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What is the evidence for cannabis use in otolaryngology?: A narrative review

William L. Valentino (MD)[a], Brian J. McKinnon (MD)[b,*]

[a] Department of Surgery, Temple University Hospital, United States of America
[b] Department of Otolaryngology - Head and Neck Surgery, Department of Neurosurgery, Drexel University College of Medicine, United States of America

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ABSTRACT

Objectives: Review of the English literature for all studies involving cannabis and Otolaryngology.
Methods: PubMed was searched using a combination of the terms cannabis, marijuana, otolaryngology, hearing, tinnitus, vestibular, rhinology, sinusitis, laryngology, voice, airway, head and neck, head and neck cancer, facial trauma, spasm, pediatric otolaryngology, sleep medicine, obstructive sleep apnea, and other variations. Literature included in the review provided substantive research on cannabis in Otolaryngology.
Results: Seventy-nine unique publications were found in the literature. The majority were published in the last decade and pertain to the subspecialty of Head and Neck; specifically, its association with incident cancers. A small number of studies exist that suggest cannabis may be a useful therapy for Otolaryngological patients suffering from blepharospasm, the effects of radiation, and the psychological sequelae of receiving a cancer diagnosis.
Conclusion: Further research is required to determine the potential therapeutic roles and adverse effects of cannabis on conditions related to Otolaryngology. This study serves the Otolaryngological researcher with the most current, comprehensive literature review for the exploration into possible projects to undertake.

1. Introduction

An increasing interest in cannabis as a medicinal can be demonstrated by numerous legislative changes permitting medical marijuana. Generally, the availability of medicinal cannabis is state-specific. Marijuana and cannabis derivatives continue to be a Schedule I illegal substance under federal law. This status requires researchers to navigate an elaborate number of review processes involving both federal and state agencies; yet, the sale of medicinal cannabis and its derivative products are skyrocketing across the country.

To give context to the challenges of cannabis as a medicinal, the National Academies of Sciences, Engineering, and Medicine (NASEM) published a book in 2017 reviewing the current evidence on the health effects of cannabis and cannabinoids. They concluded only three conditions with conclusive or substantial evidence for which cannabis or cannabinoids are effective. These conditions are 1) cannabis for the treatment of chronic pain in adults, 2) oral cannabinoids as antiemetics in the treatment of chemotherapy-induced nausea and vomiting, and 3) oral cannabinoids for the improvement of patient-reported multiple sclerosis spasticity symptoms. Their review stated that all other conditions evaluated either have limited evidence for effectiveness or insufficient evidence to support or refute effectiveness [1].

Several medical specialties (palliation, pain, and neurology) have embraced the use of medical marijuana reflecting published literature on acceptable potential uses.

The purpose of this review is to provide Otolaryngologists with a current analysis of medicinal cannabis in Otolaryngology to be utilized by those considering medicinal cannabis to their patients for therapeutic or research purposes.

2. Materials & methods

PubMed was searched using a combination of the terms cannabis, marijuana, otolaryngology, hearing, tinnitus, vestibular, rhinology, sinusitis, laryngology, voice, airway, head and neck, head and neck cancer, facial trauma, spasm, pediatric otolaryngology, sleep medicine, obstructive sleep apnea, and other variations. Literature included in the review provided substantive research, based on the authors' best judgement, on cannabis in Otolaryngology ranging from case series to meta-analyses and randomized controlled trials. Individual case reports and case series with four or less subjects were excluded from this review.

* Corresponding author at: Philadelphia Ear, Nose, & Throat Associates, Otology/Neurotology, 219 N. Broad Street, 10th Floor, Philadelphia, PA 19107, United States of America.
E-mail address: BMcKinnon@PhillyENT.com (B.J. McKinnon).
URL: https://www.PhillyENT.com (B.J. McKinnon).

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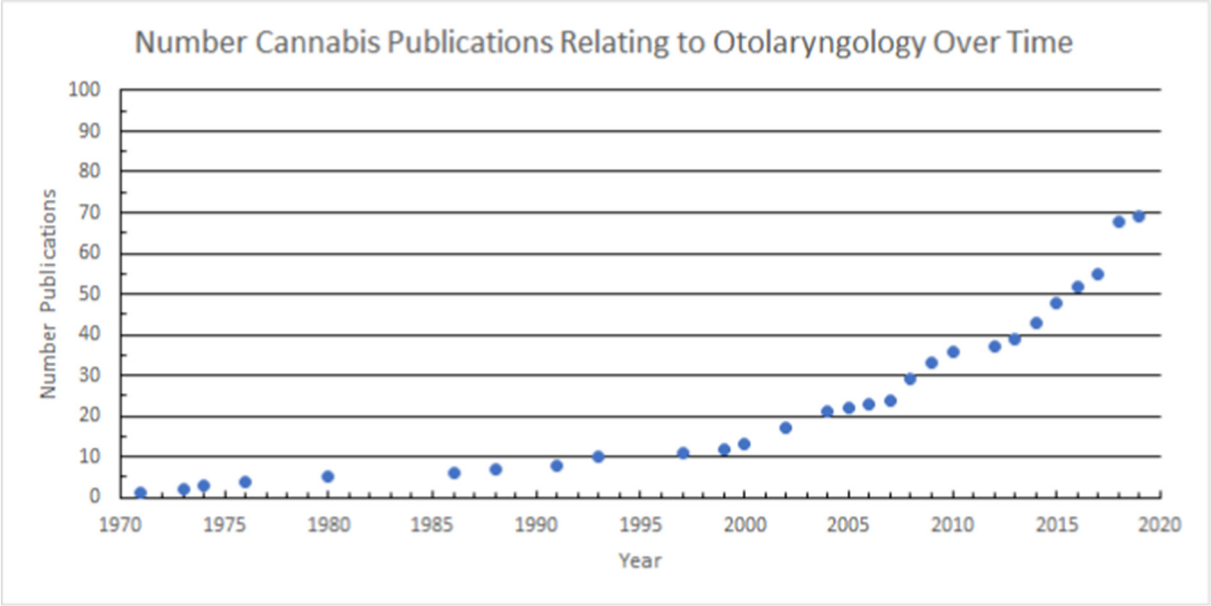

Fig. 1. Number of cannabis publications in otolaryngology over time. Note that only publications meeting this study's inclusion and exclusion criteria are included in this figure.

3. Review of the otolaryngological literature on cannabis

The number of cannabis related publications identified by the literature search are shown by year of publication in Fig. 1 and are categorized by otolaryngology subspecialty in Table 1.

3.1. General otolaryngology

Tennant and Pendergast retrospectively reported the medical complaints of 31 American soldiers stationed in West Germany who smoked illicit hashish (resin of the cannabis plant) in enormous quantities over a period of several months [2]. Complaints of bronchitis, rhinopharyngitis, acne, seborrheic dermatitis, chronic diarrhea, abdominal cramps, and weight loss were documented.

More recently, Bryant et al. published a review of the risks and benefits of cannabis use, with an emphasis on otolaryngologic disease processes; they specifically discuss the growing evidence of using cannabis to manage pain, inflammation, and cancer in the otolaryngologic patient [3].

Table 1
Number of cannabis publications by otolaryngology subspecialty.

Subspecialty	Number of publications[a]
General	2
Neurotology	13
Rhinology	0
Laryngology	1
Head and neck	38
Preclinical	4
Demographics	5
Incidence of cancer	18
Meta-analyses	1
Literature reviews	10
Pediatrics	0
Facial plastics and reconstructive surgery	2
Sleep medicine and surgery	13

[a] Only publications that meet this study's inclusion and exclusion criteria are listed here.

3.2. Neurotology

There have been several studies conducted in basic science and animal research regarding the presence of cannabinoid receptors in the dorsal and ventral cochlear nuclei. All of these studies suggest that cannabinoids may not be useful and may even exacerbate tinnitus [4–9]. However, many of these studies use the salicylate-induced or acoustic trauma-induced tinnitus animal models. Ghosh et al. determined the cochlear endocannabinoid system may have a protective role in some forms of hearing loss but an exogenous agonist may be needed to boost the activity of the system for protection against more traumatic insults, such as cisplatin-induced tinnitus [10].

Prospective, single-blinded, randomized controlled studies from the mid-1970s showed that cannabis does not have an acute effect on hearing [11] or vestibular function [12]; however, a prospective, non-randomized controlled study demonstrated chronic marijuana users may have significant vestibular changes [13]. Similarly, Mulheran et al. performed a randomized, double-blind, crossover trial to demonstrate that tetrahydrocannabinol (THC) does not have a significant effect on the auditory pathway [14].

Weich et al. designed a cross-sectional, non-experimental descriptive quantitative study by performing brainstem evoked response audiometry on former drug users. They concluded that marijuana and crack/cocaine may cause diffuse disorders in the brainstem and compromise the transmission of auditory stimuli regardless of how long these substances are used for [15].

Han et al. retrospectively analyzed the data of adults age 35–70 from the 2005–2007 National Surveys on Drug Use and Health and found a positive association between duration of marijuana use and tinnitus [16].

3.3. Rhinology

No studies were found that met the above mentioned inclusion and exclusion criteria.

3.4. Laryngology

Mueller and Wilcox performed a prospective case-control analysis of three groups (14 chronic marijuana smokers, 11 chronic cigarette

smokers, and 11 never smokers) and concluded that marijuana smokers did not differ perceptually from tobacco smokers or nonsmokers with respect to vocal pitch, quality, and fundamental frequency. However, the authors did note that the vocal folds of eight of the fourteen marijuana smokers were a much darker color, which was not seen in any of the other study group participants [17].

3.5. Head and neck

3.5.1. Basic science studies

Shi et al. demonstrated, in the mouse model using human cell lines, that the cannabinoid-2-eceptor may be a viable therapeutic target for the treatment of anaplastic thyroid carcinoma [18].

Whyte et al. demonstrated that the cannabinoid THC is a potent inhibitor of cellular respiration and thus highly toxic to cells derived from a tonsillar cancer [19].

Klein et al. performed immunohistochemical analyses of cannabinoid receptors on tissue arrays from 240 patients with squamous cell carcinoma of the head and neck (SCCHN). They were able to demonstrate that strong immunoreactivity of CB2 receptor was significantly associated with reduced disease-specific survival [20].

Bhattacharyya et al. investigated the expression pattern of key proteins linked to the EGFR pathway in laryngeal carcinoma patients with a history of cannabis smoking. They concluded that a direct association exists between cannabis smoking and increased risk of laryngeal cancer. Moreover, higher expression of the EGFR cascade in cannabis smokers revealed that cannabis smoking may be a major cause for the early onset of aggressive laryngeal cancer [21].

3.5.2. Demographics

Dahlstrom et al. performed a prospective epidemiologic study of incident SCCHN of 172 never smoker-never drinker (NSND) patients and 1131 ever smoker–ever drinker (ESED) patients. They reported 11% of NSND patients reported regular use of non-cigarette tobacco products or marijuana [22].

Muller et al. utilized a case-control study to evaluate the risk factors associated with oral human papillomavirus (HPV) and oral lesions in patients with and without human immunodeficiency virus (HIV). They determined that marijuana use (OR, 4.0; 95% CI, 1.3–12.4) was a significant risk factor for oral HPV in patients without HIV [23].

Elliott et al. conducted a non-randomized, exploratory study of 15 patients diagnosed with HNC treated with radiotherapy or chemoradiotherapy at OHSU who have enrolled in the OMMP with no evidence of recurrence or metastatic disease using retrospective chart review and data collection to survey sixteen of their patients that underwent radiation therapy that are clinically disease free who reported using medical marijuana. They found that it subjectively improved weight maintenance, depression, pain, appetite, dysphagia, xerostomia, muscle spasm, and sticky saliva. The authors therefore concluded that medical marijuana use may help with the long term side effects of radiotherapy [24].

Zhang H et al. performed a prospective cohort study assessing quality of life outcomes using the EuroQol-5D (EQ5D) and the Edmonton Symptom Assessment System (ESAS) questionnaires. They reported that there may be significant quality of life benefits, including decreased anxiety, pain, and depression and increased appetite and generalized feelings of well-being, associated with marijuana use among patients with newly diagnosed HNCs [25].

Xie et al. performed a prospective epidemiologic review of head and neck cancer (HNC) patients who are recreational marijuana users. They concluded that, compared to non-users, patients were less likely to be married, and more likely to smoke tobacco, have a p16 positive primary cancer of the oropharynx, and be treated by chemoradiation [26].

3.5.3. Incidence of cancer

Donald et al. present six cases of advanced HNC cancer in young patients who were marijuana smokers [27].

Taylor et al. retrospectively scanned all surgical pathology reports to identify ten patients under the age of 40 which were subsequently investigated for a history of marijuana use. The ten cases of respiratory tract carcinomas included two lung, four larynx, and four tongue cancers. They found eight of these cases were associated with either heavy or regular use of marijuana [28].

Donald et al. present an additional five cases of advanced HNC in young patients after reviewing the 2500 head and neck cases through his 19 years of experience [29].

aWengen et al. retrospectively reported 34 young patients (20–40 years of age) with SCC of the upper aerodigestive tract over a seven-year period. All were chronic marijuana smokers. This paper can be found in the German literature with an English abstract [30].

Endicott et al. retrospectively reported 23 cases of SCCHN in patients 41 years of age and younger in the author's sixteen years of practice. They noted that 21 of these patients reported marijuana use, one did not, and two were not questioned. The definition of marijuana use was not alluded to, however the authors provided two full case reports that were “illustrative of the history and clinical course”. These two patients used marijuana daily [31].

Zhang ZF et al. was the first epidemiologic study to demonstrate that marijuana smoking increased the risk of HNC. Their prospective, case-control design (173 cases and 176 controls) determined an odds ratio for HNCs among those who had ever smoked marijuana was 2.6 (95% CI, 1.1–6.6) after adjustment for possible confounding factors. Dose-response relationships were observed for both the frequency (use per day) and duration (years) of marijuana smoking [32].

Zhang ZF et al. published more data from their initial case-control study in 1999 investigating the relationship of environmental tobacco smoke and HNC. They analyzed this in relation to marijuana as a possible confounding factor and effect modifier [33].

Schantz and Yu retrospectively calculated the age-adjusted incidence rates for HNCs using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. They noted a higher incidence of tongue cancer in birth cohorts beginning in 1938 which, assuming a 20–30 year latency period for cancer is consistent with the similarly sharp increase in marijuana use in the United States for those born in the 1940s and 1950s. The authors noted the lack of causality and recommended the need for a well-designed study in the future [34].

Llewellyn et al. performed a case-control study of 116 patients aged 45 years and younger diagnosed with oral SCC (OSCC). They found no significance between cannabis use and OSCC but noted the highest odds ratio (OR) in female cannabis smokers [35,36].

Rosenblatt et al. performed a population-based case-control study (407 cases and 615 controls) to determine whether marijuana use was associated with the development of OSCC. They determined that there were no trends in risk of OSCC were observed with increasing duration, average frequency of use, or time since first or last use [37].

Hashibe et al. performed a population-based case-control study to reveal no association between 60 joint-years or more of marijuana smoking and the incidence of lung and upper aerodigestive cancers [38]. They did, however, note that their study may have been affected by selection bias or error in measuring lifetime exposure and confounder histories.

Aldington et al. performed a case-control study of 75 cases and 319 controls. They concluded that, while their study may have had limited power and duration, cannabis use did not appear to increase the risk of HNC [39].

Gillison et al. utilized a case-control study (240 cases and 320 controls) to reveal marijuana exposure to be independently associated with HPV16+ SCCHN, which became stronger with increased joints

per month and duration of marijuana use [40].

Liang et al. performed a population-based case-control study to determine the relationship between marijuana and SCCHN of 434 patients. They demonstrated 10–20 years of use, moderate weekly use, and beginning use at an older age significantly reduced the risk of SCCHN [41].

Berthiller et al. retrospectively pooled self-reported interview data on marijuana smoking and known HNC risk factors on 4029 cases and 5015 controls from five case-control studies within the International Head And Neck Cancer Epidemiology (INHANCE) Consortium. Subanalyses were conducted among never tobacco users (493 cases and 1813 controls) and among individuals who did not consume alcohol or smoke tobacco (237 cases and 887 controls). They determined that infrequent marijuana smoking does not confer a risk of HNC even for never tobacco smokers or never tobacco smokers *and* never alcohol drinkers [42].

Feng et al. performed a case-control study on 636 patients with nasopharyngeal carcinoma and 715 controls from North Africa and determined that marijuana smoking conferred an increased risk, independent of cigarette smoking [43].

Marks et al. performed a pooled analysis comprising individual-level data from nine case–control studies from the INHANCE consortium to determine that, compared with never marijuana smokers, those that had ever smoked marijuana had an elevated risk of oropharyngeal cancer and a reduced risk of oral tongue cancer, but after adjusting for potential confounding by HPV exposure, oropharyngeal cancers were not significant [44].

3.5.4. Systematic reviews and meta analyses

Only one study was identified as specifically within the field of Otolaryngology. De Carvalho et al. performed a systematic review to include six articles (comprising nine case-control studies) [32,38,41–44] which underwent meta-analysis. They determined that approximately 12.6% of cases and 14.3% of controls were marijuana users. The meta-analysis found no association between exposure and disease (OR = 1.021; IC 95% = 0.912–1.14; p = .718). Therefore, the authors concluded that no association between lifetime marijuana use and the development of HNC was found [45].

3.5.5. Literature reviews

Nine reviews on the literature could be found [46–54]. One publication provided an evaluation of the meta-analysis performed by de Carvalho et al. [55]

3.6. Pediatrics

No studies relating to the specific field of Pediatric Otolaryngology could be found.

3.7. Facial plastic and reconstructive surgery

Radke et al. performed a retrospective chart review with prospective data collection in order to determine the effect of medical cannabis on benign essential blepharospasm, considering its accepted use in spastic disorders [56].

Sokoya et al. determined, through a retrospective review of the medical records, there were no significant differences in the patterns of facial fractures before and after the legalization of cannabis in two hospitals in the state of Colorado [57].

3.8. Sleep

Carley et al. showed that intraperitoneal injection of THC in eleven Sprague-Dawley rats decreased the apnea index 42% and 58% in NREM and REM sleep, respectively. Oleamide (an endogenous cannabimimetic agent) and THC blocked serotonin-induced exacerbation of sleep apnea, suggesting that inhibitory coupling between cannabinoids and serotonin receptors in the peripheral nervous system may act on apnea expression [58].

Prasad et al. conducted a translational, proof-of-concept, dose-escalation study to demonstrate the safety, tolerability, and efficacy of dronabinol, an FDA-approved exogenous cannabinoid agonist. They demonstrated a mean Apnea-Hypopnea Index (AHI) change of −14 after three weeks of daily administration of dronabinol, starting at 2.5 mg and increased weekly to 5 mg then 10 mg, as tolerated. No degradation of sleep architecture or serious adverse events was noted [59].

Farabi et al. conducted an exploratory study testing the effect of dronabinol on quantitative electroencephalography (qEEG) sleep markers including power distribution and ultradian cycling in fifteen patients with severe OSA (AHI > 15). They concluded that dronabinol treatment may yield a shift in EEG power toward delta and theta frequencies and a strengthening of ultradian rhythms in the sleep EEG [60].

Calik et al. hypothesized that intra-nodose ganglion injections of a cannabinoid will attenuate serotonin-induced apnea and increase upper airway muscle tone in Sprague-Dawley rats. This is based on previous studies demonstrating the activation of these serotonin receptors in the nodose ganglion to increase afferent vagal activation thereby reducing upper airway muscle tone. The authors showed that dronabinol suppressed serotonin-induced reflex apnea, and increased phasic, but not tonic, activation of the genioglossus. Thus, the authors conclude their findings continue to demonstrate the therapeutic potential of dronabinol for the treatment of OSA [61].

Similarly, Calik & Carley demonstrated that intracerebroventricular injection of dronabinol in Sprague-Dawley rats did not decrease serotonin-induced apneas or increase genioglossus. Therefore, suggesting the dronabinol effects on serotonin-induced apneas are peripherally, not centrally, mediated [62].

Babson et al. published an excellent review of the literature on sleep and the use of cannabis and cannabinoids. They concluded that research on cannabinoids and sleep is in its infancy and studies are limited by small sample sizes, short term follow-up, and a lack of controls. However, the role of the endocannabinoid system on the circadian regulation system demonstrates the theoretical connection between cannabinoids and sleep. Thus, highlighting the critical need for continued research [63].

Carley et al. conducted a randomized, double blind controlled trial (deemed the Pharmacotherapy of Apnea by Cannabimimetic Enhancement - PACE trial) of 73 adults with moderate or severe OSA. A placebo (n = 25), 2.5 mg (n = 21), or 10 mg of dronabinol (n = 27) were administered daily, 1 h before bedtime for up to six weeks. In comparison to placebo, dronabinol dose-dependently reduced AHI by 10.7 ± 4.4 (p = .02) and 12.9 ± 4.3 (p = .003) for the 2.5 and 10 mg daily doses, respectively. Dronabinol at 10 mg/day reduced Epworth Sleepiness Scale (ESS) score by −3.8 ± 0.8 points from baseline (p < .0001) and by −2.3 ± 1.2 points in comparison to placebo (p = .05). Participants receiving 10 mg/day of dronabinol expressed the highest overall satisfaction with treatment (p = .04). Maintenance of Wakefulness Test (MWT) sleep latencies, gross sleep architecture, and overnight oxygenation parameters were unchanged from baseline in any treatment group. Most (88%) participants experienced one or more adverse events (AEs) during their participation. However, the number and severity of AEs, and treatment adherence (0.3 ± 0.6 missed doses/week) were equivalent among all treatment groups. The most frequently reported verbatim AEs included sleepiness/drowsiness (N = 25; 8% of total AEs reported), headache (N = 24; 8%), nausea/vomiting (N = 23; 8%), and dizziness/lightheadedness (N = 12; 4%). However, severity of AEs was rated as mild for 73%, moderate for 25%, and severe for only 2%. The authors, therefore, conclude that their

findings support the therapeutic potential of cannabinoids in people with OSA with the obvious need for larger scale clinical trials to clarify the best potential approaches [64].

Ramar et al. with the American Academy of Sleep Medicine, published a position statement on the use of cannabis for obstructive sleep apnea (OSA); they concluded that medical cannabis and/or its synthetic extracts should not be used for the treatment of OSA due to unreliable delivery methods and insufficient evidence of treatment effectiveness, tolerability, and safety, and that OSA should be excluded from the list of chronic medical conditions for state medical cannabis programs [65].

Two letters to the editor (2018) were published in opposition to the AASM position statement stating that there actually is sufficient evidence [66,67]. Ramar and the AASM stood by their original statement in a response to these comments [68].

Kolla et al. concluded that the approval of the use of cannabis to treat OSA is extremely premature and has the potential to result in inadequate treatment and possible harm [69]. One letter to the editor published on this study agreed with Kolla et al. and provided a deeper understanding of the background relating to the laws and regulations in the state of Minnesota [70].

4. Conclusions

The Otolaryngology community is still in its infancy in determining the efficacy and safety of cannabis among various medical conditions. Within the field of Otolaryngology, the majority of studies relating to cannabis involve its possible association with the incidence of head and neck cancer. There are a few studies present that suggest cannabis may be a useful therapy for Otolaryngological patients suffering from blepharospasm, the effects of radiation, and the psychological sequelae of receiving a diagnosis of a head and neck cancer. Further research is required to determine if cannabis has any therapeutic role in other Otolaryngologic conditions. This study provides the researcher the most up to date collection of all studies relating cannabis to the field of Otolaryngology.

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