Therapeutic Cannabis and Endocannabinoid Signaling System Modulator Use in Otolaryngology Patients

Lucas M. Bryant, MD [iD]; Kelly E. Daniels, BS [iD]; David M. Cognetti, MD; Patrick Tassone, MD [iD];
Adam J. Luginbuhl, MD; Joseph M. Curry, MD

Objectives: 1) review benefits and risks of cannabis use, with emphasis on otolaryngic disease processes; 2) define and review the endocannabinoid signaling system (ESS); and 3) review state and federal regulations for the use and research of cannabis and ESS modulators.

Methods: This manuscript is a review of the current literature relevant to the stated objectives.

Results: Cannabis (marijuana) use is increasing. It is the most widely used illicit substance in the world. There is increasing interest in its therapeutic potential due to changing perceptions, new research, and legislation changes controlling its use. The legal classification of cannabis is complicated due to varied and conflicting state and federal laws. There are currently two synthetic cannabinoid drugs that are FDA approved. Current indications for use include chemotherapy-related nausea and vomiting, cachexia, and appetite loss. Research has demonstrated potential benefit for use in many other pathologies including pain, inflammatory states, and malignancy. Data exists demonstrating potential antineoplastic benefit in oral, thyroid, and skin cancers.

Conclusions: ESS modulators may play both a causal and therapeutic role in several disorders seen in otolaryngology patients. The use of cannabis and cannabinoids is not without risk. There is a need for further research to better understand both the adverse and therapeutic effects of cannabis use. With increasing rates of consumption, elevated public awareness, and rapidly changing legislation, it is helpful for the otolaryngologist to be aware of both the adverse manifestations of use and the potential therapeutic benefits when talking with patients.

INTRODUCTION

The purpose of this review is to provide the practicing otolaryngologist with a foundational knowledge of current therapeutic uses of cannabinoids and effectors of the endocannabinoid signaling system (ECS). It includes a brief overview of the biochemical principles guiding the physiologic effects of the ECS, addresses the risks and adverse effects of cannabis use, and finally reviews current state and federal legislation.

Cannabis (marijuana) use is increasing and is currently the most widely used illicit substance both worldwide and within the United States.[1] Cannabis has been used for centuries as a treatment for myriad medical ailments. It has shown potential to be of therapeutic use in several pathologies including nausea, pain, weight/appetite loss, inflammation, anxiety, multiple sclerosis-related muscle spasticity, neuropathy, seizure, and even

cancer. [2–8] There has been a recent resurgence of interest in its therapeutic potential, which is likely due to a combination of changing societal perceptions, new scientific discoveries, and recent legislation measures relating to its regulation. The legal classification of cannabis is complicated due to conflicting legislation of the state and federal governments. At present, the federal government still classifies marijuana as a schedule I controlled substance and does not approve it for any medical uses. At the state level, 29 states and the District of Columbia have legalized comprehensive medical marijuana and cannabis programs, while an additional 17 states have highly regulated medical marijuana programs legalizing its use in more limited medical situations. This means that for patients in a majority of states, medical marijuana is increasingly becoming an accessible and entirely novel option for management of their ailments. The current increase in use for medical purposes appears to be commensurate with recent changes in state and federal legislative policies as well as international studies demonstrating a biochemical basis for the therapeutic effects seen with cannabis use. As the use of marijuana and other complementary medicine therapies continues to rise, patients may expect their physicians to explain both the potential merits and harms they may experience with its use.

Unlike many other bioceutical therapies which may be used by the otolaryngology patient, marijuana poses additional challenges due it its current federal classification as a schedule I substance. As scientific evidence of

its therapeutic benefit advances, it is vital that physicians are well informed in order to confidently provide sound guidance when questioned by patients. Additionally, the physician must be kept abreast of the current regulatory status in order to ensure they keep their practice within the rapidly changing legal boundaries of both state and federal legislation.

CANNABIS CLASSIFICATION AND BIOLOGY

Marijuana is derived from plants in the Cannabis family. There are two main species: *Cannabis sativa* and *Cannabis indica*. Hemp is a nonpsychoactive cannabis plant product that is used in beauty creams, rope, clothing and other domestic goods. There are hundreds of marijuana "chemotypes" derived from the foundational *sativa* and *indica* strains. Each strain is designed with a goal of modulating the relative concentrations of certain biologically active molecules, called phytocannabinoids. Customized variations in phytocannabinoid levels subsequently provide the user with a customized sensory experience (in the case of recreational use) or therapeutic effect (medicinal use).

Although there are many biologically active phytocannabinoids in cannabis, two predominate in the current literature. In 1964, Gaoni and Mechoulam described the psychoactive cannabinoids found in *Cannabis sativa*: Δ8-tetrahydrocannabinol (Δ8-THC) and Δ9-tetrahydrocannabinol (Δ9-THC).[9] Δ9-THC is more potent and found in higher concentrations within the plant. It is the primary cannabinoid referred to when "THC" is referenced in this paper. THC is metabolized within the lungs and liver into 11-hydroxy-Δ9-THC which is active within the CNS and elsewhere.[10] Jean-Baptiste Lamarck described *Cannabis indica* as a second strain of cannabis in 1785. *Cannabis indica* is clinically distinct from *Cannabis sativa* due to the higher relative concentration of cannabidiol (CBD), another phytocannabinoid.

THC is most commonly associated with the euphoric feelings users experience due to its psychoactive effects. In addition to a sense of euphoria, it also appears to possess anti-emetic, anti-inflammatory, analgesic, and antioxidant properties.[11] In contrast to THC, CBD has traditionally been viewed as a nonpsychoactive cannabinoid. CBD is credited for offering users analgesic, anticonvulsant, anxiolytic, antipsychotic, and sedative effects.[11–14] The anxiolytic and antipsychotic effects have been purported to participate in decreasing these adverse effects seen with THC use. This observation is one reason some proponents argue for extracts instead of synthetic cannabinoids which could ultimately cause more adverse effects through loss of this natural synergistic relationship between phytocannabinoids. When derived from hemp, and absent of THC, CBD containing products are not under federal regulation.

METHODS OF CONSUMPTION

There are several methods commonly used in cannabis consumption. The most traditional method of cannabis consumption is unfiltered smoking. This results in the user inhaling the combustion products in cannabis smoke. Smoking cannabis allows for rapid onset of effects (2–10 minutes), short duration of action, and ease of titratability.[8,15] It is important to note that smoking is the primary delivery method used in nearly all studies assessing the risks of cannabis use. Cannabis is typically smoked in an unfiltered manner and the smoke itself may reach temperatures as high as 700°C. The combustion process results in partial breakdown of cannabinoids with simultaneous production of undesirable carcinogens.[16,17] Marijuana smoke has a similar carcinogen profile as tobacco smoke, but may have higher relative concentrations of certain carcinogens.[18,19]

Another method of cannabis use is enteral consumption. Although this method avoids the carcinogen exposure of smoked cannabis, it has several downfalls. The onset of action and maximum effect is significantly more delayed (1–6 hrs) than smoking, therapeutic effects are less easily titratable secondary to inconsistent bioavailability (6–20%), and the duration of action is prolonged (20–30 hours).[8]

Recently, vaporization has gained popularity as a method of cannabis consumption. Vaporization is a process by which a material is heated to temperatures that allow for vaporization of phytocannabinoids (170–300°C). Vaporization retains the desirable pharmacokinetic profile of smoked marijuana while preventing the creation of harmful carcinogens by avoiding combustion.[15,20–22] Although vaporization appears to be a promising delivery method, it is not well studied and vaporization units are not FDA regulated, subjecting users to potential untoward exposure to heat mediated degradation products of plastics or heavy metals within the vaporizer unit.[23,24]

ENCANNABINOID SIGNALING SYSTEM

The endocannabinoid signaling system (ESS) is complex and promiscuous. In vivo, it acts as a short-range, short-term response system to acute physiologic events.[25] The ESS can be thought of as an "on demand" system, where endocannabinoids are synthesized locally in response to acute local stimuli. It is composed of ligands (cannabinoids), cell surface receptors, and several intracellular signaling pathways that induce enzymatic reactions. These enzymatic reactions may either agonize or attenuate cellular function.[25] Stimulation of the ESS can induce myriad effects, which are discussed elsewhere in this paper. Ligands of the ESS can be autogenous molecules (endocannabinoids), plant derivatives (phytocannabinoids), or synthetic cannabinoids. Phytocannabinoids, synthetic cannabinoids, and ESS modulating drugs exert their effects within the body through manipulation of normal ESS physiology.[10]

Endocannabinoids are biologic molecules made within the body that act on known cannabinoid receptors. In 1992, the first endocannabinoid, anandamide (AEA), was described.[25,26] Since then, several other arachidonic acid-derived endocannabinoids have been described, including 2-arachidonylglycerylether (2-AG), *O*-arachidonoyl-ethanolamine (virohdamine), and *N*-arachydonoyl dopamine (NADA). In general, endocannabinoids act in a paracrine fashion by binding to appropriate cell surface receptors that express appropriate cannabinoid-sensitive

Anandamide/AEA	*N*-arachidonoyl-ethanolamine
NADA	*N*-arachidonoyl-dopamine
2-AG	2-arachidonoyl glycerol
Noladin ether	2-arachidonyl glyceryl ether
Virodhamine	*O*-arachidonoyl-ethanolamine

receptors.[27–29] After internalization, endocannabinoids are metabolized by various degradatory enzymes including FAAH, DAGL, and MAGL (fatty acid amine hydrolase, diacyl glycerol lipase, monoacyl glycerol lipase) (Table I).[30,31]

There are two primary cannabinoid receptors that have been well described. They were sequentially named cannabinoid receptor 1 and 2 (CB_1, CB_2) based on timing of discovery. CB_1 was discovered and described in the late 1980s and early 1990s using a rat model. CB_2 was subsequently described in 1993 in a study using human cell cultures.[26,32,33] Both CB_1 and CB_2 are G-protein coupled receptors (GPCRs), and each of them has been shown to function in unique physiologic pathways, in part due to their distinct sites of expression.[34–38] Apart from CB_1 and CB_2, transient receptor potential vanilloid type 1 ($TRPV_1$), a lipid responsive ion channel, has also demonstrated some cannabinoid binding affinity.[39] Of note, CBD has a relatively weak affinity for both CB_1 and CB_2, which may explain the apparent antagonistic effect it has been reported to have when used with other CB receptor agonists.[25,40]

CB_1 is predominantly found within the brain and other central nervous system structures but is also expressed in other locations including the spleen, eye, and reproductive organs (Fig. 1). Upon receptor activation, CB_1 acts through a variety of intracellular mechanisms. It inhibits adenylate cyclase, resulting in decreased levels of cyclic adenosine monophosphate (cAMP). CB_1 also activates mitogen-activated protein kinase (MAPK), extracellular signal-related kinase (ERK), and phosphatidylinositol-3 kinase (PI3K) signaling pathways, among others.[6,19,34,41,42] CB_1 is able to couple with any class of receptor-activated G-proteins, including G_s, G_i, and G_q, each of which initiates its own set of unique signaling mechanisms. CB_1's diversity in effector mechanisms is further broadened by the receptor's ability to form heterodimers with other receptors. The distinct combination of g-protein pairing and heterodimerization of any one CB_1 receptor creates a nuanced structural conformation, which influences its affinity for specific ligands. Through structural modulation and diverse binding interactions, CB_1 exerts broad and complex downstream effects.[43]

Unlike CB_1, CB_2 appears to predominate peripherally within immune regulatory tissues. CB_2 expression appears to be highest in B cells and natural killer (NK) cells but is also found in T cells and polymorphonuclear (PMN, neutrophils).[44] CB_2 acts to help regulate inflammatory responses. Similar to CB_1, CB_2 induces many of its physiologic effects through MAPK and PI-3K

signaling pathways.[45,46] Unlike CB_1, which may promote a proinflammatory response, CB_2 signaling appears to decrease reactive oxygen species (ROS).[47]

OTOLARYNGIC AND GENERAL MANIFESTATIONS OF CANNABIS USE

As with other aspects of marijuana, there is conflicting data regarding the risks associated with cannabis and cannabinoid use. In general, adverse effects can be separated into those seen with acute or chronic use, and those seen with extremely high (intoxication) doses. These effects are summarized in Tables II and III. Most purported adverse effects of marijuana use appear to present in a dose-dependent manner, regardless of age.[48]

Acute physiologic effects of cannabis use include tachycardia, bronchodilation, conjunctival irritation, and decreased intraocular pressure.[49] Although previous data appears to support marijuana use having a negative effect on neural development when used in young people, a recent prospective study conducted in the UK demonstrated this tendency might be negated in moderate users when other factors such as tobacco and alcohol use are accounted for.[48,50–52] There is data supporting a correlation with mental illness, including schizophrenia, and heavy use.[50] The association between marijuana use and mental illness has not been shown to be causative. Marijuana may induce earlier or stronger psychotic events in individuals with a preexisting disposition toward mental illness.[3]

Driving impairment remains a concern in patients under the influence of marijuana. In contrast to alcohol
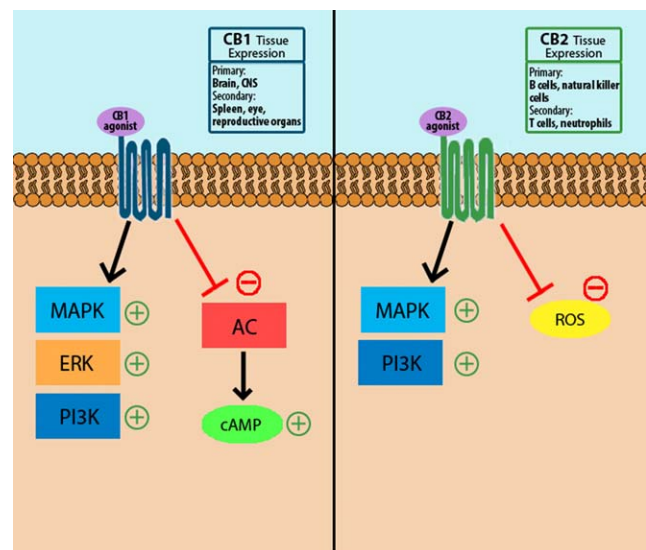

Fig. 1. CB1 and CB2 are membrane bound GPCRs. CB1 receptors (left) are found predominantly in the brain and in tissues of the central nervous system. It is expressed to a lesser degree in the spleen, eye, and reproductive organs. Upon activation, CB1 activates MAPK, ERK, and PI3K pathways, while inhibiting AC and decreasing cellular cAMP. CB2 receptors (right) are found in immune tissues, predominantly B cells and natural killer cells, with additional expression in T cells and neutrophils. Upon activation, CB2 activates MAPK and PI3K pathways while decreasing the generation of ROS.

TABLE II.
Overview of Adverse Effects of Cannabis Use.

Acute[48]	Chronic	Intoxication
Tachycardia, bronchodilation, conjunctival irritation, decreased intraocular pressure[48]	Dependence	Anxiety
Impaired judgment	Respiratory tract inflammation (smoked)	Psychosis, paranoia, mania
Impaired short-term memory	Correlation with mental illness incl. depression & schizophrenia*	Hallucinations
Increased appetite	Cognitive impairment	
Driving impairment	Depression	
Paranoia		

*Especially in patients with preexisting predisposition to mental illness.

intoxication, cannabis intoxication levels and risk of driving impairment are not as predictable due to wider levels of tolerance between users.[53] Cannabis intoxication does not appear to impair drivers to the same extent as alcohol, but has been shown to function synergistically when individuals are intoxicated by both.[53,54] This association with increased motor vehicle accidents extends to other sources of trauma as well. Gerberich et al. found that cannabis use to increase hospital admission rates for all causes of injury.[55]

Chronic effects of marijuana use include respiratory tract inflammation (primarily if smoked), dependence, depressive symptoms, and failure to achieve academically and professionally. Although less addictive than many other illicit substances, marijuana does carry a risk of dependence, with approximately 1 in 10 users demonstrating some level of dependence.[3,48,56] Marijuana does not appear to increase the rate of birth defects when used during pregnancy, but may be associated with decreased birth weight, preterm labor, and increased rate of admission to a neonatal intensive care unit after birth.[57] Finally, although the mortality risk of marijuana use remains unclear, it has also been associated with an increased risk of cardiac events and stroke.[48,58,59]

Despite the apparently similar carcinogenic profile between marijuana and tobacco smoke, current data does not clearly support marijuana smoking as a clear risk factor for lung cancer.[60–64] Studies assessing marijuana use and risk of head and neck cancers are also mixed and data is weakened by confounding factors (namely tobacco), low power, and exposure to recall bias due to their retrospective nature.[61,62,64–67] Some data shows marijuana use to be potentially protective against tongue cancers (OR 0.47, 95% CI 0.29–0.75) and other oropharyngeal cancers, while concomitantly serving as an independent risk factor for human papilloma virus (HPV)–positive oral tumors.[68,69] Gillison et al reported the possibility that the increased risk of HPV positive cancers seen in marijuana smokers may be due to certain immunomodulatory effects of cannabis. By inducing a shift from Th_1 to TH_2 immune responses, cannabinoids may decrease resistance to intracellular bacterial and viral infection. Once infected, the host would also suffer from attenuation of normal physiologic clearing of viral infection. This would ultimately result in more virulent HPV infections and increased rates of HPV-positive

cancer.[68] There are no clinical studies assessing cancer risk in users via oral ingestion or vaporization.

Although a correlation between cannabis smoking and lung cancer is non-definitive, there is data that demonstrates cannabis smoke as a mucosal irritant and source of oxidative stress to respiratory epithelium.[70] There are also reports of increased incidence of fungal sinusitis; possibly due to *Aspergillus* contaminant of the smoked plant.[71,72] Although rare, allergic reactions to marijuana have also been reported. These reactions range from type I hypersensitivity (rhinoconjunctivitis) to anaphylaxis.[73] There is also evidence that marijuana users experience increased rates of periodontal disease and dental carries.[74] Data also correlates marijuana smoking with respiratory mucosa inflammation, stomatitis, uvulitis, cough, and increased sputum production.[19,75] Fortunately, these acute respiratory inflammatory responses to smoked marijuana tend to subside soon after cessation of smoking.[76]

CURRENT CANNABINOID-BASED THERAPIES

At the time of this writing, there are no FDA approved uses for cannabis. There are currently two

TABLE III.
ENT-Specific Adverse and Therapeutic Effects Associated With Cannabinoid Use.*

Associated Increased Risk	Associated Decreased Risk
Allergic reaction (type I hypersensitivity)	Tongue cancer
HPV-related oropharyngeal cancer	Other oropharyngeal cancers
Cough, increased sputum production	Decreased intraocular pressure
Fungal sinusitis (Aspergillus)	Potential antineoplastic effects in skin cancer (melanoma, basal cell, squamous cell)
Inflammation of respiratory mucosa (rhinitis, stomatitis, uvulitis, pharyngitis, bronchitis)	Potential antineoplastic effects in thyroid cancer (anaplastic)
Peridontal disease, dental caries	
Stomatitis, xerostomia	

*Most data of adverse effects relates to smoked marijuana use and may not apply for other delivery methods.

Brand Name	Generic Name	Form	Type of Cannabinoid	Indications for Use
Marinol	Dronabinol	Capsules	Synthetic (Schedule III)	Chemotherapy induced nausea and vomiting, stimulation of appetite
Cesamet	Nabilone	Capsules	Synthetic (Schedule II)	Chemotherapy induced nausea and vomiting
*****Sativex**	Nabiximols	Liquid	Cannabis extract (THC & CBD)	MS spasticity, neuropathic pain. Not yet approved for US.
*****Epidiolex**		Liquid	Cannabis extract (98% CBD)	FDA orphan designation for Dravet Syndrome, Lennox-Gastaut Syndrome

*Not currently FDA approved for use within U.S.A.

synthetic THC formulations available within the United States, dronabinol (Marinol) and nabilone (Cesamet). Dronabinol is a schedule III cannabinoid and nabilone is a schedule II cannabinoid. Nabiximols (Sativex) is a liquid cannabis extract composed of THC and CBD. It is used as an oral spray and is approved for use in several European countries, but not currently within the United States. Indications for both dronabinol and nabilone include the treatment of recalcitrant nausea and vomiting following chemotherapy in cancer patients. Dronabinol is also approved as an appetite stimulant in diseases such as AIDS which result in severe weight loss.[77–84] (Table IV)

POTENTIAL THERAPIES FOR THE OTOLARYNGIC PATIENT

In addition to current FDA recognized indications for use of synthetic cannabinoids, there is growing evidence of therapeutic potential of both bioceutical and synthetic cannabinoids. Three of the most interesting potential uses are for the management of pain, various inflammatory disorders, and cancer.

Pain

Recently, cannabis has gained attention for use as a therapy modality for chronic pain patients, including those with inflammatory, neuropathic, and cancer-related pain.[8,77,81,83,85–93] Compared to other pain regimens, cannabinoid-based therapies appear to maintain a desirable safety profile when used for chronic pain management. Most adverse effects are mild (dizziness, xerostomia, nausea, and fatigue).[86] Cannabis typically has a moderate analgesic effect, and may function best when used synergistically with opioids for pain control.[93] Paudel showed CBD delivery for chronic, extended use could be done via transdermal methods, whereas CBD use for breakthrough pain could be achieved using an intranasal method, allowing for a more rapid onset of approximately 10 minutes.[87] The mortality and morbidity associated with narcotic use for pain control continues to be a serious concern for physicians. In 2014, Bachhuber et al. reported a nearly 25% decrease in opioid-related mortality in states which have enacted a medical marijuana program.[94] Future advances in harnessing the ESS for pain treatment may focus on the development of CB_2 preferential agonists.[85]

Inflammation

The endocannabinoid signaling system plays an active role in modulating immune and inflammatory responses within the body.[47,95–102] Cannabinoids have been shown to both stimulate and attenuate the secretion of various cytokines.[103] Most cells within both the innate and adaptive immune system either secrete endocannabinoids, express endocannabinoid receptors, or do both.[100] Anti-inflammatory activity appears to be a CBD predominant effect.[104] Decreases in several inflammatory markers, including IL-6, TNF-α, COX-2, and iNOS, prostaglandin E_2 have been demonstrated in vitro and in vivo.[104] CB_2 has been shown via in vivo animal models to inhibit Ig-E mediated mast cell activation which would otherwise result in edema and hyperalgesia.[105] CB_2 has been shown to play a role in allergic inflammatory responses, being expressed by many immunologic cells including eosinophils, neutrophils and mast cells.[95,97,98,106] As a modulator of many immune and inflammatory responses, the ESS could potentially be harnessed for use in the management of a variety of disease processes including wound healing, acute and chronic inflammatory disorders, and cancer.[103] Olah et al. demonstrated sebostatic and general anti-inflammatory effects of CBD application to skin, making it a potential treatment for acne, other inflammatory skin disorders, and possibly even wound healing.[107,108]

Cancer

Increased cannabinoid receptor expression has been demonstrated in a variety of tumor cell types. Endocannabinoids can be expressed at higher concentrations in cell populations adjacent to premalignant and malignant cells.[109] The first study to demonstrate antineoplastic activity of cannabis was completed by Munson in 1975.[110] Antineoplastic mechanisms appear to include increased reactive oxygenation species, inhibition of angiogenesis, and arrest of cell-cycle progression, as well as induction of autophagy and apoptosis.[111–114] A common basis for antineoplastic activity of cannabinoids appears to be arrest of cell cycle and inhibition of angiogenesis.[115]

Although presently absent within otolaryngology literature, there is encouraging in vitro and in vivo data demonstrating significant antineoplastic potential of the ESS within a wide variety of cancer models.[34,38,109,116] The ENT-related tumors with data demonstrating the potential antineoplastic activity of cannabinoids include

Cannabinoid	Receptor	Effect	Mechanism	Evidence	Source
varied	varied	N/A, Review	The chief events of endocannabinoids in cancer cell proliferation are reported highlighting the correspondent signalling involved in tumour processes: regulation of adenylyl cyclase, cyclic AMP-protein kinase-A pathway and MEK-extracellular signal-regulated kinase signalling cascade.	Review	Bifulco, 2008
2-AG 10; MAEA 5,	CB1	anti-proliferative	Inhibition of endocannabinoid degradation (blocking membrane transporter or FAAH mediatd degradation), causing increased AEA & 2-AG, decreasing tumor growth,	Rat thyroid xenograft in mouse	Bifulco, 2004,
MAEA 10	CB1	anti-proliferative	k-ras oncogene inhibition	Rat thyroid xenograft in mouse	Bifulco, 2001
MAEA 10	CB1	anti-proliferative	downregulate VEGF/VEGF-R, downregulation of p-21 ras, upregulation of cyclin-dependent kinase inhibitor p27 (kip1), cell cycle growth arrest at G1/S phase	Rath thyroid xenograft in mouse	Portella, 2003
CBD	CB2, TRPV	1. Pro-apoptotic, 2. Anti-proliferative	Not assessed cannabidiol, cannabigerol, cannabichromene, cannabidiol acid and THC acid, and assessed whether there is any advantage in using Cannabis extracts (enriched in either cannabidiol or THC) over pure cannabinoids	Rath thyroid xenograft in mouse	Ligresti, 2006,
Met-F-AEA	CB1	increased apoptosis	MAEA induced DNA damage following p53 activation, p21 (CDKI) expression (CIP1/WAF1)	*in vitro* human anaplastic and papillary thyroid carcinoma cells	Cozzolino, 2010
JWH133 (CB2 agonist), WIN-55, 212-2(CB1/2 agonist)	CB2, CB1	1. Increased apoptosis 2. Paclitaxel sensitization	Intratumoral injection. IL-12 and CB2 mediated antineoplastic activity. Synergy with paclitaxel therapy. Examined gene expression profile of ARO and ARO/IL-12 by microarray analysis of 3757 genes. The most highly expressed gene was cannabinoid receptor 2 (CB2), which was expressed eightfold higher in ARO/IL-12 cells than ARO cells.	*in vivo* mouse anaplastic thyroid	Shi, 2008
MFAEA	CB1	1. Dose dependent inhibition of bFGF angiogenesis 2. Induction of apoptosis	**antiangiogenic.** Endocannabinoids are now emerging as suppressors of key cell-signaling pathways involved in cancer cell growth, invasion, and metastasis. FGF, ERK, p38 MAPK, MMP-2	*in vitro & in vivo* (chick)	Pisanti, 2007

oropharyngeal and tongue cancer, thyroid cancer, lymphoma, basal cell, squamous cell, and melanoma.[5,7,27,36,38,68,79,107,117–127] Using a mouse model, Shi et al. demonstrated a strong antitumoral effect on anaplastic thyroid cancer cell lines. In addition to the direct effects observed, ESS agonism was also shown to increase paclitaxel induced apoptosis by two-fold via an unknown synergistic mechanism.[7] A summary of data relating to thyroid cancer is shown in Table V.

Unfortunately, our understanding of the antineoplastic mechanisms of cannabinoids is limited. It will be interesting to see if the pro-apoptotic, anti-proliferative, anti-migrative, anti-invasive, anti-metastatic and antiangiogenic properties of cannabinoids described in preclinical research can be translated into meaningful clinical therapies in the coming years.[114] Although the data is primarily in favor of cannabinoids functioning in an antineoplastic manner, there are some reports which suggest that cannabinoids may act as either carcinogenic or antineoplastic depending on the concentration.[25,34,128–130]

FEDERAL RESTRICTIONS RELATING TO RESEARCH OF CANNABIS AND ITS DERIVATIVES

Current federal regulations relating to research of cannabis and cannabis derivatives are highly restrictive. Currently, research can only be conducted using specific marijuana strains held at the University of Mississippi. In order to conduct marijuana research, one must obtain permission or licensure from three distinct federal entities, as well as obtaining appropriate state permissions.

Registration is obtained via the Drug Enforcement Agency (DEA), the cannabis plant material to be used for research is obtained through the National Institute on Drug Abuse (NIDA), and finally, an investigational new drug application and research protocol must be approved by the Federal Drug Administration (FDA). Most research that is approved is aimed at exploring negative effects of use, rather than therapeutic research. The current restrictions on research also prevent many modern cannabis strains (which may have varying therapeutic potential) from being studied.[131]

Interestingly, while the FDA maintains its schedule I classification (no accepted medical use, high potential for abuse), the federal government also holds one of the few patents related to cannabis. In 2003, the Department of Health and Human Services was awarded patent US1999/008769, which describes cannabinoids as having antioxidant and neuroprotective effects making "cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases."

Although the stance of physicians toward cannabis use is varied, there is a current trend by many physician groups to declassify marijuana as schedule I.[131,132] Groups such as the American Medical Association, Institute of Medicine, American College of Physicians, and the American Academy of Pediatrics support FDA reclassifying marijuana as a schedule II drug.[131] This reclassification would be promoted with the intent to increase research and allow unbiased application of the scientific method toward better understanding the marijuana plant and its potential therapeutic benefits as well as its harmful effects.

CONCLUSIONS

Much is yet to be determined in relation to both adverse and beneficial effects of cannabinoid use. New data appears to demonstrate many potentially therapeutic possibilities for modulators of the endocannabinoid signaling system. Some of the key areas of interest for the otolaryngologist include its potential effects in cases of oral cancer, thyroid cancer and skin cancer. The most compelling data has currently been achieved via in vitro or in vivo animal studies and has yet to be demonstrated in human clinical trials. Reclassification of marijuana as a schedule II substance would allow for more robust research within the United States while still maintaining a high level of regulatory oversight.

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