Received: 24 August 2020 | Revised: 7 October 2020 | Accepted: 10 October 2020

DOI: 10.1002/lio2.479

REVIEW

Laryngoscope Investigative Otolaryngology

Does *cannabis* alleviate tinnitus? A review of the current literature

Vishal Narwani MD[1] | Alexandra Bourdillon BS[2] | Keerthana Nalamada MD[3] | R. Peter Manes MD[1] | Douglas M. Hildrew MD[1,4]

[1]Division of Otolaryngology – Head and Neck Surgery, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

[2]Yale University School of Medicine, New Haven, Connecticut

[3]Department of Neurology, University of Connecticut, Farmington, Connecticut

[4]Division of Otolaryngology – Head and Neck Surgery, Department of Surgery, VA Connecticut Healthcare System, West Haven, Connecticut

Correspondence
Douglas M. Hildrew, Yale Otolaryngology, 47 College Street, PO BOX 208041, New Haven, CT 06510, USA.
Email: douglas.hildrew@yale.edu

Abstract

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.

1 | 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.[1] 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.[2-5] 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.[6]

Even if patients learn to ignore these perceived sounds, tinnitus can negatively impact quality of life.[7] 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.[2,8] Persistent symptoms can be debilitating and incur considerable psychological distress.[9-11] 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 suffer from both anxiety and depression.[12] Overall, patients with tinnitus suffer increased rates of depression and anxiety by almost 3-fold.[2] Patients who experience tinnitus are also at increased risk for insomnia and its sequalae as well as suicidal ideation.[13-16] These relationships are likely bidirectional as reduction in tinnitus symptoms has been observed after pharmacologic treatment of mood disorders with anxiolytics and antidepressants.[15,17,18] Head trauma, concussion, hypertension, smoking, and ototoxic medications have been associated with tinnitus.[3,19] However, by far the most common contributing risk factor is hearing loss, either due to acoustic trauma or presbycusis.[20,21] Literature suggests that 90% of tinnitus patients report comorbid hearing loss.[21] Furthermore, tinnitus is a predictable consequence after surgical transection of the auditory nerve during the excision of acoustic neuromas.[22] The burden of hearing loss is expected to grow with an aging population, which may be compounded by a growing prevalence of adolescents with hearing loss,[23] likely increasing the prevalence of tinnitus over the coming years.

The exact pathophysiology of tinnitus is not yet fully understood. Tinnitus appears to be caused by mechanisms that involve both the peripheral and central components of the auditory system,[24] initially triggered by trauma to the cochlea.[25,26] A commonly accepted hypothesis for the development of tinnitus is that of neuronal hyperactivity.[22] After trauma to cochlea, damage to the auditory nerve fibers synapsing with the inner hair cells undergo maladaptive neural plasticity to compensate for damage to the cochlear cells.[21] A decrease in inhibition or an increase in excitation leads to an excitatory-inhibitory imbalance that can cause neural hyperexcitability. Multiple regions of the auditory pathway become more active and neurons fire synchronously, introducing aberrant activity that creates the sensation of sound perceived as tinnitus. This neuronal hyperactivity has been observed in multiple parts of the auditory pathway, including the dorsal cochlear nucleus (DCN), ventral cochlear nucleus (VCN), the inferior colliculus, the medial geniculate body (MGB) and the auditory cortex.[27-32]

Several pharmacological and non-pharmacological approaches for the treatment of tinnitus have been studied. For patients who have concurrent significant hearing impairment, hearing aids or cochlear implants may rescue auditory sensation and prevent the progression of neuroplastic changes that contribute to tinnitus. Masking, a type of sound therapy, uses external auditory stimuli to reduce the patient's awareness of tinnitus.[33,34] Neurophysiological and cognitive behavioral therapies have also been shown to be effective against tinnitus, as these techniques attempt to modulate the patient's response or experience of tinnitus, by both reducing distress and cultivating coping strategies and distraction skills. Cognitive behavioral therapy is the best-established treatment to date for tinnitus.[35,36] Based on the evidence that tinnitus is associated with neuronal hyperactivity in the auditory brain regions, several studies have investigated the efficacy of anti-epileptic drugs, including carbamazepine,[37] gabapentin,[38-40] and lamotrigine[41] in the treatment of tinnitus. However, pre-clinical evidence supporting the use of anti-epileptic drugs in tinnitus is limited and contradictory, and are unlikely to be beneficial when compared to placebo.[42]

Given the limitations of existing therapies for the treatment of tinnitus, there is an increasing interest in exploring other pharmacotherapy. As a result of recent legislative changes, changing societal perceptions, and recent advances in the field, the potential of *cannabis* in the treatment of tinnitus is explored in this review article. With some evidence supporting that cannabinoids can suppress epileptiform and seizure activity in animals,[43-45] cannabinoid drugs may be a good candidate for the treatment of tinnitus by potentially reducing neuronal hyperactivity. In the context of otolaryngology, the role of cannabinoid drugs has been studied across various subspecialties,[46] especially in the setting of palliative care and management of chronic, cancer pain.[47]

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,

analgesic and anti-oxidant properties.[48] CBD is a non-psychoactive cannabinoid, and associated with anticonvulsant, anxiolytic and sedative effects.[49,50] There is also a growing body of evidence for the use of THC and CBD, both individually and in combination sprays (Nabiximol), for the management of chronic pain, in the setting of multiple sclerosis,[51,52] spinal cord injury-related neuropathic pain,[53] and refractory advanced cancer-related pain.[54-56]

Two classes of cannabinoid receptors have been identified, CB_1 and CB_2 receptors, which are part of the endocannabinoid system. CB_1 receptors are mainly expressed within the central nervous system,[57,58] whereas the CB_2 receptors are localized within the peripheral nervous system and the immune system.[59,60]). In the brain, endogenous cannabinoids are released postsynaptically and act in a retrograde manner on presynaptic CB_1 receptors and are thought to inhibit calcium influx at the presynaptic terminals, inhibiting neurotransmitter release.[43] In mouse and rat models of epilepsy, endocannabinoids have been shown to oppose excitatory signals during seizures, by activating $GABA_A$ receptors.[44,45,61-63] As the most widely accepted hypothesis for the pathophysiology of tinnitus is that of neuronal hyperexcitability, a mechanism that has been long observed in epilepsy, there is a potential role of cannabinoids in the management of tinnitus through its anticonvulsant effects.

3 | CB_1/CB_2 RECEPTOR EXPRESSION IN COCHLEAR NUCLEUS

Herkenham et al. first identified CB_1 receptors in the cochlear nucleus (CN) in early autoradiographic studies in a rat model.[64] The spatial distribution of CB_1 receptors in the cochlear nucleus was further elucidated by Zheng et al. utilizing immunohistochemistry studies and cell counting procedures to quantify CB_1 receptor expression.[65] The group identified high levels of CB_1 receptor expression in the DCN and VCN, suggesting a role of CB_1 receptors in auditory function, hypothesized to be likely modulating synaptic plasticity in the auditory nucleus.[66,67] Zhao et al. further demonstrated that specialized cells within the DCN expressed diacylglycerol (DAG) α and β, two enzymes necessary for the production of the endocannabinoid, 2-arachidonyl glycerol (2-AG).[67] These endocannabinoids were shown to regulate CB_1 receptor activation in the absence of exogenous cannabinoid drugs. Baek et al also reported expression of CB_2 receptor labeling in the cochlear nucleus[68]; however, conflicting data exists regarding CB_2 expression in the cochlear nucleus and still remains unclear.[69] Based on these studies, there is considerable evidence for an endocannabinoid system within the cochlear nucleus, which may be important for the development of tinnitus. These cannabinoid receptors may be targeted by exogenous drugs for the treatment of tinnitus.

4 | ANIMAL STUDIES

Literature on the effects of cannabinoid drugs on tinnitus is sparse, with only a few experimental studies performed in animal models. Zheng et al. investigated the expression of CB_1 receptors in the DCN and VCN in the salicylate model of tinnitus in rats, based on Jastreboff's tinnitus model.[65] In this model, salicylate injections was used to induce tinnitus, which was then confirmed using behavioral testing that determines whether the rats subjectively "hear" sounds in the quiet.[70] During the study, rats were water deprived, and then placed in a chamber with access to water and conditioned to drink water during episodes of silence. This was achieved by pairing a mild electric foot shock (the unconditioned stimulus) with discrete periods of silence (the conditioned stimulus) in a continuous background noise, resulting in reduced licking behavior, or decreased water consumption. The animals learnt the association between silence and the electric foot shock. After the conditioning period, control rats refrained from licking water when they were presented with silence only. On the other hand, after the injection of salicylic acid, rats who perceived tinnitus continued to lick water during periods of silence. Using immunohistochemical studies, the authors found that compared to controls, rats with tinnitus-related behavior possessed significant lower of CB_1 receptor expression in neurons in the VCN. Down-regulation of CB_1 receptors was not seen in the DCN. The findings suggested that CB_1 receptors in the cochlear nucleus may have a functional role in auditory processing and may contribute to the pathophysiology of tinnitus.

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 CB_1 non-selective, receptor agonists, WIN55,212-2 and CP55,940.[71] 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.[72,73] 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,[74] in an acoustic-trauma induced tinnitus rat model.[75] 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.[76,77] 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.[78-80]

Berger et al. investigated the effects of a highly selective, potent CB_1 receptor agonist, arachidonyl-2′-chloroe- thylamide (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 otoprotective. 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 Epidiolox (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.

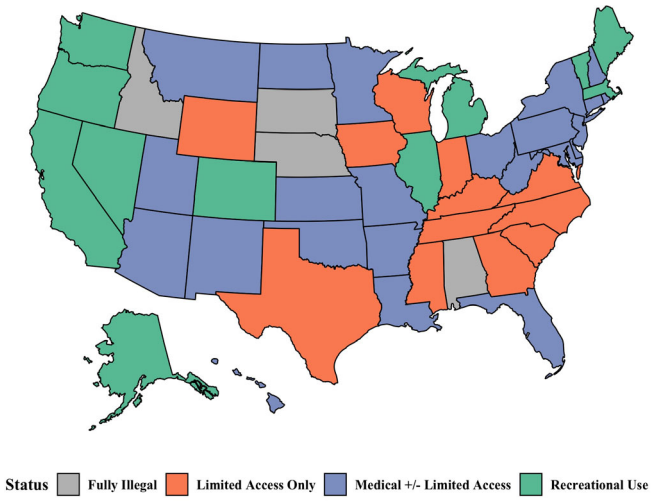

FIGURE 1 Status of *cannabis* legalization across states as characterized by: fully illegal, where there is no public *cannabis* program; limited access, where there is access to low THC and high CBD products only; medical ± program, where there is comprehensive medical *cannabis* program with state to state variability; and recreational use

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 Surgery (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

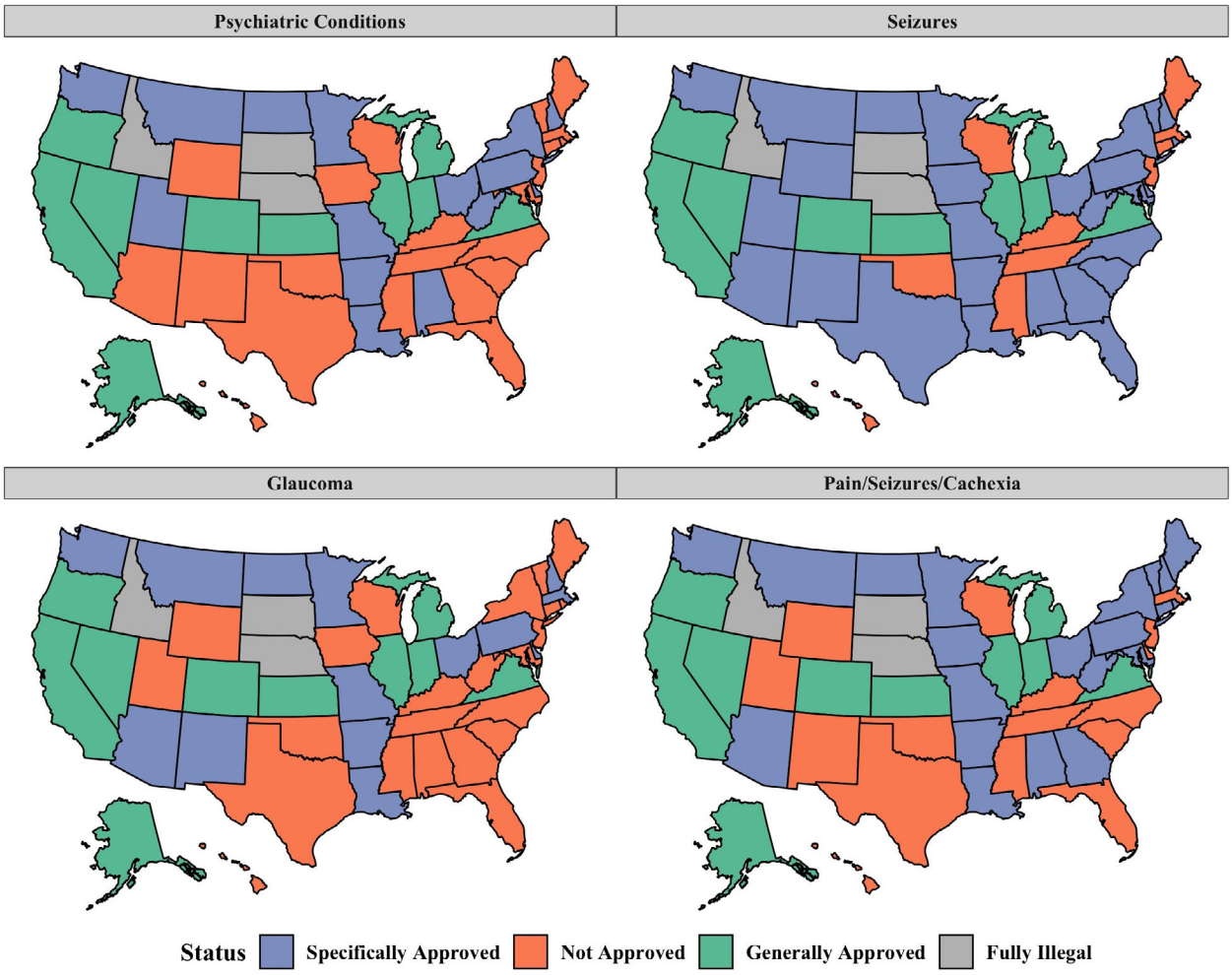

FIGURE 2 Among states that have legalized *cannabis* products for medical conditions, some have instituted laws that allow medical providers to prescribe such products generally for "any debilitating condition" (shown in green), while other states explicitly list which conditions are approved "specifically approved" (shown in blue). At this time, tinnitus is not one of the conditions that is explicitly outlined in bills passed by state legislatures

different health conditions, including tinnitus, utilizing data from the National Surveys on Drug Use and Health (NSDUH).[89] 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,[99] 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 CB_1 receptor agonist (synthetic delta-9-THC), in a patient with long-standing, symptomatic, idiopathic intracranial hypertension (IIH).[100] 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.

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*)[65]	12 (control = 6)	NA	Tinnitus is associated with downregulation of CB_1 receptors in the VCN◦, but not DCN[a].
		Zheng et al., 2010 (*Hearing Research*)[71]	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*)[80]	21	CB_1 agonist: arachidonyl-2′-chloroethylamide (ACEA)	ACAE may potentially be otoprotective but not effective in diminishing tinnitus or hyperacusis.
Acoustic Trauma	Rats	Zheng et al., 2015 (*Frontiers in Neurology*)[79]	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					
NHANES[b] 2011-2012		Qian et al., 2019 (*American Journal of Otolaryngology*)[89]	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.
NSDUH[c] 2005-2007		Han et al., 2010 (*Annals of Epidemiology*)[88]	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.
Human clinical studies and case reports					
Double-blinded cross-over study		Noyes et al., 1975 (*Clinical Pharmacology & Therapeutics*)[98]	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*)[99]	1 (patient with long-standing idiopathic intracranial hypertension (IIH))	Dronabinol (CB_1 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.
[a]DCN: dorsal cochlear nucleus.
[b]NHANES: National Health and Nutrition Examination Surgery: nationally representative cross-sectional health survey of US noninstitutionalized civilian populations.
[c]NSDUH: National Surveys on Drug Use and Health: nationally representative survey of US civilians at least 12 years of age.

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,[101] differs to that of "subjective" tinnitus. Objective tinnitus may be considered as a separate disease entity, with different treatment algorithm to subjective tinnitus.[102,103] In addition, it is difficult to draw any considerable

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 CB_1 receptors, that plays a role in the auditory pathway. The relationship between CB_1 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.[71,79,90,99] 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.

ORCID

Vishal Narwani https://orcid.org/0000-0001-8366-0255
Alexandra Bourdillon https://orcid.org/0000-0001-5111-7450
Douglas M. Hildrew https://orcid.org/0000-0003-3310-479X

BIBLIOGRAPHY

1. Jastreboff PJ, Hazell JWP. *Tinnitus Retraining Therapy: Implementing the Neurophysiological Model*. Cambridge: Cambridge University Press; 2008.
2. Bhatt JM, Lin HW, Bhattacharyya N. Prevalence, severity, exposures, and treatment patterns of tinnitus in the United States. *JAMA Otolaryngol Neck Surg*. 2016;142:959-965.
3. Tunkel DE, Bauer CA, Sun GH, et al. Clinical practice guideline: tinnitus. *Otolaryngol Head Neck Surg*. 2014;151:S1-S40.
4. Adams PF, Hendershot GE, Marano MA. Centers for Disease Control and Prevention/National Center for Health Statistics. Current estimates from the National Health Interview Survey, 1996. *Vital Health Stat 10*. 1999;10:1-203.
5. Nondahl DM, Cruickshanks KJ, Wiley TL, Klein R, Klein BEK, Tweed TS. Prevalence and 5-year incidence of tinnitus among older adults: the epidemiology of hearing loss study. *J Am Acad Audiol*. 2002;13:323-331.
6. *Veterans Benefits Administration Reports*. US Department of Veterans Affairs. 2020. https://www.benefits.va.gov/REPORTS/abr/. Accessed July 21, 2020.
7. Izuhara K, Wada K, Nakamura K, et al. Association between tinnitus and sleep disorders in the general Japanese population. *Ann Otol Rhinol Laryngol*. 2013;122:701-706.
8. Sindhusake D, Golding M, Newall P, Rubin G, Jakobsen K, Mitchell P. Risk factors for tinnitus in a population of older adults: the Blue Mountains Hearing Study. *Ear Hear*. 2003;24:501-507.
9. Sullivan MD, Katon W, Dobie R, Sakai C, Russo J, Harrop-Griffiths J. Disabling tinnitus. Association with affective disorder. *Gen Hosp Psychiatry*. 1988;10:285-291.
10. Conrad I, Kleinstäuber M, Jasper K, Hiller W, Andersson G, Weise C. The role of dysfunctional cognitions in patients with chronic tinnitus. *Ear Hear*. 2015;36:279-289.
11. Lewis JE, Stephens SD, McKenna L. Tinnitus and suicide. *Clin Otolaryngol Allied Sci*. 1994;19:50-54.
12. Hu J, Xu J, Streelman M, Xu H, Guthrie O. The correlation of the tinnitus handicap inventory with depression and anxiety in veterans with tinnitus. *Int J Otolaryngol*. 2015;2015:689375.
13. Liu YF, Hu J, Streelman M, Guthrie OW. The Epworth sleepiness scale in the assessment of sleep disturbance in veterans with tinnitus. *Int J Otolaryngol*. 2015;2015:429469.
14. Cima RFF, Vlaeyen JWS, Maes IHL, Joore MA, Anteunis LJC. Tinnitus interferes with daily life activities: a psychometric examination of the tinnitus disability index. *Ear Hear*. 2011;32:623-633.
15. Langguth B. A review of tinnitus symptoms beyond "ringing in the ears": a call to action. *Curr Med Res Opin*. 2011;27:1635-1643.
16. Malouff JM, Schutte NS, Zucker LA. Tinnitus-related distress: a review of recent findings. *Curr Psychiatry Rep*. 2011;13:31-36.
17. Gross G, Xin X, Gastpar M. Trimipramine: pharmacological reevaluation and comparison with clozapine. *Neuropharmacology*. 1991;30:1159-1166.
18. Robinson S. Antidepressants for treatment of tinnitus. *Prog Brain Res*. 2007;166:263-271.
19. Henry JA, Dennis KC, Schechter MA. General review of tinnitus: prevalence, mechanisms, effects, and management. *J Speech Lang Hear Res*. 2005;48:1204-1235.
20. Mazurek B, Stöver T, Haupt H, Gross J, Szczepek A. The role of cochlear neurotransmitters in tinnitus. *HNO*. 2007;55:964-971.
21. Shore SE, Roberts LE, Langguth B. Maladaptive plasticity in tinnitus—triggers, mechanisms and treatment. *Nat Rev Neurol*. 2016;12(3):150-160.
22. Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: the neuroscience of tinnitus. *J Neurosci*. 2010;30:14972-14979.
23. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. *Am J Med*. 2010;123:711-718.
24. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. *Trends Neurosci*. 2004;27:676-682.
25. Heffner HE, Harrington IA. Tinnitus in hamsters following exposure to intense sound. *Hear Res*. 2002;170:83-95.
26. Bauer CA. Animal models of tinnitus. *Otolaryngol Clin North Am*. 2003;36:267-285.
27. Brozoski TJ, Bauer CA, Caspary DM. Elevated fusiform cell activity in the dorsal cochlear nucleus of chinchillas with psychophysical evidence of tinnitus. *J Neurosci*. 2002;22:2383-2390.

28. Dong S, Mulders WM, Rodger J, Woo S, Robertson D. Acoustic trauma evokes hyperactivity and changes in gene expression in Guinea-pig auditory brainstem. *Eur J Neurosci*. 2010;31:1616-1628.
29. Kalappa BI, Brozoski TJ, Turner JG, Caspary DM. Single unit hyperactivity and bursting in the auditory thalamus of awake rats directly correlates with behavioural evidence of tinnitus. *J Physiol*. 2014;592:5065-5078.
30. Manzoor NF, Gao Y, Licari F, Kaltenbach JA. Comparison and contrast of noise-induced hyperactivity in the dorsal cochlear nucleus and inferior colliculus. *Hear Res*. 2013;295:114-123.
31. Middleton JW, Kiritani T, Pedersen C, Turner JG, Shepherd GMG, Tzounopoulos T. Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus hyperactivity because of decreased GABAergic inhibition. *Proc Natl Acad Sci U S A*. 2011;108:7601-7606.
32. Vogler DP, Robertson D, Mulders WM. Hyperactivity in the ventral cochlear nucleus after cochlear trauma. *J Neurosci*. 2011;31:6639-6645.
33. Vanneste S, van Dongen M, De Vree B, et al. Does enriched acoustic environment in humans abolish chronic tinnitus clinically and electrophysiologically? A double blind placebo controlled study. *Hear Res*. 2013;296:141-148.
34. Davis PB, Paki B, Hanley PJ. Neuromonics tinnitus treatment: third clinical trial. *Ear Hear*. 2007;28:242-259.
35. Martinez-Devesa P, Perera R, Theodoulou M, Waddell A. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews*. 2010;9. http://dx.doi.org/10.1002/14651858.cd005233.pub3.
36. Cima RFF, Maes IH, Joore MA, et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: a randomised controlled trial. *Lancet*. 2012;379:1951-1959.
37. Hulshof JH, Vermeij P. The value of carbamazepine in the treatment of tinnitus. *ORL*. 1985;47:262-266.
38. Bakhshaee M, Ghasemi M, Azarpazhooh M, et al. Gabapentin effectiveness on the sensation of subjective idiopathic tinnitus: a pilot study. *Eur Arch Otorhinolaryngol*. 2008;265:525-530.
39. Piccirillo JF, Finnell J, Vlahiotis A, Chole RA, Spitznagel E. Relief of idiopathic subjective tinnitus: is gabapentin effective? *Arch Otolaryngol Head Neck Surg*. 2007;133:390-397.
40. Witsell DL, Hannley MT, Stinnet S, Tucci DL. Treatment of tinnitus with gabapentin: a pilot study. *Otol Neurotol*. 2007;28:11-15.
41. Simpson JJ, Gilbert AM, Weiner GM, Davies WE. The assessment of lamotrigine, an antiepileptic drug, in the treatment of tinnitus. *Am J Otol*. 1999;20:627-631.
42. Hoekstra CEL, Rynja SP, van Zanten GA, Rovers MM. Anticonvulsants for tinnitus. *Cochrane Database of Systematic Reviews*. 2011;7. http://dx.doi.org/10.1002/14651858.cd007960.pub2.
43. Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther*. 2003;307:129-137.
44. Bhaskaran MD, Smith BN. Cannabinoid-mediated inhibition of recurrent excitatory circuitry in the dentate gyrus in a mouse model of temporal lobe epilepsy. *PloS One*. 2010;5:10683.
45. Vilela LR, Medeiros DC, Rezende GHS, de Oliveira ACP, Moraes MFD, Moreira FA. Effects of cannabinoids and endocannabinoid hydrolysis inhibition on pentylenetetrazole-induced seizure and electroencephalographic activity in rats. *Epilepsy Res*. 2013;104:195-202.
46. Valentino WL, McKinnon BJ. What is the evidence for cannabis use in otolaryngology? A narrative review. *Am J Otolaryngol*. 2019;40:770-775.
47. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med*. 2009;10(8):1353-1368.
48. Kramer JL. Medical marijuana for cancer. *CA Cancer J Clin*. 2015;65:109-122.
49. Chagas MHN, Crippa JAS, Zuardi AW, et al. Effects of acute systemic administration of cannabidiol on sleep-wake cycle in rats. *J Psychopharmacol*. 2013;27:312-316.
50. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556:75-83.
51. Conte A, Bettolo CM, Onesti E, et al. Cannabinoid-induced effects on the nociceptive system: a neurophysiological study in patients with secondary progressive multiple sclerosis. *Eur J Pain*. 2009;13:472-477.
52. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65:812-819.
53. Mondello E, Quattrone D, Cardia L, et al. Cannabinoids and spinal cord stimulation for the treatment of failed back surgery syndrome refractory pain. *J Pain Res*. 2018;11:1761-1767.
54. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain*. 2012;13:438-449.
55. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J Pain Symptom Manage*. 2013;46:207-218.
56. Sellers EM, Schoedel K, Bartlett C, et al. A multiple-dose, randomized, double-blind, placebo-controlled, parallel-group QT/QTc study to evaluate the electrophysiologic effects of THC/CBD spray. *Clin Pharmacol Drug Dev*. 2013;2:285-294.
57. Iversen L. Cannabis and the brain. *Brain J Neurol*. 2003;126:1252-1270.
58. Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. *Neuropharmacology*. 2004;47:345-358.
59. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*. 1990;346:561-564.
60. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature*. 1993;365:61-65.
61. Griebel G, Pichat P, Beeské S, et al. Selective blockade of the hydrolysis of the endocannabinoid 2-arachidonoylglycerol impairs learning and memory performance while producing antinociceptive activity in rodents. *Sci Rep*. 2015;5:7642.
62. Cristino L, Bisogno T, Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. *Nat Rev Neurol*. 2020;16:9-29.
63. Zareie P, Sadegh M, Palizvan MR, Moradi-Chameh H. Anticonvulsive effects of endocannabinoids; an investigation to determine the role of regulatory components of endocannabinoid metabolism in the Pentylenetetrazol induced tonic-clonic seizures. *Metab Brain Dis*. 2018;33:939-948.
64. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci*. 1991;11:563-583.
65. Zheng Y, Baek JH, Smith PF, Darlington CL. Cannabinoid receptor down-regulation in the ventral cochlear nucleus in a salicylate model of tinnitus. *Hear Res*. 2007;228:105-111.

66. Penzo MA, Peña JL. Endocannabinoid-mediated long-term depression in the avian midbrain expressed presynaptically and postsynaptically. *J Neurosci*. 2009;29:4131-4139.
67. Zhao Y, Rubio ME, Tzounopoulos T. Distinct functional and anatomical architecture of the endocannabinoid system in the auditory brainstem. *J Neurophysiol*. 2009;101:2434-2446.
68. Baek JH, Zheng Y, Darlington CL, Smith PF. Cannabinoid CB2 receptor expression in the rat brainstem cochlear and vestibular nuclei. *Acta Otolaryngol*. 2008;128(9):961-967.
69. Baek JH, Darlington CL, Smith PF, Ashton JC. Antibody testing for brain immunohistochemistry: brain immunolabeling for the cannabinoid CB2 receptor. *J Neurosci Methods*. 2013;216:87-95.
70. Jastreboff PJ, Brennan JF, Coleman JK, Sasaki CT. Phantom auditory sensation in rats: an animal model for tinnitus. *Behav Neurosci*. 1988;102:811-822.
71. Zheng Y, Stiles L, Hamilton E, Smith PF, Darlington CL. The effects of the synthetic cannabinoid receptor agonists, WIN55,212-2 and CP55,940, on salicylate-induced tinnitus in rats. *Hear Res*. 2010;268:145-150.
72. Cooper JC. Health and nutrition examination survey of 1971-75: part II. Tinnitus, subjective hearing loss, and well-being. *J Am Acad Audiol*. 1994;5:37-43.
73. Bauer CA, Brozoski TJ. Assessing tinnitus and prospective tinnitus therapeutics using a psychophysical animal model. *J Assoc Res Otolaryngol*. 2001;2:54-64.
74. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler*. 2006;12:639-645.
75. Zheng Y, Hamilton E, Stiles L, et al. Acoustic trauma that can cause tinnitus impairs impulsive control but not performance accuracy in the 5-choice serial reaction time task in rats. *Neuroscience*. 2011;180:75-84.
76. Zheng Y, Hamilton E, Begum S, Smith PF, Darlington CL. The effects of acoustic trauma that can cause tinnitus on spatial performance in rats. *Neuroscience*. 2011;186:48-56.
77. Zheng Y, Hamilton E, McNamara E, Smith PF, Darlington CL. The effects of chronic tinnitus caused by acoustic trauma on social behaviour and anxiety in rats. *Neuroscience*. 2011;193:143-153.
78. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. *Pharmacol Rev*. 2010;62:588-631.
79. Zheng Y, Reid P, Smith PF. Cannabinoid CB1 receptor agonists do not decrease, but may increase acoustic trauma-induced tinnitus in rats. *Front Neurol*. 2015;6:1-9.
80. Smith PF, Zheng Y. Cannabinoids, cannabinoid receptors and tinnitus. *Hear Res*. 2016;332:210-216.
81. Berger JI, Coomber B, Hill S, et al. Effects of the cannabinoid CB1 agonist ACEA on salicylate ototoxicity, hyperacusis and tinnitus in Guinea pigs. *Hear Res*. 2017;356:51-62.
82. Zheng Y, Smith PF. Cannabinoid drugs: will they relieve or exacerbate tinnitus? *Curr Opin Neurol*. 2019;32:131-136.
83. Pacula RL, Smart R. Medical marijuana and marijuana legalization. *Annu Rev Clin Psychol*. 2017;13:397-419.
84. State medical marijuana laws. National Conference of State Legistlatures. 2020. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed July 21, 2020.
85. National Academies of Sciences. *Challenges and Barriers in Conducting Cannabis Research*. Washington, DC: National Academies Press; 2017.
86. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. FDA. 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms. Accessed July 26, 2020.
87. FDA regulation of cannabis and cannabis-derived products, including cannabidiol (CBD). FDA. https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd. Accessed July 26, 2020.
88. Steele G, Arneson T, Zylla D. A comprehensive review of cannabis in patients with cancer: availability in the USA, general efficacy, and safety. *Curr Oncol Rep*. 2019;21:10.
89. Han B, Gfroerer JC, Colliver JD. Associations between duration of illicit drug use and health conditions: results from the 2005–2007 National Surveys on Drug Use and Health. *Ann Epidemiol*. 2010;20:289-297.
90. Qian ZJ, Alyono JC. An association between marijuana use and tinnitus. *Am J Otolaryngol*. 2020;41:102314.
91. National Health and Nutrition Examination Survey. 2020. https://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Accessed July 21, 2020.
92. Prince MA, Conner BT, Pearson MR. Quantifying cannabis: a field study of marijuana quantity estimation. *Psychol Addict Behav*. 2018;32:426-433.
93. van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction*. 2013;108:1801-1808.
94. van der Pol P, Liebregts N, Brunt T, et al. Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study. *Addiction*. 2014;109:1101-1109.
95. Buchan BJ, L Dennis M, Tims FM, Diamond GS. Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. *Addiction*. 2002;97:98-108.
96. Hébert S, Canlon B, Hasson D, Magnusson Hanson LL, Westerlund H, Theorell T. Tinnitus severity is reduced with reduction of depressive mood – a prospective population study in Sweden. *PloS One*. 2012;7:37733.
97. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2006;67:247-257.
98. Bhatt JM, Bhattacharyya N, Lin HW. Relationships between tinnitus and the prevalence of anxiety and depression. *Laryngoscope*. 2017;127:466-469.
99. Noyes R, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther*. 1975;18:84-89.
100. Raby WN, Modica PA, Wolintz RJ, Murtaugh K. Dronabinol reduces signs and symptoms of idiopathic intracranial hypertension: a case report. *J Ocul Pharmacol Ther*. 2006;22:68-75.
101. Meador KJ, Swift TR. Tinnitus from intracranial hypertension. *Neurology*. 1984;34:1258-1261.
102. Han BI, Lee HW, Kim TY, Lim JS, Shin KS. Tinnitus: characteristics, causes, mechanisms, and treatments. *J Clin Neurol*. 2009;5:11-19.
103. Haider HF, Bojić T, Ribeiro SF, Paço J, Hall DA, Szczepek AJ. Pathophysiology of subjective tinnitus: triggers and maintenance. *Front Neurosci*. 2018;12:1-16.

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