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The Effectiveness of Serotonin and Tricyclic Antidepressants in Tinnitus Management: A Rapid Review

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Abstract

Background: Tinnitus can be defined as a health condition characterized by the perception of sound, either in the head and/or ears, in the absence of any external acoustic stimulus. Perception is often quantified by self-report, or the use of patient reported outcome measures (PROMs). The purpose of this rapid review was to evaluate the level and quality of evidence regarding the use of serotonin and norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), and tricyclic antidepressants as measured by tinnitus patient-reported outcome measures (PROMs) and/or Visual Analog Scales (VAS). Methods: The Cochrane Rapid Review guidelines were followed. The PICO mnemonic was used to “frame” the research question. The search strategy was developed and executed in three databases: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. Inclusion and exclusion criteria were established a priori. The search, identification, and selection process were plotted using the PRISMA Flow Diagram. Results were extracted to a custom form. Critical appraisal and risk of bias assessments were completed using standard critical appraisal tools. Results: Three hundred and seventy-five publications were identified and deduplicated, 286 were screened, 266 were deemed irrelevant. Twenty publications were identified for full text review. Seven randomized controlled trials (RCT) met the inclusion criteria and were assessed for design, quality, and bias. The level and quality of the RCT studies included were rated. Statistically significant benefits for amitriptyline, nortriptyline, fluoxetine with alprazolam, and sertraline were reported for tinnitus sufferers whereas fluoxetine alone, trazodone, vestipitant or vestipitant with paroxetine, or paroxetine alone did not demonstrate significant results. A meta-analysis was not completed due to the heterogeneity of studies. Conclusions: Despite promising results, there remains insufficient rigorous high-quality research evidence to indicate that antidepressants can effectively treat subjective tinnitus at this time.

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ABSTRACT
Background: Tinnitus can be defined as a health condition characterized by the perception of sound, either in the head and/or ears, in the absence of any external acoustic stimulus. Perception is often quantified by self-report, or the use of patient reported outcome measures (PROMs). The purpose of this rapid review was to evaluate the level and quality of evidence regarding the use of serotonin and norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), and tricyclic antidepressants as measured by tinnitus patient-reported outcome measures (PROMs) and/or Visual Analog Scales (VAS). **Methods:** The Cochrane Rapid Review guidelines were followed. The PICO mnemonic was used to "frame" the research question. The search strategy was developed and executed in three databases: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. Inclusion and exclusion criteria were established a priori. The search, identification, and selection process were plotted using the PRISMA Flow Diagram. Results were extracted to a custom form. Critical appraisal and risk of bias assessments were completed using standard critical appraisal tools. **Results:** Three hundred and seventy-five publications were identified and deduplicated, 286 were screened, 266 were deemed irrelevant. Twenty publications were identified for full text review. Seven randomized controlled trials (RCT) met the inclusion criteria and were assessed for design, quality, and bias. The level and quality of the RCT studies included were rated. Statistically significant benefits for amitriptyline, nortriptyline, fluoxetine with alprazolam, and sertraline were reported for tinnitus sufferers whereas fluoxetine alone, trazodone, vestipitant or vestipitant with paroxetine, or paroxetine alone did not demonstrate significant results. A meta-analysis was not completed due to the heterogeneity of studies. **Conclusions:** Despite promising results, there remains insufficient rigorous high-quality research evidence to indicate that antidepressants can effectively treat subjective tinnitus at this time.

Keywords: tinnitus, antidepressants, intervention, effectiveness, treatment

INTRODUCTION

What did Ludwig Beethoven (1770 – 1827, German), Charles Darwin (1809-1882, English), and Vincent Van Gogh (1853-1890, Dutch) have in common? They all suffered from chronic debilitating tinnitus. Beethoven first experienced tinnitus or ringing in the ears at the age of 28 years.[1] Darwin, a true scientist, kept a journal as a daily record of the intensity and frequency of his tinnitus.[2] Van Gogh suffered immeasurably with symptoms of tinnitus, to the point that he severed his own ear in hopes of gaining some relief.[3] The first historical reports of tinnitus may date back to Babylonia times and has been attributed to the Talmudic report of Roman Emperor Titu's tinnitus.[4]

Description of the Condition

Etiology

Tinnitus, commonly known as "ringing in the ears," can be defined as a health condition characterized by the perception of sound, either in the head and/or ears, in the absence of an acoustic stimulus.[5,6] Coelho and colleagues suggest that when it comes to classifying tinnitus, there are multiple causes and multiple mechanisms, all with the same name.[7] Perceptual tinnitus is typically transitory in nature and short term. It is often characterized by temporary conditions such as cerumen, foreign body in the canal.[6,7,8] Perceptual tinnitus can also be related to a temporary threshold shift from noise exposure the previous evening at a concert or similar venue.[6,7,8] Chronic tinnitus is more debilitating and long term, characterized by an on-going condition that impacts the quality of one's life by interference with daily activities such as mental function and sensory functions.[8] It can also impact sleep, thought patterns, emotions, concentration, ability to communicate, community, social and civic life, aspects of domestic life, interpersonal relations, and learning.[7,8]

Tinnitus can be unilateral or bilateral and can be classified as subjective or objective. Another way to classify tinnitus is by the perceptual characteristics such as the type of sound, synchronicity, intensity, duration, and pitch. Additional descriptors of the nature of tinnitus include episodic versus an acute or chronic insult, and intermittent versus consistent (see Table 1).[6,7,8,9]

Table 1. Typology by Tinnitus Attributes

Classification
Primary or Secondary Primary - any phantom sound generated in the ear or the brain; Secondary - mechanical or vascular secondary issue causing it to occur
Unilateral or Bilateral Unilateral is perceived in one ear; bilateral is perceived in both ears In some cases, it cannot be localized to the ear and sounds like a head noise
Type of Sound Perceived Buzzing, Chirping, Clicking, Cracking, Crickets, Dial Tones, Frying, Hissing, Humming, Musical, Ocean, Popping, Pulsing, Ringing, Roaring, Rushing, Screeching, Static, Swishing, Tonal, Typewriter, Whistling, Whooshing
Intensity of Sound Soft, Moderately Loud, Loud, Very Loud, Extremely Loud
Perceived Pitch of Sound Low Frequency (<500 Hz); Medium Frequency (1000 – 4000 Hz), or High Frequency (8000 – 12,000 Hz)
Duration Onset: Recent (less than 6 months) or Persistent (more than 6 months) Seconds, Minutes, Hours, Days, Ongoing
Temporal Characteristics Spontaneous or Temporary Occasional, Intermittent, Constant Acute <3 month); Subacute >3 months to 6 months; Chronic >6 months

Note. Hz = hertz. Adapted from "ICF-Based Analysis of Psychological and Functional Aspects of Tinnitus," by M. James, and A. Banik, 2018, *International Journal of Health Sciences and Research, 8*(11), 226-237. https://doi.org/10.52403/ijhsr.

Pathophysiology

Coelho and colleagues suggest a typology aligned with the anatomy of the hearing mechanism (i.e., conductive tinnitus; sensorineural tinnitus, vestibular tinnitus, and somatosensory tinnitus).[7] Tinnitus that is considered "primary" is idiopathic without an identifiable cause whereas secondary tinnitus is associated with a specific underlying cause.[10] Tinnitus associated with conductive hearing loss is related to changes in the blood flow, muscles, or physiology of the middle ear.[9] Sensorineural tinnitus is linked to diverse etiologies responsible for changes in the blood flow, muscles, or physiology of the inner ear. Vestibular tinnitus is associated with conditions which affect the blood and fluid flow or physiology of the vestibular system. Lastly, somatosensory modulation of tinnitus is related to multimodal functional interaction among sensory cortical regions and includes tinnitus modulation, somatosensory tinnitus, vascular tinnitus arterial tinnitus, arteriovenous tinnitus, venous blood flow tinnitus, idiopathic intracranial hypertension, and venous hum. Examples for each type of mechanistic tinnitus is shown in Table 2.

Table 2. Typology by Tinnitus Mechanism

Classification
Conductive
Ear infections
Tympanic membrane and ossicular chain origins
Glomus tumors
Myoclonus
Tensor tympani tonicity
Sensorineural
Presbycusis tinnitus
Metabolic tinnitus
Diabetes type II
Hypothyroidism
Dyslipidemia
Anemia
Vitamin and mineral deficiencies
Noise induces tinnitus and hearing loss
Acoustic trauma or acoustic shock
Sudden hearing loss and tinnitus
Rapidly progressive bilateral sensorineural hearing loss and tinnitus
Ototoxicity
Auditory neuropathy spectrum disorder
Vestibular schwannomas
Meniere's disease
Vascular conflict of cranial nerve VIII
Visual snow syndrome
Vestibular
Vestibular migraine and tinnitus
Benign paroxysmal positional vertigo and tinnitus
Somatosensory
Tinnitus modulation
Somatosensory tinnitus
Vascular tinnitus arterial tinnitus
Arteriovenous tinnitus
Venous blood flow tinnitus
Idiopathic intracranial hypertension
Venous hum

Note. Adapted from "Classification of tinnitus: Multiple causes with the same name," by C.B. Coelho, R. Santos, K.F. Campara, and R. Tyler, 2020, *Otolaryngologic Clinics of North America*, *53*(4), 515–529. https://doi.org/10.1016/j.otc.2020.03.015

Prevalence

McCormack and colleagues conducted a systematic review of all studies between 1980 and 2015 to derive a global estimate of tinnitus prevalence.[11] The heterogeneity among 39 studies representing 16 countries which met their inclusion criteria precluded completion of a meta-analysis. Results from the qualitative synthesis revealed an overall prevalence ranging from 5.1% – 42.7% for all studies. Twelve studies used the same definition for tinnitus and prevalence for those studies were 11.9% to 30.3%. There were 8 different definitions of tinnitus, the most common used in 34.3% of the studies was "tinnitus lasting more than 5 minutes at a time". Reavis and colleagues reported on the prevalence of tinnitus by sociodemographic variable and health condition derived from the National Health and Nutrition Examination Survey data from 2009 – 2012.[12] Salazar et al reported a 33% prevalence of depression in tinnitus participants.[13] Prevalence of tinnitus by sociodemographic variable is shown in Table 3. [12]

Table 3. Characteristics of US Adults >20 Years by Tinnitus Status and Sociodemographic Variable (National Health and Nutrition Examination Survey, 2009-2012)

Characteristic	Sample size (n=5,550)	Tinnitus	No Tinnitus
Sex			
Male	2,732	17% [14%, 20%]	83% [80%, 86%]
Female	2,818	14% [12%, 16%]	86% [84%, 88%]
Age			
20–39 years	1,876	7% [5%, 9%]	93% [91%, 95%]
40–59 years	1,754	18% [16%, 21%]	82% [79%, 84%]
60–79 years	1,525	23% [19%, 27%]	77% [73%, 81%]
80+ years	395	21% [17%, 26%]	79% [74%, 83%]
Race/Ethnicity			
Non-Hispanic White Non-Hispanic Black	2,184	18% [16%, 20%]	82% [80%, 84%]
Mexican American	1,387	10% [8%, 11%]	90% [89%, 92%]
Other Hispanic	588	9% [7%, 12%]	91% [88%, 93%]
Other	524	9% [7%, 11%]	91% [89%, 93%]
	867	10% [5%, 15%]	90% [85%, 95%]
Education			
< High school	1,338	17% [13%, 21%]	83% [79%, 87%]
High school graduate	1,164	17% [12%, 22%]	83% [78%, 88%]
> High school	3,045	14% [12%, 16%]	86% [84%, 88%]
Income			
(% federal poverty level)			
≤ 100%	1,696	87% [85%, 89%]	87% [85%, 89%]
101%–200%	1,324	81% [76%, 85%]	81% [76%, 85%]
> 200%	2,530	85% [83%, 87%]	85% [83%, 87%]
Marital status			
Married	2,712	15% [14%, 17%]	85% [83%, 86%]
Widowed/divorced/separated	1,273	23% [17%, 28%]	77% [72%, 83%]
Never married	1,143	9% [7%, 12%]	91% [88%, 93%]
Living with partner	420	12% [7%, 16%]	88% [84%, 93%]
Veteran status			
Veteran	625	26% [19%, 32%]	74% [68%, 81%]
Non-Veteran	4,925	14% [12%, 16%]	86% [84%, 88%]
Occupational noise exposure			
Yes	1,870	22% [18%, 25%]	78% [75%, 82%]
No	3,678	12% [10%, 14%]	88% [86%, 90%]

Note. n = number. Adapted from "Prevalence of Self-reported Depression Symptoms and Perceived Anxiety Among community-dwelling U.S. Adults Reporting Tinnitus" by K. M. Reavis, J. A., Henry, L. M. Marshall, and K. F. Carlson, 2020, *Perspectives, 5*, 959-970. https://doi.org/10.1044/2020_PERSP-19-00178. Copyright 2020 American Speech Language Hearing Association.

Management of Tinnitus

There are five major non-invasive approaches to tinnitus management. These approaches include lifestyle, sound therapy, psychological models, alternative medicine, and pharmacologic management. Management of tinnitus falls under the scope of practice of a multitude of healthcare professionals including but not limited to physicians, audiologists, psychologists, psychiatrists, mental health specialists, and pharmacologists. *Lifestyle factors* associated with increased risk of tinnitus in adults include poor diet, smoking, alcohol consumption, and caffeine.[14,15] Reduction of these factors coupled with modifications in exercise, sleep, and stress management are strategies used to reduce the impact of tinnitus.[16] *Sound therapy* decreases the perception of tinnitus by utilizing environmental enrichment devices, amplification, and ear-level sound generators to alleviate the individual's symptoms.[9,17] *Psychological models* such as Cognitive Behavioral Therapy (CBT) and Tinnitus Retraining Therapy (TRT) are popular interventions used to address tinnitus. CBT reduces the perception of tinnitus by improving the individual's negative response to it using counseling and relaxation methods.[18] TRT separates the individual's tinnitus from their negative response using both directive counseling and ear-level noise generators which allows the individual to habituate to their tinnitus.[19] *Alternative medicine* approaches include acupuncture, herbs, hypnosis, melatonin, and vitamins.[20,21,22] *Pharmacological* agents used in tinnitus management include antianxiety, anticonvulsants, and antidepressants.[23]

Five classes of antidepressants include atypical antidepressants, monoamine oxidase inhibitors (MAOI), serotonin and norepinephrine reuptake inhibitors, (SNRI) selective serotonin reuptake inhibitors (SSRI), and tricyclic antidepressants.[24] There is a paucity of research on atypical antidepressants and MAOIs in the treatment of tinnitus.[25,26] The evidence for SNRIs, SSRIs, and tricyclic antidepressants show mixed results.[27] The objective of this review is to assess the level and quality of evidence regarding the effectiveness of serotonin and tricyclic antidepressants in the management of tinnitus.

Patient Reported Outcome Measures (PROMs)

The choice of validated tinnitus patient reported outcome measures to assess the benefits of interventions such as serotonin and tricyclic antidepressants is of critical importance. Researchers have a plethora of tinnitus assessment tools to choose from. The most used type of self-report instrument in audiology is a questionnaire. These questionnaires are used to characterize the symptoms or self-perception of any number of attributes experienced including but not limited to pitch, loudness, duration, laterality, and level of disturbance. These questionnaires often use discrete scales known as the Likert scale for responses.[28] Alternative psychometric measures known as Visual Analog Scales (VAS) are also used to assess subjective attitudes and characteristics. Described for the first time by Hayes & Patterson, this type of scale was not used in medicine until the late 1960's.[29,30] VAS are used to achieve a rapid classification of symptom severity and has been shown to be statistically measurable and reproducible.[31] When responding to a VAS item, patients specify their level of agreement with a statement by indicating a position along a continuous line between two endpoints.[31] The use of VASs for the assessment of chronic tinnitus has also been evaluated.[32,33] For example, Adamchic et al evaluated the reliability, validity, and minimally clinically identifiable difference (MCID) of the VAS loudness and VAS annoyance for tinnitus and demonstrated good test-retest reliability and validity.[32]

Patient-reported outcome measures (PROMs) are recognized as valuable tools in assessing the quality of health care and quality of life from the patient perspective.[34] Factor analyses from several tinnitus PROM validation studies have revealed multiple domains and dimensions along which reactions to and perceptions of tinnitus may fall.[35,36,37] For example, three of the earliest PROMs were the Tinnitus Effects Questionnaire (TEQ), also known as the Tinnitus Questionnaire (TQ), Tinnitus Handicap Questionnaire (THQ), and the Tinnitus Reaction Questionnaire (TRQ).[35-37] Hallam et al reported three domains in the TEQ/TQ: emotional distress, auditory perceptual difficulties, and sleep disturbance.[35] Kuk et al identified three dimensions in the THQ: emotional, social, and physical sequelae of tinnitus, effects of tinnitus on hearing sensitivity and communication; and appraisal of tinnitus.[36] Wilson et al reported four factors in the TRQ: general distress, severe distress, interferences with work and leisure, and activity avoidance. [37] In a scoping review of patients and significant other reported symptoms, Hall et al identified 42 discrete complaints spanning physical and psychological health, quality of life, and negative attributes of tinnitus sound.[38]

Both PROMs and VASs are used as outcome measures for tinnitus. Results of a recent systematic review identified 155 unique questionnaires for ear and hearing related symptoms, including 33 specific to tinnitus, 23 for vertigo, 84 specific to hearing loss, and 15 multiple complaint questionnaires.[34] Viergever and colleagues reported the author and year of the original publication, country published, a description of the assessment, the study population, item development and number of items, and language translations.[34] Although it is possible that this list of tinnitus PROMs is not all inclusive, it represents the most comprehensive list readily available to date. Table 4 is a summary of the VAS tools identified by the authors and the PROMs reported for tinnitus by Viergever et al.[34] The author and year, VAS or PROM title and abbreviation, dimensions or domains assessed, and the number of items are shown in this table.

Table 4 . Tinnitus Patient Reported Outcome Measures (PROMS)

Author/Year	PROM Name	Domains	# Items
Adamchic et al., 2012[32]	Visual Analog Scale for Annoyance (VAS-A)	Avoidance	N/A
Adamchic et al., 2012[32]	Visual Analog Scale for Loudness (VAS-L)	Loudness	N/A
Bankstahl et al., 2012[39]	Tinnitus Handicap Inventory (THI-3)	Impact on daily life Functional effect Emotional response Catastrophic response	3
Budd & Pugh, 1996[40]	Tinnitus Coping Style Questionnaire (TCSQ)	Effective coping Passive coping Maladaptive coping	40
Cima et al., 2011a[41]	Tinnitus Catastrophizing Scale (TCS)	Catastrophizing	13
Cima et al., 2011a[41]	Fear of Tinnitus Questionnaire (FTQ)	Fear	17
Cima et al., 2011a[41]	Tinnitus Vigilance and Awareness Questionnaire (TVAQ)	Vigilance and awareness	18
Cima et al., 2011b[42]	Tinnitus Disability Index (TDI)	Disability	7
Croft et al., 2013[43]	Tinnitus Response Scales (TRS)	Cognitive, behavioral, and emotional response patterns	24
Erlandsson et al., 1992[44]	Tinnitus Handicap/Support Scale (THSS)	Disability/handicap Perception and attitude Social support	28
Greimel et al., 1999[45]	Tinnitus-Beeinträchtigungs-Fragebogens (TBF-12) or Tinnitus Handicap Inventory 12 (THI-12)	Functional effect Emotional response Catastrophic response	12
Halford & Anderson, 1991[46]	Subjective Tinnitus Severity Scale (STSS)	Intrusiveness Prominence Distress	16
Hallam et al., 1988[35]	Tinnitus Effects Questionnaire (TEQ) or Tinnitus Questionnaire (TQ)	Emotional distress Cognitive distress Intrusiveness Auditory perceptual difficulties Sleep disturbances Somatic complaints	52
Hallam, 2008[47]	Shortened Tinnitus Questionnaire (STQ)	Abbreviated of TQ	33
Henry & Wilson, 1995[48]	Tinnitus Coping Strategies Questionnaire (TCSQ)	Cognitive and behavioral coping strategies	33
Henry et al., 2015[49]	Tinnitus and Hearing Survey	Disturbance Communication interference Tolerance	10
Henry et al., 2016[50]	Tinnitus Screener (TS)	Presence/absence Characteristics	4
Henry et al., 2017[51]	Self-Efficacy for Managing Reactions to Tinnitus	Confidence managing reactions	17
Hiller & Goebel, 2004[52]	Mini Tinnitus Questionnaire (Mini-TQ)	Emotional and cognitive distress Intrusiveness Auditory perceptual difficulties	12
Kaldo et al., 2006[53]	Tinnitus Stages of Change Questionnaire	Readiness to change behaviors and attitudes	23
Kennedy et al., 2005[54]	International Tinnitus Inventory (ITI)	Functional effect Emotional response Catastrophic response	8
Kleinstauber et al., 2013[55]	Tinnitus Fear-Avoidance Cognitions and Behaviors Scale (T-FAS)	Fear and avoidance	14
Kuk et al., 1991[36]	Tinnitus Handicap Questionnaire (THQ)	Physical, emotional, and social effects Hearing and communication ability Perception	27
McCombe et al., 2001[56]	Tinnitus Handicap Inventory (THI) Severity Scale	Severity of activity and participation limitations	4
Meikle et al., 2012[57]	Tinnitus Functional Index (TFI)	Intrusiveness Sense of control Cognitive interference Sleep disturbance Auditory difficulty Relaxation interference Quality of life	25

Author/Year	PROM Name	Domains	# Items
Newman et al., 1996[58]	Tinnitus Handicap Inventory (THI)	Emotional disturbance Impact on daily life Functional effect Emotional response Catastrophic response	25
Newman et al., 2008[59]	Tinnitus Handicap Inventory Screening (THI – S)	Impact on daily life Functional effect Emotional response Catastrophic response	10
Skarzynski et al., 2018[60]	Skarzynski Tinnitus Scale (STS)	Functional characteristics Psychological complaints	15
Smith & Fagelson, 2011[61]	Self-efficacy for Tinnitus Management Questionnaire (SETMQ)	Routine management Emotional response Internal thoughts and interaction with others Tinnitus concepts Use of assistive devices	40
Tyler, 1993[62]	Tinnitus Activities Questionnaire	Functional characteristics Psychological complaints	20
Tyler et al., 2014[63]	Tinnitus Primary Function Questionnaire – 20	Concentration Emotion Hearing Sleep	20
Tyler et al., 2014[63]	Tinnitus Primary Function Questionnaire – 12	Concentration Emotion Hearing Sleep	12
Westin et al., 2008[64]	Tinnitus Acceptance Questionnaire (TAC)	Activity engagement Tinnitus suppression Acceptance	12
Wilson et al., 1991[37]	Tinnitus Reaction Questionnaire (TRQ)	General distress Interference with work/leisure Severe distress Avoidance of activities	26
Wilson & Henry, 1998[65]	Tinnitus Cognitions Questionnaire (TCQ)	Positive and negative cognitive thoughts and perceptions	26

Note. Adapted from "Questions in Otology: A Systematic Mapping Review" by K. Viergever, J. T. Kraak, E. M. Bruinewoud, J. C. F. Ket, S. E. Kramer, and P. Merkus. 2021. *Systematic Reviews*, 10,111, Appendix 4. https://doi.org/10.1186/s13643-021-01659-9. Copyright 2021 Creative Commons License.

How this Intervention (Antidepressants) Might Work

There is no universally accepted theory regarding how tinnitus is generated.[9] Baldo and colleagues[27] suggest that one single underlying pathology is unlikely. Two decades of imaging studies provide electrophysiologic and metabolic evidence of hyperactivity in the auditory pathway of tinnitus participants as well as in non-auditory brain structures including the limbic system.[39] The role of the limbic system in emotional regulation and stress responses are well recognized.[66] Antidepressants work by normalizing emotional responses and are thus hypothesized to impact depression, anxiety and other psychosomatic or psychological disturbances that negatively affect the quality of life.[67,68] The overall purpose of this rapid review was to evaluate the level and quality of evidence regarding the use of serotonin and norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), and tricyclic antidepressants as measured by PROMs and VASs.

Anticipated Benefits

It is anticipated that a portion of individuals will benefit from antidepressants and enough relief from tinnitus to report significant improvements in quality of life. This benefit has often been attributed to a secondary effect of the medication in the relief of depression or anxiety as opposed to the primary effect in directly impacting the tinnitus pathophysiology.[27]

Importance of this Review

This review provides audiologists and other health care professionals with knowledge regarding patient reported outcomes relative to the use of three classes of antidepressants in the relief of tinnitus symptoms. These classes include SNRI, SSRI, and tricyclic antidepressants.[24]

METHODOLOGY

Ethics Statement

A letter of determination was submitted to the Nova Southeastern University (NSU) Institutional Review Board (IRB). Protocol # 2022-139 was determined to fall outside the jurisdiction of the IRB since it does not meet the criteria for human subject research. The methodology was consistent with the Cochrane Rapid Review guidance.[69,70]

PICO Framework

The PICO mnemonic, first proposed by Counsell, was used to "frame" the critical elements of the research question.[71] This approach is frequently used in systematic reviews. The critical elements include population, intervention, comparison, and outcome (PICO). The population for this study were individuals suffering from subjective tinnitus. The intervention included SNRIs, SSRIs, and tricyclic antidepressants. Studies were required to have a placebo control group as comparison. Outcome measures had to include a patient-reported instrument to document drug efficacy. Tinnitus questionnaires and visual analog scales were included as PROMs. The research question using the PICO framework was "Do antidepressants provide effective treatment for tinnitus participants as self-reported on tinnitus questionnaires or PROMs?"

Search Strategy

The following electronic databases were systematically searched to identify all relevant published studies: MEDLINE (Ovid), Embase.com (Elsevier), and Cochrane Central Register of Controlled Trials (EBSCOhost), from database inception to May 18, 2023. Results were limited to English language publications. Filters for identifying randomized controlled trials (RCTs) and human studies developed by the Cochrane Collaboration were applied to the Medline and Embase searches. [72,73] Search strings were developed for each database, which included keywords as well as subject headings and syntax specific to each one (see Appendix A). The search strategies were peer reviewed by another librarian prior to execution using the PRESS Checklist.[74] Results were exported to EndNote. The deduplication feature in EndNote was used and then the results were manually checked to identify the total number of unique records. Reference lists of included articles were manually screened to identify additional studies. The search identification, screening, and selection processes was plotted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), Flow Diagram (see Figure 1).[75]

Inclusion/Exclusion Criteria

Studies targeted for inclusion were those with adults over the age of 18 years suffering from subjective tinnitus who were enrolled in a clinical trial in which the intervention was a serotonin or tricyclic drug intervention. At least one of the outcome measures was required to be a self-reported tinnitus questionnaire or visual analog scale. Studies with child or adolescent tinnitus sufferers were excluded, along with any studies that included individuals with acute or chronic conditions that would limit the patient's ability to fully participate in the study. Publications were excluded if the drug was provided via intravenous (IV) administration and if there was not a comparison group with a placebo. Studies were also excluded if comparison groups used other types of treatments such as B12, Zinc or Melatonin as a comparison. Publication inclusion criteria were peer-reviewed research studies designated as an RCT and published in English. There were no limits on year of publication; however, publications were limited to those available electronically.

Data Extraction

A custom data extraction form was developed for this study. This provided a standardized method of selecting data relevant to the research question and functioned to minimize bias. One researcher served as the primary data extractor. All data extraction forms were reviewed by one other co-author. The data extraction form can be viewed in Appendix B.

Clinical Appraisal

Risk of bias was assessed using two methods. First, a critical appraisal of each article was conducted using a modified Joanna Briggs Institute (JBI) Critical Appraisal Form for Randomized Controlled Trials.[76] Secondly, the level and grade of recommendations was used by applying the JBI Level of Evidence for Effectiveness.[77] and the JBI Grade for Recommendations.[78] Level 1 is reserved for experimental designs, Level 2 for quasi-experimental, Level 3 for observational analytic designs, Level 4 for observational descriptive studies, and Level 5 for expert opinion and bench research. Grade A represents a strong recommendation for a certain health management strategy where (a) desirable effects outweigh the effects of the treatment, (b) there is evidence supporting its use, (c) there is a benefit or no impact on use, and (d) values and the patient experience have been considered. Grade B indicates a weak recommendation for a health management strategy where (a) it is not clear that desirable effects outweigh undesirable effects, (b) there is evidence supporting its use, although it may not be of high quality, (c) there is a benefit with minimal impact on resource use, and (d) patient experience has not been considered.

The GRADE method was then used to assess Risk of Bias and rate the quality level for methodological rigor and level of confidence in the results of the study. [69,70,79,80] There are four levels for the GRADE process: high, moderate, low, and very low and were defined by Balshem et al., 2011.[81] A high rating indicates that we are confident that the true effect lies close to that of the estimated effect whereas a moderate effect suggests that the true effect is likely to be close to the estimate of the effect, but the possibility exists that it could be substantially different – thus, we can only conclude a moderate level of confidence. A low-quality rating indicates that our confidence in the effect estimate is limited; the true effect could be substantially different from the estimate of the effect, and very low indicates that we have very little confidence in the effect estimate. The modified JBI Checklist with the GRADE assessment is shown in Appendix C.

Data Synthesis

Although our initial intention was to perform a meta-analysis of the results, the results were heterogeneous with multiple limitations due to methodological factors. Therefore, a qualitative analysis and synthesis of the results was completed.

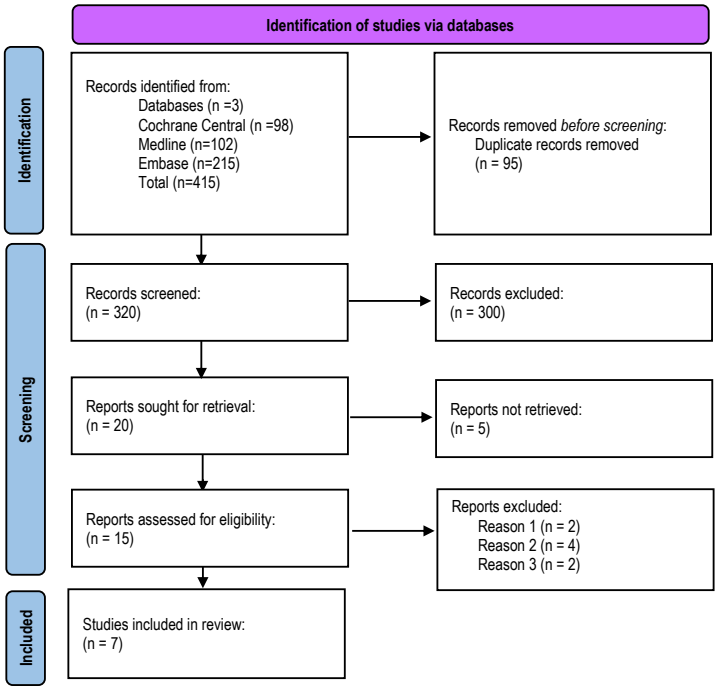
RESULTS

PRISMA Flow Diagram

The study search and selection process was tracked using the PRISMA Flow Diagram (see Figure 1).[75] The total number of records collected from the database searchers was 415. Ninety-eight records were identified from Cochrane Central; 102 from Medline and 215 from Embase. Ninety-five records were duplicates and were removed leaving a total of 320 deduplicated records. These record titles and abstracts were screened for relevance. Three hundred (300) publications were deemed irrelevant and eliminated from further consideration. Twenty records were sought for retrieval; however, five were clinical trials for which a publication was not available. Fifteen records were assessed for eligibility. Seven studies were deemed ineligible due to the following reasons: (a) used a nonpharmaceutical intervention (n = 2); (b) no patient reported tinnitus outcome measure (n = 4); and (c) was not an RCT (n = 2). Seven RCT's met the inclusion criteria and were subjected to further analysis.

Figure 1. PRISMA Flow Diagram

Figure 1. *PRISMA Flow Diagram*



Note. Reason 1 = included other forms of treatment in addition to antidepressants; Reason 2 –tinnitus patient reported outcome measure not included for outcome assessment; Reason 3 – not a randomized controlled trial. Adapted from "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews" by M. J. Page, J. E. Mckenzie, P. M. Bossuyt, I. Boutron, T. C. Hoffmann, C. D. Mulrow, L. Shamseer, J. M. Tetzlaff, A. E. Alk, S. E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hrobjartsson, M. M. Lalu, T. Li, E. W. Loder, E. Mayo-Wilson, S. McDonald, . . . D. Moher, 2021, *BMJ*, 371, n71. https://doi.org/10.1136/bmj.n71. Copyright 2023 BMJ Publishing Group Ltd.

Summary Tables

Data extracted from the RCT publications are summarized in Tables 5 -10. Table 5 shows the PICO elements for each peer-reviewed publication included in this systematic review. The 1st column shows the author and year, 2nd column displays the population, 3rd column describes the intervention, and the last column specifies the outcome measures used in each study.

Table 5. PICO Elements for Seven Peer-Reviewed Publications

Author/Year	Population	Intervention	Comparison	Outcome Measure
Bayar et al[86]	G1 = 20 G2 = 17	Amitriptyline	Placebo	American Tinnitus Association (ATA) Questionnaire
Dib et al[87]	G1 = 43 G2 = 42	Trazodone	Placebo	Analog Scale Score Questionnaire
Roberts et al[82]	G1a = 24 G1b =23 G2 = 23	Vestipitant Vestipitant + Paroxetine	Placebo	Tinnitus Handicap Inventory (THI)
Robinson et al[83]	G1 = 57 G2 = 58	Paroxetine	Placebo	Tinnitus Handicap Questionnaire (THQ)
Saberi et al[84]	G1a = 51 G1b = 56 G2 = 51	Fluoxetine Fluoxetine + Alprazolam	Placebo	Tinnitus Handicap Inventory (THI) Visual Analog Scale (VAS) Tinnitus Severity Index (TSI)
Sullivan et al[88]	G1 = 49 G2 = 43	Nortriptyline	Placebo	Tinnitus Handicap Questionnaire (THQ) MPI Tinnitus Interference (Self) MPI Tinnitus Interference (Spouse) Tinnitus Disruption
Zoger et al[85]	G1 = 29 G2 = 34	Sertraline	Placebo	Tinnitus Severity Questionnaire (TSQ)

Note. G1 = Group 1 Intervention; G1a = Group 1 Intervention (a); G1b = Group 1 Intervention (b); G2 = Group 2 Placebo

A summary of the population variables for each study is shown in Table 6. Relevant data includes the mean age, standard deviation, and range for each group in the study; along with the gender, race, and ethnicity characteristics if reported. While most studies reported age and gender, only two of the studies reported race/ethnicity.

Table 6. Population Characteristic Summary Table

Author/Year	Population	Number	Mean Age (years)	SD	Range (years)	Gender	Race/ Ethnicity
Bayar et al[86]	G1: Amitriptyline	N = 20	40.8	± 11.9	18-64	F = 10 M = 10	Not reported
	G2: Placebo	N = 17	36.9	± 11.8	21-57		Not reported
Dib et al[87]	G1: Trazodone G2: Placebo	N = 43 N = 42	Not reported	Not reported	45-80	F = 25 M = 18	Not reported Not reported
Roberts et al[82]	G1a - Vestipitant G1b - Vestipitant + Paroxetine G2 - Placebo	N = 24 N = 23 N = 23	56	Not reported	18 - 60	F = 6 M = 18	Caucasian and European Heritage
Robinson et al[83]	G1: Paroxetine G2: Placebo	N = 57 N = 58	57	Not reported	18-60	F = 66 M = 49	92% were Caucasian

Author/Year	Population	Number	Mean Age (years)	SD	Range (years)	Gender	Race/ Ethnicity
Saberi et al[84]	G1a - Fluoxetine G1b - Fluoxetine + Alprazolam G2 - Placebo	N = 51 N = 56 N = 51	Not reported	Not reported	20-65	Not reported	Not reported
Sullivan et al[88]	G1 = Nortriptyline G2 = Placebo	N =3 8 N = 54	62.0. 62.2	(8.2) (7.9)	Not reported	Not reported	Not reported
Zoger et al[85]	G1 = Sertraline G2 = placebo	N = 29 N = 34	40 46	± 14.3 ± 10.8	18 - 65	F = 14 M = 15 F = 13 M = 21	Not reported

Note. SD = standard deviation; G1 = Group 1 Intervention; G1a = Group 1 Intervention (a); G1b = Group 1 Intervention (b); G2 = Group 2 Placebo, N = number, SD = standard deviation, F = female, M = male

Descriptive data for the intervention and control groups for each study are summarized in Table 7. Characteristics include the type of medication or placebo, dose, times taken per day, and the duration of the study.

Table 7. Intervention Characteristics Summary

Author/Year	Antidepressant	Dose (mg)	Times Per day	Duration
Bayar et al[86]	G1 = Amitriptyline G2 = Placebo	50 Not reported	Once daily Once daily	6 weeks 6 weeks
Dib et al[87]	G1 = Trazodone G2 = Placebo	50 Not reported	Once daily Once daily	8.5 weeks 8.5 weeks
Roberts et al[82]	G1a = Vestipitant G1b =Vestipitant + Paroxetine G2 = Placebo	Not reported Not reported Not reported	Not reported Not reported Not reported	2 weeks 2 weeks 2 weeks
Robinson et al[83]	G1 = Paroxetine G2 = Placebo	10 increased to 50 10 increased to 50	Once daily Once daily	14 weeks 14 weeks 14 weeks
Saberi et al[84]	G1a = Fluoxetine G1b = Fluoxetine + Alprazolam G2 = Placebo	40 0.5 Same	Once daily (1week) Twice daily (3 weeks)	4 weeks 4 weeks 4 weeks
Sullivan et al[88]	G1 = Nortriptyline G2 = Placebo	50 to 150 ng/ML	Once daily	14 weeks
Zoger et al[85]	G1 = Sertraline G2 = Placebo	25 (1 week) 50 (16 weeks)	Once daily Once daily	16 weeks

Note. mg = milligrams; G1 = Group 1 Intervention; G1a = Group 1 Intervention (a); G1b = Group 1 Intervention (b); G2 = Group 2 Placebo; ng/ML = nanograms/milliliter

Characteristics of the tinnitus outcome measure or PROM and the statistical results are summarized in Table 8. For each study, the self-reported outcome measure, the pre- and posttest performance, and the statistical results are summarized.

Table 8. Outcome Measures and Results Summary

Author/ Year	Questionnaire	Groups	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	Significance ($p \leq .05$)
Bayar et al[86]	American Tinnitus Association (ATA) Questionnaire	G1 = Amitriptyline G2 = Placebo	RE: 4.25 (3.08) LE: 4.35 (3.45) RE: 4.00 (3.32) LE: 4.53 (3.28)	RE: 1.30(1.49) ** LE: 1.80(2.40) ** RE: 4.06 (± 3.44) LE: 4.71 (± 3.37)	$p < .05$
Dib et al[87]	Analog Scale Score (ASS) Questionnaire	G1 = Trazodone G2 = Placebo	6.56 6.02	5.91 5.10	$p = .77$
Roberts et al[82]	Tinnitus Handicap Inventory (THI)	G1a = Vestipitant G1b =Vestipitant + Paroxetine G2 = Placebo	32 (19) 33 (19) 33 (20)	27 (19) 29 (20) 28 (21)	$p = .02$
Robinson et al[83]	Tinnitus Handicap Questionnaire (THQ)	G1 = Paroxetine G2 = Placebo	26.84 (17.88) 26.49 (19.04)	24.74 (12.29) 25.97 (19.97)	p > 05
Saberi et al[84]	Tinnitus Handicap Inventory (THI)	G1a = Fluoxetine G1b = Fluoxetine + Alprazolam G2 = Placebo	8.65 7.73 6.57	6.69 7.00 6.1	p = .017 p = .001 p = .622 p <.001
Sullivan et al[88]	MPI Tinnitus Interference (Self)	G1 = Nortriptyline G2 = Placebo	2.8±1.1 2.2±1.3	1.8±1.3 2.4±1.3	p <.01 p <.03
Zoger et al[85]	Tinnitus Severity Questionnaire (TSQ)	G1 = Sertraline G2 = Placebo	21.96 (5.84) 22.68 (6.21)	17.28 (8.08) 19.99 (7.13)	p = .024

Note. SD = standard deviation, G1 = Group 1 Intervention; G1a = Group 1 Intervention (a); G1b = Group 1 Intervention (b); G2 = Group 2 Placebo; p = probability; RE = right ear; LE = left ear; MPI = multidimensional pain inventory

The research design, type of data analysis, level and of each study are depicted in Table 9. A modified JBI Checklist for Randomized Controlled Trials[76] was used for critical appraisal. The level of evidence for each study was rated using JBI Level of Evidence for effectiveness hierarchy.[77] The seven RCTs in this study were each rated as a Level 1.c, which is the rating assigned to RCTs. Level 1.a is a systematic review of RCT's, Level 1.b is for systematic reviews of RCTs and other study designs, and Level 1.d is for pseudo-RCTs. With this schema, the level is based on the research design. We also followed the JBI Grades of Recommendation described as Grade A or Grade B.[78] JBI Grade for Recommendations was A for four studies (n = 4;[82-85]), and B for three studies (n=3;[86-88]). The level and grade for recommendations are shown on Table 9.

Table 9. Evidence Summary

Author/Year	Research Design	Data Analysis	Level	Quality
Bayar et al[86]	Randomized, prospective, placebo-controlled parallel, single-blind trial	Not reported other than SPSS program	1.c	Grade B
Dib et al[87]	Randomized, prospective, placebo-controlled parallel, double-blind trial	Analysis of Variance (ANOVA) Chi-square; *t*-test	1.c	Grade B
Roberts et al[82]	Randomized, prospective, placebo-controlled, double-blind, crossover study	Mixed Effects Model	1.c	Grade A

Author/Year	Research Design	Data Analysis	Level	Quality
Robinson et al[83]	Randomized, prospective, placebo-controlled double-blind trial,	Repeated-measures Analyses of Variance (ANOVA)	1.c	Grade A
Saberi et al[84]	Randomized, prospective, placebo-controlled, double-blind trial	Multivariate Analysis of Covariance (MANCOVA)	1.c	Grade A
Sullivan et al[88]	Randomized, prospective, placebo-controlled, double-blind trial	Multivariate Analysis of Covariance (MANCOVA)	1.c	Grade B
Zoger et al[85]	Randomized, prospective, placebo-controlled, double-blind, clinical trial	Fisher Nonparametric Permutation Test and Pearson Product Moment Correlation Coefficients	1.c	Grade A

Note. 1c = randomized control trial; Grade A = a strong recommendation where desirable effects that outweigh undesirable effects are evident; evidence of adequate quality supporting its use, demonstrated benefit or no impact on resource use, and values, preferences and the patient experience have been considered. Grade B = a weak recommendation where desirable effects appear to outweigh undesirable effects of the strategy, although this is not as clear; there is evidence supporting its use, although this may not be of high quality; there is a benefit, no impact or minimal impact on resource use, and values, preferences and the patient experience may or may not have been taken into account. Definitions adapted from "JBI Levels of Evidence" by Joanna Briggs Institute, 2014. https://jbi.global/sites/default/files/2019-05/JBI-Levels-of-evidence_2014_0.pdf. Copyright 2014 Johanna Briggs Institute.

Risk of Bias

The risk of bias was completed for each study using GRADE process to delineate study limitations and level of confidence in the findings.[80,81] The categories considered in the risk of bias were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and an overall risk of bias judgment.[89] In the GRADE approach, RCTs are rated as high-quality evidence initially, and are rated down if evidence indicates a high risk of bias. Risk of bias can differ across studies due to design, variability in outcome measures and other factors which may suggest study limitations. For GRADE ratings, two studies were rated low indicating limited confidence in the results; one was rated as moderate indicating moderate confidence with a possibility that the true effect could be different; and four were rated as high indicating very confident that the true effect is close to that predicted.[82-88] The risk of bias, overall bias and GRADE ratings are for methodological rigor and level of confidence in findings are shown on Table 10.

Table 10. Risk of Bias

Author/Date	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Outcomes	Risk of Bias Judgment	GRADE (quality rating)
Bayar et al[86]								High	Low
Dib et al[87]								High	Low
Roberts et al[82]								Low	High
Robinson et al[83]								Low	High
Saberi et al[84]								Low	High
Sullivan et al[88]								High	Moderate

Author/Date	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Outcomes	Risk of Bias Judgment	GRADE (quality rating)
Zoger et al[85]	●	●	●	●	●	●	●	Low	High

Note: Low risk of bias = ●; High risk of bias = ●; Adapted from "Assessing Risk in a Randomized Trial" by J. P. T. Higgins, J. Savovic, M. J. Page, R. G. Elbers, & J. A. C. Sterne in the "Cochrane Handbook for Systematic Reviews of Interventions", version 6.3, 2022. Editors J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J, Page, and V. A. Welch. https://www.training.cochrane.org/handbook.Copyright 2022 by the Cochrane Collaboration; GRADE guidelines: 4: Rating the Quality of Evidence – Study Limitations Risk of Bias" by G. H. Guyatt, A. D. Oxmann, G. Vist, R. Kunz, J. Brozek, P. Alonso-Coello, V. Montori, EA Akl, B Djulbegovic, Y Falck-Ytter, SL Norris, JW Williams D Atkins Jr. J Meerpohl, and H. J. Schuemann, 2011. *Journal of Clinical Epidemiology, 64(*4), 407-415. https://doi.org/10.1016/j.jclinepi.2010.07.017. Copyright 2011 Elsevier Inc.

Study Summaries

Bayar et al conducted a six-week randomized single blind study of amitriptyline, a tricyclic antidepressant, versus a placebo (50 mg daily for the first week, then 100 mg daily for the following 5 weeks).[86] Thirty-seven adult participants with subjective tinnitus were enrolled at the Ear, Nose and Throat Department of Hacettepe University. Participants were randomly allocated to either Group 1 – amitriptyline (n = 20) or Group 2 – placebo (n = 17). The patient reported outcome measure for this study was the American Tinnitus Association (ATA) Questionnaire. Ninety-five percent of the participants in the amitriptyline group and 12% of the participants in the placebo group said that their tinnitus had decreased between pre- and posttest measures. These changes were found to be statistically significant in the amitriptyline group ($p < .05$) but not significant in the placebo group ($p > .05$). We have rated the GRADE of the methodology and level of confidence for this study as low due to the high risk of bias.

Dib et al conducted a 60-day prospective, double-blind, RCT of trazodone, a serotonin uptake inhibitor antidepressant drug, versus a placebo.[87] Eighty-five participants presenting with tinnitus were divided into one of two treatment groups: Group 1 – trazodone (n = 43) and Group 2 – placebo (n = 42). The main outcome measures for this study included an unnamed analog scale score in which tinnitus intensity, level of discomfort, and quality of life impact were rated. Although there was an improvement between pre- and posttest scores, this was not significant in either group. We have determined the GRADE of the methodology and level of confidence to be low due to the high risk of bias.

Roberts et al conducted a 14-day, double-blind placebo-controlled, RCT to assess the loudness (intensity), pitch, and distress imposed by tinnitus in addition to the handicapping effects of the disorder.[82] Vestipitant was investigated for potential effect against chronic tinnitus as a stand-alone treatment and in conjunction with a SSRI, paroxetine. Groups included two intervention groups receiving vestipitant (n=23) and vestipitant with paroxetine (n=24); and a placebo group (n = 23). The main outcome measure for this study were the VAS measurements of tinnitus characteristics, Tinnitus Handicap Inventory (THI) and plasma concentrations of trial drugs.[63] Neither vestipitant alone nor the combination of paroxetine and vestipitant were effective in reducing the perceived loudness of tinnitus in this group of patients, and nor did either regime reduce tinnitus annoyance. However, a statistically significant worsening of tinnitus intensity and distress scores were observed after Vestipitant compared with placebo for the mean data collected over the treatment period. We have rated the GRADE methodological rigor and our level of confidence in these findings as high due to the low risk of bias.

Robinson et al performed a 100-day double-blind RCT of paroxetine, a selective serotonin reuptake inhibitor used to treat depression (n = 57), versus a placebo (n=58).[83] One hundred and fifteen participants were recruited from the University of California Specialty Clinic and randomly assigned into one of two treatment groups: Group 1 – paroxetine and Group 2 – placebo. The patient reported outcome measure used in this study was Tinnitus Handicap Questionnaire (THQ).[36] The results of paroxetine compared to the placebo group were not statistically significant for the THQ score overall. However, Robinson et al reported a significant difference for one item indicating that the tinnitus was less aggravating post-treatment.[83] These results suggest there was little or no benefit for paroxetine over the placebo. We have rated the GRADE methodological rigor and our level of confidence in these findings as high due to the low risk of bias.

Saberi et al investigated the use of fluoxetine (n = 51) vs. fluoxetine plus alprazolam (n = 56) in comparison to a placebo group (n = 51) in a double-blind clinical trial study. Fluoxetine is an SSRI while alprazolam is an anti-anxiety agent.[84] This study was conducted in an academic health center in Iran with 158 participants randomized to three groups. Participants had a six-month

history of non-pulsatile tinnitus. Patient reported outcome measures included THI, VAS, and the TSI in addition to depression and anxiety scales. Results showed both treatment groups significantly improved the severity of tinnitus according to the THI and VAS scores[35], but not for the TSI.[35,58]. The authors concluded that the combination of Fluoxetine + Alprazolam should be considered in the treatment for patients with anxiety and depression problems. We have rated the GRADE methodological rigor and our level of confidence in these findings as high due to the low risk of bias.

Sullivan et al conducted a study on the antidepressant nortriptyline (n = 43) versus a placebo (n = 49).[88] This study was conducted at a university otolaryngology clinic on 92 participants with severe chronic tinnitus: 38 with current major depression and 54 with depressive symptoms and significant tinnitus-related disability. The Tinnitus Disability Measures were used for patient outcome measures in this study. Results showed that nortriptyline was more effective than the placebo for tinnitus related disability and tinnitus loudness. The authors concluded that there is a possibility of nortriptyline having a direct effect on tinnitus independent of depression however it was not statistically significant. We have determined the GRADE of the methodology and level of confidence to be moderate indicating a high risk of bias.

Zoger et al studied sertraline, a SSRI, compared to a placebo in 76 consecutively enrolled participants randomized to a treatment (n = 29) and a placebo group (n = 34).[85] Outcomes were assessed over 16 weeks using TSQ scores and VAS scales as primary and secondary measures.[91] Results indicated a significant reduction of the TSQ score and a significant reduction in tinnitus perception in comparison to the placebo group concluding that sertraline is more effective in the management of tinnitus than the placebo. We have rated the GRADE methodological rigor and our level of confidence in these findings as high due to the low risk of bias.

Effects of Interventions

Amitriptyline

Bayar et al reported pre- and posttest improvement in perception of loudness and reduction of tinnitus intensity.[86] These subjective changes were found to be statistically significant in the amitriptyline group ($p < .05$) but not significant in the placebo group ($p > .05$).

Fluoxetine

Saberi et al evaluated the impact of fluoxetine alone and fluoxetine combined with alprazolam for tinnitus handicap using the THI.[84] They reported a statistically significant improvement on the THI and VAS, but not on the TSI.

Nortriptyline

Sullivan et al evaluated the effect of nortriptyline on tinnitus disability and reported no statistically significant differences pre- and posttreatment or between treatment and placebo groups.[88]

Paroxetine

Robinson et al evaluated the impact of tinnitus handicap by comparing paroxetine to a placebo.[83] They reported no overall statistically significant difference for the THQ, although there was a significant difference for one item in the paroxetine group indicating that the tinnitus was less aggravating post-treatment

Sertraline

Zoger et al evaluated the impact of sertraline on tinnitus severity using the TSQ and VAS.[85] There was a statistically significant difference between pre- and posttest for the treatment group and in comparison, to the placebo group.

Trazodone

Dib et al report no significant differences between treatment and placebo groups for tinnitus intensity using analog scales as an outcome measure. [87]

Vestipitant

Roberts et al reported no statistically significant difference in tinnitus intensity pitch or duration using VAS ratings for vestipitant alone or combined with paroxetine.[82]

DISCUSSION

Tinnitus treatment is a complex chronic disorder, frequently accompanied by depression and/or anxiety.[12] Close alignment of tinnitus and mental health issues has sparked interest in the use of pharmaceutical treatments. The impetus of this study focused on the impact of SSRI, SSRN, and tricyclic antidepressant treatment assessed using PROMs. Several studies have explored the

potential benefits of SSRI, SSRN, and tricyclic antidepressants interventions in the treatment of subjective tinnitus with variable results.[27,63] Baldo et al conducted a systematic review of RCT's investigating the effectiveness of antidepressants in the treatment of tinnitus, including six studies in their review.[27] They concluded that high quality evidence on the positive effect of tricyclic antidepressants was lacking; however, they reported positive effects for a SSRI (paroxetine) from a high-quality study with a low risk of bias.[83] Baldo et al evaluated the outcomes of tinnitus severity and disability and secondary outcomes in tinnitus perception, depression, and global well-being.[27] In contrast, in this review the outcomes were patient perception as assessed by PROM specific to tinnitus perception.

We completed a rapid review of 7 RCTs exploring the use of SNRIs, SSRIs, and tricyclic antidepressants in the treatment of subjective tinnitus. Publications included in this review spanned almost three decades from 1993 to 2021. All the studies were RCT's; however, the studies differed in terms of intervention choices, selection of patient-reported outcome instrument, and statistical analyses. These studies employed a similar design assessing the efficacy of SSRI, SSNR, or tricyclic antidepressants on tinnitus symptoms; however, these studies were heterogenous and varied significantly in terms of number of participants, number of groups, medication dosage, duration of treatment, and PROM utilized for pre/post-treatment assessment.

Studies were selected based on randomization to treatment and placebo groups as well as their inclusion and exclusion criteria. While all included studies did have true randomization, some failed to fully detail the randomization process in the methodology section of their publication. Allocation to treatment groups was mostly concealed; however, side effects may have skewed the randomization in some studies. Moreover, most treatment groups were double blinded at the baseline. All studies demonstrated a pre- and post-intervention evaluation, and follow-up was completed with varying degrees of dropout rates. Outcomes in all cases were assessed via a series of questions to be rated using VAS regarding perception of loudness, pitch, duration, and aggravation or via a patient reported outcome questionnaire (e.g., ATA, THI, THQ, TSQ). Although patient perception and patient outcome measures can be considered subjective, they are widely recognized as the "gold standard" for effectiveness research. Statistical analyses for most of these studies tested the null hypothesis regarding differences between pre- and post-treatment performance withing and between groups. Some studies used a multivariate analysis and included other variables (e.g., performance on depression questionnaire or quality of life).

Participant Characteristics

Table 6 displays a summary of participant characteristics. The number of participants varied across studies from 37 to 115 for Bayar et al and Roberts et al respectively.[82,86] Participant ages varied across studies from 18 years to 80 years. Bayar et al, Roberts et al, Robinson et al, and Zoger et al, included a minimum age of 18 years, Saberi et al included participants aged 20 years, and the youngest participant in the Dib et al study was 45 years of age.[82-87] Sullivan et al failed to report the age range of participants; however, the mean age was 62.1 $\pm$ 8.0 years.[88]

Five studies reported the mean age of participants, whereas two studies did not.[84,87] Three studies reported SDs for age; while five studies reported gender, two did not. [84,88] Most of the studies neglected to report race and ethnic data. Only two of the studies reported race characteristics. [82,83] None of the studies reported a complete dataset of demographic and ethno-racial variables.

Pharmaceutical Interventions

The included studies were diverse in their choices of antidepressants (Table 7). Bayar et al[86] chose amitriptyline as a comparison to a placebo. The dose was 50 mg given once daily for 6 weeks. Dib et al evaluated trazodone's effect on tinnitus in comparison to a placebo.[87] They administered 50 mg once daily for 8.5 weeks. Roberts et al investigated two treatment groups with vestipitant and a combination of vestipitant with paroxetine in comparison to a placebo; however, failed to report the dose or times per day.[82] The treatment and placebo were administered for two weeks. Robinson et al administered paroxetine - 10 mg increasing to 50 mg, once daily for 14 weeks.[83] Saberi et al assessed fluoxetine and a combination of fluoxetine and alprazolam in comparison to the placebo group.[84] Their dose was 40 mg for fluoxetine once daily for 4 weeks. Sullivan et al evaluated pre and posttest performance for dosages of nortriptyline individualized and varying from 50 to 150 ng/ML once daily for 14 weeks.[88] Zoger et al studied the effectiveness of sertraline in management of tinnitus symptoms.[85] The experimental group received 25 mg once daily for one week and 50 mg once daily for the remaining 15 weeks for a total of 16 weeks of treatment.

No two RCT's used the same drug as an intervention. In addition to the variability in the drug choice for treatment, the dosage, administration, and duration across the studies varied; in some cases, researchers failed to report details. For example, Roberts et al failed to report the dose and number of times administered per day administration.[82] Dosage was measured in mg for most studies, varying from 10 mg to 50 mg; however, Sullivan et al reported the dosage in ng/mL.[88] Administration was reported as once daily for most studies, except for Saberi et al, in which administration was reported to be once daily for one week followed by

administration twice daily for three weeks.[84] All studies reported the duration of their intervention, which ranged from 2 -14 days for Roberts et al to 16 weeks or 112 days for Zoger et al.[82,85]

Patient Reported Outcome Measures (PROMS)

PROMs included VAS measures and tinnitus questionnaires. Table 7 shows the PROM and/or VAS used in each study, the experimental and placebo group pre/post-treatment mean, standard deviation, and level of significance. Of the studies included in this review four studies used VAS outcome measures that were not identified or described by Viergever and colleagues.[34,82,86-88]

VAS Measures of Tinnitus Perception

Four studies using VAS measures focused on the characteristics or perception of tinnitus such as severity, pitch, or annoyance. Bayar et al reported use of a questionnaire based on the ATA survey.[86] Their questionnaire was developed from the 1986 Tinnitus Patient Survey reported by the ATA. The Bayar et al study did not use a tinnitus PROM identified by Viergever et al, nor could the ATA Tinnitus Patient Survey be located by the authors.[34,86] Bayar et al did use a subjective rating of intensity but did not identify it as a VAS.[86] They reported a statistically significant difference in subjective ratings for pre- and posttest scores for the treatment group (amitriptyline), but not for the placebo group. Dib et al employed a VAS rating to assess the level of tinnitus discomfort. This rating scale was not referenced and was not formally identified by name but was referred to as an analog scale.[87] These authors reported a statistically significant difference in both groups after treatment (trazadone and placebo).; however, there was not a significant difference between groups. Roberts et al analyzed their results using tinnitus VAS scores for intensity and distress.[82] They reported statistically significantly worsening of perceived loudness and distress for both treatment groups compared to the placebo. Vestipitant and vestipitant with paroxetine seemed to exacerbate tinnitus symptoms. Sullivan et al assessed tinnitus disability using seven dependent variables (i.e., Sheehan Scale score, MPI tinnitus interference scale, disability scale, tinnitus disruption scale and two VAS).[88] They reported a statistically significant decrease in tinnitus disability pre and post treatment (nortriptyline) for the MPI tinnitus interference score, and one VAS scale for internal disability, and tinnitus loudness. Saberi et al used both VAS and a PROM.[84] They reported a statistically significant difference for one of the treatment groups (fluoxetine with alprazolam) between pre- and posttest performance for the VAS for tinnitus severity, and THI and a statistically significant difference between treatment and placebo groups.

Tinnitus Questionnaires

Validated

Three of the seven studies included in this review assessed handicap using validated tinnitus questionnaires identified by Viergever et al; specifically, the THI and the THQ; see Table 4).[34, 82-84] Roberts et al and Saberi et al used the 25-item version of the THI.[63,82,84] Roberts et al reported significant negative findings on the THI for vestipitant and paroxetine compared to the placebo and vestipitant alone.[82] In contrast, Saberi et al reported statistically significant findings on the THI for two treatment groups with fluoxetine and fluoxetine with alprazolam.[84] Robinson et al used the THQ and compared paroxetine to a placebo, reporting nonsignificant findings regarding the handicapping effects of tinnitus except for one item.[36,83] On a single question there was a statistically significant difference indicating the paroxetine group found tinnitus less aggravating than the placebo group.

Others

Bayar et al reportedly used a questionnaire based on the ATA survey; however, the original document could not be located.[86] Zoger et al assessed tinnitus severity using the tinnitus severity questionnaire (TSQ), which was validated by Coles et al 1991.[85,92] This questionnaire was not included in the validated tinnitus instruments identified by Viergever and colleagues.[34]

Zoger et al assessed tinnitus severity using the TSQ and reported statistically significant reductions in TSQ scores and perceived tinnitus loudness between pre and posttest for the treatment group (sertraline), but not the placebo group.[85,92,93]

Implications

VAS instruments are widely used as tools in tinnitus assessment and to monitor patient outcomes. Dib et al reports using an analog scale; however – these authors do not refer to it as a VAS.[87] Roberts et al reported using a VAS instrument for the following tinnitus indicators: loudness, pitch, and distress, reporting statistically significant 'worsening' perception of intensity and distress. In addition to the THI, Saberi et al used the Tinnitus Severity Index (TSI), which was not referenced.[63,84] However, they also used a VAS as an indicator for perceived tinnitus loudness. They reported a statistically significant change for fluoxetine alone and in combination with alprazolam. Sullivan et al reported using a Multidimensional Pain Inventory (MPI) as a tinnitus interference scale and used two VAS as indicators of internal and external disability, which were nonspecific to tinnitus.[88] They reported statistically significant results for self-reported MPI VAS scores for tinnitus interference and internal disability. Zoger et al also reported use of a VAS on tinnitus loudness and annoyance.[85] They reported a statistically significant improvement in perceived loudness. Although researchers have a plethora of validated tinnitus assessment tools to choose from, few of the studies used one of the validated

instruments reported by Viergever and colleagues.[34] More commonly used were VAS ratings as a rapid indicator of tinnitus perception. The choice of a validated tinnitus PROMs to assess the benefits of an intervention such as serotonin and tricyclic antidepressants is of critical importance and should be coupled with tinnitus specific VAS ratings. Prior to planning a clinical trial, clarity regarding the purpose of the study and overall goal of the intervention warrants attention.

Other validated PROMs that could be used to assess the change in perception of the severity of symptoms or the perceived handicap or disability include the Tinnitus Rating Scale, Tinnitus Disability Index, Tinnitus Handicap/Support Scale, Subjective Tinnitus Severity Scale, Tinnitus and Hearing Survey, or Tinnitus Functional Index.[39,42,44,46.49.57] However, if the purpose of the intervention is to decrease the psychological impact of tinnitus, the researcher might consider the Tinnitus Questionnaire/Tinnitus Effects Questionnaire, the Mini Tinnitus Questionnaire, Chronic Tinnitus Acceptance Questionnaire, Tinnitus Acceptance Questionnaire, or the Tinnitus Cognitions Questionnaire.[35,52,64,65] None of these scales were used in the RCT's included in this study.

Study Outcomes

Tinnitus Characteristics

Four studies focused on the characteristics of tinnitus as outcomes (i.e., intensity, severity, discomfort, perceived loudness, or impact on quality of life).[85-88] Three of these studies provided positive evidence of significant benefit for amitriptyline, nortriptyline, and sertraline in symptomatic relief, [85,86,88] whereas one study demonstrated no significant difference or symptomatic relief for trazodone.[87]

Tinnitus Handicap

Three studies focused on handicapping effects of tinnitus by employing the use of the THI and the THQ as outcome measures.[36,58] One study using a traditional tinnitus questionnaire to assess the handicapping effects showed positive benefit for fluoxetine combined with alprazolam, but not fluoxetine alone.[84] Two studies demonstrated no benefit for vestipitant or vestipitant combined with paroxetine and paroxetine alone (.[83,84] This evidence suggests that amitriptyline, nortriptyline, fluoxetine with alprazolam, and sertraline may provide some benefit to tinnitus sufferers[84-86,88] whereas trazodone, vestipitant, vestipitant with paroxetine, or paroxetine alone do not provide relief of tinnitus symptoms.[83,84,87]

Critical Appraisal and Limitations

Social determinants of health include race, ethnicity, gender, socioeconomic status, and education level among other variables.[94] Recognizing the need for comprehensive reporting of sociodemographic variables adds rigor to tinnitus research and enhances applicability for treatment among varying populations. Race/ethnicity was reported by Roberts et al and Robinson and colleagues.[83,84]. Other authors did not report race or ethnicity. Gender was reported in all studies except for Saberi et al and Sullivan and colleagues.[88].[84,88] Socioeconomic status and education level were not reported for participants in any of the studies included in this review.

In a recent publication, Henry et al stated that the purpose of epidemiological studies is to develop knowledge regarding the distribution and determinants of health across populations.[6] These authors suggested that one of the challenges of interpreting tinnitus research is the lack of standardization among studies in terms of definitions and use of assessment tools. Henry and colleagues provide definitions for temporal characteristics of tinnitus, functional and emotional effects of tinnitus, and the perceptual attributes of tinnitus.[6] Awareness of and adherence to these terms and definitions will facilitate comparison of studies across adult populations.

Strength and Level of Evidence

There has been an international push to adopt the GRADE process (Grading of Recommendations, Assessment, Development, and Evaluation) for assigning the strength of evidence and rigor of methodology.[77,78] The JBI Levels and Grades for Recommendations were developed keeping the GRADE approach in mind so they could be easily incorporated and used together.[77-80] Both JBI Levels of study design and grade of recommendations have been used in this study along with the GRADE process for assessing methodology.

Research Designs

All the studies were randomized prospective placebo-controlled studies and were rated as Level 1.c. One was a single-blind study, while the rest were reportedly double-blind.[86] Two were reported as parallel designs,[86,87] one was reported as a crossover study.[82] In the GRADE approach, RCTs are rated as high-quality evidence initially, and are rated down if evidence indicates a high risk of bias. The risk of bias can differ across study designs, due to variability in outcome measures and other factors which may suggest study limitations. These variables impact the JBI grade of recommendation with three studies being rated as a grade A and four

studies rated as grade B (see Table 9). The explanation delineating grade A from grade B is readily explained by the limitations noted for the risk of bias factors and the level of patient involvement in the research outcomes.[77,78]

Risk of Bias Comparisons

Seven RCTs assessing the use of antidepressants as a tinnitus treatment were included in this study. Risk of bias was assessed using the GRADE methodology. The risk of bias ratings are shown in Table 10. Four studies were rated as Low Risk of Bias.[82-85] One study was rated as Moderate Risk of Bias.[88] Two studies were rated as High Risk of Bias.[86, 87]

Heterogeneity

The heterogeneity of study characteristics precluded completion of a meta-analysis. For example, no two studies used the same drug dosage or duration of treatment (see Table 7). Few studies employed widely recognized validated tinnitus PROM measurements (see Table 8). Some studies demonstrated high risk of bias due to lack of detail in reporting patient demographics, intervention variables, blinding the outcome assessment, and statistical analysis of outcome data (Tables 9 and 10). Finally, duration of treatment was relatively short for many studies (see Table 7), and no studies reported carry over or follow-up data regarding long-term benefits (e.g., $\geq$ 6 months).

The studies included in this review failed to report specific tinnitus attributes (e.g., classification, laterality, type, sound, pitch, duration, temporal aspects). Demographic variables (e.g., age, race, ethnicity, marital status, education, income) were not reported in most studies. Details regarding recruitment, informed consent process, randomization, blinding, and treatment regimen were limited. Implementation over a longer duration with 6-month follow-up to assess carryover could be informative.

Many of the studies indicated that antidepressants can be effective for treating tinnitus symptoms; however, some lacked high-quality evidence, and some called into question the use of some antidepressants for treating tinnitus. For example, according to the study by Dib et al, trazodone, an antidepressant drug that modulates serotonin at the central nervous system (CNS) pathways, was not effective in treating tinnitus symptoms.[87] While this study was listed as an RCT, neither the explicit randomization method nor the allocation concealment were provided. Lastly, this study did not report participant dropouts, which contributes to its low-quality rating.

Although the reviewed studies were RCTs, it is important to consider the side effects antidepressants may have had on study participants. Antidepressant side effects are readily apparent in many cases; therefore, it is important to question the true blinding of these studies. Many of the placebos in the reviewed studies were not explicitly defined or described. Additionally, some studies failed to account for confounding factors, such as participants with both depression and tinnitus, which could potentially skew the data. Although some results were found to be statistically significant, evidence regarding the effectiveness of antidepressants in the treatment of tinnitus is sparse, has not been replicated, and is insufficient at this time to draw positive conclusions about efficacy.

Limitations

All efforts have been made to minimize the bias in this study; however, as a rapid review, there are inherent limitations to this study that must be recognized.[42, 43] First, a rapid review is selected when limited resources are available for the project, which was the case in this study. This rapid review was conducted over a 1-year period with four members of the team. Comprehensive systematic reviews typically have a large team collaborating on the project. Secondly, the rapid review was limited by the number of databases used in the study. The databases were limited to those recommended in the Cochrane Rapid Review Interim Guidelines.[42,43] Three databases were used, and grey literature was not included in the review. It is possible that additional studies that may have met the inclusion criteria could have been missed. A third limitation is that a pharmacist, psychiatrist, or a physician who is knowledgeable and experienced in pharmaceutical interventions and treatment using antidepressants was not included in the study team.

Implications for Policy, Practice, and Future Research

Some studies exploring the use of SNRIs, SSRIs, and tricyclic antidepressants in the management of tinnitus reported a statistically significant decrease in in handicapping effects or benefit in symptom severity for tinnitus sufferers in experimental conditions and no benefit for tinnitus sufferers in placebo control groups,[82,84,86,88] while some did not.[83,84,85] Amitriptyline, nortriptyline, fluoxetine with or without alprazolam, and sertraline may provide some benefit to tinnitus sufferers,[84-86,88] whereas trazodone, vestipitant, vestipitant with paroxetine, or paroxetine alone did not demonstrate significant benefit.[82,83,85] However, these conclusions are based on a limited number of heterogeneous studies that implemented different interventions, different data collection methods, a variety of outcome measures, and different statistical analyses. These limitations must be addressed to improve the level and quality of the data reported in future studies.

Clinical Implications

Audiologists play a key role in tinnitus management as they have the ability and knowledge to provide tinnitus counseling, suggest strategies through lifestyle adjustments and audiometrically evaluate the patient's tinnitus severity and pitch. While audiologists cannot prescribe these medications, they must be aware of the current trends of pharmacological treatments for tinnitus and its symptoms. In some cases, a referral to an otologist, neurologist, psychiatrist, or psychologist may be the most appropriate plan of care. Currently, there is no FDA-approved pharmacological treatment for tinnitus and there is insufficient evidence to indicate that antidepressants can effectively treat subjective tinnitus.

Future Research

Currently, there is limited research available on the efficacy of antidepressant treatment with SSRI, SSNI, for tinnitus sufferers. There is a need for additional research to conduct double-blind randomized control trials with drug choice, dose, length of treatment, use of scales/questionnaires, and follow-up clearly specified based on a solid rationale. Future studies may focus on higher doses, longer trials of treatment, and extended periods of follow-up to assess the potential for long-term benefit to chronic tinnitus sufferers who are compromised by co-existing conditions of anxiety and depression. Well-designed RCTs with complete participant datasets including age, gender, race, and ethnicity are critical. Future studies should focus on describing the psychological and functional aspects of tinnitus more fully. Studies reporting the methodology in enough detail to be replicated would help provide high-quality evidence that could be independently verified. did not provide a detailed methodology so that the study could be replicated. Future randomized clinical control trials should adhere to the CONSORT (Consolidated Standards of Reporting Trials) to ensure the highest quality of RCT.[95] An audiologist should be included on the investigative team when participants with hearing related symptoms are the study population. Standardized definitions of terminology should be utilized across studies to reduce the heterogeneity and improve consistency across the literature. A rationale should be provided for the selection of PROMs with a complete description of psychometric properties and a full reference to the publication. Outcome measures aligned with the World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF) should be considered.[96] Many of the tinnitus PROMs are available in multiple languages which would increase the generalizability of the results or create the opportunity for international trials.

CONCLUSIONS

Despite promising results, there remains insufficient rigorous high-quality research evidence to indicate that antidepressants can effectively treat subjective tinnitus at this time. Further research is needed to reduce or eliminate this unremitting problem.

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Appendix A
Search Strategy

Searches run on July 8, 2021; Updated May 18, 2023

Totals:
Cochrane Central: 98
Medline: 102
Embase: 215
Total: 415
Deduplicated total: 320

Embase.com (ELSEVIER)		
1	Tinnitus/de	22,277
2	(tinnit* OR ((ear OR ears OR hear OR hears OR heard OR hearing) near/3 (buzz* OR chirp* OR click* OR hiss* OR puls* OR ring* OR sizzl*))):ti,ab,kw	16,804
3	#1 OR #2	25,782
4	“Antidepressant agent”/de OR “serotonin uptake inhibitor”/exp OR 'tricyclic antidepressant agent'/exp	374,098
5	(antidepress* OR “anti-depress*” OR ssri OR ssris OR snri OR snris OR ssnri OR ssnris OR (Serotonin* near/4 inhibitor*) OR (“5-hydroxytryptamine” near/2 inhibitor*) OR (“5-HT” near/2 inhibitor*) OR (noradrenalin* near/3 inhibitor*) OR (norepinephrine near/3 inhibitor*) OR (dual near/3 inhibitor*) OR (triple near/3 inhibitor*)):ti,ab,kw	136,848
6	(Alaproclate OR amfebutamone OR Amoxapine OR ampreloxetine OR cericlamine OR chlorphentermine OR Citalopram OR Clomipramine OR dapoxetine OR escitalopram OR femoxetine OR Fenfluramine OR Fluoxetine OR Fluvoxamine OR hydroxynefazodone OR hyperforin OR ifoxetine OR indalpine OR litoxetine OR lubazodone OR medifoxamine OR moxifetin OR nefazodone OR nefopam OR nomelidine OR norcitalopram OR Norfenfluramine OR norfluoxetine OR norsertraline OR Olanzapine OR omiloxetine OR Paroxetine OR Sertraline OR tedatioxetine OR Trazodone OR vilazodone OR Vortioxetine OR Zimeldine):ti,ab,kw	62,832
7	(Amitriptyline OR Ammuxetine OR “brompheniramine plus dextromethorphan” OR “carbinoxamine maleate plus dextromethorphan” OR clomipramine OR desvenlafaxine OR deudextromethorphan OR “dextromethorphan plus guaifenesin plus pseudoephedrine” OR dosulepin OR doxepin OR duloxetine OR imipramine OR Levomilnacipran OR liafensine OR Milnacipran OR nefazodone OR sibutramine OR tramadol OR venlafaxine):ti,ab,kw	45,981
8	(Amitifadine OR bicifadine OR brasofensine OR centanafadine OR cocaine OR diclofensine OR indatraline OR methamphetamine OR tesofensine OR toludesvenlafaxine):ti,ab,kw	62,526
9	(“2 hydroxydesipramine” OR “10 hydroxynortriptyline” OR “adinazolam mesilate” OR amineptin OR amineptine OR Amitriptyline OR amitriptylinoxide OR Amoxapine OR butriptyline OR cianopramine OR Clomipramine OR cyclobenzaprine OR danitracen OR demexiptiline OR Desipramine OR desmethyldoxepin OR dibenzepin OR dimetacrin OR dosulepin OR Dothiepin OR Doxepin OR etizolam OR Imipramine OR imipraminoxide OR Iprindole OR Lofepramine OR melitracene OR metapramine OR nitroxazepine OR norclomipramine OR nordoxepin OR nortrimipramine OR Nortriptyline OR noxiptilin OR noxiptiline OR Opipramol OR propizepine OR Protriptyline OR quinupramine OR “s 3344” OR tampramine OR tandamine OR tianeptine OR Trimipramine):ti,ab,kw	33,924

10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	434,121
11	#3 AND #10	1,058
12	('randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab,tt OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab,tt OR compare:ti,tt OR compared:ti,tt OR comparison:ti,tt OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEXT/1 label):ti,ab,tt) OR (((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt) OR 'double blind procedure'/de OR ((parallel NEXT/1 group*):ti,ab,tt) OR crossover:ti,ab,tt OR 'cross over':ti,ab,tt OR (((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt) OR assigned:ti,ab,tt OR allocated:ti,ab,tt OR ((controlled NEAR/8 (study OR design OR trial)):ti,ab,tt) OR volunteer:ti,ab,tt OR volunteers:ti,ab,tt OR 'human experiment'/de OR trial:ti,tt) NOT (((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt) OR ('cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)) OR ('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)) OR ('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)) OR (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt) OR 'random field*':ti,ab,tt OR (('random cluster' NEAR/4 sampl*):ti,ab,tt) OR (review:ab AND review:it NOT trial:ti,tt) OR ('we searched':ab AND (review:ti,tt OR review:it)) OR 'update review':ab OR ((databases NEAR/5 searched):ab) OR ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))	4,935,572
13	#11 AND #12	199
14	#11 AND #12 AND [english]/lim	193

Database:
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to July 07, 2021>

#	Query	Results from 8 Jul 2021
1	Tinnitus/	8,388
2	(tinnit* or ((ear or ears or hear or hears or heard or hearing) adj3 (buzz* or chirp* or click* or hiss* or puls* or ring* or sizzl*))).mp.	14,613
3	1 or 2	14,613
4	Antidepressive Agents/ or Serotonin Uptake Inhibitors/ or "Serotonin and Noradrenaline Reuptake Inhibitors"/ or Antidepressive Agents, Tricyclic/	69,634
5	(antidepress* or anti-depress* or ssri or ssris or snri or snris or ssnri or ssnris or (Serotonin* adj4 inhibitor*) or (5-hydroxytryptamine adj2 inhibitor*) or (5-HT adj2 inhibitor*) or (noradrenalin* adj3 inhibitor*) or (norepinephrine adj3 inhibitor*) or (dual adj3 inhibitor*) or (triple adj3 inhibitor*)).mp.	121,691
6	(Alaproclate or amfebutamone or Amoxapine or ampreloxetine or cericlamine or chlorphentermine or Citalopram or Clomipramine or dapoxetine or escitalopram or femoxetine or Fenfluramine or Fluoxetine or Fluvoxamine or hydroxynefazodone or hyperforin or ifoxetine or indalpine or litoxetine or lubazodone or medifoxamine or moxifetin or nefazodone or nefopam or nomelidine or norcitalopram or Norfenfluramine or norfluoxetine or norsertraline or Olanzapine or omiloxetine or Paroxetine or Sertraline or tedatioxetine or Trazodone or vilazodone or Vortioxetine or Zimeldine).mp.	51,001
7	(Amitriptyline or Ammuxetine or brompheniramine plus dextromethorphan or carbinoxamine maleate plus dextromethorphan or clomipramine or desvenlafaxine or deudextromethorphan or dextromethorphan plus guaifenesin plus pseudoephedrine or dosulepin or doxepin or duloxetine or imipramine or Levomilnacipran or liafensine or Milnacipran or nefazodone or sibutramine or tramadol or venlafaxine).mp.	39,446
8	(Amitifadine or bicifadine or brasofensine or centanafadine or cocaine or diclofensine or indatraline or methamphetamine or tesofensine or toludesvenlafaxine).mp.	56,558
9	(2 hydroxydesipramine or 10 hydroxynortriptyline or adinazolam mesilate or amineptin or amineptine or Amitriptyline or amitriptylinoxide or Amoxapine or butriptyline or cianopramine or Clomipramine or cyclobenzaprine or danitracen or demexiptiline or Desipramine or desmethyldoxepin or dibenzepin or dimetacrin or dosulepin or Dothiepin or Doxepin or etizolam or Imipramine or imipraminoxide or Iprindole or Lofepramine or melitracene or metapramine or nitroxazepine or norclomipramine or nordoxepin or nortrimipramine or Nortriptyline or noxiptilin or noxiptiline or Opipramol or propizepine or Protriptyline or quinupramine or s 3344 or tampramine or tandamine or tianeptine or Trimipramine).mp.	34,526
10	4 or 5 or 6 or 7 or 8 or 9	219,860
11	3 and 10	162
12	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)	4,394,822
13	11 and 12	99
14	limit 13 to english language	92

Cochrane Central Register of Controlled Trials (EBSCO)		
1	MH Tinnitus	108
2	(tinnit* OR ((ear OR ears OR hear OR hears OR heard OR hearing) N2 (buzz* OR chirp* OR click* OR hiss* OR puls* OR ring* OR sizzl*))	2,739
3	1 OR 2	2,739
4	MH Antidepressive Agents OR MH Serotonin Uptake Inhibitors OR MH “Serotonin and Noradrenaline Reuptake Inhibitors” OR MH Antidepressive Agents, Tricyclic	510
5	antidepress* OR anti-depress* OR ssri OR ssris OR snri OR snris OR ssnri OR ssnris OR (Serotonin* N3 inhibitor*) OR (5-hydroxytryptamine N1 inhibitor*) OR (5-HT N1 inhibitor*) OR (noradrenalin* N2 inhibitor*) OR (norepinephrine N2 inhibitor*) OR (dual N2 inhibitor*) OR (triple N2 inhibitor*)	22,957

6	Alaproclate OR amfebutamone OR Amoxapine OR ampreloxetine OR cericlamine OR chlorphentermine OR Citalopram OR Clomipramine OR dapoxetine OR escitalopram OR femoxetine OR Fenfluramine OR Fluoxetine OR Fluvoxamine OR hydroxynefazodone OR hyperforin OR ifoxetine OR indalpine OR litoxetine OR lubazodone OR medifoxamine OR moxifetin OR nefazodone OR nefopam OR nomelidine OR norcitalopram OR Norfenfluramine OR norfluoxetine OR norsertraline OR Olanzapine OR omiloxetine OR Paroxetine OR Sertraline OR tedatioxetine OR Trazodone OR vilazodone OR Vortioxetine OR Zimeldine	20,175
7	Amitriptyline OR Ammuxetine OR “brompheniramine plus dextromethorphan” OR “carbinoxamine maleate plus dextromethorphan” OR clomipramine OR desvenlafaxine OR deudextromethorphan OR “dextromethorphan plus guaifenesin plus pseudoephedrine” OR dosulepin OR doxepin OR duloxetine OR imipramine OR Levomilnacipran OR liafensine OR Milnacipran OR nefazodone OR sibutramine OR tramadol OR venlafaxine	14,686
8	Amitifadine OR bicifadine OR brasofensine OR centanafadine OR cocaine OR diclofensine OR indatraline OR methamphetamine OR tesofensine OR toludesvenlafaxine	5,094
9	“2 hydroxydesipramine” OR “10 hydroxynortriptyline” OR “adinazolam mesylate” OR amineptin OR amineptine OR Amitriptyline OR amitriptylinoxide OR Amoxapine OR butriptyline OR cianopramine OR Clomipramine OR cyclobenzaprine OR danitracen OR demexiptiline OR Desipramine OR desmethyldoxepin OR dibenzepin OR dimetacrin OR dosulepin OR Dothiepin OR Doxepin OR etizolam OR Imipramine OR imipraminoxide OR Iprindole OR Lofepramine OR melitracene OR metapramine OR nitroxazepine OR norclomipramine OR nordoxepin OR nortrimipramine OR Nortriptyline OR noxiptilin OR noxiptiline OR Opipramol OR propizepine OR Protriptyline OR quinupramine OR “s 3344” OR tampramine OR tandamine OR tianeptine OR Trimipramine	8,305
10	4 OR 5 OR 6 OR 7 OR 8 OR 9	48,769
11	3 AND 10	90

Appendix B

Data Extraction Form

General Information

Date form completed (dd/mm/yyyy)	
Name person extracting data	
Title of Article	
Authors	
Year	
Publication Journal (where was it published?)	
Reference Citation (APA)	

Study Eligibility

Eligibility Questions	Eligibility criteria	Yes - Eligibility criteria met	No- Eligibility criteria not met
Is the publication available in English?	English only	Include	Exclude
Is the publication in a peer-reviewed journal?	Peer-reviewed	Include	Exclude
Is this study a randomized controlled trial?	Randomized Controlled Trial	Include	Exclude
Does the study contain tricyclic antidepressants & SSRI?	Both	Include	Exclude
Patient reported outcome?	Tinnitus Report	Include	Exclude
Patient Age	Adult	Include	Exclude

Study Setting

	Detail Specifics
Setting (location & social context)	
Study inclusion criteria?	
Study exclusion criteria	
Ethics statement	
Method of Recruitment	

Participants

	Group 1a Treatment	Group 1b Treatment	Group 2 Placebo
Participants (n=xx)			
Age Range, SD, Mean			
Education			
Occupation			
Income			
Sex			
Race/Ethnicity			
Hearing Loss			

History of Depression			
Severity of Tinnitus			
Reactivity of Tinnitus			
Duration of Tinnitus (Constant/intermittent)			
Intensity of Tinnitus			
Unilateral or Bilateral			
Comorbidities			
Other			

Intervention

	Group 1a -Treatment	**Group 1b -Treatment**	**Group 2 - Placebo**
What was the intervention?			
What was the treatment regimen?			
What was the dose of the treatment? (Mg)			
How many times per day was the intervention administered?			
How long was the duration of the treatment period?			

Outcomes

Add more rows as needed for outcomes	**Group 1a -Experimental**	**Group 1b -Experimental**	**Group 2 - Placebo**
What was the pre- outcome measure?			
What were post outcome measure results?			
Mean Results			
Standard Deviation			
Confidence Interval			
Level of Significance			
What was the pre- outcome measure?			
What were post outcome measure results?			
Mean Results			
Standard Deviation			
Confidence Interval			
Level of Significance			

Risk of Bias Assessment

Domain	Risk of Bias	Support for judgement
Random sequence generation	Low/High/Unclear	
Allocation concealment	Low/High/Unclear	
Blinding of participants & personnel	Low/High/Unclear	
Blinding of outcome assessment	Low/High/Unclear	
Incomplete outcome data	Low/High/Unclear	
Overall risk of bias	Low/High/Unclear	
Other bias: specify	Low/High/Unclear	

Level, Quality, and Strength

Reference	Rating	Support for judgement
JBI 2014b (Level)	1c	**Randomized prospective placebo-controlled trial**
JBI 2014a (Recommendation strength)	Grade A Strong/Grade B Weak	
GRADE	High/Moderate/Low/Very Low	
Comments		

Note: Adapted from "Assessing Risk in a Randomized Trial" By J. P. T. Higgins, J. Savovic, M. J. Page, R. G. Elbers, and J. A. C. Sterne in the "*Cochrane Handbook for Systematic Reviews of Interventions*", version 6.3, 2022. J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, and V. A. Welch (Editors). https://www.training.cochrane.org/handbook Copyright 2023 Cochrane Collaboration.

Appendix C

JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer_____ Date_____

Author_____Year_____

Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment	□	□	□	□
2.	Was allocation to treatment groups concealed?	□	□	□	□
3.	Were treatment groups similar at the baseline?	□	□	□	□
4.	Were participants blind to treatment assignment?	□	□	□	□
5.	Were those delivering treatment blind to treatment assignment?	□	□	□	□
6.	Were outcomes assessors blind to treatment assignment?	□	□	□	□
7.	Were treatment groups treated identically other than the intervention of interest?	□	□	□	□
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	□	□	□	□
9.	Were participants analyzed in the groups to which they were randomized?	□	□	□	□
10.	Were outcomes measured in the same way for treatment groups?	□	□	□	□
11.	Were outcomes measured in a reliable way?	□	□	□	□
12.	Was appropriate statistical analysis used?	□	□	□	□
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments: (Including reason for exclusion)

Note. Adapted from "Critical Appraisal Checklist for Randomized Controlled Trials" by Johanna Briggs Institute. 2022, https://jbi.global/critical-appraisal-tools.

GRADE Scoring System (Grading quality of evidence and strength of recommendations) System		
Full Citation:		
Date/Reviewer:		
Directions: Circle the value associated with each indicator. Total the rating at the bottom of the page.		
Type of Evidence		
Initial score based on type of evidence	+4	RCTs/SR of RCTs +/- other types of evidence
	+2	Observational evidence (e.g., cohort, case-control)
Quality		
Based on	Blinding and allocation process *(lack of clearly randomized allocation sequence, lack of blinding, lack of allocation concealment)*	
	Follow-up and withdrawals *(failure to adhere to intention-to-treat analysis, trial is cut short)*	
	Sparse data *(large losses to follow-up)*	
	Other methodological concerns *(e.g., incomplete reporting, subjective outcomes)*	
Score	0	No problems
	-1	Problem with 1 element
	-2	Problems with 2 elements
	-3	Problems with 3 or more elements
Consistency		
Based on	Degree of consistency of effect between or within studies	
Score	+1	Evidence of dose response across or within studies (or inconsistency across studies is explained by a dose response); also 1 point added if adjustment for confounders would have increased the effect size
	0	All/most studies show similar results
	-1	Lack of agreement between studies (e.g., statistical heterogeneity between RCTs, conflicting results)
Directness		
Based on	The generalizability of population and outcomes from each study to our population of interest	
Score	0	Population and outcomes broadly generalizable
	-1	Problem with 1 element
	-2	Problem with 2 or more elements
Effect Size		
Based on	The reported OR/RR/HR for comparison	
Score	0	Not all effect sizes >2 or <0.5 and significant; or if OR/RR/HR not significant
	+1	Effect size >2 or <0.5 for all studies/meta-analyzes included in comparison and significant
	+2	Effect size >5 or <0.2 for all studies/meta-analyses included in comparison and significant

Total		
GRADE	+4	High
	+3	Moderate
	+2	Low
	+1	Very low
Recommendation		
Strength	Strong for using	
	Weak for using	
	Strong against using	
	Weak against using	

Note: Adapted from "Understanding GRADE: An Introduction," by G. Goldet and J. Howick, 2013, *Journal of Evidence-based Medicine, 6*(1), p. 52. https://doi.org/10.1111/jebm.12018 Copyright 1999-2023 John Wiley & Sons, Inc.