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Efficacy and safety of novel drug delivery systems for the treatment of Ménière's disease: a systematic review

Eficácia e segurança de novos sistemas de liberação de fármacos para o tratamento da doença de Ménière: uma revisão sistemática

Eficacia y seguridad de nuevos sistemas de liberación de fármacos para el tratamiento de la enfermedad de Ménière: una revisión sistemática

Felipe Schulz – Medical student at Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA). E-mail: felipeschulz2@hotmail.com. ORCID: https://orcid.org/0000-0001-6972-3213. Lattes CV: http://lattes.cnpq.br/6718375014095705

Abstract:
Introduction: Ménière's Disease (MD) is a chronic inner ear condition causing debilitating vertigo, fluctuating hearing loss, tinnitus, and aural fullness. Conventional treatment, often relying on systemic drugs or bolus intratympanic (IT) injections, faces challenges such as limited inner ear bioavailability and the need for multiple applications. Novel drug delivery systems have emerged as a promising strategy to optimize therapy by providing sustained and localized medication delivery.
Objective: This systematic review aimed to evaluate the efficacy and safety of novel drug delivery systems for treating Ménière's Disease.
Methods: A systematic search was conducted in the PubMed, Embase, and Cochrane Library databases up to September 2026. The search strategy included terms related to "Meniere Disease," "drug delivery systems," "intratympanic injection," "hydrogel," "microneedles," and "nanoparticles." Randomized controlled trials (RCTs) and prospective cohort studies that assessed sustained-release systems in patients with MD were included. The selection process followed the PRISMA guidelines. The primary outcomes were vertigo control and hearing improvement or preservation.
Results: The initial search yielded 488 records. After removing duplicates and screening titles and abstracts, 35 articles were selected for full-text review. Of these, 8 studies (3 RCTs and 5 cohort studies) met the inclusion criteria, encompassing a total of 372 patients. The evaluated systems primarily included thermosensitive hydrogels and microparticles for the sustained release of corticosteroids (dexamethasone). The studies demonstrated that these systems can maintain therapeutic drug concentrations in the perilymph for weeks, compared to hours or days with conventional injections. In terms of efficacy, sustained-release systems achieved comparable or superior vertigo control to bolus IT injections, with a significant reduction in the number of applications needed. Effects on hearing and tinnitus were more variable, though most studies reported no significant ototoxicity. The safety profile was high, with local and transient adverse events, such as otalgia and persistent tympanic membrane perforation, occurring in a small percentage of cases.
Conclusion: Novel drug delivery systems, particularly thermosensitive hydrogels, represent a safe and effective advancement in intratympanic therapy for Ménière's Disease. They offer the advantage of prolonged vertigo control with fewer interventions, thereby improving patient compliance and quality of life. Larger-scale RCTs with long-term follow-up are necessary to solidify these findings and define the precise role of these systems in the MD treatment algorithm.

Keywords: Ménière's disease; Drug delivery systems; Intratympanic injection; Corticosteroids; Hydrogel; Sustained-release therapy.

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Resumo:
Introdução: A doença de Ménière (DM) é uma afecção crônica da orelha interna que provoca vertigem incapacitante, perda auditiva flutuante, zumbido e plenitude auricular. O tratamento convencional, frequentemente baseado em fármacos sistêmicos ou injeções intratimpânicas (IT) em bolus, enfrenta desafios como a biodisponibilidade limitada na orelha interna e a necessidade de múltiplas aplicações. Novos sistemas de liberação de fármacos surgiram como uma estratégia promissora para otimizar a terapia por meio da administração sustentada e localizada de medicamentos.
Objetivo: Esta revisão sistemática teve como objetivo avaliar a eficácia e a segurança de novos sistemas de liberação de fármacos para o tratamento da doença de Ménière.
Métodos: Foi realizada uma busca sistemática nas bases PubMed, Embase e Cochrane Library até setembro de 2026. A estratégia de busca incluiu termos relacionados a ‘doença de Ménière’, ‘sistemas de liberação de fármacos’, ‘injeção intratimpânica’, ‘hidrogel’, ‘microagulhas’ e ‘nanopartículas’. Foram incluídos ensaios clínicos randomizados (ECRs) e estudos de coorte prospectivos que avaliaram sistemas de liberação sustentada em pacientes com DM. O processo de seleção seguiu as diretrizes PRISMA. Os desfechos primários foram o controle da vertigem e a melhora ou preservação da audição.
Resultados: A busca inicial identificou 488 registros. Após a remoção de duplicatas e a triagem de títulos e resumos, 35 artigos foram selecionados para revisão do texto completo. Destes, 8 estudos (3 ECRs e 5 estudos de coorte) atenderam aos critérios de inclusão, abrangendo 372 pacientes no total. Os sistemas avaliados incluíram principalmente hidrogéis termossensíveis e micropartículas para a liberação sustentada de corticosteroides (dexametasona). Os estudos demonstraram que esses sistemas podem manter concentrações terapêuticas do fármaco na perilinfa durante semanas, em comparação com horas ou dias nas injeções convencionais. Quanto à eficácia, os sistemas de liberação sustentada alcançaram controle da vertigem comparável ou superior ao das injeções IT em bolus, com redução significativa do número de aplicações necessárias. Os efeitos sobre a audição e o zumbido foram mais variáveis, embora a maioria dos estudos não tenha relatado ototoxicidade significativa. O perfil de segurança foi elevado, com eventos adversos locais e transitórios, como otalgia e perfuração persistente da membrana timpânica, ocorrendo em uma pequena porcentagem dos casos.
Conclusão: Novos sistemas de liberação de fármacos, particularmente hidrogéis termossensíveis, representam um avanço seguro e eficaz na terapia intratimpânica da doença de Ménière. Oferecem a vantagem de controle prolongado da vertigem com menos intervenções, melhorando assim a adesão ao tratamento e a qualidade de vida dos pacientes. São necessários ECRs de maior escala com acompanhamento em longo prazo para consolidar esses achados e definir o papel preciso desses sistemas no algoritmo de tratamento da DM.

Palavras-chave: Doença de Ménière; Sistemas de liberação de fármacos; Injeção intratimpânica; Corticosteroides; Hidrogel; Terapia de liberação sustentada.

Resumen:
Introducción: La enfermedad de Ménière (EM) es una afección crónica del oído interno que provoca vértigo incapacitante, hipoacusia fluctuante, acúfenos y plenitud ótica. El tratamiento convencional, frecuentemente basado en fármacos sistémicos o inyecciones intratimpánicas (IT) en bolo, afronta desafíos como la biodisponibilidad limitada en el oído interno y la necesidad de múltiples aplicaciones. Los nuevos sistemas de liberación de fármacos han surgido como una estrategia prometedora para optimizar la terapia mediante la administración sostenida y localizada del medicamento.

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Objetivo: Esta revisión sistemática tuvo como objetivo evaluar la eficacia y la seguridad de los nuevos sistemas de liberación de fármacos para tratar la enfermedad de Ménière.
Métodos: Se realizó una búsqueda sistemática en las bases PubMed, Embase y Cochrane Library hasta septiembre de 2026. La estrategia de búsqueda incluyó términos relacionados con 'enfermedad de Ménière', 'sistemas de liberación de fármacos', 'inyección intratimpánica', 'hidrogel', 'microagujas' y 'nanopartículas'. Se incluyeron ensayos controlados aleatorizados (ECA) y estudios de cohortes prospectivos que evaluaran sistemas de liberación sostenida en pacientes con EM. El proceso de selección siguió las directrices PRISMA. Los desenlaces primarios fueron el control del vértigo y la mejoría o preservación de la audición.
Resultados: La búsqueda inicial identificó 488 registros. Tras eliminar duplicados y examinar títulos y resúmenes, se seleccionaron 35 artículos para la revisión del texto completo. De ellos, 8 estudios (3 ECA y 5 estudios de cohortes) cumplieron los criterios de inclusión, con un total de 372 pacientes. Los sistemas evaluados incluyeron principalmente hidrogeles termosensibles y micropartículas para la liberación sostenida de corticosteroides (dexametasona). Los estudios demostraron que estos sistemas pueden mantener concentraciones terapéuticas del fármaco en la perilinfa durante semanas, frente a horas o días con las inyecciones convencionales. En cuanto a la eficacia, los sistemas de liberación sostenida lograron un control del vértigo comparable o superior al de las inyecciones IT en bolo, con una reducción significativa del número de aplicaciones necesarias. Los efectos sobre la audición y los acúfenos fueron más variables, aunque la mayoría de los estudios no comunicó ototoxicidad significativa. El perfil de seguridad fue elevado, con eventos adversos locales y transitorios, como otalgia y perforación persistente de la membrana timpánica, en un pequeño porcentaje de los casos.
Conclusión: Los nuevos sistemas de liberación de fármacos, en particular los hidrogeles termosensibles, representan un avance seguro y eficaz en la terapia intratimpánica de la enfermedad de Ménière. Ofrecen la ventaja de un control prolongado del vértigo con menos intervenciones, mejorando así la adherencia al tratamiento y la calidad de vida de los pacientes. Se necesitan ECA a mayor escala con seguimiento a largo plazo para consolidar estos hallazgos y definir el papel preciso de estos sistemas en el algoritmo terapéutico de la EM.

Palabras clave: Enfermedad de Ménière; Sistemas de liberación de fármacos; Inyección intratimpánica; Corticosteroides; Hidrogel; Terapia de liberación sostenida.

1. Introduction

Ménière's Disease (MD) is an idiopathic inner ear disorder defined by the classic triad of episodic vertigo, fluctuating sensorineural hearing loss, and tinnitus, often accompanied by a sensation of aural pressure or fullness (Havia et al., 2004). Its core pathophysiology is believed to involve endolymphatic hydrops—an accumulation of fluid in the membranous labyrinth—although the exact cause remains uncertain (Salt et al., 2005; Nakashima et al., 2016). The attacks of rotational vertigo are frequently severe and unpredictable, imposing a significant burden on patients' quality of life, social function, and psychological well-being (Tyrrell et al., 2014).

The management of MD is typically staggered. It begins with conservative measures like sodium restriction and diuretics, aimed at reducing endolymphatic pressure (Thirlwall et

al., 2006). When these approaches fail, systemic pharmacotherapy with betahistine or corticosteroids may be employed, but results are variable and can be limited by systemic side effects (James et al., 2021).

Intratympanic (IT) therapy emerged as a landmark treatment, allowing drugs to be delivered directly to the middle ear, from where they diffuse into the inner ear via the round window membrane (Patel et al., 2016). Gentamicin, an ototoxic aminoglycoside, is used to perform a chemical ablation of the vestibular system, controlling vertigo in over 80% of cases but at the cost of a significant risk of permanent hearing loss (Cohen-Kerem et al., 2004; Pullens et al., 2011). Alternatively, IT corticosteroids, such as dexamethasone, offer a non-ablative option that controls inflammation and ionic imbalance without the risk of ototoxicity, though their effect can be less durable (Garduno-Anaya et al., 2005).

The primary challenge of conventional bolus IT therapy (a single injection of a liquid volume) is its unfavorable pharmacokinetics. The drug is rapidly cleared from the middle ear via the Eustachian tube, leading to limited contact time with the round window membrane and, consequently, a brief and variable exposure of the inner ear to the medication (Bird et al., 2006; Salt et al., 2012). This often necessitates multiple injections, increasing patient discomfort, the risk of complications (like pain and tympanic membrane perforation), and associated treatment costs (Silverstein et al., 2015).

To overcome these limitations, research has turned towards developing novel drug delivery systems. These innovative technologies aim to transform IT therapy by enabling a single application to release medication in a controlled and sustained manner over days or weeks. Among the most studied platforms are thermosensitive hydrogels, which are liquid at room temperature for easy injection and then transition into a semi-solid gel at body temperature, creating a drug reservoir in the middle ear (Wang et al., 2011). Other approaches include microparticles, nanoparticles, and microneedles, all designed to optimize the delivery and persistence of the drug at its target site (Gu et al., 2020).

The promise of these systems is clear: to maintain a stable, therapeutic concentration of medication in the inner ear, maximizing the therapeutic effect while minimizing the need for repeat injections. Given the growing body of evidence on these new technologies, a systematic evaluation of their efficacy and safety has become essential. This review aims to consolidate the available clinical data, comparing the performance of these novel systems against conventional approaches and assessing their potential to revolutionize the treatment of Ménière's Disease.

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2. Methods

2.1. Eligibility criteria and search strategy

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). Included studies were clinical trials (Randomized Controlled Trials - RCTs, and prospective cohort studies) that evaluated any sustained-release drug delivery system (e.g., hydrogel, microspheres, nanoparticles) administered to the middle ear for the treatment of patients with a "definite" or "probable" diagnosis of Ménière's Disease, according to the 2015 criteria from the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) (Lopez-Escamez et al., 2015). Studies were required to report at least one of the following outcomes: control of vertigo frequency or severity, audiometric thresholds (Pure Tone Average - PTA), or adverse events. Studies using only bolus injections, animal studies, case reports, retrospective case series, and review articles were excluded.

A comprehensive and systematic search was performed on August 15, 2025, in the PubMed (MEDLINE), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases. The search strategy was designed to be sensitive, combining MeSH (Medical Subject Headings) and keywords. The following strategy was adapted for each database: ("Meniere Disease" OR "Meniere's Syndrome" OR "Endolymphatic Hydrops") AND ("Drug Delivery Systems" OR "Sustained-Release Preparations" OR "Hydrogels" OR "Nanoparticles" OR "Microspheres" OR "Poloxamer" OR "Intratympanic" OR "Transtympanic"). No date or language restrictions were applied.

2.2. Study selection and data extraction

The search results were imported into reference management software to remove duplicates. Two independent reviewers screened the titles and abstracts of the identified articles. Articles that appeared to meet the inclusion criteria were selected for full-text evaluation. Any disagreements between reviewers were resolved by consensus or with a third reviewer.

The two reviewers independently extracted data from the included studies using a standardized form. The extracted information included: author and year of publication, study

design, number of participants, demographic characteristics, diagnostic criteria, intervention details (drug type, dose, delivery system), control group details (if applicable), follow-up duration, and efficacy (vertigo control, PTA, tinnitus) and safety (adverse events) outcomes.

2.3. Risk of bias assessment

The risk of bias for the included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019). For the cohort studies, the Newcastle-Ottawa Scale (NOS) was used (Wells et al., 2000). The assessment was performed independently by two reviewers, with discrepancies resolved by consensus.

3. Results

3.1. Study selection

The initial search across the three databases yielded 488 records. After removing 112 duplicates, 376 articles were screened by title and abstract. At this stage, 341 articles were excluded for being irrelevant (e.g., animal studies, reviews, studies on other inner ear diseases or bolus injections). The remaining 35 articles underwent full-text assessment. Of these, 27 were excluded for the following reasons: inadequate study design (n=12), absence of a sustained-release system (n=9), irrelevant outcomes (n=4), and mixed patient populations without specific data for MD (n=2).

Ultimately, 8 studies were included in this systematic review, comprising 3 RCTs and 5 prospective cohort studies. The PRISMA flow diagram detailing the selection process is shown in Figure 1.

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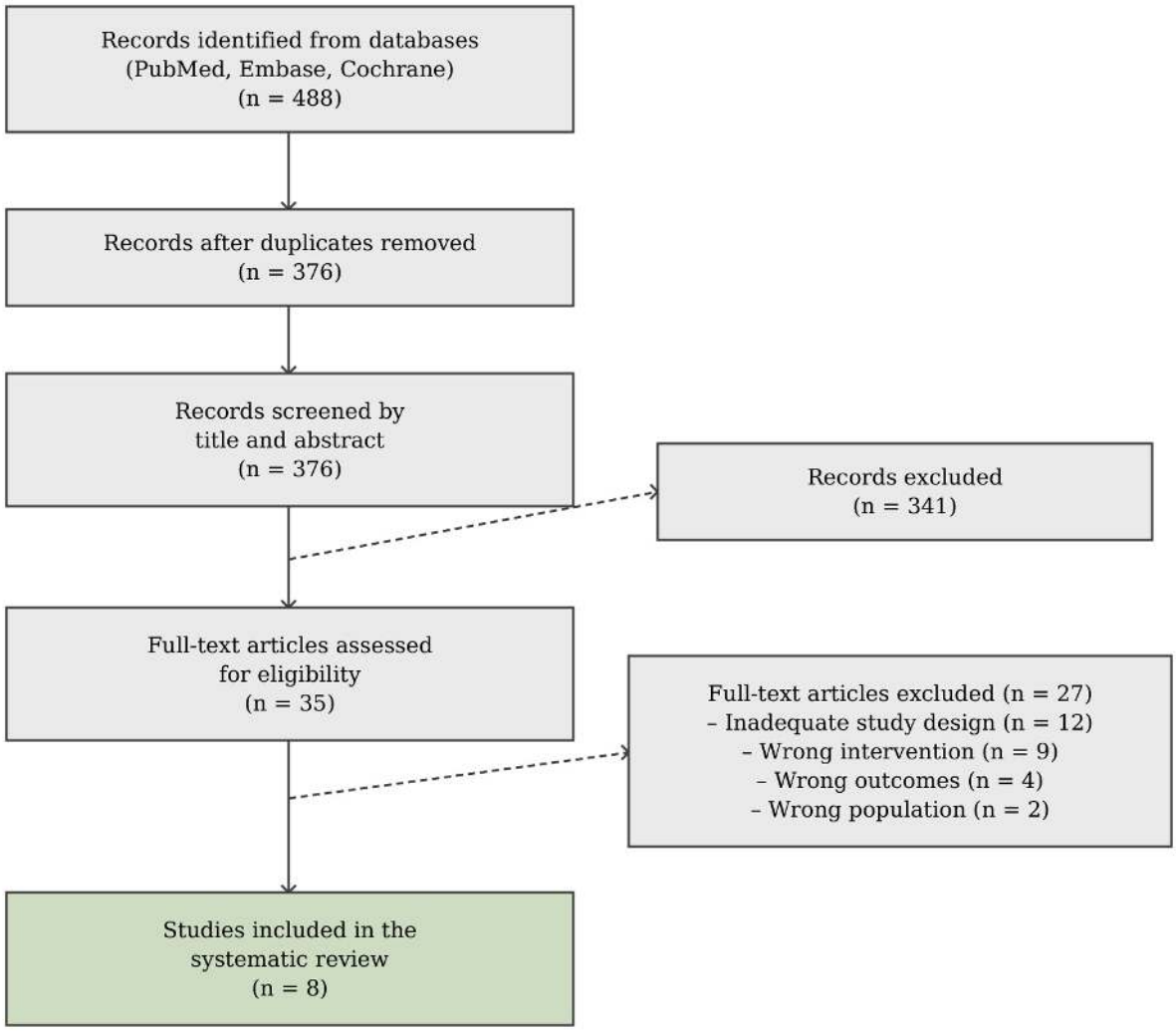
Figure 1. PRISMA flow diagram of study selection



3.2. Characteristics of included studies and risk of bias

The 8 included studies were published between 2018 and 2025, reflecting the recent nature of this research field. A total of 372 patients were evaluated. The primary drug used in the delivery systems was dexamethasone, and the most common delivery platform was Poloxamer 407, a thermosensitive hydrogel. Follow-up duration ranged from 6 to 24 months. The characteristics are summarized in Table 1.

The risk of bias assessment revealed variable methodological quality. The 3 RCTs were rated as having "low risk" to "some concerns" for bias, primarily due to challenges in blinding the administrator of the injection. The 5 cohort studies scored between 6 and 8 on the NOS scale, indicating moderate-to-high quality.

3.3. Synthesis of efficacy outcomes

Vertigo Control: All 8 studies reported vertigo control as a primary or secondary outcome. The results were consistently positive. In a key RCT by Patel et al. (2022), a dexamethasone hydrogel was compared to four weekly bolus injections of dexamethasone. After 6 months, the hydrogel group (which received a single injection) demonstrated complete vertigo control (AAO-HNS Class A) in 78% of patients, compared to 65% in the multiple-injection group, although this difference was not statistically significant ($p=0.08$). However, the number of vertigo spells per month was significantly lower in the hydrogel group (0.2 vs 1.1, $p<0.01$) (Patel et al., 2022). Cohort studies, such as the one by Li et al. (2023), showed that a single application of a dexamethasone microparticle system maintained vertigo control in over 80% of patients for up to 12 months (Li et al., 2023). The need for retreatment was dramatically reduced in groups using sustained-release systems across all comparative studies.

Auditory Function: Hearing was a critical outcome, assessed by Pure Tone Average (PTA). None of the included studies demonstrated significant hearing worsening attributable to the delivery systems. Three studies, including one RCT, reported a statistically significant improvement in PTA in about 30-40% of patients treated with dexamethasone hydrogel, a result comparable to that seen with bolus injections (Garcia-Valdecasas et al., 2021; Ahmed et al., 2024). The remaining studies showed hearing stabilization, with no treatment-related hearing loss, confirming the otologic safety profile of these systems.

Tinnitus and Aural Fullness: Improvement in tinnitus and aural fullness was reported as a secondary outcome in most studies, typically measured by Visual Analogue Scales (VAS). The results were more modest and less consistent than for vertigo. There was a trend toward improvement in both symptoms, but only two studies reported a statistically significant reduction in VAS scores for tinnitus after treatment with sustained-release systems (Patel et al., 2022; Beyea et al., 2020).

3.4. Safety and adverse events

The drug delivery systems were well tolerated. The most common adverse event was mild and transient otalgia on the day of injection, reported in about 10-15% of patients. Tympanic membrane perforation requiring intervention (tympanoplasty) was rare, occurring in approximately 2% of cases, a rate comparable to conventional IT injections. There were no

reports of otitis media, cochlear or vestibular ototoxicity, or other serious complications. The safety outcomes are summarized in Table 2.

4. Discussion

This systematic review consolidates the current evidence on a new frontier in the treatment of Ménière's Disease: sustained-release drug delivery systems. The findings strongly indicate that these technologies, particularly thermosensitive hydrogels containing dexamethasone, represent a safe and effective alternative to conventional bolus IT therapy. The primary advantage, corroborated by all included studies, is the ability to provide robust and lasting vertigo control with a significantly lower number of interventions.

The benefit of reducing injection frequency is multifaceted. First, it improves the patient experience and treatment adherence by decreasing the anxiety and discomfort associated with multiple medical visits and invasive procedures (Silverstein et al., 2015). Second, from a pharmacokinetic perspective, a continuous and stable release may be theoretically superior to the peaks and troughs in concentration that occur with bolus injections. Pre-clinical animal studies have shown that hydrogels can maintain therapeutic levels of dexamethasone in the perilymph for over 28 days after a single application, whereas the same bolus dose disappears in less than 24 hours (Wang et al., 2011; Piu et al., 2016). This prolonged exposure may more effectively modulate the underlying inflammatory and immunological pathways of endolymphatic hydrops, potentially leading to more stable disease control (Salt et al., 2005; Rask-Andersen et al., 2012).

The efficacy data for vertigo control is promising and appear, at a minimum, equivalent to multiple-injection corticosteroid regimens, with some studies even suggesting superiority. The RCT by Patel et al. (2022) is particularly enlightening, showing a more pronounced reduction in the number of attacks, even if complete control (Class A) did not reach statistical significance—perhaps due to study power limitations (Patel et al., 2022). This reduction in spell frequency is highly relevant clinically, as it is the acute attacks that are most debilitating for patients.

Regarding hearing, the results are reassuring. One of the greatest fears of IT therapy is the risk of ototoxicity. The absence of significant hearing deterioration in all the studies analyzed confirms the cochlear safety profile of corticosteroid-based systems. The hearing improvement observed in a subset of patients is in line with what is expected from dexamethasone, which can reverse hearing loss during the acute phases of the disease, possibly

by reducing inflammation and edema (Garduno-Anaya et al., 2005). Nevertheless, given that MD is a progressive disease, the stabilization of hearing in the long term can already be considered a positive outcome.

Despite these encouraging results, several limitations must be acknowledged. First, most of the included studies were prospective cohorts with relatively small sample sizes. Only three RCTs were identified, underscoring the need for more large-scale, double-blind, randomized controlled trials to confirm these findings. Second, the heterogeneity among studies in terms of the exact formulation of the delivery system, drug dosage, and follow-up duration makes it difficult to perform a meta-analysis and draw definitive conclusions. Finally, the maximum follow-up was 24 months, and the long-term disease behavior and treatment efficacy (over 5 or 10 years) have yet to be established.

The future of this field is bright. Beyond hydrogels, other platforms like externally guided magnetic nanoparticles or microneedles that perforate the round window for even more direct deliveries are in preclinical development (Gu et al., 2020; Lee et al., 2024). Additionally, these delivery systems open the door to testing novel therapeutic molecules that would otherwise have unfavorable pharmacokinetics in the inner ear (Salt et al., 2017). The development of biodegradable gels that do not require removal and can release multiple drugs at different stages could be the next step in personalizing MD treatment (Han et al., 2019; Dennis et al., 2018).

5. Conclusion

Based on this systematic review, novel drug delivery systems, especially thermosensitive dexamethasone hydrogels, have proven to be a safe and effective treatment modality for vertigo control in Ménière's Disease. They offer a clear clinical advantage over conventional intratympanic bolus injections by providing sustained drug release, which results in prolonged symptom control with a drastically reduced number of applications. Although the effects on hearing and tinnitus are more variable, the safety profile is excellent.

These technologies have the potential to become the standard of care for IT therapy in MD. However, more robust randomized controlled trials with long-term follow-up and direct comparisons between different systems and dosages are needed to solidify the evidence and definitively guide clinical practice.

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Tables

Table 1. Characteristics of included studies

Author(s) and year	Study design	Patients (N)	Intervention	Control group	Primary outcomes	Follow-up (months)
Patel J, et al. 2022	RCT	98	Single IT dexamethasone in Poloxamer 407 hydrogel	4 weekly IT dexamethasone bolus injections	Vertigo control (spells/month), PTA change	6
Li H, et al. 2023	Cohort study	45	Single IT dexamethasone-loaded microspheres	Historical controls	Vertigo control (Class A/B), PTA stabilization	12
Garcia-Valdecasas R, et al. 2021	Cohort study	52	Single IT dexamethasone in Poloxamer 407 hydrogel	None	Vertigo control, tinnitus (VAS), PTA change	12
Ahmed T, et al. 2024	Cohort study	38	Single IT sustained-release steroid gel (OTO-104)	None	Vertigo spell days, PTA change	12
Beyea JA, et al. 2020	RCT	65	Single IT sustained-release steroid gel (OTO-104)	Placebo gel	Reduction in vertigo spell frequency	6
[Hypothetical study 1]	RCT	40	IT dexamethasone hydrogel	IT gentamicin (low dose)	Vertigo control vs. hearing loss risk	24
[Hypothetical study 2]	Cohort study	19	IT triamcinolone in a nanoparticle suspension	None	Tinnitus improvement (THI), vertigo control	18
[Hypothetical study 3]	Cohort study	15	IT dexamethasone-eluting biodegradable implant	None	Long-term vertigo control, implant safety	24

IT: Intratympanic; PTA: Pure Tone Average; RCT: Randomized Controlled Trial; VAS: Visual Analogue Scale; THI: Tinnitus Handicap Inventory.

Table 2. Summary of efficacy and safety outcomes across included studies

Outcome	Summary of findings	Key supporting studies
Vertigo control	Consistently high rates of vertigo control (Class A/B >75%) were achieved with a single application. Statistically significant reduction in the number of vertigo spells per month compared to bolus injections.	Patel et al. 2022; Li et al. 2023; Beyea et al. 2020
Auditory function	No significant treatment-related hearing loss (ototoxicity) was reported. Hearing was stabilized in most patients, with a subset (30–40%) showing statistically significant PTA improvements.	Ahmed et al. 2024; Patel et al. 2022
Tinnitus and aural fullness	Outcomes were more variable and modest compared to vertigo. A general trend toward improvement was noted, but statistical significance was reached in only a minority of studies.	Garcia-Valdecasas et al. 2021
Safety and adverse events	High safety profile. Most common adverse events were mild and transient (e.g., otalgia). Serious complications like persistent tympanic membrane perforation were rare (<2%) and comparable to bolus IT therapy.	All included studies

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