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SYSTEMATIC REVIEW

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Prevention and treatment of cisplatin-induced ototoxicity in adults: A systematic review

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Abstract

Objectives: Ototoxicity is a common disabling side effect of platinum-based chemotherapy. This study aimed to assess the evidence on the management of platinum-induced ototoxicity in adult cancer patients.

Methods: Four databases were searched up to 1 November 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 via two grading scales.

Results: Nineteen randomised controlled trials and five quasi-experimental studies with 1673 patients were analysed. Eleven interventions were identified, nine pharmacological and two non-pharmacological. Six of the interventions (sodium thiosulphate, corticoids, sertraline, statins, multivitamins and D-methionine) showed mild benefits in preventing cisplatin-induced ototoxicity. Only one trial assessed corticoids as a potential treatment. Overall, only six trials were deemed with a low risk of bias. The majority of studies inadequately documented intervention-related adverse effects, thereby limiting safety conclusions.

Conclusions: Current interventions have mild benefits in preventing cisplatin-induced ototoxicity in adult cancer patients. Sodium thiosulphate is the most promising intervention as a preventive strategy. Rigorous, high-quality research is warranted, encompassing an evaluation of all potential symptoms and innovative treatment modalities.

KEYWORDS
chemotherapy-related adverse events, cisplatin-induced ototoxicity, hearing loss, otoprotection, platinum chemotherapy

1 | INTRODUCTION

Platinum chemotherapy agents are the cornerstone of several oncologic and haematologic protocol treatments given their high effectiveness, cost and accessibility.[1] These benefits are tied to unwanted side effects. Ototoxicity is a well-known adverse effect of platinum compounds,

The content of this manuscript has not been previously shared in conferences or seminars, and it will only be published when approved.

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.[1,2] 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 and 225 mg/m^2), concomitant radiotherapy treatments or even the patient's stress level.[3–8] Current knowledge has shown platinum-induced ototoxicity is a multifactorial process where free radical oxygen species and inflammation induce endogenous anti-oxidants depletion and increase lipid peroxidation, causing rupture of the outer hair cell stereocilia in the organ of Corti.[9,10] 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.[11] Depending on the hearing loss frequency and the severity of speech impairment, more than 10 grading systems have been proposed to better characterise patients' affection.[12] Moreover, accurate prediction models of posttreatment hearing alterations with good performance (e.g., sensitivity of 80% and specificity of 75%) and follow-up screening audiometric test analysis have been proposed to diagnose platinum ototoxicity.[2,13,14] Numerous studies on animals have been conducted and a guideline to treat cisplatin-induced ototoxicity (CiO) in children has been published, albeit the evidence solely recommends the pharmacologic treatment of sodium thiosulphate in non-metastatic hepatoblastoma or in other non-metastatic cancers, and is against its routine use in metastatic cancers. Amifostine, sodium diethyldithiocarbamate and intratympanic therapy are discouraged as the modification of cisplatin infusion duration to reduce ototoxicity.[15] Meanwhile, there is a paucity in the adult population about the safety and effectivity of pharmacological or non-pharmacological interventions to prevent or treat platinum-induced ototoxicity, without inhibiting antitumor effects.[16] Even so, ototoxicity prevention and treatment is a major research priority due to the symptom burden and diminishing quality of life patients experience.[17] Thus, we conducted the first comprehensive systematic literature review encompassing pharmacological and non-pharmacological interventions to prevent or treat platinum-induced ototoxicity in adult cancer patients. Our hypothesis is that mirroring the scenario in the paediatric population, sodium thiosulphate could potentially stand as the sole intervention exhibiting a commendable efficacy and safety profile, applicable to both the treatment and prevention of platinum-induced ototoxicity.

Key Points

1. Cisplatin-induced ototoxicity is a well-known adverse effect that has not been sufficiently studied in the adult population.
2. Pharmacological and non-pharmacologic interventions to prevent cisplatin-induced hearing loss are controversial given their mild efficacy and potential side effects.
3. Pharmacological and non-pharmacologic interventions to treat cisplatin-induced hearing loss are scarce.
4. Sodium thiosulphate for preventing cisplatin-induced ototoxicity is currently the most promising intervention.
5. Tinnitus and vertigo are distressing symptoms overlooked in cisplatin-induced ototoxicity research.

2 | METHODOLOGY

2.1 | 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.

2.2 | Search strategy

We developed a search strategy using Medical Subject Headings (MeSH) related to chemotherapy-induced ototoxicity. We searched four databases (Medline, CINHAL, PubMed and Cochrane Central) 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 (Juan Esteban Correa-Morales and Nidia Mantilla-Manosalva) 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. Furthermore, 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; Figure 1).

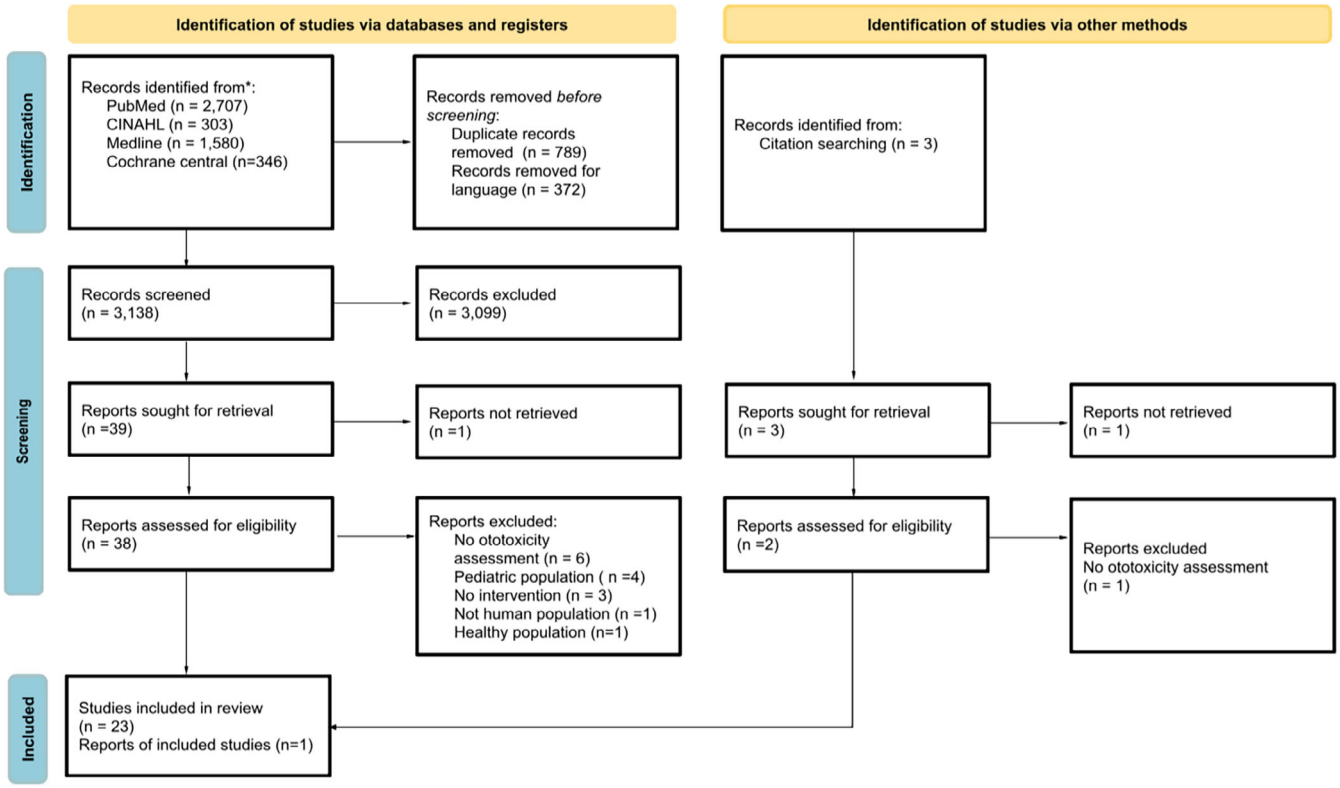

FIGURE 1 PRISMA flow chart to illustrate the flow of studies through the review and the selection process.

2.3 | Study selection

Eligible studies had to be (1) original investigations published in a peer-reviewed journal before 1 November 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 and Spanish; (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. Grey literature, editorials, commentaries, case series with 10 or fewer patients, case studies and protocols were excluded from the review.

2.4 | Data extraction

Four reviewers (Elias Quintero-Muñoz, Juan Esteban Correa-Morales, Oscar Felipe Borja-Montes and Lennis Jazmin Bedoya-Muñoz) 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.

2.5 | Quality appraisal

Four reviewers (Laura Cuellar-Valencia, Sara Giraldo-Moreno, Nidia Mantilla-Manosalva and María Fernanda Iriarte-Aristizábal) independently assessed each included study for the risk of bias. A third reviewer arbitrated possible differences. Randomised controlled trials (RCT) were evaluated using the Cochrane Collaboration's Risk-of-Bias Tool 2 and non-randomised studies were assessed with the Newcastle Ottawa Scale.[18,19] No study was disregarded for its quality.

2.6 | Data synthesis and analysis

The synthesis of results was performed using the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews.[20] 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 are 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 analysing and interpreting the results and vouched for their completeness and accuracy.

3 | RESULTS

The search rendered 4936 studies, 752 duplicates were removed, and 3777 were deemed ineligible after screening titles and abstracts. The reference review resulted in the addition of one article. The resulting 40 full texts were screened, of which 24 studies were selected for data extraction and analysis.[21-43] Figure 1 depicts the PRISMA complete screening process. Publication dates were 1995–2022, with studies conducted in 15 different countries, with five studies from the United States, four from the Netherlands, two from Canada and Italy, and one study from Sweden, Turkey, Greece, Spain, Israel, Japan, United Kingdom, Chile, Egypt, Iran and India. Studies consisted of 19 controlled trials.[21-23,25,27-31,33-38,40,41,43,44] 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 19 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. Figure 2 and Table 1 presents the quality assessment for all the studies. In total, 11 interventions were used for cisplatin-ototoxicity, 9 pharmacological interventions were assessed in 20 studies[21-40] and 2 non-pharmacological interventions assessed in 4 studies.[41-44] All of the studies assessed platinum-ototoxicity prevention, except for one that evaluated ototoxicity

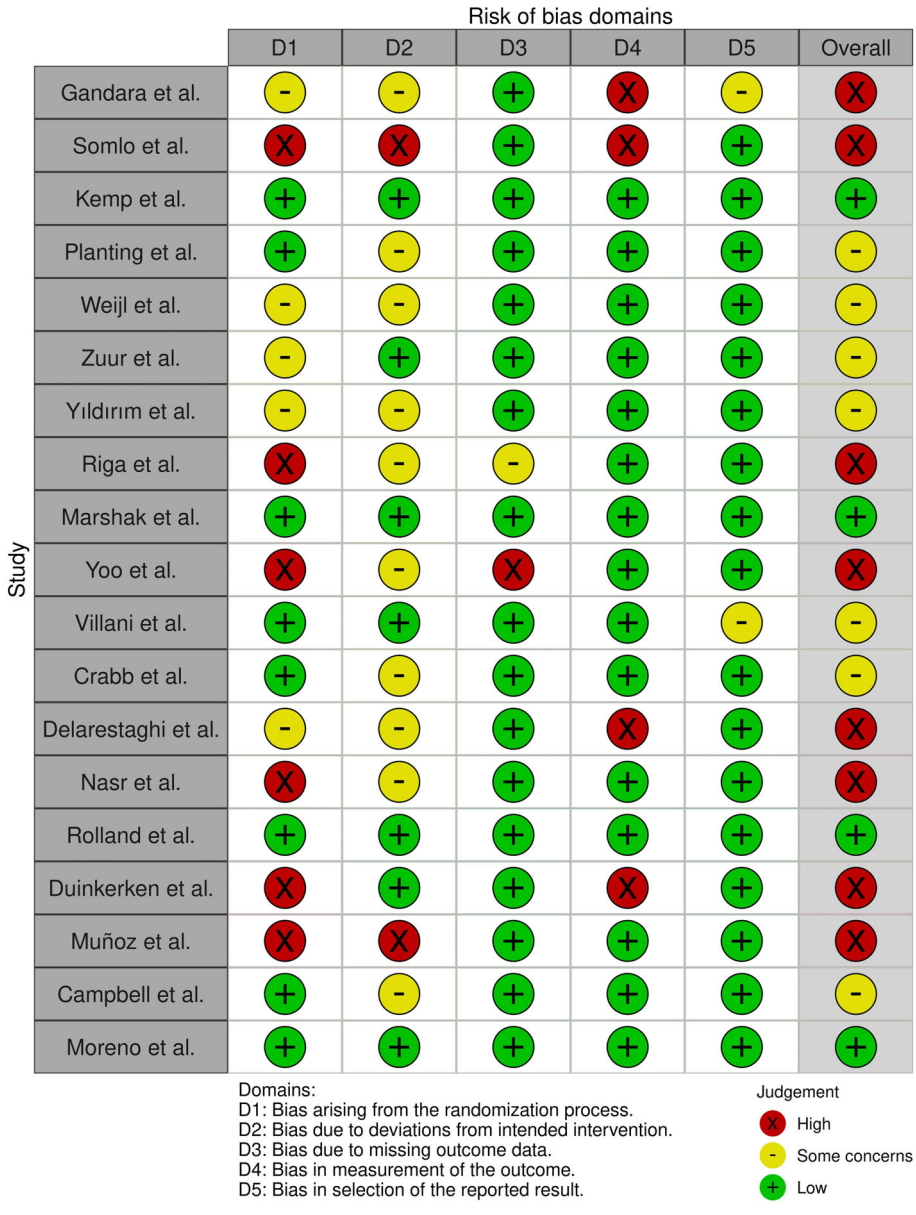

FIGURE 2 Assessment of the risk of bias in clinical trials. Quality tool used: Cochrane risk-of-bias tool for randomised trials Version 2.[45]

TABLE 1 Quality assessment of cohorts and cases–control studies.

Study	Type of study	Selection	Comparability	Outcome/exposure	Overall
Madasu et al.	Cohort	2	1	0	Poor quality
Scasso et al.	Case and controls	3	0	1	Poor quality
Fernandez et al.	Cohort	3	1	3	High quality
Ishikawa et al.	Cohort	3	1	3	High quality
Ekborn et al.	Cohort	2	0	1	Poor quality

Note: Quality tool used: Newcastle–Ottawa quality assessment scale.

treatment.[34] 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 CiO outcome as hearing loss and five studies also considered tinnitus,[24,25,30,32,42] and only two included vestibular disturbances.[24,32] All of the studies used an audiometry test to examine ototoxicity. The study's characteristics for the pharmacologic and non-pharmacologic interventions appear in Tables 2 and 3, respectively.

3.1 | Patient characteristics

Study populations included adults 18–82 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 12 studies.[24,25,27,29,30,32,33,36-39,43] Other types were ovarian, bladder, germ cell, gastric, lung, breast, sarcoma, thymus, mesothelioma, oesophagus, 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 and 517 mg/m^2, an average of 138 mg/m^2. 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. Regarding this last condition, there was great heterogeneity between studies, 10 studies demanded or allowed concomitant radiotherapy,[24,25,27,30,32,36,37,39,42,43] while 13 considered radiotherapy as an exclusion criterion. For those studies that reported follow-up time, the mean was 6.4 months.

3.2 | Pharmacological interventions

3.2.1 | Diethyldithiocarbamate

A randomised placebo-controlled multicentre study used diethyldithiocarbamate for chemoprotection against CiO 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. The patients also had a trend for a greater reduction in auditory acuity at 3000 Hz ($p = .095$).[21]

3.2.2 | Dopamine

In a randomised, 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 favour of the dopamine group when audiogram results were analysed at 2000, 4000 or 8000 Hz ($p = .27$, .14 and .49, respectively).[22]

3.2.3 | Amifostine

Three studies assessed amifostine in CiO prevention. None of them found favourable results with amifostine as a pretreatment strategy. The first study was a randomised 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 ($p = .095$).[23] The second randomised 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 ($p = .24$).[25] Finally, in a prospective cohort of 15 patients with different types of cancer, 11 out of 12 patients displayed auditory symptoms despite amifostine treatment.[26] 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.[23,25,26]

3.2.4 | Sodium thiosulphate

Five articles researched sodium thiosulphate for CiO prevention.[24,27,32,36,37] The first one was a prospective cohort of 70 patients with head and neck cancer, who received cisplatin, radiotherapy (dose was not specified) and systemic sodium thiosulphate. The baseline audiometric analysis comparison to the audiometry after the fourth cisplatin infusion did not appear to confer a protective hearing effect from sodium thiosulphate. Tinnitus or vestibular loss were not

TABLE 2 Characteristics of the studies assessing pharmacological interventions.

Author	Type of study and number of patients	Type of cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse reactions
Gandara et al., 1995	RCT; 214	Lung cancer; ovarian cancer	100 mg/m^2	Clinical grading scale and audiometry	Diethyldithiocarbamate	Not reported	Patients in the intervention group had a greater but not significant reduction in auditory acuity at 3000 Hz ($p = .095$)	No difference between groups
Somlo et al., 1995	RCT; 42	Sarcoma; breast	125 mg/m^2	Audiometry	Dopamine infusion 2 ug/kg/min over 48 h	1 month	No differences were observed in favour of the dopamine group when audiogram results were analysed at 2000, 4000 or 8000 Hz ($p = .27, .14$ and .49, respectively).	Not reported
Kemp et al., 1996	RCT; 242	Ovarian	100 mg/m^2	Audiometry	Amifostine, 910 mg/m^2	41 months	Amifostine had a 43% reduction in the incidence of ototoxicity ($p = .108$). Ototoxicity required cisplatin dose reduction or discontinuation 16% in the control arm versus 9% in the amifostine arm	Nausea and/or vomiting, hypotension, flushing, sneezing, dizziness, sleepiness, hiccups and chills
Madasu et al., 1997	Prospective cohort; 70	Head and neck	150 mg/m^2	Audiometry	Sodium thiosulphate	22 days	Sodium thiosulphate did not appear to confer protection. There were no cases of debilitating tinnitus or vestibular loss	Not reported
Planting et al., 1999	RCT; 74	Head and neck	70 mg/m^2	Audiometry	Amifostine; 740 mg/m^2	6 months	Hearing loss was only seen at the high-frequencies (4000 and 8000 Hz). No difference in hearing or tinnitus occurrence ($p = .24$)	Hypotension, dizziness, flushing, anxiety, palpitations and sneezing

TABLE 2 (Continued)

Author	Type of study and number of patients	Type of cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse reactions
Ekborn et al., 2004	Prospective cohort; 15	Melanoma oesophagus cancer	125–150 mg/m^2	Audiometry	Amifostine; 50 mg/mL	Not reported	92% of patients (11 of 12) had auditory symptoms. Ototoxicity was unacceptable despite amifostine treatment.	Nausea and vomiting, ototoxicity, neurotoxicity, oliguria and hypotension
Zuur et al., 2007	RCT; 158	Head and neck	150 mg/m^2	Audiometry	Intravenous sodium thiosulphate 9 g/m^2 (30 min) followed by 12 g/m^2 (2 h)	3 months	Approximately 10% less hearing loss at frequencies vital for speech perception ($p = .001$)	No difference between groups
Yıldırım et al., 2010	RCT; 54	Solid organ tumours	Not reported	Audiometry and auditory brainstem response	*N*-acetylcysteine 600 mg/day or salicylate 300 mg/day	2 months	Cisplatin-ototoxicity could be reduced in *N*-acetylcysteine group in 10 000 and 12 000 Hz ($p < .005$) compared to placebo	Not reported
Riga et al., 2013	RCT; 20	Gastric; melanoma; head and neck; Ewing sarcoma; small cell lung cancer	50–100 mg/m^2	Audiometry	Transtympanic *N*-acetylcysteine (10%)	Not reported	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 ($p = .008$).	Almost all patients had pain after application but it decreased gradually. One patient had an ear infection.
Yoo et al., 2014	RCT; 11	Head and neck	100 mg/m^2	Audiometry	Transtympanic L-N-Acetylcysteine (2%) 200 mg/mL	2 months	The difference in hearing preservation did not reach significance	Not reported
Marshak et al., 2014	RCT; 26	Any cancer	517 mg/m^2	Audiometry and DPOAE	Intratympanic dexamethasone (10 mg/mL solution)	Not reported	Significant increase in the pure tone threshold for 6000 Hz was observed in the control ($p < .02$) but not in the study group. Groups' comparison showed a difference in the DPOAE average signal-to-noise ratio ($p < .04$)	Slight pain and short mild vertigo during application

(Continues)

TABLE 2 (Continued)

Author	Type of study and number of patients	Type of cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse reactions
Ishikawa et al., 2015	Prospective cohort; 18	Head and neck	100–180 mg/m^2	Audiometry	Sodium thiosulphate; 14 g/m^2/4 h	2 months	Intra-arterial cisplatin with sodium thiosulphate caused relatively less severe cisplatin ototoxicity than usual intravenous cisplatin chemoradiation	Not reported
Crabb et al., 2017	RCT; 94	Bladder; germ cell; head and neck; lung	200 mg/m^2	Audiometry	Aspirin; 975 mg three times a day for 4–5 days	3 months	Aspirin did not protect patients receiving cisplatin. Patients demonstrated mean combined hearing loss of 49 dB versus 36 dB ($p = .233$)	Renal toxicity affected more patients in the aspirin arm (17.8% vs. 10.2%), the rest of toxicities were similar between arms
Nasr et al., 2018	Non-randomised clinical trial	Any cancer	Average cumulative cisplatin dose 546.3 ± 111.58 mg	Audiometry	Intra-tympanic methylprednisolone; 40 mg/mL	After cisplatin dose reached 400 mg.	Significant increases in the average pure-tone thresholds at 6000 Hz were found in both the study and control groups ($p \leq .001$ and <.001, respectively) at 6000 and 8000 Hz	Not reported
Delarestaghi et al., 2018	RCT; 79	Lymphoma; gastric	75 mg/m^2	Audiometry and otoacoustic emissions	Sertraline 25–50 mg/day	3 months	Level of distortion product otoacoustic emissions was unchanged 57.1% and 17.1% in the sertraline and placebo groups, respectively ($p = .000$)	11.4% had severe nausea and vomiting in the sertraline group
Rolland et al., 2019	RCT; 13	Head and neck	100 mg/m^2	Audiometry and bone conduction audiograms	Transtympanic sodium thiosulphate (dose 0.1 mL)	18 months	The average loss of hearing was 1.3 dB less for treated ears compared to control ears ($p = .61$) 3 and 10 Hz.	Three patients reported dizziness and one patient had vertigo. Pain in the middle ear was noted for four patients

TABLE 2 (Continued)

Author	Type of study and number of patients	Type of cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse reactions
Duinkerken et al., 2021	Single-blind placebo controlled study. 12	Lung; head and neck; mesothelioma; thymus carcinoma	75–100 mg/m^2	Audiometry	Transtympanic sodium thiosulphate 0.5%; 2.0 mL	3 months	Shift pure-tone average at 8–12.5 Hz was 18.4 dB less in treated ears compared to untreated ears ($p = .068$).	Vertigo, pain and tinnitus
Muñoz et al., 2021	RCT; 45	Head and neck	240 mg/m^2	Audiometry	*N*-acetylcysteine 1200 mg followed by 600 mg/day		Protective role of *n*-acetylcysteine from cisplatin-induced ototoxicity in patients with head and neck cancer: randomised placebo controlled clinical trial	Not reported
Fernandez et al., 2021	Observational study; 277	Head and neck	200 mg/m^2	Audiometry	Various statins at different doses	3 months	Atorvastatin use was significantly associated with reduced cisplatin-induced hearing loss ($p \leq .01$) (OR = 0.47; 95% CI: 0.30–0.78)	Not reported
Moreno et al., 2022	RCT; 23	Lung; bladder; unknown origin	70–100 mg/m^2	Audiometry	Intratympanic dexamethasone; 8 mg	2 months	Audiometric analysis showed a higher hearing threshold in the study group at frequencies of 500, 1000 and 6000 Hz: 4.9, 5.5 and 16 dB ($p < .05$)	Infections 8.6% and permanent perforation 34.8%

Abbreviations: DPOAE, Distortion Product Otoacoustic Emissions; RCT, randomised control trial.

TABLE 3 Characteristics of the studies assessing non-pharmacological interventions.

Author	Type of study	Type of cancer	Cisplatin dose	Ototoxicity assessment	Intervention	Follow-up time	Outcome	Adverse reactions
Weijl et al., 2004	RCT; 50	Any cancer	100 mg/m^2	Audiometry	1000 mg vitamin C, 400 mg vitamin E, 100 mg selenium	12 months	Patients with the highest micronutrient antioxidant score had less loss of high-tone hearing (conduction threshold at 8.0 Hz 2.8 versus 14.4 dB; $p = .028$)	Not reported
Villani et al., 2016	RCT; 108	Solid malignancies	Not reported	Audiometry and evoked brainstem responses	400 mg vitamin E per day	3 months	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	Not reported
Scasso et al., 2017	Case–control study; 26	Any cancer	100 mg/m^2	Audiometry	Coenzyme Q10 + multivitamins	4 months	A higher hearing impairment in the control patients occurred in six out of eight patients (75.0%). Otherwise, only 2 out of 18 patients (11.1%) who took the supplement daily were affected ($p < .01$)	Not reported
Campbell et al., 2022	RCT; 27	Head and neck; genitourinary; oesophagus	50 mg/m^2	Audiometry	D-methionine (100 mg/kg) fractionated into two doses	Five cycles of cisplatin	Placebo group showed a threshold shift from baseline to post-treatment at 10 Hz (−13.65 dB; $p = .008$), 11.2 Hz (−16.15 dB; $p = .008$) and 12.5 Hz (−11.46 dB; $p = .03$). The intervention group showed no significant threshold shifts.	No difference between groups

Abbreviation: RCT: Randomised control trial.

reported, nor were adverse reactions.[24] A similar prospective cohort of 18 patients with the same kind of cancer and receiving 60–70 Gray of radiotherapy assessed sodium thiosulphate otoprotection. The sodium thiosulphate group had significant hearing loss at ultra-high frequencies of 10 and 12 kHz ($p = .028$ and .039, respectively), whereas the group not receiving sodium thiosulphate had significant hearing loss at high frequencies of 8 and 10 kHz ($p = .016$ and .027, respectively). During follow-up, one patient presented with subjective tinnitus. Vertigo episodes and adverse reactions were not reported for any patient.[32] Later, a pilot non-randomised control trial using transtympanic sodium thiosulphate 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 ($p = .068$).[37] This positive finding was further explored in a randomised control trial that tested intravenous sodium thiosulphate 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 ($p = .14$), but the intervention group had 10% less hearing loss at frequencies vital for speech perception ($p = .001$). No difference in adverse reactions between groups was observed.[27] Finally, a second randomised control trial tested trans-tympanic injections of sodium thiosulphate 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 ($p = .61$) nor clinically significant, the difference was in favour of the treated ears for all frequencies between 3 and 10 kHz. Injections caused dizziness in three patients, vertigo in one patient and pain in four patients.[36]

3.2.5 | *N*-acetylcysteine

Four randomised placebo-controlled trials have explored if *N*-acetylcysteine can avert CiO administered intratympanic[29,30] or orally.[28,38] A RCT used intratympanic *N*-acetylcysteine at 10% in 20 patients with different types of tumours. 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 ($p = .008$) with cisplatin.[29] 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.[30] 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,[29] while the trial with a lower concentration of *N*-acetylcysteine did not report adverse reactions.[30] The third RCT compared the protective hearing effect of placebo, oral *N*-acetylcysteine, and salicylate in 54 patients with solid organ tumours 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 ($p < .005$) compared to placebo. Nonetheless, safety outcomes between study interventions were not reported.[28] The fourth RCT compared the protective hearing effect of oral *N*-acetylcysteine in 45 patients with head and neck cancer receiving cisplatin. Audiometry did not show a significant difference between placebo and oral *N*-acetylcysteine in the prevention of ototoxicity, but it did modify the course of installation and progression.[38]

3.2.6 | Corticoids

Three investigations have evaluated the role of intratympanic corticosteroids in preventing CiO.[31,34,40] Two studies used dexamethasone and one methylprednisolone. In a controlled trial, prior to each cisplatin treatment session, intratympanic dexamethasone was injected 0.7–1.0 mL (10 mg/mL) into randomly assigned ears. A significant attenuation in the hearing loss at 6000 Hz ($p < .02$) and decreased outer hair dysfunction in the range of 4000–8000 Hz ($p < .04$) was observed in the intervention group.[31] These positive findings of intratympanic dexamethasone protecting the hearing capacity were corroborated by a second randomised 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 ($p < .05$).[40] 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.[31,40] Finally, 0.3 mL (40 mg/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.[34]

3.2.7 | 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 ($p = .233$).[33]

3.2.8 | 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 ($p < .001$). 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.[35]

3.2.9 | 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 six 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 ($p \leq .01$; 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.[39]

3.3 | Non-pharmacological interventions

3.3.1 | Multivitamins

Three investigations evaluated multivitamin supplementation in CiO.[41,42,44] A multivitamin beverage that contained vitamin C, vitamin E and selenium was used as CiO prophylaxis 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; $p = .028$).[41] 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: $p = .05$; left ear: $p = .04$) and 8000 HZ (right ear: $p = .04$; left ear: $p = .03$) 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 were not completed because of a 37% patient drop-out.[44] 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 ($p < .05$) and a stable range of blood antioxidants ($p < .05$) 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 ($p < .05$). Similarly, tinnitus incidence was higher in the control group (62.5% vs. 11.1% $p < .05$). In this study, 69% of patients received concomitant head radiation (dose was not specified).[42] None of the studies reported adverse effects due to vitamin supplementation, only the patient's dislike for the taste of the supplementation product.

3.3.2 | D-methionine

A RCT assessed the otoprotective effect of D-methionine in CiO in 27 patients receiving chemoradiotherapy for head and neck, genitourinary and oesophagus cancer. Radiotherapy was used on 37% of the patients (dose was not specified). While the placebo group showed significant hearing threshold decline from baseline to post-treatment at 10 kHz (−13.65 dB; $p = .008$), 11.2 kHz (−16.15 dB; $p = .008$) and 12.5 kHz (−11.46 dB; $p = .03$), the intervention group showed no significant hearing threshold shift. There was no difference in side effects between the groups.[43]

4 | DISCUSSION

This systematic review is a comprehensive synthesis of all the interventions that have been used in adult patients to mitigate CiO. Previous systematic reviews have described the evidence on potential therapeutic targets based on animal models,[46] have noted the effectiveness of a particular intervention[47] or have focused on the paediatric population.[15] This is the first systematic review in the adult population with CiO that gathers evidence from a broad range of studies 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, 11 interventions (nine pharmacological and two non-pharmacological) for CiO in adults were identified. Based on the authors' information, this review analyses 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.[34] This finding may be relevant to explaining the ineffective results of some interventions. The action of free radical oxygen species may take time to occur as cisplatin accumulates in the cochlea, while in the meantime, the prophylactic effect of the otoprotective intervention may be lost thus not coinciding with the nadir damage on the ear function.[10,11]

We encounter four pharmacological and two non-pharmacological interventions with positive results that merit further investigation. Of the pharmacological interventions, sodium thiosulphate, corticoids, sertraline and statins showed a preserving hearing effect. Nonetheless, based on the existing evidence, only sodium thiosulphate emerges as a viable intervention for preventing CiO in adults, aligning with our initial hypothesis. Despite the studies demonstrating mild benefits, sodium thiosulphate stands out for the consistency in averting CiO among adults undergoing cisplatin therapy. These results are similar to what has been found in high-quality RCT in the paediatric population, where

sodium thiosulphate reduced the incidence of cisplatin-induced hearing loss among children with standard-risk hepatoblastoma, without jeopardising overall or event-free survival.[48] A recent systematic review and meta-analysis, based on four studies with mixed paediatric and adult populations, confirms the otoprotective effect of sodium thiosulphate.[49] The remaining interventions have several limitations to consider that cannot be overlooked. For instance, a considerable number and severity of side effects were reported in the intratympanic corticoids trial, a single trial was conducted with sertraline and statins, and the statins trial had a heterogeneous intervention, which limits the robustness of these results. 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 regimens 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.[50]

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 mild hearing loss that occurs above the frequency range of human speech (0.25–8 kHz) that may go undetected,[51] 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 ($p = .007$) and in older populations ($p = .007$).[2] Investigators have also found cisplatin-induced tinnitus is significantly correlated with reduced hearing per frequency (0.25–12 kHz, $p < .0001$) and vertigo (OR = 6.47; $p < .0001$),[4] 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, haematology or palliative care consultations. Currently, four clinical trials in adult patients with CiO risk are underway to evaluate sodium thiosulphate and mannitol, rosuvastatin and intratympanic *N*-acetylcysteine.[52-55] Only one of them considers the apparition of tinnitus in their outcomes. Therefore, future high-quality randomised clinical trials should consider the shortcomings and successes of existing evidence to improve their internal validity.

4.1 | Limitations

There are a number of limitations to our review. First, one article about the protective effect of ginkgo biloba extract on CiO was retrieved by the manual research on clinicaltrial.gov, but was not available in its full-text format. Second, our review is based on studies with a high risk of bias, small and heterogeneous samples, who were followed-up on different time ranges. The nature of these characteristics rendered the undertaking of a meta-analysis unfeasible. Nonetheless, it is plausible that an adept statistician with more experience could execute quantitative assessments, thus supplementing our findings with valuable insights. Third, adverse effects were reported verbatim in most articles that were reviewed. Unfortunately, few articles reported percentages of adverse effects in the experimental arm, constraining an accurate idea of the intervention's toxicity profile. Safety outcomes were not mentioned in 10 out of 24 studies at all. Fourth, 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. Since most of the interventions contain mild benefits and uncertain risks, our results should be taken as preliminary findings that need to be corroborated by further research.

5 | 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 summarises 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 randomised clinical trials are warranted to clarify the significance of these preliminary findings. Future research should include patients' reported outcomes and avoid overlooking otic symptoms like tinnitus and vertigo.

AUTHOR CONTRIBUTIONS

Juan Esteban Correa-Morales: Conceptualization; Methodology; Validation; Investigation; Data curation; Writing—review and editing; Resources; Supervision; Visualization. **Sara Giraldo-Moreno, Nidia Mantilla-Manosalva, Laura Cuellar-Valencia, Lennis Jazmin Bedoya-Muñoz, and María Fernanda Iriarte-Aristizábal**: Methodology; Validation; Investigation; Data curation; Writing—original draft. **Elias Quintero-Muñoz** and **Andrea Marcela Zuluaga-Liberato**: Writing—review and editing. **Oscar Felipe Borja-Montes:** Investigation; Data curation; review and editing.

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The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study did not require ethical approval. The authors followed the journal's citation and reference style in the text.

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