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REVIEW ARTICLE

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The role of selective serotonin reuptake inhibitors and tricyclic antidepressants in addressing reduction of Meniere's disease burden: A scoping review

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Abstract

Objective: To assess the effect of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in reducing vertigo, tinnitus, and hearing loss among patients with Meniere's disease (MD).

Data Sources: The following databases were utilized in this scoping review: Ovid Medline, PubMed-NCBI, CINAHL, Cochrane Library, Web of Science, and Clinicaltrials.gov.

Method: Studies were identified through the following search phrases: "serotonin specific reuptake inhibitors" OR "tricyclic antidepressants" AND "Meniere's disease." References from included manuscripts were examined for possible inclusion of additional studies.

Results: The literature search yielded 23 results, which were screened by three independent reviewers. Seventeen studies and three duplicates were excluded. An examination of references from the included studies yielded two additional publications. A total of four published studies assessing SSRIs and TCAs among 147 patients with MD were ultimately included. Four studies described significant reductions in vertigo attack frequency among patients treated with either SSRIs or TCAs compared to their pretreatment baseline. Three studies assessed the drugs' effects on hearing, of which none found a significant difference among patients treated with SSRIs or TCAs. One study found a significant decrease in patient-reported tinnitus following treatment with TCAs or SSRIs compared to their pretreatment baseline.

Conclusions: Data exploring SSRIs and TCAs among patients with MD suggests that these medications may reduce the frequency of tinnitus and vertigo, although there was significant heterogeneity in outcome reporting. There remains a need for larger-scale prospective studies that emphasize objective data to evaluate their effectiveness in reducing common MD symptoms.

Alexander A. Missner and Mana Sheykhsoltan contributed equally to this study.

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KEYWORDS
aural fullness, clinical trials, Meniere's disease, scoping review, sensorineural hearing loss, serotonin specific reuptake inhibitors, tricyclic antidepressants, vertigo

Key points

Serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are potentially effective in relieving the burden of a chronic inner ear disorder, Meniere's disease. These medications may help reduce vertigo and tinnitus symptoms. There remains a need for larger-scale prospective studies to further evaluate their effectiveness.

INTRODUCTION

The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) defines a definite diagnosis of Meniere's Disease (MD) with the following criteria: two or more spontaneous attacks of vertigo, each lasting 20 min to 12 h; audiometrically documented low-to mid-frequency sensorineural hearing loss in the affected ear on at least one occasion before, during, or after one episode of vertigo; fluctuating aural symptoms in the affected ear; and other causes excluded.[1,2] The prevalence of MD in the United States is estimated to be 190 per 100,000 individuals. MD is associated with significant morbidity and psychological sequelae.[1,3]

Common therapies for patients with MD include conservative measures such as changes in diet and sleep patterns for potential reductions of pressure in the endolymphatic system.[1,4] Other treatments involve diuretics, intratympanic (IT) gentamicin, oral high-dose betahistine, IT steroids, and IT steroids plus high-dose betahistine.[5] These interventions have been studied in systematic reviews and Meta-analyses, yet there is a lack of strong data to support their use in effectively controlling vertigo and optimizing hearing preservation among patients with MD.[5] Therefore, there is a need to investigate alternative treatments for improv medical management of MD.

Pharmacological treatment of vestibular migraine (VM) including tricyclic antidepressants (TCAs) and serotonin-specific reuptake inhibitors (SSRIs) has been proposed to treat MD based on the similarities of these two disorders.[6–8] VM is diagnosed by at least five episodes of vestibular symptoms of moderate or severe intensity lasting between 5 min and 72 h, and a current or previous history of migraine with one or more migraine features in at least 50% of the vestibular episodes.[9] It is estimated that 51% of patients with MD experience headaches and among that cohort, at least half experience vestibular symptoms simultaneously with migraines.[10–12] Furthermore, patients with VM tend to have evidence of motion intolerance to environments with complex visual stimuli or moving objects, as well as sensitivity to light and/or sound during vestibular symptom episodes. Fluctuation in hearing at the time of dizziness is less common in the setting of VM compared to in MD, which may be distinguished from aural fullness. MD presents more often with fluctuating aural symptoms of tinnitus or fullness in the affected ear, rarely involving bilateral ears as VM can.[2] The clinical similarities between these two disorders suggest a potential mechanistic overlap, prompting research into the use of VM treatments for patients with MD.[13] Nonetheless, there is limited data to support the use of SSRIs and TCAs among patients with MD.

Established clinical practice guidelines for the treatment of MD are aimed at (1) preventing or reducing vertigo attacks, (2) improving hearing loss, aural fullness, and tinnitus, and (3) enhancing QOL.[1] Since there is currently a poor understanding of the etiology of MD and a lack of effective therapies, there is tremendous variation in MD treatments.[1] The objective of this scoping review is to evaluate the role of SSRIs and TCAs in treating patients with MD and in turn provide a more evidence-based recommendation for their potential use.

MATERIALS AND METHODS

A scoping review of studies published on the use of TCAs and/or SSRIs in MD was adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search of Ovid Medline, PubMed-NCBI, CINAHL, Cochrane Library, Web of Science, and Clinicaltrials.gov from January 1997 through August 2022 was performed.

Search strategies

A literature search was conducted using the following keywords or phrases: [serotonin-specific reuptake inhibitors] OR [tricyclic antidepressants] AND [Meniere's disease]. Further search strategies included the use of journal features, such as “Explode” to include all subheadings and individual drugs pertinent to these classes. References were restricted to those written in the English language. Abstracts of studies yielded from the database search were investigated by three independent reviewers for inclusion or exclusion. References from the included studies were examined for possible inclusion of additional studies.

Inclusion and exclusion criteria

Studies that met inclusion criteria described the effect of either TCA, SSRI, or a combination thereof among patients with a diagnosis of

MD. All agents within the listed drug classes were sufficient to include. Studies that concurrently examined TCA or SSRI alongside other drug classes were included in this study. Exclusion criteria included studies in which patients did not have MD or were not taking TCAs or SSRIs designated for the treatment of their MD. Therefore, these agents had to be taken for the treatment of MD.

RESULTS

Figure 1 shows the flow chart of the search results. Initial literature search yielded 23 results. A total of 17 studies and three duplicates were excluded. An examination of references from the included studies yielded two additional publications. As such, four published studies assessing SSRIs and TCAs among 147 MD patients were ultimately included.[13–16]

Table 1 provides the characteristics of the four studies. Table 2 discusses the effects of the TCA or SSRI interventions on tinnitus, hearing loss, and vertigo severity.

Two studies examined the role of TCAs and two studies investigated SSRIs in MD.

Vertigo

Four studies described significant reduction in vertigo attack frequency among patients treated with either SSRIs or TCAs, although the measurements of vertigo attacks differed. Kıroğlu et al.[14] found that among all 12 patients included in their study, the average patient-reported vertigo attacks decreased from approximately three to zero attacks per year after initiating Escitalopram 10 mg between 12 and 24 months. Ghavami et al.[13] demonstrated an average decrease in patient-reported vertigo attacks from approximately eight to less than one attack per year after treatment with Nortriptyline (10–75 mg), Verapamil (120–240 mg), a combination of Nortriptyline and Verapamil, or Topiramate 150 mg. In a case series by Goto et al.,[15] three patients reportedly had completely controlled vertigo symptoms after initiating Sertraline 50 mg per day, although

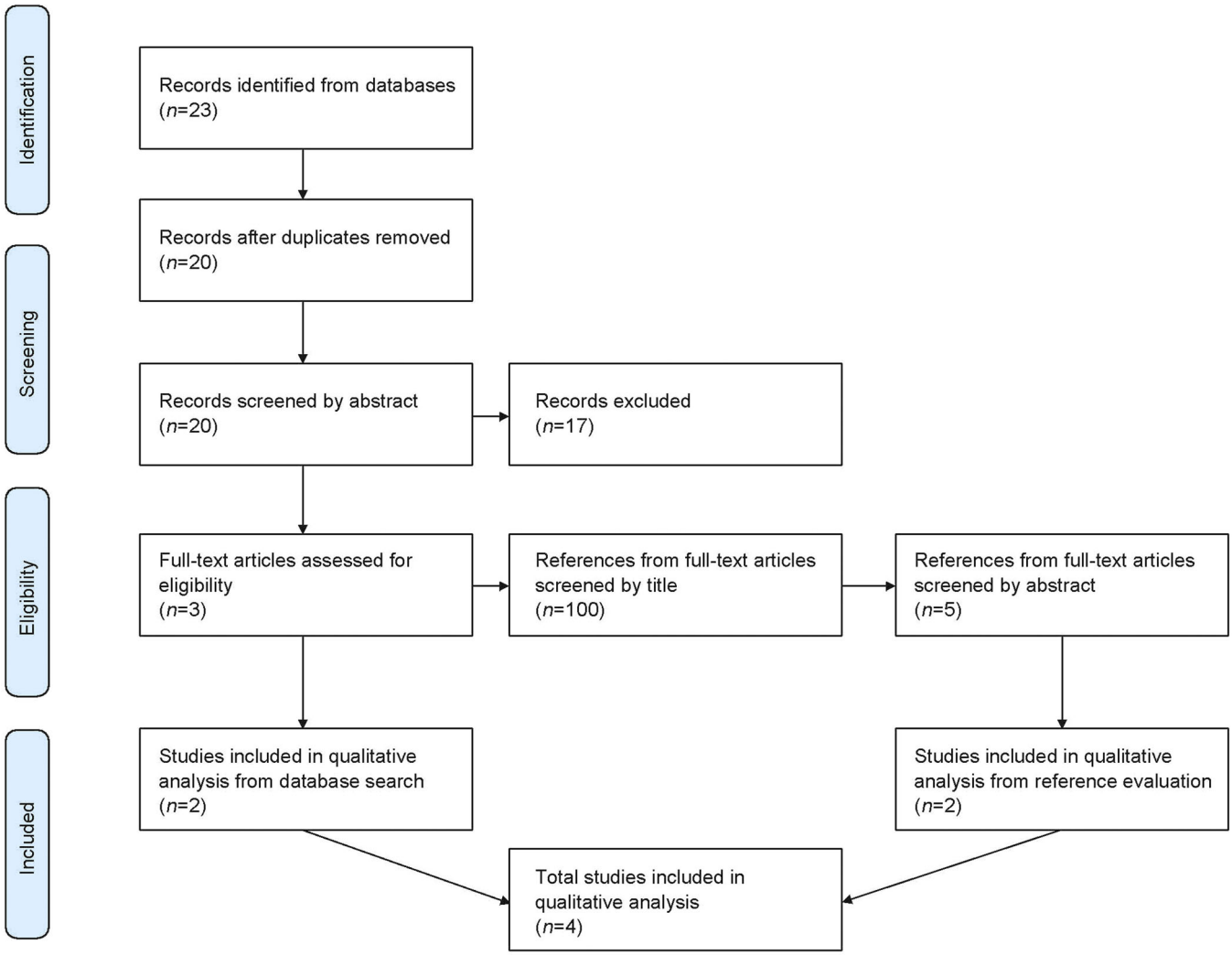

FIGURE 1 Flow diagram of systematic review process.

TABLE 1 Characteristics of included studies.

Authors, year (country)	Type of study	No. of MD pts	Diagnosis of MD pts	Intervention	Intervention duration and follow up-period	Measurement
Kıroğlu et al.,[14] 2017 (Turkey)	Cohort study	12	MD and GAD	Escitalopram 10 mg/d	23.5 months (12.0–36.0 months) compared to pretreatment baseline	Neurotologic examination, videonystagmography, audiological tests, and inner ear magnetic resonance imaging.
Ghavami et al.,[13] 2018 (USA)	Cohort study	27	MD	(1) Nortriptyline 25 mg qhs - with escalation of 25 mg every 3 weeks up to 75 mg if symptoms had not improved. (2) Verapamil SR 24 h 120 mg qhs with escalation to 180 mg and then 240 mg every 2 weeks if symptoms were not improved. (3) Combination of above medications. (4) Topiramate 25 mg qhs with weekly escalation of 25 mg up to 150 mg qhs.	24 months compared to pretreatment baseline	MDOQ-R after migraine prophylactic therapy to assess QOL.
Goto et al.,[15] 2013 (Japan)	Case report	3	MD- relapsed	Sertraline 50 mg/d	24 months compared to pretreatment baseline	PTA, DHI, HADS, and FL.
Rajamani et al.,[16] 2018 (India)	Randomized, double-blinded, placebo controlled trial	105	MD	Amitriptyline 10 mg/d or placebo (generic Vitamin B tablet)	10 days compared to 10 days on placebo	University of Virginia Vestibular and Balance Centre Dizziness Questionnaire, which has a Visual Analogue Scale.

Abbreviations: DHI, Dizziness handicap inventory; FL, Functional level score; HADS, Hospital anxiety and depression scale; MDOQ-R, Meniere's Disease Outcomes Questionnaire-Retrospective; PTA, Pure tone audiometry.

TABLE 2 Effects of SSRI/TCA interventions in included studies.

Authors, year (country)	Effect on hearing loss	Effect on vertigo	Effect on tinnitus
Kıroğlu et al.,[14] 2017 (Turkey)	Not reported	No vertigo attacks observed posttreatment	Not reported
Ghavami et al.,[13] 2018 (USA)	Posttreatment audiograms showed no change in hearing in the affected ear ($P = 0.15$). Self-reported decrease in "bothered by hearing loss" ($P < 0.001$)	Reduced vertigo FLS posttreatment ($P = 0.006$). 92% showed improvements in every QOL metric measured	Reduced tinnitus
Goto et al.,[15] 2013 (Japan)	Hearing thresholds, measured by PTA at 0.5, 1, 2, and 4 kHz did not alter	Vertigo attacks controlled posttreatment	Not reported
Rajamani et al.,[16] 2018 (India)	Hearing levels were reported to not be affected	Vertigo improved posttreatment ($P < 0.001$). 88.3% showed improvement in QOL	Not reported

Abbreviations: FLS, Functional level score; QOL, quality of life; SSRI, serotonin-specific reuptake inhibitors; TCA, tricyclic antidepressants.

their baseline symptoms were not quantified. Rajamani et al.[16] demonstrated a significant improvement in patient-reported vertigo symptoms based on a visual analog scale among patients who received Amitriptyline 10 mg compared to controls.

Hearing loss

Three studies assessed the drugs' effects on hearing, of which none found a significant difference among patients treated with SSRIs or TCAs. Two of these studies investigated hearing loss through audiometric data; however, only Ghavami et al.[13] compared pretreatment and posttreatment hearing thresholds and found no statistically significant change in hearing in the affected ear. No study evaluated control of hearing fluctuations.

Tinnitus

Ghavami et al.[13] found a significant decrease in patient-reported tinnitus among 25 patients treated with Nortriptyline (10–75 mg), Verapamil (120–240 mg), a combination of Nortriptyline and Verapamil, or Topiramate 150 mg.

Quality of life (QOL)

Two studies discussed improvements in QOL following drug intervention. Ghavami et al.[13] used the Meniere's Disease Questionnaire-Retrospective, while Rajamani et al.[16] used the Visual Analogue Scale and dizziness inventory handicap to comment on QOL.

DISCUSSION

TCAs and SSRIs have been reported to be used by otolaryngologists in the treatment of MD as well as concurrent MD and VM.[7,13] There are no seminal studies in the literature that support this use, but the lack of efficacious treatment options and disability associated with MD has led to the off-label use of these medications to potentially alleviate symptoms. In this scoping review, we found four manuscripts that suggest a possible role of these medications to alleviate vertigo, tinnitus, and overall QOL among patients with MD.

Several studies have shown reduction in migraine and vertigo when VM patients are treated with TCAs and SSRIs.[7,8,17] Although the mechanism of how these therapies exert their effects in treatment of VM and/or MD is largely unknown, a proposed mechanism may be through modulation of a potassium channel subunit, Kir4.1, found in cells of the stria vascularis and cochlear ganglion.[18] It is thought that Kir4.1 regulates endocochlear potential by maintaining concentration gradients between the endolymph and perilymph, in addition to maintaining endocochlear potential.[18] Both TCAs and SSRIs have been shown to inhibit this subunit in astrocytes, which is postulated to contribute to its therapeutic value.[19] Another potential mechanism of action of TCAs, specifically amitriptyline, may be through neuroprotective properties as a TrkB agonist and an inducer of glial cell line-derived neurotrophic factor, which together may regenerate and protect cochlear synapses.[20,21] Likewise, investigated serotonergic activity in the vestibular nuclei, inferior olive, and midline cerebellar nuclei may suggest the therapeutic potential of serotonin on central vestibular pathways.[22,23] Treatments that affect levels of serotonin may thus help reduce vertigo symptoms through these pathways.

Although both TCAs and SSRIs have adverse effects (AEs), including but not limited to TCAs' potential to cause cardiac toxicity and anticholinergic effects, and SSRIs' rare precipitation of serotonin syndrome,[24,25] they are widely prescribed and tolerated to treat migraine, neuropathic pain, vestibular migraine, and depression.[26–28] Both drug classes are known to cross the blood-brain barrier, and neither are ototoxic. These favorable safety profiles provide further motivation to investigate these drugs for MD.

Our review demonstrates that TCAs and SSRIs may improve QOL among patients with MD. A recently published systematic-review and meta-analysis found that 50% of patients with MD experience depression, and that many of these patients are not properly treated for this debilitating condition.[29] In diseases such as neuropathic pain

and depression, TCAs and SSRIs alleviate chronic discomfort, improve disability, and are respectively first-line agents.[26–28] These drugs may be associated with higher QOL due to improvement of underlying depression often seen in MD. However, the doses of TCAs and SSRIs utilized in the included studies are well below doses used for depression and anxiety. Ghavami et al. found that patients had significant improvement in memory function, depression, concentration, and self-confidence after SSRI/TCA treatment. A greater effect was seen in subjective improvement in physical symptoms of MD, such as hearing loss and tinnitus. Goto et al. noted that the utility of these medications may be due to treating comorbid depression, demonstrating subjective improvement in patients' anxiety and depression via a verified scale. Neither of these studies delineated whether improvement in MD was due to direct action of the drugs, addressing underlying comorbidity, or a combination of these mechanisms. This hypothesis should be further explored in future studies to assess how treating psychological comorbidity of MD improves patients' QOL. Furthermore, since over half of patients with MD experience headache, these therapeutics' role in reducing headache may suggest that they target another underlying symptom of MD.[10]

One of the limitations of this study is the significant heterogeneity among the included studies, which hindered a more robust statistical analysis of outcomes. One of the studies only had a follow-up of 10 days posttreatment, while three of the studies continued for approximately 2 years. All the studies used subjective metrics for reporting measures of symptoms, and the specific questionnaires varied between studies. Therefore, there is a lack of standardized and objective assessments of symptoms of MD following TCA or SSRI interventions. The interventions also varied widely between studies with respect to medication(s) and doses. Another limitation is the small sample sizes of the studies. The four studies yielded a total of only 147 MD patients. The standard for MD diagnosis has evolved overtime, and studies included in this analysis span from the years 2013–2018.[1] Therefore, we were unable to conclude if the criteria of diagnosis of MD was consistent throughout all studies as they were not explicitly addressed in all studies. In addition, the diagnosis of VM in MD patients was not thoroughly addressed in the included studies. Ghavami et al. specified that their MD patient cohort did not have a VM diagnosis, but the other studies did not specify whether patients with MD met the diagnostic criteria for VM. We encourage future studies to be transparent about the criteria used for the clinical diagnosis of MD and to screen for possible VM.

Altogether, the lack of effective treatment options and significant disability associated with MD necessitates drug-discovery for safe, effective treatments that potentially improve MD symptoms. Although the results from this study cannot establish that TCAs or SSRIs are a preferred treatment modality for MD, they have shown that they may reduce vertigo and tinnitus, and enhance QOL in MD patients. This data supports the notion that future studies should investigate TCAs and SSRIs in MD in larger scale, randomized controlled trials (RCTs) with objective metrics to assess vertigo, hearing thresholds, and quality of life.

CONCLUSION

The review of the literature suggests that SSRIs and TCAs are potentially effective in relieving the burden of MD through reduction of vertigo and tinnitus. Although the mechanisms of action of SSRIs and TCAs are largely unknown in MD, the postulated effects of antidepressants on subunit channels in the inner ear provide a potential mechanistic explanation for the reduction of MD symptoms by these interventions. There is a significant limitation in analysis due to sample sizes, variability in medication and regimen used, and heterogeneous outcome measures. Future research should utilize RCTs with long-term follow-ups and objective metrics of outcomes such as audiometric data analysis and validated questionnaires.

AUTHOR CONTRIBUTIONS

Mana Sheykhsoltan and Alexander A. Missner contributed equally to the conception or design of the work; acquisition, analysis, and interpretation of the data; and drafting of the manuscript. Amir Hakimi and Michael Hoa contributed to the study design, drafting or revising of the work, and approval of the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

This review article features previously published data, which are openly available in the articles cited in the reference section.

ETHICS STATEMENT

The authors have nothing to report.

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