Prevention and treatment of platinum ototoxicity in adults: A systematic review

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Abstract

Background: Ototoxicity is a common disabling side effect of platinum-based chemotherapy. This study aimed to systematically assess the evidence on the management of platinum-induced ototoxicity in adult cancer patients. Methods: Three databases were searched up to November 1, 2022. Original studies were included if they reported on a pharmacologic or non-pharmacologic intervention to prevent or treat platinum ototoxicity in adults. The articles’ quality was assessed with two grading scales. Results: Eighteen randomized controlled trials and five quasi-experimental studies with 1673 patients were analyzed. Eleven interventions were identified, nine pharmacological and two non-pharmacological. Six of the interventions (sodium thiosulfate, corticoids, sertraline, statins, multivitamins, and D-methionine) showed mild benefit preventing cisplatin-induced ototoxicity. The data must be carefully analyzed due to the low quality and underreporting of side effects. Conclusions: Current interventions have mild benefits preventing cisplatin-induced ototoxicity in adult cancer patients. High-quality research is required to clarify the significance of these findings.
Keywords: Cisplatin-induced ototoxicity, platinum chemotherapy, chemotherapy-related adverse events, hearing loss, otoprotection.

Key Messages

1. Chemotherapy ototoxicity is a well-known adverse effect that has few treatment options and that has not been sufficiently studied in the adult population.
2. Tinnitus and vertigo are distressing symptoms overlooked in cisplatin-induced ototoxicity research.
3. Pharmacological interventions to prevent cisplatin-induced hearing loss are controversial given their mild efficacy and potential side effects. Future investigations of sodium thiosulfate for preventing cisplatin-induced ototoxicity are warranted.

Introduction

Platinum chemotherapy agents are the cornerstone of several oncologic and hematologic protocol treatments given their high effectiveness, cost, and accessibility (Dillard et al., 2022). These benefits are tied to unwanted side effects. Ototoxicity is a well-known adverse effect of platinum compounds, such as cisplatin and carboplatin, that may cause permanent hearing loss, tinnitus, or vestibular disturbances in 40–80% of treated adult patients, which is globally estimated to be half a million cases per year (Dillard et al., 2022, Frisina et al., 2016). Ototoxicity type and degree vary depending on sex, age, genetic predisposition, changes in protein expressions, previous neuro-otological symptoms, chemotherapy interval of administration, dose regimen (up to 100% of patients have been found to be affected in a dose range between 150–225 mg/m2), concomitant radiotherapy treatments, or even the patient’s stress level (Kirkim et al., 2015, Charif et al., 2019, Coling et al., 2007, Bielefeld et al., 2021, Chan et al., 2018, Miaskowski et al., 2018). Current knowledge has shown platinum-induced ototoxicity is a multifactorial process where free radical oxygen species and inflammation induce endogenous antioxidants depletion and increase lipid peroxidation, causing rupture of the outer hair cell stereocilia in the organ of Corti (Gentilin et al., 2019, Tang et al., 2021). This process may have an acute or progressive onset, as cisplatin is retained in the cochlea indefinitely, activating the apoptotic pathway in the marginal cells on the stria vascularis region that maintains the endolymph composition (Breglio et al., 2017). Depending on the hearing loss frequency and the severity of speech impairment, more than ten grading systems have been proposed to better characterize patients’ affection (Waissbluth et al., 2017). Moreover, accurate prediction models of posttreatment hearing alterations with good performance (eg. sensitivity of 80% and specificity of 75%) and follow-up screening audiometric test analysis have been proposed to diagnose platinum ototoxicity (Shuette et al., 2020, Frisina et al., 2016, Ardeshirrouhanifard et al., 2022). However, there is a paucity of safe and effective pharmacological or non-pharmacological options to prevent or treat platinum-induced ototoxicity in adults, without inhibiting antitumor effects. Numerous studies on animals have been conducted with relative success and a guideline to treat cisplatin-induced ototoxicity in children has been published (Freyer et al., 2020), albeit the evidence concerning the adult population is sparse, non-pharmacologic treatments have not been systematically researched, and the use of otoprotecting strategies for other chemotherapy agents besides platinums is anecdotal (Desilets et al., 2020). Even so, ototoxicity prevention and treatment is a major research priority due to the symptom burden and diminishing quality of life patients experience (Miaskowski et al., 2018). Thus, we conducted a comprehensive systematic literature review on pharmacological or non-pharmacological interventions to prevent or treat platinum-induced ototoxicity in adult cancer patients.

Methodology

Objective

The primary aim was to systematically review the effectiveness and safety of pharmacological or non-pharmacological interventions used to prevent or treat platinum-induced ototoxicity in adult cancer patients. Even though ototoxicity is a less common adverse effect of other chemotherapy agents, we consider that studies could report ototoxicity interventions for multiple chemotherapy regimens. So our secondary aim was to assess pharmacological or non-pharmacological interventions for ototoxicity caused by other chemotherapy agents in adult cancer patients.
Search Strategy

We developed a search strategy using Medical Subject Headings (MeSH) related to chemotherapy-induced ototoxicity. We searched three databases (Medline, CINHAL, and PubMed) using the following search string:

(Ototoxicity OR Drug-Induced Ototoxicity OR Drug-Related Otological Toxicities OR Drug-Induced Cochleotoxicity OR Drug Induced Cochlear Toxicity OR Drug Induced Vestibulotoxicity OR vertigo OR tinnitus) AND (Antineoplastic Agent OR Anticancer Agent OR Antineoplastic Drug OR Antineoplastic OR Antitumor Drug OR Cancer Chemotherapy Agent OR Antitumor Agent OR Cancer Chemotherapy Drug OR Chemotherapeutic Anticancer Agents OR Chemotherapeutic Anticancer Drug OR Combined Antineoplastic Agents OR Antineoplastic Combined Chemotherapy Regimens).

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42022376324). The search results were downloaded into Endnote software to remove duplicates. The debugged search was uploaded to Rayyan where two reviewers (JEC and NM) screened abstracts and selected relevant titles with a 0.43 inter-rater agreement. In the event of a conflict of views, a consensus was reached through discussion. Further to ensure consistency in eligibility criteria the full texts were reviewed by the seven authors. There was a vote in case of disagreement. References from selected articles were also included. We report the results following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Study Selection

Eligible studies had to be 1) original investigations published in a peer-reviewed journal before November 1, 2022; 2) include human patients over 18 years old; 3) report an intervention as prophylaxis or treatment for ototoxicity induced by any chemotherapy agent; 4) be published in English; 5) use an experimental or quasi-experimental research design, and 6) report treatment outcomes, either their safety or efficacy. Ototoxicity induced by chemotherapy was considered as hearing loss, tinnitus, or vestibular disturbances after chemotherapy treatment. Gray literature, editorials, commentaries, case series with ten or fewer patients, case studies, and protocols were excluded from the review.

Data extraction

Three reviewers (EQ, JEC, and LB) independently extracted data into a Microsoft Excel spreadsheet. Data extracted included the year of publication, country, study design, number of participants, inclusion/exclusion criteria, sample characteristics, type of cancer, patient’s functionality, chemotherapy agent, dose average, number of cycles, concomitant radiotherapy exposure, audiometric measurements, kind of ototoxicity, type of intervention, comparator, time of follow-up, and efficacy and safety outcomes. To ensure consistency, extracted data were compared between reviewers, and disagreements were discussed until a consensus was reached.

Quality Appraisal

Four reviewers (LC, SG, NM, and MFI) independently assessed each included study for the risk of bias. A third reviewer arbitrated possible differences. Randomized controlled trials (RCT) were evaluated using the Cochrane Collaboration’s Risk-of-Bias Tool 2 and non-randomized studies were assessed with the Newcastle Ottawa Scale (Higgins et al., 2021, Wells et al., 2016). No study was disregarded for its quality.

Data Synthesis and Analysis

The synthesis of results was performed using the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews (Popay et al., 2006). The outcomes regarding platinum ototoxicity symptom ease were reported using means (or difference in means) ± standard deviations or means with confidence intervals (CIs) and p values. Epidemiological statistics were reported according to the original articles. The data is presented regarding the efficacy and safety of each intervention. Furthermore, to improve intervention comparisons, the summary information underlines the intention of the intervention (prevention/treatment), the type of assessed ototoxicity (hearing loss, tinnitus, and/or vestibular disturbances), and if other ototoxic treatments...
were associated with the platinum treatment (e.g. radiotherapy with Gray dose). All authors were involved in analyzing and interpreting the results and vouch for their completeness and accuracy.

**Results**

The search rendered 4590 studies, 742 duplicates were removed, and 3442 were deemed ineligible after screening titles and abstracts. The reference review resulted in the addition of one article. The resulting 35 full texts were screened, of which twenty-three studies were selected for data extraction and analysis (Gandara et al., 1995, Somlo et al., 1995, Kemp et al., 1996, Madasu et al., 1997, Planting et al., 1999, Ekborn et al., 2004, Zuur et al., 2007, Yıldırım et al., 2010, Riga et al., 2013, Yoo et al., 2014, Marshak et al., 2014, Ishikawa et al., 2015, Crabb et al., 2017, Nasr et al., 2018, Delarestaghi et al., 2018, Rolland et al., 2019, Duinkerken et al., 2021, Fernandez et al., 2021, Moreno et al., 2022, Weijl et al., 2004, Villani et al., 2016, Scasso et al., 2017, Campbell et al., 2022). Figure 1 depicts the PRISMA complete screening process. Publication dates were 1995–2022, with studies conducted in 14 different countries, with 5 studies from the United States, 4 from the Netherlands, 2 from Canada and Italy, and one study from Sweden, Turkey, Greece, Spain, Israel, Japan, United Kingdom, Egypt, Iran, and India. Studies consisted of 18 controlled trials (Gandara et al., 1995, Somlo et al., 1995, Kemp et al., 1996, Planting et al. 1999, Zuur et al. 2007, Yıldırım et al. 2010, Riga et al. 2013, Yoo et al. 2014, Marshak et al. 2014, Crabb et al. 2017, Nasr et al. 2018, Delarestaghi et al. 2018, Rolland et al. 2019, Duinkerken et al. 2021, Moreno et al. 2022, Weijl et al. 2004, Villani et al. 2016, Campbell et al. 2022) and 5 quasi-experimental studies (Madasu et al. 1997, Ekborn et al. 2004, Ishikawa et al. 2015, Fernandez et al. 2017, Scasso et al. 2017, Campbell et al. 2022). The median number of patients per study was 73 and ranged from 11 to 277. Of note, only four RCT had a low risk of bias, seven had some concern of bias, and seven had a high risk of bias. Across the 18 RCT, the most common sources of bias were related to the outcome measurement and the selection of results. In the quasi-experimental studies quality assessment, two studies were of high quality and three were rated as having poor methodological quality. The source of bias came from the comparability and outcome evaluations. Table 1 and Table 2 presents the quality assessment for all of the studies. In total 11 interventions were used for cisplatin-ototoxicity, 9 pharmacological interventions were assessed in 19 studies(Gandara et al., 1995, Somlo et al., 1995, Kemp et al., 1996, Madasu et al. 1997, Planting et al. 1999, Ekborn et al. 2004, Zuur et al. 2007, Yıldırım et al. 2010, Riga et al. 2013, Yoo et al. 2014, Marshak et al. 2014, Ishikawa et al. 2015, Fernandez et al. 2021, Scasso et al. 2017) and 2 non-pharmacological interventions assessed in 4 studies( Weijl et al. 2004, Villani et al. 2016, Scasso et al. 2017, Campbell et al. 2022). All of the studies assessed platinum-ototoxicity prevention, except for one that evaluated ototoxicity treatment (Nasr et al. 2018). Although we searched for platinum-induced ototoxicity, all studies assessed cisplatin and none of the studies included other platinum agents or other types of chemotherapy agents. All of the studies interpreted cisplatin-induced ototoxicity (CiO) outcome as hearing loss, five studies also considered tinnitus (Planting et al., 1999, Madasu et al., 1997, Ishikawa et al., 2015, Yoo et al., 2014, Scasso et al., 2017), and only two included vestibular disturbances(Madasu et al., 1997, Ishikawa et al., 2015). All of the studies used an audiometry test to examine ototoxicity. The study’s characteristics for the pharmacologic and nonpharmacologic interventions appear in Table 3 and Table 4, respectively.

Table 1. Assessment of the risk of bias in clinical trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Bias Arising From the Randomization Process</th>
<th>Bias caused by Deviations From Intended Interventions</th>
<th>Bias caused by Missing Outcome Data</th>
<th>Bias in Measurement of the Outcome</th>
<th>Bias in Selection of the results</th>
<th>Overall risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandara et al.</td>
<td>Some concerns</td>
<td>Some concerns</td>
<td>Low</td>
<td>High</td>
<td>Some concerns</td>
<td>High</td>
</tr>
<tr>
<td>Somlo et al.</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Kemp et al.</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Study | Bias Arising From the Randomization Process | Bias caused by Deviations From Intended Interventions | Bias caused by Missing Outcome Data | Bias in Measurement of the Outcome | Bias in Selection of the results | Overall risk of bias
---|---|---|---|---|---|---
Planting et al. | Low | Some concerns | Low | Low | Low | Some Concerns
Weijl et al. | Some concerns | Some concerns | Low | Low | Low | Low
Zuur et al. | Some concerns | Low | Low | Low | Some Concerns
Yıldırım et al. | Some concerns | Low | Low | Low | Some Concerns
Riga et al. | High | Some concerns | Low | Low | Some Concerns
Marshak et al. | Low | Low | Low | Low | Low
Yoo et al. | High | Some concerns | High | Low | Low | High
Villani et al. | Low | Low | Low | Low | Low | Some Concerns
Crabb et al. | Low | Some concerns | Low | Low | Low | Some Concerns
Delareastagli et al. | Some concerns | Low | Low | High | Low | Some Concerns
Nasr et al. | High | Some concerns | Low | Low | Low | High risk
Rolland et al. | Low | Low | Low | Low | Low | Low
Duinkerken et al. | High | Low | Low | High | Low | High
Campbell et al. | Low | Some concerns | Low | Low | Low | Some Concerns
Moreno et al. | Low | Low | Low | Low | Low | Low

Quality tool used: Cochrane risk-of-bias tool for randomized trials Version 2

Table 2. Quality assessment of Cohorts and Cases-Control studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome/exposure</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madasu et al.</td>
<td>Cohort</td>
<td>2 (*)</td>
<td>1 (*)</td>
<td>0 (*)</td>
<td>Poor Quality</td>
</tr>
<tr>
<td>Scasso et al.</td>
<td>Case and controls</td>
<td>3 (*)</td>
<td>0 (*)</td>
<td>1 (*)</td>
<td>Poor Quality</td>
</tr>
<tr>
<td>Fernandez et al.</td>
<td>Cohort</td>
<td>3 (*)</td>
<td>1 (*)</td>
<td>3 (*)</td>
<td>High Quality</td>
</tr>
<tr>
<td>Ishikawa et al.</td>
<td>Cohort</td>
<td>3 (*)</td>
<td>1 (*)</td>
<td>3 (*)</td>
<td>High Quality</td>
</tr>
<tr>
<td>Ekborn et al.</td>
<td>Cohort</td>
<td>2 (*)</td>
<td>0 (*)</td>
<td>1 (*)</td>
<td>Poor Quality</td>
</tr>
</tbody>
</table>

Quality tool used: Newcastle - Ottawa quality assessment scale

*Patient characteristics*
Study populations included adults 18 to 82 years. Almost all studies include both female and male participants. Several types of cancers were accepted for participation, for instance, four studies included all types of cancers. The most prevalent type was head and neck cancer in 11 studies (Planting et al., 1999, Madsu et al., 1995, Ishikawa et al. 2015, Duinkerken et al., 2021, Zuur et al., 2007, Rolland et al., 2019, Yoo et al., 2014, Riga et al. 2013, Crabb et al., 2017, Fernandez et al., 2021, Campbell et al. 2022). Other types were ovarian, bladder, germ cell, gastric, lung, breast, sarcoma, thymus, mesothelioma, esophagus, melanoma, and cancer of unknown origin. Most of the studies recruited patients about to begin chemotherapy, with no prior history of auditory surgery, affection, or disease, and good performance status. Cisplatin dose ranged between 75 to 517 milligrams per square meter (mg/m²), an average of 138 mg/m². Study exclusion criteria varied, with some studies excluding patients with metastasis in the central nervous system, hepatic or renal insufficiency, hearing asymmetry, hearing aid users, and concomitant neuropathy or radiotherapy. In regards to this last condition, there was great heterogeneity between studies, 10 studies demanded or allowed concomitant radiotherapy (Planting et al., 1999, Madsu et al., 1995, Ishikawa et al. 2015, Duinkerken et al., 2021, Zuur et al., 2007, Rolland et al., 2019, Yoo et al., 2014, Fernandez et al., 2021, Scasso et al. 2017, Campbell et al. 2022) while 13 considered radiotherapy as an exclusion criterion. For those studies that reported follow-up time, the mean was 6.4 months.

**Pharmacological interventions**

**Diethyldithiocarbamate**

A randomized placebo-controlled multicenter used diethyldithiocarbamate for chemoprotection against ClO in patients with lung or ovarian cancer. Patients who received diethyldithiocarbamate received lower cumulative doses of cisplatin, were more likely to be withdrawn from treatment early due to chemotherapy-related toxicities, and had a trend for a greater reduction in auditory acuity at 3000 Hz (P = 0.095)(Gandara et al., 1995).

**Dopamine**

In a randomized, placebo-controlled, double-blind trial, the protective effect of low-dose dopamine given as a continuous infusion in cisplatin toxicity was evaluated. No differences were observed in favor of the dopamine group when audiogram results were analyzed at 2,000, 4,000, or 8,000 Hz (P = 0.27, 0.14, and 0.49, respectively)(Somlo et al., 1995).
Amifostine

Three studies assessed amifostine in CIo prevention. None of them found favorable results with amifostine as a pretreatment strategy. The first study was a randomized trial of patients with advanced ovarian cancer, the amifostine group required less dose reduction or discontinuation of cisplatin and reported a 43% reduction in ototoxicity incidence, however, this difference did not reach a statistical difference ($P = 0.095$) (Kemp et al., 1996). The second randomized trial used a weekly course of amifostine in patients with head and neck cancer, 21% of the patients received concomitant radiotherapy. There was no difference in hearing or tinnitus occurrence ($P = 0.24$) (Planting et al., 1999). Lastly, in a prospective cohort of 15 patients with different types of cancer, 11 out of 12 patients displayed auditory symptoms despite amifostine treatment (Ekborn et al., 2004). Amifostine treatment was poorly tolerated, all three studies report patients experienced nausea and/or vomiting, hypotension, flushing, sneezing, dizziness, sleepiness, hiccups, anxiety, palpitations, and chills (Kemp et al., 1996, Planting et al., 1999, Ekborn et al., 2004).

Sodium Thiosulfate

Five articles researched sodium thiosulfate for CIo prevention (Madasu et al., 1995, Ishikawa et al. 2015, Duinkerken et al., 2021, Zuur et al., 2007, Rolland et al., 2019). The first one was a prospective cohort of 70 patients with head and neck cancer, who received cisplatin, radiotherapy (dose not specified), and systemic sodium thiosulfate. The baseline audiometric analysis comparison to the audiometry after the fourth cisplatin infusion did not appear to confer sodium thiosulfate a protection hearing effect. Tinnitus or vestibular loss were not reported, nor were adverse reactions (Madasu et al., 1995). A similar prospective cohort of 18 patients with the same kind of cancer and receiving 60-70 Gray of radiotherapy assessed sodium thiosulfate otoprotection. The sodium thiosulfate group had significant hearing loss at ultra-high frequencies of 10 and 12 kHz ($p = 0.028, 0.039$, respectively), whereas the group not receiving sodium thiosulfate had significant hearing loss at high frequencies of 8 and 10 kHz ($p = 0.016, 0.027$, respectively). During follow-up, one patient presented with subjective tinnitus. Vertigo episodes and adverse reactions were not reported for any patient (Ishikawa et al. 2015). Later a pilot non-randomized control trial using transtympanic sodium thiosulfate in 12 adults for cisplatin and radiotherapy (maximum cochlear dose 30 Gray) was performed. The pure-tone average shift at 8 -12.5 kHz was 18.4 dB less in treated ears compared to untreated ears ($p=0.068$) (Duinkerken et al., 2021). This positive finding was further explored in a randomized control trial that tested intravenous sodium thiosulfate for CIo in 158 patients. All patients received concomitant radiotherapy (mean dose 70 Gray). In both treatment arms, the incidence of CIo did not deviate ($P =0.14$), but the intervention group had 10% less hearing loss at frequencies vital for speech perception ($P = 0.001$). No difference in adverse reactions between groups was observed (Zuur et al., 2007). Finally, a second randomized control trial tested trans-tympanic injections of sodium thiosulfate for CIo prevention in 13 patients with head and neck cancer. Although all of the patients received radiotherapy no dose information was provided. After 18 months of follow-up, the average hearing loss was 1.3 dB less for treated ears compared to control ears. Although not statistically ($p = 0.61$) nor clinically significant, the difference was in favor of the treated ears for all frequencies between 3 and 10 kHz. Injections caused dizziness in 3 patients, vertigo in one patient, and pain in 4 patients (Rolland et al., 2019).

N-acetylcysteine

Three randomized placebo-controlled trials have explored if N-acetylcysteine can avert CIo administered intratympanic (Riga et al., 2013, Yoo et al., 2014) or orally (Yıldırım et al., 2010). A RCT used intratympanic N-acetylcysteine at 10% in 20 patients with different types of tumors. They found that treated ears with N-acetylcysteine had no significant changes in auditory thresholds while the control ears had a significant decrease in auditory thresholds at the 8000 Hz frequency band ($P = 0.008$) with cisplatin (Riga et al., 2013). Another RCT assessed the effectiveness of intratympanic N-acetylcysteine at 2% to prevent hearing and tinnitus due to cisplatin in 11 patients with head and neck cancer receiving concomitant radiotherapy. No benefit in hearing preservation or tinnitus incidence was found (Yoo et al. 2014). The concentration difference of N-acetylcysteine may have influenced the disparity of the results as the occurrence of side effects. For instance, the highest concentration of N-acetylcysteine was associated with pain application among almost
all patients (Riga et al., 2013), while the trial with a lower concentration of N-acetylcysteine did not report adverse reactions (Yoo et al., 2014). The third RCT compared the protective hearing effect of placebo, oral N-acetylcysteine, and salicylate in 54 patients with solid organ tumors receiving cisplatin. Audiometry and auditory brainstem parameters showed no significant difference between placebo and salicylate. On the other hand, the N-acetylcysteine group did have a reduction in cisplatin hearing ototoxicity at 10,000 and 12,000 Hz (p<0.005) compared to placebo. Nonetheless, safety outcomes between study interventions were not reported (Yıldırım et al., 2010).

Corticoids

Three investigations have evaluated the role of intratympanic corticosteroids to prevent CiO (Marshak et al., 2014, Moreno et al., 2022, Nasr et al., 2018). Two studies used dexamethasone and one methylprednisolone. In a controlled trial, prior to each cisplatin treatment session, intratympanic dexamethasone was injected 0.7 to 1.0 ml (10mg/ml) into randomly assigned ears. A significant attenuation in the hearing loss at 6000 Hz (P<0.02) and decreased outer hair dysfunction in the range of 4000 to 8000 Hz (P<0.04) was observed in the intervention group (Marshak et al., 2014). These positive findings of intratympanic dexamethasone protecting the hearing capacity were corroborated by a second randomized controlled phase IIIB trial. Dexamethasone was administered via a passive diffusion device to an ear and the contralateral ear was used as the control. Audiometric analysis showed a higher hearing threshold in the study group than in the control group with significant differences at frequencies of 500, 1000, and 6000 Hz (p < 0.05)(Moreno et al. 2022). Safety outcomes for both trials reported slight pain and mild vertigo during the application, otological infections, and permanent tympanic perforation in 34.8% of the patients (Marshak et al., 2014, Moreno et al., 2022). Lastly, 0.3ml (40mg/ml) of intratympanic methylprednisolone was also assessed for CiO treatment in a prospective cohort of 20 patients with any type of cancer. Intratympanic corticosteroid injections appeared to have minimal therapeutic effect diminishing cisplatin-induced hearing loss at 6000 and 8000 Hz. The adverse effects of this trial were not reported (Nasr et al., 2018).

Aspirin

A phase II double-blind placebo RCT recruited 94 patients to receive aspirin 975 mg twice daily, before and after their cisplatin dose. Patients in the aspirin arm were more commonly affected by aspirin renal toxicity (17.8% vs 10.2%) and no protective hearing effect was observed (p= 0.233)(Crabb et al., 2017).

Sertraline

A double-blind placebo RCT assessed if oral sertraline (50 mg/day) can contribute to preserving the hearing threshold among patients with lymphoma and gastric cancer exposed to cisplatin. The two groups were distributed homogeneously. The ototoxicity grade for the sertraline group was lower compared to the placebo group (p<0.001). The level of distortion product otoacoustic emissions was unchanged among 57.1% in the sertraline group versus 17.1% in the placebo group (p=0.000). However, 11.4% of the patients in the sertraline group reported severe nausea and vomiting (Delarestaghi et al., 2018).

Statins

Previous studies in mice have demonstrated statins reduce CiO. Their effect was tested on 277 adults (546 ears) treated with cisplatin and concurrent radiotherapy for head and neck cancer in an observational study. Of the 6 types of statins tested in this observational study, 44% of patients took atorvastatin. The mixed-effect model analysis showed atorvastatin was significantly associated with reduced cisplatin hearing loss (P = 0.01) (OR = 0.47; 95% CI, 0.30–0.78). No significant correlation was found between high-frequency hearing loss and atorvastatin dose. Adverse effects were not reported (Fernandez et al., 2021).

Table 3. Characteristics of the studies assessing pharmacological interventions.
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study &amp; number of patients</th>
<th>Type of Cancer</th>
<th>Cisplatin dose</th>
<th>Ototoxicity assessment</th>
<th>Follow-up time</th>
<th>Outcome</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandara et al. 1995</td>
<td>RCT 214</td>
<td>Lung cancer</td>
<td>100 mg/m²</td>
<td>Clinical grading scale &amp; audiometry</td>
<td>Not reported</td>
<td>Patients in the intervention group had a greater but not significant reduction in auditory acuity at 3000 Hz (P = 0.095).</td>
<td>No difference between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian cancer</td>
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<td></td>
</tr>
<tr>
<td>Somlo et al. 1995</td>
<td>RCT 42</td>
<td>Sarcoma</td>
<td>125 mg/m²</td>
<td>Audiometry</td>
<td>1 month</td>
<td>No differences were observed in favor of the dopamine group when audiogram results were analyzed at 2,000, 4,000, or 8,000 Hz (P = 0.27, 0.14, and 0.49, respectively).</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast</td>
<td></td>
<td>Dopamine infusion 2 ug/kg/min over 48 hours</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Author</td>
<td>Type of study &amp; number of patients</td>
<td>Type of Cancer</td>
<td>Cisplatin dose</td>
<td>Ototoxicity assessment</td>
<td>Follow-up time</td>
<td>Outcome</td>
<td>Adverse Reactions</td>
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</tr>
<tr>
<td>Kemp et al. 1996</td>
<td>RCT 242</td>
<td>Ovarian</td>
<td>100 mg/m2</td>
<td>Audiometry</td>
<td>41 months</td>
<td>Amifostine had a 43% reduction in the incidence of ototoxicity (P = 0.108). Ototoxicity required cisplatin dose reduction or discontinuation. 16% in the control arm vs 9% in the amifostine arm.</td>
<td>Nausea and/or vomiting, hypotension, flushing, sneezing, dizziness, sleepiness, hiccups, and chills.</td>
</tr>
<tr>
<td>Madasu et al. 1997</td>
<td>Prospective Cohort 70</td>
<td>Head and neck</td>
<td>150 mg/m2</td>
<td>Audiometry</td>
<td>22 days</td>
<td>Sodium thiosulfate did not appear to confer protection. There were no cases of debilitating tinnitus or vestibular loss.</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Sodium thiosulfate did not appear to confer protection. There were no cases of debilitating tinnitus or vestibular loss.
<table>
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<tr>
<th>Author</th>
<th>Type of study &amp; number of patients</th>
<th>Type of Cancer</th>
<th>Cisplatin dose</th>
<th>Ototoxicity assessment</th>
<th>Follow-up time</th>
<th>Outcome</th>
<th>Adverse Reactions</th>
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</thead>
<tbody>
<tr>
<td>Planting et al. 1999</td>
<td>RCT 74 Head and neck</td>
<td>70 mg/m²</td>
<td>Audiometry</td>
<td>Amifostine 740 mg/m²</td>
<td>6 months</td>
<td>Hearing loss was only seen at the high-frequencies (4000 and 8000 Hz). No difference in hearing or tinnitus occurrence (P = 0.24).</td>
<td>Hypotension, dizziness, flushing, anxiety, palpitations, sneezing.</td>
</tr>
<tr>
<td>Ekborn et al. 2004</td>
<td>Prospective Cohort 15 Melanoma Esophagus Cancer</td>
<td>125 - 150 mg/m²</td>
<td>Audiometry</td>
<td>Amifostine 50 mg/mL</td>
<td>Not reported</td>
<td>92% of patients (11 of 12) had auditory symptoms. Ototoxicity was unacceptable despite amifostine treatment.</td>
<td>Nausea and vomiting, ototoxicity, neurotoxicity, oliguria, and hypotension.</td>
</tr>
</tbody>
</table>
| Zuur et al. 2007    | RCT 158 Head and neck           | 150 mg/m²      | Audiometry     | Intravenous Sodium Thiosulfate 9 g/m² (30 minutes) followed by 12 g/m² (2 hours) | 3 months       | Approximately 10% less hearing loss at frequencies vital for speech perception (P = 0.001). | }
<table>
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<th>Author</th>
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<tr>
<td>Yıldırım et al. 2010</td>
<td>RCT 54</td>
<td>Solid organ tumors</td>
<td>Not reported</td>
<td>Audiometry &amp; auditory brainstem response</td>
<td>2 months</td>
<td>Cisplatin ototoxicity could be reduced in N-acetylcysteine group in 10,000 and 12,000 Hz (p&lt;0.005) compared to placebo.</td>
<td>Not reported</td>
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<tr>
<td>Riga et al. 2013</td>
<td>RCT 20</td>
<td>Gastric Melanoma Head and neck Ewing Sarcoma Small cell lung cancer</td>
<td>50 - 100 mg/m²</td>
<td>Audiometry Transtympan N-acetylcysteine (10%)</td>
<td>Not reported</td>
<td>In treated ears no significant changes in auditory thresholds were recorded. In the control ears cisplatin induced a significant decrease of auditory thresholds at the 8000 Hz frequency band (P = 0.008).</td>
<td>Almost all patients had pain after application but it decreased gradually. One patient had an ear infection.</td>
</tr>
<tr>
<td>Yoo et al. 2014</td>
<td>RCT 11</td>
<td>Head and neck</td>
<td>100 mg/m²</td>
<td>Audiometry Transtympan L-N-Acetylcysteine (2%)</td>
<td>2 months</td>
<td>The difference in hearing preservation did not reach significance.</td>
<td>Not reported</td>
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<tr>
<td>Author</td>
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<td>Marshak et al. 2014</td>
<td>RCT 26</td>
<td>Any cancer</td>
<td>517 mg/m²</td>
<td>Audiometry and DPOAE</td>
<td>Intratympanic</td>
<td>Ototoxicity assessment: Not reported. Outcome: Significant increase in the pure tone threshold for 6000 Hz was observed in the control (P&lt;0.02) but not in the study group. Groups’ comparison showed a difference in the DPOAE average signal-to-noise ratio (P&lt;0.04).</td>
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<tr>
<td>Ishikawa et al. 2015</td>
<td>Prospective Cohort 18 Head and neck</td>
<td>100 - 180 mg/m²</td>
<td>Audiometry</td>
<td>Sodium Thiosulfate 14 g/m²/4 h</td>
<td>2 months</td>
<td>Intra-arterial cisplatin with sodium thiosulfate caused relatively less severe cisplatin ototoxicity than usual intra-venous cisplatin chemoradiation.</td>
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<tr>
<td>Author</td>
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<tr>
<td>Crabb et al. 2017</td>
<td>RCT 94</td>
<td>Bladder, Germ cell, Head and neck, Lung</td>
<td>200 mg/m2</td>
<td>Audiometry</td>
<td>3 months</td>
<td>Aspirin did not protect patients receiving cisplatin. Patients demonstrated mean combined hearing loss of 49 dB vs 36 dB (p = 0.233) between arms.</td>
<td>Renal toxicity affected more patients in the aspirin arm (17.8% vs 10.2%), the rest of toxicities were similar between arms.</td>
</tr>
<tr>
<td>Nasr et al. 2018</td>
<td>Non-randomized clinical trial</td>
<td>Any cancer</td>
<td>Average cumulative cisplatin dose 546.3 ± 111.58 mg</td>
<td>Audiometry</td>
<td>After cisplatin dose reached 400 mg,</td>
<td>Significant increases in the average pure-tone thresholds at 6000 Hz were found in both the study and control groups (P = &lt;0.001 and &lt;0.001, respectively) at 6000 and 8000 Hz.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Author</td>
<td>Type of study &amp; number of patients</td>
<td>Type of Cancer</td>
<td>Cisplatin dose</td>
<td>Ototoxicity assessment</td>
<td>Intervention time</td>
<td>Follow-up time</td>
<td>Outcome</td>
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<tr>
<td>Delarestatghi et al. 2018</td>
<td>RCT 79</td>
<td>Lymphoma</td>
<td>75 mg/m²</td>
<td>Audiometry &amp; otoacoustic emissions</td>
<td>Sertraline 25 - 50 mg/d</td>
<td>3 months</td>
<td>Level of distortion product otoacoustic emissions was unchanged 57.1% and 17.1% in the sertraline and placebo groups, respectively (p=0.000).</td>
</tr>
<tr>
<td>Rolland et al. 2019</td>
<td>RCT 13</td>
<td>Head and neck</td>
<td>100 mg/m²</td>
<td>Audiometry and Bone conduction audiograms</td>
<td>Transtympani 8 months Sodium Thiosulfate (dose 0.1 ml).</td>
<td>18 months</td>
<td>The average loss of hearing was 1.3 dB less for treated ears compared to control ears (p = 0.61) 3 and 10 Hz.</td>
</tr>
<tr>
<td>Duinkerken et al. 2021</td>
<td>Single-blind placebo controlled study, 12</td>
<td>Lung Head and neck Mesothelioma Thymus carcinoma</td>
<td>75 - 100 mg/m²</td>
<td>Audiometry</td>
<td>Transtympani 8 months Sodium Thiosulfate 0.5% 2.0 ml</td>
<td>Shift pure-tone average at 8 -12.5 Hz was 18.4 dB less in treated ears compared to untreated ears (p=0.068).</td>
<td>Vertigo, pain and tinnitus</td>
</tr>
<tr>
<td>Author</td>
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<td>Cisplatin dose</td>
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<tr>
<td>Fernandez et al. 2021</td>
<td>observational study 277</td>
<td>Head and neck</td>
<td>200 mg/m²</td>
<td>Audiometry</td>
<td>3 months</td>
<td>Atorvastatin use was significantly associated with reduced cisplatin-induced hearing loss (P &lt; 0.01) (OR = 0.47; 95% CI, 0.30–0.78).</td>
<td>Not reported</td>
</tr>
<tr>
<td>Moreno et al. 2022</td>
<td>RCT 23</td>
<td>Lung Bladder Unknown origin</td>
<td>70-100 mg/m²</td>
<td>Audiometry Intratympanic dexamethasone 8mg</td>
<td>2 months</td>
<td>Audiometric analysis showed a higher hearing threshold in the study group at frequencies of 500, 1000, and 6000 Hz: 4.9 dB, 5.5 dB, and 16 dB (p &lt; 0.05).</td>
<td>Infections 8.6% and permanent perforation 34.8%.</td>
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</table>

RCT: Randomized control trial Hz: Hertz dB: decibel DPOAE: Distortion Product Otoacoustic Emissions

Table 4. Characteristics of the studies assessing non-pharmacological interventions.
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Type of Cancer</th>
<th>Cisplatin dose</th>
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<th>Intervention time</th>
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<tbody>
<tr>
<td>Weijl et al. 2004</td>
<td>RCT 50</td>
<td>Any cancer</td>
<td>100mg/m²</td>
<td>Audiometry</td>
<td>1000mg Vitamin C, 400mg Vitamin E, 100mg selenium</td>
<td>12 months</td>
<td>Patients with the highest micronutrient antioxidant score had less loss of high-tone hearing (conduction threshold at 8.0 Hz 2.8 vs. 14.4 dB; p=0.028).</td>
<td>Not reported</td>
</tr>
<tr>
<td>Villani et al. 2016</td>
<td>RCT 108</td>
<td>Solid malignancies</td>
<td>Not reported</td>
<td>Audiometry and evoked brainstem responses</td>
<td>400mg Vitamin E per day</td>
<td>3 months</td>
<td>A significant hearing loss in the control group at both 2000 Hz and 8000 Hz. Conversely, audiograms did not show significant changes in the active group at 2000, 4000, and 8000 Hz.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Author</td>
<td>Type of study</td>
<td>Type of Cancer</td>
<td>Cisplatin dose</td>
<td>Ototoxicity assessment</td>
<td>Follow-up time</td>
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<tr>
<td>Scasso et al. 2017</td>
<td>Case-control study 26</td>
<td>Any cancer</td>
<td>100 mg/m²</td>
<td>Audiology</td>
<td>4 months</td>
<td>Coenzyme Q10 + Multivitamins</td>
<td>A higher hearing impairment in the control patients occurred in 6 out of 8 patients (75.0%). Otherwise, only 2 out of 18 patients (11.1%) who took the supplement daily were affected (P &lt; 0.01).</td>
<td>Not reported</td>
</tr>
<tr>
<td>Campbell et al. 2022</td>
<td>RCT 27</td>
<td>Head and neck Genitourinary Esophagus</td>
<td>50 mg/m²</td>
<td>Audiology</td>
<td>5 cycles of cisplatin</td>
<td>D-methionine (100 mg/kg) fractionated into two doses</td>
<td>Placebo group showed a threshold shifts from baseline to post-treatment at 10 Hz (-13.65 dB p =0.008), 11.2 Hz (-16.15dB p=0.008) and 12.5 Hz (-11.46dB p=0.03). The intervention group showed no significant threshold shifts.</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>
RCT: Randomized control trial Hz: Hertz dB: decibel

Non-pharmacological interventions

Multivitamins

Three investigations evaluated multivitamin supplementation in CiO (Weijl et al., 2004, Villani et al., 2016, Scasso et al., 2017). A multivitamin beverage that contained vitamin C, vitamin E, and selenium was used as CiO profilaxis in a RCT. At 12 months they did not find any difference between the occurrence of nephrotoxicity and ototoxicity induced by cisplatin. However, patients with the highest micronutrient antioxidant values at the start of chemotherapy had significantly less loss of high-tone hearing than patients with low values (conduction threshold at 8.0 kHz 2.8 vs. 14.4 dB; p=0.028) (Weijl et al., 2004). Another RCT compared the protective effect of vitamin E supplementation for 3 months against placebo in CiO. At 1 month the control group had significant hearing loss at both 2000 Hz (right ear: p=0.05; left ear: p=0.04) and 8000 HZ (right ear: p=0.04; left ear: p=0.03) when compared with baseline values. Audiograms did not show significant changes in the active group at 2000, 4000, and 8000 Hz. Evoked brainstem responses remained unchanged in both groups. The planned follow-up evaluations weren’t completed because of a 37% patient drop-out (Villani et al., 2016). Ultimately a case-control study tested if dietary supplementation with coenzyme Q10 plus multivitamins could preemptively reduce reactive oxygen species and consequently CiO. They found that patients on dietary supplementation, 7 days before and 21 days after chemotherapy, had a significantly lower amount of reactive oxygen metabolite derivatives (P < 0.05) and a stable range of blood antioxidants (P < 0.05) compared to the control group. Moreover, the intervention group showed lesser augmentation on the hearing threshold level at 8000 Hz frequency 6.9 ± 11.8 dB compared to the control group 20.0 ± 16.2 dB (P < 0.05). Similarly, tinnitus incidence was higher in the control group (62.5% vs 11.1% P < 0.05). In this study, 69% of patients received concomitant head radiation (dose not specified)(Scasso et al., 2017). None of the studies reported adverse effects due to vitamin supplementation, only the patient’s dislikeness for the taste of the supplementation product.

D-methionine

A RCT assessed the otoprotective effect of D-methionine in CiO in 27 patients receiving chemoradiotherapy for head and neck, genitourinary, and esophagus cancer. Radiotherapy was used on 37% of the patients, the delivered dose was not stated. While the placebo group showed significant hearing threshold decline from baseline to post-treatment at 10 kHz (-13.65 dB p =0.008), 11.2 kHz (-16.15dB p=0.008), and 12.5 kHz (-11.46dB p=0.03), the intervention group showed no significant hearing threshold shift. There was no difference in side effects between the groups (Campbell et al., 2022).

Discussion

This systematic review is a comprehensive synthesis of all the interventions that have been used in adult patients to mitigate cisplatin-induced ototoxicity. Previous systematic reviews have described the evidence on potential therapeutic targets based on animal models (Mukherjea et al., 2020), have noted the effectiveness of a particular intervention (Duval et al., 2012), or have focused on the pediatric population (Freyer et al., 2020). This is the first systematic review in the adult population with CiO that broadly recopilates the evidence on pharmacological and non-pharmacological interventions. Our study approach allowed us to search for ototoxicity caused by other types of platinum and chemotherapy agents, albeit the retrieved studies only focused on cisplatin ototoxicity. In total eleven interventions (nine pharmacological and two non-pharmacological) for CiO in adults were identified. Based on the authors’ information, this review analyzes the most interventions to date. All of the interventions have been tested as a preemptively otoprotective strategy and only one (corticosteroids) has been assessed in one study as a treatment strategy once the hearing deficit is established due to cisplatin administration (Nasr et al., 2018). This finding may be relevant to explain the ineffective results of some interventions. The action of free radical oxygen species may take time to occur as cisplatin accumulates in the cochlea, meantime the prophylactic effect of the otoprotective intervention may be lost, not coinciding with the nadir damage on the ear function(Breglio et al., 2017, Tang et al., 2021).
We encounter four pharmacological and two non-pharmacological interventions with positive results that merit future investigation. Of the pharmacological interventions, sodium thiosulfate, corticoids, sertraline, and statins showed a preserving hearing effect. Nevertheless, the current evidence on these interventions has limiting aspects to consider. A considerable number and severity of side effects were reported in the intratympanic corticoids trial, a single trial has been conducted with sertraline and statins, and the statins trial had a heterogeneous intervention which limits the confidence of the results. Although the studies showed a partial benefit, sodium thiosulfate appears as the most promising intervention to prevent CiO in adults undergoing cisplatin therapy. These results are similar to what has been found in high-quality RCT in the pediatric population, where sodium thiosulfate reduced the incidence of cisplatin-induced hearing loss among children with standard-risk hepatoblastoma, without jeopardizing overall or event-free survival (Brock et al., 2018). A recent systematic review and meta-analysis, based on four studies with mixed pediatric and adult populations, confirms the otoprotective effect of sodium thiosulfate (Chen et al., 2021). On the other hand, the two non-pharmacological interventions that showed positive results were multivitamins and D-methionine. As with the pharmacological interventions, this too has limiting considerations. The multivitamins regimen tested vary widely among the studies, and the evidence regarding D-methionine consists of a unique pilot trial. None of the studies testing non-pharmacological interventions had a good quality rating. However, the safety profile of these dietary supplements seems to be superior and could make them a good option depending on future trials. Moreover, the low number of participants reduces the chances of detecting significant adverse events and increases the likelihood of Type II errors. (Faber et al., 2014).

Additionally, our results highlighted the focus and gaps of CiO research. Even though tinnitus and vertigo are symptoms that may considerably affect patients’ quality of life, even more than the mild hearing loss that occurs above the frequency range of human speech (0.25 – 8 kHz) that may go undetected (Chauhan et al., 2011), few studies in our review documented them. Moreover, none showed that any kind of intervention could prevent or palliate these symptoms. It is not clear why the studies did not take the whole spectrum of CiO symptoms into account, given that cisplatin-induced tinnitus is reported to be prevalent with high cumulative cisplatin doses (p<0.007) and in older populations (p=0.007) (Frisina et al., 2016). Investigators have also found cisplatin-induced tinnitus is significantly correlated with reduced hearing per frequency (0.25-12 kHz, p< 0.0001) and vertigo (OR = 6.47; p< 0.0001) (El Charif et al., 2019), which means it is uncommon for patients to experience hearing loss without tinnitus and vertigo. This suggests that these symptoms are likely underdiagnosed or overlooked in oncology, hematology, or palliative care consultations. Currently, four clinical trials in adult patients with CiO risk are underway to evaluate sodium thiosulfate and mannitol, rosvastatin, and intratympanic N-acetylcysteine (Dizon et al., Kasem et al., Sajenio et al., Cavelier et al.). Only one of them considers the apparition of tinnitus in their outcomes. Therefore, future high-quality randomized clinical trials should consider the shortcomings and successes of existing evidence to improve their internal validity.

**Limitations**

There are a number of limitations to our review. Relevant articles might be missed because the search was conducted only in three databases, in one language, and excluded grey literature. One article about the protective effect of ginkgo biloba extract on CiO was retrieved by the manual research on clinicaltrial.gov, but wasn’t available in its full-text format. The conclusions of our review are based on studies with small and heterogeneous samples, who were followed on different time ranges, and whose analysis had low quality, so our results should be taken as preliminary findings that need to be corroborated in the future. None of the trials took into account patients’ quality of life or reported outcomes to assess the intervention’s benefit. So a comprehensive understanding of the effectiveness of any intervention is missing. Finally, the safety outcomes of the interventions were not mentioned in 10 out of 23 studies. Since most of the interventions contain mild benefits and uncertain risks, underreporting of side effects limits the power of our conclusions.

**Conclusions**

Ototoxicity is a known side effect of platinum-based chemotherapeutics. Eleven pharmacological and non-pharmacological strategies have been proposed to address this issue in the adult cancer population. This
review summarizes the effectiveness of each intervention for the prevention and treatment of hearing loss associated with cisplatin. Current studies’ results are limited by their suboptimal methodological quality and underreporting of safety outcomes. High-quality randomized clinical trials are warranted to clarify the significance of these preliminary findings. Future research should ensure to include patients’ reported outcomes and overlooked otic symptoms like tinnitus and vertigo.

References:


