Cannabis Use and Endocannabinoid Signaling System Modulators in the Otolaryngology Patient

Bryant, Lucas M; Tassone, Patrick T; Secking Serin I; Cognetti, David M; Curry, Joseph M
Thomas Jefferson Hospital, Philadelphia, PA

Abstract

Objectives:

1. **Review data regarding benefits and risks of cannabis use, with emphasis on disease processes seen by the otolaryngologist.**
2. **Define and review the biomolecular mechanisms of the endocannabinoid signaling system.**
3. **Review current state and federal regulations for the medical use and research of cannabis and modulators of the endocannabinoid system (ESS).**

Introduction

Cannabis (marijuana) is the most widely used illicit substance worldwide and in the United States[1]. There is increasing interest in its therapeutic potential due to changing societal perceptions, new data, and changes in regulatory legislation.

Cannabis and its derivatives act on pre-existing signaling systems within the body called the **endocannabinoid signaling system (ESS).** The ESS is composed of ligands which bind cell surface receptors and activate several intracellular pathways. Ligands may be endogenous (endocannabinoid), plant derived (phytocannabinoid), or synthetic. The most well defined cannabinoid receptors are from the g-protein coupled receptor family and are named by the order of their discovery **(CB_1, CB_2).** Modulators of the ESS (cannabis and cannabis derivatives), have shown therapeutic effects in many pathologies [2-8].

The legal classification of cannabis is complicated because of conflicting legislation between state and federal governments. Cannabis and cannabis derivatives are currently classified as schedule I, even though over half of state legislations have legalized its use in some form. As political and social climates shift toward legalization, it is increasingly important that physicians understand potential risks and benefits with the use of cannabis and cannabis derivatives.

Methods

This project is a thorough review of the best-available current literature. We also review current legal regulations at the state and federal levels.

Results & Discussion

There are two FDA approved cannabinoid drugs (Table 1). Other ESS modulators are available within Europe/UK, and have orphan designation within the US. Areas of potential benefit include pain, inflammation, and malignancy.

Table 1.
Currently Available Cannabinoid Pharmacotherapies

Name (generic), form	Derivation	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** (nabixomols), liquid	Cannabis extract (THC & CBD)	MS spasticity, neuropathic pain.
***Epidiolex**, liquid	Cannabis extract (98% CBD)	FDA orphan designation for Dravet Syndrome, Lennox-Gastaut Syndrome

**Not FDA approved for use within USA*

In vitro and *in vivo* models have demonstrated antineoplastic effects of ESS modulators, including cannabis derivatives[9-18]. These studies include skin cancers (squamous cell, basal cell, melanoma), lymphoma, and thyroid cancer [5,7,10,19-34]. Some of the strongest current data come from research on thyroid cancer and are summarized here (Table 2).

Adverse effects of cannabis use can be classified into acute, chronic, and intoxication (Table 3). Many of the known adverse effects of cannabis use are related to cognitive function. Although there is a correlation between cannabis use and schizophrenia, causation has not yet been clearly demonstrated[35-39].

Results & Discussion (cont.)

Table 2. ESS Modulators and Their Effects on Thyroid Cancer

Cannabinoid	Receptor	Effect	Mechanism	Evidence Type	Author
varied	varied	N/A	The chief effects of endocannabinoids in cancer cell proliferation are reported highlighting the correspondent signaling involved in tumor processes: regulation of adenylyl cyclase, cyclic AMP-protein kinase-A pathway and MEK-extracellular signal-regulated kinase signaling cascade.	Review	Bifulco, 2008
2-AG 10; MAEA 5,	CB1	anti-proliferative	Inhibition of endocannabinoid degradation (blocking membrane transporter or FAAH mediated 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	Pro-apoptotic, 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	increased apoptosis, 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

Table 3.
Overview of Adverse Effects of Cannabis Use

Acute	Chronic	Intoxication
Tachycardia, bronchodilation, conjunctival irritation, decreased intraocular pressure	Dependence	Anxiety
Impaired judgement, paranoia	Respiratory tract inflammation (smoked)	Psychosis
Impaired short term memory	Correlation with schizophrenia and depression	Paranoia
Increased appetite	Decreased professional and academic achievement	Mania
Driving impairment	Cognitive impairment	Hallucinations

Cannabis smoke is a mucosal irritant and source of oxidative stress to respiratory epithelium[50]. There are reports of increased incidence of fungal sinusitis (in part due to Aspergillus contaminant) in marijuana smokers[51-52]. Allergic reactions to marijuana have been shown (although rare). These include Type I hypersensitivity reactions (rhinoconjunctivitis) and even anaphylaxis[53].

Marijuana users experience increased rates of periodontal disease and dental caries[54]. Data also correlate marijuana smoking with respiratory mucosa inflammation, stomatitis, uvulitis, cough, and increased sputum production[55-56]. (Table 4)

Table 4.
ENT Specific Adverse and Therapeutic Effects Associated With Cannabinoid Use*

**Most data of adverse effects relates to smoked product and may not apply to other delivery methods*

Associated With Increased Risk	Associated With 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	

Conclusions

Effectors of the endocannabinoid signaling system may play both a causal and therapeutic role in several disorders seen in otolaryngology patients. New data appear to demonstrate many potentially exciting therapeutic possibilities for modulators of the ESS. Areas of interest for the otolaryngologist include the potential benefit in cases of oral cancer, thyroid cancer and skin cancer, and the possible use in regulation of inflammatory conditions such as rhinosinusitis and wound healing.

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 and public awareness, it is vital for the otolaryngologist to be aware of both the adverse manifestations of use, and the potential therapeutic benefits. The importance of open discussion and appropriate patient education cannot be overstated.

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