

*The Terror of
Tinnitus &
Cannabis*

The Terror of Tinnitus and a Potential Treatment

***With millions of Americans suffering daily,
Could Cannabis be the most effective Treatment?***

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Every day millions of Americans experience a terrible intrusion in their lives. It occurs as a phantom noise, negatively impacting overall well-being and interfering with daily function. Some describe it as a high pitch ringing in their ears that can cause various medical conditions ranging from migraine headaches to partial high-frequency hearing impairment. This is tinnitus. It has no known medical cure and few surgical options. Here, we look into a potential and natural treatment for this debilitating condition: Cannabinoids. An effective cannabinoid treatment option has been estimated to gross billions of dollars while being cost-effective for individuals suffering from tinnitus. While there are limited evidence to support the effects of cannabinoids for tinnitus treatment due to FDA restrictions on clinical trials examining Schedule I substances, there has been pre-clinical evidence exhibiting the benefits of cannabinoid use for related and co-occurring medical conditions. Further, with a growing number of states legalizing cannabis, investigating cannabinoids as a treatment for tinnitus is the next logical step to help individuals suffering and develop a practical, accessible, and lucrative treatment option.

What is Tinnitus, why is it a Problem, and who is affected?



Tinnitus is a remarkably prevalent and often disabling condition for which there is no known cure and few treatment options. This debilitating condition affects the hearing and quality of life for millions across the USA alone (1). Approximately 25% of the American population has reported being affected by tinnitus at some stage, with up to 8% suffering chronically (2). It is one of the most widespread health conditions and can occur across all ages (3). The prevalence of tinnitus often increases with age (4) and may affect as many as

one in three older adults (5). Additionally, tinnitus is associated with lower quality of life and increased levels of depression (6). Around 50% of people suffering from tinnitus experience depression (7), which is notably higher than the rates of depression suffered by the general population at 6.7% (8).

Tinnitus is the occurrence of an involuntary, perceived sound sensation (e.g., ringing, buzzing, humming in the ears) without an external stimulus (9). Individuals with tinnitus can experience a range of sound sensation intensities, from subtle noise marginally above the hearing threshold to severely intense sounds, nearly eliminating outside noises. It is typically expressed as a symptom in many different medical issues or disorders, such as noise-induced hearing loss, various diseases (e.g., diabetes), ear infections, ear nerve damage, stress, consumption of certain medications (e.g., aspirin, platinum-based cancer chemotherapy, loop diuretics, aminoglycosides, etc.), head/neck injuries, and psychological conditions (10).

Know More

- Tinnitus sounds differ from person to person. There are four different types: subjective, objective, neurological, and somatic.
- Objective pulsatile tinnitus: The doctor, apart from the patient, will be able to hear the sound during the examination. It is a rare type of tinnitus.
- Subjective pulsatile tinnitus: Only the patient can hear the most common type of tinnitus sound.
- Neurological tinnitus is usually caused by a disorder, such as Meniere's disease, primarily affecting the brain's auditory functions.
- Somatic tinnitus: Related to the sensory system. This form is caused, worsened, or otherwise related to the sensory system.

The most significant risk factors for developing tinnitus have an existing hearing impairment, increasing age, being male, and cancer chemotherapy (1). Individuals also found to be at risk of tinnitus are those who already suffer from comorbidities where tinnitus may be a symptom, work in loud environments (e.g., construction), engage in leisure activities with excessive noise (e.g., hunting, concerts, using headphones), as well as those who have a history of mental health issues (e.g., anxiety disorder) (2). Also, due to increased occupational and leisure exposure to noise, tinnitus is projected to increase (4) drastically.

Furthermore, due to the nature of war, tinnitus is one of the most common sequelae to impact our active and retired service men and women (12), who are already acutely prone to experience greater psychological (e.g., PTSD) and physical hardships (e.g., chronic pain from injuries) (13). The cause, traits, and associated symptoms of tinnitus are pretty heterogeneous. While tinnitus is not a disease, it is categorized as a frequent symptom of several pathologies (e.g., trauma injuries, neurological issues, noise trauma, and reaction to medication) (7, 14).

Tinnitus typically develops due to cochlear lesions such as unexpected hearing loss/impairment, presbycusis (age-related hearing loss), or consumption of certain drugs (10). An existing theory is that tinnitus is a type of sensory epilepsy that occurs in specific parts of the auditory central nervous system due to neuronal hyperactivity (e.g., 15, 16). Another theory attempting to explain the cause of tinnitus is thalamocortical dysrhythmia (17). Tinnitus is generated through many different avenues and has a range of effects on people's lives.

Many individuals suffering from tinnitus describe experiencing various symptoms like frustration, annoyance, irritability, hearing problems, hyperacusis, insomnia, and concentration issues (18). Subsequently, the presence of these symptoms is exceedingly relevant in determining the severity of the tinnitus (e.g., the worse the insomnia is, the worse the tinnitus is). Tinnitus has also been linked to significant distress and lowered functionality in social, work, and other daily activities (19), increased stress (20, 21), cognitive problems (22,23), lower quality of life (24, 25), depression (26, 27), disturbed sleep/insomnia (28, 29). Many individuals consider their tinnitus so severe that they feel debilitated (30), sometimes leading to suicide (31).

Living with any medical concern can significantly impact an individual's life in many ways, but to have an additional symptom as invasive and irritating as tinnitus, only further negatively impacts overall well-being, leading to an increase in adverse health outcomes, as well as negative effects on society. The American Tinnitus Association estimated that in 2013 the annual costs to society for the care and lost economic activity directly attributable to tinnitus were over \$26 billion (32). Additionally, its socioeconomic significance is noted by the markedly increased likelihood of eligibility for disability pensions among those suffering from tinnitus (33).

What are the current Treatment Options?

A few national organizations (e.g., American Tinnitus Association) advocate for enhanced services and research into relieving the suffering of such a large population affected by tinnitus. However, there are currently limited medical, behavioral, and surgical treatment options for tinnitus, with no universally effective treatment. The available tinnitus treatments are often expensive, mildly effective, and can have adverse side effects.

Current treatment options include Cognitive Behavioral Therapy, Mindfulness-Meditation, Tinnitus Retraining Therapy, antidepressants, and various sound-based combination therapies (refer to reviews for extended lists of treatments and treatment details: (34-36)). Cognitive Behavioral Therapy can range anywhere from \$5 to \$300 a session and is often time-consuming. With this therapy (like many others), attrition tends to be high. Still, those who completed the therapy reported improvement in tinnitus severity of the symptom and, in select studies, decreased depression (34). Tinnitus Retraining Therapy, which incorporates sound therapy and counseling, can cost around \$3000. This therapy has also shown to improve tinnitus symptoms as well as reduce depression and anxiety when compared to the control groups (34).

While the FDA currently approves no medications specifically for treating tinnitus, some medications, like antidepressants, have been trialed. Hoare et al. conducted a retrospective meta-analysis that described mixed findings for using antidepressants as another treatment option for tinnitus, indicating that two out of three randomized control trials found no improvement in tinnitus symptoms. Some study participants experienced adverse effects from the medications, such as sexual dysfunction and excessive sleepiness. While there is some hope with the existing tinnitus treatments, they can be expensive, time-consuming, infrequently available, and have potentially undesirable side effects. Thus, with an estimated 10% of the population seeking treatment for tinnitus, there is a need to explore alternative treatment solutions, creating a lucrative opening in the market for a tinnitus relief product.

Tinnitus Treatment Market Research Projections

The Royal National Institute for Deaf People collected epidemiologic data, customer and market research, and market data on some products used to manage their tinnitus (37). The market value of tinnitus treatments like retraining therapy and other pharmaceuticals was projected to be \$127 million in 2003. The data also showed that many people suffering from tinnitus had halted their search for medical treatments simply because of the lack of effective treatments. Further, The Royal National Institute for Deaf People has estimated that an innovative treatment option for tinnitus, in its first year on the market, could be valued at \$689 million (38) with an article from Drug Discovery Today Journal reporting the industry's revenue could be at least \$10 billion (39).

With this in mind, we are proposing one possible candidate for a source of promising tinnitus treatments: cannabis, more specifically, one of its chemical compounds, cannabinoids. With the

momentum in the acceptance of medicinal uses of cannabis, especially with states continuing to legalize its production and distribution, there has been no better time to explore and invest in this potential, especially one that has already helped many people suffering from a range of ailments.

Cannabis/Cannabinoids in the Medical and Research Industry

Cannabis is not new to the pharmaceutical world. Its medical use has been documented as far back as 2900 BC by the Chinese Emperor, who referred to it as “a top-rated medicine that possessed both yin and yang” (40). In more recent years, Pfizer (1980’s, New York) had developed a compound to treat emesis or involuntary vomiting. However, this product, Levonantrodol, was later dropped because of its psychoactive side effects due to its seemingly greater potency than Delta-9-THC, a psychoactive ingredient in cannabis. Eli Lilly and Company (Indiana-based) also developed a Delta-9-THC analog called Nabilone. It was also intended to treat emesis and had some dysphoric side effects. Available in the UK and Canada for over 30 years without documented abuse, it remains available in the US only by prescription since it is classified as a narcotic. Marinol (dronabinol), an oral capsule from Unimed Pharmaceuticals (Illinois), is the only FDA-approved cannabis derivative available in the U.S.A. but not indicated for tinnitus. Sativex (a combination of THC and cannabidiol) is a spray from plant extracts approved only in Canada and not available in the U.S.A. produced by GW Pharmaceuticals (London, UK) with no labeled indication for tinnitus.

Even though there is excellent potential for cannabinoid treatment, it has been difficult to receive approval to conduct controlled clinical trials on its effects on medical conditions, particularly for tinnitus. This is due primarily to two factors. Firstly, studies have been non-clinical, animal studies. Since tinnitus is essentially a subjective experience and is limited in its objective measurements, it is difficult for the researcher to ascertain the extent and severity of tinnitus in animals. It is known that there is extreme variability in the genesis and progression of tinnitus in humans exposed to similar stimuli. Therefore, inducing tinnitus and obtaining treatment feedback in laboratory animals is a great challenge. The second deterrent is the regulations.

Even if it was possible to obtain meaningful experimental results in animals, the next challenge a researcher faces with doing a human subject study is that they must contend with cannabis’ classification as a Schedule 1 drug by the Drug Enforcement Agency. As an illegal substance in a shrinking number of states, researchers have limited access to a legal supply of the plant and its chemical compounds. Not surprisingly, much research investigating possible treatments and examining cannabinoids’ effectiveness in combatting various ailments is occurring outside of the U.S.A. Even so, some major pharmaceutical companies have been searching for new cannabinoid therapeutics.

For applicability to tinnitus, researchers need to determine the overlap between where cannabinoids are effective with the locales involved in the subjective experience of tinnitus. One key area for research is to isolate and identify the mechanism of cannabis’ effects. Cannabis has over 545 different types of chemicals, leaving the unlimited potential to explore various

chemicals, alone or in unique combinations, to address numerous maladies.

Some of the questions that need to be answered include which specific chemicals within cannabis are the most compatible with tinnitus or deliver the desired effect and which neurotransmitter receptors should be targeted. THC (tetrahydrocannabinol), or delta-9-THC, is one of the best-known psychoactive ingredients in cannabis since it has long been associated with the plant's euphoric effects. However, there are many other cannabinoids, with the two most commonly researched being cannabitol (CBN) and cannabidiol (CBD). The two classes of cannabinoid receptors are CB1 and CB2. CB1 is expressed in the central nervous system, while CB2 can be found in locales such as the immune or peripheral nervous systems (41).

Understanding the receptors and their effects on the brain and body could open up greater understanding and insights into how to utilize cannabinoids for treatments. CB1 receptors have been identified in the cochlear nucleus (42), suggesting there may be an application in this area for treating tinnitus by cannabinoids. However, minimal literature currently explores these cannabinoid receptors in the auditory brain systems and how they may affect auditory functionality.

Medical cannabis/cannabinoid treatments have been explored for other conditions that are often related to tinnitus in some way. For example, studies (15, 16) have theorized that tinnitus is a form of sensory epilepsy. In a recent study exploring the use of a cannabinoid as a seizure treatment for children resistant to standard epilepsy treatments, a reduced number of seizures was observed with cannabinoid treatment (43). A study by Smith and Zheng (44) explored whether cannabinoid receptor agonists in the cochlear nucleus would act pro- or anti-epileptic, further attempting to understand the relationship between induced tinnitus and cannabis and cannabinoids in rats. Their results were unclear, stating that the cannabinoids may worsen tinnitus. The results were difficult to determine since the subjects were animals, and the tinnitus exacerbation could be due to tinnitus-related neuronal hyperactivity or some redemptive response to it. While these studies are few with mixed findings, they are the start of a much more extensive exploration of the effects of cannabinoid treatment, not just for tinnitus but many other disorders.

While much of the praise of cannabis/cannabinoid treatment is anecdotal, data collections have revealed that medical cannabis is frequently used to treat various symptoms and conditions. A recent review examined cannabinoid medical use in the neurological field, explicitly examining its effects on individuals with Parkinson's disease, Alzheimer's disease, multiple sclerosis, and Huntington's disease, among others (45). The available pre-clinical evidence revealed various beneficial effects for individuals who have Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

Further, cannabis/cannabinoids have been documented to treat medical issues like chronic pain, problems sleeping, inflammation, skin disorders, headaches, nausea, anxiety, and depression, to name a few (46). Currently, cannabis retailers are known to recommend many different strains of cannabis specifically targeted toward relieving issues like anxiety, pain, nausea, and even tinnitus. Though some studies on cannabis treatment have reported mixed findings, there have been studies and reviews showing cannabis/cannabinoids to be effective in treating a variety of a

range of conditions, for example, neurological conditions (47), inflammation (48), and psychological issues (49, 50). Moreover, these conditions are often found to be comorbidities of tinnitus. They tend to be closely associated, only further paving the road toward the use of cannabinoids as the next logical step for tinnitus relief.

Furthermore, tinnitus is often accompanied by an emotional component. The emotional component typically brought on by tinnitus can be expressed in various ways, such as concentration issues from lack of sleep, feelings of anxiety, or even from pain resulting from comorbidities like diabetes or head injury, all of which could also have reduced symptoms from medical cannabis/cannabinoid treatment. Not only could potential relief for tinnitus and its symptoms occur, but medical cannabis/cannabinoid treatment could also benefit the original pathology, which in turn could reduce the number of medications, which are often accompanied by adverse side effects, and allow individuals to experience relief and to reclaim their lives.

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