Clinical Pharmacology of Tinnitus: Design and Evaluation

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Abstract

Tinnitus – the perception of phantom sound – is estimated to seriously affect the quality of life of about 3% of the entire world population, making it an attractive target for pharmacotherapy. However, none of the so far conducted clinical trials with the use of pharmacological substances could be called a thrilling success. There are multiple reasons for this, which are discussed in this chapter. Moreover, a comprehensive overview of factors that should be taken under consideration when designing clinical pharmacological study for tinnitus is presented in an anticipation to help design trials producing meaningful clinical data and identifying clinically relevant substances effective in tinnitus treatment.

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Purpose and Rationale

The purpose of this chapter was to review and to present contemporary information regarding the design of clinical trials for tinnitus. In addition, the aim was to distinguish the two main different directions that are being developed in tinnitus pharmacology, namely, the treatment of tinnitus percept and the treatment of tinnitus-related distress. Although the American Academy of Otolaryngology-Head and Neck Surgery recommended *against* the contemporary medial therapy of tinnitus (antidepressants, anticonvulsants, anxiolytics, or intratympanic medications (Tunkel et al. 2014)), the need to explore pharmacological intervention remains. The method: data from clinical studies that were performed between 2006 and 2016 and were analyzed in a recent systematic review (Hall et al. 2015, 2016) were included in the present study. Sixty-five studies that used pharmacological approach for tinnitus treatment were extracted. In these particular 65 studies, the pharmacological substances used, the outcome domains, and the outcome measure

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instruments were analyzed, presented, and discussed.

Tinnitus

Tinnitus Characteristics

Tinnitus is a *symptom* of various diseases that manifests itself as a sound percept without an external source (Jastreboff 1990). *Objective tinnitus* can be heard by other persons (often only with an aid of amplification) because it is caused by internal bodily noises (e.g., pulse that could be heard if the diseased blood vessel is located in the proximity of the ear). *Subjective tinnitus* is a phantom sound heard exclusively by the affected person. Illnesses capable of inducing subjective tinnitus include, but are not limited to, the head and neck injuries and all diseases that induce hearing impairment (middle ear inflammation, meningitis, otosclerosis, Meniere's disease, presbyacusis, ototoxicity, noise-induced hearing loss, vestibular schwannomas, meningioma, intracranial pressure, atherosclerosis, diabetes, and other diseases) (Baguley et al. 2013). The grade of hearing loss has been suggested to correlate with the grade of tinnitus impairment (Mazurek et al. 2010). Recently, cochlear synaptopathies that cause *hidden hearing loss* are being considered as a possible reason underlying tinnitus (Guest et al. 2017; Liberman and Kujawa 2017). Unfortunately, in many cases, the direct cause of tinnitus remains unknown making causative therapy approaches difficult.

Box 1
Tinnitus often associates with hearing loss (Henry et al. 2014), but pharmacological intervention for hearing loss has a very small therapeutic time window, as the auditory hair cells are postmitotic, and in mammals, they are unable to regenerate (Seymour and Pereira 2015). Successful attempts of therapy against noise-induced hearing loss included using steroids, magnesium, coenzyme Q10, or D-methionine (Sakat et al. 2016). Importantly, all of the clinical studies were either using protective approach (prior to noise exposure) or an intervention immediately after noise exposure. Non-pharmacological approach of treating hearing loss (hearing aids, implantable hearing aids, and cochlear implants) is effective not only in restoring the ability to hear but also in reducing tinnitus-related distress (Olze et al. 2011; Ramos Macias et al. 2015).

There are several clinical terms used in the descriptive diagnostics of tinnitus that relate to the duration or to the severity of tinnitus – the most common ones are presented in Table 1.

Regardless of the specific cause of tinnitus, the common denominator for all types of tinnitus is the *activation of auditory cortex under acoustically sterile conditions*. This activation results from the stimulation of auditory pathway that may take place in various parts of auditory circuits, starting from the periphery and ending in the auditory cortex.

Influence of Tinnitus on Nonauditory Systems

In addition to activating the auditory system, processed acoustic signals stimulate also other structures. A good example is the reaction of a central nervous system to nonverbal acoustic stimuli, such as music (Koelsch 2014). The sound of music activates not only the auditory but also the somatosensory, autonomic, vestibular, and limbic systems (Fig. 1).

Likewise, simple auditory stimuli such as the sound of chimes or a beep were shown to stimulate several structures in the central nervous system in addition to the auditory brain (Georgiewa et al. 2016). Interestingly, neuroimaging of tinnitus patients determined an increased cortical activity in the auditory brain of tinnitus patients

Table 1 Various types of tinnitus used in clinical descriptions.

Type of tinnitus		Remarks
Constant	Intermittent	Refers to the presence of tinnitus (continuous and noncontinuous)
Distressing (decompensated)	Non-distressing (compensated)	Refers to the psychological effect of tinnitus on the affected person
Acute	Chronic	Refers to the duration of tinnitus, where tinnitus is considered acute when occurring no longer than 3 months and chronic when longer than 3 months. In some countries or societies, the duration of tinnitus is regarded as chronic when longer than 6 or even 12 months
Peripheral	Central	Refers to the anatomical place (but not the cause!) of tinnitus origin, where "peripheral tinnitus" is considered to originate from cochlea and "central tinnitus" from anywhere between the cochlear nucleus and auditory cortex
With mental comorbidities	Without mental comorbidities	Refers to comorbid mental conditions such as anxiety and depression of phobias
Unilateral	Bilateral	Refers to the affected side

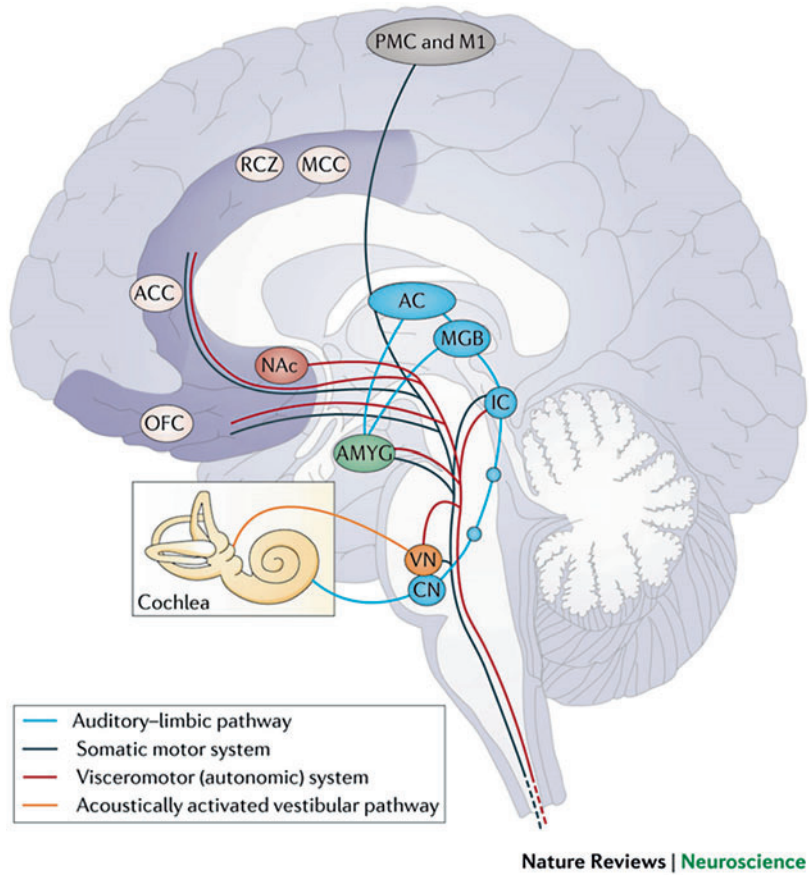

Fig. 1 The main pathways underlying autonomic and muscular responses to music. The auditory cortex (AC) also projects to the orbitofrontal cortex (OFC) and the cingulate cortex (projections not shown). Moreover, the amygdala (AMYG), OFC, and cingulate cortex send numerous projections to the hypothalamus (not shown) and thus also exert influence on the endocrine system, including the neuroendocrine motor system. *ACC*, anterior cingulate cortex; *CN*, cochlear nuclei; *IC*, inferior colliculus; *M1*, primary motor cortex; *MCC*, middle cingulate cortex; *MGB*, medial geniculate body; *NAc*, nucleus accumbens; *PMC*, premotor cortex; *RCZ*, rostral cingulate zone; *VN*, vestibular nuclei (Reprinted with permission from Springer Nature from (Koelsch 2014))

(Arnold et al. 1996) as well as different reactions to the sound of the nonauditory areas (Georgiewa et al. 2016) suggesting *altered neuronal connectivity in the tinnitus brain* (Leaver et al. 2016).

Box 2
Acoustic signals induce auditory and non-auditory brain stimulation.

Acoustic stimulation can be viewed as an auditory signal that induces neuronal auditory and nonauditory reactions, of which the evoked emotional reactions can be of positive or negative nature. In addition, sound may occasionally induce responses from the autonomic nervous system. In people *suffering* from tinnitus, the phantom sound perceived by the auditory system comes to be *negatively labeled* in terms of emotional load. Because of this, the *sound of tinnitus becomes a stressor* for the affected person. As such, it activates hypothalamus-pituitary-adrenal (HPA) axis inducing the release of stress hormones and provoking tinnitus-specific stress reactions that are referred to as *tinnitus-induced distress*. These reactions include but are not limited to nervousness, insomnia, problems with concentrations, and other secondary and tertiary responses to stress. Some of the reactions may induce the development or an aggravation of already existing mental conditions, such as anxiety (Pattyn et al. 2016) or depressive symptoms (Hoare et al. 2011). In turn, these conditions may worsen tinnitus percept and tinnitus-related distress (Fig. 2).

Multidisciplinary Aspects of Tinnitus

Tinnitus is a sensation of a sound and as such it often takes the tinnitus sufferers to the office of audiologist. However, the profession of audiologist as a health-care professional is known only in some countries (e.g., the United Kingdom, Sweden, the USA, Canada, Australia, Malaysia, India, or Portugal), whereas in other countries (e.g., Germany, Austria, Poland, France, or Czech Republic), people experiencing tinnitus or other hearing problems are examined by the ORL specialists and then optionally referred to other medical professionals. Persons suffering from a long-term (chronic) tinnitus, who in addition to perceiving a phantom sound react to it in a negative emotional way, are often referred to clinical psychologists. In addition, patients with bothersome tinnitus who have comorbid metal conditions may be attended to by psychiatrist, while patients with so-called somatosensoric tinnitus (Haider et al. 2017) will be attended to also by a physiotherapist. As a result, numerous health professionals deal with tinnitus patients: general practitioners, ORL specialists, audiologists, psychologists, psychiatrists, cardiologists, neurologists, physical therapists, and dentists (Tunkel et al. 2014). Because of distinct education and partitioned competences, although focused on tinnitus treatment, these specialists will have different clinical expertise on the subject. During the design of clinical study, one needs to take this under consideration when involving health practitioners.

Contemporary Studies Involving Pharmacological Interventions for Tinnitus

Recent systematic review that analyzed outcome domains and instruments used to measure outcome of clinical trials for tinnitus has identified 228 trials meeting the review criteria and performed between the years 2006 and 2016 (Hall et al. 2016). Of these trials, 65 involved pharmacological agents. The drugs could be generally split into two categories (for the precise listing, see Table 2):

- **Targeting the auditory pathway** (substances aiming at the auditory pathway glutamate receptors, substances blocking sodium or potassium pumps)
- **Targeting the tinnitus-related distress and/or comorbid disorders** (substances aiming at serotonin uptake, dopamine receptors, antagonists at the μ-opioid receptor, etc.)

Only about a 40% of the drugs used in tinnitus-related clinical trials aim at the tinnitus percept via targeting the auditory pathway, while the remaining 60% are directed against the comorbid diseases and/or tinnitus-related distress (Fig. 3).

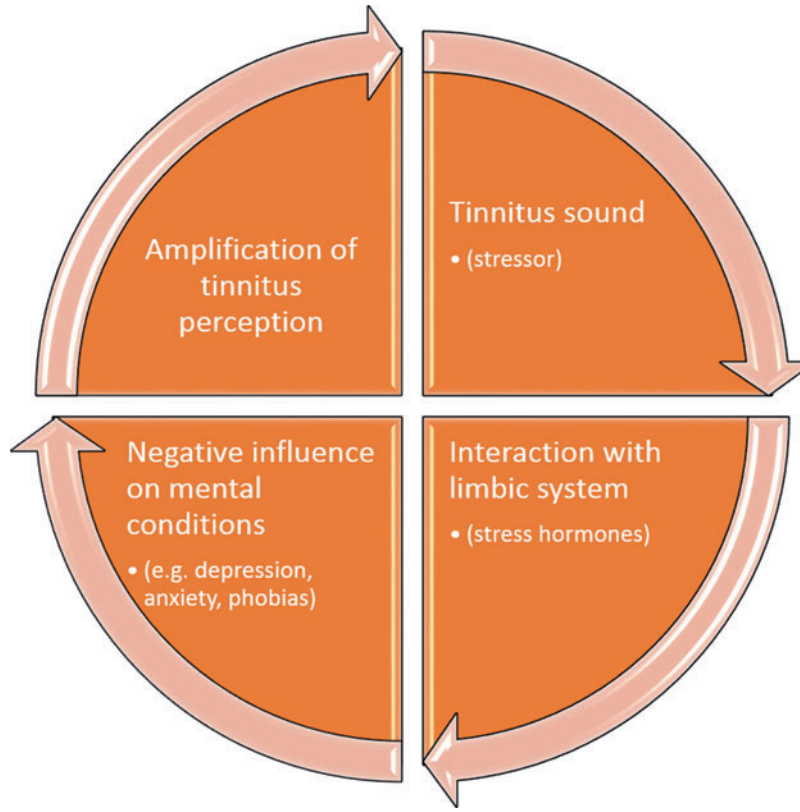

Fig. 2 Tinnitus as stressor that amplifies other mental conditions as well as its own related distress

The Design of Pharmacological Intervention for Tinnitus

The design of clinical intervention for tinnitus depends on several factors, such as sample homogeneity, choice of pharmacological target, or effect measured (Table 3). Sample homogeneity could be achieved by choosing one subtype of tinnitus in an age- and gender-matched group of patients. However, despite the attempts to standardize tinnitus diagnostic and classification procedure (Crummer and Hassan 2004; Langguth et al. 2011), there is still lack of internationally acknowledged and scientifically and clinically verified tinnitus subtypes.

Pharmacological trials for tinnitus use standard trial design (parallel, crossover, blinding, etc.). However, several crucial factors need to be taken under consideration when designing tinnitus trial:

1. That tinnitus is a subjective symptom
2. That the acoustic properties of tinnitus are measured with subjective methods
3. That perceiving tinnitus must not mean suffering from tinnitus
4. That all the accepted means to measure the degree of tinnitus-induced distress (or degree of suffer) are subjective
5. That targeting the disease, which presumably caused tinnitus, must not necessarily target tinnitus itself

Three further issues are of vast importance when designing the pharmacological trial for tinnitus:

Target Selection

General target selection discriminates between tinnitus percept and tinnitus-induced distress. One-third of the previous studies targeted tinnitus-induced distress, and roughly equal number

Table 2 Drugs used in the analyzed pharmacological trials in the period between 2006 and 2016[a]

Drug	Number of trials	Mode of action
Acamprosate	1	The mechanism of action of acamprosate is unknown and controversial. Targets NMDA
Alprazolam	2	A potent, short-acting anxiolytic of the benzodiazepine class – a minor tranquilizer
AM-101	6	Esketamine hydrochloride, an N-methyl-D-aspartate (NMDA) receptor antagonist
Atorvastatin	1	Atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in the liver tissue that plays a key role in the production of cholesterol in the body
AUT00063	1	Small-molecule modulator of Kv3 potassium channels
Betahistine dihydrochloride	2	Betahistine has a very strong affinity as an antagonist for histamine H_3 receptors and a weak affinity as an agonist for histamine H_1 receptors
BGG492A	1	Competitive antagonist of the AMPA and kainate receptors
Cannabis	1	Cannabinoid is one of a class of diverse chemical compounds that acts on cannabinoid receptors in cells that alter neurotransmitter release in the brain
Carbamazepine	1	Carbamazepine is a blocker of voltage-gated sodium channels that binds to activated voltage-gated sodium channels, preventing repetitive and sustained firing of an action potential
Caroverine	2	Acts as an N-type calcium channel blocker, competitive AMPA receptor antagonist, and noncompetitive NMDA receptor antagonist (Arnold et al. 1996). It also has potent antioxidant effects (Baguley et al. 2013)
Cilostazol	1	Cilostazol is a phosphodiesterase inhibitor with therapeutic focus on cyclic adenosine monophosphate (cAMP)
Cinnarizine	1	Cinnarizine is an antihistamine and a calcium channel blocker; it is also known to promote cerebral blood flow
Cyclobenzaprine	1	Cyclobenzaprine is a muscle relaxer medication used to relieve skeletal muscle spasms and associated pain in acute musculoskeletal conditions
D-cycloserine	1	Is an antibiotic used to treat tuberculosis and target the glycine-binding site of N-methyl-D-aspartate (NMDA) receptors in humans
Deanxit	1	Deanxit is made up of two components: **flupentixol** 0.5 mg (or flupenthixol, an antipsychotic) and **melitracen** 10 mg (a tricyclic antidepressant)
Dexamethasone	1	Corticosteroid medication
Escitalopram	1	An antidepressant of the selective serotonin reuptake inhibitor (SSRI) class
Fluoxetine	1	An antidepressant of the selective serotonin reuptake inhibitor (SSRI) class
Fluvoxamine	1	Selective serotonin reuptake inhibitor (SSRI) and σ_1 receptor agonist
Gabapentin	5	Mimics the chemical structure of the neurotransmitter gamma-aminobutyric acid (GABA)
Ginkgo biloba	3	A possible treatment for dementia and Alzheimer's disease, possibly improving cerebral circulation
Hangekobokuto	2	A lignan isolated from the bark, seed cones, and leaves of trees belonging to the genus *Magnolia*. Used as analgesic and to treat anxiety and mood disorders

(*continued*)

Table 2 (continued)

Drug	Number of trials	Mode of action
Lidocaine	2	Lidocaine alters signal conduction in neurons by blocking the fast voltage-gated Na+ channels in the neuronal cell membrane responsible for signal propagation
Lyophilized powder of enzymolyzed honeybee larvae	1	Unknown
Magnesium	1	NMDA antagonist
Melatonin	4	N-Acetyl-5-methoxy tryptamine: a hormone that is produced by the pineal gland in animals and regulates sleep and wakefulness
Memantine	1	NMDA antagonist
Naltrexone	1	Naltrexone and its active metabolite 6β-naltrexol are antagonists at the μ-opioid receptor
Neramexane	6	A drug related to memantine (Arnold et al. 1996), which acts as an NMDA antagonist (Baguley et al. 2013) and has neuroprotective effects
Paroxetine	1	An antidepressant of the selective serotonin reuptake inhibitor (SSRI) class
Piribedil	1	D_2 and D_3 receptor agonist
Pramipexole	1	Dopamine agonist
Prednisolone	1	Steroid medication
Q10	2	Antioxidant, part of mitochondrial respiratory chain
Simvastatin	1	Simvastatin inhibits 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase
Trazodone	1	Serotonin antagonist and reuptake inhibitor (SARI) class
Vardenafil	1	PDE5 inhibitor
Vestipitant	2	Selective antagonist for the NK1 receptor (substance P receptor)
Zinc	1	NMDA antagonist

[a]Based on the supplementary data from (Hall et al. 2016)

targeted tinnitus percept (Fig. 4). The rest of the studies either have not officially stated their target or targeted other domains, such as quality of life or comorbid symptoms. In addition, the molecular identity of the target needs to be specified. Few genetic studies that were performed to identify possible candidate genes associated with tinnitus rather than doing just that pointed the need of better phenotyping or subtyping of tinnitus (Vona et al. 2017).

Sample Selection (Inclusion and Exclusion Criteria and Sample Size)

Stringent inclusion and exclusion criteria supported by up-to-date diagnostic criteria should be set to assure sample homogeneity. The sample should be composed based on gender distribution, age, duration of tinnitus (in the analyzed trials, duration of tinnitus ranged from less than 3 months up to a year; 19 trials either did not report or reported ambiguously the tinnitus duration (Hall et al. 2016)), possible cause of tinnitus, the degree of tinnitus-induced distress (39 of 65 trials in the past did not report this (Hall et al. 2015)), and the degree of hearing loss. In addition, comorbid mental conditions and other conditions must be taken under account. The method for calculation of sample size should be stated (in the trials analyzed, the sample size varied from 10 to 821 subjects, and the method of calculation was stated only in 9 of 65 trials (Hall et al. 2016)).

Choice of Methods to Measure the Trial Outcome

In the pharmacological tinnitus trials analyzed in the past 10 years (2006–2016), various outcome

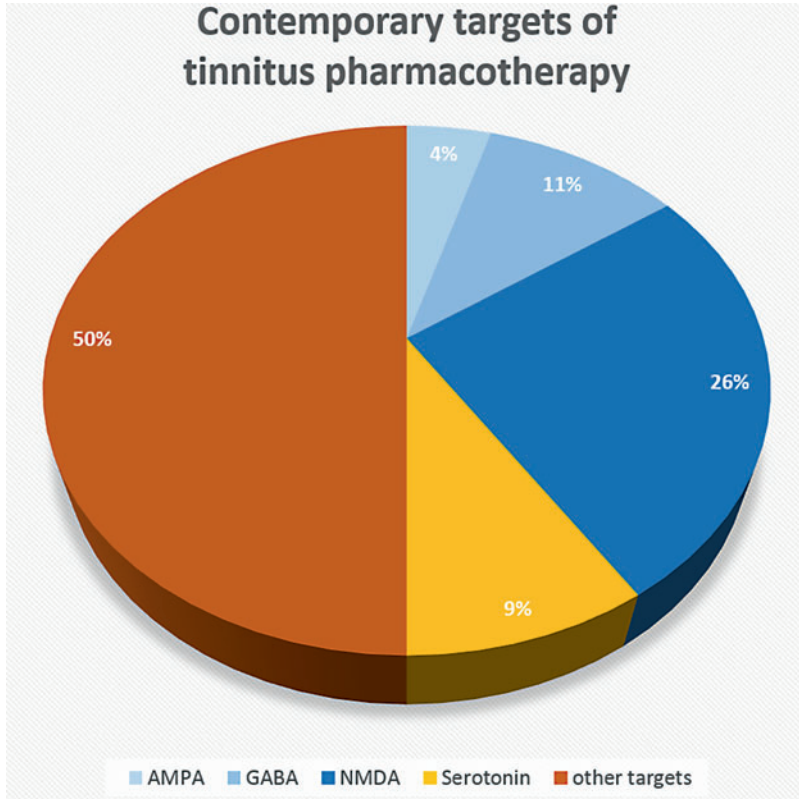

Fig. 3 Targets of pharmacotherapy (2006–2016)

Table 3 Factors particularly important during the design of clinical trial for tinnitus

Sample homogeneity	Age
	Gender
	Duration of tinnitus
	Presence of tinnitus
	Cause of tinnitus (known/ unknown)
	In case of known cause – central or peripheral origin
	Comorbid conditions
	Equal degree of psychological effect of tinnitus on the affected individual
Choice of pharmacological target	The cause of tinnitus
	Tinnitus-related distress
	Comorbid conditions
Observed effect	Choice of outcome measures (domains measured, tools used for measurement)
	Clinical significance of the measured changes
	Time course of the treatment
	Time course of the follow-up

measures were used (Hall et al. 2016) and included psychometric questionnaires, numerical scales, and audiometric measurements (Fig. 5). The psychometric questionnaires were predominantly used when targeting the tinnitus-induced distress, whereas audiometric methods and numerical scales were used when the primary target consisted of tinnitus percept (Meikle et al. 2007).

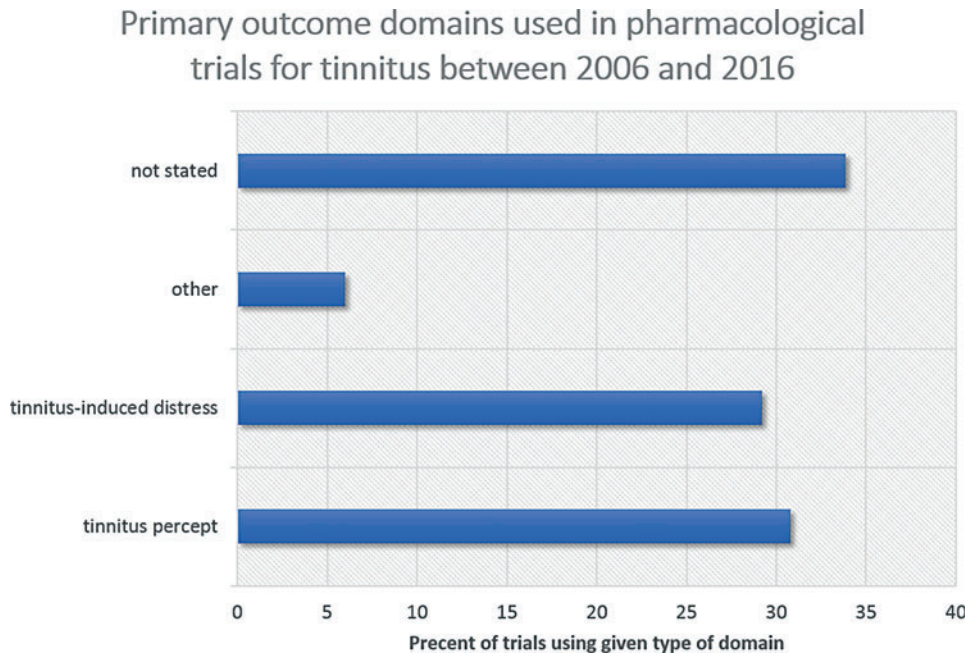

Fig. 4 Primary outcome domains used in the past trials (2006–2016)-based on supplementary data from (Hall et al. 2016).

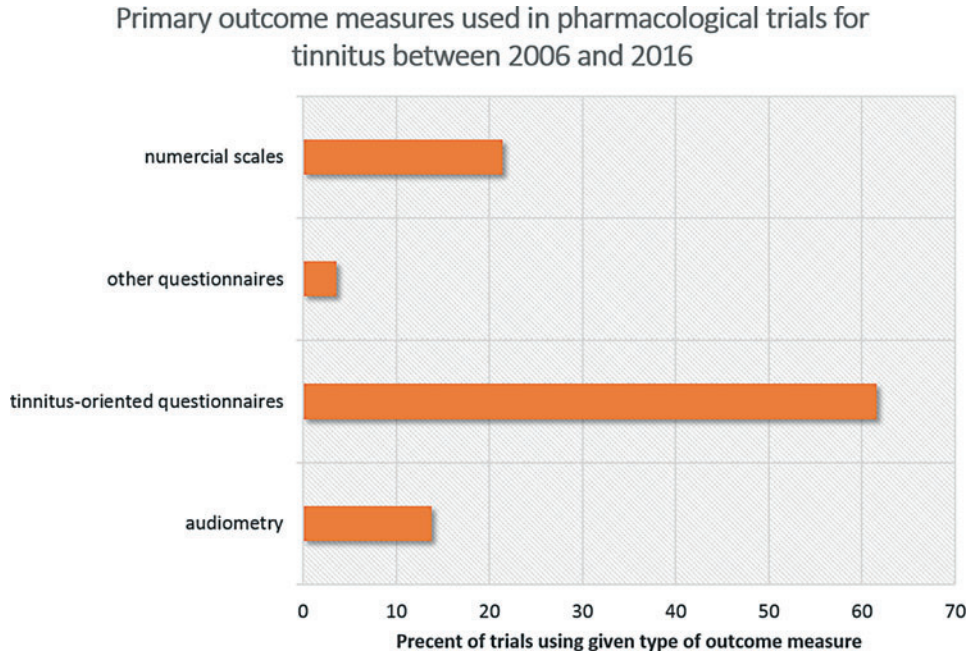

Fig. 5 Primary outcome measures used in the past trials (2006–2016)-based on supplementary data from (Hall et al. 2016).

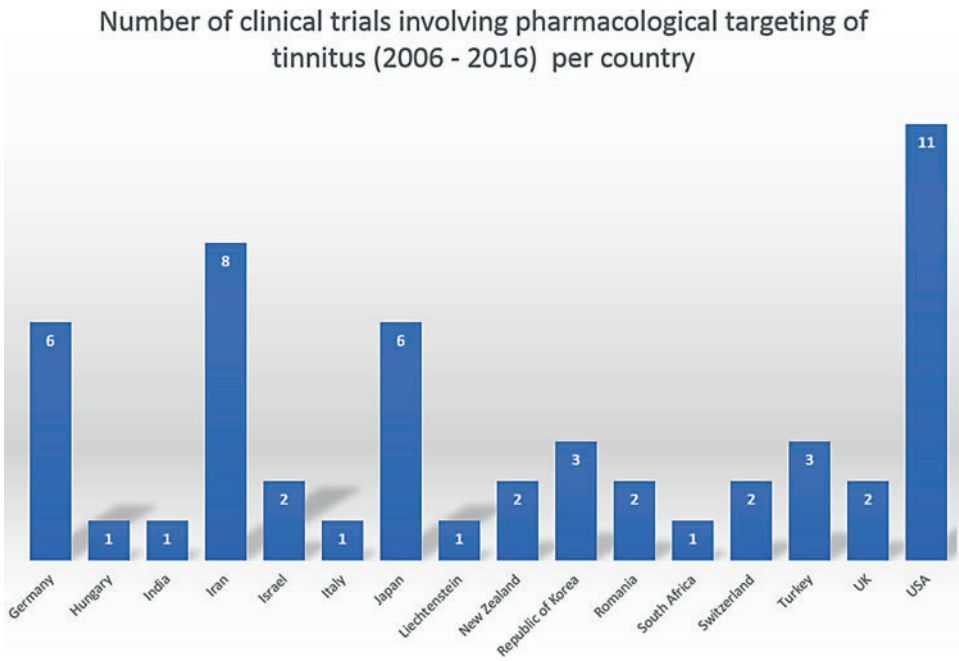

Fig. 6 Countries in which the clinical trials were conducted in the past (2006–2016)-based on supplementary data from (Hall et al. 2016).

There are several psychometric instruments that measure tinnitus-related distress. However, one needs caution when choosing the instrument, as they are not identical and often measure different domains with various sensitivities. In addition, the majority of tinnitus-related questionnaires are available in English and not in other languages. The most used tinnitus questionnaires worldwide in the past 10 years (Hall et al. 2016) include English version of Tinnitus Questionnaire (Hallam et al. 1988) and its German version (Hiller and Goebel 1992), Tinnitus Handicap Inventory (Newman et al. 1996) and Tinnitus Functional Index (Meikle et al. 2012). In addition, new questionnaires are being developed to address emerging issues, such as acceptance of tinnitus (Weise et al. 2013) To date, many questionnaires were validated and translated into other languages, e.g., Tinnitus Functional Index is presently available in German (Bruggemann et al. 2017), Swedish (Hoff and Kahari 2017), Polish (Wrzosek et al. 2016), and Dutch (Rabau et al. 2014), but it still remains to be offered in several other tongues, especially considering where the clinical pharmacological trials are being conducted (Fig. 6).

The study design in the past was predominantly randomized controlled (Fig. 6) (Hall et al. 2016), which is a general trend in the clinical research (Fig. 7).

Although clinical trials for tinnitus that were conducted in the past have not delivered a breakthrough in medical research (Beebe Palumbo et al. 2015; Plein et al. 2016; Savage and Waddell 2012), they delivered a lot of information that can be used to design an improved and well-focused trial, in which a variety of tinnitus phenotypes would be recognized (Fig. 8).

The therapeutic avenues that have in the past been explored for tinnitus include acupuncture, electromagnetic stimulation, hearing aids, hypnosis, psychotherapy, tinnitus masking devices, cognitive behavioral therapy, and tinnitus retraining therapy (Savage and Waddell 2014). For the design of the future trials, it should not be excluded that a drug therapy could be combined with one or more of the above approaches. In fact, the effectiveness of cognitive behavioral therapy

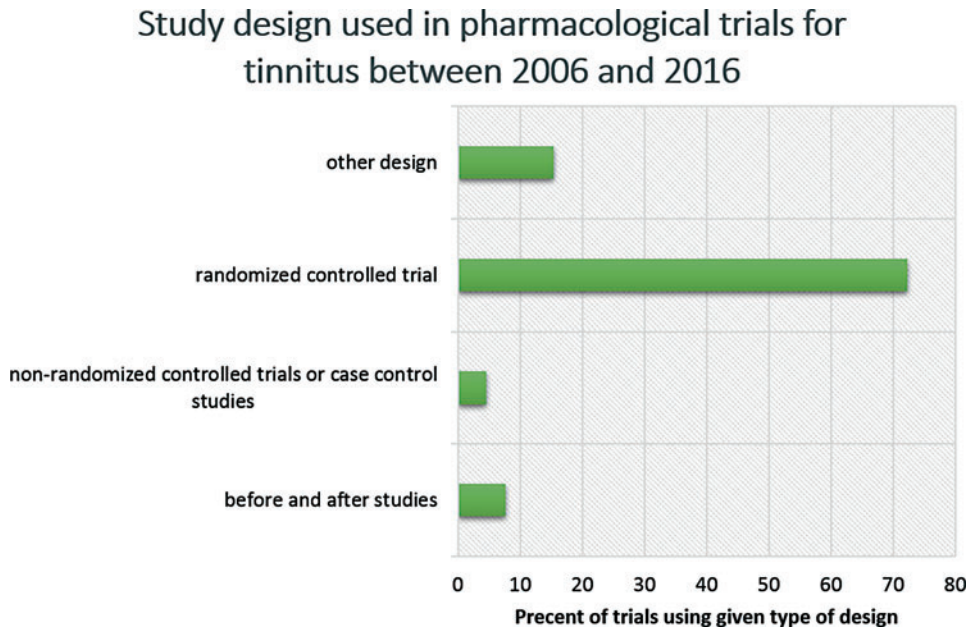

Fig. 7 Types of study design used in the past trials (2006–2016)-based on supplementary data from (Hall et al. 2016).

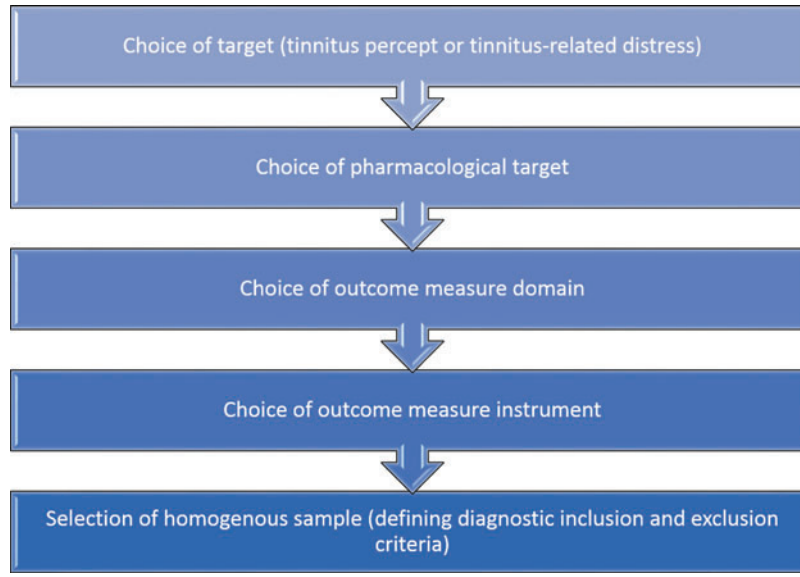

Fig. 8 General design scheme of pharmacological trial for tinnitus

in tinnitus management indicated by Cochran (Martinez-Devesa et al. 2010) and other systematic reviews (Hesser et al. 2011) could be a starting point for such combination therapy.

Taken together, the pharmacological trails were in the past anticipated to pinpoint a substance that would universally cure millions of people suffering from tinnitus. However, rather than providing a quick and uncomplicated solution, pharmacological trials uncovered the enormous diversity among tinnitus sufferers and a consequent need for rigorous tinnitus classification. Introduction of tinnitus taxonomy would improve the choice of inclusion and exclusion

criteria. This should also have positive impact on the selection of outcome domains and their measurement. Discovery or design of a universal medication against tinnitus, which would be comparable with a pain killer reducing discomfort of a headache as well as a stomachache or a toothache, is a Holy Grail of the clinical tinnitus research. However, improving the design of clinical pharmacological trials for tinnitus may result in obtaining partial answers and putting together step by step the 1000 pieces tinnitus puzzle.

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