Chapter 7
Past, Present, and Future Pharmacological Therapies for Tinnitus

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Abstract Tinnitus, the perception of a sound that has no external acoustic source in the environment, is a challenging condition to manage clinically because its etiology, perceptual characteristics (e.g., pitch and loudness), and accompanying symptoms (e.g., insomnia, anxiety, and/or depression) vary greatly among patients. Despite the long history of tinnitus, its considerable prevalence, and economic burden, there currently exists no approved drug or widely accepted treatment. As such, previous pharmacological attempts to manage tinnitus have used drugs that are approved for other medical conditions in what is considered an "off-label" approach. Broadly, these drugs have included anesthetics, antidepressants, anxiolytics, anticonvulsants, glutamate-receptor antagonists, and muscle relaxants. This chapter provides readers who are new to the field an introduction to the specific off-label drugs that have been administered for tinnitus management as well as the associated experimental rationale, patient outcomes, and relevant animal research. Furthermore, the results and recommendations of systematic reviews are summarized. Finally, where possible, discussion on each drug concludes with the treatment recommendations of the American Academy of Otolaryngology—Head and Neck Surgery Foundation. Ultimately, the authors hope that readers gain an awareness of

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C.G. Le Prell et al. (eds.), *Translational Research in Audiology, Neurotology, and the Hearing Sciences*, Springer Handbook of Auditory Research 58,
DOI 10.1007/978-3-319-40848-4_7

the history of drug therapies for tinnitus as well as the reasoning for why a certain drug may not be currently recommended, whether it be its apparent inefficacy, potential for harm, or shortcomings in the associated experimental design of the clinical trials.

Keywords Anticonvulsants • Anxiolytics • Etiology • Glutamate-receptor antagonists • Laboratory animal models • Muscle relaxants • Off-label drug therapy • Prevalence • Tinnitus • Tricyclic antidepressants

7.1 Introduction

Tinnitus, derived from the Latin word *tinnire* ("to ring"), is a condition characterized by the perception of a sound with no corresponding external acoustic source. *Objective* tinnitus represents a rare form of the condition in which an individual (and perhaps an observer using a stethoscope) can hear a real sound that is generated by his or her own internal structures, such as blood vessels or musculature near the middle ear. These sounds can be pulsatile and synchronized with respiration or heartbeat or can be continuous such as in cases of venous hum. Conversely, *subjective* tinnitus is a much more common condition that describes a phantom sensation that can be heard only by the afflicted individual. Often, subjective tinnitus is perceived as a ringing or buzzing in one or both ears. Objective and subjective forms of tinnitus are not mutually exclusive, as some individuals have described experiencing both types of auditory sensations.

As described in the following sections, subjective tinnitus, henceforth referred to only as "tinnitus," is a challenging condition to manage clinically because its etiology, perceptual characteristics (e.g., pitch and loudness), and accompanying symptoms (e.g., insomnia, anxiety, and/or depression) vary greatly among patients. Ultimately, translational research on tinnitus is focused on identifying its neural basis as well as finding safe and effective treatment strategies, as both of these goals remain elusive. To this end, researchers have developed laboratory animal models capable of screening treatment strategies in hopes of translating these findings into improved therapies for tinnitus sufferers.

Moving beyond anecdotal reports, several clinical trials have been conducted to determine the efficacy of various drugs at suppressing tinnitus. However, because there currently exists no approved drug treatment for tinnitus, these previous pharmacological attempts to manage tinnitus have used drugs that are approved for other medical conditions in what is considered an "off-label" approach. It has been estimated that more than four million off-label prescriptions are written for tinnitus each year in the United States and Europe (Vio and Holme 2005), and there are likely even more supplements sold commercially without a prescription. Off-label drugs requiring a prescription have included anesthetics, antidepressants, anxiolytics, anticonvulsants, glutamate-receptor antagonists, and muscle relaxants.

This chapter provides an introduction to the specific off-label drugs that have been investigated for tinnitus management as well as the associated experimental rationale, patient outcomes, and relevant animal research. In addition to providing an update to previous comprehensive articles on the pharmacotherapy of tinnitus (Salvi et al. 2009; Langguth and Elgoyhen 2012), this chapter also summarizes the results and recommendations of available articles from the Cochrane Database of Systematic Reviews, as these review articles are recognized as providing an in-depth critique of the primary research devoted to evidence-based healthcare (http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html). Finally, where possible, the discussion on each drug concludes with recommendations from the American Academy of Otolaryngology–Head and Neck Surgery Foundation, which published an exhaustive, evidence-based Clinical Practice Guideline for the evaluation and treatment of tinnitus (Tunkel et al. 2014).

As outlined in Sect. 7.4, most of the clinical trials examining off-label drugs have failed to provide compelling evidence that tinnitus can be routinely managed with pharmacotherapy in the majority of patients. It is important to note, however, that a considerable degree of the uncertainty regarding the efficacy of these various drugs likely can be attributed to methodological limitations in the clinical trials themselves (e.g., randomization or inadequate placebo controls). Thus, this chapter provides the reasoning for why a certain drug may not be currently recommended, whether because of its apparent inefficacy, potential for harm, or shortcomings in the associated experimental design of the clinical trials, as these collective reasons have contributed to the difficulty in translating drug therapies for tinnitus into evidence-based practice (Weaver 2014).

7.1.1 Tinnitus Prevalence

A large proportion of adults will experience tinnitus at some point in their life, albeit perhaps only for a short time and likely as a consequence of exposure to loud noise or transient vascular changes. However, in approximately 10 % of the general population (Heller 2003), tinnitus is a chronic condition that can lead to difficulty concentrating, insomnia, and, in some cases, severe forms of anxiety and depression, all of which can negatively affect quality of life (Erlandsson and Hallberg 2000). According to data derived from the 2011–2012 National Health and Nutrition Examination Survey (NHANES), conducted by the US Centers for Disease Control and Prevention, it is estimated that approximately 20 million Americans experience chronic tinnitus, with 2 million people suffering from extreme and debilitating cases (https://www.ata.org/understanding-facts). Other analyses of NHANES data (1994–2004), which is based on a sample of 14,178 completed surveys, estimate that approximately 50 million American adults have experienced some form of tinnitus, with 16 million experiencing frequent tinnitus within the past year (Shargorodsky et al. 2010). Similar rates of tinnitus prevalence and disturbance ($\sim$5–16 % of population, with $\sim$1–4 % disabled) have been

reported in European (Axelsson and Ringdahl 1989; McCormack et al. 2014), African (Khedr et al. 2010), Asian (Xu et al. 2011; Jalessi et al. 2013), and South American (Oiticica and Bittar 2015) countries, making tinnitus a global concern.

7.1.2 Tinnitus Diagnosis and Measurement

A comprehensive tinnitus diagnosis should involve a multidisciplinary approach because tinnitus can be a symptom of various underlying pathologies (e.g., hearing loss, neurovasculature abnormalities, head/neck trauma, retrocochlear pathology, etc.) and it can be accompanied by several different comorbidities (e.g., anxiety, depression, and/or insomnia) (Langguth et al. 2013). Although it is beyond the scope of the present chapter to provide a detailed description of the recommended diagnostic procedures, it is worth introducing the stepwise decision-tree approach for clinical management of tinnitus that has been proposed from the Tinnitus Research Initiative (TRI)—a leading, nonprofit foundation dedicated to supporting collaborative research to improve the understanding of the pathophysiology of tinnitus as well as the development of effective treatments. Ultimately, the TRI recommends that the basic diagnostic steps include a case history, clinical ear examination, audiologic testing, and assessment of tinnitus severity (Langguth et al. 2013).

Regarding the measurement of tinnitus, there are two important components: perception and reaction (Tunkel et al. 2014). Tinnitus perception refers to the acoustic aspects of the phenomenon, such as its loudness, pitch, and temporal features. These can be, and often are, assessed with psychoacoustic measures, including matches to real acoustic stimuli (Henry et al. 2014). In contrast, the patient's reaction to his or her tinnitus encompasses the person's emotional well-being and is reflected in subjective measures of how bothersome his or her tinnitus is (i.e., its severity), measures usually derived from in-depth interviews or questionnaires (Shi et al. 2014). Several questionnaires are available for assessing the severity and effects of tinnitus. These include the Tinnitus Handicap Questionnaire (Kuk et al. 1990); the Tinnitus Reaction Questionnaire (Wilson et al. 1991); the Tinnitus Handicap Inventory (Newman et al. 1996), which is the most commonly used questionnaire in the United Kingdom (Baguley et al. 2013); and more recently, the Tinnitus Functional Index (Meikle et al. 2012; Henry et al. 2015).

Because the psychoacoustic measurements of tinnitus do not fully explain the subjective "feelings" or emotional toll of its severity (Meikle et al. 1984; Folmer et al. 1999), clinicians are encouraged to include measures of both the patient's perception and reaction to his or her tinnitus in a comprehensive evaluation (Langguth et al. 2011). The use of a validated tinnitus questionnaire is important in providing a baseline for assessing the efficacy of treatment in clinical trials related to the subjective elements of tinnitus (Tunkel et al. 2014). That said, given the number of questionnaires available, it can be difficult to compare across studies if

each clinical trial evaluates the treatment outcome using a different, albeit validated, questionnaire. Also important to consider when evaluating the potential efficacy of putative treatments is the potential for placebo effects to confound the interpretation (Duckert and Rees 1984).

7.1.3 Tinnitus Etiology

Tinnitus is a difficult condition to manage clinically because its perceptual characteristics, accompanying symptoms, and etiology vary considerably among patients. For example, tinnitus is often comorbid with other conditions such as noise- or age-related hearing loss, hyperacusis, head/neck injury or age-related issues, temporomandibular joint disorders, neurovascular complications, or insult to the auditory nerve (e.g., via microvasculature compression or vestibular schwannoma) (Langguth et al. 2013). Further contributing to the heterogeneity of tinnitus and its associated symptoms is the finding that approximately 40 % of patients report that there was "no related onset factor" associated with their tinnitus (for review, see Elgoyhen and Langguth 2010).

It is commonly acknowledged that hearing impairment and increasing age are significant risk factors for tinnitus (Ahmad and Seidman 2004). Furthermore, a study among American adults reported that a history of loud leisure-time, firearm, or occupational noise exposure is also associated with increased odds of experiencing tinnitus (Shargorodsky et al. 2010). As exposure to loud noise is a pervasive hazard for military personnel (Grantham 2012), it is well established that servicemen and servicewomen find themselves at increased risk for tinnitus (Theodoroff et al. 2015). Among returning veterans from conflicts in Iraq and Afghanistan, 49 % of personnel exposed to blast trauma developed tinnitus (Cave et al. 2007).

In further considering the relationship between hearing loss and tinnitus, a retrospective observational study on 286 tinnitus patients found that the tinnitus pitch was in the same range and correlated significantly with the frequency of the maximum hearing loss (Schecklmann et al. 2012). That said, an abnormal audiogram is not always detected in tinnitus patients (Langguth et al. 2013), particularly if the pure tones used are within the conventional range of audiometric testing (125–8,000 Hz). Several studies have confirmed, however, that when the hearing thresholds of these tinnitus patients are assessed above 8,000 Hz, hearing impairments are indeed revealed and the pitch of the tinnitus is near or at the region of these higher frequencies (for review, see Henry et al. 2014), findings that further support the role of hearing loss in tinnitus etiology.

In addition to hearing loss, symptoms of depression are also commonly reported in patients who seek medical attention for their tinnitus. It remains challenging, however, to accurately estimate the prevalence of depression in patients with tinnitus from the general population because of research selection bias. Patients recruited for studies are often those who are actively, and sometimes aggressively, seeking treatment for their tinnitus and its associated symptoms (e.g., depression,

anxiety, and/or insomnia). This self-selection bias may lead to an overestimation of prevalence of depression among individuals with tinnitus. Despite variability in the rates of depression documented in the literature (14–80 %; Langguth et al. 2011), several studies report a positive correlation between depression and tinnitus-related severity and annoyance (for review, see Pinto et al. 2014). From these findings, an important clinical question emerges: Is there directionality to this comorbidity of tinnitus and depression? For example, are patients with depression more vulnerable to developing tinnitus? Or is depression simply a reflection of a learned distress response brought on by tinnitus? In a comprehensive review of the literature, Langguth and colleagues (2011) proposed that the comorbidity of tinnitus and depression does not likely occur by chance nor does depression simply manifest as a reaction to one's tinnitus. Instead, they contend that tinnitus and depression are pathophysiologically interrelated because the two disorders share similar alterations in neurotransmitter systems, and imaging studies have revealed overlap of brain circuits that are activated in both tinnitus and depression (see Sect. 7.3 for the putative mechanisms of tinnitus). That said, the extent to which there may be interrelation will need to be thoroughly evaluated given that the majority of individuals with depression do not have tinnitus. In addition, there are many individuals with tinnitus who are not being treated for depression by a healthcare provider. Thus, it is possible that those subjects who actively seek treatment are suffering from both tinnitus and depression, but their symptoms, although related, do not share a common pathway. It is reasonable, however, to consider that tinnitus can exacerbate and/or lead to depression and that depression can make coping with tinnitus more difficult or render individuals more susceptible to tinnitus distress.

Anxiety, another psychological condition, has also been identified as a significant risk factor for tinnitus severity (for review, see Langguth et al. 2011). For example, in a study of patients deemed to be at high risk for severe or disabling tinnitus (via the Tinnitus Severity Questionnaire), it was estimated that approximately 50 % had a concurrent anxiety disorder (Zöger et al. 2006). Subjects included in this study had pure-tone averages better than 50 dB hearing level (HL) in their worse-hearing ear (Zöger et al. 2006). Additional studies have identified a relationship between tinnitus distress and *anxiety sensitivity*, whereby anxious patients misattribute the bodily sensations of their tinnitus as a sign of a potentially harmful underlying condition that serves to heighten their anxiety (Hesser and Andersson 2009; Gül et al. 2015). Given the comorbidity of anxiety and tinnitus, it is not surprising that the intensity of a patient's tinnitus can be exacerbated by stressful events (Hébert and Lupien 2009). Moreover, a large-scale epidemiological study reported a linear association between the presence of tinnitus and the magnitude of long-term stress (Hasson et al. 2011). It is worth noting, however, that such human correlational studies are unable to distinguish cause and effect, such as whether tinnitus increases stress levels, if stress causes tinnitus, or if both are related to some third unmeasured factor (Mazurek et al. 2012; Canlon et al. 2013).

7.1.4 Economic Burden of Tinnitus

According to a 2013 report, tinnitus and hearing loss have emerged as the top two service-related disabilities for which American veterans received compensation from the US Department of Veterans Affairs (2014). Consequently, the financial cost associated with tinnitus compensation for the military has soared, totaling $300 million for the 2010 fiscal year under the major disability only for hearing loss category and $920 million overall individual claims (Department of Veterans Affairs Compensation Benefits Report FY 2010). It is important to note, however, that the economic burden of tinnitus-related disability is likely not restricted to military agencies, as it has been estimated that approximately 1 % of the general population suffers from debilitating tinnitus (McCombe et al. 2001) that can impair their workplace productivity and earning potential (Henry et al. 2005). For example, based on a large cohort study, patients with tinnitus have a greater than a threefold increased risk of going on to receive a disability pension compared to individuals who went on sick leave for a non-otology/audiology diagnosis (Friberg et al. 2012).

7.2 Laboratory Animal Models of Tinnitus

Over the past approximately 25 years, a number of laboratory animal models have been developed to investigate the pathophysiology of tinnitus, with the vast majority using rodents (e.g., rats, mice, and hamsters). It is important to note that before assessing any changes in cochlear function or brain activity that may underlie tinnitus, it was necessary that researchers first overcome the challenge of developing behavioral tests that were capable of determining whether or not animals were actually experiencing tinnitus. Jastreboff and colleagues (1988) were the first to establish an animal model of tinnitus in the rat. Subsequently, a variety of behavioral paradigms have been developed to screen rats and other laboratory animals for noise- and drug-induced tinnitus (for review, see Heffner and Heffner 2012; Stolzberg et al. 2012; Hayes et al. 2014). In general, the majority of the initial behavioral paradigms involved training an animal to perform a distinct behavior when sound was present in its environment and a different behavior during quiet conditions. Then, following a noise or drug exposure, if the animal mistakenly behaved during quiet conditions as though it was "hearing" an acoustic stimulus, the researchers concluded that the animal was experiencing tinnitus. There are a number of inherent challenges in developing these models in that the conditions under which animals are trained to respond or withhold responding are absent of acoustic stimuli. Then, presumably, when the animal no longer perceives quiet because of tinnitus, it behaves as if there were a real sound in the background. Ultimately, based on these behavioral paradigms, it is now well established that, similar to humans, excessive exposure to loud noise or ototoxic drugs (e.g., sodium

salicylate, the active component of aspirin) can induce tinnitus in laboratory animals.

To date, one of the most commonly used behavioral tools to screen animals for noise-induced tinnitus has been the gap prepulse inhibition of the acoustic startle (GPIAS) paradigm. The technique was developed by Turner and colleagues (2006) and was based, in part, on earlier work by Ison and colleagues (Ison 1982; Ison et al. 2002). In contrast to the aforementioned behavioral tests that involved training animals before inducing tinnitus, the GPIAS paradigm does not require overt training, as it is based on an animal's reflexive motoric response (a "flinch") to a loud sound. The amplitude of this reflexive acoustic startle response can be modified by presenting an audible acoustic cue before the onset of a startling stimulus. In the GPIAS paradigm, the cue is a silent gap in a continuous background noise. Alternatively, acoustic cues such as tones and noise bursts in quiet presented prior to a startling stimulus can also modify the acoustic startle reflex amplitude. A key feature of the GPIAS paradigm is the consistent finding that if an animal is able to detect a brief silent gap in a background sound before the loud startle stimulus, its acoustic startle amplitude will be attenuated or abolished (i.e., it "flinches" less in response to the loud sound). Supporters of the GPIAS paradigm suggest that if the animal's tinnitus pitch is qualitatively similar to the background sound, then it should be unable to detect the silent gap, and consequently, its acoustic startle amplitude will not be suppressed or will be suppressed to a lesser degree. This difference is important because changes in startle amplitudes after "tinnitus" induction could result from generalized changes across all trials or the results of trial averages that include trials in which animals detected the cue and trials in which the animals completely failed to detect the cue.

It should also be noted that the notion of tinnitus "filling in" the silent gap has been seriously challenged in human (Fournier and Hébert 2013; Boyen et al. 2015) and laboratory animal studies (Hickox and Liberman 2014; Radziwon et al. 2015). Moreover, a study on rats identified an additional caveat of the GPIAS paradigm: it is susceptible to "false positives" for tinnitus following hearing loss (Lobarinas et al. 2013). To illustrate this point, a temporary and reversible unilateral, conductive hearing loss was produced in rats by plugging one ear with a silicone elastomer. When tested under the GPIAS, paradigm animals showed behaviors consistent with "tinnitus" as evidenced by a lack of difference between the trials that contained a gap, relative to trials with no gap (i.e., it appeared that the animals could not detect the gap). However, on closer inspection, the presence of the earplug had significantly reduced the response to the loud acoustic startle stimulus under both cued and uncued trials. If the startling stimulus no longer produced a startle response, there was nothing from which to inhibit and thus a lack of difference. It did not matter whether the trial was cued or not as the animals no longer exhibited a robust startle response. When the same earplugged animals were tested under the same gap or no-gap conditions but with a startle response induced with a tactile stimulus (i.e., a 10–12 PSI airpuff to the back of the neck), the animals readily detected the gap cue prior to the air puff and showed robust inhibition. These results highlight some of the challenges associated with developing animal models and the

need to both build robust evidence and critically evaluate existing evidence. Clearly, a failure to accurately screen animals for the presence/absence of tinnitus is a significant and persistent concern for researchers who intend to subsequently investigate its pathophysiology or possible drug therapies for translational research aims.

In addition to the challenges of accurately screening laboratory animals for tinnitus (for review, see Heffner and Heffner 2012; Eggermont 2013), it is important to note that current models were designed to assess the perception of tinnitus. In contrast, the emotional and/or cognitive effects of tinnitus have not been explored in animals. This could be viewed as either an advantage or a disadvantage. If the goal is to determine whether a particular therapy reduces the actual sound of tinnitus, then the current animal models may be an attractive tool to determine efficacy. However, if tinnitus is defined by the negative psychological reaction experienced by patients who are unable to habituate to the sound of tinnitus, then animal models would be of limited use. These different viewpoints also significantly affect efforts at studying tinnitus, as efficacy may be defined by a reduction or elimination of the tinnitus sound or by a reduction in the psychological reaction to tinnitus.

Despite the aforementioned challenges, there are still significant and distinct benefits of using laboratory animal models for translational tinnitus research. For example, animal models allow researchers to (1) precisely control how tinnitus is induced; (2) invasively record neural activity from various brain regions using microelectrodes; and (3) safely evaluate the efficacy of novel treatments for reducing the tinnitus percept. In Sect. 7.4, we present the outcomes of various animal studies that have either screened drugs that had already been administered to humans for tinnitus (e.g., memantine and cyclobenzaprine) or drugs that have yet to be tested in clinical trials for tinnitus (e.g., retigabine).

7.3 Putative Mechanisms of Tinnitus

At present, the mechanisms underlying tinnitus continue to remain elusive. It is unlikely that the signal for tinnitus simply originates in the cochlea and travels to the brain via the auditory nerve because, although some patients' tinnitus improved after their auditory nerve had been surgically transected, other patients experienced persistent (or worsened) tinnitus following surgery (House and Brackman 1981). These data suggest that some forms of tinnitus are generated centrally or perpetuated even in the absence of a connection to the cochlea (Eggermont et al. 2012). Further support of a central generator for some forms of tinnitus has emerged from several neuroimaging studies (Melcher 2012). These studies show that brain activity is enhanced in auditory and nonauditory areas in patients with tinnitus relative to control subjects without tinnitus (for review, see Adjamian et al. 2009;

Lanting et al. 2009). Ultimately, it has been suggested that although tinnitus may indeed be triggered by cochlear damage, tinnitus can be perpetuated by the subsequent plastic changes that occur in the central auditory system independent of the periphery (Henry et al. 2014).

Based on several decades of research using both invasive neural recordings in laboratory animals as well as noninvasive recordings and neuroimaging techniques in humans, a variety of central mechanisms of tinnitus have been proposed (see Eggermont et al. 2012). In a comprehensive review, Henry et al. (2014) outlined these putative tinnitus mechanisms within a framework of various neural models, including (1) dorsal cochlear nucleus hyperactivity, (2) tonotopic reorganization, (3) central gain, (4) neural synchrony, and (5) network models. The dorsal cochlear nucleus (DCN) hyperactivity model of tinnitus suggests that hearing impairment causes a loss of inhibition in this early relay nucleus, leading to an increase in spontaneous neural activity that ascends along subsequent structures in the central auditory system and ultimately manifests as tinnitus (Kaltenbach et al. 2005; Dehmel et al. 2012). Tonotopic map reorganization occurs at each relay nucleus throughout the central auditory system as a consequence of the sensory deafferentation caused by the hearing loss. There is speculation that this reorganization, typically characterized by an expansion of the representation of frequencies spared after cochlear damage, results in the phantom perception of tinnitus (Rauschecker 1999). The central gain model of tinnitus proposes that following the reduction in sensory input from the cochlea, structures in the central auditory system become hyperactive owing to homeostatic mechanisms that are triggered to preserve neural sensitivity but do so at the expense of also amplifying "neural noise" (i.e., tinnitus) (Noreña 2011). Based on results from electro- and magnetoencephalography in humans, neural synchrony models refer to the aberrant cortical oscillatory activity that is believed to arise from hyperpolarization of the thalamus following sensory deafferentation (Llinas et al. 1999; De Ridder et al. 2015). These changes in the thalamus result in a synchronized, bursting pattern of activity of neurons that project to the cortex, which ultimately causes abnormally synchronized cortical activity believed to contribute to the tinnitus percept (Llinas et al. 1999; De Ridder et al. 2015). Finally, network models of tinnitus are founded on neuroimaging data that reveal that more than one brain region demonstrates aberrant activity or morphology in patients with tinnitus (Leaver et al. 2011; Elgoyhen et al. 2012). For example, frontal, temporal, and parietal cortical areas have been implicated in the perception of tinnitus, whereas tinnitus distress appears to be associated with synchronized activity in the subcallosal anterior cingulate cortex, the insula, parahippocampal area, and amygdala (Langguth et al. 2011). Overall, it should be noted that the proposed neural models of tinnitus may not be mutually exclusive. For example, a loss of inhibition early in the auditory pathway or "central gain" due to homeostatic mechanisms may ultimately manifest as changes in large-scale network activity.

7.4 Off-Label Approach to Pharmacotherapy for Tinnitus

Despite the long history of tinnitus suffering and its considerable prevalence and economic burden, there is currently no FDA-approved drug for the treatment of tinnitus. Previous pharmacological attempts to manage tinnitus have instead used drugs approved for other medical conditions. Broadly, these off-label drugs have included anesthetics, antidepressants, anxiolytics, anticonvulsants, glutamate-receptor antagonists, and muscle relaxants.

Other attempts have used various dietary supplements for the treatment of tinnitus. Many of these "supplements" carry disclaimers such as, "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (US Food and Drug Administration 2015). Such statements are included because, under the Dietary Supplement Health and Education Act of 1994 (DSHEA) and current FDA regulations, these formulations are considered food and thus exempt from the rigorous labeling and testing standards applied to drugs. Because of the lack of scientific support for the use of dietary supplements (Tunkel et al. 2014), this chapter provides an overview of the off-label prescription drugs that have been examined in clinical trials as well as the scientific rationale underlying their use and the associated patient outcomes.

7.4.1 Anesthetics

Bárnáy (1935) inadvertently found that tinnitus could be suppressed with intravenous administration of the anesthetic procaine, which is commonly known as Novocain. Similar promising findings were reported over the next several decades (for review, see Melding et al. 1978). In the early 1980s, a series of clinical trials investigated the effect of intravenous administration of the voltage-gated sodium channel blocker lidocaine on tinnitus. As summarized and critiqued by Bauer and Perring (2008), these studies monitored the effect of intravenous lidocaine on tinnitus (versus a saline placebo control) 5–30 min postinfusion using a within-subjects design and found that lidocaine reduced the loudness, pitch, and annoyance of tinnitus in the majority of subjects. However, these effects were transient, and 9–32 % of subjects included in the various studies reported that their tinnitus *worsened* after lidocaine. Furthermore, the study design was compromised because most subjects experienced side effects (e.g., imbalance and speech disorders) to the lidocaine, preventing them from remaining blind to the treatment.

It has long been known that the inclusion of appropriate placebo controls is important in clinical trials that seek to evaluate drug therapies for tinnitus. Duckert and Rees (1984) suggested to patients who had previously participated in a lidocaine study that they were to again receive an injection of lidocaine but instead were unknowingly administered saline. The placebo effect influenced 40 % of subjects,

as they reported a change in their tinnitus following the placebo (saline) injection. These findings reach far beyond the evaluation of the proposed efficacy of lidocaine and serve as a cautionary note that the effectiveness of drug therapies for tinnitus may be subject to strong bias by the placebo effect.

Studies have also sought to elucidate the mechanism(s) by which intravenous lidocaine suppresses tinnitus. For example, Kalcioglu et al. (2005) investigated whether the effect of lidocaine on tinnitus suppression was due to its effect on altering otoacoustic emissions in the cochlea. Ultimately, having found similar changes in distortion product otoacoustic emission (DPOAE) measures in subjects whose tinnitus lessened with lidocaine treatment versus those whose did not, the authors concluded that lidocaine-induced suppression of tinnitus was not likely due to altered DPOAEs. Using positron emission tomography, Reyes et al. (2002) measured regional cerebral blood flow (rCBF) before and after lidocaine infusion and found that there was reduction in rCBF (and presumably neural activity) in the auditory cortex of patients who experienced a decrease in tinnitus loudness, findings that were consistent with the authors' hypothesis that tinnitus originates in the central auditory pathway rather than the periphery. It is important to note, however, that these conclusions cannot rule out potential peripheral effects of lidocaine on auditory nerve fibers, synapses, or inner hair cells.

With respect to efficacy, the potential usefulness of intravenous lidocaine as a treatment for tinnitus is strongly diminished by its unwanted side effects, transient nature, increase in tinnitus among some participants, and impractical intravenous route of delivery outside a clinical setting. Despite these limitations, because a significant proportion (40–82 %) of subjects in the studies summarized by Bauer and Perring (2008) reported a reduction of tinnitus following intravenous lidocaine administration, these findings have been put forth in general support of the contention that tinnitus may indeed be treated with pharmacotherapy (Langguth and Elgoyhen 2012). Perhaps future studies will be able to offset the clear drawbacks of intravenous lidocaine administration while preserving its promising effects at silencing tinnitus.

7.4.2 Tricyclic Antidepressants

If, as suggested, tinnitus and depression share similar pathophysiology (Langguth et al. 2011), it is reasonable to ponder whether the drugs that effectively treat depressive symptoms may also be effective at managing tinnitus loudness and/or severity. To date, a variety of tricyclic antidepressants have been evaluated in clinical trials to treat tinnitus, including trimipramine, nortriptyline, and amitriptyline. In a double-blind crossover trial versus placebo, trimipramine was found to be ineffective at reducing tinnitus disability owing to a lack of statistically significant results coupled with a large placebo effect (Mihail et al. 1988). Sullivan et al. (1993) found that nortriptyline showed a nonstatistically significant trend to decrease functional disability and tinnitus loudness in a 12-week, double-blind,

randomized controlled trial that included subjects with either major depression or depressive symptoms. The effectiveness of amitriptyline (10 mg; 3 times/day) was evaluated in a 10-week, randomized, open-label, placebo-controlled trial (Podoshin et al. 1995) and a 6-week, randomized, parallel, placebo-controlled single-blind study (50 mg/day for first week; 100 mg/day for 5 weeks) (Bayar et al. 2001). According to Podoshin and colleagues (1995), the majority of patients reported no improvement in tinnitus with amitriptyline treatment, whereas Bayar et al. (2001) found that a higher dose of amitriptyline resulted in a significant reduction in the subjective rating of tinnitus and its loudness as well as a reduction in tinnitus by the end of the study in 95 % of the patients (compared to 12 % of the placebo group).

Baldo et al. (2012) published a Cochrane Review on the effectiveness of antidepressants for tinnitus treatment and provided a comprehensive critique of the aforementioned studies and their outcomes. It is worth noting that Baldo and colleagues excluded additional studies that administered antidepressants because of issues such as high participant dropout rate (Zöger et al. 2006; Holgers et al. 2011), lack of randomization (Sullivan et al. 1989), or failure to include a placebo control (Roberts et al. 2011). Considering the primary outcome measure to be a change in tinnitus disability, Baldo et al. (2012) concluded that the four randomized controlled trials investigating tricyclic antidepressants yielded only a slight improvement, and thus there was insufficient evidence in support of antidepressant therapy for tinnitus.

Ultimately, the clinical practice guideline published by the American Academy of Otolaryngology–Head and Neck Surgery Foundation does not recommend antidepressants for treating tinnitus (Tunkel et al. 2014). That said, given the possibility that tinnitus patients who have sought medical attention may also have depressive symptoms, it has been suggested that a multidisciplinary diagnostic approach be used. A team approach involving collaboration between audiologists, otolaryngologists, and mental health professionals is strongly recommended for patients with severe tinnitus as well as those with histories suggestive of comorbidity with anxiety or depression (Pinto et al. 2014).

7.4.3 Benzodiazepines

Based on the proposed relationship between stress and tinnitus, researchers have sought to determine the efficacy of anxiolytic (antianxiety) drugs on tinnitus and its associated symptoms. Several clinical trials for tinnitus have been conducted using benzodiazepines, a class of psychoactive drugs with anxiolytic (as well as anticonvulsant and sedative) properties. Benzodiazepines act as positive allosteric modulators of γ-aminobutyric acid ($GABA_A$) receptors, thereby enhancing GABA-mediated inhibition. In addition to their anxiolytic effects, it has been suggested that benzodiazepines could suppress tinnitus by increasing inhibitory neurotransmission in the central auditory system, thereby offsetting the

hyperexcitability that has been implicated in tinnitus pathophysiology (Jufas and Wood 2015). In further support of the possible therapeutic potential of benzodiazepines, an imaging study found that patients with tinnitus have a reduction in benzodiazepine-binding sites in the medial temporal cortex, as assessed with single-photon emission computed tomography and a benzodiazepine radioligand (Shulman et al. 2000).

In a systematic review, Jufas and Wood (2015) considered the strength of the evidence for benzodiazepine use in tinnitus management and weighed that against the associated risks. The authors summarized and critiqued six studies (outlined below) investigating various benzodiazepines, including diazepam (Valium), alprazolam (Xanax), and clonazepam. Collectively, these studies used a variety of outcome measures, such as audiometry, visual analogue scales, the Tinnitus Handicap Inventory, and an assessment of tinnitus loudness, to determine the efficacy of the drug therapy.

Diazepam is mainly used to treat anxiety and insomnia. Studies conducted in the early 1980s found that diazepam was ineffective at managing tinnitus in a double-blind crossover trial (Kay 1981), as well as in a single-blind comparison of participants (Lechtenberg and Shulman 1984).

Alprazolam significantly reduced tinnitus loudness in a 12-week, double-blind, placebo-controlled study where the dosage was adjusted (0.5–1.5 mg/day) for each participant (Johnson et al. 1993). Although the majority of participants improved, this study has been challenged because of its individualized dosing regimen and lack of inclusion of a validated tinnitus questionnaire as an outcome measure (Salvi et al. 2009). It appears that these concerns are warranted, as Jalali and colleagues (2009) reported that alprazolam (1.5 mg/day) did not significantly improve the Tinnitus Handicap Inventory score or tinnitus loudness in a randomized, triple-blind, cross-over, placebo-controlled trial. Ultimately, the conflicting results between these two studies could partly arise from differences in the patient populations. Because Jalali and colleagues (2009) excluded tinnitus patients with depressive or anxiety disorders, it is possible that the beneficial effect on tinnitus loudness observed by Johnson et al. (1993) was due to alprazolam's general anxiolytic properties on patients in their study rather than its direct effect on tinnitus pathophysiology (Jufas and Wood 2015).

Of the benzodiazepines used in clinical trials, clonazepam, which has a long plasma half-life of 20–40 h, has shown the most favorable results in reducing tinnitus. For example, in a randomized, single-blind comparison study using clonazepam, 18 of the 26 tinnitus patients experienced reduction in tinnitus volume, with more than half of these patients reporting a better than 50 % improvement in tinnitus volume using a patient assessment rating scale (1–5) (Lechtenberg and Shulman 1984). A follow-up study found that clonazepam reduced tinnitus annoyance and intensity in a randomized, single-blind, placebo-controlled trial (Bahmad et al. 2006). Similarly, Han et al. (2012) conducted a randomized, open-label, crossover comparison study and reported that 3 weeks of clonazepam significantly reduced tinnitus annoyance and loudness as well as scores on the Tinnitus Handicap Inventory.

When considering benzodiazepines for tinnitus management, it is important to be mindful of potential confounds in the aforementioned clinical trials as well as the likelihood of adverse side effects. For example, Jufas and Wood (2015) cautioned that, despite the evidence supporting the efficacy of clonazepam in three studies, none of them adequately described sufficient participant blinding to the treatment, and this may have resulted in an overestimation of the positive effects reported by the participants. It is difficult to keep participants blinded to the experimental conditions because benzodiazepines have a considerable side effect profile, including sedation, memory impairment, and slurring of speech. Benzodiazepines also carry a risk of drug dependency. Of the benzodiazepines discussed previously, alprazolam is perhaps of greatest concern because its relatively short plasma half-life (12–15 h) makes it difficult for patients to withdraw from use (Wolf and Griffiths 1991). Finally, there are reports that tinnitus can *emerge* after discontinuation of long-term use of benzodiazepines (Busto et al. 1986, 1988; Ashton 1991). Based on the results available and the potential for adverse effects, previous review articles (e.g., Langguth and Elgoyhen 2012; Jufas and Wood 2015) as well as the published Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014) have cautioned against the use of anxiolytics, such as benzodiazepines, for the treatment of tinnitus.

7.4.4 Anticonvulsants

The use of anticonvulsants is not restricted to epileptic conditions, as this class of drugs has been prescribed for various psychiatric disorders and pain syndromes (Langguth and Elgoyhen 2012). The two most commonly used anticonvulsants in clinical trials for tinnitus management have been carbamazepine and gabapentin. Carbamazepine, which is structurally similar to tricyclic antidepressants, effectively inhibits high-frequency neuronal firing by binding to voltage-gated sodium channels and stabilizing the sodium inactivation state so that fewer channels can subsequently open (Ambrósio et al. 2002). At present, the mechanism(s) underlying gabapentin's actions as an antiepileptic and antinociceptive drug is not completely understood. It has been suggested that its actions may be mediated by multiple cellular effects, which likely involve blockage of voltage-gated calcium channels (Sills 2006). Ultimately, the use of anticonvulsants in clinical trials for tinnitus management has been rationalized based on their actions in reducing the neuronal hyperexcitability proposed to underlie tinnitus.

In the late 1970s, it was reported that the subset of tinnitus patients who benefitted from intravenous lidocaine also responded positively to carbamazepine (Shea and Harell 1978; Melding and Goodey 1979). As a follow-up to these studies, Donaldson (1981) conducted a randomized, crossover trial comparing the effect of carbamazepine versus placebo. Unlike the studies in which 600–1,000 mg/day of carbamazepine was effective in approximately half of the patients tested (for review, see Salvi et al. 2009), the lower dose used in the study by Donaldson (1981)

(200 mg/day) resulted in a nonsignificant effect on tinnitus. Using a higher dose (450 mg/day) in a randomized, double-blind trial, Hulshof and Vermeij (1985) found that carbamazepine actually *worsened* tinnitus compared to placebo (albeit nonsignificantly), and the majority of patients experienced side effects such as dizziness, nausea, and headache. Finally, 300–600 mg/day of carbamazepine did not show a significant benefit in tinnitus patients as assessed with visual analog scale and Tinnitus Severity Index in a randomized, double-blind clinical trial of patients with nonpulsatile tinnitus (Gerami et al. 2012). Despite these equivocal results, carbamazepine has been reported to be effective at managing *pulsatile* tinnitus (Rahko and Hakkinen 1979; Mardini 1987), a rare form of tinnitus related to auditory nerve vascular compression in which the phantom sensation is described as sounding like clicking or a typewriter (i.e., "typewriter tinnitus"; Levine 2006).

In a series of randomized, double-blind, placebo-controlled trials, the anticonvulsant gabapentin was found to be no more effective than placebo at improving scores on the Tinnitus Handicap Inventory (Piccirillo et al. 2007; Witsell et al. 2007) or Tinnitus Severity Index (Dehkordi et al. 2011). Similarly, Bakhshaee et al. (2008) found no significant difference in the Tinnitus Severity Index or loudness perception between gabapentin and placebo in a double-blind crossover trial. In an attempt to determine the efficacy of gabapentin on different subpopulations of tinnitus patients as well as find an optimum dose for each patient, Bauer et al. (2015) conducted a double-blind crossover trial. This trial specifically segregated patients whose tinnitus was attributed to high-level sound exposure and included entry and washout placebo phases that bracketed escalating (800, 1,800, and 2,400 mg) and decreasing drug dose (900 mg) series for 3–4 weeks. Consistent with the earlier studies, Bauer et al. (2015) confirmed the limited efficacy of gabapentin in decreasing the loudness and impact of tinnitus.

Similar to the aforementioned carbamazepine clinical trials where efficacy was reported to differ with various daily dosage regimens, Zheng et al. (2008) used an animal model and found that carbamazepine at 15 mg/kg but not at lower or higher doses could reduce salicylate-induced tinnitus in rats that were assessed with a conditioned lick suppression paradigm. In contrast to the aforementioned human studies, Bauer and Brozoski (2006) found that gabapentin was effective at reversibly attenuating tinnitus in noise-exposed rats using a psychophysical procedure based on each animal's auditory discrimination ability. In fact, Bauer and colleagues (2015) acknowledged that it was the promising findings from their earlier animal work that directly informed their decision to investigate the effect of gabapentin in humans with noise-induced tinnitus. In the clinical trial, because the objective, psychometric assessment of tinnitus loudness paralleled the subjective, questionnaire-based measures of loudness, the authors suggested that gabapentin primarily impacts the "sensory" features of tinnitus. Perhaps the positive effects of both carbamazepine and gabapentin observed in animal studies relate to the fact that the behavioral paradigms assess whether or not an animal perceives a (phantom) sound, and as such, the "sensory" nature of tinnitus is measured without the secondary features commonly reported in humans, such as the attentional and emotional reaction to tinnitus. Consequently, even if the intensity of the tinnitus is

reduced, it may not be sufficient to reduce the reaction to any residual tinnitus. Alternatively, if the tinnitus signal is abolished, as some animal data suggest, there should no longer be any reaction as the phantom sound is no longer present. The discrepancies between the animal and human data highlight significant challenges and the need for the systematic steps of the translational research process.

In addition to carbamazepine and gabapentin, animal studies that focused on potential peripheral effects have investigated the anticonvulsant retigabine on tinnitus and cochlear function. Retigabine is an unconventional anticonvulsant that exerts its effects through voltage-gated potassium channels. More specifically, retigabine acts as an activator of neuronal KCNQ/Kv7 potassium channels, which on opening cause hyperpolarization, thereby lessening neuronal excitability. Retigabine was found to prevent the reduction in the compound action potential (CAP) that occurs following salicylate administration in rats, findings that the authors suggested could protect against salicylate-induced or other forms of tinnitus (Sheppard et al. 2015). Similarly, noise-exposed mice that were injected with retigabine (starting 30 min after noise exposure and continuing for 5 days) were less likely to develop tinnitus than saline-injected mice that received the same noise exposure (Li et al. 2013). It was reasoned that retigabine prevented tinnitus by offsetting the neuronal hyperexcitability and reduction of KCNQ activity that occurs in the dorsal cochlear nucleus following noise exposure and CAP suppression (Li et al. 2013). In a follow-up study from the same laboratory (Kalappa et al. 2015), the novel KCNQ-channel activator SF0034 was found to be a more potent and less toxic anticonvulsant than retigabine in rodents, which also appeared to prevent noise-induced tinnitus in mice. It is worth noting that in both studies (Li et al. 2013; Kalappa et al. 2015), the noise-exposed mice were screened for tinnitus using the gap prepulse inhibition of the acoustic startle (GPIAS) paradigm. Because the GPIAS paradigm has been challenged as a screening tool for tinnitus (see Sect. 7.2 for details), the promising therapeutic effects of KCNQ-channel activators would be strengthened by additional studies that screened for tinnitus in drug-treated animals using paradigms that rely on carefully designed, behaviorally conditioned responses that can control for the confounding effects of hearing loss. That said, the study by Li et al. (2013) has provided important first steps in understanding potassium-channel pathologies following noise exposure and may one day lead to novel pharmacotherapy for tinnitus patients (Kaltenbach 2013).

In 2011, Hoekstra et al. published a Cochrane Review evaluating the effectiveness of anticonvulsants in tinnitus patients. After excluding several studies from consideration due to such factors as lack of randomization or use of only a single dose of a given drug, seven clinical trials (encompassing 453 patients) were reviewed. Based on a meta-analysis, it was concluded that anticonvulsants showed only a small effect of doubtful clinical significance in the treatment of tinnitus, and 18 % of patients experienced side effects. Consequently, according to the Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014), anticonvulsants are not presently recommended for treating tinnitus, as they failed to show a preponderance of benefit over harm.

7.4.5 Glutamate-Receptor Antagonists

As an alternative to administering drugs aimed at enhancing GABAergic inhibition in tinnitus patients, clinical trials have also attempted to dampen tinnitus-related hyperexcitability by antagonizing glutamatergic (excitatory) neurotransmission. To this end, a variety of glutamate-receptor antagonists have been used, including memantine, neramexane, caroverine, acamprosate, and AM-101. To date, a Cochrane Review has not summarized and critiqued the previous clinical trials of glutamate-receptor antagonists, and the Clinical Guideline of Tinnitus (Tunkel et al. 2014) provides only limited commentary on acamprosate as a treatment option for tinnitus (see below).

Memantine acts as a glutamatergic antagonist by blocking *N*-methyl-D-aspartate (NMDA) channels once they have already opened rather than competing to bind at the actual glutamate-receptor site (Johnson and Kotermanski 2006). Memantine has been proposed as a putative therapeutic agent for tinnitus of cochlear origin because it is known to suppress the excitotoxicity mediated by NMDA receptors on cochlear hair cells (Oestreicher et al. 1998). Using a conditioned lick suppression paradigm in rats, Lobarinas et al. (2006) found that a low dose of memantine (3 mg/kg) failed to completely suppress tinnitus induced by sodium salicylate. However, when this same laboratory increased the dose of memantine (up to 5 mg/kg) and tested animals using the GPIAS paradigm, memantine appeared to suppress salicylate-induced tinnitus (Ralli et al. 2014). Furthermore, Zheng et al. (2012a) found that memantine treatment at the higher dose (5 mg/kg) reduced the proportion of rats that showed behavioral evidence of noise-induced tinnitus using a conditioned lick suppression model (Zheng et al. 2012a).

To date, only one clinical trial has investigated the effect of memantine on tinnitus. In a randomized, double-blind crossover design, 90 days of treatment with memantine did not improve scores on the Tinnitus Handicap Inventory beyond that of the placebo condition, and 9 % of patients experienced side effects (Figueiredo et al. 2008). Suckfüll et al. (2011) performed a double-blind clinical trial to investigate the effect of neramexane, a compound related to memantine that acts as a noncompetitive NMDA antagonist as well as a nicotinic acetylcholine-receptor antagonist, on patients with moderate to severe tinnitus. The various neramexane treatment groups (25, 50, and 75 mg/day) as well as the placebo group all showed trends for improvements in the scores reported for the Tinnitus Handicap Inventory questionnaire (THI-12) at the 16-week study end point, but the results did not reach statistical significance. At 4 weeks after the end of treatment, however, there was a significant improvement in THI-12 scores in the 50 mg/day group compared to the placebo group (Suckfüll et al. 2011). Additional clinical trials investigating the efficacy, safety, and tolerability of neramexane were completed (NCT00405886; NCT00955799) or terminated (NCT00827008) from 2006 to 2012, but it does not appear that any results have been made available as of this writing (https://clinicaltrials.gov/).

Caroverine, in addition to acting as a noncompetitive NMDA antagonist and a competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antagonist, is a calcium channel blocker and antioxidant. Beginning in the late 1990s, a series of clinical trials investigated the efficacy of caroverine on tinnitus. These were conducted based on the rationale that tinnitus of cochlear origin occurs due to excessive glutamate neurotransmission in inner hair cells. In a placebo-controlled single-blind study, a single intravenous injection of caroverine immediately reduced both the subjective rating and psychoacoustic measurement of tinnitus in 63 % of patients in the treatment but not in the placebo control group (Denk et al. 1997). However, a separate study that used the same patient selection and treatment conditions as the protocol of Denk et al. (1997) did not find a positive effect of caroverine administration (Domeisen et al. 1998). Finally, in a proof-of-concept study, when caroverine was applied noninvasively as a 1 % topical solution to the tympanic membrane of the affected ear, 57 % of patients reported an improvement in tinnitus severity (Ehrenberger 2005).

Acamprosate, a drug approved to aid in the withdrawal of alcohol dependency, has been investigated in clinical trials for tinnitus management based on its putative actions as both a glutamate antagonist and positive allosteric modulator of GABA. In a double-blind study, 87 % of patients treated with acamprosate for 90 days reported tinnitus relief compared to 44 % of patients in the placebo group (Azevedo and Figueiredo 2007). Furthermore, a randomized, double-blind, placebo-controlled crossover trial found that there was a significant improvement in both objective measures (psychoacoustic matching of tinnitus loudness) as well as subjective measures of tinnitus (visual analog scale of tinnitus loudness and quality of life questionnaires), with more than 90 % of subjects reporting improvement in their tinnitus (Sharma et al. 2012). Moreover, these positive effects seemed to persist when the acamprosate group discontinued their treatment and crossed over to the placebo phase for an additional 45 days (Sharma et al. 2012). Despite acknowledging these seemingly favorable results, the Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014) does not recommend acamprosate treatment because of insufficient evidence of its efficacy.

Systemic administration of NMDA antagonists can cause considerable undesirable side effects, which ultimately restricts the dosing that can be administered to patients with tinnitus. As reviewed by Meyer (2013), local drug delivery via intratympanic membrane injections can be used to increase the drug concentration in the inner ear while limiting the side effects associated with systemic administration (see Chap. 5 by Lynch, Kil, and Le Prell for additional discussion). In 2011, Muehlmeier et al. evaluated the safety and local tolerance of intratympanic delivery of the noncompetitive NMDA antagonist AM-101 as a therapy for patients who have had tinnitus for less than 3 months. In a randomized, double-blind, placebo-controlled, Phase 1/2a study, they reported that intratympanic AM-101 was well tolerated by study participants (n = 16) irrespective of the administered dose, and there was some preliminary evidence of its efficacy at managing tinnitus. Based on these results, a follow-up Phase 2 clinical trial was conducted on 248 patients

(van de Heyning et al. 2014). Intratympanic administration of AM-101 resulted in a statistically significant, dose-dependent improvement in the subjective measures of tinnitus loudness, annoyance, and sleep difficulties in patients with acute acoustic trauma- or otitis media-triggered tinnitus; however, there was no overall treatment benefit on the objective measure of minimum masking level of the patients' tinnitus, suggesting that whereas patients were less distressed, the tinnitus sound itself remained unchanged (van de Heyning et al. 2014). In support for AM-101 as a potential treatment for acute noise exposure, a study on rats found that local administration of AM-101 in the cochlea reduced the level of noise-induced trauma to the inner hair cells and lessened the decline of signal transmission in the auditory nerve (Bing et al. 2015). At the time of publication of this chapter, subjects were being recruited to participate in Phase 3 clinical trials to investigate the efficacy of AM-101 to treat acute tinnitus that started as the result of an injury to the inner ear or otitis media (NCT01803646) as well as to test the safety and local tolerance of repeated treatment cycles of AM-101 (NCT01934010; NCT02040207). According to information on the NIH-sponsored website (https://clinicaltrials.gov/), final data collection from these studies is estimated to be completed in 2016.

7.4.6 Muscle Relaxants

The efficacy of muscle relaxants such as baclofen and cyclobenzaprine to treat tinnitus has been assessed in clinical trials as well as in animal studies. Baclofen is a derivative of GABA that acts as an agonist of the $GABA_B$ receptor. Although baclofen was found to reverse the noise-induced hyperexcitability of neurons in the rat inferior colliculus in a dose-dependent manner (Szczepaniak and Møller 1996), a double-blind placebo-controlled study found that 3 weeks of baclofen administration (10 mg orally twice daily for 1 week, 20 mg orally twice daily for the second week, and 30 mg orally twice daily for the third week) was no more effective than a placebo in ameliorating tinnitus in patients, as it failed to show any clinical or statistical advantage over the placebo for both subjective and objective measures of tinnitus (Westerberg et al. 1996). However, this study was challenged based on the inclusion of subjects with different types of tinnitus, which may have rendered the study underpowered (Møller 1997) and because a less effective form of baclofen containing both the L- and D-isomers was administered to patients (Smith et al. 2012). In rats, when the more potent form of baclofen (L-isomer) was administered in the days *immediately following* noise exposure, the animals still went on to develop tinnitus (Zheng et al. 2014). In contrast, in a different group of rats that had *already* screened positive for noise-induced tinnitus, the administration of L-baclofen was found to reduce their tinnitus (Zheng et al. 2012b). Finally, to further complicate the actions of baclofen on tinnitus, case reports have been published in which baclofen was found to *induce* severe tinnitus in patients who were taking the medication for alcohol dependence (Auffret et al. 2014). One must be cautious

when interpreting these case reports, however, because additional medications may have confounded the relationship between baclofen and tinnitus in these patients.

In a 12-week, open-label pilot study, the centrally acting muscle relaxant cyclobenzaprine was found to significantly reduce tinnitus severity as assessed by scores on the Tinnitus Handicap Inventory (Coelho et al. 2012). A separate pilot study found that cyclobenzaprine positively affected both the distress and intensity of tinnitus in a subset of patients; 25 % of patients responded with a 55 % reduction in tinnitus distress, whereas 24 % of patients responded with a 53 % reduction in tinnitus intensity (Vanneste et al. 2012). Consistent with the effects of cyclobenzaprine on tinnitus intensity, a study using the GPIAS paradigm found that rats with noise-induced tinnitus showed a reduction in behavior consistent with tinnitus following cyclobenzaprine treatment (Lobarinas et al. 2015). At present, the pharmacological actions of cyclobenzaprine are not completely understood. As suggested previously (Lobarinas et al. 2015), perhaps cyclobenzaprine exerts its seemingly positive effects on tinnitus by acting as an attenuator of phantom pain or as a modulator of attentional mechanisms via its effects on the locus coeruleus, a brainstem region associated with awareness, arousal, and attention. Based on the promising findings in the open-label pilot studies, it was suggested that a randomized, double-blind, placebo-controlled clinical trial was warranted to evaluate the efficacy of cyclobenzaprine as a treatment for tinnitus (Coelho et al. 2012; Vanneste et al. 2012). At the time of publication of this chapter, no clinical trial was yet underway according to an NIH-sponsored website (https://clinicaltrials.gov/).

7.5 Methodological Considerations

Collectively, the preceding sections reveal the considerable challenges associated with translating drug therapies for tinnitus management. For example, it can be difficult to even interpret the seemingly equivocal results of many of the aforementioned clinical trials owing to experimental insufficiencies and/or inconsistencies across studies. Ultimately, these methodological shortcomings contribute to the general lack of support for drug therapies in tinnitus management (Weaver 2014).

In the coming years, it is expected that there will continue to be an increase in the number of investigations devoted to uncovering the neural basis of tinnitus as well as in studies seeking to determine the efficacy of novel or off-label drugs. Moving forward, researchers using animal models are encouraged to scrutinize the validity and reliability of their chosen model for screening animals for tinnitus-like behavior, as failure to do so could confound the assessment of the efficacy of novel drugs for tinnitus treatment. When testing novel or off-label drugs in tinnitus patients, it is clear that future clinical trials should strive to avoid the methodological shortcomings of the studies discussed in this chapter, such as inadequate placebo controls or participant blinding. To that end, Jufas and Wood (2015) acknowledged that successful participant blinding can be achieved if the placebos

used in clinical trials share similar side-effect profiles to the drug under investigation.

In a much-needed call to attention, Landgrebe et al. (2012) have proposed an international standard regarding the methodological aspects of clinical trials for tinnitus. Importantly, the authors have identified several critical aspects of trial design that should be considered in future studies, some of which include (1) limiting the heterogeneity of included participants so as to reduce the variability in the findings (e.g., including/excluding tinnitus patients who also suffer from insomnia, anxiety, and/or depression); (2) using validated subjective and objective outcome measures to comprehensively assess the auditory features of the tinnitus percept, emotional features such as distress and attentional features like awareness; and (3) adjusting the treatment duration and the follow-up period to accurately assess the putative efficacy of the therapy (Landgrebe et al. 2012).

7.6 Potential Alternatives to Drug Treatment for Tinnitus

In addition to drug treatment, a variety of alternative strategies have been attempted for the clinical management of tinnitus, including sound therapy, cognitive behavioral therapy, and repetitive transcranial magnetic stimulation (rTMS). A brief outline of each of these therapies is included in Sects. 7.6.1–7.6.3. For more information, interested readers are encouraged to consult with comprehensive reviews that summarize and critique the effectiveness of sound therapy (Hobson et al. 2012), TRT (Phillips and McFerran 2010), cognitive behavioral therapy (Martinez-Devesa et al. 2010), and rTMS (Meng et al. 2011) for the clinical management of tinnitus.

7.6.1 Sound Therapy

Sound therapy for tinnitus generally refers to the use of sound generators, hearing aids, or combined devices to partially or completely mask tinnitus, with the aim of reducing the patient's awareness and/or associated reactions. Licensed audiologists who have undergone specialized training usually perform these therapies. One such approach, Tinnitus Retraining Therapy (TRT), developed by Pawel Jastreboff, combines counseling with maskers, when needed, as part of a comprehensive treatment strategy (Jastreboff and Hazell 2004). The masking is set to the "mixing" point so that patients can still hear the tinnitus, but it is mixed with competing background noise. This strategy facilitates adaptation as opposed to simply covering up the tinnitus transiently, while the counseling focuses on reducing tinnitus reaction. Another sound therapy approach was developed by Neuromonics™ Inc., a device that was the first of its kind to be approved by the US Food and Drug Administration (FDA). Whereas TRT focuses on counseling with sound generation

providing a supportive role, Neuromonics™ is centered on extensive use of a customized sound generator under the guidance of a healthcare provider.

7.6.2 Cognitive Behavioral Therapy

Beyond TRT and Neuromonics™, more formal psychological treatment for tinnitus can be provided by a mental health professional. One of the most widely used strategies is cognitive behavioral therapy. This approach seeks to manage the suffering associated with tinnitus by training patients to restructure their negative thoughts, enhance coping strategies, and encourage them to face situations that may initially exacerbate their negative feelings to promote habituation. This form of therapy can sometimes reduce the reaction to tinnitus even when the acoustic percept shows no significant change (Martinez-Devesa et al. 2010).

7.6.3 Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is an experimental tool for stimulating cortical neurons via brief magnetic pulses delivered to the scalp, with the goal of interfering with the tinnitus-related neural activity (Langguth et al. 2012). This form of treatment requires physician oversight and has been applied to central disorders such as migraine and stroke. Repetitive transcranial magnetic stimulation (rTMS) was approved as a treatment for major depression by the FDA in the United States in 2008 for patients unresponsive to antidepressant pharmacotherapy. Although rTMS has been successful in a subset of tinnitus patients, the associated costs and specialized facilities have limited its widespread use.

7.7 Summary

Given that tinnitus etiology, as well as its perceptual characteristics and associated symptoms, can vary considerably among patients, perhaps it is not surprising that no single drug has been widely accepted as being effective at either quieting tinnitus or eliminating its distress. Although some drugs have shown promising effects in a subset of patients (e.g., carbamazepine for “typewriter tinnitus” or AM-101 for acute noise-induced tinnitus), there is limited support from the aforementioned clinical trials and Cochrane Reviews that any specific off-label drugs are capable of fully treating tinnitus. Ultimately, based on the systematic reviews and acknowledgment of the methodological concerns of several of the clinical trials, the Clinical Practice Guideline for Tinnitus (Tunkel et al. 2014) stated that clinicians should not *routinely* recommend antidepressants, anxiolytics, anticonvulsants, or

intratympanic medications for the primary goal of treating persistent, bothersome tinnitus. That said, it is acknowledged that their recommendation to avoid the routine use of medications for tinnitus does not apply to those patients with comorbid disorders, such as depression, anxiety, or seizure disorder, in which such drugs could be indicated and useful (Tunkel et al. 2014).

In the future, it is expected that validated animal models will continue to serve a crucial role in uncovering the neural basis of tinnitus as well as providing opportunities to screen novel therapies for tinnitus suppression. As discussed earlier, translating these findings from animal studies to the improved treatment for tinnitus patients will ultimately require the collaboration of scientists, audiologists, otolaryngologists, and mental health professionals to fully address the worldwide problem of tinnitus.

Compliance with Ethics Requirements

Brian L. Allman declares that he has no conflict of interest.

Ashley L. Schormans declares that she has no conflict of interest.

Marei Typlt declares that she has no conflict of interest.

Edward Lobarinas received 1-year postdoctoral funding for research on AM-101 from Auris Pharmaceuticals.

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