Research Paper

Efficacy of pharmacologic treatment in tinnitus patients without specific or treatable origin: A network meta-analysis of randomised controlled trials

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ABSTRACT

Background: Although tinnitus has a prevalence between 20 and 42.8%, the currently recommended management for tinnitus, such as tinnitus support and psychologic therapies, are relatively time-consuming and expensive. Several new pharmacologic treatments designed for tinnitus patients without specific origin had been developed but their efficacy remains unclear.

Methods: The current Network Meta-Analysis (NMA) of randomised controlled trials (RCTs) was conducted to evaluate the efficacy of different pharmacologic treatments for tinnitus management in tinnitus patients without specific or treatable origin (i.e. primary tinnitus). Databases were searched from inception to April 5th, 2021. All network meta-analytic procedures were conducted under the frequentist model. We calculated the effect size of outcomes with different rating scales with standardized mean difference. PROSPERO registration: CRD42020177742.

Findings: Overall, 36 RCTs were included with 2,761 participants. The main results revealed that pharmacologic interventions with brain-acting effect (for example, amitriptyline, acamprosate, and gabapentin) and those with anti-inflammation/anti-oxidant effect (for example, intra-tympanic dexamethasone injection plus oral melatonin) were associated with superior improvement in tinnitus severity and response rate compared to placebo/control. Oral amitriptyline were associated with the highest improvement in tinnitus severity and the fourth highest response rate. None of the investigated interventions was associated with different changes in quality of life compared to placebo/control. All the investigated treatments were associated with similar drop-out rate to placebo/control.

Interpretation: The current NMA suggests a potential role for treatments with brain-acting effect (for example, amitriptyline, acamprosate, and gabapentin) or anti-inflammation/anti-oxidant effect (for example, intra-tympanic dexamethasone injection plus oral melatonin) as the preferable effective treatments for tinnitus without specific or treatable origin.

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Research in context

Evidence before this study

Although tinnitus has a high prevalence and frequent comorbid complications, tinnitus management, including tinnitus support and psychological therapy, is relatively time-consuming and expensive. Several new pharmacologic treatments designed for tinnitus patients without specific origin (i.e. primary tinnitus) have been developed but their efficacy and superiority remain unclear.

Added value of this study

Based on 36 randomized controlled trials with 2761 participants, pharmacologic interventions with brain-acting effect (for example, amitriptyline, acamprosate, and gabapentin) and those with anti-inflammation/anti-oxidant effect (for example, intra-tympanic dexamethasone injection plus oral melatonin) were associated with superior improvement in tinnitus severity and response rate compared to placebo/control in tinnitus patients without specific or treatable origin. All the investigated treatments were associated with similar drop-out rate to placebo/control.

Implications of all the available evidence

The pharmacologic management of tinnitus with brain-acting effects (for example, amitriptyline, acamprosate, and gabapentin) and those with anti-inflammation/anti-oxidant effect (for example, intra-tympanic dexamethasone injection plus oral melatonin) appear to serve as the preferable effective treatments for tinnitus without specific or treatable origin (i.e. primary tinnitus) in situations where tinnitus support and/or psychologic therapy was unavailable or unpracticable.

1. Introduction

Among the adult population, tinnitus has a global prevalence of approximately 20% [1]. Moreover, the economic burden to manage tinnitus resulted in a total healthcare bill of GB£750 million per annum in the United Kingdom in 2016 [2] and estimated healthcare costs at US$660 per patient per year in the United States [3]. Tinnitus has been recognised as a difficult disease to define and manage owing to controversy regarding its definition and treatment [4].

Several potential aetiological sources underlie tinnitus symptoms development, including [1] the peripheral auditory system [5], [2] the tinnitus auditolimbic dopaminergic pathway [6] or [3] overt oxidative stress or imbalance of antioxidant enzyme [5,7]. Although somatic treatments can be effective in cases of tinnitus with a specific origin (such as palatal myoclonus, deafferentation of the auditory system, loss of cochlear hair cells, and ototoxic drugs), the efficacy of traditional pharmacologic treatment to reduce tinnitus severity has been controversial in tinnitus with unknown etiology [1,8].

The currently recommended management to tinnitus, such as tinnitus support and psychologic therapies, are relatively time-consuming and expensive [8,9]. Furthermore, the management of tinnitus support and psychologic therapy involved prolonged person-to-person contact, which would increase the risk of infection during the CoVID19 pandemic era. Several pharmacologic treatments or nutrient supplementation strategies have been developed in recent decades. For example, antioxidant supplementation, such as melatonin, ginkgo biloba, and vitamin C, have been widely investigated for tinnitus management [10]. Local treatment with steroid injection has also been considered as an alternative to traditional oral pharmacologic treatment. Furthermore, in tinnitus patients without specific or treatable origin, there were abnormal hyperactivity in brain multiple regions [11]. Therefore, new pharmacologic strategy for managing brain abnormal hyperactivities had been proposed [12]. However, there is a lack of clarity regarding the evidence about the efficacy for most of these alternative treatments.

Previous pairwise meta-analyses and systematic reviews have investigated the effects of Ginkgo biloba [13], zinc supplementation

[14] and vitamin supplementation [15] but failed to demonstrate a significant benefit in tinnitus treatment. Some of those interventions were designed for management to specific situation (i.e. zinc supplementation to the rationale of zinc deficiency) [14] but the others did not [13,15]. Only melatonin [5] and intra-tympanic corticosteroid injections [16] have shown promising results in some investigations. Similarly, the intra-tympanic corticosteroid injection had the preference to focus on situation of local inflammation [16]. Because there were a lack of enough comparative evidence, the current guidelines declined the recommendation of pharmacologic interventions for tinnitus management [8,9]. However, it had become more and more difficult conducting a large-scale randomized controlled trial to multiply compare different pharmacologic interventions at a time.

Network meta-analysis (NMA) are conducted based on statistical method to calculate the direct and indirect comparison between multiple treatments. The evidence of direct comparison enables comparison between original randomized controlled trials (RCTs). The evidence of indirect comparison mainly came from the hypothesis of transitivity, which was one of the key component of NMA. The NMA of existing RCTs enables estimation of the comparative efficacy and understanding of the relative merits of multiple interventions and maximises statistical power, which cannot be done in traditional pairwise meta-analysis. Furthermore, based on the multiple comparison, the network meta-analysis could provide new statistical evidence to guide the future studies. Considering these issues, we conducted an NMA of the published RCTs to estimate the relative efficacy of different pharmacologic treatments in patients with tinnitus. The PICO of the current NMA was: (1) Patient or Problem: tinnitus patients without specific or treatable origin; (2) Intervention: pharmacologic intervention or nutrition supplement to manage tinnitus severity; (3) Comparator: placebo-controlled or active-controlled; and (4) Outcome: changes of tinnitus severity.

2. Methods

2.1. General guidelines of the study

The current network meta-analysis (NMA) followed an a priori defined unpublished protocol (available upon reasonable request to the corresponding author) and was performed according to the latest preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guideline [17] and AMSTAR2 (Assessing the methodological quality of systematic reviews) Guidelines [18]. The current study had been approval by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No. B-109–29). The current study had been registered in PROSPERO (CRD42020177742) with the first submission date of April 1st, 2020 and final approval of registration date by July 5th, 2020.

2.2. Target of investigated medication, search strategy and selection criteria

In order to improve the reliability of the current NMA, we choose the pharmacologic treatments which were intended to include from the list of recommendations in the current review articles or clinical guidelines [1,8,9,13,19–23]. A systematic review was carried out using ClinicalKey, Cochrane CENTRAL, Embase, ProQuest, PubMed, ScienceDirect, Web of Science, and ClinicalTrials.gov databases from inception to April 5th, 2021 (eTable 1). No language restriction was used. In addition, manual searches were performed for potentially eligible articles selected from the reference lists of review articles, clinical guidelines, and pairwise meta-analyses [1,8,9,13,19–23]. The definition of "tinnitus without specific or treatable origin" followed the definition of primary tinnitus addressed in the important guideline by Tunkel, D.E. (2014) [22].

2.3. Inclusion and exclusion criteria

We included published randomized controlled trials (RCTs) with placebo-controlled, waiting-list controlled or active-controlled design, conducted in tinnitus patients. In the initial registration in PROSPERO, the target participants were those with chronic tinnitus and the target of comparison was pharmacologic treatment only. However, in order to reduce the potential heterogeneity of the recruited participants and to expand the potential treatment strategy, we changed to only included published RCTs to compare different pharmacologic treatments or nutrient supplements in tinnitus patients without specific or treatable origin. That is, in the current NMA, non-invasive brain/nerve stimulation methods were not investigated. Further, tinnitus patients with specific or treatable origin would not be included in the current study. The targets of comparison arms were set to be pharmacologic treatments or nutrient supplements in patients with tinnitus. That is, in the current NMA, non-invasive brain/nerve stimulation methods were not investigated.

The exclusion criteria were [1] not a clinical trial, [2] not an RCT, [3] not reporting the target outcomes (defined below), [4] not related to pharmacologic treatment or nutrient supplements mentioned earlier and [5] studies investigating central or peripheral non-invasive brain/nerve stimulation therapy. In cases of duplicated usage of data (i.e., different articles based on the same sample sources), we included only the article with the largest sample source. In addition, the network meta-analysis was based on two KEY hypotheses (i.e. transitivity and similarity), which had to be fulfilled by the good randomization. It will violate these important hypotheses of network meta-analysis if we included the study with poor randomization [i.e. had significantly different baseline tinnitus severity between the groups after randomization]. In order to improve the quality of similarity/transitivity hypothesis, we excluded those poor randomization RCTs with significantly different severity in baseline.

2.4. Data extraction

Three authors (JJ Chen, YW Chen and BY Zeng) independently screened the studies and extracted the relevant information from the manuscripts. In cases of discrepancy, the corresponding author (PT Tseng) mediated. If data of outcomes of interest were missing from published reports, the corresponding authors or co-authors were approached to obtain the additional data. If the data of outcomes of interest still were unavailable, we will only count the other available outcomes of interest from this RCT in the network meta-analysis of other outcomes. We followed an a priori defined unpublished protocol (available upon reasonable request to the corresponding author) and the flowchart used in previous NMAs [11,24–30].

2.5. Outcomes

2.5.1. Primary outcome

The primary outcome was change in the severity of tinnitus after treatment in patients with tinnitus.

2.5.2. Secondary outcomes

Secondary outcomes were change in quality of life and response rate related to the treatment in patients with tinnitus. The response rate was defined on the basis of the criteria applied in the included studies. Finally, we assessed the dropout rate, which was defined as the percentage of patients dropping out for any reason before study completion.

2.6. Cochrane risk-of-bias tool and Grade ratings

Three independent authors (JJ Chen, YW Chen and BY Zeng) evaluated the risk of bias (interrater reliability, 0.85) for each domain

Table 1
League table of the improvement of severity of tinnitus

_The table is a large network meta-analysis league table (rotated to landscape on the page) of pairwise comparisons (mean difference with 95% CI) between treatments. The diagonal carries the treatment abbreviations: Ami, Aca, GaLid, DeMel, Nor, Oxc, Dex, Par, Zinc, Car, MeSul, Met, Gab, Bet, VePar, Ozone.

Ami
-0.21 (-1.20,0.78); -0.26 (-1.36,0.84); -0.40 (-1.72,0.91); -0.55 (-1.62,0.51); -0.57 (-1.77,0.63); -0.61 (-1.35,0.62); -0.70 (-1.66,0.44); -0.70 (-1.70,0.31); -0.74 (-1.24,0.26); -0.74 (-1.73,0.24); -0.52 (-1.26,0.19); -0.73 (-1.92,0.46); -0.58 (-1.50,0.45); -0.79 (-1.88,0.30); -0.81 (-1.43,0.27); -0.85 (-1.91,0.30); -0.64 (-1.47,0.27); -0.83 (-1.34,0.06); -0.96 (-2.00,0.33); -0.94 (-1.58,0.32); -1.00 (-2.09,0.17); -0.99 (-1.66,0.16); *-0.79 (-1.52,-0.05); -1.01 (-2.11,0.22); -0.81 (-2.44,0.44); *-0.80 (-1.31,-0.29); -0.85 (-2.06,0.47); -0.89 (-2.00,0.01); -0.94 (-2.13,0.10); *-0.93 (-1.78,-0.08); -1.05 (-1.76,0.06); -1.06 (-2.20,0.08); *-1.12 (-2.19,-0.05); -1.14 (-2.84,0.55); *-1.14 (-2.23,-0.05); -1.25 (-2.49,0.61); *-1.13 (-2.18,-0.09); *-1.26 (-2.71,0.20); -1.33 (-2.33,0.24); *-1.15 (-2.09,-0.20); -1.39 (-2.71,0.05); *-1.36 (-2.51,-0.20); -1.18 (-2.32,0.08); *-1.43 (-2.72,-0.15); *-1.23 (-2.32,-0.14); *-1.43 (-2.69,-0.18); *-1.23 (-2.29,-0.17)

Aca
-0.05 (-0.92,0.82); -0.20 (-1.32,0.93); -0.34 (-1.16,0.48); -0.36 (-1.77,0.63); -0.40 (-1.35,0.62); -0.49 (-1.21,0.40); -0.54 (-1.24,0.26); -0.52 (-1.26,0.19); -0.58 (-1.56,0.62); -0.60 (-1.47,0.27); -0.64 (-1.34,0.06); -0.63 (-1.58,0.32); -0.75 (-1.66,0.16); -0.74 (-1.68,0.21); -0.80 (-2.06,0.47); -0.73 (-1.62,0.15); -0.76 (-1.76,0.25); -0.80 (-1.83,0.23); -0.85 (-1.76,0.06); -0.89 (-2.49,0.61); -0.86 (-1.91,0.48); -0.88 (-1.82,0.10); -1.00 (-1.86,0.10); -1.07 (-2.13,0.14); -1.12 (-2.32,0.08); -1.13 (-2.50,0.24); -1.08 (-2.24,0.07); -1.18 (-2.37,0.02)

GaLid
-0.14 (-1.37,1.08); -0.29 (-1.25,0.66); -0.31 (-1.41,0.79); -0.35 (-1.29,0.59); -0.44 (-1.32,0.44); -0.49 (-1.34,0.37); -0.47 (-1.56,0.62); -0.53 (-1.51,0.45); -0.55 (-1.55,0.45); -0.59 (-1.29,0.11); -0.58 (-1.64,0.49); -0.70 (-1.73,0.33); -0.69 (-1.75,0.38); -0.75 (-1.83,0.74); -0.73 (-2.10,0.61); -0.76 (-1.62,0.15); -0.80; -0.86 (-2.51,1.03); *-1.10 (-2.15,-0.05); -1.18; *-1.18 (-2.34,-0.01)

DeMel
-0.15 (-1.34,1.04); -0.17 (-1.48,1.14); -0.21 (-1.39,0.98); -0.29 (-1.43,0.85); -0.34 (-1.46,0.78); -0.33 (-1.64,0.98); -0.38 (-1.39,0.62); -0.41 (-1.64,0.82); -0.44 (-1.56,0.67); -0.43 (-1.72,0.85); -0.56 (-1.81,0.70); -0.54 (-1.83,0.74); -0.60 (-2.14,0.94); -0.59 (-1.73,0.55); -0.61 (-1.85,0.62); -0.66 (-1.61,0.40); -0.74 (-1.92,0.60); *-0.74 (-1.47,0.00); -0.85; -0.86 (-2.20,0.49); -0.93 (-2.41,0.56); -0.99; -0.94; -0.96; *-1.03 (-2.03,-0.03); -1.03 (-2.40,0.34)

Nor
-0.02 (-1.08,1.04); -0.06 (-0.96,0.84); -0.14 (-0.98,0.69); -0.19 (-1.01,0.62); -0.18 (-1.23,0.88); -0.24 (-1.39,0.62); -0.26 (-1.17,0.70); -0.29 (-1.21,0.70); -0.28 (-1.31,0.75); -0.41 (-1.40,0.58); -0.39 (-1.42,0.63); -0.45 (-1.78,0.88); -0.44 (-1.28,0.40); -0.46 (-1.43,0.50); -0.51 (-1.50,0.49); -0.59 (-1.92,0.60); -0.57 (-2.19,1.01); -0.70 (-2.05,0.64); -0.71 (-1.81,0.39); -0.78 (-2.04,0.49); -0.84 (-2.18,0.51); -0.79 (-1.91,0.33); -0.81 (-1.82,0.21); -0.88 (-2.04,0.28); -0.88 (-2.01,0.25)

Oxc
-0.04 (-1.09,1.01); -0.13 (-1.13,0.88); -0.17 (-1.15,0.81); -0.16 (-0.99,0.67); -0.22 (-1.30,0.87); -0.24 (-1.34,0.87); -0.27 (-1.24,0.70); -0.26 (-1.43,0.90); -0.39 (-1.52,0.74); -0.37 (-1.54,0.79); -0.43 (-1.87,1.01); -0.42 (-1.42,0.58); -0.44 (-1.55,0.67); -0.49 (-1.28,0.41); -0.57 (-1.62,0.65); -0.55 (-1.61,0.52); -0.57 (-1.66,0.52); -0.68 (-2.05,0.64); -0.69 (-1.92,0.54); -0.76 (-2.13,0.62); -0.82 (-2.27,0.63); -0.77 (-2.02,0.48); -0.79 (-1.91,0.33); -0.86 (-2.15,0.42); -0.86 (-2.12,0.39)

Dex
-0.09 (-0.91,0.74); -0.13 (-0.93,0.66); -0.12 (-1.16,0.92); -0.18 (-1.10,0.75); -0.20 (-1.14,0.75); -0.24 (-1.02,0.55); -0.22 (-1.24,0.79); -0.35 (-1.33,0.63); -0.33 (-1.35,0.68); -0.39 (-1.71,0.93); -0.38 (-1.21,0.44); -0.40 (-1.55,0.67); -0.45 (-1.43,0.53); -0.53 (-2.13,1.06); -0.51 (-1.41,0.39); -0.53 (-1.46,0.40); -0.64 (-1.98,0.69); -0.65 (-1.74,0.44); -0.72 (-1.97,0.54); -0.78 (-2.11,0.55); -0.73 (-1.84,0.38); -0.75 (-1.75,0.25); -0.82 (-1.97,0.33); -0.82 (-1.94,0.30)

Par
-0.05 (-0.74,0.64); -0.03 (-1.03,0.96); -0.09 (-0.96,0.78); -0.11 (-1.00,0.78); -0.15 (-1.14,0.75); -0.14 (-0.86,0.56); -0.22 (-1.11,0.83); -0.26 (-1.19,0.66); -0.25 (-1.21,0.72); -0.31 (-1.59,0.97); -0.30 (-1.06,0.46); -0.32 (-1.22,0.58); -0.36 (-1.22,0.58); -0.45 (-2.01,1.11); -0.42 (-1.26,0.42); -0.44 (-1.31,0.43); -0.56 (-1.86,0.74); -0.56 (-1.60,0.48); -0.63 (-1.85,0.58); -0.69 (-1.99,0.60); -0.65 (-1.71,0.42); -0.66 (-1.61,0.29); -0.74 (-1.84,0.37); -0.74 (-1.81,0.34)

Zinc
0.01 (-0.96,0.99); -0.04 (-0.89,0.80); -0.06 (-0.93,0.80); -0.10 (-0.78,0.58); -0.09 (-1.03,0.86); -0.22 (-1.12,0.69); -0.20 (-1.14,0.74); -0.26 (-1.52,1.01); -0.25 (-0.98,0.48); -0.27 (-1.14,0.61); -0.31 (-1.36,0.55); -0.40 (-1.95,1.15); -0.37 (-1.19,0.45); -0.40 (-1.24,0.45); -0.51 (-1.79,0.77); -0.51 (-1.53,0.51); -0.58 (-1.78,0.61); -0.65 (-1.93,0.63); -0.60 (-1.64,0.44); -0.61 (-1.54,0.31); -0.69 (-1.77,0.40); -0.69 (-1.74,0.37)

Car
-0.06 (-1.14,1.02); -0.08 (-1.17,1.02); -0.10 (-1.08,0.85); -0.09 (-1.26,1.06); -0.23 (-1.36,0.90); -0.21 (-1.37,0.94); -0.27 (-1.70,1.16); -0.26 (-1.26,0.73); -0.28 (-1.39,0.82); -0.31 (-1.11,0.56); -0.33 (-1.46,0.80); -0.41 (-2.10,1.27); -0.39 (-1.45,0.67); -0.41 (-1.49,0.67); -0.52 (-1.97,0.92); -0.53 (-1.75,0.70); -0.60 (-1.97,0.78); -0.66 (-2.11,0.79); -0.61 (-1.85,0.63); -0.63 (-1.77,0.52); -0.70 (-1.98,0.57); -0.70 (-1.95,0.55)

MeSul
-0.02 (-1.01,0.96); -0.05 (-1.10,1.01); -0.17 (-1.19,0.85); -0.16 (-1.21,0.90); -0.22 (-1.56,1.13); -0.21 (-1.08,0.66); -0.23 (-1.22,0.77); -0.22 (-1.22,0.81); -0.27 (-1.29,0.75); -0.36 (-1.97,1.26); -0.33 (-1.27,0.61); -0.35 (-1.13,0.54); -0.47 (-1.83,0.90); -0.47 (-1.60,0.65); -0.54 (-1.83,0.75); -0.60 (-1.97,0.76); -0.55 (-1.70,0.59); -0.57 (-1.61,0.47); -0.65 (-1.61,0.32); -0.65 (-1.80,0.51)

Met
-0.04 (-0.89,0.82); -0.03 (-1.10,1.05); -0.15 (-1.19,0.88); -0.14 (-1.21,0.93); -0.19 (-1.56,1.17); -0.18 (-1.07,0.71); -0.21 (-1.22,0.81); -0.20 (-0.91,0.51); -0.25 (-1.29,0.79); -0.34 (-1.96,1.29); -0.31 (-1.27,0.65); -0.33 (-1.32,0.65); -0.45 (-1.82,0.93); -0.45 (-1.59,0.69); -0.52 (-1.82,0.78); -0.58 (-1.96,0.79); -0.53 (-1.69,0.62); -0.55 (-1.61,0.51); -0.62 (-1.82,0.57); -0.63 (-1.79,0.54)

Gab
0.01 (-0.92,0.95); -0.11 (-1.01,0.78); -0.10 (-1.03,0.83); -0.16 (-1.41,1.10); -0.15 (-0.86,0.57); -0.17 (-1.03,0.69); -0.16 (-0.64,0.31); -0.21 (-1.11,0.68); -0.30 (-1.84,1.24); -0.27 (-1.08,0.53); -0.29 (-1.13,0.54); -0.41 (-1.68,0.87); -0.41 (-1.42,0.60); -0.48 (-1.67,0.71); -0.54 (-1.82,0.73); -0.50 (-1.53,0.54); -0.51 (-1.43,0.40); -0.59 (-1.66,0.49); -0.59 (-1.63,0.46)

Bet
-0.13 (-1.23,0.98); -0.11 (-1.58,1.24); -0.17 (-1.12,0.81); -0.16 (-1.26,0.90); -0.18 (-0.98,0.63); -0.22 (-1.33,0.88); -0.31 (-1.98,1.36); -0.28 (-1.32,0.75); -0.31 (-1.36,0.75); -0.42 (-1.85,1.01); -0.42 (-1.62,0.78); -0.49 (-1.85,0.86); -0.56 (-1.98,0.87); -0.51 (-1.73,0.71); -0.52 (-1.65,0.60); -0.60 (-1.86,0.66); -0.60 (-1.83,0.63)

VePar
0.02 (-1.08,1.12); -0.04 (-1.43,1.34); -0.03 (-0.96,0.89); -0.05 (-1.10,0.99); -0.05 (-0.80,0.70); -0.10 (-0.85,0.66); -0.18 (-1.83,1.46); -0.16 (-1.15,0.84); -0.18 (-1.20,0.84); -0.29 (-1.74,1.12); -0.30 (-1.51,0.88); -0.37 (-1.73,0.97); -0.43 (-1.87,0.98); -0.38 (-1.57,0.80); -0.40 (-1.49,0.69); -0.47 (-1.70,0.75); -0.47 (-1.67,0.72)

Ozone
-0.11 (-0.65,0.43); -0.06 (-1.47,1.35); -0.05 (-1.01,0.92); -0.07 (-1.15,1.01); -0.07 (-0.87,0.73); -0.11 (-1.22,0.99); -0.20 (-1.87,1.47); -0.17 (-1.20,0.86); -0.20 (-1.25,0.86); -0.31 (-1.74,1.12); -0.31 (-1.51,0.88); -0.38 (-1.73,0.97); -0.45 (-1.87,0.98); -0.40 (-1.61,0.82); -0.41 (-1.53,0.71); -0.49 (-1.74,0.76); -0.49 (-1.72,0.74)

Additional off-diagonal estimate: -0.55 (-1.12,0.02); -0.16 (-0.82,0.50)

Pooled / bottom-row estimates:
*-1.01 (-1.70,-0.32); *-0.80 (-1.33,-0.26); *-0.79 (-1.37,-0.21); *-0.74 (-1.47,0.00); *-0.46 (-0.87,-0.04); -0.44 (-1.13,0.25); *-0.74 (-1.29,-0.19)

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Table 1 (*Continued*)

Clo	Ner	Pir	Pla	Ves	ClD	Tra	Mel	KRG	PaVitE	Pen	DeGin	ALVitC	Var	Ser	Gin
			*-1.01 (-1.70,-0.32)												
			*-0.40 (-0.79,-0.01)												
			-0.38 (-1.10,0.35)												
			-0.28 (-0.81,0.25)												
			-0.28 (-0.96,0.40)												
			-0.22 (-0.70,0.25)				-0.35 (-0.13,0.83)								
			-0.20 (-0.71,0.31)												
			-0.15 (-0.46,0.16)												
			-0.18 (-0.81,0.46)												
			-0.05 (-0.62,0.52)	-0.10 (-0.67,0.47)											
			-0.07 (-0.70,0.57)												
Clo					-0.14 (-0.88,0.60)										-0.43 (-0.92,0.06)
0.01 (-1.27,1.29)	**Ner**		-0.02 (-0.23,0.20)												
-0.01 (-1.38,1.36)	-0.02 (-0.92,0.88)	**Pir**	0.00 (-0.52,0.53)												
-0.01 (-1.17,1.16)	-0.02 (-0.55,0.52)	0.00 (-0.72,0.72)	**Pla**	-0.05 (-0.63,0.53)		-0.11 (-0.53,0.32)	-0.13 (-0.61,0.35)	-0.25 (-0.99,0.50)					-0.33 (-1.10,0.44)	-0.35 (-0.96,0.26)	-0.42 (-1.21,0.37)
-0.06 (-1.44,1.33)	-0.07 (-1.00,0.86)	-0.05 (-1.09,1.00)	-0.05 (-0.81,0.71)	**Ves**											
-0.14 (-1.03,0.75)	-0.15 (-1.71,1.41)	-0.13 (-1.76,1.50)	-0.13 (-1.60,1.33)	-0.08 (-1.73,1.56)	**ClD**										
-0.11 (-1.45,1.22)	-0.12 (-0.97,0.72)	-0.10 (-1.07,0.87)	-0.11 (-0.76,0.54)	-0.06 (-1.06,0.94)	0.03 (-1.58,1.63)	**Tra**									
-0.14 (-1.49,1.21)	-0.15 (-1.02,0.72)	-0.13 (-1.12,0.87)	-0.13 (-0.81,0.55)	-0.08 (-1.10,0.94)	0.00 (-1.61,1.62)	-0.02 (-0.97,0.92)	**Mel**							-0.29 (-0.76,0.18)	-0.18 (-0.72,0.36)
-0.25 (-1.26,0.76)	-0.26 (-1.56,1.04)	-0.24 (-1.62,1.14)	-0.24 (-1.43,0.94)	-0.20 (-1.60,1.21)	-0.11 (-1.46,1.24)	-0.14 (-1.49,1.21)	-0.11 (-1.48,1.25)	**KRG**					-0.08 (-0.83,0.66)		-0.18 (-0.94,0.58)
-0.25 (-1.40,0.89)	-0.27 (-1.31,0.78)	-0.24 (-1.39,0.90)	-0.25 (-1.14,0.64)	-0.20 (-1.37,0.97)	-0.11 (-1.56,1.33)	-0.14 (-1.24,0.96)	-0.12 (-1.24,1.01)	-0.00 (-1.17,1.16)	**PaVitE**						-0.11 (-0.39,0.17)
-0.32 (-1.22,0.57)	-0.34 (-1.55,0.88)	-0.31 (-1.62,0.99)	-0.32 (-1.41,0.77)	-0.27 (-1.60,1.06)	-0.18 (-1.45,1.08)	-0.21 (-1.48,1.06)	-0.19 (-1.47,1.10)	-0.07 (-1.00,0.85)	-0.07 (-1.14,1.00)	**Pen**					
-0.39 (-1.39,0.62)	-0.40 (-1.69,0.90)	-0.38 (-1.76,1.00)	-0.38 (-1.56,0.80)	-0.33 (-1.73,1.07)	-0.25 (-1.59,1.10)	-0.27 (-1.62,1.07)	-0.25 (-1.61,1.11)	-0.14 (-1.17,0.89)	-0.13 (-1.29,1.03)	-0.06 (-0.98,0.86)	**DeGin**				-0.04 (-0.58,0.49)
-0.34 (-1.50,0.82)	-0.35 (-1.41,0.71)	-0.33 (-1.49,0.84)	-0.33 (-1.25,0.58)	-0.28 (-1.47,0.91)	-0.20 (-1.66,1.26)	-0.22 (-1.35,0.90)	-0.20 (-1.34,0.94)	-0.09 (-1.27,1.09)	-0.08 (-0.97,0.81)	-0.01 (-1.10,1.07)	0.05 (-1.13,1.22)	**ALVitC**			-0.09 (-0.88,0.69)
-0.36 (-1.76,1.05)	-0.37 (-1.32,0.58)	-0.35 (-1.41,0.72)	-0.35 (-1.13,0.43)	-0.30 (-1.39,0.79)	-0.22 (-1.88,1.45)	-0.24 (-1.26,0.78)	-0.22 (-1.26,0.82)	-0.10 (-1.52,1.31)	-0.10 (-1.29,1.09)	-0.03 (-1.37,1.31)	0.03 (-1.38,1.45)	-0.02 (-1.22,1.19)	**Var**		
-0.43 (-1.94,1.08)	-0.44 (-1.55,0.66)	-0.42 (-1.62,0.78)	-0.42 (-1.39,0.54)	-0.37 (-1.60,0.85)	-0.29 (-2.04,1.46)	-0.32 (-1.48,0.85)	-0.29 (-0.97,0.39)	-0.18 (-1.71,1.35)	-0.18 (-1.49,1.14)	-0.11 (-1.56,1.35)	-0.04 (-1.57,1.48)	-0.09 (-1.42,1.24)	-0.07 (-1.32,1.17)	**Ser**	
-0.43 (-1.13,0.27)	-0.44 (-1.52,0.63)	-0.42 (-1.60,0.76)	-0.42 (-1.35,0.51)	-0.37 (-1.57,0.83)	-0.29 (-1.42,0.84)	-0.32 (-1.45,0.82)	-0.29 (-1.45,0.86)	-0.18 (-0.91,0.55)	-0.18 (-1.08,0.73)	-0.11 (-0.67,0.46)	-0.04 (-0.77,0.68)	-0.09 (-1.02,0.83)	-0.07 (-1.29,1.14)	-0.00 (-1.34,1.34)	**Gin**

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of improvement in severity of tinnitus in patients with tinnitus. Interventions are reported in order of mean ranking of severity of tinnitus improvement, and outcomes are expressed as standardised mean difference (SMD) (95% confidence intervals). For the pairwise meta-analyses, SMD of less than zero indicates that the treatment specified in the row realized more improvement than that specified in the column. For the network meta-analysis (NMA), SMD of less than zero indicates that the treatment specified in the column realized more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

Abbreviation: 95%CIs: 95% confidence intervals; Aca: acamprosate; Alp: alprazolam; ALVitC: alpha-lipoic acid plus vitamin C; Ami: amitriptyline; Bet: betahistine; Car: carbamazepine; Chl: chlorpheniramine; ClD: clonazepam plus deanxit; CLES: common language effect size; Clo: clonazepam; DeGin: intra-tympanic dexamethasone injection plus ginkgo biloba; DeLid: intra-tympanic dexamethasone injection plus lidocaine; DeMel: intra-tympanic dexamethasone injection plus melatonin; Dex: intra-tympanic dexamethasone injection; Gab: gabapentin; GABA: gamma-Aminobutyric acid; GaLid: gabapentin plus intradermal lidocaine injection; Gin: ginkgo biloba; GRADE: Grading of Recommendations Assessment, Development and Evaluation; KRG: Korean red ginseng; Mel: melatonin alone; MeSul: melatonin and sulodexide; Met: intra-tympanic methylprednisolone injection; Mis: misoprostol; Ner: neramexane; NMA: network meta-analysis; Nor: nortriptyline; Oxc: oxcarbazepine; Ozone: ozone exposure; Par: paroxetine; PaVitE: papaverine hydrochloride plus vitamin E; Pen: pentoxifylline; Pir: piribedil; Pla: placebo; Pra: pramipexole; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomised controlled trials; RR: rate ratio; Ser: sertraline; SMD: standardized mean difference; SUCRA: surface under the cumulative ranking curve; THI: tinnitus handicap inventory; Tra: trazodone; Tri: postaurical subcutaneous triamcinolone injection; Var: vardenafil; VAS: visual analogue scale; VePar: vestipitant and paroxetine; Ves: vestipitant; Zinc: zinc supplementation

described in the Cochrane risk-of-bias tool [31]. We evaluated the certainty of the evidence, including transitivity, precision, and coherence, according to the GRADE framework and the article by Cipriani, et al. [32,33]

2.7. Statistical analysis

We estimated the standardised mean difference (SMD) with a 95% confidence interval (95%CIs) for continuous variables (i.e., the primary outcome of tinnitus severity and the secondary outcome of quality of life). For the categorical variables, we used the rate ratio (RR) and 95%CIs (i.e., the secondary outcome of response rates and drop-out rate) and applied a 0.5-zero-cell correction during the meta-analysis procedure. However, if zeroes were present in both the intervention and control arms of one study, we did not apply such a correction procedure because of the risk of increasing the bias; instead, such studies were excluded from our analysis [34,35]. We used the frequentist model of NMA to compare the effect sizes of studies with similar interventions. All comparisons were performed using a two-tailed *t*-test, and $p < 0.05$ was considered statistically significant. Heterogeneity among the included studies was evaluated using the tau value, which is the estimated standard deviation of the effect across the included studies.

We used mixed comparison with generalised linear mixed models to make direct and indirect comparisons [36]. To compare multiple treatment arms, we combined direct and indirect evidence from the included studies [37]. STATA version 16.0 (StataCorp LLC Statistics/ Data Analysis StataCorp, TX, USA) was used in our NMA with the *mvmeta* command [38]. The restricted maximum likelihood method was used to evaluate the between-study variance [39]. To provide additional information for clinical applications, we calculated the relative ranking probabilities of the treatment effects of all treatments for the target outcomes. In brief, the surface under the cumulative ranking curve (SUCRA) indicated the percentage of the mean rank of each treatment relative to an imaginary intervention that was the best without uncertainty [40]. When the area under the curve was smaller, the treatment deserved a higher rank of benefit in the treatment of tinnitus.

We evaluated the potential inconsistencies between the direct and indirect evidence within the network by using the loop-specific approach and identified local inconsistencies by using the node-splitting method. The design-by-treatment model was used to evaluate global inconsistencies across the entire NMA [41]. We used the comparison adjusted funnel plot and Egger regression to evaluate the potentially small study effects in the order of efficacy of individual treatments [42]. Finally, following the rationale of previous NMA study [43], we assessed the efficacy of the different kinds of placebo therapy or control (treatment as usual or waiting list) as additional proof of transitivity by computing the severity of tinnitus (Hedges' *g*) and response rate (event rate) for an oral form of placebo therapy, injection form of placebo therapy, and controls (treatment as usual or waiting list) on the platform of Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ). If significant evidence of different effects of placebo therapy or control (treatment as usual or waiting list) by specific placebo therapy/control was found [44], we arranged sensitivity tests by removing the trial(s) of that specific placebo therapy/control and repeated the main analysis. In addition, in order to investigate the potential impact of different disease duration of the tinnitus symptom on the current NMA, we arrange further evaluation of the potential different placebo effect in the subgroups of different disease duration of the tinnitus symptom as additional proof of transitivity. In order to reduce the potential heterogeneity of the study design, we arranged subgroup analysis focusing on RCTs with placebo-controlled. Finally, in order to improve the methodology reliability of the included RCTs, we arranged subgroup analysis focusing on RCTs with multiple domain rating scales, such as tinnitus

handicap inventory, tinnitus handicap questionnaire, and tinnitus severity index.

2.8. Role of funding source

None of the funding source had any role in study design and/or data analysis or interpretation.

3. Results

A total of 87 articles were considered for full-text review (Fig. 1), of which 51 were excluded for various reasons (eTable 2). Finally, 36 articles were included in the current study (eTable 3). Fig. 2 depicts the entire geometric distribution of the treatment arms. To be specific, in the Fig. 2, the lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network.

3.1. Characteristics of the included studies

A total of 2761 participants were included, with mean age = 52.3 years (range: 39.0 to 72.6 years) and mean female proportion = 45.5% (range: 10.7 to 65.9%). The mean treatment duration was 11.9 weeks (range: 2 to 24 weeks). The baseline characteristics of the included participants are summarised in eTable 3. The definition of response varied among the recruited studies: subjective relief, Tinnitus Handicap Inventory improvement at least 1/3 from baseline, Visual Analogue Scale reduction >50%, 15 dB or greater decrease in loudness from baseline, increase in global improvement of at least 4, THI less than 36, THI reduction of more than 10 or improvement of 20 points or more in tinnitus handicap questionnaire scores.

3.2. Risk of bias, publication bias, inconsistency assessment, and grade ratings

We found that 66.7% (168/252 items), 25.8% (65/252 items) and 7.5% (19/252 items) of the included studies had a low, unclear, and high risk of bias, respectively. Unclear reporting of 'Allocation concealment' and 'Blinding of outcome assessment' were the most often encountered reasons for unclear risk of bias (eFigure 4A-4B).

Funnel plots of the publication bias (eFigure 5A–5H) revealed general symmetry, and the results of Egger's test indicated no significant publication bias among the articles included in the NMA. In general, the NMA did not demonstrate inconsistencies in terms of either loop-specific approach, node-splitting method, or design-by-treatment method (eTable 6−7). The results of GRADE evaluation have been listed in the appendix. In brief, the overall quality of evidence of the overall NMA, direct evidence, and indirect evidence were low to medium (eTable 8).

3.3. Primary outcome: Change in tinnitus severity

Changes in tinnitus severity for all treatments can be found in Table 1/Fig. 3. The NMA revealed that the oral amitriptyline, oral acamprosate, and oral gabapentin plus intradermal lidocaine injection were associated with significant improvement in the severity of tinnitus in comparison to the placebo/control (Table 1 and Fig. 3). According to the SUCRA, oral amitriptyline was associated with the largest improvement, followed by oral acamprosate and oral gabapentin plus intradermal lidocaine injection (eTable 4A). Finally, the heterogeneity among the included studies did not reveal any significant heterogeneity detected using the tau value (eTable 9).

There was no significant different placebo effect between the injection form placebo, oral form placebo, and controls without
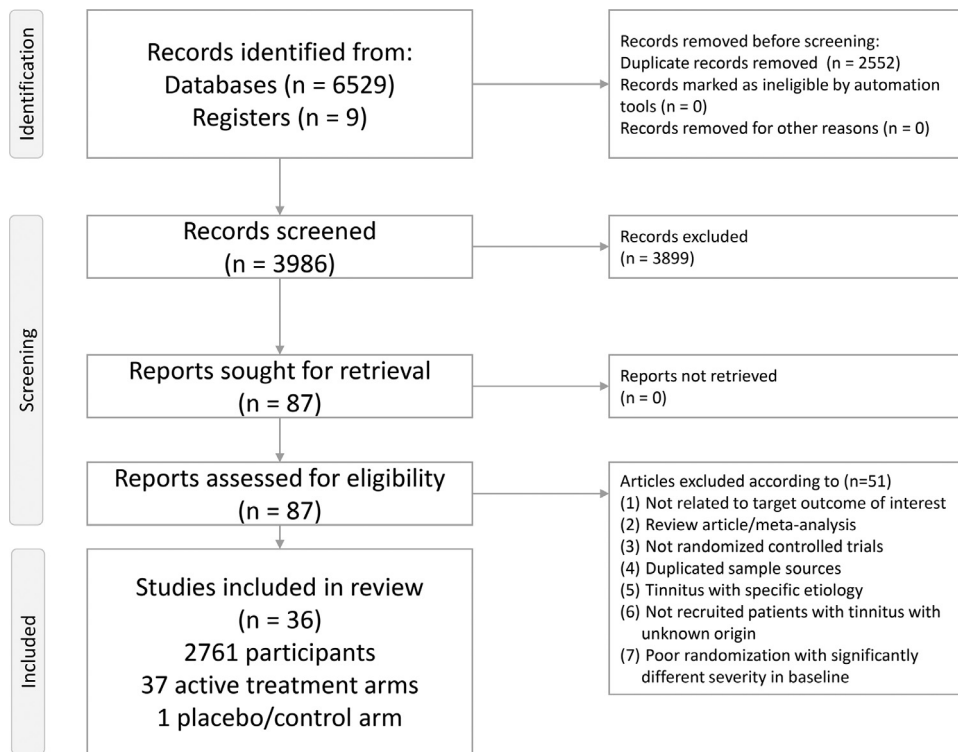
Fig. 1. Flowchart of the current network meta-analysis. Fig. 1 depicts the entire flowchart of the current network meta-analysis.

placebo (i.e. waiting-list) ($p = 0.97$, eFig. 3A). However, if we examined the individual placebo effect in specific placebo group, we detected a significant placebo effect in the oral form of placebo therapy ($p < 0.001$). Furthermore, the main result of primary outcome would not change after removing non-placebo controlled trials (eFig. 1D and eFig. 2D).

About the subgroup of different disease duration of tinnitus symptom, there was no significant different placebo effect between the subgroups of disease duration 1−2 months, 2−3 months, 3−6 months, 6−12 months, and > 12 months ($p = 0.80$, eFig. 3B).

However, if we examined the individual placebo effect in specific subgroup, we detected a significant placebo effect in the subgroup of tinnitus symptoms disease duration between 6 and 12 months ($p = 0.02$).

Finally, in the subgroup analysis focusing on RCTs with multiple domain rating scales, the main results of superiority rankings revealed similar findings. To be specific, the intradermal lidocaine injection plus oral gabapentin (GaLid) were associated with significant improvement in the severity of tinnitus in comparison to the placebo/control (SMD=−0.75, 95%Cis: −1.39 to −0.11) (eTable 5D,
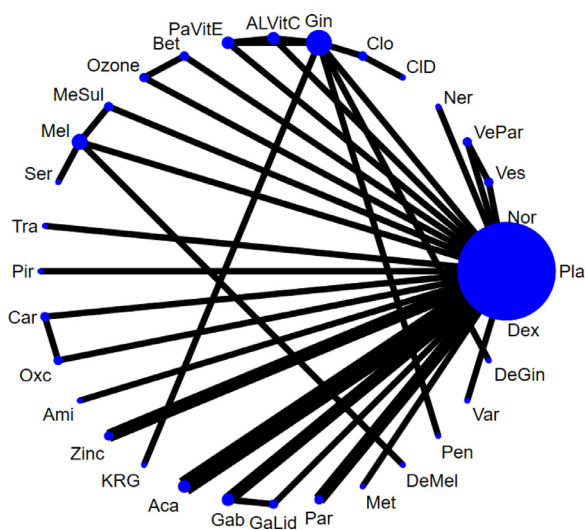
Fig. 2. Network structure of changes in severity of tinnitus. Fig. 2 depicts the overall network structure of the current network meta-analysis of changes in severity of tinnitus. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network.
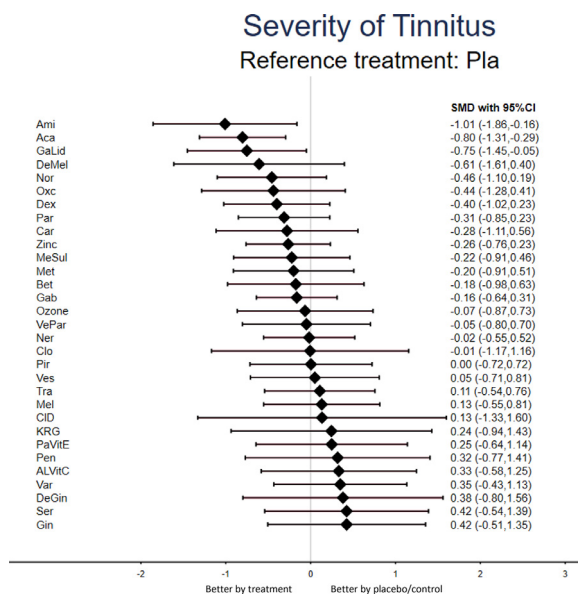
Fig. 3. Forest plot of the changes in severity of tinnitus. Fig. 3 indicates that, when the effect size is less than zero, the specified treatment was associated with higher improvement in severity of tinnitus than placebo/controls did.

eFig. 1F, and eFig. 2F). According to the SUCRA, the GaLid was associated with the largest improvement (eTable 4E).

3.4. Secondary outcome: Response rate and change in quality of life

The NMA revealed that intra-tympanic dexamethasone injection plus oral melatonin, oral melatonin plus sulodexide, oral melatonin alone, oral amitriptyline, oral acamprosate, zinc supplementation, and oral gabapentin plus intradermal lidocaine injection were associated with significantly higher response rates than the placebo/control was (eTable 5A, eFig. 1A, and eFig. 2A). According to the SUCRA, intra-tympanic dexamethasone injection plus oral melatonin was associated with the highest response rate, followed by oral melatonin plus sulodexide and oral melatonin alone (eTable 4B).

Regarding assumptions of transitivity, there was no significant difference between the investigated placebo therapy/waiting-list groups ($p = 0.79$, eFig. 3C). Furthermore, the main result of secondary outcome would not change after removing non-placebo controlled trials (eFig. 1E and eFig. 2E). To provide a more clinical-relevant information to clinicians, we transformed the response rate into Common Language Effect Size (CLES). To be specific, the value of CLES represent the probability of one random observation from the treated population being larger than another random observation from the control population [45]. The application of CLES would help the clinicians to communicate with ordinary people more easily. The calculated CLES of response rates of control without placebo, injection form placebo, and oral form placebo were 16.9%, 26.4%, and 24.5% respectively. That is, the prescription of injection form placebo and oral form placebo will have the probability of 26.4% and 24.5% to get response for tinnitus symptoms.

On the other hand, none of the investigated pharmacologic treatments were associated with a significant difference in the outcome of quality of life in patients with tinnitus in comparison to the placebo/control groups (eTable 4C, eTable 5B, eFig. 1B, and eFig. 2B).

3.5. Dropout rate

In the NMA, none of the investigated pharmacologic interventions were associated with significantly different dropout rates compared to placebo/control. (eTable 4D, eTable 5C, eFig. 1C, and eFig. 2C).

4. Discussion

To our knowledge, this is the first NMA addressing the efficacy of different pharmacologic management in tinnitus without specific/treatable origin (i.e. primary tinnitus). The main findings of the current NMA were that regimens of pharmacologic interventions with brain-acting effect, such as amitriptyline, acamprosate, gabapentin, and melatonin, were associated with significantly better improvement in tinnitus severity or response rate than the placebo/waiting-list groups. Several mechanisms support the effects found in this NMA. Another important finding of the current NMA was the significantly higher response rate of intra-tympanic dexamethasone injection plus oral melatonin than the placebo/waiting-list group. Most treatments showed similar drop-out rate compared to placebo/control.

The severe tinnitus perception exerted similar abnormal neurotransmitter secretion found in the pain perception in the somatosensory system, which was associated with decreased GABAergic inhibition [46]. Therefore, the prescription of gabapentin, which bound at calcium channel proteins and exerted widely suppressing effect, could imitate the GABAergic effect [47]. Similarly, the amitriptyline, one of the tri-cyclic antidepressant family, had been found to exert its role on nociceptive perception in the central somatosensory system through multiple neurotransmitter system, such as GABA and alpha1-adrenergic receptors [48]. In addition to the theory of abnormal nociceptive perception, the previous systematic review and

network meta-analysis had demonstrated that tinnitus patients without specific or treatable origin had been found to have significant hyperactivity in brain multiple regions [11]. Therefore, the strategy to reduce the abnormal hyperactivity would exert potential beneficial effects to reduce tinnitus severity. For example, the acamprosate is thought to stabilize chemical signaling in the brain through blocking glutaminergic N-methyl-D-aspartate receptors and GABA receptors [49], which efficacy in improving tinnitus would reflect the potential new direction for guiding future research of tinnitus management.

Another important finding of the current NMA was the significantly higher response rate of intra-tympanic dexamethasone injection plus oral melatonin than the placebo/waiting-list group. Melatonin has both dopaminergic antagonist effects [50] and antioxidant effects [51]. The description of the tinnitus auditolimbic dopaminergic pathway, located within the prefrontal, primary temporal, temporoparietal associative areas and the limbic system [6], share cerebral structures with tinnitus perception; thus it was considered a novel approach to tinnitus management [52]. The overt oxidative stress [5] and imbalance antioxidant enzyme [7] is considered one possible etiology of tinnitus. The supplementation of antioxidants such as melatonin has been shown to be effective in tinnitus management [53]. Although the findings of potential benefits of melatonin in tinnitus management could support the hypothesis of a tinnitus auditolimbic dopaminergic pathway and overt-oxidative stress in tinnitus, future clinical trials should focus on the etiology of tinnitus.

Based upon the hypothesis of triggers of cochlear damage to the early development of tinnitus [54], an intra-tympanic steroid injection (i.e., dexamethasone) theoretically is a promising treatment modality for early-stage tinnitus with origin of cochlear damage [55]. The beneficial effects of dexamethasone on tinnitus might be derived from immune suppression, anti-inflammation and sodium reabsorption in the inner ear through action on steroid receptors in the human temporal bone [55]. The intra-tympanic administration route could result in regionally high peri-lymphatic dexamethasone levels compared to a systematic administration route, which could reduce the risk of systemic adverse events [55]. However, since the current NMA recruited tinnitus patients without specific or treatable origin, the potential beneficial effect of intra-tympanic dexamethasone injection alone did not achieve significant level (Fig. 3). Therefore, combined with the findings in the current NMA, the intra-tympanic dexamethasone injection plus oral melatonin would be ranked superior to the intra-tympanic dexamethasone injection alone in tinnitus patients without specific or treatable origin.

In comparison with the previous clinical guidelines [8,9,22], the current NMA did not focus on the traditional management (i.e. tinnitus support and psychologic therapy) to tinnitus, which was relatively time-consuming and expensive. Rather, the current NMA focus on the pharmacologic interventions to manage the tinnitus severity. In addition, the current NMA also focus on the potential placebo effect in the tinnitus management. To be specific, the current NMA found that the oral form placebo exerted significantly beneficial effects in participants with tinnitus ($p < 0.001$) (eFig. 3A). However, the CLES of response rates of oral form placebo (i.e. the probability of one random observation from the treated population being larger than another random observation from the control population) was only 24.5%, which was relatively low compared to that of neuropsychiatric disease, such as depression (i.e. 35%−40%) [56]. However, the unavoidable placebo effect could also be at least partly explained by the fact that most studies applied subjective rating scales and there was a relative lack of reliable objective investigating tools. Therefore, to develop up an conclusive objective measurements for the severity of tinnitus without specific/treatable origin should be warranted [57].

Several potential limitations should be considered. First, this NMA may have been underpowered due to the heterogeneity of the participants (e.g., comorbidities, mood disorder, baseline severity of

tinnitus, duration of tinnitus onset, wearing hearing-aids, treatment duration in each study and follow-up duration), variety in the definition of response, variety in tinnitus severity or quality-of-life rating scales, and high risk of bias in 'Random sequence generation' and 'Blinding of participants' in some of the included RCTs. In order to overcome the potential bias on the primary outcome, we arranged subgroup to exclude RCTs without placebo-control, in which the main results would not change. Further, in the subgroup of different duration of tinnitus symptoms, there was no significant difference of placebo effect between the subgroups with different disease duration of tinnitus symptom ($p = 0.80$), which suggest potentially less impact by the different duration of tinnitus symptom on the primary outcome. As for the heterogeneity of the outcome reporting (i.e. variety in tinnitus severity or quality-of-life rating scales), this was an unavoidable limitation of any NMA investigating subjective outcomes. The tinnitus, just like the depressive symptoms, quality of life, or pain symptoms [58], was a subjective symptom and lack of objective measurement to measure its severity or to define its treatment response. Currently, there had not been any conclusive golden rating scales to measure its severity [8,9]. Also, there had been no conclusive evidence to approve the superiority of one rating scales to the others [8,9,22]. The choice or selection of one specific rating scales would become an potential source of bias in the network meta-analysis of subjective symptoms. Based on this limitation, we highly recommend future studies to address the need for a gold standard measurement of tinnitus severity, which would appear to be a significant limitation in the tinnitus research field. Further, the results of the future study would be recommended to be rated according to a standardized multi-measure scale. Therefore, the clinicians may pay attention when applied the results of current study in their clinical practice because of the potential difference between the rating scales and the variety of definition of response rate. Second, although the most of the RCTs included a placebo control in their study design, some of the included trials applied waiting list as their control groups. However, the main findings were unchanged after excluding those trials (eFig. 1D-1E and 2D-2E). Third, given the relatively small number of patients and RCTs, the main results of this NMA should perhaps be conservatively applied in clinical practice. Fourth, despite some heterogeneity among RCTs regarding the control group, when trials were restricted to an oral form of placebo therapy, results were similar. Further, the potential placebo effect was an unavoidable issue in any clinical studies investigating disease of subjective symptoms, such as tinnitus. The overall placebo of the injection form placebo and oral form placebo were 26.4% and 24.5%, which was relatively low compared to that of neuropsychiatric disease, such as depression (i.e. 35%−40%) [56]. Fifth, because of small numbers of included RCTs and insufficient direct/indirect comparison between treatment arms, there would be different findings between the primary outcome (i.e. changes of tinnitus severity) and secondary outcome (i.e. response rate). Sixth, although the De Ridder et al. (2021) [4] had provided the clear concept of "tinnitus disorder", the most included RCTs (published from 1993 to 2020) in the current NMA did not apply the concept of "tinnitus disorder". Therefore, we could not make distinguish between the target of "tinnitus vs tinnitus disorder" in the current study. Finally, we only investigated the drop-out rate but not by an adverse events profile because too few studies provided data about adverse events to form a network. Also, there were some other important factors associated with the baseline tinnitus severity, such as quality of life, anxiety mood, depressive mood, and so on. However, we could only perform network meta-analysis of quality of life but not the others because there were too few RCTs providing such data to form a network structure.

In conclusion, this NMA found that pharmacologic interventions with brain-acting effects (i.e., amitriptyline, acamprosate, and gabapentin) and those with anti-inflammation/anti-oxidant effect (i.e., intra-tympanic dexamethasone injection plus oral melatonin) were associated with superior improvement in tinnitus severity and response rate compared to placebo/control in tinnitus patients without specific or treatable origin. The main results did not change when focusing RCTs with placebo-controlled. Most treatments showed similar drop-out rate compared to placebo/control. However, because some of the intervention comparisons were based on only a few RCTs and the rating scales of tinnitus severity and other subjective symptoms had widely varied, clinicians should select specific treatments with caution. Based on the statistical result found in the current NMA, we would like to recommend future RCTs investigating brain-acting regimens/modulations targeting abnormal brain hyperactivities and overt oxidative stress in tinnitus without specific or treatable origin.

Declaration of Competing Interest

The authors report no financial interests or potential conflicts of interest.

Data sharing statement

The all data of the current study would be available upon reasonable request.

Author contributions

Jiann-Jy Chen, Yen-Wen Chen, Bing-Yan Zeng, and Chao-Ming Hung, who contributed equally as first authors, independently screened the studies and extracted the relevant information from the manuscripts, evaluated the risk of bias, and drafted the current manuscript.

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Ming-Kung Wu and Ping-Tao Tseng, who contributed equally as the corresponding authors, took the responsibility of data deposit, collection of all information from the other authors, and submitting the current manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101080.

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