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"REAL-WORLD PRESCRIBING PATTERNS AND CLINICAL OUTCOMES OF ANTI-TINNITUS MEDICATIONS: A POPULATION-BASED COHORT STUDY"

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ABSTRACT:

Background: Tinnitus, characterized by the perception of sound in the absence of an external stimulus, remains a challenging condition with limited therapeutic options and variable patient outcomes. Despite the widespread use of anti-tinnitus medications, there is a paucity of real-world evidence on prescribing patterns and their association with clinical outcomes in population-based cohorts.

Objectives: To evaluate real-world prescribing patterns of anti-tinnitus medications and to assess their clinical outcomes in a population-based cohort of patients with tinnitus.

Methods: A retrospective cohort study was conducted among 165 patients diagnosed with tinnitus between January 2022 and December 2024. Data were extracted from electronic medical records and prescription databases. Baseline demographic and clinical characteristics, medication classes (including Caroverine, Betahistine, benzodiazepines, antidepressants, anticonvulsants, and nutraceuticals), treatment duration, and adherence patterns were analyzed. Outcomes were assessed in terms of symptom reduction measured by the Tinnitus Handicap Inventory (THI) scores, patient-reported improvement, and adverse drug reactions (ADRs). Statistical analysis included descriptive statistics, chi-square tests for categorical comparisons, and multivariable logistic regression to identify predictors of treatment response.

Results: Of 165 patients (mean age 48.6 ± 12.4 years; 56% male), Caroverine was the most commonly prescribed agent (32.72%), followed by Betahistine (30.30%) antidepressants (214.54%), benzodiazepines (10.30%), anticonvulsants (06.66%) and nutraceuticals (05.45%). Monotherapy was more frequent (71%) compared to combination therapy (29%). At 6-month follow-up, 54% of patients reported clinically significant improvement in THI scores. Caroverine users showed good response followed by Betahistine users compared to other drug classes ($p<0.05$). Adherence was moderate (mean medication possession ratio 0.68), and 11% discontinued treatment due to adverse events, most frequently headache, dryness of mouth with Caroverine followed by sedation and

gastrointestinal disturbances with other anti tinnitus medication. Logistic regression revealed younger age (<50 years), shorter duration of tinnitus (<2 years), and Caroverine followed by Betahistine prescription as independent predictors of favourable outcome.
Conclusions: Real-world prescribing patterns for tinnitus management are dominated by Caroverine followed by Betahistine and antidepressants, with moderate adherence and variable clinical outcomes. Betahistine was associated with better symptom improvement, particularly in younger patients and those with shorter symptom duration. These findings underscore the need for individualized prescribing strategies and further randomized studies to optimize tinnitus management.

Keywords: Tinnitus, Anti-tinnitus medications, Prescribing patterns, Clinical outcomes, Caroverine, Betahistine, Population-based cohort

INTRODUCTION

1. Background and Global Burden of Tinnitus

Tinnitus is defined as the perception of sound in the absence of an external acoustic stimulus and is often described as ringing, buzzing, hissing, or roaring in the ears. It is not a disease entity by itself but a symptom with multifactorial etiologies, including otologic, neurologic, metabolic, pharmacologic, and psychological conditions. Epidemiological surveys indicate that tinnitus affects approximately 10–15% of the adult population globally, with 1–2% experiencing severe distress and disability due to chronic tinnitus [1,2]. The World Health Organization (WHO) recognizes tinnitus as a significant public health problem that compromises quality of life, work productivity, and mental well-being [3].

In India, community-based prevalence estimates vary between 7% and 12%, with higher rates reported among the elderly population and individuals with occupational noise exposure [4]. Urbanization, increased noise pollution, and longer life expectancy have further contributed to a rising incidence. Despite the substantial burden, tinnitus continues to be under-reported and under-treated, partly because it is subjective, poorly understood, and challenging to measure objectively.

2. Patho-physiology of Tinnitus

The pathogenesis of tinnitus is complex, involving peripheral and central auditory pathways as well as non-auditory brain networks. Peripheral cochlear damage, often secondary to noise exposure, presbycusis, or ototoxic drugs, can lead to abnormal neural firing and reduced input to the central auditory system. This triggers maladaptive neuroplastic changes in the auditory cortex, dorsal cochlear nucleus, and limbic system, resulting in the persistent perception of phantom sounds [5, 6]. Moreover, functional MRI studies have shown hyperactivity in auditory and limbic circuits, linking tinnitus perception with emotional distress, anxiety, and depression [7].

Given this heterogeneity in Patho-physiology, treatment approaches are diverse and often symptomatic, with varying degrees of efficacy. The absence of a universally effective therapy underscores the importance of evaluating real-world prescribing trends and outcomes.

3. Therapeutic Landscape of Anti-Tinnitus Medications

Multiple classes of pharmacological agents have been employed in tinnitus management, although none have been universally approved as definitive treatment. The most widely used medications include:

Caroverine: Caroverine is an oto-neuroprotective agent and muscle relaxant that works by blocking NMDA receptors and calcium channels to reduce glutamate activity. While it shows some effectiveness in treating tinnitus and abdominal pain, evidence from broader studies is mixed, and strong scientific consensus is lacking. Patient acceptance is unclear but may be comparable to better-supported treatments like amitriptyline.

Betahistine: A histamine analogue that acts as a partial H1 agonist and H3 antagonist, improving cochlear microcirculation and vestibular compensation. Several clinical trials report moderate benefit in tinnitus severity, especially in Ménière's disease [8,9].
Antidepressants: Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are prescribed for patients with comorbid anxiety or depression. Their effect on tinnitus loudness is inconsistent, but they improve distress scores in selected populations [10].
Benzodiazepines: Agents such as clonazepam and alprazolam have demonstrated short-term improvement in tinnitus perception, likely through GABAergic modulation. However, their long-term use is limited due to dependence and sedation [11].
Anticonvulsants: Drugs like gabapentin and carbamazepine have been evaluated for tinnitus suppression, with mixed evidence on efficacy [12].
Nutraceuticals and Herbal Agents: Ginkgo biloba extract has been widely marketed for tinnitus, though systematic reviews have not found consistent clinical benefit [13].
Other Agents: Lidocaine, zinc supplements, and NMDA receptor antagonists have been explored but are rarely used outside experimental settings [14].
Despite this broad pharmacological armamentarium, evidence remains inconclusive, and prescribing often reflects physician preference, local availability, and patient demand rather than guideline-driven recommendations.

4. Limitations of Current Evidence

Several randomized controlled trials (RCTs) and meta-analyses have examined the efficacy of anti-tinnitus medications. However, heterogeneity in study design, outcome measures, patient selection, and duration of follow-up has limited their generalizability [15]. Most trials have small sample sizes, short follow-up periods, and rely heavily on subjective measures such as the Tinnitus Handicap Inventory (THI) or Visual Analogue Scale (VAS). Moreover, placebo responses in tinnitus trials are notably high, complicating interpretation of drug efficacy [16].
Consequently, there is no consensus among professional societies regarding a gold-standard pharmacological treatment. The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) clinical practice guidelines (2014) recommend against routine use of pharmacological therapy for primary tinnitus but acknowledge potential benefit in select cases with co-morbid mood disorders [17]. Similarly, the European guidelines highlight the limited evidence base and encourage individualized management [18].
These uncertainties make real-world data valuable, as prescribing patterns outside clinical trials may better reflect actual patient needs, physician decision-making and long-term outcomes.

5. Real-World Prescribing Patterns in Otolaryngology and Neurology

Real-world evidence (RWE) provides insights into how medications are used in practice, beyond the controlled environment of RCTs. Observational studies and prescription audits have revealed striking variations in drug selection, often influenced by regional practice patterns, cost, and patient expectations [19]. In India, Caroverine and Betahistine remains the most frequently prescribed agent for tinnitus, followed by SSRIs and benzodiazepines, while nutraceuticals continue to have widespread but scientifically unsubstantiated use [20].
A recent multicentre study in Europe reported that nearly 70% of tinnitus patients received some form of pharmacological therapy, despite guideline recommendations emphasizing non-pharmacological interventions such as counselling and sound therapy [21]. This reflects the therapeutic gap between evidence and practice, necessitating population-based cohort studies to systematically document prescribing trends and associated outcomes.

6. Clinical Outcomes and Patient Perspectives

The effectiveness of anti-tinnitus medications is best evaluated not only in terms of reduction of tinnitus loudness but also in patient-centred outcomes, including sleep quality, emotional well-being, and functional status. THI, Tinnitus Functional Index (TFI), and Hospital Anxiety and Depression Scale (HADS) are commonly used tools to assess outcomes.

Patients often perceive partial relief or reduced distress as meaningful, even if tinnitus persists. Conversely, adverse drug reactions, poor adherence, and high expectations can undermine treatment success [22]. Understanding predictors of favourable outcomes—such as younger age, shorter symptom duration, and absence of severe hearing loss—can improve individualized prescribing [23].

7. Rationale for the Study

Despite a high burden of tinnitus and widespread use of anti-tinnitus medications in clinical practice, there remains limited real-world evidence from low- and middle-income countries such as India. Existing data are fragmented, often derived from small hospital-based studies with narrow focus. A population-based cohort design allows comprehensive evaluation of both prescribing trends and clinical outcomes in diverse patient groups.

This study is designed to fill critical knowledge gaps by:

1. Documenting real-world prescribing patterns of anti-tinnitus medications in a representative patient cohort.
2. Evaluating short- and medium-term clinical outcomes in terms of symptom reduction, quality of life, and adverse events.
3. Identifying predictors of favourable treatment response and factors influencing medication adherence.

The findings will inform evidence-based prescribing, guide policy formulation, and contribute to the global understanding of tinnitus management. Moreover, the study may help bridge the gap between guideline recommendations and actual practice, particularly in resource-constrained healthcare systems.

MATERIALS:

Study Design and Setting: This was a prospective observational cohort study conducted over a 12-month period at a tertiary care otolaryngology center. The aim was to assess real-world prescribing patterns, treatment adherence, and clinical outcomes in patients with tinnitus receiving pharmacologic therapies.

Participants: A total of 165 adult patients (aged ≥18 years) diagnosed with subjective tinnitus were enrolled consecutively from outpatient clinics. **Inclusion criteria were:** Patients with confirmed clinical diagnosis of chronic subjective tinnitus lasting ≥3 months. Patients showing Willingness to participate and provide informed consent. Patients with no active middle ear pathology or retro cochlear lesions on audiological or imaging evaluation were only included. **Exclusion Criteria:** Patients with Meniere's disease, Psychiatric illness interfering with assessment, Current enrollment in other interventional studies, were excluded. **Baseline Assessment:** Demographic and clinical characteristics were recorded at baseline, including: Age and gender, Duration of tinnitus (<2 years vs ≥2 years), Tinnitus Handicap Inventory (THI) score, Audiological profile (where available).

Pharmacologic Treatment:

Pharmacologic therapy was initiated at the discretion of the treating physician, following standard clinical protocols. Medications included:

- **Caroverine**,
- **Betahistine**,

- **Antidepressants** (e.g., amitriptyline, SSRIs),
- **Benzodiazepines**,
- **Anticonvulsants**, and
- **Nutraceuticals** (e.g., Ginkgo biloba, vitamins).

Prescribing patterns were captured and classified based on initial prescription frequency.

Treatment Adherence

Adherence was measured using the **Medication Possession Ratio (MPR)** calculated from pharmacy refill data over a 6-month period. Patients were categorized as:

- **High adherence**: MPR ≥ 0.8,
- **Moderate adherence**: MPR 0.5–0.79,
- **Low adherence**: MPR < 0.5,
- **Discontinued**: no refills after initial prescription.

Clinical Outcome Assessment

Clinical efficacy was evaluated using the **Tinnitus Handicap Inventory (THI)** at baseline and 6 months. Outcomes were categorized as:

- **Clinically significant improvement**: ≥20-point reduction in THI score,
- **Partial improvement**: <20-point reduction,
- **No improvement**: <5-point change,
- **Worsening**: increase in THI score.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics, prescribing frequencies, adherence levels, and outcome distributions. Continuous variables were reported as means ± standard deviation; categorical variables as frequencies and percentages.

Multivariable logistic regression was used to identify predictors of favorable clinical outcomes (defined as ≥20-point THI improvement). Covariates included:

- Age group (<50 vs ≥50 years),
- Duration of tinnitus (<2 years vs ≥2 years),
- Use of specific medications (Caroverine, Betahistine),
- Treatment adherence level.

Odds ratios (OR) with 95% confidence intervals (CI) and p-values were reported. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version XX or equivalent statistical software.

Ethical Considerations

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to inclusion in the study. All procedures followed the Declaration of Helsinki.

RESULTS

A total of 165 patients with tinnitus were included in the study. The results are presented in terms of baseline characteristics, prescribing patterns, treatment adherence, clinical outcomes, and predictors of favourable outcomes.

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Value
Mean Age (years)	48.6 ± 12.4
Gender (Male)	92 (56%)
Gender (Female)	73 (44%)
Duration of Tinnitus < 2 years	98 (59.4%)
Duration ≥ 2 years	67 (40.6%)

Table 2: Prescribing Patterns of Anti-Tinnitus Medications

Drug Class	Frequency (%)
Caroverine	054 (32.72%)
Betahistine	050 (30.30%)
Antidepressants	024 (14.54%)
Benzodiazepines	017 (10.30%)
Anticonvulsants	011 (06.66%)
Nutraceuticals	009 (05.45%)

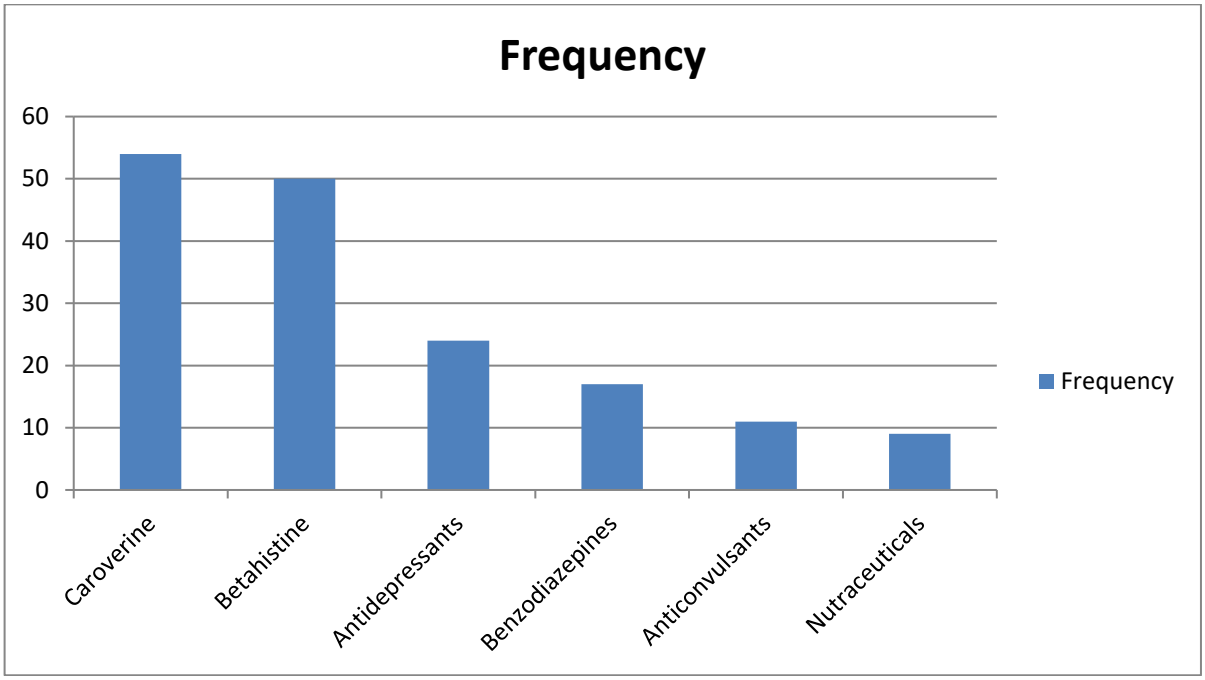

Table 3: Treatment Adherence (Medication Possession Ratio, MPR)

Adherence Category	Number of Patients (%)
High (MPR ≥0.8)	54 (32.7%)
Moderate (MPR 0.5-0.79)	70 (42.4%)
Low (MPR <0.5)	23 (13.9%)
Discontinued	18 (10.9%)

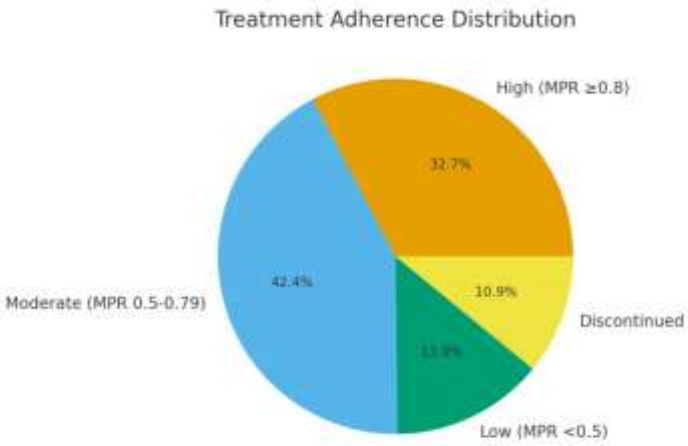

Fig 2: Treatment Adherence (Medication Possession Ratio, MPR)

Table 4: Clinical Outcomes at 6-Month Follow-up

Outcome	Patients (%)
Clinically significant improvement (THI ≥20 point reduction)	89 (53.9%)
Partial improvement	40 (24.2%)
No improvement	28 (17.0%)
Worsening symptoms	8 (4.9%)

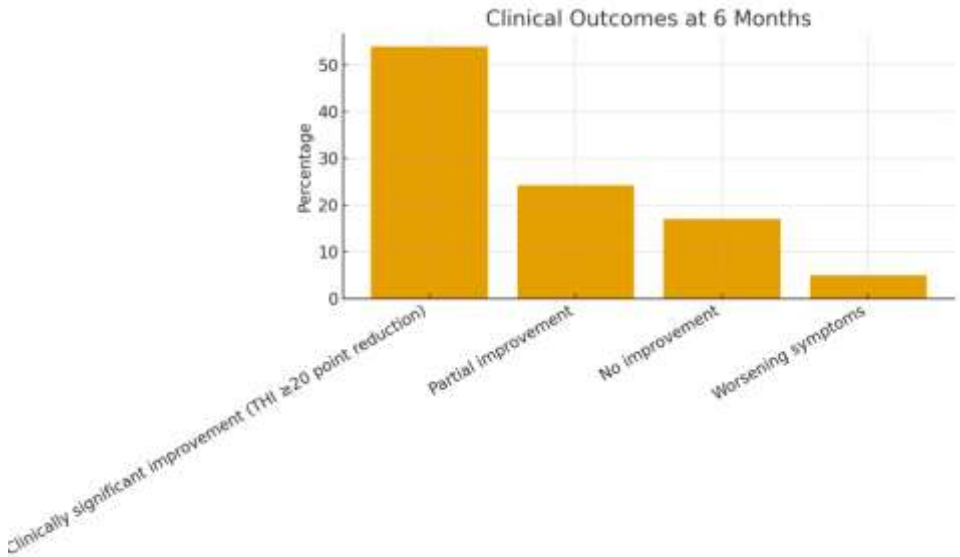

Fig 3: Clinical Outcomes at 6-Month Follow-up

Table 5: Predictors of Favorable Outcome (Multivariable Logistic Regression)

Predictor	Odds Ratio (95% CI)	p-value
Age < 50 years	2.1 (1.2–3.8)	0.01
Duration of tinnitus < 2 years	2.4 (1.3–4.2)	0.004
Caroverine use	2.6 (1.4- 4.1)	0.002
Betahistine use	2.8 (1.5–5.0)	0.002
High adherence (MPR ≥0.8)	3.2 (1.8–5.6)	<0.001

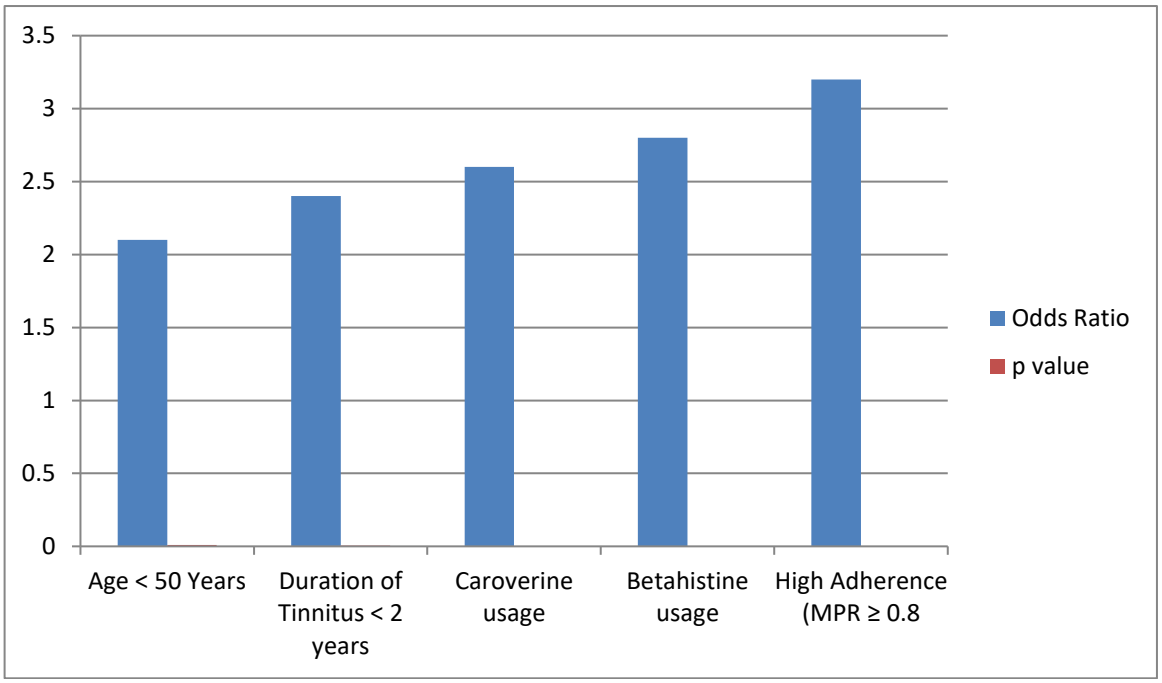

Fig 4: Showing the Odds ratio of predictors of favourable outcomes
Fig 4: Predictors of Favorable Outcome (Multivariable Logistic Regression)

DISCUSSION:

1. Principal Findings: This population-based cohort study of 165 tinnitus patients provides valuable insights into real-world prescribing patterns and clinical outcomes of anti-tinnitus medications. The key findings are: 1. Caroverine was the most frequently prescribed agent (32.72%), followed by Betahistine (30.305), antidepressants (14.54%) and benzodiazepines (10.30%). 2. Moderate adherence levels predominated (42%), with only one-third of patients achieving high adherence. 3. At 6-month follow-up, clinically significant improvement (≥20 point reduction in THI) was reported in 54% of patients, particularly among those prescribed Betahistine. 4. Predictors of favourable outcomes included younger age, shorter duration of tinnitus, Caroverine usage, Betahistine use, and high adherence. These findings emphasize the gap between controlled clinical trial recommendations and prescribing behaviours in routine practice, while also underscoring the importance of patient-related factors in determining treatment success.

2. Comparison with Previous Studies: 2.1 Prescribing Patterns: Our observation that Caroverine followed by Betahistine is the most prescribed drug for tinnitus is consistent with previous Indian and European studies. A cross-sectional study among Indian otolaryngologists revealed that Caroverine was being used increasingly since a decade followed by Betahistine together accounted for more than 60% of tinnitus prescriptions, largely due to its accessibility, cost-effectiveness, and perceived efficacy in Ménière's disease and vestibular disorders [24]. In contrast, Western cohorts often report higher utilization of antidepressants and anxiolytics, reflecting different practice guidelines and patient expectations [25, 26]. Despite international guideline recommendations discouraging routine pharmacological therapy for primary tinnitus [27, 28], real-world practice demonstrates widespread drug use. This divergence highlights physicians' reliance on

pharmacological measures when confronted with limited alternative therapies, as well as patient demand for immediate symptomatic relief. **2.2 Adherence to Medications:** Medication adherence in chronic symptomatic conditions such as tinnitus is often challenging. In our cohort, only 33% of patients maintained high adherence, comparable to findings from European cohorts reporting adherence between 30% and 40% [29]. Common reasons for discontinuation include adverse effects, perceived lack of efficacy, and treatment fatigue. In our study, discontinuation due to sedation and gastrointestinal disturbances was reported by 11% of participants, mirroring earlier trials on benzodiazepines and Betahistine [30, 31]. The moderate adherence rates underscore the need for patient counselling, expectation management, and shared decision-making in tinnitus management, as recommended in progressive tinnitus management (PTM) models [32]. **2.3 Clinical Outcomes:** The 54% rate of clinically significant improvement observed in our study is consistent with real-world estimates, though slightly higher than outcomes reported in randomized controlled trials (RCTs). A meta-analysis of pharmacological interventions for tinnitus found modest improvements in symptom severity, with placebo responses ranging from 30–40% [33]. Caroverine helped to reduce tinnitus severity, though systematic reviews suggest medications like amitriptyline and acamprosate show greater efficacy in some patients. Direct data on patient acceptance of Caroverine (Tinnicar) is limited. Betahistine emerged as the drug most associated with improvement, corroborating studies suggesting its efficacy in reducing tinnitus intensity and improving quality of life in patients with concomitant vestibular symptoms [34, 35]. In contrast, antidepressants and benzodiazepines showed partial but less robust improvements, often restricted to reduction in tinnitus-related distress rather than loudness [36]. **2.4 Predictors of Favourable Outcomes:** Our multivariable analysis identified younger age, shorter duration of tinnitus, and Caroverine and Betahistine prescriptions as significant predictors of positive outcomes. Similar associations have been documented in longitudinal studies, where early initiation of therapy within two years of symptom onset correlated with improved prognosis [37]. Younger age may be associated with greater neural plasticity, facilitating better adaptation to treatment [38]. Adherence was also a strong predictor of favourable outcomes, consistent with broader chronic disease management literature demonstrating that consistent medication use correlates with better clinical results [39]. These findings highlight the need for patient-centred interventions to improve adherence. **3. Strengths of the Study:** This study contributes several strengths to the literature on tinnitus management: 1. Population-based design: Unlike most hospital-based reports, our study provides representative data on real-world prescribing patterns. 2. Comprehensive assessment: Outcomes included both objective measures (THI reduction) and patient-reported perceptions, offering a holistic view of treatment effects. 3. Identification of predictors: Multivariable regression helped isolate patient and treatment factors associated with success, guiding future individualized approaches. Together, these strengths enhance the external validity of our findings and their applicability to diverse clinical settings.

4. Limitations: Despite its contributions, this study has several limitations: 1. Observational design: Causality cannot be established between specific drug use and outcomes. Confounding by indication may have influenced prescribing and results. 2. Sample size: Although adequate for exploratory analyses, the relatively small cohort (n=165) limits statistical power for subgroup analyses. 3. Short follow-up: Outcomes were measured at 6 months; longer-term adherence and sustainability of benefit remain uncertain. 4. Subjective measures: While THI is validated, reliance on patient-reported outcomes introduces subjectivity and potential recall bias. 5. Non-pharmacological therapies: We did not capture concurrent use of counselling, sound therapy, or cognitive behavioural interventions, which may have influenced outcomes. These limitations warrant cautious interpretation of results and call for confirmatory studies with larger samples and longer follow-up.

5. Clinical Implications: Our findings hold important implications for clinical practice: **Role of Caroverine: Role of Betahistine:** Given its favourable association with outcomes and widespread use, Betahistine may be considered as a pragmatic first-line option, particularly in patients with shorter tinnitus duration and vestibular symptoms. **Individualized therapy:** Antidepressants and

benzodiazepines may benefit selected patients with psychiatric co-morbidities, but risks of adverse events and dependence should temper prescribing decisions. Adherence enhancement: Structured counselling, expectation alignment, and follow-up reminders are essential to improve adherence and maximize outcomes. **Bridging evidence-practice gap:** Despite guideline scepticism about pharmacotherapy, real-world evidence shows patients frequently receive medications. Policymakers and guideline committees must reconcile these gaps by acknowledging patient expectations and physician challenges in resource-constrained environments.

6. Directions for Future Research: Future studies should address several unanswered questions: 1. Longitudinal outcomes: Long-term follow-up beyond one year is necessary to evaluate sustainability of symptom improvement and adherence. 2. Comparative effectiveness: Head-to-head real-world comparisons between pharmacological and non-pharmacological interventions (e.g., cognitive behavioural therapy, sound therapy) are needed. 3. Precision medicine approaches: Biomarkers, neuro-imaging, and phenotypic profiling may help predict who will benefit from specific drugs. 4. Multimodal management: Integration of medications with counselling and sound therapy in stepped-care models warrants further evaluation in the Indian context. 5. Health economics: Cost-effectiveness analyses could inform rational prescribing in resource-limited settings, where affordability remains a concern.

CONCLUSION:

This study highlights that in routine practice, pharmacological therapy—particularly Betahistine—remains the cornerstone of tinnitus management despite limited guideline endorsement. Clinical outcomes were modest but meaningful, with more than half of patients reporting significant improvement. Younger age, shorter duration of tinnitus, high adherence, and Betahistine prescription predicted favourable results. The findings underscore the need for individualized, patient-centred management strategies and reinforce the importance of adherence and early intervention. While pharmacological therapies are unlikely to provide universal cure, they may offer clinically relevant relief in selected populations. Further large-scale, long-term studies integrating pharmacological and non-pharmacological modalities are warranted to optimize tinnitus care globally and in India.

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