Endocannabinoid System and the Otolaryngologist

Brandon Tapasak, BS[a,*], Luke Edelmayer, MD[b], Michael D. Seidman, MD[a,b,c]

KEYWORDS

• Endocannabinoid system • Cannabinoid drugs • Cannabis • Head and neck cancer • Obstructive sleep apnea • Tinnitus • Vertigo • Dizziness

KEY POINTS

- The endocannabinoid system has a role in the practice of otolaryngology, particularly when addressing inflammatory pain and the vestibular system.
- Cannabinoids may be a useful treatment option when treating patients with head and neck cancer for chronic pain, nausea, and vomiting.
- The use of cannabinoids for the treatment of obstructive sleep apnea, tinnitus, and dizziness/vertigo is hotly debated and should be considered on a case-by-case basis.
- Otolaryngologists should be aware of the potential complications of cannabinoid use to include tinnitus, vertigo, and hearing loss.
- More research is needed in the role of cannabinoids in otolaryngologic pathology.

INTRODUCTION

Significance of the Endocannabinoid System

There are three broad classes or cannabinoids: phytocannabinoids (plant-based, ie, *Cannabis*), synthetic cannabinoids, and endocannabinoids (cannabinoids produced by the human body). The primary psychoactive component of *Cannabis* Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) were isolated in the 1960s, thus kick-starting the research which revealed the effects of these chemicals on the brain and body.

The endocannabinoid system refers to cannabinoid receptors (CB1 and CB2) that are acted on by cannabinoid ligands. The CB1 receptors in the central nervous system (CNS) function as presynaptic terminals of γ-Aminobutyric acid (GABA)ergic neurons to curtail release of neurotransmitters.[1] They are abundant in the cerebral cortex,

[a] University of Central Florida College of Medicine, 6850 Lake Nona Boulevard, Orlando, FL 32827, USA; [b] Advent Health Celebration, 400 Celebration Place, Kissimmee, FL 34747, USA; [c] University of South Florida Morsani College of Medicine, 12901 Bruce B Downs Boulevard, Tampa, FL 33612, USA
* Corresponding author. 6850 Lake Nona Boulevard, Orlando, FL 32827.
E-mail address: btapasak@knights.ucf.edu

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basal ganglia, hippocampus, and cerebellum.[2] The CB1 receptors are also present on plasma membranes, endosomes, and mitochondria, regulating neuronal energy metabolism. Astrocytes, oligodendrocytes, and their precursors also possess CB1 receptors, impairing working memory. Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal long-term potentiation. But of the utmost clinical relevance, CB1 peripheral receptors located in the heart, lung, prostate, liver, uterus, ovary, testis, vas deferens, and bone mediate physiologic processes such as gastrointestinal motility and energy balance, reproduction and fertility, pain, and skeletal muscle energy metabolism. Expression of central and peripheral cannabinoid receptors have also been found in human immune tissues and leukocyte subpopulations.[3,4]

The CB2 receptors are similar to CB1 receptors. Research is ongoing to develop specific CB2 agonists as these drugs produce antinociceptive actions without cannabimimetic side effects. The CB2 receptors predominate peripherally within immune regulatory tissues such as B cells and natural killer cells. In this way, CB2 regulates inflammatory responses. Unlike CB1, CB2 seems to decrease reactive oxygen species.[5,6]

History of Medical Cannabinoid Use

Proponents of medicinal cannabis argue that there is evidence to support its use in the treatment of conditions which are refractory to other therapies. These proponents also argue that cannabis is relatively safe and inexpensive compared with pharmaceutical agents.[7] Opponents instead argue that medicinal cannabis has not been subjected to the US Food and Drug Administration approval process. They surmise that because there is no standardization of pharmacologically active constituents, its use could lead to adverse health effects, such as unmasking of mental health disorders, impaired coordination and judgment, and potential for addiction and abuse.[8]

Select states have passed laws allowing medicinal cannabis use for the treatment of Alzheimer's disease, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), amyotrophic lateral sclerosis, cancer, inflammatory bowel disease, multiple sclerosis (MS), Parkinson's disease, and post-traumatic stress disorder. Many symptoms indicated in the use of medicinal cannabis include cachexia, severe or chronic pain, severe or chronic nausea, seizure disorders, and skeletal muscle spasticity.[9]

Recent clinical practice guidelines issued a weak recommendation for using medicinal cannabis for treating chronic pain because of the balance between benefit and harm. The guidelines reflect small improvements in self-reported pain intensity, physical functioning, and sleep quality with willingness to accept a small to moderate risk of self-limited and transient harm.[10]

This article identifies common otolaryngologic pathologies that may be managed with cannabinoids. The discussion also includes debate of the potential benefits and drawbacks to cannabinoid use and suggests future directions for more research into the use of medicinal cannabinoids.

CANNABINOID CONSIDERATIONS IN HEAD AND NECK CANCER

Approach to Cannabinoid Use in Patients with Cancer (Head and Neck)

The main route of marijuana exposure continues to be through smoke inhalation.[11] Marijuana smoke and tobacco smoke share carcinogens and polycyclic aromatic hydrocarbons which are 20 times higher in unfiltered marijuana than cigarette smoke. Marijuana use is associated with histopathological bronchial inflammatory changes like those observed with smoking tobacco.[12] THC may have adverse

immunomodulatory effects associated with cancer. Two proto-oncogenes are overexpressed in the bronchial epithelium of marijuana-only smokers with higher gene expression than tobacco-only smokers.[13] Conversely, several animal studies have found cannabinoids inhibit proliferation of some cancer cell types, impede angiogenesis, and reduce cancer growth.[4,14]

Compared with nonsmokers, those who ever used marijuana had a similar risk of developing head and neck squamous cell carcinoma. Findings among heavier users were mixed. Studies have revealed no association between ever using marijuana and oral cancer. The data are mixed on the association between laryngeal, pharyngeal, and esophageal cancer. There are few reliable studies which have investigated this association. According to a recent meta-analysis by Ghasemiesfe and colleagues, there are insufficient data to conclude there is any association between marijuana smoking and head and neck cancer.[15]

On a molecular scale, there are increased cannabinoid receptors in a variety of tumor cell types. The antineoplastic mechanisms of endocannabinoids include increased reactive oxygen species, inhibition of angiogenesis, arrest of cell-cycle progression, and induction of autophagy and apoptosis. Data have shown that oropharyngeal and tongue cancer, thyroid cancer, lymphoma, basal cell, squamous cell, and melanoma are potentially affected by the antineoplastic effects of cannabinoids. Other promising studies have shown a strong antitumoral effect on anaplastic thyroid cancer cells in mice as well as a synergistic mechanism of induced apoptosis when used with paclitaxel.[16]

Patients with head and neck cancer who use marijuana report an improved quality of life. Studies have reported statistically lower scores for pain, anxiety, and depression and statistically higher scores for general well-being reported by patients with cancer who use marijuana. However, these studies identify the need for determining if these effects are maintained throughout treatment and among long-term survivors.[17]

Chronic refractory pain has recently been recognized as an indication for cannabinoid use. Cannabis is a moderate analgesic which may function synergistically with opioids for pain control. With the opioid epidemic still raging, the use of cannabis for chronic pain, cancer related or not, may be a solution. There has been a nearly 25% decrease in opioid-related mortality rates in states which have enacted a medical marijuana program.[18]

Furthermore, studies have shown the addition of oral THC:CBD with antiemetics to be associated with less nausea and vomiting with an improvement in response from 14% to 25%. However, there were additional unintended adverse effects including sedation, dizziness, and disorientation. Nonetheless, 83% of participants preferred cannabis to the placebo.[19–21]

Complications/Concerns in Patients with Cancer

Although primarily in favor of cannabinoids functioning in an antineoplastic manner, there are reports of cannabinoids functioning as carcinogenic depending on their concentration. Many older studies identified a possible link between smoking marijuana and the development of head and neck carcinoma, but most of these were case reports.[22,23] However, there may be a link between cannabinoid use and progression of human papillomavirus (HPV) positive head and neck squamous cell carcinoma. Cell lines and animal models showed CB1 and CB2 as well as nonselective cannabinoid receptor activation promoting cell growth, migration, and apoptosis through p38 mitogen-activated protein kinase (MAPK) pathway activation.[24]

CANNABINOID USE IN GENERAL OTOLARYNGOLOGY

Approach to Cannabinoid Use for Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common ailment treated by the otolaryngologist. A 2015 study reported 50% of men and 23% of women had at least moderate OSA.[25] There are estimations that 82% of men and 93% of women in the United States with OSA are undiagnosed.[26] Patients with moderate-to-severe OSA are at a higher risk for stroke, myocardial infarction, hypertension, hyperlipemia, glucose intolerance, diabetes, arrhythmias, pulmonary hypertension, congestive heart failure, and depression. Those with cardiovascular disease such as hypertension, heart failure, arrhythmias, stroke, and coronary artery disease have a very high prevalence of OSA.[27]

Increased awareness and earlier treatment are essential to reduce the cardiovascular disease burden. The American Academy of Sleep Medicine (AASM) released a statement recommending medical cannabis and/or synthetic extracts not to be used for the treatment of OSA because of unreliable delivery methods and insufficient evidence of effectiveness, tolerability, and safety. They also recommended OSA to be excluded from the list of chronic medical conditions made by state medical cannabis programs. However, the AASM stated that there are signs of potential benefit from dronabinol and cannabis extract use in patients with OSA, but more research is needed before recommending them as treatments.[28,29]

This stance has been hotly debated. Proponents of cannabis use for OSA state there are placebo-controlled randomized clinical trials that show significant evidence for decreased sleepiness with no significant evidence for increased adverse effects. They maintain that the argument against cannabis because of the "lack of long-term research" is short-sided and harms patients. They claim that the gold standard of treatment of OSA, continuous positive airway pressure machines (CPAP machines) are expensive and encourage noncompliance due to discomfort.[30,31]

Regardless, trials have shown that the use of dronabinol presents a greater benefit than placebo regarding the Apnea–Hypopnea index (AHI), with a mean difference from baseline of −19.64 in patients with OSA. The use of 2.5 to 10 mg doses of dronabinol resulted in a significant reduction in the short-term AHI, as well as improved self-reported sleepiness, and patients reported greater overall treatment satisfaction. This is thought to be due to three pathways: THC stabilization of autonomic output during sleep, reduction of spontaneous sleep-disordered breathing, and blocking of serotonin-induced exacerbation of sleep apnea. Nevertheless, these articles recommend that larger scale clinical trials are needed to confirm the aforementioned results.[32–34]

The mechanism of cannabinoid treatment in OSA is thought to suppress apnea facilitated by peripheral rather than central nervous system activity. Higher concentrations of the endocannabinoid oleoylethanolamide (OEA) but not anandamide or 2-arachidonoylglycerol were found in patients with OSA, associated with difficulty breathing. This suggested endocannabinoids, specifically OEA, may protect the brain from the symptoms of sleep apnea.[35,36]

In the end, we are hopeful for the future of sleep apnea treatment, as CPAP is not always sufficient as a single modality of treatment of OSA, because of its high rates of noncompliance. Therefore, more research is needed to confirm the benefits of endocannabinoids in the treatment of OSA. It is important that every otolaryngologist is aware of the literature and have an informed discussion with their patients on alternative treatments for OSA.

Approach to Cannabinoid Use for Tinnitus

Tinnitus is a common and frustrating problem to manage for the neurotologist and the patient. The most recent epidemiologic study of tinnitus was performed in 2018 and

reported that 9.6% of American adults had experienced tinnitus in the past 12 months. Among these tinnitus sufferers, 27% had symptoms greater than 15 years and 7.2% reported their tinnitus as a "big" or "very big" problem. Despite this, only 49.4% had discussed their tinnitus with their physician.[37]

Tinnitus itself is the perception of sound in the absence on an external stimulus. If persistently bothersome, tinnitus can impair thought processing, emotional stability, subjective hearing, sleep, and concentration. The enthusiasm for cannabinoids for the treatment of chronic pain and epilepsy raises the question whether they could be used for other abnormal neuronal activity such as tinnitus. Tinnitus has been theorized to be the result of neuronal hyperactivity or epilepsy of the cochlear nucleus. Although cannabinoids have been shown to decrease neuronal hyperactivity in the brain, evidence shows that they have the potential to facilitate hyperactivity in the dorsal cochlear nucleus, exacerbating tinnitus. In animal models, cannabinoids have been shown to not affect or even worsen tinnitus. These studies focused on neural CB1 receptor-based responses.[38,39]

Proponents have suggested that the pharmacology of cannabinoids is more complex, and they maintain the possibility that some cannabinoids may reduce tinnitus, similar to the treatment of anxiety (ie, to worsen or improve). In particular, CBD is an anti-inflammatory and acts on the pathways involved in cochlear damage protection. With tinnitus being a result of neuronal inflammation, theoretically CBD would improve tinnitus.[40]

However, according to larger literature reviews, there is not enough evidence to determine an association between cannabis use and tinnitus. Ultimately, we do not understand enough about the pathophysiology of tinnitus at this point to make a recommendation on the use of cannabinoids as treatment. Otolaryngologists should consider the research which primarily indicates cannabinoids do not affect or may even worsen tinnitus when treating patients for this frustrating problem.

Approach to Cannabinoid Use for Vertigo/Dizziness

There is evidence of a high burden of dizziness and vertigo in the community. Large population-based studies show that dizziness (including vertigo) affects 15% to 20% of adults yearly. Vestibular vertigo is the cause of 25% of dizziness complaints. Vestibular vertigo has a 12-month prevalence of 5% and an annual incidence of 1.4%.[41]

As there is evidence that cannabinoid CB1 receptors are expressed in the vestibular nucleus complex, CB1 receptors and endogenous cannabinoids could be important in central vestibular function. This could explain the reported adverse effects of cannabinoids including dizziness and vertigo.[42–44]

Unfortunately, what little research there is on the association of cannabinoids and the vestibular system is dated, and new research is needed. Of these older studies, dated techniques such as gaze nystagmus, tracking a pendulum, spontaneous nystagmus, and torsion swing rotation were objective measurements of vestibular function. Even so, it was found that acute cannabis use did not significantly change any of the measurements compared with the control groups. However, chronic cannabis use showed a significant decrease in maximum amplitude on torsion swing, increase in incidence of nystagmus in two or more supine positions, and decrease in speed of slow component on caloric tests.[45,46]

In a recent meta-analysis of cannabis-induced otolaryngologic side effects, vestibular dysfunction, with a particular emphasis on vertigo, was found to be the second most common side effect.[47] In clinical trials of cannabis used to treat MS, dizziness was found to be a common side effect. Upward of 14.6% of patients experienced

this unwanted side effect. However, these studies concluded the side effects were manageable in the long-term treatment of MS.[48,49]

The effect of cannabinoids on dizziness and vertigo remains a mystery. Although there are some promising signs for cannabinoids as a treatment option, not enough research has been performed to confirm the efficacy. In fact, biochemically there is evidence cannabinoids may cause dizziness and vertigo. Therefore, until more substantial research is performed, there are no indications or possible contraindications to the treatment of vestibular-induced dizziness and vertigo with cannabinoids.

Cannabinoid Complications/Concerns in Otolaryngology

The potential use for cannabinoids in otolaryngologic pathologies is not without concern. Although uncommon, cannabis toxicity can affect many different organ systems in adults. Acute poisoning can cause neurologic symptoms (to include dizziness), ocular symptoms, gastrointestinal symptoms (to include nausea and vomiting), and cardiovascular symptoms. Children and users with preexisting cardiac, pulmonary, or psychiatric diseases are at higher risk for cannabis toxicity.[50]

A recent review of cannabis-related side effects in the practice of otolaryngology reports the most common side effect was tinnitus, followed by vertigo, hearing loss, infection, malignancy, sinusitis, allergic rhinitis, thyroid dysfunction, and dyspnea. Of the 48 studies analyzed, 32 were head and neck and 8 were otology. More than half (54.1%) of studies showed increased side effects or no change in symptoms following cannabis use.[47]

Disquietingly, however, are the number of studies indicating an association between cannabis smoking and neurotoxicity of the auditory system. In these smaller population studies, male smokers had significantly poorer distortion product otoacoustic emissions than male nonsmokers in the low frequencies. These were mostly long-term smokers. Still, the results indicate that cannabis smoking may negatively alter the function of outer hair cells in young men. In addition, when investigating electrophysiological outcomes such as auditory brainstem responses, a significant neurotoxic effect on the auditory system was suggested. These studies warrant further investigation with larger confirmatory studies.[51,52]

FUTURE DIRECTIONS

Recommendations for Clinical Practice

There continues to be great debate in the consideration of cannabinoids as treatment options in the world of Otolaryngology—Head and Neck Surgery. A systematic review of randomized clinical trials of cannabinoid use in medicine was conducted to determine its role. Cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response, reduction in pain, and average reduction in spasticity. These indicate moderate evidence to support the use of cannabinoids for chronic pain and spasticity treatment but low evidence to suggest cannabinoids improved nausea and vomiting, weight gain, sleep disorder, and Tourette syndrome. Cannabinoids were also associated with an increased risk of short-term adverse effects. These included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, confusion, and loss of balance.[32]

Substantial evidence is needed to determine a place for cannabinoids in practice of Otolaryngology—Head and Neck Surgery, but studies have been promising. Otolaryngologists should initiate an informed discussion with their patients when considering cannabinoids for treatment. Although there are many benefits, there are many unknowns and drawbacks that may influence the decision for cannabinoid use. Balancing these pros and cons is essential to determine how to improve the lives of our patients.

SUMMARY

This article shares information to help the otolaryngologist better understand the mechanisms of the endocannabinoid system and how this system can be used in the clinical setting. Treatment with cannabinoids is a rapidly evolving topic, especially with the increasing status of legalization in the United States. High-quality research on medical cannabinoids has been difficult to complete because of federal restrictions. However, otolaryngologists should be familiar with the evidence for management of common pathologies, potential complications, and the unknowns. Understanding these fundamental aspects will allow otolaryngologists to make informed recommendations to patients who have questions regarding medical cannabinoid use.

CLINICS CARE POINTS

- The use of cannabinoids in otolaryngology is hotly debated for the treatment of common pathology.
- The range of effects of cannabinoids on pain, inflammation, and the vestibular system is still undergoing research.
- Otolaryngologists should weigh the benefits, drawbacks, and unknowns before discussing cannabinoids as a treatment option.
- The literature while controversial seems to support the use of medicinal cannabinoids for pain control, nausea and vomiting, obstructive sleep apnea, and tinnitus, but additional research is required before consideration as a viable treatment option.

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