the collecting duct, where they inhibit Na^+ reabsorption by directly blocking the epithelial sodium channel (ENaC) on the lumen and therefore prevent the concomitant exit of potassium from the principal cell (potassium-sparing diuretic). Another class of potassium sparing diuretics is the aldosterone antagonist, such as spironolactone, which are antagonists of the mineralocorticoid receptor, in which biological targets like aldosterone cannot bind. However, relatively recent work has demonstrated that the mechanism involved in improvements in MD outcomes from salt reduction is likely due to increased aldosterone (Miyashita et al., 2017; Mori et al., 2017). Hence, any drug which reduces aldosterone, like spironolactone, may counter this benefit. Therefore, the combination of Thiazides and potassium-sparing diuretics, not antagonizing aldosterone, may be of utility.

Another class of diuretics used in the second line of therapy for Meniere's disease treatment is the Carbonic anhydrase inhibitor (Basura et al., 2020b). These work in the proximal convoluted tubule by inhibiting the carbonic anhydrase enzyme, thereby preventing the formation of carbonic acid (H_2CO_3), which is needed for the reabsorption of Na^+ via H^+. Acetazolamide is an example carbonic anhydrase inhibitor, which is used to reduce intraocular pressure in glaucoma. Given that hydropic pressure is a theorized cause of dysfunction associated with MD, Acetazolamide could also help alleviate ELH, like glaucoma.

Osmotic diuretics may also be used in the treatment of MD such as glycerol, urea, mannitol, and isosorbide. These work in the proximal convoluted tubule and loop of Henle of the nephron and function to increase the solute concentration within the tubules and therefore cause water to be retained within the tubules, preventing its reabsorption. That is, when there is a higher concentration of solute within a particular area of the tubule lumen, more water will be drawn to this region instead of out into the bloodstream. This will reduce plasma volume and blood pressure.

An example of osmotic diuretic use in MD is Isosorbide (90 ml/day), which can be used as an alternative to other diuretics to prevent vertigo attack recurrence (Iwasaki et al., 2021). This drug has been used for MD treatment to decrease the volume of endolymph without recurrence (Kakigi et al., 2004; Matsubara et al., 1985; Padoan, 2003; Yamashita et al., 2023). It has also shown good outcomes in reducing symptoms and improving hearing clinically (Kakigi et al., 1995; Kitahara et al., 1982; Larsen, 1984) and has been used as drug therapy for MD in Japan and Korea (Kim et al., 2014; Kitahara et al., 1982; Yamazaki et al., 1982). Although the oral administration of the drug was efficient in clinical settings, it has indicated several adverse effects (Kakigi et al., 2006; Nozawa et al., 1995). Another option is intratympanic administration, on which Kim, 2020 have focused and investigated in an animal model. It reduced hydrops and preserved symmetrical vestibular function in chronic and acute models, respectively, indicating a new therapeutic candidate for MD.

In regard to another diuretic, glycerol has been used in a concentration of 10% per weight volume for a duration of six months (0.5 g/kg once a day for two consecutive days every 15 days). This resulted in the improvement of vertigo and tinnitus (Scarpa et al., 2020a). Glycerol is an osmotic agent and draws water out of the scala media, thereby reducing hydrops (Scarpa et al., 2020a). Most notably, glycerol is used in the Glycerol Test, which is a simple and rapid method for identifying and diagnosing endolymphatic hydrops in MD. Here, 1.5 g/kg of glycerol is ingested in early MD patients with sensorineural hearing loss, and pure-tone audiometry measurements are compared before and after ingestion. Glycerol routinely results in significant improvement of hearing thresholds, likely due to the osmotic improvement of endolymph pressure and volume.

3.2.1.5. Corticosteroids. Corticosteroid drugs are common medications used in the treatment of MD. Common examples include dexamethasone, methylprednisolone, and triamcinolone (Salt and Plontke, 2020). It is claimed that corticosteroids, with a not-well-known mechanism, are capable of decreasing inflammation while increasing labyrinth circulation. Moreover, steroids have shown some impacts on the salt metabolism in the inner ear (Bogaz et al., 2017; Chi et al., 2011). They may be taken orally or intravenously for systemic administration or locally via intratympanic injections into the middle ear space. However, studies have revealed intratympanic (IT) delivery is associated with higher drug concentrations to the ear, compared to systemic administration. For this

reason, IT corticosteroids are often used to reduce the severity and frequency of vertigo spells in MD. Unfortunately, standard IT corticosteroids only provide short-term relief, necessitating repeated injections. To solve this problem, researchers are developing sustained-release corticosteroids, such as the use of corticosteroids in hydrogels, which may be inserted into the middle ear space for more sustained and stable pharmacokinetics. Interestingly, different formulations of corticosteroids have vastly different pharmacokinetics, such as dexamethasone vs. dexamethasone phosphate (Salt et al., 2019).

Intratympanic steroid administration is also another option (Iwasaki et al., 2021) by which the vascular endothelium is stabilized, the blood flow of the cochlear increases (anti-inflammatory influence), and fluid homeostasis is preserved (Millennie et al., 2021). However, unfortunately, this treatment is effective only for weeks to months, requiring repeated injections (Froehlich and Lambert, 2020). The treatment is deemed the second-line therapy by the International Consensus (ICON) on Meniere's disease therapy when medical therapies have failed (Nevoux et al., 2018). Moreover, it has been suggested that Intratympanic steroid therapy is effective for the refractory period of the disease (de Cates and Winters, 2021; Patel et al., 2016). Methylprednisolone and dexamethasone are commonly prescribed, of which 0.4–0.8 ml is injected into the space of the middle ear every three to seven days (once to four times) (Basura et al., 2020b).

3.2.2. Non-ablative surgery

3.2.2.1. Ventilation tubes. In 1966, Tumarkin was the first to suggest that the insertion of a grommet or ventilation tube may improve MD symptoms (Tumarkin, 1966). This stemmed from the belief that Eustachian tube obstruction created negative pressure in the middle ear cavity, resulting in abnormal endolymphatic pressure within the inner ear and the development of ELH and MD. Subsequent studies reported improvements in outcomes with the insertion of transtympanic ventilation tubes, which prevented vertigo in 82% of patients (Montandon et al., 1988), which may suggest this therapy may have some effect on modulating endolymphatic hydrops within the inner ear. Following this, Kimura and Hutta (1997) confirmed reduced endolymphatic hydrops development, which they theorized was due to pressure release into the middle ear and/or increased oxygenation of both the middle and inner ear. Furthermore, a larger, recent study demonstrated long-term ventilation tube placement was effective in controlling vertigo in 62% of patients (Marcelli et al., 2021). Overall, these works suggest that the use of a ventilation tube or grommet is a safe and effective management option in definite, intractable MD, and importantly may be used to prevent more invasive procedures.

3.2.2.2. Middle ear positive pressure treatment. For patients failing to respond to conventional first-line therapies in MD, such as Betahistine and diuretics, alternative approaches may be used. One example is the use of positive pressure delivered to the middle ear. The idea that pressure changes can assist a Meniere's sufferer is not a new one. For example, Tumarkin's pressure relief theory in 1966, and subsequent reports that ambient pressure changes cause modulations in hearing thresholds in MD patients in the 1970–80s. Specifically, the use of 'local overpressure' was used to improve hearing outcomes in the advanced stages of MD (Densert and Densert, 1982). Since this time, there have been several devices and patents which aim to deliver positive pressure into the middle ear space to treat MD. Examples include US patent no. 4754748 (Antowski, 1988), and US patent no. 4757807 (Densert and Densert, 1988). More recently, Densert et al. introduced the Meniett pressure pulse generator in the US patent no. 6159171 (Densert et al., 2000). Since this time, the Meniett device has been used in a range of studies as a treatment approach for Meniere's disease (Ahsan et al., 2015; Densert et al., 1975, 1997; Ingelstedt et al., 1976; Shojaku et al., 2011). In most cases, the Meniett device delivers pressure to the middle ear directly via a transtympanic ventilation tube, whilst in other cases, pressure is delivered directly to the ear canal. Interestingly, serval studies have revealed improvements in MD patients with the Meniett device. That is, a systematic review and meta-analysis of 18 studies from literature sources between 1996 and 2012 revealed improvements in MD patient outcomes (Ahsan et al., 2015). Specifically, 8 of the studies reported hearing improvements, whilst 6 studies demonstrated reduced vertigo attacks after Meniett treatment (Ahsan et al., 2015). Despite these improvements, the mechanism of action of the Meniett device is still unclear. However, low-pressure air pulses through the tympanic membrane onto the round window are believed to reduce endolymph pressure. Specifically, it is hypothesized that the Meniett device stimulates endolymph flow (or longitudinal flow) within the inner ear to normalize pressure and help MD relieve symptoms (van Sonsbeek, 2015). The Meniett Device is currently approved by the Food and Drug Administration in the United States but lacks approval from the Pharmaceuticals and Medical Devices Agency in Japan. Although the meta-analysis and systematic review revealed positive outcomes with the use of the Meniett device in MD patients, it is important to note there have been contrary findings (Ahsan et al., 2015; Clyde et al., 2017; Mattox and Reichert, 2008b; Russo et al., 2017)and more research is needed to ascertain the effectiveness and the mechanism of action of such a device.

3.2.2.3. Endolymphatic sac surgery. As endolymph overaccumulation and/or malabsorption may lead to MD, sac decompression and drainage might assist in relieving excess endolymph, and as a result, reducing hydrops and compensating for inner ear dysfunction. This procedure aims at reducing pressure in the area of the endolymphatic sac (Bento and Lopes, 2019). Inserting silastic sheeting and administering high-dose steroids into the sac can increase the effectiveness of this procedure (Kitahara, 2018; Sajjadi and Paparella, 2008). Endolymphatic sac decompression is performed based on several methods (Bento and Lopes, 2019) such as sac shunting, sac drainage, sac decompression, and duct blockage (Li et al., 2021b). During endolymphatic sac drainage and duct blockage, endolymphatic pressure is reduced following sac opening (sac drainage) (Portmann, 1991), and the endolymph coming from the sac decreases following duct blockage by small titanium clips (Bento and Lopes, 2019; Saliba et al., 2015). These two were assessed for their efficacy in MD treatment, and the findings indicated their potential to decrease endolymphatic hydrops (Jiang et al., 2020). Moreover, sac decompression has been performed alone and with shunting. The results indicated the effectiveness of both techniques with no considerable difference (Sood et al., 2014). Importantly, endolymphatic sac surgery preserves the function of the inner ear and can be an option against vertigo attacks prior to more destructive surgery (Iwasaki et al., 2021; Sood et al., 2014). Nonetheless, a shortage of evidence still exists regarding the efficiency of the surgery in providing symptom relief for MD patients (Devantier et al., 2019b).

3.2.2.4. Plugging surgery (semicircular canal occlusion). In plugging surgery, cupular movement and receptor cell stimulation are inhibited through semicircular canal occlusion (Li et al., 2021b). Following a mastoidectomy, three bony semicircular canals are exposed, and a fenestra is formed. Afterwards, the fenestration is covered by bone wax, and the incision is closed (Li et al., 2021b). Two types of surgery are performed, notably posterior and superior semicircular canal occlusions. These offer relief from vertigo and also maintain hearing and otolith function; however, imbalance might be lasting in a minority of patients (Beyea et al., 2012; Welgampola et al., 2008). Initially, this type of surgery was used for the treatment of benign paroxysmal positional vertigo (BPPV) (Parnes and McClure, 1990). Subsequently, it was applied to intractable peripheral vertigo, and in a study, 75% of the patients with vertigo were healed (Charpiot et al., 2010). Another study using triple semicircular canal plugging demonstrated that vertigo was

substantially or completely improved (Yin et al., 2008).

Importantly, this type of surgery has been performed in patients with intractable MD. Gill et al. (2021) demonstrated plugging surgery can be an alternative to vestibular sectioning, with low levels of morbidity, reduced hospitalization periods, long-term symptomatic control, and hearing preservation. In regard to triple semicircular canal plugging (TSCP) in intractable MD, it has recently been shown that vertigo control and hearing preservation were nearly 99% and around 70%, respectively. This indicates TSCP has high operation efficacy and safety. (Li et al., 2021b; Zhang et al., 2016). It is worth mentioning that steroids, like dexamethasone, are suggested to be used after TSCP to reduce the possibility of inflammation and hearing loss following the procedure (Lyu et al., 2020).

3.2.3. Destructive medicine

Finally, if conservative medical and non-ablative approaches provide no assistance for patients, destructive treatments may be used to control debilitating vertigo attacks. The first ablative approach is usually the ototoxic medicine, gentamicin, followed by destructive surgeries such as a labyrinthectomy, vestibular neurectomy, and succulotomy. Additionally, patients may also suffer from hearing impairment and might require cochlear implantation.

3.2.3.1. Gentamicin (aminoglycoside). If the above measures do not improve vertigo attacks, an ablative therapy may be used. One such example is a chemical labyrinthectomy of the vestibular system via intratympanic gentamicin (El Shafei and Qotb, 2020; Liu et al., 2020b). Gentamicin is a well-known, FDA-approved class of aminoglycoside (AG) antibiotic. AGs work as antibacterial drugs that inhibit protein synthesis in certain gram-negative bacteria (Krause et al., 2016). Other AGs include streptomycin, neomycin, tobramycin, kanamycin, and amikacin, with clinical uses such as tuberculosis, pneumonia, meningitis, endocarditis, sepsis, and conjunctivitis. Besides their effective antimicrobial activity, all AGs have toxic side effects on the inner ear and kidneys. While toxicity to the kidneys is reversible, toxicity to the inner ear is not. This drug-induced damage to the inner ear is termed 'ototoxicity'. Interestingly, specific AGs are more ototoxic to the cochlea, such as neomycin, kanamycin, and amikacin, whereas others such as gentamicin are predominately vestibulotoxic. For this reason, gentamicin is used to treat vestibular dysfunction and vertigo attacks in intractable Meniere's disease by chemical ablation of the mechanosensory hair cells, preventing aberrant signals in the postsynaptic afferent neurons. However, the precise mechanism of action of vestibular damage is not clear. The proposed mechanism of AG transport into hair cells is hypothesized via the apical mechanoelectrical transduction (MET) channel, endocytosis on apical and basal membranes, TRP channels, or ATP receptors. Additionally, damage to the hair cells is proposed to occur via directly blocking the MET channel, cell-induced apoptosis, the formation of Reactive Oxygen Species (ROS), inhibition of mitochondrial protein synthesis, and reduced ATP (Huth et al., 2011). Besides its potent ototoxic activity on hair cells, gentamicin has also been shown to also affect the primary afferent neurons at the vestibular neuroepithelia, with specific vulnerability to the central and striola zone neurons in mammalian preparations (Sultemeier and Hoffman, 2017). Specially, gentamicin results in non-apoptotic loss of vestibular calyces, which does not seem to be mediated by hair cell loss. Both these ablative pathways make gentamicin an ideal candidate for treating intractable vertigo in Meniere's sufferers, which is not responsive to other conservative therapies. By damaging the hair cells and primary afferents at the vestibular neuroepithelium, gentamicin prevents aberrant signals or vertiginous information being sent to the brain.

Local intratympanic administration of AGs into the inner ear has the advantage of improved pharmacokinetics and drug delivery, when compared to oral and systemic routes, and reduced adverse effects, such as avoiding kidney damage and ototoxicity to the intact, contralateral ear. For this reason, gentamicin is routinely administered to MD patients via intratympanic injection. Two protocols are often used: shot-gun and titration. "Shot-gun" involves a large up-front dose of gentamicin, such as three injections per day for four consecutive days (Carey, 2004), whilst "Titration" involves spacing out of the doses over a longer time, such as one injection per week for four weeks, or until there was evidence of inner ear damage (Carey, 2004). Interestingly, both protocols showed no disparity in vertigo control; however, the "Shot-gun" approach resulted in much more hearing deterioration than the "Titration" method (57% vs 19%, respectively) (Carey, 2004). Note, there is still no accepted guideline regarding dose and duration for intratympanic gentamicin administration (Yaz et al., 2020). Despite this, researchers continue to search for the optimal dosing regimen. For example, Ishizaki et al. used a once-off dose of 26.7 mg/ml (Magnan et al., 2018), whereas Molnar et al. used a smaller dose of 8 mg/ml two to four times on alternate days, which seemed to improve vertigo attacks without a high risk of hearing loss (Molnár et al., 2020). Others report better hearing improvement with 10 mg of gentamicin every two weeks (Scarpa et al., 2019).

Overall, gentamicin has shown effectiveness in treating debilitating vertigo attacks and vestibular dysfunction in patients with intractable MD. However, several caveats exist such as the possibility of causing irreversible hearing impairment and uncertain dosing regimens. It may also be a risky therapy in patients with bilateral MD, as ablating both labyrinths may result in permanent, irreversible vestibular hypofunction, with gait, gaze, and postural instability, with no ability for compensation from the contralateral labyrinth.

3.2.4. Destructive operations

Destructive surgery such as vestibular neurectomy and labyrinthectomy is used in intractable MD when other treatments have given no relief (Li et al., 2021b). The International Consensus (ICON) on the treatment of Meniere's disease (Nevoux et al., 2018), the guideline of French Otorhinolaryngology Head and Neck Surgery Society (SFORL) for Meniere's disease (Nevoux et al., 2017), and the European position statement on diagnosis and treatment of Meniere's disease (Magnan et al., 2018) recommend surgical procedures after the failure of noninvasive treatment and take the surgical option into account as the last remaining option.

3.2.4.1. Labyrinthectomy. In this fully destructive surgery, neurosensory epithelia of the otoliths and SCCs are removed (Basura et al., 2020b), leading to irreversible ablation and impairment of the vestibular system. Since the cochlea is adjacent to the vestibular end organs, this procedure may lead to hearing impairment (Alrowythy et al., 2020). Therefore patients with moderate to extreme sensorineural hearing loss may benefit from labyrinthectomy (Liu et al., 2020b). This procedure has demonstrated good effectiveness in vertigo control, and a recent report indicated vertigo attacks were well controlled, and the life quality of the patients improved. Nonetheless, this type of treatment should be reserved for intractable vertigo in severe cases where other treatments have failed (Liu et al., 2020b; Yu et al., 2019). In comparison with vestibular neurectomy and endolymphatic sac surgery, labyrinthectomy, is a gold standard treatment which is superior in vertigo control (Yilmaz et al., 2020).

3.2.4.2. Vestibular/vestibulocochlear neurectomy. During vestibular neurectomy, vestibular nerves are surgically sectioned to prevent noxious vestibular signals from being sent to the central nervous system – which the brain interprets as vertigo (Sajjadi and Paparella, 2008). Importantly, this type of treatment only involving a vestibular nerve section conserves hearing and may be chosen after failures in the other conservative treatments (Iwasaki et al., 2021; Lemnos et al., 2019). Nonetheless, some adverse effects can take place, such as cerebrospinal fluid leakage, meningitis, and epidural hematoma (Alrowythy et al.,

2020).

3.2.4.3. Sacculotomy. This procedure is used in patients with unilateral idiopathic endolymphatic hydrops, with intractable, severe episodic vertigo. During this surgery, a fenestra is formed in the stapes footplate or round window membrane to provide a permanent shunt for saccular drainage. Because of these surgical manipulations of auditory structures, cochlear dysfunction is a likely outcome (Bento and Lopes, 2019; Kinney et al., 1995; Wielinga and Smyth, 1989), and hence it is best used in patients with established sensorineural deafness that cannot be helped by a hearing aid (McDonald and Cody, 1994). When compared with endolymphatic sac decompression, sacculotomy showed better results in the control of vertigo, albeit with significant hearing deterioration (Soheilipour et al., 2015). Hence, it is no surprise a cochleosacculotomy is indicated for the elderly with hearing loss (Yilmaz et al., 2020). Overall, this procedure has been shown to control vertigo in approximately 80% of patients, and importantly hearing can often be maintained or improved (McDonald and Cody, 1994).

Due to the progressive, fluctuating nature of MD, with phases of acute attacks and quiescence, researchers must be cautious in their interpretation of novel therapies for MD, given that symptoms have the capacity to fluctuate (and improve) naturally over time. Because of this, potential therapies must be assessed in large sample sizes, under rigorous testing conditions. Recently, several promising future therapies have been identified; however, many of these are undergoing recruitment or active status in clinical trials.

3.2.5. Drug therapeutics in clinical trials

Several clinical trials are underway to find effective drug therapies for MD, including local or systemic administration. Early results have been promising, and some studies have passed phase three and four clinical trials. To determine the safety and efficacy of interventions in the treatment of MD, clinical trials are often performed as randomized, double-blind, placebo-controlled trials. Many drug formulations are delivered systematically, via oral or intravenous routes, such as Montelukast, Betahistine, Famciclovir, and Venlafaxine. For example, Venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), which is classically used in the treatment of mood disorders such as depression and anxiety (Liu et al., 2017), has shown promise in reducing vertigo attacks and is currently recruiting in a randomized, placebo-controlled, double-blind, crossover, pilot trial for the treatment of MD (gov Identifier: NCT04218123). Moreover, there are several therapeutic approaches being studied in phase 4 such as Montelukast, previously an FDA-approved drug, known to help with allergies). Others include Betahistine, and Sildenafil (Viagra, vasodilator). Local drug interventions include stellate ganglion block, OTO-104, and pressure equalizer (PE) tubes/devices, such as devices such as the Meniett device. Of these, OTO-104, a steroid encapsulated in hydrogel, has attracted attention among researchers. However, after recent hype, it has been terminated after completing phase 3 clinical trials, due to negative results; gov Identifier NCT02612337.

Of all the interventions listed in Table 2, there are few non-pharmacological devices developed for MD treatment. A ventilation tube, which is at the clinical trial stage (NCT04835688), is a potential device and could be implanted following the myringotomy of the tympanic membrane (Yilmaz et al., 2019). In 1966, Tumarkin was the first doctor who introduced ventilation tubes as treatment alternatives (Tumarkin, 1966). Recently in a clinical study, Ogawa et al. (2015) reported that the ventilation tube could be advantageous and initially prevent invasive operations. Literature reviews have further demonstrated positive outcomes, with minimal invasiveness and a low rate of complications (Yilmaz et al., 2019). However, due to evidence shortage, the SFORL, ICON's guidelines, and the European Position Statement on Diagnosis and Treatment of Meniere's disease have not recommended this type of treatment (Magnan et al., 2018; Nevoux et al., 2017, 2018). All in all, it is worth performing this surgery owing to some reports with positive results and fewer complications (Yilmaz et al., 2019). Another device is the Meniett device, which works as a ventilation tube delivering controlled pressure pulses to the middle ear. This is theorized to help alleviate endolymphatic hydrops in the inner ear. However, it is not clear how low-amplitude pressure pulses would do this (Mattox and Reichert, 2008a; Russo et al., 2017). In practice, low-frequency or infrasonic tones delivered to the ear canal at non-damaging levels may produce a similar pressure modulation of the oval window (OW). Although this probably modulates the resting position of the basilar membrane, like low-frequency biasing (Pastras et al., 2020a), it will likely not influence the mechanics and function of the vestibular system, as most of the hydroacoustic energy passes through to the cochlea (Pastras et al., 2020a). Based on the experimental evidence, this would likely mean such a device would be ineffective at modulating vestibular function and symptoms, but rather would modulate auditory sensitivity via mechanical biasing. Other less studied devices include the Otoband (transcranial vibrating system), transcutaneous auricular vagus nerve stimulator (taVNS), and the mastoid oscillator. These have shown promise and are being clinically investigated. More systematic research is required to further demonstrate their potential for MD treatment. The TinniTool (Dismark@, Maur, Switzerland) is another device (Teggi et al., 2008), which operates on safe low-level laser therapy. It is assumed that laser irradiation with low intensity enhances cellular proliferation, ATP and collagen synthesis, growth factor release, and local inner ear blood flow, to trigger repair mechanisms (Teggi et al., 2008; Wang et al., 2019). Overall, MD device-based treatment can decrease vertigo symptoms with a positive impact on hearing status, with fewer sick days and improvements in functional levels. To analyze the advantages of this treatment, excess long-term follow-up studies are required (Wang et al., 2019). Further information related to other therapeutic methods, drugs, and devices can be found in Table 2 and at https://www.clinicaltrials.gov.

3.2.6. Drug delivery

Several delivery systems have been proposed for MD treatment including systematic, intratympanic, direct inner ear, and nano-based drug delivery routes, as shown in Table 3. Nonetheless, some of them (direct inner ear and nano-based drug delivery) have only shown potential for use in MD as an inner ear disease. Systemic drug delivery has demonstrated effectiveness in the management of inner ear disorders, such as MD (Zhang et al., 2022a). For instance, the corticosteroid prednisolone, taken orally in MD patients, demonstrated reduced frequency and periods of vertigo episodes by 50% and 30%, respectively (Morales-Luckie et al., 2005). Moreover, a meta-analysis showed oral administration of betahistine is safe and effective for vertigo treatment in MD (Nauta, 2014). However, conflicting results also suggest oral steroids) only produced temporary improvement for several months. Therefore, short-term oral steroid administration might be ineffective for hearing and/or vestibular improvement in MD patients (Fisher et al., 2012). These varied outcomes might be due to shortcomings of systemic delivery, such as the blood–labyrinth barrier (BLB) and low blood supply, preventing the absorption of effective drug concentrations in the inner ear tissue. If drug concentrations were to be increased in the bloodstream, this may lead to systemic toxicity (Zhang et al., 2022a). These disadvantages encouraged other delivery approaches., such as local drug delivery, specifically intratympanic (in the middle ear cavity) and direct inner ear drug delivery (intracochlear or intravestibular). The advantages of intratympanic (IT) administration are the delivery of greater concentrations of medications into the inner ear, slower drug release, and reduced side effects (Bird et al., 2007). However, IT administration can result in drug loss via the Eustachian tube and lymphatic absorption (Froehlich and Lambert, 2020), requiring multiple injections (Hu and Parnes, 2009). Another important parameter in the success of IT delivery is Round Window Membrane (RWM) permeability, which is varied in different patients and affects drug retention and

Table 2
Clinical trials (clinicaltrials.gov) related to new emerging therapeutic approaches for MD.

NCT Number	Title	Status	Conditions	Interventions	Mechanism	Phases
NCT04815187	Repurposed Use of Allergic Rhinitis and Allergic Asthma Drug to Reduce Vertigo and Hearing Loss in Meniere's Disease	Recruiting	Meniere's Disease, Allergic Rhinitis, and Vertigo	Drug: Montelukast Systematic intervention: One pill at night for 90 days	Leukotriene receptor antagonist	Phase 4
NCT02718846	Isobide Solution and Meniace Tablets Compared to Monotherapy with Meniace Tablets	Completed	Meniere's Disease	Meniace and Isobide Systematic intervention: 6 mg of Meniace tablets administered 3 times per day after meals and an initial dosage of 90 ml of Isobide solution administered orally 3 times a day after meals	Isobide: oral hyperosmotic diuretic Meniace: histamine H1 receptor agonist and a potent histamine H3 receptor antagonist	Phase 4
NCT01574313	Effect of Stellate Ganglion Block on Meniere's Disease	Completed	Vertigo and Meniere Disease	Procedure: local intervention via Stellate Ganglion Block (SGB) Active Comparator: Drugs: 0.25 mg fludiazine, 25 mg cephadol@ (diphenidol), and 200 mg kentons@ (tocopherol nicotinate).	SGB: sympathetic block via anesthetic injection in the neck	Phase 4
NCT00831688	Efficacy of Local Overpressure Treatment for Meniere's Disease	Completed	Meniere's Disease	Device: Meniett(C) device by MedTronic Local intervention	Positive pressure therapy	Phase 4
NCT00160238	Effects of Betaserc on Vestibular Compensation in Patients Suffering from Disabling Meniere's Disease and Having Undergone Vestibular Neurotomy	Completed	Meniere's Disease	Drug: Betahistine 24 mg twice a day (Betaserc) Systematic intervention	Histamine H1 receptor agonist and a potent histamine H3 receptor antagonist	Phase 4
NCT00145483	Sildenafil for Meniere's Disease	Completed	Meniere's Disease	Drug: Sildenafil Systematic intervention	Phosphodiesterase-5 (PDE5) inhibitor	Phase 4
NCT03664674	Phase 3 Study of OTO-104 in Subjects with Unilateral Meniere's Disease	Completed	Meniere Disease	Drug: OTO-104 (dexamethasone in glycol polymer, poloxamer 407) Intratympanic injection 12 mg dexamethasone	Anti-inflammation	Phase 3
NCT02768662	A 6-Month Extension Study of OTO-104 in Meniere's Disease	Terminated (Negative Efficacy Results from the recently completed Phase 3 study 104–201,506)	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 3
NCT02717442	Study of OTO-104 in Subjects with Unilateral Meniere's Disease	Terminated (Negative Efficacy Results from the recently completed Phase 3 study 104–201,506)	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 3
NCT02706730	A 6-Month Extension Study of OTO-104 in Meniere's Disease	Terminated (Negative Efficacy Results from the recently completed Phase 3 study 104–201,506)	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 3
NCT02612337	Study of OTO-104 in Subjects with Unilateral Meniere's Disease	Completed	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 3
NCT02158585	Study of Lamotrigine to Treat Meniere's Disease	Completed	Meniere's Disease, Meniere's Vertigo, Vertigo (Intermittent), and Vertigo (Aural)	Drug: Lamotrigine Systematic intervention 25 mg twice a day, 50 mg twice a day, and 100 mg twice a day during titration 150 mg twice a day for the 12-week study period 150 mg once a day for Week 1 of the taper 75 mg once a day for Week 2 of the taper	Antiepileptic	Phase 3
NCT01526408	Famvir for Treatment of Hearing in Unilateral Meniere's Disease	Terminated (House Research Institute (HRI) no longer	Meniere's Disease	Drug: Famciclovir Systematic intervention Six 250 mg pills orally for the first 7 days	Anti-herpetic with potent activity against Herpes Simplex Virus Types 1 and 2 (HSV-1 and HSV-2), Epstein-	Phase 3

(*continued on next page*)

Table 2 (*continued*)

NCT Number	Title	Status	Conditions	Interventions	Mechanism	Phases
		conducting research.)		One 250 mg pill twice a day for 77 days	Barr Virus (EBV), and Varicella-Zoster Virus (VZV)	
NCT01454726	Clinical Trial of Traditional Chinese Diaoshi Jifa Therapy of Meniere's Disease	Completed	Meniere's Disease	Other: Diaoshi Jifa Therapy (a well-known traditional Chinese Medicine approach to treating dizziness in patients with chronic diseases) plus the Western Medical Treatment Systematic intervention Western medical treatment: Ginkgo 20 ml once a day IV, Merision (betahistine mesylate) 6 mg three times a day orally	Diaoshi Jifa: finger press of the acupuncture points, massage of the acupuncture points, and dynamic manipulation of the acupuncture points (Sun et al., 2014). Ginkgo: antioxidant and vasoactive Merision: histamine H1 receptor agonist and a potent histamine H3 receptor antagonist	Phase 3
NCT04218123	Assessing the Efficacy of a Serotonin and Norepinephrine Reuptake Inhibitor for Improving Meniere's Disease Outcomes	Recruiting	Meniere's Disease	Drug: Venlafaxine Systematic intervention Daily oral intake 37.5 mg	Serotonin and norepinephrine reuptake inhibitor	Phases 2 and 3
NCT00802529	Transtympanic Gentamicin vs. Steroids in Refractory Meniere's Disease	Completed	Meniere's Disease	Drugs: Methylprednisolone and Gentamicin Intratympanic injection	Anti-inflammation	Phases 2 and 3
NCT03587701	Effects of Anakinra in Subjects with Autoimmune Inner Ear Disease	Recruiting	Autoimmune Inner Ear Disease, Corticosteroid-Resistant Autoimmune Inner Ear Disease (CR-AIED), and Corticosteroid-Resistant Meniere's Disease (CR-MD)	Drug: Anakinra Systematic intervention 100 mg/0.67 ml self-administered by patients daily	IL-1 receptor antagonist	Phase 2
NCT03325790	SPI-1005 for the Treatment of Patients with Meniere's Disease	Completed	Meniere's Disease	Drug: 200 mg SPI-1005 and 400 mg SPI-1005 (both used twice a day)	SPI-1005 (Ebselen): Glutathione peroxidase mimetic	Phase 2
NCT02740387	Open Label Study of OTO-104 in Subjects with Meniere's Disease	Terminated (Negative Efficacy Results from the recently completed Phase 3 study 104–201,506)	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 2
NCT02265393	A 1-Year Safety Study of OTO-104 in Subjects with Unilateral Meniere's Disease Located in United Kingdom	Completed	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 2
NCT01950312	The Effects of Gevokizumab in Corticosteroid-resistant Subjects with Autoimmune Inner Ear Disease	Completed	Autoimmune Inner Ear Disease	Drug: Gevokizumab Systematic intervention Subcutaneous injection	Humanized recombinant antibody anti-IL1β	Phase 2
NCT01412177	OTO-104 for the Treatment of Meniere's Disease	Completed	Meniere's Disease	Drug: OTO-104	Anti-inflammation	Phase 2
NCT04766853	Verification of the Efficacy/Safety of the Dual Drug Delivery for Hearing Loss	Recruiting	Hearing Loss (Sudden), Hearing Loss (Ototoxic), Hearing Loss (Noise-Induced), and Meniere's Disease	Drug: Dexamethasone and Hyaluronic acid Intratympanic injection Dexamethasone 5 mg/ml Hyaluronic Acid 20mg/2 ml	Dexamethasone: Anti-inflammation	Phases 1 and 2
NCT02603081	Study to Evaluate SPI-1005 in Adults with Meniere's Disease	Completed	Meniere's Disease	Drug: SPI-1005	SPI-1005 (Ebselen): Glutathione peroxidase mimetic	Phases 1 and 2
NCT01267994	A Clinical Trial of Anakinra for Steroid-Resistant Autoimmune Inner Ear Disease	Completed	Sensorineural Hearing Loss and Autoimmune Inner Ear Disease	Drug: Anakinra	IL-1 receptor antagonist	Phases 1 and 2
NCT01084525	OTO-104 for Meniere's Disease	Completed	Meniere's Disease	Drug: OTO-104 (steroid) 3 mg and 12 mg	Anti-inflammation	Phase 1
NCT04902963	What is the Tympanic Membrane Healing Time After Insertion of a Gelfoam Pressure Equalizer (PE) Tube?	Completed	Eustachian Tube Dysfunction, Sudden Hearing Loss, Meniere's Disease	Device: PE tube Local intervention	Middle ear ventilation and preventing fluid accumulation behind the tympanic membrane	N/A
NCT04869020	Evaluation of the OtoBand in Subjects with Self-reported Vertigo to Reduce Severity of Vertigo in a Real-world Setting	Recruiting	Vertigo	Device: Otoband Local intervention	Transcranial vibrating system	N/A
NCT04847700	Minimally Invasive Vestibular Neurectomy	Recruiting	Meniere's Disease	Procedure: Surgical Treatment Local intervention		N/A

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Table 2 (*continued*)

NCT Number	Title	Status	Conditions	Interventions	Mechanism	Phases
	Versus Tenotomy of the Stapedius and Tensor Tympani Muscles in the Management of Patients with Unilateral Meniere's Disease					
NCT04835688	Ventilation Tube Insertion for Unilateral Meniere's Disease	Recruiting	Meniere's Disease	Procedure: Transmyringeal Ventilation Tube Insertion		N/A
NCT04686695	Transcutaneous Auricular Vagus Nerve Stimulation Treatment on Meniere Disease	Completed	Meniere's Disease	Device: taVNS Local intervention	Transcutaneous electrical nerve stimulation	N/A
NCT03795675	CI Following VS Removal or Labyrinthectomy	Recruiting	Vestibular Schwannoma and Meniere's Disease	Device: Cochlear Implant	Auditory nerve stimulator	N/A
NCT03520322	A Study of a Mastoid Device in Subjects with Meniere's Disease	Enrolling by invitation	Meniere's Disease	Device: Mastoid Oscillator		N/A
NCT02309099	Cochlear Implantation After Labyrinthectomy or a Translabyrinthine Surgical Approach	Completed	Unilateral Acoustic Neuroma and Meniere's Disease	Device: Cochlear Implant	Auditory nerve stimulator	N/A
NCT00500474	Effects of Endolymphatic Sac Drainage with Steroids for Meniere's Disease	Completed	Meniere's Disease	Procedure: Endolymphatic Sac Drainage with Steroids Local intervention Intra-endolymphatic sac application of large doses of steroids	Anti-inflammation	N/A

elimination rates (Zhang et al., 2022a). In terms of IT drug delivery in MD patients, several drugs, namely steroids and gentamicin have been used. Gentamicin is an effective therapy for vertigo treatment with a risk of hearing loss. However, for IT gentamicin administration, many parameters such as drug dose, administration intervals, patient selection, and contraindications should be taken into consideration (Yongchuan and Hongzhe, 2019).

IT delivery devices including the Silverstein Microwick and Microcatheter have been designed to enhance the effect of drug delivery. The MicroWick is a polyvinyl acetate wick inserted into a ventilation tube placed in the tympanic membrane to make contact with the round window. After the patient self-administers the drug through the external ear, it is absorbed by the wick and passively diffuses to the round window (Patel et al., 2019; Silverstein et al., 2004). The Microcatheter consists of an external end with two lumens for fluid infusion and withdrawal, and an internal end, with a bulbous tip. To use this device, a tympanomeatal flap is performed to expose the round window niche, where the bulbous tip is positioned and compressed. The external end exits from the outer ear canal and connects to a pumping system for drug infusion (El Kechai et al., 2015; Swan et al., 2008). Compared with the MicroWick, the Microcatheter provides better control over the concentration of drug infused into the round window (El Kechai et al., 2015). Several clinical studies used both the Microwick and Microcatheter devices. For the Microwick, Gentamicin and ganciclovir were administered in patients with MD, resulting in vertigo control in over 75% of cases (Guyot et al., 2008; Hill et al., 2006). Another study used the Microcatheter for gentamicin administration into the inner ear in MD patients, leading to long-term vertigo control (95% of the patients) and preservation of hearing (77% of the patients) and vestibular function (86% of the patients) (Suryanarayanan and Cook, 2004).

In addition to these, there are several intracochlear delivery systems (Table 3), including direct injections, cochlear implants, osmotic minipumps, and reciprocating perfusion systems. The first pathway involves direct drug injection via a syringe into the cochlea, with higher and more consistent levels of drug when compared with IT injection (Patel et al., 2019; Szeto et al., 2020). In patients with profound hearing loss, cochlear implants are used, and drugs can be delivered through the implant to decrease inner ear trauma or to prevent further hearing loss following implantation (Liu et al., 2013; Patel et al., 2019; Rejali et al., 2007; Richardson et al., 2007). The implant can be coated with biodegradable eluting polymers or incorporate an active infusion pump (Borenstein, 2011; El Kechai et al., 2015). For example, a flexible disposable intracochlear catheter has been used for delivering a single bolus of iodine, demonstrating effective drug delivery during cochlear implantation in animal models (Ibrahim et al., 2011).

For more control of drug delivery, osmotic pumps and reciprocating microfluidic reservoirs have been developed. An osmotic pump transfers the drug through a cannula into the inner ear at a determined rate, using an osmotic gradient between the perilymph and the canister containing the drug. Some drugs and gene vectors have been delivered through this mechanism in various animal models (Borenstein, 2011; Pararas et al., 2012). Nonetheless, there are challenges in using osmotic pumps, such that, after starting the pump, drug delivery is continuous with no on/off control, and the flow rate cannot be changed (Pararas et al., 2012). Further, only a limited drug volume can be delivered through the pump in a specified time period, due to the low clearance rate of cochlear fluid (Patel et al., 2019). To overcome these challenges, a reciprocating microfluidic reservoir has recently been developed, which provides automated drug delivery with constant drug volume infusion and withdrawal (net zero volume delivery), preventing an increase in the perilymph volume of the cochlea (Tandon et al., 2016). This system has shown its potential for the treatment of hearing loss and other associated diseases in preclinical research (Sewell et al., 2009). Generally, the negatives of this direct drug delivery technology are the need for surgical procedures and their possible device performance issues following implantation (Piu and Bishop, 2019).

One emerging approach to improve direct drug delivery is a trans-OW, silicon-based implant, which is mounted on the stapes to deliver drugs to the inner ear (Sircoglou et al., 2015). Furthermore, small implants known as ear cubes have been developed for direct drug delivery into the cochlea and vestibule through the OW. These silicone-based implants are comprised of a cylinder inserted into an OW and a connecting cuboid inserted into the middle ear, which contains the inner ear medications (Gehrke, 2016).

To improve the efficiency of IT drug delivery, biopolymers or macromolecular structures as therapeutic carriers are being used for targeted delivery. It has been shown that the use of hydrogels helps in the continuous delivery of drugs to the inner ear. Some of the latest

Table 3
Comparison of drug delivery routes for MD and/or inner ear disorders (El Kechai et al., 2015; Kashizadeh et al., 2022; Li et al., 2022; Nyberg et al., 2019; Zhang et al., 2022a).

Delivery route	Advantages	Disadvantages	Examples
Systemic	•Non-invasive delivery •Easily operated •Ability to target Blood-Labyrinth Barrier (BLB) transporters •Ability to design smart drug delivery vehicles[a] •Varied administration routes (oral, intravenous or drip injection, and intramuscular injection) •Clinical use	•BLB limits success •Off-target effects •Lower concentrations of used therapeutics (compared •to local delivery) •Protein fouling[b]	•Oral betahistine for MD patients (Lezius et al., 2011; Nauta, 2014) •Oral Steroid for MD patients (Fisher et al., 2012)
Intratympanic	•Beneficial for middle ear and inner ear treatment •Reduced systemic exposure •Precluding systemic targeting issues •Precluding premature systemic clearance •Short- and middle-term therapeutic delivery (days to weeks) •Normally outpatient procedure •Suited for hydrogels, nanocarriers, and medical devices	•Invasive •Diffusion through the round window is required to access the cochlea •Inter-individual variability of drug levels (probably due to different round window thickness and/or its potential blockage) •Drug elimination by the Eustachian tube •Unsuited for liquid formulations •Risk of pathogen transmission in the middle ear •Danger of tympanic membrane perforation •The main delivery barrier is the round window membrane	•Intratympanic steroid for MD patients (Devantier et al., 2019a) •Intratympanic dexamethasone for MD patients (Rogha et al., 2019) •Intratympanic gentamicin for MD patients (Yongchuan and Hongzhe, 2019)
Direct inner ear delivery (intracochlear and vestibular)	•Inner ear treatment •Reduced systemic exposure •Long-term drug delivery (months to years) •Suited for liquid formulations, nanocarriers, and medical devices •Ability to deliver drugs along with a cochlear implant •Bypassing the BLB •Reduction in systemic drug side effects •Proper drug targeting •Precluding systemic targeting issues •Precluding premature systemic clearance •Direct access to perilymph	•Highly invasive •Surgical access to the cochlea is required •The danger of trauma and postoperative complications (protein fouling and inflammation) •Hospitalization •Potential toxicity of high drug levels in the cochlea •Risk of pathogen transmission	•Microfluidics-based intracochlear drug delivery (Sewell et al., 2009) •Flexible disposable intracochlear catheter in animal models (Ibrahim et al., 2011)
Nano-based	•High biocompatibility •High drug stability •Sustained drug release •Drug targeting •Biodegradable •No damage induction to the blood-brain barrier •Transport of hydrophilic and/or hydrophobic agents •Easy functionalization •Easy fabrication; •Low toxicity •Versatile surface modifications	•Tendency to aggregation •Modifications in size or shape might lead to delivery efficacy changes •Eustachian tube leakage •Toxicity	•Solid lipid nanoparticles Loaded with glucocorticoids for inner ear drug delivery (in vitro) (Cervantes et al., 2019) •Dexamethasone encapsulated in polyethylene glycol-coated polylactic acid nanoparticles locally applied onto the RWM of guinea pigs (Sun et al., 2015)

[a] Nanoscale engineering of delivery systems generates smart drug delivery vehicles to solve main concerns for systemic delivery such as targeting, toxicity, and premature elimination from the bloodstream (Nyberg et al., 2019).

[b] Protein fouling is a process in which serum proteins attach to the surface of a drug delivery vehicle or therapeutic agent, leading to a decrease in bioavailability and phagocytosis (Nyberg et al., 2019).

delivery formulations proposed for MD treatment include hyaluronic acid (HA), chitosan (CS), and poloxamer 407 (P407) (Magdy et al., 2022; Nguyen et al., 2017). Poloxamers are considered efficient drug delivery carriers for different sizes of therapeutic compounds in the inner ear. For example, thermosensitive hydrogels have been injected intratympanically in a liquid form and then converted to a solid phase after injection, leading to more drug retention and sustained drug release within the inner ear (Salt and Plontke, 2018). Another promising technique is corticosteroid-bound hyaluronic acid for IT administration, which has been shown to improve hearing outcomes (Rogha et al., 2019; Selivanova et al., 2005). For example, dexamethasone-bound hyaluronic acid. Chitosanase, which degrades the hydrogel, could also be used to better control sustained drug release using chitosan (CS). Thus, a mixture of CS (2–10% w/w) combined with glycerol phosphate (5–30% w/w) for continuous release of gentamicin has been disclosed. The procedure consists of two phases: first, gradual drug release from the hydrogel, and then release termination through chitosanase degradation (Nguyen et al., 2017).

Nanoparticles (NPs) are highly stable and biocompatible making them a promising solution to accomplish selective and controlled medication release, bringing new opportunities for smart, targeted drug delivery approaches (Quaranta and Picciotti, 2020). The nano-encapsulation of medicinal pharmaceuticals may effectively enhance their absorption and internalization by cells/tissues, resulting in lower doses and fewer side effects. Moreover, medications with low soluble and degradable drugs with a short shelf-life can be adjusted by NP-based delivery methods (Pritz et al., 2013). In addition to NP-based drug delivery, gene therapy using nanoparticle carriers has been emerging as an

approach in the treatment of hearing loss (Pyykkö et al., 2011; Yang et al., 2018) (Fig. 5), serving as an emerging potential therapeutic for Meniere's disease. Despite the promise of NPs in the future treatment of MD, an evaluation of their safety and health characteristics is necessary in order to properly evaluate hazards for patients undergoing NP-based therapy and characterize safe procedures, regarding the reported ototoxicity of these materials (Feng et al., 2015; Leso et al., 2019; Zou et al., 2014).

Additional clinical factors need to be considered affecting pharmacological treatment with regards to MD. For example, the analysis of cytokine profiles of MD patients has revealed that there may be two MD patient subgroups with different immune responses or functional immune system status (Frejo et al., 2018), which might influence the outcome of clinical trials on treatments for MD. Thus, according to the current evidence indicating a relationship between proinflammatory cytokines (high levels of IL1 beta, TNFalpha, IL4, and IgE) and MD (Frejo et al., 2018; Moleon et al., 2021; Zhang et al., 2022b), the cytokine profile of MD patients is suggested to be tested prior to enrolling them in clinical trials.

4. Potential therapeutic options with low-level evidence

Several studies exist in the form of non-controlled cohort studies. This is problematic given that MD patients display a 60–80% therapeutic benefit to any treatment provided - the so-called Meniere's 'placebo effect'. Hence, in order to reliably test the therapeutic response in MD patients, more rigorous placebo-controlled clinical trials are needed (Bretlau et al., 1984; Cooper and Kaylie, 2020). In the following, some of the therapeutic options are briefly discussed, which need more controlled clinical trials to better prove their efficiency.

4.1. Anti-secretory factor (AF)

In the last decade, researchers have focused on Specially Processed Cereals (SPCs) as a treatment for MD. SPCs have been postulated to induce the endogenous synthesis of anti-secretory factor (AF) and ion modulator, which is a protein secreted by the pituitary gland after infection (Scarpa et al., 2020b, 2020c). SPCs have been recently used for MD treatment and reported to reduce vertigo attacks and tinnitus (Viola et al., 2020), suggesting potential utility for continued use. Note that additional evaluations may be required to validate their application in clinical practice (De Luca et al., 2020a).

4.2. Anti-viral drugs

Anti-viral drugs are not recommended for Meniere's disease therapy (Iwasaki et al., 2021). However, Velusamy and colleagues stated that antiviral medications should be used in MD care (Velusamy et al., 2020). Another study by Beigh et al. (2017) showed that antiviral drugs can decrease the dose of vestibular sedatives needed to achieve vertigo reduction in MD and vestibular neuronitis (VN). Nonetheless, more investigation is required for the verification of anti-viral treatment (Beigh et al., 2017).

4.3. Selective serotonin Re-uptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have been utilized to treat mood disorders such as depression and anxiety (Gunasekara et al., 1998). They hold several advantages, such as tolerability and low complication rates, and have been shown to improve dizziness in patients suffering from various psychiatric symptoms (Staab et al., 2002). Moreover, SSRIs have also been used for the treatment of neurological disorders such as migraine-related vertigo and panic disorders. With regards to MD, Goto et al. used sertraline (an SSRI) to control vertigo attacks in Meniere's patients (Goto et al., 2014). SSRIs were also used in patients with both MD and generalized anxiety disorder. In this study, escitalopram was selected as an SSRI. Results demonstrated that SSRIs might directly affect the vestibular system, and escitalopram may control vertigo (Kıroğlu et al., 2017). However, more studies are needed to understand the mechanistic effects of SSRIs in MD and confirm their use as a treatment.

4.4. Combined treatment

Combined treatment strategies refer to the staggering of two or more MD therapies together in one treatment regimen. A recent example of successful combined treatment in MD includes endolymphatic sac decompression and posterior tympanotomy with local steroid injection (Xu et al., 2020). After implementing this treatment method, vertigo episodes declined, and nearly 90% complete vertigo control was achieved. In another study, dexamethasone was combined with the ototoxic drug gentamicin for MD treatment. After six months, the effect on vertigo attacks disappeared, potentially highlighting the success of the therapy (Geng et al., 2020). Recently, triple semicircular canal plugging and cochlear implantation were simultaneously applied in patients with Meniere's disease at advanced stages, and subsequently, vertigo was effectively controlled in these patients, with improvements in hearing function and tinnitus (Zhang et al., 2017). In 2021, Fang et al. compared several treatment regimens including (1) traditional Chinese medicine (TCM), (2) acupuncture, (3) combined treatment, and (4) western medicine groups (Fang et al.). These groups included: 1) Modified Zhenwu decoction, 2) acupuncture at Taichong acupoints, 3) combined treatment (Modified Zhenwu decoction and acupuncture at Taichong acupoints), and 4) betahistine mesylate, respectively. Interestingly, group three, receiving combined treatment, showed better results than the other groups. As a result, combined treatment is likely to be beneficial for the treatment of MD.

5. Gaps, challenges, and future perspectives

There exist several gaps in MD research that need to be addressed. The precise root of MD is still unknown; however, it is thought to be associated with ELH. The specific triggers and underlying mechanisms are not absolutely comprehended. In terms of MD diagnosis, it remains a challenge since MD symptoms can overlap with other inner ear disorders. Currently, there is no definitive testing for MD, and it is typically diagnosed based on the patient's medical history, symptoms, and ruling out other conditions. Another gap is related to symptom heterogeneity. There are various symptoms, including vertigo, tinnitus, hearing loss, and a feeling of fullness in the ear, and the severity and combination of these symptoms might differ among individuals, making it difficult to establish standardized treatment approaches. In this regard, current treatments are mainly concentrated on managing symptoms and preventing attacks. It is essential to have a therapy capable of stopping or slowing down the disease progression. Perhaps, research on the complex interplay between genetic and environmental factors can be helpful for potential therapeutic breakthroughs.

Some challenges have been raised in this field of study. MD research may face inadequate funding to foster large-scale studies and clinical trials. Additionally, recruiting a sufficient number of participants for clinical trials can be difficult due to the rarity of MD and the variability of its symptoms. For conducting some research, such as genetic studies or experimental treatments, ethical concerns need to be considered when it comes to patient consent and safety. In the field of diagnosis, reliable biomarkers are essential to definitively diagnose MD or predict its course. Biomarker identification would vastly assist in early diagnosis and personalized therapy.

Due to the research gaps and challenges, future works could be focused on different aspects of the disease. Genetics and genomics need to be more investigated. This could provide valuable insights into MD pathogenesis, risk factors, and potential therapeutic targets. Personalized treatment approaches tailored to each patient's specific symptoms

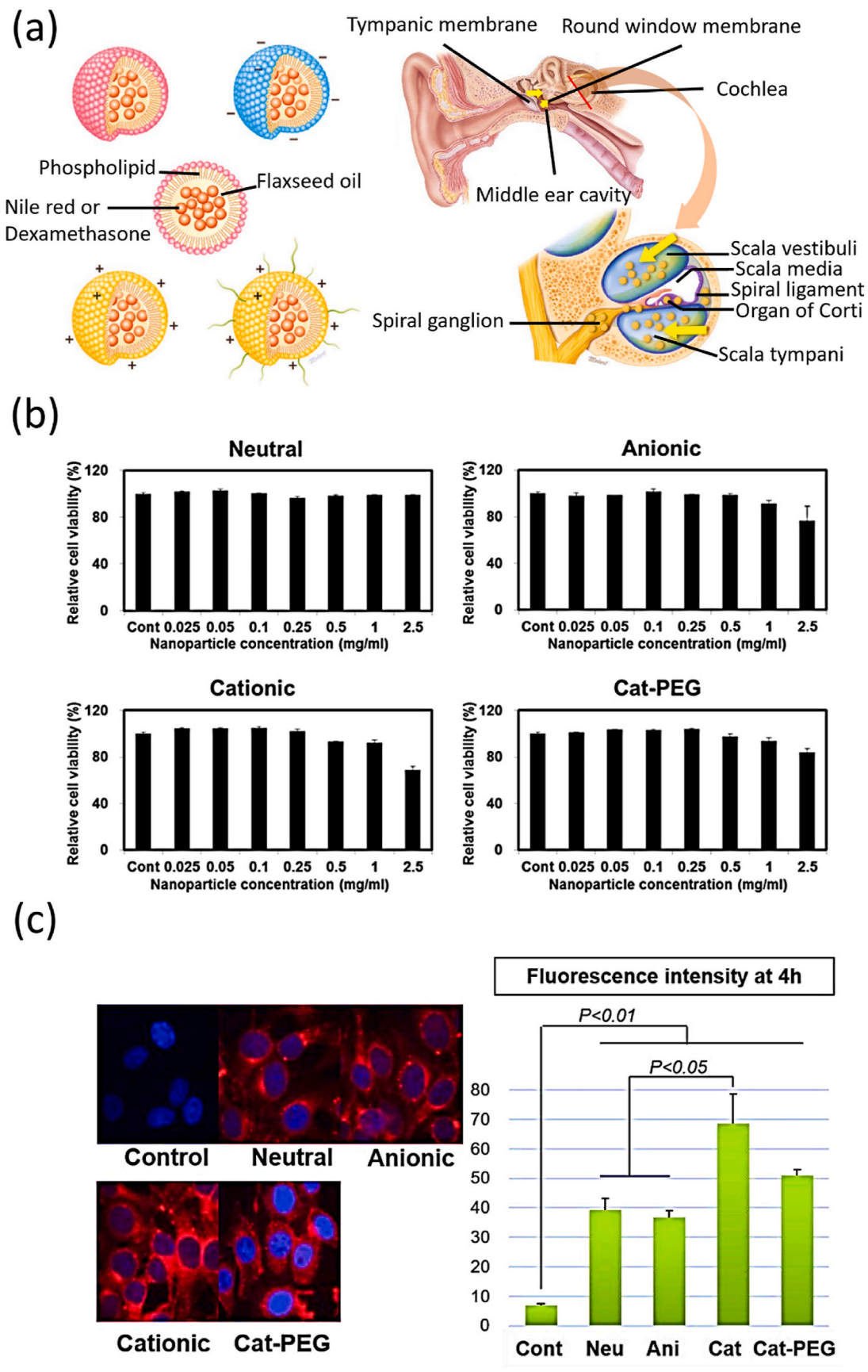

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Fig. 5. Nanoparticles as an emerging treatment candidate for MD. (a) Representation of the four candidate nanoparticles (NPs) (neutral, anionic, cationic, and cat-PEG), and a schematic of the ear (outer, middle, and inner), and distributions of NPs following intratympanic administration to the cochlea. (b) Tested cytotoxicity of four candidate NP carriers on HEI-OC1 cells measured using the commercial 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The levels at which nanoparticles did not affect cell viability (compared with untreated cells) were 0.5 mg/ml for anionic, 0.25 mg/ml for cationic, and 0.5 mg/ml for Cat-PEG nanoparticles, and neutral nanoparticles were not toxic up to 2.5 mg/ml. (c) The cellular updates of Nile Red-loaded NPs (0.5 mg/ml) by HEI-OC1 cells were tested and quantified using confocal microscopy. Cationic NPs had the most intense cellular uptake, followed by the Cat-PEG, neutral, and anionic nanoparticle carriers after 4 h. However, 16 h later, Cat-PEG nanoparticles showed uptake of nanoparticles similar to cationic nanoparticles. Reproduced with permission (Yang et al., 2018)

and underlying causes are expected to be taken into account in the near future. Further research into the inner ear fluid dynamics might uncover mechanisms of MD development and progression. Novel therapeutic methods are being explored, and gene therapies, targeted drug delivery systems, or regenerative medicine have the potential to change MD management. Emerging technologies such as artificial intelligence (AI) could also be applied to MD in the near future to assist in early MD diagnosis and prediction by analyzing patient symptoms, genetic markers, and risk factors.

Research on MD would be beneficial for other related inner ear diseases. MD and other inner ear diseases share some similarities but also exhibit distinct features that set them apart. For instance, both involve abnormalities or dysfunction within the inner ear structures, such as the cochlea and vestibular system. Vertigo is a common symptom shared by MD and various inner ear disorders. Hearing loss or changes in hearing are frequently observed in inner ear diseases. Patients with MD and certain inner ear disorders may experience tinnitus. Nonetheless, there are some differences in terms of etiology, associated symptoms, symptom patterns, and progression. Thus, understanding the overlaps and differences between these conditions is crucial for accurate diagnosis and appropriate management and can be generalized to benefit other conditions.

6. Conclusion

Despite more than a century of research, Meniere's disease remains a challenging and enigmatic condition, with its underlying causes and mechanisms still unknown. The lack of comprehension at the cellular level within the inner ear has impeded the development of effective and targeted treatments. Nonetheless, the scientific community continues to explore various avenues, focusing on factors like endolymphatic hydrops as a key element in the development of the disease and the identification of different subsets of MD specific to individual patients. Encouraging advancements, such as direct inner ear delivery systems and micro/nano-particles, show promise as potential treatment approaches for the future. Additionally, therapeutic approaches with low-level evidence are to be considered for more randomized clinical trials. Currently, general areas of research and potential developments to help patients with Meniere's disease are focused on genetic and molecular studies, imaging and diagnostic techniques, precision medicine, therapeutic advances, vestibular rehabilitation and management, inner ear delivery systems, neurostimulation and neuromodulation, and regenerative medicine. However, further dedicated basic science and clinical research are indispensable to truly expand therapeutic options. While challenges persist and answers remain elusive, the process of exploration and research is ongoing, illuminating a path toward a future where more efficient management and therapeutic strategies are within reach. Hope prevails as the driving force, propelling the collective efforts of the scientific community toward a new dawn in Meniere's disease treatment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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