

The Use of Lipo-Flavonoid® in the Management of Tinnitus

THE EVOLUTION OF A STANDARD TREATMENT REGIMEN

This White paper addresses the history of the use of eriodictyol glycoside, a natural agent to help manage tinnitus, a potentially debilitating condition that can affect both quality of life and health.

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INTRODUCTION

Hearing is one of the major senses and an essential aspect of communication. Hearing occurs when vibration is perceived as sound and is converted by the ear into nervous impulses. Tinnitus significantly interferes with hearing and is derived from the Latin word “tinnire” meaning to ring or ringing. Tinnitus patients report a variety of acoustic sounds besides ringing (for example, buzzing, clicking, hissing, roaring, chirping, or squealing) and of differing pitches. While the cause of tinnitus is not well understood, it has been suggested that hearing impairment may be caused by chronic effects on the inner and outer hair cell and the acoustic nerve function of the ear. Tinnitus may also be associated with inflammation resulting in vascular or neural damage. [Nondahl 2010]

Flavonoid compounds have been used therapeutically for many years. These agents are widely believed to exhibit a variety of pharmacologic properties including anti-viral, anti-inflammatory, anti-oxidant and anti-platelet effects. [Ishikawa 2000] The use of Lipo-Flavonoid®, containing a lemon bioflavonoid complex, has become a primary or adjunctive first course of treatment for many tinnitus sufferers.

In 2010 the owners of the Lipo-Flavonoid® dietary supplement commissioned an independent study of practicing ENTs. More than 50% reported that they recommended dietary supplements to patients complaining of ringing in the ears. In more than 90% of the cases, the specific brand recommended was Lipo-Flavonoid®. In December 2014, another independent survey was conducted with 250 practicing Otolaryngologists regarding their use of supplements. All employed supplements as an adjunct therapy for tinnitus or Meniere’s syndrome. M3 Research also reported that 85% recommend Lipo-Flavonoid® most often for these conditions. [Data on file]

Definition of Tinnitus

Tinnitus is largely self-reported and subjective in nature. There is no standard definition of tinnitus but it is generally considered to be the perception of sound where there is no audible source. This “phantom” sound can be heard in one or both ears. Patients are generally considered to have tinnitus if they hear these noises chronically with some studies defining it as 3 or more months, [NIDCD 2010] while recent guidelines define tinnitus as 6 months or more of persistent symptoms. [Tunkel 2014]

Tinnitus is not itself a disease but a symptom of other medical conditions. Tinnitus can be identified as *primary* (idiopathic) or *secondary* (associated with a particular underlying condition). Ringing in the ears may be temporary or permanent.

To diagnose tinnitus accurately, it is important to categorize it appropriately as either *subjective* tinnitus (which is heard only by the patient and is the most common form) or *objective* tinnitus, which is rare. These patients usually have a vascular abnormality that can be heard using a stethoscope. [Tunkel 2014]

Although the cause of tinnitus is often unknown, otologic issues are primarily associated with subjective tinnitus. Several conditions commonly associated with it are impacted cerumen, infections (ex., otitis media), and diseases or syndromes such as Meniere’s which presents with episodic vertigo and is associated with low-pitched tinnitus. [Lockwood 2002]

Prevalence of Tinnitus

Tinnitus is not uncommon, particularly among older adults. Because there is no agreed upon definition, it is difficult to accurately estimate the number of tinnitus sufferers. *Incidence*, or the risk of developing the condition over time, is 12.7% cumulatively over 10 years. [Nondahl 2010] Adding to the complexity of describing this condition, tinnitus can improve spontaneously and severity may fluctuate as patients develop a tolerance to the symptoms. [Tunkel 2014]

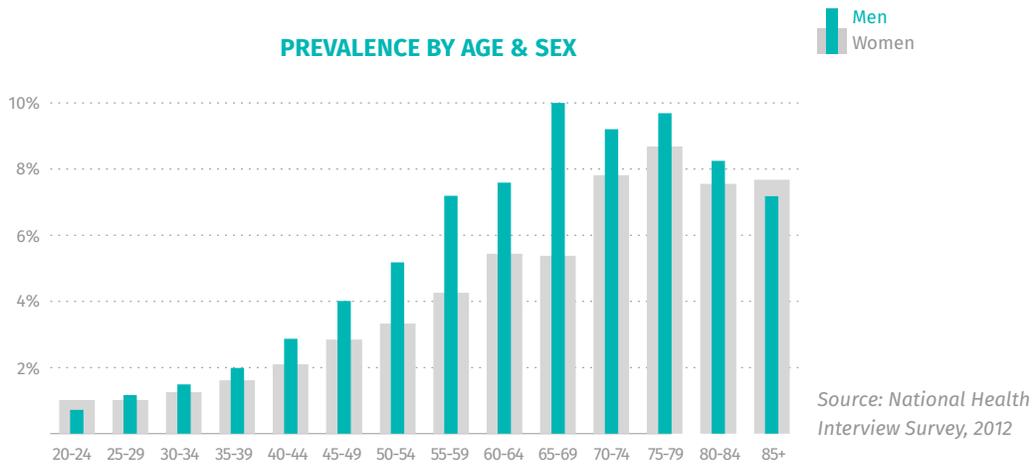
Prevalence for tinnitus is estimated at 25.3%. A 1996 National Health Interview Survey estimated that 35-50 million adults have tinnitus, with 12 million seeking medical help and 2-3 million experiencing severely debilitating symptoms. [NIDCD Nov 2012] Non-Hispanics are more likely to report having tinnitus than Hispanics and non-Hispanic blacks. These distinctions between race and ethnicity suggests that tinnitus may be caused by something independent of hearing impairment. [Shargorodsky 2010]

Tinnitus is often associated with some level of hearing loss although 13 million people with tinnitus reported no loss. [Kochkin 2011] Older adults and males are more likely to have tinnitus than women and there is a strong correlation with exposure to occupational noise. Because males are affected at a statistically higher rate, it is often attributed to their greater exposure to environmental noise [NIDCD 2012] in occupations such as the military, construction or musicians.

- **MEN** have higher rates of tinnitus
- **AGE RELATED**, increasing around 40 years old, peaking at 65-79 years old, declining after 80 years
- Approximately **27% OF PEOPLE 65-84 YEARS** have tinnitus
- Almost 40% of tinnitus sufferers experience it **80% OF THEIR DAY**
- **1 IN 4** report their tinnitus as loud
- **1 IN 5** report their tinnitus is disabling or nearly disabling
- **NON-HISPANIC BLACKS AND HISPANICS** had a lower prevalence than non-hispanic whites

Source: Kochkin 2011; NIDCD 2012; Nondahl 2010

Tinnitus is age related generally beginning around age 40 for both sexes, and peaking at 65 to 79 years old. Men consistently demonstrate higher rates in every age group. It then begins to decline after the age of 80.



Impact of Tinnitus

Tinnitus is recognized as debilitating, affecting a patient’s overall health status and quality of life. Tinnitus patients are at risk for anxiety and depression, with 48 - 60% of tinnitus patients reporting depression. [Tunkel 2014] It is linked to a variety of risk factors including co-morbid conditions such as autoimmune disease, hypertension, diabetes, dyslipidemia and arthritis. [Nondahl 2010] There are over 550 drugs that are known to be ototoxic, some causing transient and reversible tinnitus and others resulting in permanent damage. [Bauman 2013]

Current and past smokers may have a higher likelihood of tinnitus but this is not universally agreed upon. Patients with a higher body mass index (BMI ≥ 30 kg/m²) are also believed to be at greater risk. [Tunkel 2014]

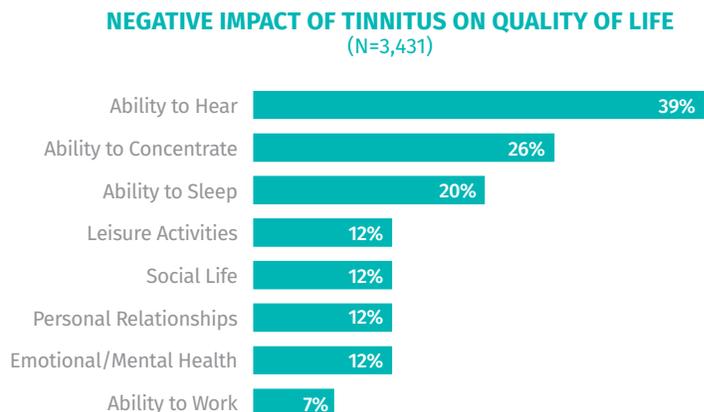
Tinnitus patients have problems with social interactions and other lifestyle issues. They often experience difficulty with work and bouts of insomnia. [Shargorodsky 2010] The impact of tinnitus is considerable because it affects hearing, concentration and sleep, as well as other social activities.

SELECTED RISK FACTORS (ASSOCIATED WITH DEVELOPING TINNITUS):

- **Head trauma** or neurologic disorders (5-10%)
- **Otologic** (ex., Meniere’s)
- **Arthritis**
- **Metabolic abnormalities** (ex., hyperlipidemia, hyperthyroidism)
- **Ototoxic drugs** (antibiotics such as gentamicin, analgesics such as aspirin and ibuprofen)
- Long term **noise exposure**

Source: Tunkel 2014; Nondahl 2010; Bauman 2013

More than half (55%) of patients reporting tinnitus experienced some negative effect on quality of life.



Source: Adapted from American Tinnitus Association [Kochkin 2011]

Tinnitus is a serious economic burden in the U.S. Not only does it negatively impact workplace productivity, it is a major source of disability and health care costs. Among U.S. veterans, disability payments related to tinnitus have increased 16.5% annually. It is estimated that 1.5 million U.S. veterans will receive disability compensation by 2016 at a cost to taxpayers of more than \$2.75 billion. [Tunkel 2014]

Making a Differential Diagnosis

Physical examination and patient history are essential in making a differential diagnosis due to the subjective nature of tinnitus. Distinguishing subjective from objective tinnitus and identifying underlying disease is essential to developing a treatment plan.

Patient evaluation begins with a thorough history to determine symptom onset, location, and possible causes (environmental or medical). If a medical cause is suggested, laboratory tests are indicated (thyroid studies, complete blood chemistry, lipid levels, etc).

Patients reporting tinnitus should undergo audiometric assessment including diagnostic testing such as a baseline audiogram, speech discrimination testing, and tympanometry. Additional audiologic measures may be needed to determine appropriate therapy.

An otologic exam should also be performed to determine cerumen impaction, perforation, infection, cranial nerve damage or vascular involvement. [Crummer 2004]

Treating an underlying condition may improve tinnitus. Cerumen impaction or other obstructions can be relieved and infection can be treated. [Tunkel 2014] It is important to find mechanisms to improve quality of life for as long as tinnitus is an issue.

Treatment: Lipo-Flavonoid®

Lipo-Flavonoid® is a lemon bioflavonoid product that contains eriodictyol glycoside and has been used extensively for decades as part of a multiple treatment approach for the treatment of Meniere's and tinnitus. The efficacy of this product was first documented by Dr. Williams of the Mayo Clinic in the 1960's in a series of papers evaluating the use of citrus bioflavonoids in the treatment of patients presenting with symptoms consistent with Meniere's.

Prior to the publication by Williams of his "preliminary report" of treatment of 160 patients, the use of citrus bioflavonoids to address ringing in the ears was virtually unknown in medical practice.

Over time, Dr. Williams detailed in a subsequent paper that all citrus bioflavonoids were not alike. Specifically, eriodictyol glycoside (the lemon bioflavonoid complex) provided relief of the signs and symptoms of Meniere's and that the lemon bioflavonoid was critical to successful treatment. Williams speculated that eriodictyol glycoside inhibits histidine decarboxylase thereby improving the impaired endolymphatic flow and the quality of microcirculation in the inner ear.

Dr. Williams' observations were accepted by other ENTs and additional observations followed. Today, ENTs regularly employ supplementation with Lipo-Flavonoid® as a primary or adjunctive therapy in most cases where ringing in the ears is involved. [Data on file]

The summary of Dr. Williams' work is noted in the chart below.

Author/Reference

Description

Williams HL & Hedgecock LD

Citrus bioflavonoid, ascorbic acid and other B vitamins in the treatment of certain types of neurosensory deafness: preliminary report.

Staff meeting of the Mayo Clinic 1962

Summary of the positive results of studies evaluating the efficacy of citrus bioflavonoid, ascorbic acid and Vitamin B in the treatment of 160 people with Meniere's. In some cases, Vitamin B complex may improve hearing; application of citrus bioflavonoid (6 capsules/day) may enhance hearing improvement.

Williams HL et al:

Eriodictyol glycoside in the treatment of Meniere's disease.

Ann Otol Rhinol Lar 1963, 72(4):1082-101.

(Follow up to the 1962 "preliminary report")

The paper explores the composition of bioflavonoid noting the importance of lemon. Lemon bioflavonoid complex contains eriodictyol glycoside. The author hypothesizes that it may act on histidine decarboxylase or acts on the amines or polypeptides that play a role in microcirculation. Reviewing 122 cases of Meniere's disease, and 75 cases of deafness from other causes, the author concludes that eriodictyol glycoside (lemon bioflavonoid complex) exerts a beneficial therapeutic effect.

Williams HL

The episodic vertigoes.

Minn Med 1967; 50:1008-12

Meniere's or "episodic vertigoes" can be relieved by eriodictyol glycoside which acts by blocking histidine decarboxylase.

Williams HL.

Dizziness in the older age group.

Postgraduate Medicine 1963; 606-609.

Dizziness in the geriatric patient is reviewed. True vertigo is difficult to distinguish from Meniere's. When vertigo is associated with end-organ or nerve cell degeneration, symptomatic relief may be obtained by giving large doses of water soluble vitamins with lemon bioflavonoid complex containing eriodictyol. The product, taken 2 capsules, 3 times a day requires 2-6 weeks to take effect. Symptoms reoccur if therapy is discontinued.

Williams HL

Eriodictyol glycoside in Meniere's disease.

Trans Am Academy Ophthal Otol

1964; 45-56.

Eriodictyol glycoside (in lemon bioflavonoid complex) was given to patients with Meniere's at a dosage of 2400 mg/day. The author reports eriodictyol glycoside is the active substance in Lipo-Flavonoid® that improves symptoms and acts by inhibiting histidine decarboxylase.

Mechanism of Action

The human ear is an enormously complex system which depends on tiny hair-like sensors in the inner ear to convert external vibrations into recognizable sounds. Inflammation, irritation or trauma can be very disruptive in the inner ear. The blood vessels which serve this area are extremely small, so much so that physicians sometimes refer to ‘micro-circulation’ when talking about blood circulation in the inner ear.

Various hypotheses have been offered by clinical observers to explain the mechanism by which the micronutrient support provided by Lipo-Flavonoid® provides benefit to many tinnitus sufferers.

Some have speculated that the lipotropic agents contained in Lipo-Flavonoid® may help to prevent abnormal accumulation of fatty deposits, thereby improving circulation. In 1973, Rubin theorized that “the [successful] use of eriodictyol glycoside (bioflavonoids) is possibly based on improving vascular permeability.”

Dosing and Administration

Lipo-Flavonoid® contains lemon bioflavonoids and vitamins. The product provides a safe, and often effective treatment for tinnitus sufferers. The recommended dosage to initiate treatment is two caplets three times a day following meals for a total of six caplets daily. Treatment is recommended to continue for 60 days or until the patient obtains noticeable improvement. Patients are advised to then switch to the maintenance regimen of one caplet three times a day following meals (total of three caplets daily).

Literature Review

More than 50 years of clinical data support the notion that Lipo-Flavonoid® provides symptom improvement and relief from vertigo and tinnitus. In addition to the papers published by Dr. Williams, there is a substantial body of medical literature documenting the successful use of lemon bioflavonoid in the treatment of tinnitus.

The professional acceptance of this course of therapy was built over time by clinical observation by prominent ENT clinicians. Reports in the medical literature have created a slow but steady acceptance of this treatment regimen by the professional ENT community.

A survey of 250 geographically diverse ENTs in 2014 showed that 100% of the survey participants reported that they recommended nutritional supplements for patients presenting with either tinnitus or Meniere’s syndrome. And, 85% of those surveyed identified Lipo-Flavonoid® as the brand recommended most often. [Data on file]

This wide acceptance of what was a previously unknown regimen was achieved primarily by the ENT professional community’s practice of sharing clinical observations relating to Meniere’s symptoms in the published medical literature.

INGREDIENTS IN LIPO-FLAVONOID®

- **Eriodictyol glycoside** (lemon citrus bioflavonoid)
- **Vitamin C** (as ascorbic acid)
- **Vitamin B-1** (thiamine mononitrate)
- **Vitamin B-2** (riboflavin)
- **Niacin** (niacinamide)
- **Vitamin B6** (pyridoxine HCl)
- **Vitamin B12** (cyanocobalamin)
- **Pantothenic acid** (as calcium pantothenate)
- **Choline Bitartrate**
- **Inositol**

Source: www.LipoFlavonoid.com

Literature Review of Lipo-Flavonoid® Data

Author/Reference

Description

Ishikawa Y. et al Bioflavonoid quercetin inhibits mitosis and apoptosis of glomerular cells in vitro and in vivo. <i>Biochem Biophys Res Commun</i> 2000, 279(2):629-34.	Bioflavonoids have been regarded as therapeutic agents for a wide variety of diseases particularly in inflammation.
Slattery WH, Fayad JN Medical treatment of Meniere's disease. <i>Otolaryngologic Clinics of North America</i> 1997; 30:1027-37.	Nonsurgical intervention is considered effective in approximately 80% of patients with Meniere's. Eriodictyol glycoside (lemon bioflavonoid extract) may act on histidine decarboxylase or act on the amines or polypeptides that play a role in microcirculation.
Fetterman BL, Saunders JE, Luxford WM Prognosis and treatment of sudden sensorineural hearing loss. <i>Am J Otol</i> 1996; 17:529-36	Treatment options for sudden sensorineural hearing loss are discussed. Lemon bioflavonoid complex, following intravenous histamine as part of multiple therapies, may be effective.
Arenberg IK, Bayer RF Therapeutic Options in Meniere's Disease. <i>Arch Otolaryngol</i> 1977;103: 589-93.	Author discusses Meniere's and shift from treating vertigo to improving hearing. The use of lipoflavonoids and bioflavonoids possibly fortify oxidative phosphorylation in the inner ear or block histidine decarboxylase, improving hearing.
Shaia FT, Sheehy JL Sudden sensori-neural hearing impairment: a report of 1,220 cases. <i>Laryngoscope</i> 1976; 86:389-98.	Author reviewed 1,220 patient cases and recommends treatment should start immediately, especially in patients with recent onset. The investigators treat patients empirically and include large dose preparation of Vitamin C and lemon bioflavonoid complex (Lipo-flavonoid®), 2 capsules twice a day.
Herschberg S Meniere's disease. <i>J Am Osteopathic Association</i> 1974; 73:540-6.	Treatment of Meniere's is mostly symptomatic and supportive. To prolong remission of symptoms, vitamin supplementation with bioflavonoid complex (Lipo-flavonoid®) has been used satisfactorily.
Rubin W: Vestibular suppressant drugs. <i>Arch Otolaryngol</i> 1973; 97:135-8.	Author reviews the pharmacologic rationale for the use of vestibular suppressant agents. The use of eriodictyol glycoside (bioflavonoids) is possibly based on improving vascular permeability.
Goffin FB Lipoflavonoids in Meniere's disease. <i>Eye, Ear, Nose & Throat Monthly</i> 1970; 49:290-1.	12 patients with Meniere's were treated with Lipo-flavonoid® for several months and subjective improvement in vertigo was reported.
Wolfson, RJ Treatment of Meniere's disease. <i>Mod Treat</i> 1969; 6:553-67.	Meniere's is characterized by a triad of symptoms: vertigo, tinnitus, and deafness. Treatment for Meniere's includes Lipo-flavonoid® which includes lemon bioflavonoid complex with a mixture of B vitamins. Surgical management is required in 5 to 15% of patients.
Abdo CJ Jr Vertigo: the patient and the doctor. <i>J La State Med Soc</i> 1968; 120:79-90.	The author reviews vertigo, its causes, diagnosis and treatment. He discusses eriodictyol glycoside in the lemon bioflavonoid fraction of Lipo-flavonoid® and its suggested activity on histidine decarboxylase and its use in Meniere's.
Shea Jr., JJ The treatment of Meniere's disease. <i>Miss St Med Assoc</i> 1965; 6:411-4.	Lipo-flavonoid® complex and lemon bioflavonoid complex or eriodictyol glycoside reduced frequency of vertigo in patients with Meniere's. Dosing: 2 capsules 2 times a day for 2-6 months.

Treatment: Therapeutic Recommendations

Although no cure for tinnitus exists, there are a variety of therapeutic modalities available to provide relief of symptoms. Biofeedback (a relaxation technique), cochlear implants/electrical stimulation and TMJ (temporomandibular joint) treatment when tinnitus is a symptom of jaw joint dysfunction have been tried.

Recent guidelines published by the American Association of Otolaryngologists evaluated currently available treatment options and issued recommendations for these non-pharmacologic treatments. [Tunkel 2014]

Recommended

Hearing Aid/Amplification – Robust clinical data is lacking so recommendation on hearing aid use is primarily empirical because many tinnitus patients do experience hearing loss. Hearing aids may improve quality of life and reduce symptoms for many tinnitus patients.

Sound Therapy – The use of sound to change tinnitus perception and reaction is known as tinnitus masking therapy (TMT) and has been around since the 1970's. Partial or total masking has been used although rigorous studies are lacking. Music therapy has also been used as an alternative to sound therapy.

Cognitive Behavioral Therapy (CBT) has been used for 30 years to ameliorate the negative thoughts and actions associated with tinnitus and helping patients put them in a more productive framework. There is extensive literature supporting CBT even though strong clinical data is lacking.

Not Recommended: Prescription Drug Products

Medical treatment with antidepressants, anticonvulsants and anxiolytics is not recommended. These prescription agents have not demonstrated efficacy and may lead to serious adverse events. No medications have been approved by the FDA for the treatment of tinnitus.

Although **antidepressants** have been used for tinnitus, studies have demonstrated only modest benefits which may be due to their effect on depression and anxiety. These agents all have serious side effects.

Anticonvulsants have been prescribed to modulate neurotransmitters such as GABA (gamma-aminobutyric acid) but these drugs demonstrated little effect and have significant side effects.

Anxiolytics such as alprazolam have been used but clinical data is lacking and these agents have side effects, particularly in older patients. [Tunkel 2014]

Not Recommended: Ginko Biloba, Melatonin and Zinc

Alternative treatments such as Ginko biloba, melatonin and zinc are available over-the-counter without a prescription. Despite anecdotal information, their use is not recommended.

Ginko biloba is a commonly used supplement taken for tinnitus but there is insufficient clinical data supporting its use. It is associated with gastrointestinal side effects, headache and nausea. There is also the potential for clinically significant drug interactions. Older patients on anticoagulants and analgesics should avoid taking Ginko biloba because its antiplatelet activity could lead to serious bleeding.

Melatonin is a hormone that regulates the sleep cycle. It may alleviate tinnitus for patients experiencing insomnia and sleep disturbance but there is limited data on its efficacy in tinnitus.

Zinc plays an important role in the central nervous system and prevalence rates for zinc deficiency in patients with tinnitus can be quite high (2 to 69%). However, there is insufficient evidence of its efficacy in tinnitus and it too has gastrointestinal side effects. [Tunkel 2014]

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Conclusion

Tinnitus is a complex condition that is not well understood but is increasingly prevalent in the United States. It has now become a financial burden as many patients experience difficulty in maintaining employment and must deal with concomitant disease states. Otolaryngologists are faced with patients who require treatment to resume active and productive lives but therapeutic options available are limited. Experts recommend against many pharmacologic agents as lacking evidence of efficacy while exposing patients to significant adverse events.

Recommendations for the management of tinnitus are primarily nonpharmacologic options that pose little risk to patients and include noninvasive treatment options such as hearing aids and sound therapy. Further study would benefit patients who suffer from this debilitating condition. Physicians recommending Lipo-Flavonoid® supplementation frequently see symptomatic improvement in their patients and it has become a primary or adjunctive therapy for tinnitus sufferers.

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