



Letter to the Editor

## Is antidepressant gaining recognition in the treatment of Meniere's disease?

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Dear Editor,

Meniere's disease (MD) remains a challenging inner ear disorder with multifaceted symptomatology, including vertigo, tinnitus, fluctuating hearing loss, and often neuropsychiatric comorbidities such as anxiety and depression, complicating both diagnosis and management. Despite advancements over the last several decades, the pathophysiology of MD is not fully elucidated, and existing treatments primarily aim to reduce vertigo episodes, often neglecting other symptom domains, including hearing loss and tinnitus.

The wide variability in the symptomatology, affecting population and diagnostic measures, makes the diagnosis process difficult. With the recent classification, MD has been grouped into five types, which may reduce the complexities of diagnosing the disease, but all the treatment options available focus on reducing the vertigo episodes, leaving behind the other symptoms.

It was believed that the rupture of the membranous labyrinth is responsible for the vertigo episodes. The distortion of the endolymphatic duct with inadequate drainage causes endolymphatic hydrops, and its rupture alters the chemical milieu of endolymph and perilymph, substantiated by the presence of scars. Recent studies show that the sudden shift of endolymph to the pars superior is the reason for vertigo attacks rather than the recurrent membrane breaks.<sup>[1]</sup> Furthermore, the neuroimaging studies found that endolymphatic hydrops is not absolutely to MDs but is also noted in subjects of vestibular migraine, isolated sensory neural hearing loss and in healthy volunteers.<sup>[2]</sup> MD also shares its pathophysiology with vestibular migraine, another disease of the inner ear. Trials also point to the immunological basis of the disease pathology. Those patients diagnosed with MD also have an autoimmune pathology.<sup>[3]</sup> Trials with allergic desensitisation in patients with MD show a positive response. The immunological profile also shows variations in the levels of cytokines and biomarkers in various clinical trials. However, the major hindrance to the clinical trials of MD is the placebo effect, which affects the outcome and validity of any trial. This paves the way for so many treatment options without specificity.

Current standard therapies, such as diuretics, vestibular suppressants, betahistine and invasive procedures, while offering some vertigo control, have variable efficacy and do not address the broader symptom burden associated with MD. Moreover, the overlap in clinical features with vestibular migraine and emerging evidence suggesting an immunological basis of MD highlight the need for alternative, multifactorial therapeutic strategies.

Antidepressants—particularly selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)—have shown promise not only as treatments for vestibular migraine but

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also potentially for MD due to shared pathophysiological mechanisms and symptom overlap. A recent scoping review by Missner *et al.* synthesised the limited but growing literature on SSRIs and TCAs in MD, reporting significant reductions in vertigo frequency and tinnitus severity among treated patients, though no significant impact on hearing thresholds was observed.<sup>[4]</sup> These agents were also associated with improvements in quality of life, likely through both direct symptom amelioration and treatment of comorbid depression, which is prevalent in MD populations.<sup>[4]</sup>

Mechanistically, antidepressants may exert beneficial effects in MD through modulation of ion channel subunits such as Kir4.1 in the inner ear, neuroprotective properties and central vestibular pathway serotonergic activity. Importantly, these medications have a favourable safety profile and are non-ototoxic, supporting their off-label use in refractory cases or when psychiatric symptoms coexist.<sup>[4]</sup>

In addition, venlafaxine, a serotonin–norepinephrine reuptake inhibitor with an immunomodulatory effect and efficacy in vestibular migraine prophylaxis, has been explored as a candidate for repurposing in MD. Preliminary trials suggest long-term benefits in reducing vertigo and stabilising hearing loss progression, though larger randomised controlled trials with detailed immunological and pharmacogenomic profiling are warranted to confirm these findings.

Venlafaxine is available as extended-release or immediate-release (IR) formulations, which achieve a steady state within 3 days, with the fastest onset of action. Its antidepressant effect is known to last for a year.<sup>[5]</sup> Venlafaxine was successfully tried in the prophylaxis of vestibular migraine<sup>[6]</sup> which shows more or less the same clinical picture of MD. Trials also show that this drug reduces the level of epithelial neutrophil-activating protein 78 (ENA-78), an immunological biomarker in major depressive disorder.<sup>[7]</sup> ENA-78 is a member of the CXC chemokines and acts as a potent chemoattractant and activator of neutrophil function, which is released in inflammatory diseases.<sup>[8]</sup> With limited or no action on cholinergic, histaminergic and  $\alpha$  receptors, venlafaxine gives a better safety profile. Major adverse reaction noted is the rise in blood pressure, more with the usage of IR. Furthermore, studies proved that the adverse events of venlafaxine were tolerated over time.<sup>[9]</sup> All these point to a chance of venlafaxine being a suitable candidate for repurposing for MD.

A recent trial of venlafaxine versus placebo with a short-term follow-up MD cleared the non-superiority of venlafaxine to placebo.<sup>[10]</sup> However, longitudinal follow-up of the trial shows the benefits of venlafaxine in the participants on long-term off-label use, though the number of participants who used the drug after the trial was lower. There was a significant reduction in the vertigo attacks, and the hearing loss was also reduced.

Cognitive improvement was also noted in the subjects. The inflammation biomarker, ENA78, is reduced while tumour necrosis factor-alpha and interferon gamma are elevated in this population in the short-term analysis. This highlights the long-term benefit of venlafaxine, and needs further research exploring the long term benefits of venlafaxine on the biomarkers at different dose strengths (37.5mg, 75mg, 150mg). Since the immunological basis of the disease is under evaluation,<sup>[3]</sup> a detailed study of various cytokines and the biomarkers in a large population is advisable. Including magnetic resonance imaging in large trials may phase out the confusion in the pathology of MD.<sup>[2]</sup> Adding to that, studies earlier noted that the variation in CYP2D6 phenotypes (EM AND PM) contributes to the pharmacodynamic responses and adverse effects of venlafaxine.<sup>[11]</sup> Taking into account, pharmacogenomic analysis of the trial is also recommended for the future personalised management of MD.

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