Original Article

The effect of Adjunctive Memantine Added to Betahistine on symptoms and quality of life in chronic tinnitus: A randomized, single-blind clinical trial

Hamed Ghavimi, Azam Maleki, Haleh Shirvani, Mehdi Maghbooli*

1. Hamed Ghavimi: Assistant professor, Pharm.D, Ph.D. of Pharmacology, Zanjan University of Medical Sciences Faculty of Pharmacy, Department Pharmacology, Zanjan, Iran, Orcid ID: 0000-0001-8404-1544;Email: Hamed.Ghavimi@gmail.com

2. Azam Maleki: Assistant professor, Social Determinants of Health Research Center, Health and Metabolic Diseases Research Institute, Zanjan University of Medical Sciences, Zanjan, Iran, Orcid ID: 0000-0001-7888-1985; Email: malekia41@yahoo.com

3. Haleh Shirvani: Ph.D. of Pharmacology**,** Departments of Pharmacology and Toxicology, School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran, Orcid ID: 0009-0008-7059-1324; Email:H.sh.halleh@gmail.com

4. Mehdi Maghbooli: Associate professor of neurology, Iran, Zanjan University Of Medical Sciences, Vali-e-Asr Hospital, Neurology Department, Orcid ID: 0000-0003-0482-9062 ; E-mail: m.maghbooli@zums.ac.ir

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Criteria for inclusion in the authors'/ contributors' list:

I. Hamed Ghavimi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing.

II. Azam Maleki: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing.

III. Haleh Shirvani: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

IV. Mehdi Maghbooli: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Corresponding author: Mehdi Maghbooli, MD; Associate Professor of neurology, Vali-e-Asr university Hospital, Zanjan University of medical sciences, Zanjan, Iran

Tel: +98 24 33444182, +98 914 4910131

Fax: +98 24 33449553

Email: m.maghbooli@zums.ac.ir

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Abstract

Background: Tinnitus affects approximately 10–15% of adults and remains a significant medical challenge. Given the role of glutamate excitotoxicity in tinnitus pathophysiology, N-methyl-D-aspartate receptor antagonism represents a promising pharmacological target. This study aimed to evaluate the effect of adjunctive memantine, added to betahistine, on tinnitus severity, insomnia, and quality of life among patients with primary tinnitus.

Methods: A single-blind, randomized controlled trial was conducted on 60 patients with primary tinnitus. All participants received conventional treatment with betahistine (8 mg/day) for 90 days. The intervention group additionally received memantine, titrated up to 20 mg/day, while the control group received a placebo. Outcomes were assessed at baseline and three months post-intervention using the Tinnitus Handicap Inventory, Insomnia Severity Index, and Short Form-36 Health Survey (SF-36). Data analysis was conducted using chi-square and independent samples t-tests with statistical significance set at $P < 0.05$.

Results: At the end of follow-up, the intervention group showed a significant shift toward lower tinnitus severity, with 50% reporting mild and 31% slight tinnitus, while the control group showed no improvement, and 60% remained in the severe category. The between-group difference in the tinnitus severity distribution was statistically significant ($P = 0.001$). The intervention group demonstrated significantly greater improvements in health-related quality of life across multiple SF-36 domains and a significant reduction in insomnia severity compared with the control group, with between-group results favoring the memantine-plus-betahistine group ($P < 0.05$).

Conclusion: Adding memantine to betahistine may improve tinnitus-related outcomes compared with betahistine alone. Larger double-blind trials are needed to confirm these findings.

Key Words: Tinnitus, Memantine, Quality of life, Insomnia

1. Introduction

Tinnitus is the perception of sound in the absence of an identifiable internal or external auditory stimulus. Chronic tinnitus is a common problem among adults, particularly among women and individuals older than 60 years, leading to impaired quality of life [1]. A recently reported systematic

review and meta-analysis estimated that the global prevalence of any tinnitus among adults was 14.4%, with no significant difference between men and women [2].

Whereas the majority of the global population who experience tinnitus do not have significant life, work, or family interference with tinnitus, a significant proportion of affected individuals experience disabling tinnitus that negatively affects their social and occupational functioning. It is worth noting that tinnitus is strongly associated with depression, exacerbates cognitive disabilities, and negatively impacts an individual's quality of life [3-5]. Moreover, sleep disturbance is a common comorbidity among individuals with severe tinnitus and can further exacerbate the burden of the morbidity [6].

Currently, there are no Food and Drug Administration (FDA) approved drugs to treat tinnitus, and its management is a difficult and frustrating problem in clinics. Although a wide variety of substances, such as local anesthesia [7], anti-epileptics [8], tricyclic antidepressants [9], selective serotonin reuptake inhibitors (SSRIs) [10,11], and benzodiazepines [12], have been applied, no consensus has yet been reached regarding effective pharmacological treatments for tinnitus. Several pathophysiological models have been proposed to demonstrate the mechanism of tinnitus (e.g., peripheral model, central model, somatosensory model, inflammatory model, and psychological model), but its pathophysiology is incompletely understood [13]. Considerable attention has been paid to the possible involvement of the excitatory neurotransmitter glutamate in tinnitus pathophysiology via activation of N-methyl-D-aspartate (NMDA) receptors. It has been proposed that pathologically released glutamate at the terminals of the auditory pathways leads to overexpression of NMDA receptors. Upregulation of NMDA receptors in the auditory pathway provides a significant facilitation of glutamate overstimulation, leading to auditory system epilepsy and, consequently, tinnitus [14]. In this regard, several medications that antagonize the NMDA receptors, such as memantine, acamprosate, caroverine, and flupirtine, have been investigated in different clinical trials and animal studies for tinnitus treatment [15-18]. Memantine works as a noncompetitive antagonist of the NMDA receptor. Memantine has demonstrated efficacy in neurodegenerative disorders such as Alzheimer’s disease and has been shown to have a favorable tolerability profile [19].

Memantine has been examined as a potential treatment for tinnitus, but results across different animal models and clinical trials have been inconsistent. While some animal studies suggest that memantine can reduce tinnitus-related behaviors [20,21], randomized, double-blind, prospective

crossover clinical trial found no significant improvement in tinnitus symptoms compared to placebo. In the Figueiredo et al. clinical trial, participants (60 patients) received memantine, titrated to a maximum dose of 20 mg/day, and placebo for 90 days each, with a 30-day washout period between treatment periods. The primary treatment effect was evaluated using the Tinnitus Handicap Inventory (THI), and monotherapy with memantine did not produce a statistically significant improvement in THI scores compared with placebo [22].

The aim of this study was to assess the effect and safety of memantine in a clinically different context and to address several limitations in the assessment of treatment response. Unlike the Figueiredo et al. trial, the present study evaluated memantine as an adjunct to betahistine in a randomized, two-arm, parallel-group, single-blind clinical trial. Moreover, we aimed to examine not only tinnitus severity but also sleep and broader health-related functioning during adjunctive treatment.

2. Materials and Methods

2.1. Study setting

This study was a single-blind, two-arm, parallel-group randomized clinical trial conducted on 60 patients with primary tinnitus who attended the neurology clinic of Vali-e-Asr University Training Hospital in Zanjan between July 2022 and July 2023. Initially, all subjects were informed of the study protocol, and those who agreed signed the Free and Informed Consent form before enrollment.

2.2. Ethical Considerations

This study was approved by the Ethical Committee of Zanjan University of Medical Sciences under protocol number IR.ZUMS.REC.1402.103 and Iranian Clinical Trial Registration Center under the protocol number IRCT20190427043389N4.

2.3. Participants and eligibility criteria

The inclusion criteria for this study were patients aged 18-60 years with primary tinnitus lasting more than 3 months and were referred to the neurology outpatient clinic of Vali-e-Asr University Training Hospital in Zanjan, Iran and provision of written Free and Informed Consent. Non-inclusion criteria included prior use of memantine or other medications known to affect tinnitus,

such as steroids and vasodilators, within the last four weeks. Patients who had difficulty completing the questionnaires, such as difficulty understanding the questions, any otologic condition other than tinnitus, tinnitus caused by external or middle ear diseases, a history of psychiatric illness, anemia, diabetes mellitus, hypothyroidism, or other chronic and life-threatening chronic diseases, were also excluded from the study.

2.4.Intervention

Patients in the intervention group received memantine (Hakim Pharmaceutical Co., Tehran, Iran) and betahistine (8 mg: Actover Pharmaceutical Co., Karaj, Iran) daily, while the control group received placebo (formulated and produced at the pharmaceutical department of Zanjan University of Medical Sciences, Faculty of Pharmacy) and 8 mg betahistine daily. It is worth noting that, based on the recommendations of the local Ethics Committee and empirical usage and commonly prescribed medication in Iranian and other country clinical settings for tinnitus treatment, betahistine was administered as a baseline treatment in both groups [23]. The memantine dosing schedule was as follows: 1) days 1 to 7: 5 mg; 2) days 8 to 14: 5 mg twice a day; 3) days 15 to 21: 5 mg at 8 am and 10 mg at 8 pm; 4) days 22 to 90: 10 mg twice a day. It is worth noting that the dose of memantine was chosen from the previous study [22]. Moreover, the control group was administered a visually equivalent placebo tablet similar to the intervention group protocol for 90 days following a schedule similar to the intervention group's protocol. The patients, but not the outcome assessors were blinded with respect to the nature of the medications during the study. This study included demographic data collection through interviews with all participants. The collected data included age, gender, occupation, education level, marital status, and whether the participant resided in an urban or rural area.

2.5.Outcomes

The primary outcome of the study was the change in tinnitus severity, assessed using the validated Tinnitus Handicap Inventory (THI) questionnaire from baseline to the end of the 3-month intervention period. The secondary outcomes included**:** Insomnia severity, measured using the Insomnia Severity Index (ISI), to evaluate the impact of treatment on sleep disturbances. Quality of life, assessed using the 36-Item Short Form Health Survey (SF-36), to determine the broader effects of the intervention on participants' well-being. The THI is a self-report questionnaire designed to assess the severity and impact of tinnitus on patients' quality of life. The THI consists

of 25 questions, each scored using a three-point Likert scale: Yes (4 points), Sometimes (2 points), and No (0 points). The total score ranges from 0 to 100, with higher scores indicating greater tinnitus severity. According to this questionnaire, those patients who scored from 0 to 16 were defined as slight tinnitus or Grade 1, patients who scored from 18-36 were defined as mild tinnitus or Grade 2, patients who scored from 38 to 56 were defined as moderate or Grade 3, patients who were also scored 58-76 defined as severe or grade 4 and those patients who scored 78-100 were defined as catastrophic or Grade 5 tinnitus [24, 25]. The ISI is a brief self-report tool that assesses a patient's perception of their insomnia severity. The ISI is a sensitive instrument for measuring changes following insomnia treatment and has demonstrated reliability and validity in multiple studies. The questionnaire includes seven items that evaluate difficulties such as initiating sleep, maintaining sleep (frequent awakenings), early morning awakenings, satisfaction with sleep patterns, daytime functioning impairment, the noticeable impact of insomnia on others, and distress caused by sleep problems. Each item is rated on a 5-point Likert scale ranging from 0 (very satisfied) to 4 (very dissatisfied). The total score is calculated by summing the item scores, yielding a range of 0 to 28, with higher scores indicating more severe insomnia. Scores between 15 and 21 reflect moderate clinical insomnia, while scores between 22 and 28 indicate severe insomnia [26]. The Quality-of-Life Questionnaire (SF-36) assesses quality of life across two main domains: physical health and mental health, each comprising four subdomains, for a total of eight areas. The physical health domains include: physical functioning (10 items), physical role limitations (4 items), body pain (2 items), general health perceptions (5 items), the mental health domains include: social functioning (2 items), emotional role limitations (3 items), vitality/energy and fatigue (4 items), mental health/emotional well-being (6 items). Additionally, one question assesses the patient's overall perception of their health quality. Items are scored on a 5-point Likert scale, and scores for each domain are transformed to a scale ranging from 0 to 100, where higher scores indicate better functioning [27]. Safety profile data were collected from patients' follow-up visits over the three months of the intervention, and the frequency of any new adverse effects related to the treatment was documented.

2.6. Randomization and allocation concealment

Participants were recruited using convenience sampling from patients routinely referred to the neurology clinic of Vali-e-Asr University Training Hospital, Zanjan, Iran. A neurologist assessed potential participants for eligibility according to the predefined inclusion and exclusion criteria.

After providing written informed consent, eligible participants were randomly assigned in a 1:1 ratio to the memantine plus betahistine (the intervention group) or placebo plus betahistine (the control group) group using permuted block randomization with a block size of four. The random allocation sequence was generated by an independent individual who was not involved in participant recruitment, clinical assessment, outcome assessment, or data analysis. Allocation codes were placed in sealed, opaque envelopes. After enrolment, each participant selected one sealed envelope, and the enclosed code determined the assigned treatment regimen.

2.7. Blinding procedures

This was a single-blind randomized controlled trial with blinded data analysis. Participants were unaware of whether they had received memantine or placebo. The treating neurologist had access to the allocation code for prescribing purposes. Study medications were prepared in coded packages, and the dispensing staff provided the package corresponding to the participant's study code without access to the allocation key. The dispensing staff member was not involved in outcome assessment or data analysis. To maintain participant blinding, the placebo was matched to memantine in physical appearance and size. Outcome assessment was performed by a study researcher who was aware of treatment allocation; however, statistical analyses were conducted by an analyst blinded to group assignment.

2.8. Sample size calculation

In this study, the sample size was calculated using an independent two-sample *t*-test based on Cohen's effect size. Cohen's thresholds for effect sizes are defined as 0.2 for small, 0.5 for medium, and 0.8 for large effects. Considering the importance of a large effect, an effect size of 0.8 was selected. Assuming 80% statistical power and a significance level of 5%, the required sample size was estimated as 30 participants per group, totaling 60 participants. These calculations were performed using G*Power software. At the end of the intervention, the between-group difference corresponded to a large standardized effect (Cohen's d = 2.19, 95% CI: 1.52 to 2.85; $P < 0.001$).

2.9. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics Version 26. Descriptive statistics, including means and standard deviations, were calculated to summarize demographic and personal

characteristics of the study population. Group differences in demographic variables were assessed using chi-square tests for categorical data and independent-samples t-tests for continuous variables, as appropriate. The Kolmogorov–Smirnov test confirmed that the data were normally distributed. Consequently, independent t-tests were used to compare outcome measures between the intervention and control groups, and paired-samples t-tests were used to evaluate within-group changes from baseline to follow-up. A *P* value less than 0.05 was considered statistically significant. Efficacy analyses were performed using a complete-case approach and included participants with available baseline and post-intervention outcome data. Participants who withdrew before the post-intervention assessment were excluded from the efficacy analysis. No imputation was performed for missing post-intervention outcome data. For the primary outcome, an analysis of covariance (ANCOVA) was performed to compare post-intervention THI scores between the intervention and control groups, with baseline THI score included as a covariate. The assumption of homogeneity of error variances was satisfied, as indicated by Levene's test ($F_{(1,53)} = 0.097$, $P = 0.757$). The adjusted between-group difference was reported with its 95% confidence interval, together with the F statistic, *P* value, and partial eta squared (η^2p) as a measure of effect size.

3. Results

A total of 82 individuals were assessed for eligibility at the enrollment stage. Of these, 22 participants were excluded, including 12 who did not meet the inclusion criteria, 8 who declined to participate, and 2 for other reasons. Consequently, 60 participants were randomized and equally allocated to the two study arms, with 30 participants assigned to the intervention group and 30 participants to the control group. During the follow-up period, no participants were lost to follow-up in the control group. In contrast, in the intervention group, four participants withdrew from the study during the first two weeks due to adverse effects (one patient due to stomachache and three patients due to psychological side effects). Ultimately the complete-case efficacy analysis included 26 participants in the memantine-plus-betahistine group (the intervention group) and 30 participants in the placebo-plus-betahistine group (the control group) (**Figure 1**).

3.1. Baseline Characteristics

The intervention and control groups were comparable at baseline, with no significant differences in demographic characteristics ($P > 0.05$; **Figure 2**). The mean age of participants in the intervention group was 52.63 ± 10.89 years, while the mean age in the control group was 54.07 ±

8.45 years. There was no statistically significant difference in mean age between the two groups ($P = 0.687$), indicating that the intervention and control groups were comparable in terms of age at baseline.

3.2. Tinnitus Handicap Inventory

The mean THI score at baseline was 66.08 ± 15.7 in the intervention group and 59.13 ± 15.5 in the control group, with no significant between-group difference ($P = 0.103$). Similarly, the distribution of tinnitus severity levels (slight to catastrophic) did not differ significantly between the two groups at baseline ($P = 0.206$).

At the end of the intervention, a significant between-group difference was observed. The intervention group demonstrated a marked shift toward lower severity categories (**Table 1**), with 50% of participants reporting mild tinnitus and 31% reporting slight tinnitus, whereas the control group showed no improvement and a higher proportion remained in the severe category (60%). The difference in severity distribution between the two groups at the end of follow-up was statistically significant ($P = 0.001$).

After adjustment for baseline THI scores, the between-group difference in post-intervention THI scores remained statistically significant. ANCOVA showed a significant effect of treatment group on post-intervention THI scores, $F_{(1,53)} = 72.16$, $P < 0.001$, partial $\eta^2 = 0.577$. The adjusted mean difference between the intervention and control groups was −34.01 points (95% CI: −42.05 to −25.98), favoring the intervention group (**Table 2**).

3.3. Quality of Life Questionnaire

At baseline, there were no statistically significant differences between the intervention and the control groups across any of the SF-36 quality-of-life domains and the total score ($P > 0.05$). At the end of follow-up, the intervention group had higher mean scores than the control group in physical functioning ($P = 0.003$), bodily pain ($P = 0.043$), general health ($P = 0.019$), social functioning ($P = 0.012$), and mental health ($P = 0.048$). No statistically significant differences were found between the two groups in the domains of role limitations due to physical problems, vitality, or role limitations due to emotional problems at the end of follow-up ($P > 0.05$). The overall SF-36 score was also higher in the intervention group (75.24 ± 14.00 vs. 63.01 ± 15.19; $P = 0.003$). These comparisons were not adjusted for multiple testing; therefore, the domain-specific findings, particularly those with P values close to 0.05, should be interpreted cautiously (**Table 3**).

Insomnia Severity Index

At baseline, the mean ISI score was 12.62 ± 5.04 in the intervention group and 14.37 ± 4.90 in the control group, with no significant between-group difference ($P = 0.192$). Likewise, the baseline distribution of insomnia categories (absence, subthreshold, moderate, and severe insomnia) was comparable between the two groups ($P = 0.759$).

At the end of follow-up, a favorable shift toward lower insomnia severity was observed in the intervention group. The proportion of participants reporting absence of insomnia increased to 38.5% in the intervention group compared with 20.0% in the control group, while the proportion of moderate insomnia decreased to 11.5% in the intervention group versus 30.0% in the control group. However, the between-group difference in categorical distribution of insomnia severity at the end of follow-up did not reach statistical significance (P = 0.144). In contrast, analysis of continuous outcomes revealed a statistically significant reduction in mean ISI score in the intervention group compared with the control group at the end of follow-up (9.62 ± 4.01 vs. 12.07 ± 4.56, respectively; P = 0.042; **Table 4**).

3.4. Within-Group Comparison of Study Outcomes (Before and After)

Within-group analyses using paired *t*-tests revealed significant improvements across all outcomes in the intervention group following the intervention. Specifically, tinnitus severity showed a marked reduction in the intervention group, with a mean difference of 41.69 ± 20.86 (t = 10.19, P = 0.001). In contrast, no significant change was observed in the control group (P = 0.453). Similarly, insomnia severity (ISI score) significantly decreased in the intervention group (P = 0.003), whereas the reduction observed in the control group did not reach statistical significance (P = 0.06). Regarding quality of life, the intervention group experienced a significant improvement after the intervention (P = 0.001). Although a statistically significant change was also detected in the control group (P = 0.003), the magnitude of improvement was notably greater in the intervention group (**Table 5**).

3.5. Evaluation of Safety Profile

Adverse effects were assessed through face-to-face interviews and clinical examinations during follow-up visits. In the intervention group, 10 of the 30 randomized participants (33.3%) experienced at least one adverse effect. Four participants (13.3%) discontinued treatment within the first two weeks because of adverse effects, including psychological symptoms (n = 3) and gastrointestinal discomfort (n = 1), and were therefore excluded from the complete-case analysis. The remaining six participants reported adverse effects, including dizziness, elevated blood

pressure, insomnia, and psychological symptoms, but continued treatment through the end of the follow-up period. These six participants represented 20.0% of the randomized intervention group and 23.1% of those who completed the study. No adverse effects were reported in the control group.

4. Discussion

The aim of this study was to investigate the possible beneficial effects of adding memantine as a non-competitive NMDA receptor antagonist to betahistine on insomnia, quality of life, and tinnitus severity among patients with primary tinnitus. Our study results indicated that adding memantine to betahistine may improve tinnitus severity. Consistent with our findings, Pourayyoubi et al. (2025) demonstrated the effectiveness of memantine in reducing tinnitus severity in a double-blind, randomized placebo-controlled trial. In their study, 70 patients (age range 18-65 years) were randomly assigned to intervention (n= 35) and control groups (n= 35), with both groups receiving routine treatment consisting of cinnarizine 25 mg twice daily; however, memantine was added to the intervention group at an initial dose of 5 mg daily. The dose gradually increased to a maximum of 20 mg per day during the final weeks of the 60-day treatment period. In the Pourayyoubi et al. trial, tinnitus severity was evaluated using the Tinnitus Severity Index (TSI) and the Numerical Rating Scale (NRS) at baseline and after a 60-day follow-up period, without assessing sleep or broader quality-of-life domains. It is worth noting that previous comparative research has shown that THI is more closely associated with psychological measures and may provide a more comprehensive representation of patients' overall tinnitus-related status than NRS [28]. Despite the absence of significant baseline differences between the groups, Pourayyoubi et al. reported a significant reduction in TSI in the memantine group at the end of the treatment period, supporting the potential role of memantine as an effective adjunctive therapy alongside routine treatment. Nevertheless, they reported that the mean NRS improved significantly in both the intervention and control groups [29]. In contrast, Salembier et al. found no statistically significant improvement in tinnitus symptoms following treatment with flupirtine, another functional NMDA receptor antagonist, highlighting the inconsistent clinical evidence supporting NMDA receptor antagonism as a treatment strategy for tinnitus[15].

Consistent with the results of the Pourayyoubi et al. study, these findings are consistent with a possible role of NMDA-mediated glutamatergic mechanisms in the pathophysiology of tinnitus and highlight NMDA receptor antagonism as a rational therapeutic approach. Inner ear cell

damage, may be a common underlying cause of tinnitus, leads to dysregulated glutamate release, the primary excitatory neurotransmitter in the auditory system, which may induce neurotoxicity and neuronal hyperexcitability. By antagonizing NMDA receptors, memantine may attenuate this pathological glutamatergic overactivation. Supporting this mechanism, preclinical evidence has demonstrated that memantine exerts protective effects against salicylate-induced tinnitus, potentially through downregulation of the NMDA receptor NR2B subunit [21].

In line with these findings, it is also reported that a combination of memantine could attenuate the salicylate-induced tinnitus in rats [30]. Zheng *et al.'s* study mentions that memantine reduces chronic tinnitus caused by acoustic trauma in rats [20]. Lobarinas *et al.* utilized the salicylate- and quinine-induced tinnitus model in rats and reported the beneficial effects of memantine [31]. In contrast to our findings, Figueiredo et al. reported that memantine was ineffective in treating tinnitus in human subjects [22].

The results of the present study suggested a possible beneficial effect of memantine add -on betahistine treatment in tinnitus. To the best of our knowledge, this was among the few trials, if not the only one, to evaluate insomnia and health-related quality of life alongside tinnitus severity during adjunctive memantine treatment, and the results indicated a beneficial effect of adjunctive memantine added to betahistine in improving quality of life and insomnia severity among patients with primary tinnitus. Importantly, because betahistine was administered to both study groups, the present trial evaluated the additional effect of memantine when added to betahistine, rather than the efficacy of memantine as monotherapy. Similarly, because the study did not include a group receiving neither betahistine nor memantine, it was not designed to establish the efficacy of betahistine itself for tinnitus. Therefore, the observed between-group differences should be interpreted as the effects associated with adding memantine to the background betahistine regimen.

Commonly, patients suffering from tinnitus have sleep and psychological difficulties that affect sleep quality and quality of life. Accumulating data reported that insomnia occurs in up to 50% of patients with severe tinnitus. In line with these observations, Mori et al. (2021) reported that initiation of low-dose memantine led to a significant short-term increase in sleep duration, despite no baseline differences in sleep scores compared with the galantamine group, supporting a potential role for memantine in sleep modulation [32]. In another study, four weeks of memantine treatment significantly improved sleep continuity, as evidenced by longer total sleep time, higher sleep efficiency, and fewer nocturnal awakenings, and was accompanied by a reduction in

behavioral and psychological symptoms of dementia (BPSD), particularly anxiety and irritability, suggesting that its sleep benefits may be partly mediated through attenuation of neuropsychiatric hyperarousal [33].

Omranifard et al. demonstrated that add-on memantine, titrated up to 20 mg/day over four weeks, led to significant improvements in global functioning and quality of life in patients with schizophrenia receiving stable doses of atypical antipsychotics. These findings suggest that memantine may exert broad functional and quality-of-life benefits, potentially through modulation of glutamatergic neurotransmission and reduction of neuropsychiatric symptom burden [34]. Regarding insomnia, our results indicated that the mean ISI score at the end of follow-up was significantly lower in the intervention group than in the control group. However, the between-group difference in the categorical distribution of insomnia severity was not statistically significant. Thus, although the findings suggest a possible improvement in self-reported insomnia symptoms associated with adjunctive memantine, they do not establish a clinically meaningful improvement in insomnia severity or a definitive shift between insomnia categories. The magnitude and clinical relevance of this difference should be further evaluated in larger studies using prespecified clinical response criteria.

The present study also explored health-related quality of life using the SF-36 questionnaire. At the end of follow-up, the intervention group had higher mean scores in several SF-36 domains and in the overall score than the control group. However, these findings should be interpreted cautiously because multiple comparisons were performed without adjustment for multiplicity. In particular, the results for bodily pain, general health, social functioning, and mental health, which had *P* values close to the conventional significance threshold, should be considered exploratory. Although the observed differences suggest a potential benefit of adjunctive memantine on selected aspects of self-reported health status, the present findings do not establish that these differences are clinically meaningful. In a large randomized trial of patients undergoing whole-brain radiotherapy, memantine (20 mg/day) showed a significant association between baseline cognitive function and health-related quality of life (HRQoL) [35]. Taken together, these findings indicate that the effects of memantine on quality of life are highly context-dependent. While add-on memantine improves global functioning and quality-of-life in chronic neuropsychiatric conditions such as schizophrenia, where symptom burden, emotional regulation, and sleep disturbance play central roles, similar benefits are not consistently observed in patients with brain metastases undergoing

whole brain radiotherapy (WBRT), a population characterized by progressive neurological injury and limited functional reserve. This distinction is particularly relevant to the present tinnitus study, in which improvements in quality of life may be partly mediated by reductions in insomnia severity and hyperarousal rather than through direct cognitive enhancement. These mechanisms may partly explain why memantine produces measurable quality-of-life benefits in functional sensory disorders but not in conditions dominated by structural brain damage.

An important tolerability finding was that four participants (13.3%) in the intervention group discontinued the study within the first two weeks because of adverse effects and poor tolerability. Overall, 10 of the 30 participants (33.3%) in the intervention group experienced at least one adverse event, although six continued treatment despite these events. These findings highlight the importance of considering treatment tolerability alongside potential therapeutic benefits when evaluating adjunctive memantine for chronic tinnitus.

Several limitations of this study should be considered when interpreting the findings. The sample size was relatively small. In addition, participants were recruited from a single secondary neurology clinic, which may limit the generalizability of the results to more diverse tinnitus populations or other clinical settings. Furthermore, all outcomes were assessed using self-reported instruments (THI, ISI, and SF-36), which are susceptible to reporting bias and may not fully reflect objective changes in auditory processing or sleep physiology. In addition, the outcome assessor was aware of participants' treatment allocation, although data analysis was conducted under blinded conditions. Given the self-reported nature of the outcome measures, the possibility of assessment- or response-related bias cannot be completely excluded. Because four participants in the memantine-plus-betahistine group discontinued treatment early due to adverse effects and lacked post-intervention outcome data, the complete-case analysis may have been affected by differential attrition bias; thus, the findings should be interpreted cautiously. Future studies involving larger, multicenter cohorts, extended follow-up durations, and objective neurophysiological or sleep-related measures are warranted to more comprehensively elucidate the role of memantine in tinnitus-associated insomnia and quality-of-life impairment.

5. Conclusion

In conclusion, the outcomes of the present investigation suggest that adding memantine, a drug used to treat Alzheimer's disease, to a background regimen of betahistine may help alleviate primary tinnitus, patients' quality of life and self-reported insomnia compared with betahistine

alone. However, the clinical relevance of the insomnia findings and the robustness of the SF-36 domain-specific results remain uncertain, particularly because the categorical insomnia analysis was not statistically significant and multiple SF-36 comparisons were performed without adjustment. Given the small sample, single-center design, differential attrition and short follow-up, current results are preliminary and require confirmation in larger, adequately blinded trials. This research could help expand our options for treating tinnitus.

Authors Contributions

Hamed Ghavimi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. Azam Maleki: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. Haleh Shirvani: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. Mehdi Maghbooli: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Ethics Statement

All procedures in this study were conducted in accordance with the protocols approved by the Zanjan University of Medical Sciences ethics committee (IR.ZUMS.REC.1402.103) and the Iranian Clinical Trial Registration Center under the protocol number IRCT20190427043389N4, for research involving human participants.

Patient Consent Statement

Written informed consent was obtained from all participants. Due to institutional confidentiality policies, signed consent forms are securely archived and cannot be shared externally.

Clinical Trial Registration

This study was approved by the Iranian Clinical Trial Registration Center under the protocol number IRCT20190427043389N4.

Conflict of Interest

The authors declare no relevant financial or non-financial interests.

Data Availability Statement

Data will be provided upon reasonable request.

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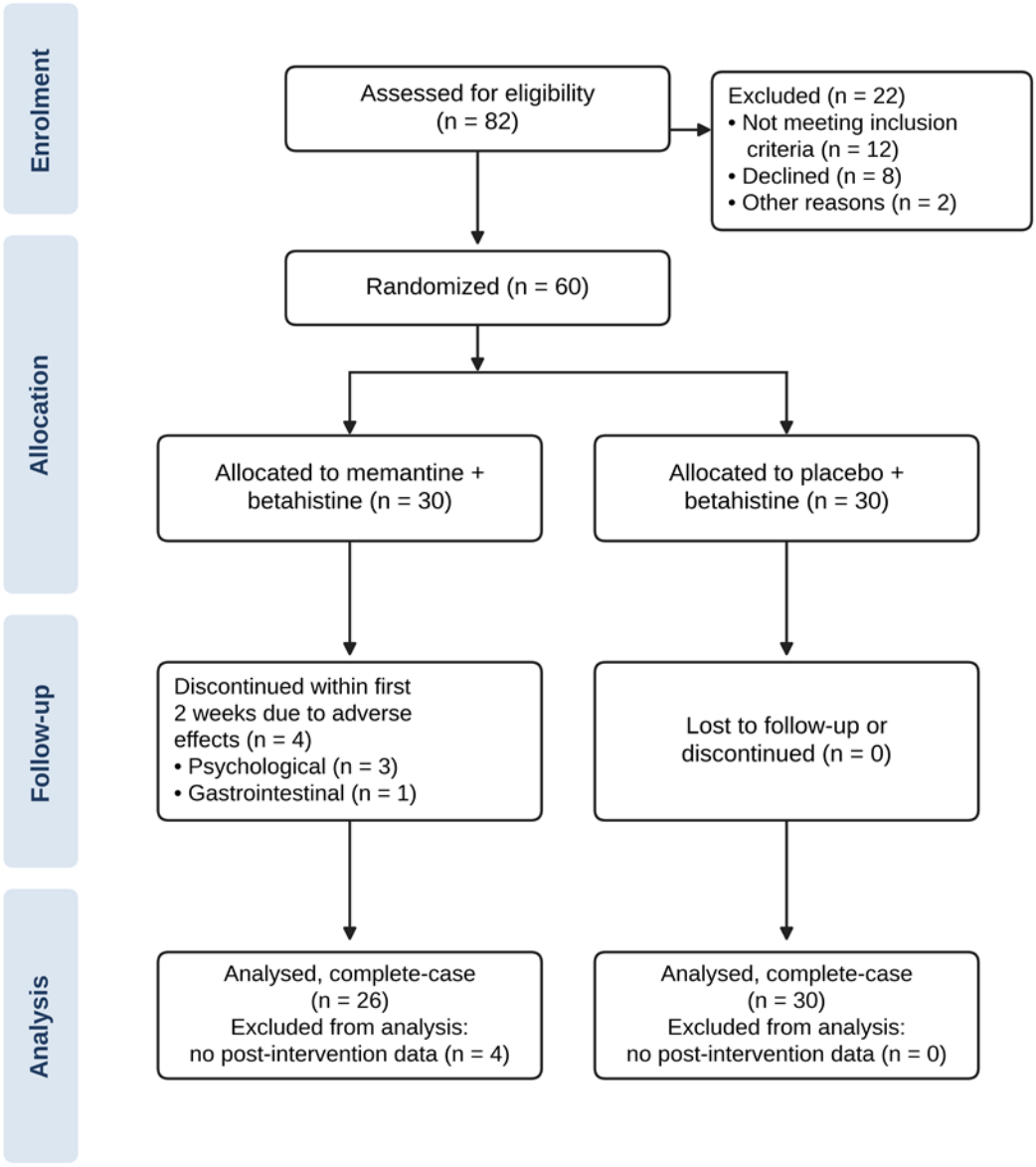
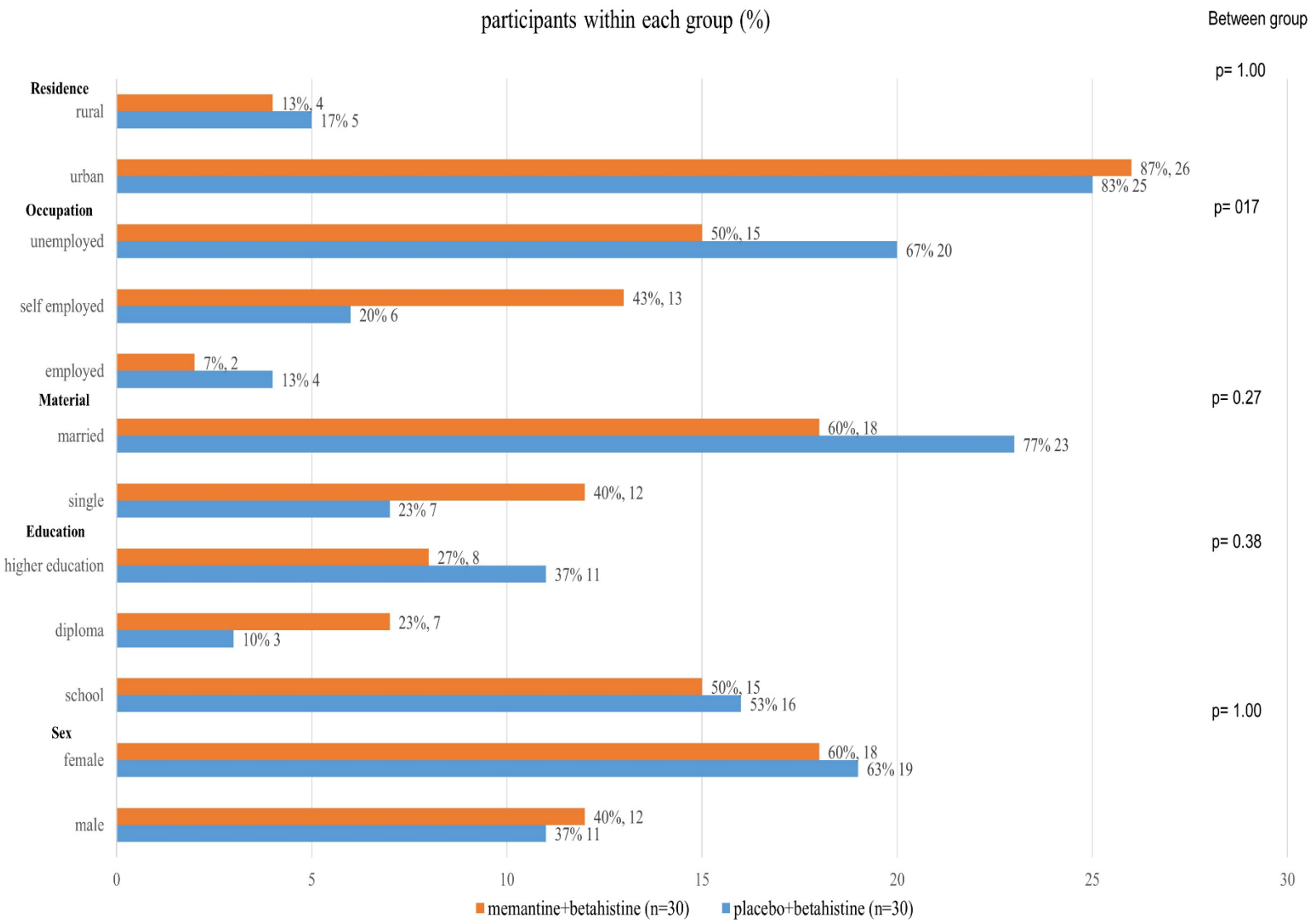


Figure 1. Diagram of the flow of patients through every stage of the study.



Values are n (%) of the 30 participants randomized to each arm. P values: Fisher's exact test (2 categories) or permutation chi-square test (3 categories).

Figure 2. Demographic and epidemiological characteristics of patients in both the intervention and control group

Table 1. Between-Group Comparisons of Tinnitus Severity Categories and THI Scores at Baseline and Post-Intervention

Number of severities	Baseline			EndPoint		
	Intervention group (%)	Control group (%)	*P* Value	Intervention group (%)	Control group (%)	*P* Value
Slight	0	0		8 (30.77)	0	
Mild	2 (7.7)	3 (10)		13 (50)	3 (10)	
Moderate	3 (11.5)	9 (30)	0.206	4 (15.38)	9 (30)	0.001
Severe	14 (53.8)	15 (50)		1 (3.85)	18 (60)	
Catastrophic	7 (26.9)	3 (10)		0	0	
Total	26 (100)	30 (100)		26 (100)	30 (100)	
	Mean ± SD			Mean ± SD		
Between-Group Comparison	66.08 ± 15.7	59.13 ± 15.5	0.103	24.38 ± 14.7	56.8 ± 14.9	0.001

The independent *t*-tests and Chi-Square test were employed to compare outcome measures between the intervention and control groups.

Table 2. ANCOVA Results for Post-Intervention THI Scores Adjusted for Baseline THI

Source	df	F	*P* value	Partial η^2
Baseline THI	1	3.28	0.076	0.058
Treatment group	1	72.16	<0.001	0.577
Error	53	—	—	—

Table 3. Between-Group Comparison of Mean health-related quality-of-life scores at the baseline and endpoint

SF-36 Domain	Baseline			EndPoint		
	Intervention group (n=26)	Control group (n=30)	*P*	Intervention group (n=26)	Control group (n=30)	*P* Value
Physical function	78.65±20.62	69.50±21.06	0.107	85.38±18.22	69.02±21.09	0.003
Role physical	48.08±33.85	39.17±33.91	0.331	81.73±33.04	67.08±34.5	0.122
Body pain	69.62±26.3	62.00±19.72	0.222	80.00±24.17	67.33±21.49	0.043
General health	54.81±24.19	45.00±20.09	0.103	63.27±22.22	49.83±19.32	0.019
Vitality	58.08±22.36	55.33±18.00	0.613	49.04±10.96	43.67±11.29	0.077
Social function	63.94±21.6	61.67±17.35	0.664	80.29±20.36	67.08±17.82	0.012
Role emotional	34.62±43.7	50.00±39.88	0.174	78.21±35.2	68.89±38.09	0.349
Mental health	61.69±19.17	57.33±18.98	0.397	69.85±13.54	62.27±14.31	0.048
Total SF-36 score	61.49 ± 17.74	56.4 ± 13.1	0.224	75.24 ± 14	63.01 ± 15.19	0.003

Independent-samples t-tests were used to compare SF-36 scores between the intervention and control groups.

Table 4. Between-Group Comparison of Mean Insomnia Severity Scores at baseline and endpoint

Distribution of insomnia	Baseline			EndPoint		
	Intervention group (n=26)	Control group (n=30)	*P* Value	Intervention group (n=26)	Control group (n=30)	*P* Value
Absence of insomnia	5 (19.2%)	4 (13.3%)		10 (38.5%)	6 (20.0%)	
Subthreshold insomnia	9 (34.6%)	8 (26.7%)	0.759	13 (50.0%)	15 (50.0%)	0.144
Moderate insomnia	11 (42.3%)	17 (56.7%)		3 (11.5%)	9 (30.0%)	
Severe insomnia	1 (3.8%)	1 (3.3%)		•	•	
Between-Group Comparison	Mean ± SD			Mean ± SD		
	12.62 ± 5.04	14.37 ± 4.9	0.192	9.62 ± 4.01	12.07 ± 4.56	0.042

The independent *t*-tests were employed to compare ISI score between the intervention and control groups.

Table 5. Within-Group Comparison of Study Outcomes Before and After the Intervention Using Paired-Samples t-Test

Variable	Group	Comparison	Mean Difference	SD	*T* Value	*P* Value
Tinnitus Severity	Intervention	Pre – Post	41.69	20.86	10.19	0.001
	Control	Pre – Post	2.33	16.78	0.76	0.453
Insomnia Severity (Isi)	Intervention	Pre – Post	3.00	4.57	3.35	0.003
	Control	Pre – Post	2.30	3.20	0.94	0.06
Quality of Life	Intervention	Pre – Post	−13.75	12.59	−5.57	0.001
	Control	Pre – Post	−6.61	11.06	−3.28	0.003

Within-group comparisons were performed using paired-samples t-tests. Mean differences were calculated as baseline minus post-intervention scores. *P* values are two-sided.