Pharmacologic interventions for tinnitus: Challenges in drug development

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Otolaryngology Head and Neck Surgery
Southern Illinois University School of Medicine
Overview

Part 1.
History of tinnitus drugs
Challenges of drug development

Part 2.
Animal models, mechanisms and drug trials
Which drugs and which brain regions.....

Part 3.
Translating models to people
Goals of drug treatments for tinnitus

Part 4.
Clinical trial design – pearls and pitfalls
Hippocrates treating woman, 5th c. B.C.E. relief, Archaeological Museum of Piraeus.
Dr. Thomas' Eclectic Oil:

WHAT IT HAS DONE.

WHAT IT WILL DO.

IT WILL POSITIVELY CURE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cure Time</th>
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<tbody>
<tr>
<td>Toothache</td>
<td>in 5 Minutes</td>
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<tr>
<td>Earache</td>
<td>2 “</td>
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<tr>
<td>Backache</td>
<td>2 Hours</td>
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<tr>
<td>Lameness</td>
<td>2 Days</td>
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<tr>
<td>Coughs</td>
<td>20 Minutes</td>
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<tr>
<td>Hoarseness</td>
<td>1 Hour</td>
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<td>Colds</td>
<td>24 Hours</td>
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<tr>
<td>Sore Throat</td>
<td>12 “</td>
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<tr>
<td>Deafness</td>
<td>2 Days</td>
</tr>
<tr>
<td>Pain of Burn</td>
<td>5 “</td>
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<tr>
<td>Scald</td>
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Croup it will cease in 5 minutes, and positively cure any case when used at the outset.

Remember that Dr. Thomas' Eclectic Oil is only 50 cents per bottle, and one bottle will go farther than half a dozen of an ordinary medicine.

Presented By
Thompson Barnes
Freemont N H
The “breakthrough” tinnitus treatment

‘Cures’ several pts in a few clinics

Gabapentin significantly improves new onset tinnitus
(Zapp 2001)

Significant improvement in open-label trial of gabapentin and clonazepam in patients with hypoperfusion
(Shulman et al. 2002)
The “breakthrough” tinnitus treatment

When tested .....using standardized measures

-elimination in 10% -
- 30-50% reduction in 30-50% -

-variable outcomes with replication-
The “breakthrough” tinnitus treatment

40 percent of placebo subjects report global benefit with reductions in tinnitus loudness and disability

(Dobie 1999)
Pathways of drug development

Serendipitous observation

Lidocaine
Minoxidil
Sildenafil
Gabapentin

Effects are unpredictable, rarely hold up to large-scale trials

Barany 1935
i.v. infusion Procaine

Clinical trials of lidocaine, bupivacaine, oral tocanide

Imaging studies: bivariate activity with lidocaine modulation of tinnitus

Duckert 1984: 40% placebo response
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Perhaps useful in specific targeted populations
Rare successful placebo controlled, replicated studies
## Pathways of drug development

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Rare successful placebo controlled, replicated studies

**Megwalu**: Open label

**Hurtuk**: DBPC; 84 enrolled

Loudness match
Severity index
Self-rated tinnitus

~57% improvement defined as a ‘decrease’ on at least 2 of 3 parameters
Moving from ‘serendipity’ to salient targets

Boris Odintsov, PhD
Beckman Institute
U Illinois Urbana
Champaign

Varian
600 NMR,
14.1 T.
Advantages of an animal model

• Uniform population
• Control causal factors
• Eliminate confounding factors
• Utilize invasive measures
Using an animal model to understand tinnitus

1. Establish a behavioral task
Psychophysical testing using conditioned suppression to detect tinnitus

(1) Establish a behavioral task

(2) Expose the animal to a tinnitus inducing event
Psychophysical testing using conditioned suppression to detect tinnitus

(1) Establish a behavioral task

(2) Expose the animal to a tinnitus inducing event

(3) Train animal to listen to auditory cues. Stop lever pressing during “silence”.

Tinnitus ≠ Silence
Behavioral evidence of noise-induced tinnitus in animals

Bauer and Brozoski, JARO 2001
Is there a critical pattern of hair cell damage?

- Behavioral training
- Control
  Unilateral 4 kHz 1 hour
  RW Cisplatin
  RW Carboplatin
- Cochlear histology
Is there a critical pattern of hair cell damage?

1 kHz tinnitus develops in all subjects with cochlear damage.

No correlation between tinnitus induced by noise, cisplatin or carboplatin and the pattern of damage.

Is there a critical pattern of hair cell damage?

Strong correlation (r=0.91) between tinnitus and degeneration of high spontaneous rate primary neurons

Bauer, Brozoski, Myers

*J Neurosci Res 2007*
Central changes associated with tinnitus

**Dorsal cochlear nucleus**

Brozoski, Bauer & Caspary *J Neuro Res* 2002

- Increased bursting
- Increased regularity of bursting
- Peak frequency within burst matching tinnitus frequency

**Inferior colliculus**

Bauer et al. *Neuro Res* 2008

- Increased bursting
- Increased regularity of bursting
- Peak frequency within burst matching tinnitus frequency
Loss of primary afferent activity leads to compensatory changes within the central auditory pathway.
Increased spontaneous neural activity
Increased synchronous activity
Increased regularity of action potentials
Over-representation of “lost” frequency bands
Potential mechanism (s)....

Down-regulation of inhibitory neurotransmitters, such as γ-amino butyric acid (GABA) and glycine

Up regulation of excitatory neurotransmitters, eg. glutamate (Glu).
Auditory neurotransmitters

- Glutamate
- Acetylcholin
- GABA
- Dopamine
- Enkephalins
- Dynorphins
- CGRP

Cochlear complex
Dorsal nuclei
Ventral nuclei
Inferior cerebellar peduncle (restiform body)
Cochlea
Spiral ganglion
Cochlear nerve
Trapezoid body
Superior olivary nucleus
Auditory neurotransmitters

- Glutamate
- Glycine
- GABA

Syka J.
Auditory neurotransmitters

Glutamate

Serootonin

Salience

Significance

Glycine

GABA
Auditory neurotransmitters

Glutamate
- Attention
- Learning
- Memory

Dopamine

Glycine

GABA
### Pathways of drug development

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Rare successful placebo controlled, replicated studies
Alprazolam
Modulate GABA receptors (agonist): anxiolytic, hypnotic, anticonvulsant properties

Johnson et al. 1993

- Double-blind, placebo controlled (n=40)
- Chronic tinnitus, unspecified severity
- No depression or anxiety
- Loudness (dB and VAS)
Alprazolam  (Johnson et al. 1993)

- **Objective loudness (dB)**
- **Subjective loudness (VAS)**

**Decreased loudness match**
**Deceased subjective loudness (clinically significant?)**
**No change in MML**
Jalali et al. 2009

- Randomized, triple-blind, crossover, placebo-controlled
- Chronic tinnitus, no depression/anxiety
- Outcomes: THI, VAS severity, loudness (dB)
Alprazolam  (Jalali et al. 2009)

Figure 3. THI pre- and post-treatment scores  
A Alprazolam;  B  Placebo
The use of benzodiazepines for tinnitus: a systematic review  NE Jufas, R Wood J of Laryngology and Otology 2015

Results: Six clinical trials were included. Clonazepam was found to be effective in three studies, but these studies had limitations regarding adequate blinding. The effectiveness of alprazolam was equivocal.

Conclusion: Benzodiazepine use for subjective tinnitus does not have a robust evidence base. Clonazepam has the most evidence to support its use and is relatively less likely to lead to abuse because of its longer half-life, but caution is still needed given the other serious side effects.
Pathways of drug development

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**Dual mechanism of action**
- glutamate antagonist
- GABA agonist

**DBPC** *
50% improvement in 50% of subjects vs 11% on placebo

**DBPC, crossover**
~50% improvement
Pathways of drug development

Off-label use of an existing compound

**Acamprosate**
Azevedo & Figueirido 2005
Sharma et al 2012

Dual mechanism of action
- glutamate antagonist
- GABA agonist

**DBPC** *
Pre 6.75  Post 2.87
Pre 5.72  Post 5.17

**DBPC, crossover**
VAS Pre 7.1 Post 4.05
QOL Pre 66 Post 36
TLM Pre 50 Post 43 (dB)

Multisite DBPC trial
Data unpublished
Pathways of drug development

**Novel drug development**

- Autifony 0063 (2011)

**Antagonist of voltage-gated K channels**

- S-Ketamine cochlear infusion
Pathways of drug development

Novel drug development

- Autifony 0063 (2011)

S-Ketamine cochlear infusion
Locate and investigate critical brain areas associated with tinnitus
Manganese-enhanced Magnetic Resonance Imaging (MEMRI) and MRS
Vigabatrin effect on Mn+ uptake

![Graph showing the effect of vigabatrin on Mn+ uptake in different brain areas.](image)

VIGABATRIN : GABA-transaminase inhibitor
Pre-Drug

Vigabatrin, Low Dose

Tinnitus Returns After 7-week Washout

Neurotransmitter levels and tinnitus?

Measure endogenous GABA, glutamate, and choline levels using volume-localized proton magnetic resonance spectroscopy (\(^1\)H-MRS).
A. Free induction decay (FID) of molecular resonance induced by a tuned RF pulse. Average of 128 FIDs.

B. Fourier transform of the FID with 1-Hz line broadening. The x axis is the frequency difference in Hz between the reference and the resonant frequencies of the three pairs of methylene protons of GABA.

C. A relative proton spectrum: The Fourier transform of the FID has line widths broadened to 7-Hz (widths expected of the GABA protons in vivo). The scale of the x-axis is in parts/megahertz (ppm), which is a relative scale of molecular resonance, independent of the field strength of the magnet. The index numbers under each peak correspond to the methylene proton groupings shown below in the GABA structure.
Quantifying Spectra: Use a peak **not** confounded by other compounds.

Blue: Representative spectrum (MGB, right)
Green: GABA phantom, 10 mM; Red: Glu phantom, 10 mM
Dorsal cochlear nucleus (DCN)
Inferior Colliculus (IC)

Glu

GAB A
Medial Geniculate Body of the Thalamus (MGB)
Primary Auditory Cortex (A1)

Glu

GAB
RESULTS

Dramatic GABA level decreases were NOT seen in tinnitus.

Small GABA increases were seen in the contralateral (re exposure) DCN and A1. Glu increases in the ipsi DCN and contra A1 with tinnitus.

[Graphs showing changes in Glutamate and Choline levels in A1 before and after tinnitus]
MRS profile (in the rat):

- mixed GABA alterations
- selective Glu increases
and a potential cholinergic component

present a picture of interactive neurotransmission in the "tinnitus" brain.
Can animal models facilitate drug development?
from The Better Hearing Institute: Self-Reported Efficacy of Treatments, Kochkin et al. 2011
I can’t remember how long I have had ringing in my ears. It may have started 5 or 10 years ago. It has always been very soft. I am worried now that it is louder and it is making it very hard to hear. Everyone has to repeat what they say to me because I don’t understand them and if we are in a store or with family it is even worse.

It doesn’t bother me at night – it’s like having summer crickets outside all year round. I can knit and read books without it bothering me.

The biggest problem is the crickets blocking my ability to hear.
It just happened one night last year to be honest. For the first 10 days, it was constant. I felt extremely depressed and lost 11 pounds from not eating. I wasn't taking it seriously as I still smoked marijuana the first few days and once a week for 3 weeks until I resented pot because it just made the sound louder. Drinking alcohol also made my whole head ring.

Anyways, after the first ten days it has been on and off (or not noticeable). I have often thought finally, this is going away and I can do things normally again. It would usually come back though. Now I constantly test myself to hear if it is there or not.
I got tinnitus 12 weeks ago. I went to a concert and the 'music' was very, very loud. I realized part way through that I had been standing next to one of the speakers for 2 hours. The next morning I woke up with ringing in my left ear. I thought it would go away but it didn’t. By the following week I knew I was in trouble.

Since then its been three months of hell. I can’t think about anything else and am kicking myself for not moving away from that speaker. I feel terrified that I will have this all my life and am so worried about the effect of it on my job (self-employed computer programmer). I can’t focus on my work because of the constant distracting sound.
Reverse hearing loss, prevent hearing loss, prevent onset of tinnitus

Magnesium AM 101
Eliminate the percept
Reduce the loudness

Requires knowledge of mechanisms
- peripheral tinnitus generator-
- central tinnitus generators -
Address the co-morbid reactions to tinnitus
### Clinical trials: antidepressants for tinnitus
*(from S. Robinson, PBR 2007)*

| Study            | Antidepressant | Severity | Duration | Subject Selection | Response
|------------------|----------------|----------|----------|-------------------|---------|
| Sullivan et al.  | Nortriptyline  | Unspecified | > 6 months | No specified severity or duration | Significant improvement in MPI, HRSD
| Robinson et al.  | Paroxetine     | Unspecified | > 6 months | No associated depression | Decreased loudness and severity (TSQ) correlated with improvements in depression, anxiety
| Zoger et al.     | Sertraline     | Severe   | No specified duration | 57% with depression | No change on 7 pt tinnitus severity scale
| Mihail et al.    | Trimipramine   | No selection criteria | | | 8 dB increase in loudness

Robinson et al. 2009
- Participants with more severe tinnitus show greater response to treatment particularly with co-morbid depression and anxiety
Clinical trials: antidepressants for tinnitus

*Clinical Practice Guideline (AAOHNS 2014)*: 7 RCTs and 1 Cochrane review fail to demonstrate preponderance of benefit over harm, not recommended

*AHRQ (2013)*: reviewed RCTs of antidepressants, etc; 6 studies with benefit in tinnitus specific QoL and 5 for subjective loudness... no recommendation based on low/insufficient strength of evidence

*Cochrane review (Baldo 2012)*: low quality evidence, no significant benefit, not recommended
Address the co-morbid reactions to tinnitus
Ketamine Therapy Provides Hope for Tinnitus Sufferers

Tinnitus (Chronic “Ringing in the Ears”)
To the millions of Americans who suffer from Tinnitus, a constant low or high-pitched ringing in the ears, it is more than an annoyance. Tinnitus is a psychological and emotional assault on the senses that taxes and exhausts those with this disorder. It can affect sleep and concentration, and can inhibit the ability and desire to interact socially.

Until now, Tinnitus treatments have focused on helping sufferers cope with the condition. Cognitive behavioral training is used to learn how to tune out the sound, and physical therapies help individuals learn to manipulate the pitch and tone of the ringing by clenching the muscles around the neck and ear. Standard medication therapies, in general, are minimally effective for Tinnitus sufferers.

“...It seems the more severe the tinnitus, the better it works, because many of the same problems—pain and phantom noises—can predispose to depression and PTSD.”

Dr. David E. Potter, Chairman of Pharmaceutical Sciences, Texas A&M University's Rangel College of Pharmacy
Important points for developing – testing – using drugs for tinnitus
Important points for developing – testing – using drugs for tinnitus

Clearly identify the target to be treated

- the perception (quality, loudness)
- the reaction/emotion
- the attention/vigilance directed towards tinnitus
Important points for developing -- testing -- using drugs for tinnitus

Measure what you are modulating
Clearly define the target population:
  - acute vs chronic
  - associated hyperacusis
  - stratified for severity, other factors
Must have a placebo arm
Account for stability of subjective ratings and changes with study enrollment
Important points for developing – testing – using drugs for tinnitus
STATEMENT 10. MEDICAL THERAPY: Clinicians should not routinely recommend antidepressants, anticonvulsants, anxiolytics, or intratympanic medications for a primary indication of treating persistent, bothersome tinnitus. **Recommendation against** based on systematic reviews and randomized controlled trials with methodological concerns, with a preponderance of benefit over harm.

THIS DOES NOT MEAN THAT DEPRESSION, ANXIETY, AND SEIZURE DISORDERS SHOULD NOT BE TREATED WITH MEDICATIONS

THESE MEDICATIONS HAVE NOT BEEN SHOWN TO IMPROVE TINNITUS SPECIFIC MEASURES
Developing a drug for tinnitus

What is the treatment goal?
Measure what you intend to modulate
Define your patient population
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Tom Brozoski, PhD
Donald Caspary, PhD
Larry Hughes, PhD
Louisa Ciobanu, PhD
Boris Odintsov, PhD
Kurt Wisner, BA