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To cite this article: Berthold Langguth & Ana Belén Elgoyhen (2011) Emerging pharmacotherapy of tinnitus, Expert Opinion on Emerging Drugs, 16:4, 603-606, DOI: [10.1517/14728214.2011.644273](https://doi.org/10.1517/14728214.2011.644273)

To link to this article: <https://doi.org/10.1517/14728214.2011.644273>



Published online: 08 Dec 2011.



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# Expert Opinion

1. Background
2. Current pharmacologic treatment
3. Future pharmacological agents
4. Expert opinion

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## Emerging pharmacotherapy of tinnitus

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One in ten adults has clinically significant subjective tinnitus, and for one in hundred, tinnitus severely affects their quality of life. Despite the significant unmet clinical need for a safe and effective drug targeting tinnitus relief, there is currently not a single FDA-approved drug on the market. Even a drug that produces a small but significant effect would have a huge therapeutic impact. In the last few years, there have been significant advances in i) the understanding of the pathophysiology of the different forms of tinnitus, ii) the establishment of valid animal models and iii) the development of clinical trial methodology. A glimpse of hope is appearing in the horizon as an increasing number of pharmaceutical industries now have compounds targeting tinnitus in their pipeline.

**Keywords:** animal models, anticonvulsants, antidepressants, anxiolytics, auditory system, GABA, glutamate, hearing, inner ear, NMDA, pain, phantom perception, randomized clinical trials

*Expert Opin. Emerging Drugs* (2011) 16(4):603-606

### 1. Background

Tinnitus is a common and distressing symptom that is characterized by the perceived sensation of sound in the absence of an external stimulus. Based on recent data, tinnitus occurs in 25.3% of American adults (50 million people), with 7.9% experiencing it frequently (16 million people) [1]. Epidemiological studies reveal comparable prevalence rates for Europe, Asia and Africa [2]. Most important risk factors for tinnitus are increasing age, male gender and hearing loss. These prevalence rates are expected to increase due to demographic development, warfare and increasing occupational and leisure noise. Two years ago, we reviewed pharmacotherapeutic options for tinnitus, the potential of new emerging compounds and the difficulties and challenges in their development [3]. Here we provide an update, based on the recent increasing literature regarding tinnitus pathophysiology and treatment.

Many patients with tinnitus report symptoms such as frustration, annoyance, anxiety, depression, irritation, concentration difficulties and sleep disturbances. These symptoms are highly relevant for the perceived tinnitus severity [2]. Thus, tinnitus represents a highly prevalent and distressing condition that places a huge burden on patients and significantly impairs quality of life.

Although often arising from peripheral hearing loss, tinnitus persists after auditory nerve transection, suggesting the critical involvement of central mechanisms. In recent years, animal studies and neuroimaging data have contributed to a more detailed identification of the neuronal alterations in the central nervous system underlying tinnitus [4]. Governed by mechanisms of homeostatic plasticity [5], reduced auditory input results in reduced inhibitory and increased excitatory function in central auditory pathways. This in turn leads to increased neuronal firing rates, increased neuronal synchrony and tonotopic reorganization [4]. Most relevant for the tinnitus percept is the synchronized neuronal activity in the central auditory pathway. However, this activity alone is not sufficient for conscious tinnitus

perception [6,7] and coactivated ‘(self-)awareness’ and ‘salience’ brain networks are required. In addition, activation of a non-specific distress network accounts for the perceived annoyance and distress [7]. Moreover, memory mechanisms might play a role in the persistence of the awareness of the phantom percept, as well as in the reinforcement of the associated distress [7]. Thus, different dynamic overlapping brain networks should be considered as targets for the treatment of this disorder.

Several tinnitus animal models have been established, but their behavioral validation is currently still restricted to the perceptual aspects of tinnitus. Thus, whereas the available models probably reflect tinnitus-related alterations in central auditory pathways leading to the phantom percept, changes in nonauditory brain areas underlying tinnitus-associated distress are probably not recapitulated. Activity changes in the central auditory pathways are mediated by alterations in GABAergic [5], glycinergic [8] and glutamatergic neurotransmission. Serotonergic axons from the dorsal raphe nucleus, the nucleus accumbens and other paralimbic regions innervate the thalamic reticular nucleus and the dorsal thalamus and have been proposed to modulate tinnitus-related activity in auditory pathways [6].

There is an increasing consensus that subtypes of tinnitus exist. These differ in their pathophysiology and in the response to specific treatments. The lack of well-established clinical criteria to differentiate pathophysiologically distinct subtypes represents a major challenge for clinical research. Moreover, since tinnitus is a purely subjective condition, outcome measurement of therapeutic interventions is not trivial. Systematic assessment of treatment effects across clinical trials, together with standardized assessment of clinical characteristics of participating patients and the collection of these data in a large database, has been proposed in order to identify outcome predictors for specific treatments and useful characteristics for subtyping of tinnitus patients [9]. An increasing number of assessment instruments have been developed and validated, and there is a consensus initiative underway to standardize methodological aspects of clinical tinnitus trials. Efficient criteria for subtyping patients and an increase in the methodological quality of clinical trials will be essential for the identification of efficient pharmacologic treatments.

## 2. Current pharmacologic treatment

Although a wide variety of compounds have been (and still are) used off-label to treat tinnitus patients, there is still no US Food and Drug Administration (FDA)- or European Medicines Agency (EMA)-approved drug on the market [3]. The long list of used compounds includes anxiolytics, anticonvulsants, antidepressants, *N*-methyl *D*-aspartate (NMDA) antagonists, cholinergic antagonists, antihistamines, vasodilators, antipsychotics, sodium and calcium channel antagonists, antidiuretics and herbal medicines, among others [3]. In some cases, like in the case of anticonvulsants and the calcium antagonist gabapentin, the rationale behind their use derives from their effectiveness in pathologies thought to share

underlying neural substrates with tinnitus, like epilepsy and neuropathic pain, respectively. In other cases, their use aims to treat the comorbidities that accompany tinnitus, such as depression, anxiety and sleep disorders. Even further, some drugs such as NMDA receptor antagonists and GABA<sub>A</sub> agonists are used based on known underlying neuronal changes seen in tinnitus, with the hope of reversing the increased neuronal excitability observed in several regions of the auditory pathway [4]. Some drugs have been reported to provide moderate relief of symptoms in a subset of patients. However, most drugs have not proven sufficient effectiveness in randomized controlled clinical trials in order to be marketed specifically for tinnitus [3]. Thus, novel pharmacological approaches for treating tinnitus are required in order to address a widely recognized, yet largely underserved and unmet, clinical need.

## 3. Future pharmacological agents

### 3.1 Animal studies

Recent animal research has focused on the neurochemistry of tinnitus-related changes in synaptic plasticity in the dorsal cochlear nucleus (DCN), a site of integration of acoustic and multimodal sensory inputs. In animal models of tinnitus, changes of inhibitory glycinergic neurotransmission have been demonstrated [8]. In a DCN slice preparation from mice with behavioral evidence of tinnitus, flavoprotein autofluorescence imaging was used to measure evoked circuit activity, revealing a decrease in GABAergic inhibition [10]. Consistent with these findings, behavioral signs of tinnitus are attenuated in rats when taurin, a partial agonist of glycine and GABA<sub>A</sub> receptors, is supplemented to their diet [11]. Moreover, it has been demonstrated that synaptic plasticity in the DCN is modulated by muscarinic cholinergic receptors interacting with endocannabinoid signaling [12]. However, two different cannabinoid receptor agonists (WIN55,212-2 and CP55,940) do not reduce behavioral manifestations of salicylate-induced tinnitus in rats [13].

A very recent study has tried to identify which changes in the auditory cortex are critically relevant for tinnitus perception [5]. Cortical changes after high-frequency hearing loss depended on the exact cortical region analyzed. The ‘normal hearing’ cortical area, which corresponded to the representation of low frequencies, showed increase in inhibitory and excitatory transmission and map reorganization. By contrast, in the sensory-deprived high-frequency area, only GABAergic inhibitory transmission was decreased and excitatory neurotransmission was not changed. Drugs that enhance GABAergic inhibition such as vigabatrin, but not those that reduce excitation (such as ketamine), reversibly eliminated the tinnitus behavior, indicating that reduced inhibition in the sensory-deprived area may be causally related to tinnitus [5]. This finding indicates that pharmacologically targeting GABAergic synapses or the cellular mechanisms underlying homeostatic plasticity might alleviate tinnitus symptoms.

Kv7 potassium channels, which are present in the peripheral and central auditory system, may represent an alternative target for modulating tinnitus-related increases in neural activity. In a pilot study Maxipost, a compound that attenuates hyperexcitability via modulation of Kv7 potassium channels, reduced behavioral signs of salicylate-induced tinnitus in rats [14]. In addition, for some forms of acute tinnitus, intratympanic steroid injections have proven beneficial. Since repeated intratympanic injections are difficult to perform and inner ear drug exposure is limited after single injections, there is a need for sustained-release formulations. Such an option may be the sustained-release dexamethasone hydrogel OTO-104 for which therapeutic perilymph levels of dexamethasone have been reported up to 3 months after intratympanic injection in guinea pigs [15].

### 3.2 Clinical studies

An increasing number of new compounds with diverse actions on the central nervous system are under investigation for tinnitus, indicating that the headquarters of big pharmaceutical companies are perceiving tinnitus as a potential indication for new central acting drugs.

GlaxoSmithKline investigated the neurokinin-1 receptor antagonist vestipitant, which has anxiolytic properties, for the treatment of chronic tinnitus. Although well-tolerated, vestipitant, alone or in combination with paroxetine, was not effective in ameliorating tinnitus [16]. By contrast, neramexane, an antagonist of NMDA receptors and of  $\alpha 9\alpha 10$  cholinergic nicotinic receptors developed by Merz, has shown promising results in a Phase II trial [17] and has entered Phase III [18]. Further compounds that have entered Phase II programs, are the AMPA antagonist BGG492A from Novartis [19], which is also under investigation for the treatment of migraine and epilepsy, and Cilostazol from Otsuka Pharma, which selectively inhibits phosphodiesterase type 3 and increases cyclic adenosine monophosphate concentrations by inhibiting its degradation [20]. Moreover, deanxit, the combination of the antidepressant mirtazapine and the antipsychotic flupentixol, has proven superior to placebo in a crossover trial as add-on medication to clonazepam [21].

Based on the assumption that glutamatergic excitotoxicity in the cochlea might play a role in tinnitus generation, intratympanic injections of the NMDA receptor antagonist AM-101, from Auris Medical, were applied in patients with acute tinnitus (less than 3 months duration) in a double-blind, randomized, placebo-controlled Phase I/II clinical trial. Intratympanically injected AM-101 was well tolerated and demonstrated a trend toward a reduction of the minimal masking level compared with placebo. However, no effects on tinnitus loudness and severity were observed, as measured by visual analog scales and the TBF-12 questionnaire, respectively [22]. The safety and efficacy of another intratympanically applied antiglutamatergic agent (NST001, Neurosystec) is currently being tested in a further pilot study [23].

### 4. Expert opinion

Since our last review [3], there have been important advances in tinnitus research. Many difficulties that have hampered the search for effective pharmacologic compounds in the past have been successfully addressed. This is evidenced by a more detailed understanding of the pathophysiology of the different forms of tinnitus, better elaborated and validated animal models and improvements in clinical trial methodology. Promising new agents are under investigation. It is expected that further compounds will follow, enhancing the possibility that the first FDA- or EMA-approved drug effective in the treatment of tinnitus and its debilitating symptoms will enter the market soon.

### Declaration of interest

B Langguth has received sponsorship from Deutsche Forschungsgemeinschaft, the Tinnitus Research Initiative and AstraZeneca. He has also received honoraria for consultancy from Sanofi, Novartis and Merz. AB Elgoyhen has received sponsorship from the Tinnitus Research Initiative and the Howard Hughes Foundation.

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