Tinnitus psychopharmacology: A comprehensive review of its pathomechanisms and management

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Background: Subjective tinnitus is a frequent, impairing condition, which may also cause neurotransmitter imbalance at the cochlea. Psychopharmacologic agents, although not being the first-line treatment for tinnitus, may modulate cochlear neurotransmission, thereby influencing the subjective tinnitus experience.

Method: A comprehensive review of MEDLINE literature (from January 1990–January 2010) was performed searching for: “tinnitus”, major classes of psychopharmacological agents, and psychiatric disorders. The most relevant clinical evidence is reported briefly along with a concise description of the main neurotransmitters purported to be involved in tinnitus, in order to provide the reader with a rational evaluation of tinnitus therapy with psychopharmacological agents.

Results: Although strong methodological issues limit the reliability of the current results, a broad number of psychopharmacological agents have already been considered for tinnitus, both as candidate triggers or potential therapies.

Conclusions: Selected psychopharmacological drugs may play a role in the clinical management of this disorder. While the rational use of these agents for the treatment of tinnitus should not be overlooked, research should be undertaken on their neuromodulating actions at the cochlea.

Keywords: tinnitus, psychopharmacology, cochlea

Introduction
Tinnitus, from the Latin word “tinnitus” meaning “ringing”1 is a perception of sound in the absence of external sounds (ICD-10 code, H93.1).2 This phenomenon can be divided into two broad groups: objective and subjective tinnitus. Objective tinnitus is provoked by sound generated in the body reaching the ear through conduction in body tissues, while subjective tinnitus is meaningless sounds that are not associated with any physical sound and it can be heard only by the suffering person. Although subjective tinnitus represents a far more prevalent condition compared to objective tinnitus,3 and thereby constitutes a more accessible phenomenon for investigators, current information available on its etiology is unsatisfactory. In fact, while a broad number of heterogeneous pathomechanisms and causes have been postulated (Table 1), no univocal consensus has been reached to date and its management is still a well debated issue. Furthermore, since there are many kinds of subjective tinnitus, the search for a (unique) cure is futile. As consequence, both researchers and clinicians have progressively extended the portfolio of potential therapies (including nonfirst-choice treatments such as psychopharmacological agents) especially for those patients whose tinnitus may be related to comorbid psychological stressors.4
Since some forms of tinnitus may be exacerbated or moderated by psychopharmacological agents, the aim of the present paper is to provide the reader with an updated survey on their rational use in subjective tinnitus.

**Data source and selection**
A comprehensive review of English-written MEDLINE results was retrieved using the following queries: “Tinnitus AND neurobiology”; “Tinnitus AND therapy”; “Tinnitus AND antidepressant”; “Tinnitus AND SSRI”; “Tinnitus AND venlafaxine”; “Tinnitus AND duloxetine”; “Tinnitus AND bupropion”; “Tinnitus AND tricyclic”; “Tinnitus AND benzodiazepine”; “Tinnitus AND lithium”; “Tinnitus AND antiepileptic”; “Tinnitus AND anxiety”; “Tinnitus AND depression”; “Tinnitus AND bipolar disorder”; “Tinnitus AND schizophrenia”; “Tinnitus AND ADHD”; and “Tinnitus AND dementia”. Results were kept within a January 1990–January 2010 time limit. Finally, meta-analysis and randomized clinical trials (RCTs) data were prioritized when available.

**Pathophysiology**
The changes in the auditory nervous system, especially at the dorsal (DCN) and ventral cochlear nucleus (VCN) underpinning tinnitus are often represented by a reduction in the inhibitory rather than an excitatory input, resulting in a shift in the balance between inhibition and excitation.

Deprivation of input may cause neural plasticity to change the relationship between inhibition and excitation and protein synthesis and finally, impact on neurotransmission—especially at the DCN, the inferior colliculus (IC), together with the primary and secondary auditory cortices—eventually affecting the thalamic and dorsal cortex transmission, the amygdala, and other structures. The rerouting of information may cause structures of the central nervous system (CNS) that are not normally involved in processing auditory information to become activated by sound stimulation (ie, the abnormal involvement of the nonclassical–nonspecific/extralemniscal–pathways). Yet to date, no univocal or exhaustive appreciation of tinnitus determining neural abnormalities has been...
reached; with its pathophysiological correlates still remaining a debated issue.

Among others, the following evidence and hypotheses have been postulated:7

**Peripheral auditory system**

**Spontaneous otoacoustic emissions**
Small acoustic signals presumed to be generated by the electromotile activity of the outer hair cells (OHCs) of the cochlea and propagated into the external auditory canal may be abnormally perceived as tinnitus.8

**Edge theory**
Increased spontaneous activity in the edge area, which represents a transition from normal OHCs on the apical side of a lesion to OHCs toward the basal side that are missing or altered, may contribute to tinnitus perception.9

**Discordant theory**
The discordant dysfunction of damaged OHCs and intact inner hair cells (IHCs) may result in the disinhibition and increased spontaneous activity of neurons in the DCNs, that receive excitation from IHCs, but with no inputs from the damaged OHCs, therefore playing a role in tinnitus phenomenon.10

**Central auditory system**

**The dorsal cochlear nucleus**
Hyperactivity by disinhibition or plastic readjustments of the DCN, triggered for instance by OHC damage or a reduction in auditory nerve input have been supposed to concur in tinnitus genesis.11

**Auditory plasticity theory**
Damage to the cochlea enhances neural activity in the central auditory pathway, such as the IC and the temporal lobe of the auditory association cortex (similar to the phantom limb sensation in amputees).12

**Crosstalk theory**
The compression from blood vessels or a tumor on auditory nerve causes ephaptic coupling between nerve fibers, which may result in the phase-locking of spontaneous activity of groups of auditory neurons that may be perceived as sound.13

**Somatosensory system**
Abnormal DCN activity could also be influenced by the stimulation of the somatosensory system. Furthermore, pain signals from the cochlea carried by the cochlear C fibers may be interpreted by the CNS as tinnitus.14

**Neurotransmitters**
It has been postulated that numerous cochlear neurotransmitters play a role in tinnitus sensation.

**GABA**
It is known that the number of gamma-aminobutyric acid (GABA) immunoreactive neurons in the auditory nuclei decreases with age;15 together with its concentration and release, the glutamatergic acid decarboxylase activity (the rate-limiting enzyme in the formation of GABA), GABAA receptor binding and the presynaptic GABA releasing terminals availability.16 This trend has been postulated to be a higher risk of noise-induced hearing loss as an important tinnitus etiological factor, especially in older men17, and has prompted both researchers and clinicians to consider GABAergic modulators as a candidate therapy for tinnitus patients. Anxiolytic benzodiazepines (BDZ), as well as antiepileptic drugs that enhance GABAA receptors (including those used as mood-stabilizers); or GABAB agonists (eg, baclofen, a drug used for multiple sclerosis and proposed for morphine withdrawal syndrome) have all been suggested both for animal and human models of tinnitus.19,20 Finally, while anxiety per se does not produce tinnitus, it may strongly exacerbate its perception, and may be modulated by GABAergic neurotransmission enhancers with the final result of tinnitus relief.

**Serotonin**
Serotonergic (5-HTergic) modulation (eg, by salicylate administration) has been reported to provoke tinnitus,21 although human genetic studies on the regulatory region of the 5-HT transporter (5-HTTLPR) SLC6A4 gene failed to show any significant effect on the susceptibility to chronic tinnitus, thus indicating an indirect, rather than a direct, modulating role of 5-HT in tinnitus etiology and CNS-adaptive mechanisms.22 Modulation of 5-HT is a core mechanism of a very large number of routinely prescribed drugs including the selective serotonin reuptake inhibitor (SSRI) antidepressants, thus their putative role in increasing the sensation of tinnitus should therefore be taken into account.23 Nonetheless, the biological theory of depression provides a rationale for the association of emotional distress and chronic tinnitus determined by the respective impact of dysfunctional neural reorganization on limbic and auditory structures, with a specific role of brain-derived...
neurotrophic factor (BDNF) in promoting plasticity-induced recovery, has been postulated in depressive states, which could make some affective (or anxiety) disordered individuals more genetically prone or stress-vulnerable for developing tinnitus.

**Dopamine**

Tinnitus perception takes place in prefrontal, primary temporal and temporoparietal associative areas, as well in the limbic system. Dopamine (DA) neurotransmission acts through prefrontal, primary temporal, temporoparietal associative areas and the limbic system. Tinnitus perception and DA-ergic pathway share the same cerebral structures, which control attention, stress, emotions, learning, memory and motivated behavior. Distress from tinnitus emanates from these same cerebral functions, and could therefore be potentially modulated by either DA-blockers (ie, typical and atypical antipsychotics) or DA-agonists (eg, bupropion, a norepinephrine/DA reuptake inhibitor, antidepressant and by many anti-Parkinson drugs such as levodopa, bromocriptine, pramipexole and others).

**Glutamate**

N-methyl d-aspartate (NMDA) glutamate receptor is most likely involved in tinnitus, as it is involved in many forms of central neuropathic pain. Specifically, it has been shown that acetylsalicylic acid activates cochlear NMDA receptors and that the use of NMDA-antagonists at the round window abolishes tinnitus, while NMDA receptor agonists may induce tinnitus-like behaviors. Memantine, used to treat neuropathic pain and mild to moderate forms of Alzheimer’s disease, blocks NMDA transmission in hair cells (the same as salicylate acts upon) also modulating the cholinergic transmission. Acamprosate, a drug acting as both a NDMA-blocker and GABA-enhancer is used for alcohol withdrawal maintenance, recently proposed as an (augmentation) strategy to improve cognitive depressive symptoms, has recently been trialed for the management tinnitus with some success. Salicylate amplifies cochlear NMDA-mediated responses but has little or no effect on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) glutamate receptor and glutamatergic kainite-mediated responses. AMPA receptors (AMPA) are both glutamate receptors and cation channels that are integral to plasticity and synaptic transmission at many postsynaptic membranes. AMPA receptors mediate the excitotoxic effect of excessive noise trauma, leading to excessive amounts of glutamate in the synaptic cleft that results in neurite loss, and are also able to upregulate themselves through plastic changes. Application of NMDA antagonists onto the round window membrane abolishes tinnitus, even in animals receiving treatment with the 5-HT₂C anxiogenic agent 1-(-3-chlorophenyl) piperazine (mCPP), suggesting NMDA blocking, even for depressed or chronically anxious tinnitus patients.

**Ion channel and others**

The inner cells of the cochlea have only the L-type of calcium (Ca²⁺) channels, that are involved in the regulation of in situ glutamate release and are blocked by salicylate. In the IC, the current through the L-type channels, although unable to directly trigger the neurotransmitter release, contributes to GABAergic transmission by activating the second messenger system and/or by increasing the intracellular Ca²⁺ connection; while salicylate also blocks the outward and delayed rectifier potassium (K⁺) channels in rat IC, hence decreasing the GABAergic transmission.

Glycine receptors (whose number significantly decreases with age in DCN) along with acetylcholine muscarinic and nicotinic receptors (whose number also decreases with age in the VCN and IC) antagonism has also been investigated for their implication in the genesis of tinnitus and may lead to new pharmacological strategies (such as with varenicline, a smoking-cessation drug and often prescribed to psychiatric patients) in the treatment of tinnitus.

**Psychopharmacological treatment**

Many drugs, including psychopharmacological agents, are routinely employed in the treatment of tinnitus (Table 2). Such drugs could be prescribed as both a potential therapy for tinnitus, or just to patients with psychopathological problems who may also present with tinnitus, or to patients with psychopathological problems who may develop tinnitus (possibly as iatrogenic phenomenon).

**Antidepressants**

Baldo and colleagues performed a meta-analysis in 2006 on tricyclic antidepressants (TCAs) and SSRIs, which questioned substantially their efficacy in the treatment of tinnitus, although most evidence may have been invalidated by methodological bias or the reliance on single case reports. In 2007, an analysis of four RCTs by Robinson found that higher doses of SSRIs and TCAs appear to work for tinnitus patients who also exhibit depression and anxiety or insomnia, both of which are frequent comorbidities among chronic otologic patients. What appears to be irreversible disability of otologic origin may, in part, be a reversible disability of...
### Table 2: Main pharmacological agents for subjective tinnitus

| Drugs          | Rationale                                                                 | Evidence                                                                 |
|----------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| **Antidepressants** |                                                                            |                                                                          |
| TCAs           | NA- and 5HT-ergic transmission modulation, anticholinergic action, BDNF synthesis enhancement | Nortriptyline Superior to placebo (RTC) (higher doses of TCAs and SSRIs appear to work for tinnitus patients who also exhibit depression and anxiety or insomnia) | Amitriptyline Some success (case reports and a single blind study). Low doses sometimes related to tinnitus onset |
|                |                                                                            |                                                                          |
|                |                                                                            |                                                                          |
| SSRIs          | 5HT-ergic transmission modulation, BDNF synthesis enhancement               | Paroxetine No significant improvement for nondepressed patients (RTC)     |
|                |                                                                            |                                                                          |
|                |                                                                            |                                                                          |
| SNRIs          | NA- and 5HT-ergic transmission modulation, BDNF synthesis enhancement       | Duloxetine Withdrawal has been seldom associated with tinnitus           |
|                |                                                                            |                                                                          |
|                |                                                                            |                                                                          |
| NDRIs          | NA- and DA-ergic transmission modulation, BDNF synthesis enhancement        | Bupropion Limited-sample reports indicated its potential induction of tinnitus |
|                |                                                                            |                                                                          |
| Heterocyclics  |                                                                            |                                                                          |
|                |                                                                            |                                                                          |
| Sedative-hypnotics | GABA-A-ergic transmission modulation                                     | Alprazolam Superior to placebo in the treatment of severe disabling tinnitus of predominantly cochlear origin (effective especially for those patients presenting high levels of co-morbid anxiety) |
| Benzodiazepines| (alprazolam, clonazepam, midazolam: short half/average-life and pro 5-HT-ergic features) | Clonazepam Superior to placebo (effective also for pulsatile tinnitus when associated with beta-blocker agents) |
|                |                                                                            |                                                                          |
|                |                                                                            |                                                                          |
| GABA-B agonists| Muscle relaxing and antispastic action                                     | Midazolam Superior to placebo                                           |
| Mood stabilizers|                                                                            |                                                                          |
| Antiepileptics | GABA-ergic transmission enhancement, GABA transaminase inhibition, alpha (2) delta calcium channel antagonism, others (histone deacetylases role, GSK-3 remodeling and synapsin I clustering) | Carbamazepine Some success in case reports and trials (limited sampled reports indicated its potential induction of objective tinnitus) |
|                |                                                                            |                                                                          |
| Lithium        | Inhibitory effect on the phosphoinositide cascade, proserotonergic at higher doses? Others | Gabapentin Effective in reducing subjective or objective tinnitus, especially in individuals with associated acoustic trauma (RTC) |
|                |                                                                            |                                                                          |
| Glutamatergic compounds | NDMA receptor blockade and GABA-ergic transmission enhancing | Superior than placebo in a double-blind study (potentially effective even for depressed or chronically anxious tinnitus patients) |
| Acamprosate    |                                                                            |                                                                          |
| Memantine      | Hair cells NMDA transmission blockade and cholinergic modulation           | Not yet investigated in humans for tinnitus treatment                    |

(Continued)
### Table 2 (Continued)

| Drugs | Rationale | Evidence |
|-------|-----------|----------|
| **Antipsychotics** | | |
| Typical | Auditolimbic D₂, DA-ergic modulation | Cases of schizophrenic patients treated with antipsychotics for tinnitus-like sensations |
| Atypical | Dose-depending D₂ receptor antagonism (postsynaptic D₂-blockade at high doses and presynaptic auto-inhibitory D₂-blockade at low doses with DA release instead of reduction), D₁ partial agonism, others | Sulpiride Superior to placebo in a single blind (low doses) placebo-controlled study and in a RTC + hydroxyzine or melatonin |
| Lidocain | L-type CA++ channels blockade, indirectly contributing to glutamatergic, GABA-ergic and cholinergic transmission modulation | Partially effective |
| Melatonin | Pineal neurohormone with melatonergic agonism and anti-DA-ergic actions | Partially effective, especially in patients with sleep disturbance |
| Botulinum toxin | Inhibition of acetylcholine release at the neuromuscular junction | Partially effective in somatic tinnitus |
| **Zinc, antioxidants, minerals, vitamins, ginko biloba and other herbal remedies** | Different mechanisms of action | Alternate results or ineffective |
| **Unassessed potential targets** | | |
| Agomelatine | MT1/MT2 melatonergic agonism and 5-HT₂C-ergic antagonism | No evidence to date |
| Varenicline | Nicotinic acetylcholine receptor partial agonism | No evidence to date |

**Abbreviations:** DA, dopamine; TCA, tricyclic antidepressants; CA, calcium; GABA gamma-aminobutyric acid; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; NDRI s, serotonin norepinephrine and dopamine reuptake inhibitors; NMDA, N-methyl D-aspartate; RTC, relaxation training control; BDNF, brain-derived neurotropic factor; NA, noradrenaline; GSK-3, glycogen synthase kinase-3; MT, metallothionen.

Psychiatric origin when treated with drugs proven to be effective antidepressants such as nortriptyline.

Some TCAs have proven not to be effective for tinnitus, or were even less effective than placebo (or possibly being associated with tinnitus onset with high doses of clomipramine).

A possible dose effect may exist as lower doses have sometimes been related to tinnitus onset, even when the same agents were reported as being effective (as in non-TCA heterocyclic antidepressants such as trazodone and mianserin).

Sertraline was found to be more effective than placebo for severe refractory tinnitus cases although its discontinuation was associated with tinnitus onset. Other SSRIs (eg, paroxetine) provided no significant improvement for nondepressed patients or even exacerbated tinnitus (eg, fluoxetine).

While newer antidepressants have not been investigated as thoroughly as SSRIs and TCAs, little data on their role in the treatment of tinnitus has been reported and which has sometimes led to inhomogeneous evidence.

Serotonin norepinephrine reuptake inhibitors (SNRIs) withdrawal has seldom been associated with tinnitus (both for venlafaxine and duloxetine), while the norepinephrine dopamine reuptake inhibitor (NDRI) bupropion may mimic a transient ischemic attack that may induce tinnitus, that is most likely due to DA-ergic enhancement.

### Antipsychotics

Although pharmacological treatment is well-established for tinnitus in clinical practice systematic, rigorous literature evidence on antipsychotics is lacking, especially with regard to recently introduced atypical compounds.

Also, it is sometimes difficult to separate tinnitus from psychotic symptoms, thus increasing the cases of schizophrenic patients who may receive antipsychotics for tinnitus-like sensations or hallucinations.

To date the most accurately investigated antipsychotic medication for tinnitus is sulpiride.

A 2007 prospective, randomized, single blinded, placebo-controlled study by Lopez-Gonzalez on sulpiride plus hydroxyzine (an antihistamine derivate and subcortical sedative attenuating the limbic system) indicated the efficacy of the antipsychotic drug in reducing the sensation of tinnitus, possibly mediated by the auditolimbic D₂ DA-ergic modulation. An RCT investigation from the same group also reported the efficacy of sulpiride in association with melatonin (a pineal hormone with anti-DA-ergic actions) in attenuating tinnitus sensation. Remarkably, both studies used...
low doses of sulpiride (up to 50 mg/8 hours) and this should be taken into account when using (atypical) antipsychotics, since the presynaptic autoinhibitory D₂-blockade should lead to DA release instead of reduction (as evidenced by high dose-mediated postsynaptic D₂ heteroreceptors blockade).

The melatonergic role has also been considered for associations with antipsychotics other than sulpiride, and is worthy of further investigation, even for other classes of drugs (ie, the newly introduced antidepressant agomelatine, acting as metallothionen-1 (MT1)/MT2 melatonergic agonist and 5-HT₂c-ergic antagonist).76

Mood stabilizers

Many antiepileptics used as mood stabilizers have been considered for the treatment of tinnitus, although almost all available evidence does not come from systematic investigations and therefore do not lead to an univocal consensus.

Among others, carbamazepine has been proposed both as stand-alone treatment for subjective tinnitus or with lidocaine, salicylate, or steroid augmentation/switch option, while limited-sampled reports indicate its potential induction of objective tinnitus (by auditory nerve vascular compression).81,82

Valproate, an another popular antiepileptic/mood-stabilizer, has also been investigated as a candidate for tinnitus therapy.83,84 However a singlecase has been reported suggesting its potential role in inducing tinnitus (eventually by magnesium metabolism impairment).85,86 with tinnitus eventually being misinterpreted as psychotic symptom.87 The only RCT evidence for lamotrigine concluded it to be ineffective for tinnitus.88

To date, gabapentin is the most thoroughly investigated antiepileptic drug for tinnitus. A placebo-controlled trial by Bauer and colleagues reported its effectiveness in reducing subjective or objective tinnitus, especially in individuals with associated acoustic trauma.89 However, more recent, placebo-controlled studies using high doses of gabapentin (1800 mg/day and 900–3600 mg/day respectively) have disproved its efficacy versus placebo.90–92 Remarkably, no systematic studies on the use of pregabalin (a gabapentin-related GABA-B-agonist agent).103 While no systematic trials have been conducted on the long half-life BDZs, it has been observed that the chance of protracted tinnitus due to abrupt discontinuation of diazepam (30 mg/day long-term treatment)104 or oxazepam105 is most likely due to a receptor upregulation phenomena.

Sedative-hypnotics

Benzodiazepines (BDZs) and other sedative-hypnotics agents are among the most prescribed drugs worldwide and the pivotal role of BDZ receptor distribution in severe, intractable tinnitus has been studied by Daftary and colleagues.99 It is therefore unsurprising that BDZ GABA-A-ergic modulation has repeatedly been considered for treating severe disabling tinnitus of predominantly cochlear origin.98

Although systematic investigations are lacking, the majority of evidence suggests their potential role in tinnitus management, especially for those patients presenting with high levels of comorbid anxiety. Placebo-controlled trials for alprazolam,99 midazolam,100 and clonazepam101 have produced the most promising results (remarkably, these drugs share the short half/average-life and the pro-5-HT-ergic features). Clonazepam has also been reported as being effective for the treatment of pulsatile tinnitus when associated with beta-blocker agents,102 although less effective than baclofen (a muscle relaxer and an antispasmodic GABA-B-agonist agent).103 While no systematic trials have been conducted on the long half-life BDZs, it has been observed that the chance of protracted tinnitus due to abrupt discontinuation of diazepam (30 mg/day long-term treatment)104 or oxazepam105 is most likely due to a receptor upregulation phenomena.

Conclusions

Tinnitus pharmacological therapies include a wide range of proposed medicaments. Among others, zinc, melatonin, lidocaine, botulinum toxin, antioxidants minerals, vitamins, ginkgo biloba, and other herbal remedies, have been considered in the treatment of tinnitus.

Indeed, psychological (eg, cognitive behavioral therapy) and retraining approaches have been suggested repeatedly as preferred integrative or stand-alone treatments. However,
psychopharmacological agents are often considered choices as well, although it is difficult to assess their efficacy.

In fact, major limits influence the validity of available literature evidence. Few studies follow RCT standards and most reports rely on small-sized samples or are just single-case reports, with the literature evidence considered by this review relying on MEDLINE.

Also clinical diagnosis of tinnitus are extremely heterogeneous and could be “influenced” by concomitant comorbidities/therapies, especially in case of anxious and depressed patients. These considerations inevitably limit the comprehension of the underpinning neurobiological substrates of tinnitus, further reducing the chance of developing selective pharmacological agents.

Nonetheless, while psychopharmacological agents include a heterogeneous, broad number of compounds, the rational acknowledgment of studies in the current literature and hypothesized biological causes should be considered mandatory in order to avoid iatrogenic phenomena or to effectively consider the psychopharmacological treatment strategy.

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