Tinnitus: Partial success and failures of pharmacoagents

Edward Lobariñas Ph.D. CCC-A

University of Florida
Department of Speech Language and Hearing Sciences
Gainesville, FL
Tinnitus

- **Subjective Tinnitus** - the perception of sound in the absence of a corresponding external sound

- **Objective Tinnitus** -
  - muscle spasms that cause clicks or crackling around the middle ear
  - pulsatile tinnitus resulting from altered blood flow or turbulence near the ear or as a subjective phenomenon from increased awareness of blood flow in the ear.
Modern Commercial “Drug” Therapies

- Therapies are varied but none have been conclusively shown to be effective across a wide range of patients
Why does the problem of tinnitus persist?

• Tinnitus is a symptom with often unknown etiology

• Tinnitus is strongly associated with hearing loss but not all individuals with hearing loss have tinnitus

• Tinnitus definition unclear because of discrepancy between percept and disability

• Two competing viewpoints
  1. The reaction to the sound
  2. The tinnitus sound signal itself
Aspects of Tinnitus

Subjective Tinnitus

+++

Emotional Component

Perceptual Component
Drug Therapies

- Extensive review showed that no drug reliably reduced tinnitus in the majority of patients and no drug exceeded placebo control (Dobie 1999)

- **Tocainide** (lidocaine analog, Na channel blocker) and related drugs
- **Carbamazepine** (anticonvulsant, Na channel inactivator, potentiates GABA receptors)
- **Benzodiazepines** (enhance GABA-A)
- **Tricyclic antidepressants** (serotonin-norepinephrine reuptake inhibitors)
- **Caroverine** (AMPA receptor antagonist)
- **Zinc** (antioxidant)
- **Melatonin** (sleep aid)
- **Baclofen** (GABA-B agonist)
- **Flunarizine** (Calcium channel blocker, reduces migraines)
- **Betahistine** (Histamine mixed agonist/antagonist, may increase serotonin)
Acamprosate

- Treatment of tinnitus with acamprosate
- Andréia Aparecida de Azevedo and Ricardo

Acamprosate, a drug used to treat alcohol dependence, was first reported as a potential treatment for tinnitus in 2005. The drug may improve tinnitus by a dual mechanism of action, acting both as a glutamate antagonist and as a GABA agonist. It is suggested that its action may be both on the ear and the nervous system.
Cyclobenzaprine

- Muscle Relaxant with tri-cyclic antidepressant action

- On-going open label trial

- High-dose cyclobenzaprine (30 mg) resulted in a significant reduction in the Tinnitus Handicap Inventory (THI) score between baseline and week 12

- A 2\textsuperscript{nd} study by Vanneste, Fiqueiredo, and De Ridder shows
  - In 24\% of the tinnitus patients a reduction of 53\% on tinnitus intensity
  - In 25\% a clear response to cyclobenzaprine with a reduction of 55\% on tinnitus distress
  - Particular subgroups, namely pure tone tinnitus patients and unilateral tinnitus patients, responded better to cyclobenzaprine
Modeling Tinnitus in Animals
Gap Prepulse Inhibition of the Acoustic Startle (GPIAS)
Schematic of GPIAS

No gap condition

Carrier Noise (6, 12, 16, or 24 kHz NBN)

75 ms silent gap

50 ms gap condition

Carrier Noise (6, 12, 16, or 24 kHz NBN)

Startle Stimulus

Startle Response

Tinnitus

Startle Response
Gap Prepulse Inhibition

- No Gap = Large Startle
- Gap = Small Startle
- Gap + Tinnitus = Large Startle
Unilateral Noise Exposure

- 126 dB SPL, 16 kHz NBN, Left ear 1h
Noise Burst Prepulse Inhibition

Effect of Noise on NBPIAS

- Baseline
- Post Noise

Frequency (Hz):
- 6k
- 12k
- 16k
- 20k
- 24k

% NBPIAS:
- 0%
- 20%
- 40%
- 60%
- 80%
- 100%
Effect of Noise on GPIAS

![Graph showing the effect of noise on GPIAS at different frequencies (6k, 12k, 16k, 20k, 24k). The graph compares baseline and post-noise conditions, with error bars indicating variability. The x-axis represents frequency in kHz, and the y-axis represents percentage of GPIAS. The graph highlights a trend of increased GPIAS after noise exposure, labeled as "Tinnitus." ]
Tinnitus Treatment 1

- **L-838417**
  - **Mechanism**: GABA(A) partial agonist $\alpha_2$, $\alpha_3$ and $\alpha_5$ subtypes, antagonist to $\alpha_1$ subtype, low affinity for $\alpha_4$ or $\alpha_6$ subtypes
  - **Uses**: non-benzodiazepine anxiolytic
Effects of L838417 on Noise Induced Tinnitus (TR4)

Percent Inhibition

Carrier Noise Frequency kHz

Baseline
Post Noise
Post Noise L-838417 10mg/kg (1)
Post Noise 4 day

6 12 16 20 24
Tinnitus Treatment 2

- **Tonabersat**
  - **Mechanism**: gap junction blocker (connexin 26)
  - **Uses**: migraines with auras (clinical trials)
Effects of Tonabersat on Noise Induced Tinnitus

- Baseline
- Post Noise
- Tonabersat 10 mg/kg Post Noise

Frequency (Hz): 6k, 12k, 16k, 20k, 24k

% GPIAS
Tinnitus Treatment 3

- **Cyclobenzaprine**
  - **Mechanism**: structured like tricyclic antidepressant, shown in rats to activate the Locus Coeruleus in the brainstem (stress and panic)
  - **Uses**: muscle relaxant sleep aid and treatment for fibromyalgia
Cyclobenzaprine from clinical observation to systematic evaluation

- **Uses**: muscle relaxant sleep aid and treatment for fibromyalgia

- **Mechanism**: structured like tricyclic antidepressant, shown in rats to activate the Locus Coeruleus in the brainstem (stress and panic)

Supported by a grant from the Tinnitus Research Initiative
Effect on the Startle Reflex

Startle Input-Output Function

- 20 days post noise
- Cyclobenzaprine 0.5
Effect on Hearing
Effect on GPIAS

Effect of Cyclobenzaprine on Noise Induced Tinnitus

- Baseline
- 20 days post noise
- Cyclobenzaprine .5 mg/kg

Percent GPIAS

Frequency (Hz)
- 6k
- 12k
- 16k
- 20k
- 24k
How is Cyclobenzaprine Attenuating Tinnitus?

• Attenuation of muscular component of reflex?

• Antidepressant action?

• Vigilance or awareness of deafferented region of hearing?
Summary

• Measures of tinnitus reaction do not appear to be correlated with perceptual characteristics of tinnitus

• Hearing loss is *strongly* correlated with tinnitus

• Animals exposed to noise develop similar hearing loss and tinnitus patterns as humans

• Animal models can provide a reliable alternative to study novel drug therapies for tinnitus and can help identify neural correlates
Special Thanks

- Karlee Pusch
- Courtney Campbell
- Carrie Shillitoe
- Laura Lewicki
- Dr. Richard Salvi

- The American Tinnitus Association
- The National Institute of Health
- Tinnitus Research Initiative
Questions?