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# Tinnitus: Pathophysiology, Management with Glutamate Receptor Antagonists and Antioxidants – A Clinical Study.

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**ABSTRACT**

**Background:** Tinnitus, the perception of sound without an external stimulus, is a common symptom in sensorineural hearing loss (SNHL). It is frequently associated with excitotoxicity caused by excessive glutamate release and reactive oxygen species (ROS), leading to cochlear and neuronal damage. **Objective:** To evaluate the efficacy of caroverine and antioxidant combination therapy in patients with cochlear-origin subjective tinnitus associated with SNHL. **Methods:** This prospective study included 20 patients aged 20–66 years with subjective tinnitus of cochlear/synaptic origin. Exclusion criteria included objective tinnitus, retrocochlear pathology, Meniere's disease, drug-induced ototoxicity, and middle ear disease. All patients underwent clinical ENT evaluation, audiometry, and were treated with caroverine (20 mg twice daily) and a combination of rebamipide (100 mg), alpha-lipoic acid (100 mg), and acetylcysteine (100 mg), twice daily for 8 weeks. Those with giddiness received cinnarizine (25 mg) and dimenhydrinate (40 mg). Patients were followed up at 15, 30, and 60 days with repeat pure tone audiometry and clinical evaluation. **Results:** Of the 20 patients (10 male, 10 female), complete resolution of tinnitus was observed in 11 cases, partial improvement in 7, and no improvement in 2. Hearing improved in 4 cases and partially in 8; 2 showed no improvement. Giddiness improved completely in 2, partially in 1, and was persistent in 1 case. Thirteen patients were fully satisfied, 3 partially satisfied, and 4 not satisfied with treatment outcomes. **Conclusion:** Caroverine and antioxidant combination therapy significantly improved tinnitus symptoms in SNHL patients by antagonizing NMDA and AMPA glutamate receptors and reducing oxidative stress. This approach may offer a safe and effective management option for cochlear-synaptic tinnitus. **Keywords:** Tinnitus; Sensorineural Hearing Loss; Glutamic Acid; Antioxidants.

## INTRODUCTION

Tinnitus is defined as the perception of sound without an external auditory stimulus. Subjective tinnitus, the most common type, results from aberrant activity in the auditory pathway, whereas objective tinnitus arises from physical sources such as vascular anomalies and can be audible to others.

Sensorineural hearing loss (SNHL) is commonly associated with tinnitus, where excessive glutamate release and N-methyl-d-aspartate (NMDA) or $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation contribute to excitotoxicity and neuronal depolarization. Free radicals, including reactive oxygen species (ROS), further damage cochlear and neural tissues by lipid peroxidation and DNA damage.

### Pathophysiological Mechanism of Tinnitus and Cell Death

The pathogenesis of tinnitus, particularly in cases of sensorineural origin, involves a cascade of excitotoxic and oxidative events leading to neuronal dysfunction and ultimately cell death. (see Figure 1)

**Initiating Factors – Noise and ROS:** Prolonged or intense noise exposure, coupled with increased levels of reactive oxygen species (ROS), causes damage to cochlear and auditory neuronal cells. This injury triggers the excessive release of glutamate, a major excitatory neurotransmitter in the auditory pathway.

**Glutamate Excitotoxicity:** Elevated extracellular glutamate accumulates in the neuronal synaptic cleft, especially in the cochlear and central auditory structures. This leads to hyperactivation of AMPA ($\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, causing neuronal depolarization.

**Ion Influx and Tinnitus Generation:** The activation of AMPA receptors results in an influx of sodium ions ($Na^+$) and passive calcium ions ($Ca^{2+}$) entry into neurons. This abnormal ionic influx contributes to neuronal hyperexcitability, which is perceived clinically as tinnitus.

**Sustained Stimulation and NMDA Receptor Activation:** If the glutamatergic stimulus persists, continued depolarization occurs. The sustained depolarization removes the magnesium block from NMDA (N-methyl-D-aspartate) receptors, leading to further calcium influx into the neuronal cytoplasm.

**Chronic Excitation and Enzyme Activation:** Prolonged elevation of intracellular calcium activates several neuro-destructive enzymes, including: Phospholipase A2: damages cellular membranes; Nitric oxide synthase: produces nitric oxide, a free radical; Xanthine oxidase: generates additional ROS

**Cellular Breakdown and Neuronal Death:** These enzymatic cascades lead to disrupted cellular homeostasis, mitochondrial dysfunction, and ultimately neuronal

apoptosis or necrosis. The chronicity of this process is believed to perpetuate tinnitus and may also exacerbate sensorineural hearing loss.

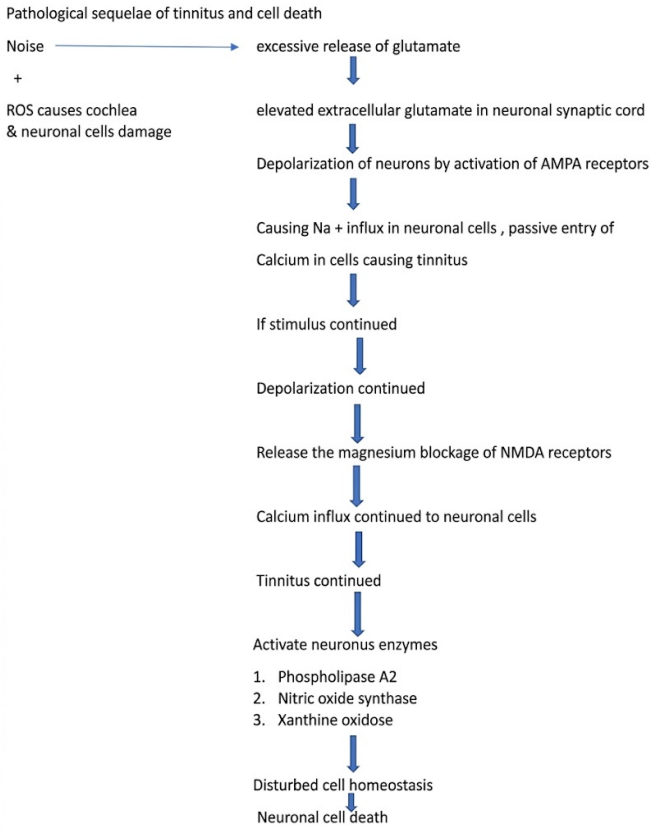


**Figure 1.** Flowchart: Mechanism of Glutamate-Induced Tinnitus and Neuronal Cell Death

## MATERIALS AND METHODS

### Inclusion Criteria:

- Patients with subjective, cochlear-origin tinnitus associated with SNHL
- All age groups and genders

### Exclusion Criteria:

- Objective tinnitus
- Retrocochlear pathology (e.g., acoustic neuroma, demyelination)
- Meniere's disease
- Drug-induced ototoxicity
- Middle ear disease

### Diagnostic Workup:

- Detailed history and ENT examination
- Pure tone audiometry and impedance audiometry to rule out middle ear pathology
- Evaluation of comorbidities (diabetes, hypertension, hypothyroidism)

### Treatment Protocol:

- Caroverine 20 mg twice daily – calcium channel blocker and NMDA receptor antagonist
  **Antioxidant combination:** Rebamipide 100 mg; Alpha-lipoic acid 100 mg; N-acetylcysteine 100 mg (twice daily for 8 weeks)
  **For associated giddiness:** Cinnarizine 25 mg + Dimenhydrinate 40 mg twice daily, then tapered
- Reassessment at 15, 30, and 60 days

## RESULTS

### Demographics:

**Total patients:** 20 (10 male, 10 female)
**Study duration:** May 2024–May 2025 (1 year)
**Age range:** 20–66 years (mean: 44.65 years)
**Occupations:** Teachers (3), Nurses (2), Businessmen (3), Housewife (4), Students (3), Labourers (2), Carpenter (1), Farmer (1), Govt. employee (1)

### Tinnitus Characteristics:

**Duration:** 7 days–1 year (mean: 2 months)
**Laterality:** Bilateral (10), Right (3), Left (7)

- Giddiness present in 4 cases

### Audiological Findings:

**27 ears:** SNHL
**2 ears:** Mixed hearing loss
**11 ears:** Normal hearing threshold
**Tympanic membranes:** Normal in all cases

- Middle ear pathology excluded by impedance audiometry

### Comorbidities:

- Hypertension (4), Diabetes (3), Hypothyroidism (3), Atrophic rhinitis (1)

## STATISTICAL ANALYSIS AND REVIEW OF RESULTS

### Study Population Overview:

**Total Patients:** 20
**Mean Age:** 44.65 years
**Gender Distribution:** Equal (10 male, 10 female)
**Duration of Tinnitus:** 7 days–1 year (mean ≈ 2 months)
**Laterality:** Bilateral – 50%, Left ear – 35%, Right ear – 15%
**Comorbidities:** Hypertension (20%), Diabetes (15%), Hypothyroidism (15%), Atrophic rhinitis (5%)

### Tinnitus Symptom Relief

Ninety percent of patients reported some degree of relief, with 55% achieving complete remission of tinnitus symptoms following 8 weeks of treatment. This suggests significant clinical efficacy of caroverine and antioxidant therapy in subjective tinnitus of cochlear origin.

### Hearing Improvement

Among 14 patients with hearing loss, 12 (85.7%) showed improvement (complete or partial). The use of caroverine in combination with antioxidants may help to attenuate early cochlear synaptic damage and improve auditory threshold in SNHL-related tinnitus.

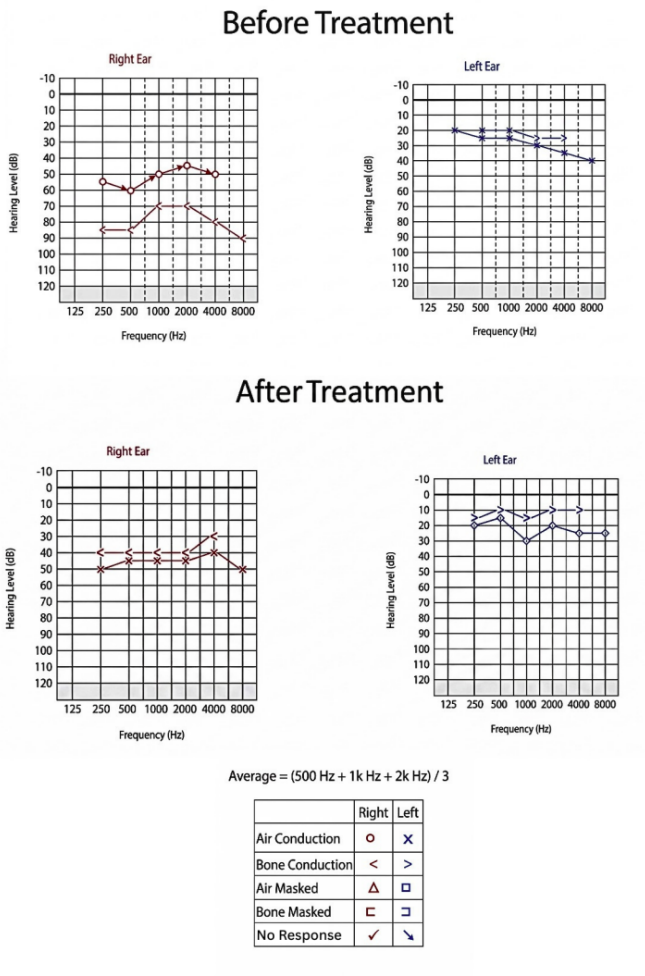


**Figure 2.** Pre- and Post-treatment Audiogram of a patient presenting with symptoms of Tinnitus

### Giddiness Relief

Among 4 patients with giddiness, 3 experienced benefits, suggesting that calcium channel blockade and central vestibular modulation by cinnarizine/dimenhydrinate combination may be effective in treating coexisting vestibular symptoms.

### Patient Satisfaction

Satisfaction correlates strongly with the degree of tinnitus relief and hearing improvement. Thirteen patients were fully satisfied, 3 partially, and 4 not satisfied.

**Table 1.** Summary of Clinical Outcomes

| Clinical Outcome | Complete | Partial | None/Not Satisfied |
|---|---|---|---|
| Tinnitus Relief | 11 | 7 | 2 |
| Hearing Improvement | 4 | 8 | 2 |
| Giddiness Relief | 2 | 1 | 1 |
| Patient Satisfaction | 13 | 3 | 4 |

**Table 2.** Hearing Outcomes

| Ear | Type of Hearing Loss (Before) | Improvement (After) | Interpretation Summary |
|---|---|---|---|
| Right | Moderate SNHL (AC ≈ 60 dB, flat) | Improved to moderate-mild (AC ≈ 40–50 dB) | Partial recovery; sensorineural loss persists |
| Left | Mild SNHL (AC ≈ 25–35 dB) | Improved to near-normal (AC ≈ 20–30 dB) | Near-complete recovery; normal functional range |

## DISCUSSION

The present study evaluated the efficacy of caroverine combined with a triple antioxidant regimen (rebamipide, alpha-lipoic acid, and N-acetylcysteine) in managing subjective tinnitus of cochlear origin associated with SNHL. Our findings demonstrate a substantial rate of symptomatic improvement, with 90% of patients reporting some degree of tinnitus relief and 55% achieving complete resolution within 8 weeks of therapy.

### Pathophysiological Rationale for Treatment

The underlying mechanism of tinnitus in SNHL involves glutamate-mediated excitotoxicity and oxidative stress-induced neuronal injury. Excessive glutamate release leads to hyperactivation of AMPA and NMDA receptors, causing abnormal ion influx, sustained depolarization, and eventual cochlear and central auditory neuron apoptosis. Concurrently, ROS generation exacerbates lipid peroxidation, mitochondrial dysfunction, and DNA damage. [1,2,3,4]

Caroverine, by antagonizing NMDA and AMPA receptors and acting as a calcium channel blocker, interrupts this excitotoxic cascade. [5,6] The antioxidants employed—rebamipide, alpha-lipoic acid, and N-acetylcysteine—provide synergistic free radical scavenging, membrane stabilization, and mitochondrial protection, potentially enhancing neuronal survival. This dual pharmacological strategy targets both neurochemical excitation and oxidative injury, which explains the observed clinical benefits, suggesting that modulation of glutamate pathways is a promising therapeutic approach.

### Comparison with Literature

Our results are consistent with earlier reports demonstrating the potential of NMDA receptor antagonists in tinnitus therapy. Studies by Denk et al. [5] and Ehrenberger et al. [6] have shown that caroverine can improve tinnitus perception in cases linked to cochlear synaptic dysfunction. Similarly, antioxidant therapy—especially alpha-lipoic acid and N-acetylcysteine—has been documented to attenuate oxidative cochlear injury in both experimental and clinical contexts. [7] However, most previous studies investigated these agents individually, whereas our combined regimen appears to yield higher remission rates, suggesting a possible additive or synergistic effect when targeting both excitotoxic and oxidative mechanisms simultaneously. [8]

### Clinical Outcomes and Implications

The high percentage of complete tinnitus relief (55%) and partial relief (35%) is notable, especially given the refractory nature of tinnitus in many SNHL cases. Hearing improvement in 85.7% of patients with baseline loss suggests that early intervention may help reverse or stabilize cochlear synaptic dysfunction, potentially preventing further auditory decline. Additionally, improvement in vestibular symptoms in 3 out of 4 patients indicates ancillary benefits in cases with concurrent labyrinthine involvement.

### Strengths of the Study

- Mechanism-based treatment approach addressing both excitotoxicity and oxidative damage.
- Prospective design with regular follow-up at 15, 30, and 60 days.
- Use of objective audiometric parameters alongside subjective symptom reporting.

### Limitations

Several limitations should be acknowledged. First, the study included a relatively small sample size (n=20), limiting statistical power. Second, the absence of a placebo or control group restricts definitive attribution of symptom improvement solely to the intervention. Third, the short follow-up duration precludes assessment of long-term recurrence rates. Additionally, while the improvement in hearing thresholds and tinnitus perception is promising, psychoacoustic tinnitus measures and validated quality-of-life scores were not employed, which may have added further objectivity.

### Future Directions

Larger randomized controlled trials are warranted to confirm these findings and determine the optimal treatment duration, dosage, and patient selection criteria. Incorporating tinnitus handicap inventories, psychoacoustic profiling, and neuroimaging correlates could refine assessment and elucidate neuroplastic changes post-treatment. Given the encouraging results, exploration of earlier intervention in acute SNHL-related tinnitus and combination regimens with cognitive or sound therapy may enhance overall management outcomes.

This study reinforces the hypothesis that targeting glutamatergic excitotoxicity and oxidative stress concurrently offers a viable therapeutic approach in managing cochlear-origin tinnitus associated with SNHL. Caroverine combined with antioxidant therapy produced meaningful symptom relief, hearing improvement, and high patient satisfaction, warranting further research to establish this protocol as a standard clinical option.

## CONCLUSION

Cochlear synaptic tinnitus and sudden SNHL are amenable to treatment using glutamate receptor antagonists like Caroverine, coupled with antioxidants. This therapeutic strategy stabilizes neuronal membranes, restores physiological signaling, and significantly improves patient quality of life, supporting its potential role as a standard treatment modality in cochlear-origin tinnitus.

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