Does cannabis alleviate tinnitus? A review of the current literature

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Objective(s): Endocannabinoid pathways have been proposed to affect the underlying pathophysiology of tinnitus. The aim of this study is to evaluate the scope and findings of existing literature on the relationship between cannabis and cannabinoid pathways and tinnitus.

Methods: We conducted a review of animal, clinical and survey studies investigating the relationship between the use of cannabis-derived agents and tinnitus. Using pertinent keywords and MeSH terms on PubMed, relevant studies were identified, yielding four animal studies, two large cross-sectional survey studies, one clinical crossover study, and one case report.

Results: Animal studies revealed that cannabinoid receptor expression in the cochlear nucleus varied with tinnitus symptomatology and the use of cannabinoid agents either increased or had no effect on tinnitus-related behavior. Survey studies yielded conflicting results between cannabis use and tinnitus in the general population. Clinical data is largely lacking, although a small cohort study showed a dose-dependent relationship between tetrahydrocannabinol consumption and frequency of tinnitus episodes in patients receiving treatment for cancer.

Conclusion: While animal studies have revealed that cannabinoid receptors likely have a role in modulating auditory signaling, there is no compelling data either from animal or human studies for the use of cannabinoids to alleviate tinnitus. Further research is necessary to elucidate their precise role to guide development of therapeutic interventions.

Level of Evidence: NA.

KEYWORDS
- cannabinoid receptors
- cannabis
- cochlear nucleus
- endocannabinoid
- hearing loss
- marijuana
- otolaryngology
- THC
- tinnitus

Vishal Narwani and Alexandra Bourdillon contributed equally to this work.
INTRODUCTION

Tinnitus is the perception of sound that results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea, and not related to external stimulation of any kind. These perceived sounds can manifest a variety of symptoms, such as ringing, buzzing, whirring, humming, whooshing, static, insects, and hissing sounds. Most tinnitus is subjective, perceived only by the patient as a phantom sound. In contrast, objective tinnitus refers to the perception of acoustic, vibratory activity generated mechanically within the body, that can be heard by the patient and the examiner. Objective tinnitus is a rare entity and is not the focus of this review. Tinnitus has been reported to affect approximately 1 in 10 US adults, with a prevalence as high as 30% amongst adults over 50, making it one of the most common chronic conditions. In the veteran population, tinnitus and hearing loss are the #1 and #2 most prevalent service connected disabilities with 1,971,201 veterans listed as service connected for hearing loss and 1,228,936 veterans listed as service connected for tinnitus.

Even if patients learn to ignore these perceived sounds, tinnitus can negatively impact quality of life. Survey data suggests that half of adults who experience tinnitus approach a physician for a medical consultation, and approximately 15% try any type of treatment. Persistent symptoms can be debilitating and incur considerable psychological distress. In the veteran population, it has been described that 71.9% of those with tinnitus suffer from anxiety, 59.3% with tinnitus suffer from depression, and 58.2% with tinnitus described that 71.9% of those with tinnitus suffer from anxiety, and the examiner. Objective tinnitus is a rare entity and is not the focus of this review. Tinnitus has been reported to affect approximately 1 in 10 US adults, with a prevalence as high as 30% amongst adults over 50, making it one of the most common chronic conditions. In the veteran population, tinnitus and hearing loss are the #1 and #2 most prevalent service connected disabilities with 1,971,201 veterans listed as service connected for hearing loss and 1,228,936 veterans listed as service connected for tinnitus.

2 CANNABIS BIOLOGY AND RECEPTOR DISTRIBUTION

Cannabis, also known as marijuana, is a generic term for the psychoactive drug derived from plants of the Cannabis family, including Cannabis sativa and Cannabis indica. Cannabis contains over 400 different chemicals. The biologically active molecules unique to cannabis are known as phytocannabinoids; approximately 120 different phytocannabinoids have been identified, many of which directly modulate the endogenous cannabinoid system. Two of the phytocannabinoids that predominate in literature and by far the most well-understood are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the principal psychoactive constituent of cannabis, associated with the euphoric feeling users experience. It also possesses antiemetic, anti-inflammatory,
CB1 receptors are mainly expressed within the central nervous system, with only a few experimental studies performed in animal models. Literature on the effects of cannabinoid drugs on tinnitus is sparse, and CB2 receptors, which are part of the endocannabinoid system, are expressed in the cochlear nucleus and still remains unclear. Based on this evidence, Zheng et al. further explored the relationship of cannabinoid receptors and tinnitus, by investigating the effect of tinnitus with two different CB1 non-selective, receptor agonists, WIN55,212-2 and CP55,940. In this experiment, both receptor agonists at different concentrations were injected in the salicylate-induced tinnitus rat model and in controls. Neither WIN55,212-2 (at 3 mg/kg) or CP55,940 (at 0.1 mg/kg or 0.3 mg/kg) significantly reduced the conditioned behavior associated with tinnitus in the rat model. On the contrary, injection of WIN55,212-2 at 3 mg/kg, and CP55,940 at 0.3 mg/kg in control animals significantly increased tinnitus-related behavior, suggesting that cannabinoids may induce tinnitus. The association between cannabinoid receptors in rats and tinnitus-like behavior was further elucidated by using the acoustic trauma-induced tinnitus rat model, which is believed to be more closely related to human tinnitus than the salicylate rat model since noise trauma is one of the more common causes of tinnitus in humans. In a follow up study, Zheng et al. investigated the effect of delta-9-THC and CBD in a 1:1 to ratio, equivalent to Nabiximols (Sativex), used in the treatment of spasticity and chronic pain in multiple sclerosis, in an acoustic-trauma induced tinnitus rat model. Tinnitus was induced by unilateral acoustic trauma applying a 16 kHz pure tone with an intensity of 115 dB, and tinnitus-related behavior observed using the conditioned lick suppression paradigm. Zheng et al found that the administration of delta-9-THC and CBD significantly increased tinnitus-related behavior compared to controls. Following a 2-week washout period, the tinnitus-related behavior decreased in the experiment group. The cannabinoid agonists used in both studies were non-selective and it has been hypothesized that they may have interacted with opioid, vanilloid, or muscarinic receptors, obscuring the interpretation of the results.
Berger et al. investigated the effects of a highly selective, potent CB2 receptor agonist, arachidonyl-2’-chloroethylamide (ACEA), on a salicylate-induced and noise-induced tinnitus model in guinea pigs.81 Following administration of ACEA, the group found no significant reduction or reversal of tinnitus-like behavior in guinea pigs. Interestingly, the group found that ACEA seemed to reverse the decrease in auditory brainstem-evoked response amplitudes induced by salicylate, compared to the control group, suggesting that ACEA may be potentially ototprotective. Overall, using both the salicylate-induced tinnitus model and acoustic trauma-induced tinnitus model, it appears that cannabis may reversibly exacerbate or induce tinnitus.82 Based on animal models, there is no evidence that cannabis or cannabinoid drugs can alleviate tinnitus.

5 | SURVEY AND CLINICAL STUDIES

At present, there are no systematic studies or randomized controlled trials in humans that have examined the effects of cannabinoids on tinnitus. Although cannabis for medical use is legal in 33 states in the US (Figure 1), cannabis remains as a Schedule I controlled substance at the federal level.83,84 This status requires researchers to face several, strict regulatory barriers, such as obtaining licensure from three different federal entities as well as obtaining appropriate state permissions, to undertake research.85 As a result, research on the health effects of cannabis and cannabinoids has been limited in the US.

To date, the only FDA approved cannabis-derived or cannabis-related products for medical use are Epidiolex (cannabidiol), used for seizures in rare epileptic syndromes, Marinol and Syndros (THC dronabinol formulations) for anorexia in AIDS patients, and Cesamet (nabilone, a THC analog) for treating chemotherapy-associated nausea.86-88 Nabiximol is currently available in Canada for cancer pain management, but not in the US.88 Some states have passed legislation allowing the prescription of cannabis products for certain conditions (Figure 2).84,85 Tinnitus, however, is not among commonly approved conditions, which contributes to the challenges of conducting relevant investigative clinical studies.

Nevertheless, some epidemiological studies have examined associations between recreational cannabis use and tinnitus in a non-controlled setting.89,90 Table 1 illustrates an overview of animal and human studies investigating the relationship of cannabis and tinnitus. Qian et al. recently published a cross-sectional study evaluating the association between cannabis use and occurrence of tinnitus utilizing the National Health and Nutrition Examination Survey (NHANES) survey.90 NHANES is an ongoing, nationally representative series of cross-sectional health surveys of the US non-institutionalized civilian population designed to provide estimates of health and nutritional status.91

An association was reported between the regular use of cannabis (at least once per month over the previous 12 months) and the experience of tinnitus during that 12-month period (P < .001). No significant dose-response relationship was observed with the frequency (P = .716) or quantity (P = .560) of cannabis consumed and frequency of tinnitus. The association was present after controlling for other variables in multivariate analysis (OR = 1.75, 95% CI 1.02-3.01, P = .043). However, the presence of hearing loss, history of work noise exposure, and anxiety were also found to be associated with prevalent tinnitus; these variables had a stronger correlation to the presence of tinnitus than cannabis use.90

Although this study describes a statistically significant association between tinnitus and cannabis use in humans, large survey databases such as NHANES surveys must be interpreted with caution. A major limitation of the study is that both key variables examined, cannabis use and presence of tinnitus, are self-reported variables and may be subject to recall bias. Literature suggests patients tend to underreport cannabis use, and inaccurately estimate the quantity of cannabis consumed.92-95 The NHANES surveys also lack data on the potency, specific cannabis strain, and lifetime cannabis use of individuals. The survey also presents insufficient data on the characterization of tinnitus; no data on the severity of tinnitus and the impact on quality of life were assessed, making comparisons between participants difficult. Furthermore, an inherent weakness of the study design is the inability to determine directionality or causal pathways of the findings observed. The study found that anxiety was strongly associated with tinnitus and cannabis use. Several studies have shown mood disorders to be correlated with both tinnitus perception and cannabis use.96-98 Due to the cross-sectional design, the study cannot exclude the possibility of tinnitus leading to increased cannabis use as a mechanism for this association. The lack of standardization of cannabis use, the insufficient information of the severity of tinnitus and the cross-sectional nature of the study, limits the ability to draw major conclusions from this study.

A similar epidemiological, cross-sectional study was undertaken by Han et al. Investigating the association of illicit drug use with
different health conditions, including tinnitus, utilizing data from the National Surveys on Drug Use and Health (NSDUH). The study investigated the lifetime use of cannabis and other illicit drugs of 29,195 participants between the age of 35 and 49. After controlling for confounding factors, no statistically significant associations were found between tinnitus and cannabis use. Similar to other cross-sectional surveys, the study is subject to recall bias and causative conclusions are unable to be made due to the design of the study.

Noyes et al. first described an association between cannabis and tinnitus in 1975, where the group performed a double-blinded cross-over study evaluating the analgesic effects of different doses of THC and codeine in patients with cancer. 11 patients from a total of 34 patients from the study cohort reported tinnitus as an adverse event after the administration of 10 mg or 20 mg of THC, compared to 3 patients reporting tinnitus in the placebo group. The data also show a likely dose-response relationship, with patients who received the higher concentration THC reporting tinnitus more frequently. Since the objective of the study was to assess the analgesic effects, no statistical analyses were performed comparing the tinnitus and non-tinnitus group, nor the severity of tinnitus characterized. Despite the small sample size, the study is one of the first studies in literature that provides objective data on the adverse side-effect profile of THC in humans in a controlled environment.

The first published study using a cannabinoid for the treatment of tinnitus was undertaken by Raby et al. The group presented a case report describing the use of dronabinol, a CB1 receptor agonist (synthetic delta-9-THC), in a patient with long-standing, symptomatic, idiopathic intracranial hypertension (IIH). The patient had previously reported symptom control of IIH when smoking cannabis, but wanted to seek an alternative medication to minimize the psychoactive effects related to it. Treatment with dronabinol, 5 mg twice daily, increased to 10 mg twice a day after 7 days, resulted in the resolution of her headaches and decreased perception of tinnitus. She remained free of symptoms over 30 months with a maintenance dosage of 5 mg twice a day. Resolution of her IIH-related symptoms was also objectively correlated with improvement of papilledema on fundoscopic exam.

FIGURE 2 Among states that have legalized cannabis products for medical conditions, some have instituted laws that allow medical providers to prescribe such products generally for "any debilitating condition" (shown in green), while other states explicitly list which conditions are approved "specifically approved" (shown in blue). At this time, tinnitus is not one of the conditions that is explicitly outlined in bills passed by state legislatures.
Although an improvement of tinnitus was observed, the pathophysiology of objective tinnitus in this patient, caused by increased turbulent, venous flow secondary to intracranial hypertension, differs to that of “subjective” tinnitus. Objective tinnitus may be considered as a separate disease entity, with different treatment algorithm to subjective tinnitus. In addition, it is difficult to draw any considerable

| TABLE 1 | Overview of preclinical, survey and human clinical studies investigating the relationship between tinnitus and cannabis agonists |
|----------|---------------------------------------------------------------------------------------------------------------|
| Study model | Study | n | Agent | Findings |
| Preclinical animal studies | | | | |
| Salicylate Model | Rats | | Zheng et al., 2007 (Hearing Research) | 12 (control = 6) | NA | Tinnitus is associated with downregulation of CB1 receptors in the VCN, but not DCN. |
| | | | Zheng et al., 2010 (Hearing Research) | 24 | Cannabinoid receptor agonists: 1. WIN55,212 (3.0 mg/ kg s.c) 2. CP55,940 (0.1 mg/ kg s.c) 3. CP55,940 (0.3 mg/ kg s.c) | Agents (1) and (3) significantly increased tinnitus-related behavior while none of the treatments reduced tinnitus-induced conditioned behavior. |
| Guinea Pigs | | | Berger et al., 2017 (Hearing Research) | 21 | CB1 agonist: arachidonyle-2,0-chloroethylamide (ACEA) | ACEA may potentially be otoprotective but not effective in diminishing tinnitus or hyperacusis. |
| Acoustic Trauma | Rats | | Zheng et al., 2015 (Frontiers in Neurology) | 50 (control = 20) | Combination treatment of delta-9-THC and CBD (1:1 ratio) | Cannabinoids increased the number of tinnitus animals in the acoustic-trauma induced tinnitus group compared to the sham controls. |
| Human survey studies | | | Qian et al., 2019 (American Journal of Otolaryngology) | 2705 (ages 20-69) | Use of cannabis at least once per month for the past 12 months | Cannabis use was significantly associated with tinnitus, although severity of tinnitus and quality of life measures were not assessed. |
| Human clinical studies and case reports | | | Han et al., 2010 (Annals of Epidemiology) | 29 195 (ages 35-49) | Categorized duration of cannabis usage by: 1. Never usage 2. ≤1 year 3. 2-10 years 4. ≥11 years | No statistically significant association was observed between cannabis usage and tinnitus. |
| Double-blinded cross-over study | Noyes et al., 1975 (Clinical Pharmacology & Therapeutics) | 34 (patients with cancer) | Delta-9-THC | Tinnitus was more frequently observed in patients receiving the agent compared to placebo (11 vs 3). |
| Case Report | Raby et al., 2006 (Journal of Ocular Pharmacology & Therapeutics) | 1 (patient with long-standing idiopathic intracranial hypertension (IIH)) | Dronabinol (CB1 receptor agonist) | Patient’s IIH-related symptoms, including tinnitus, resolved after a course of 5 mg twice daily over 7 days followed by 10 mg twice daily for 2 days. |

Abbreviation: VCN, ventral cochlear nucleus.  
1DCN: dorsal cochlear nucleus.  
2NHANES: National Health and Nutrition Examination Surgery: nationally representative cross-sectional health survey of US noninstitutionalized civilian populations.  
3NSDUH: National Surveys on Drug Use and Health: nationally representative survey of US civilians at least 12 years of age.
conclusions from the case report given that the evidence is anecdotal in nature.

6 | CONCLUSION

Based on the findings from animal studies, there is evidence of an endocannabinoid system, mediated chiefly by CB1 receptors, that plays a role in the auditory pathway. The relationship between CB1 receptors and tinnitus is likely complex, and not fully understood. At present, there is no compelling data either from animal or human studies for the use of cannabinoids to alleviate tinnitus. On the contrary, evidence suggests that cannabinoids may induce or worsen tinnitus. As high quality prospective research for the effect of cannabis on tinnitus is lacking, evidence can neither support nor refute the use of cannabis in controlling symptoms of tinnitus. Once we overcome restrictive regulatory barriers for undertaking cannabis research in the US, future prospective trials may help provide data to further elucidate the association between cannabis and tinnitus.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Vishal Narwani, Alexandra Bourdillon, Keerthana Nalamada, R. Peter Manes, Douglas M. Hildrew: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. Vishal Narwani, Alexandra Bourdillon, Keerthana Nalamada, R. Peter Manes, Douglas M. Hildrew: Drafting the work or revising it critically for important intellectual content. Vishal Narwani, Alexandra Bourdillon, Keerthana Nalamada, R. Peter Manes, Douglas M. Hildrew: Final approval of the version to be published. Vishal Narwani, Alexandra Bourdillon, Keerthana Nalamada, R. Peter Manes, Douglas M. Hildrew: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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How to cite this article: Narwani V, Bourdillon A, Nalamada K, Manes RP, Hildrew DM. Does cannabis alleviate tinnitus? A review of the current literature. Laryngoscope Investigative Otolaryngology. 2020;5:1147–1155. https://doi.org/10.1002/lio2.479