International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 03 Issue 12 Dec 2018, ISSN: 2455-8737, Imp. Factor - 4.102
Available online at - www.ijirms.in

Open Access Journal | Research Article | DOI: 10.23958/ijirms/vol03-i12/490

Marijuana: To Use or Not to Use

Sonal Banzal [1], Udaya M Kabadi [1,2]

[1]Broadlawns Medical Center, Des Moines, Iowa
[2]University of Iowa, Iowa City, Iowa

Address for Correspondence:

Udaya M Kabadi
MD, FACP, FRCP(C), FACE
Adjunct Professor of Medicine, University of Iowa, Iowa City, Iowa
And
Chief, Endocrinology, Broadlawns Medical Center, Des Moines, Iowa
1801 Hickman Road, Des Moines, Iowa 50314
Tele No. 5152823041
Email: ukabadi@gmail.com

Several state legislatures legalized marijuana for medicinal and recreational purposes despite federal government's refusal to decriminalize it. Moreover, usage by over 9 % of population ages ≥ 12 years documented by CDC in 2016 may have promoted smuggling across state lines.[1,2]

History and Physiology

Initial endogenous cannabinoids, Anandamide and 2-AG discovered in 1990s are generated from phospholipids and synthesized in postsynaptic cell membrane. ligands can also bind and activate both CBR1 and CBR2 receptors.[6-9] Activation leads to generation of cyclic AMP, stimulation of mitogen-activated protein kinase and Inhibition of voltage gated Ca^{2+} channels (CB_1-R only). However, they bind to and activate CBR1 presynaptically and are promptly degraded by inhibition of transmitter release on binding sites.[10-12] Potential effects include ECS over activation promoting lipogenesis in liver and adipose tissue, inhibiting glucose uptake by skeletal muscle and adiponectin release by adipocyte. ECS activity in the GI tract interferes with feelings of satiety.[3-16] All of these central and peripheral effects contribute to the increased risk of obesity and metabolic syndrome including dyslipidemia, insulin resistance, glucose intolerance and increased cardiometabolic risk.[13-16] Several animal studies have demonstrated role of endocannabinoids in decreasing body weight and adiposity with confirmation by documentation of leanness and resistance to diet induced obesity in CB knockout mice.[2,17] ECS is overdriven in livers of diet induced obese animals resulting in fatty liver in wild type but not in CB1 knockout counterparts.[12] Mutation in enzyme degrading ECS is also associated with increased food intake and weight gain in humans.[2,17,18] Thus, ECS is modulatory in nature and its overactivity in brain in other organs may be a contributors to obesity and its consequences.

Therapeutic Use Of Marijuana

Marijuana or cannabis is an extract derived from the dried flowers and leaves of plant cannabis sativa. The plant produces 60 different molecules but only 2 binding to CBR1 in CNS. Tetrahydrocannabinol induces acute psychosis whereas Cannabidiol acts as an antipsychotic.[19] Therefore, the effect of street cannabis depends on proportion of these molecules.

Based on endocannabinoids physiology, beneficial effects of CBR1 blockade for obesity and exogenous cannabinoids in several disorders were anticipated. However, CBR1 blockers were not approved for therapy of obesity or metabolic syndrome due to serious neuropsychiatric and psychological untoward effects including severe depression leading to suicides and homicides as well as acute and chronic psychotic behavior.[19-21] In contrast, marijuana with 2 major active cannabinoids is legalized by individual state authorities as a supplement for medicinal usage for many disorders. it is apparent that marijuana use fits in with vitamin D supplementation. Vitamin D deficiency is promulgated to be a 'root cause' of almost all human evils and disorders.[22] However, there is not even a semblance of an evidence documenting improvement in morbidity or morality of these disorders with vitamin D supplementation even in megadoses, only exceptions being improvements in bone mineralization and muscle integrity, especially aches and strength both well established outcomes for decades.[22] In the same vein, marijuana is being advertised as a remedy for almost all human evils despite lack of valid rigorous scientific evidence. A few clinical trials have indicated improvement in manifestations of certain disorders. The disorders include neurodegenerative diseases e.g. dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis as well as neuropathic pain.[23-27] Marijuana therapy is also proposed for management of autism, glaucoma as well as onset of nausea and vomiting during pregnancy as well as radiation or chemotherapy for cancers. Finally, marijuana administration has also been tested for relief of pain in subjects with terminal cancer as well as subjects being treated with opioids and other narcotic agents.[26,27] However, almost all these studies employed retrospective designs. Alternatively, few prospective trials documented improvement in pain when added to opioids or symptoms of other aforementioned neurodegenerative disorders as well as autism, glaucoma and pregnancy while using concurrently with established therapies. However, none of these trials used parallel randomized designs and

hence failed to include comparative data generated in subjects administered placebo or comparators. Therefore, national regulatory agencies including Federal Bureau of Investigation denied approval for marijuana based therapies due to absence of robust and rigorous evidence based on extensive clinical trials falling short of convincing scientific scrutiny. However, adverse effects of marijuana use irrespective for medicinal or recreational purposes are rarely described in these reports despite extensive documentation elsewhere in several independent studies in the literature.[28-31] The adverse outcomes include onset of psychotic behavior and hyperemesis syndrome on acute administration.[29-32] Moreover, chronic medicinal or recreational usage has resulted in disorders of multiple organ systems; central nervous system, adverse psychiatric and psychological outcomes, respiratory system with reduction in lung volumes and capacities, cardiovascular system with arrhythmia and cardiomyopathy with consequential congestive heart failure, incase risk of ketoacidosis in subjects with diabetes, sexual dysfunction including lack of libido, erectile dysfunction and gynacomastia etc.[30-33]

Therefore, in light of aforementioned data, marijuana therapy for chronic disorders may not be encouraged with a reluctant exception being 'palliative therapy' for relief of 'suffering' in subjects with terminal illnesses with a short survival period. Alternatively, recreational use although discouraged, may be left to discretion of individuals after a thorough discussion about presumed questionable benefits and side effects especially because use of equally or more harmful agents such as alcohol and tobacco are legalized.

References

[1] Sarah S. Stith, Jacob M. Vigil, Franco Brockelman, Keenan Keeling, Branden Hal. Patient-Reported Symptom Relief Following Medical Cannabis Consumption. Front. Pharmacol., 28 August 2018 | https://doi.org/10.3389/fphar.2018.00916

[2] Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest.* 2003;112:423-431.

[3] Kaur R, Ambwani singh S, Endocannabinoid system; A mulitfacet therapeutic target, Curr Clinical Pharmacol. 2016; 11(2): 110-7. Review

[4] Schrot RJ, Hubbard JR et al. Cannabinoids: medical implications. Ann Med. 2016; 48 (3): 128-41.

[5] Ford TC, Hayley AC, Downey LA, Parrott AC. Cannabis: An overview of its adverse acute and chronic effects and its implications. Curr Drug Abuse Rev 2017; 10(1): 6-18. Doi: 10.2174/1874473710666170712113042

[6] Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature.* 1993;365:61-65.

[7] Sugiura T, Kondo S, Sukagawa A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Commun.* 1995;215:89-97.

[8] Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptor. *Pharmacol Ther.* 1997;74:129-180.

[9] Ameri A. The effects of cannabinoids on the brain. *Prog Neurobiol.* 1999;58:315-348.

[10] Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci.* 1998;21:521-528.

[11] Wilson RI, Nicholl RA. Endocannabinoid signaling in the brain. *Science.* 2002;296:678-682.Di Marzo V, Matias I. Endocannabinoid control of food intake and energy balance. *Nat Neurosci.* 2005;8:585-589.

[12] De Petrocellis L, Cascio MG, Di Marzo V. The endocannabinoid system: a general view and latest additions. *Br J Pharmacol.* 2004;141:765-774.

[13] Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. *Mol Pharmacol.* 2003;63:908-914.

[14] Pagotto U, Vicennati V, Pasquali R. The endocannabinoid system and the treatment of obesity. *Ann Med.* 2005;37:270-275.

[15] Osei-Hyiaman D, DePetrillo M, Pacher P, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. *J Clin Invest.* 2005;115:1298-1305.

[16] Liu YL, Connoley IP, Wilson CA, Stock MJ. Effects of the cannabinoid CB1 receptor antagonist SR141716 on oxygen consumption and soleus muscle glucose uptake in Lep(ob)/Lep(ob) mice. *Int J Obes (Lond).* 2005;29:183-187.

[17] Kirkham TC, Williams CM, Fezza F, Di Marzo V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. *Br J Pharmacol.* 2002;136:550–557.

[18] Ravinet Trillou C, Delgorge C, Menet C, Arnone, M, Soubrie P. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int J Obes Relat Metab Disord.* 2004;28:640-648.

[19] Lattanzi S, Brigo F, Trinka E et al, Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. Drugs (2018). https://doi.org/10.1007/s40265-018-0992-5

[20] Buckner JD, Zvolensky MJ, Ecker AH et al. Integrated cognitive behavioral therapy for comorbid cannabis use and anxietydisorders: A pilot randomized controlled trial. Behav Res Ther. 2018 Oct 26. pii: S0005-7967(18)30167-0. doi: 10.1016/j.brat.2018.10.014.

[21] Hosseini S, Oremus M. The Effect of Age of Initiation of Cannabis Use on Psychosis, Depression, and Anxiety among Youth under 25 Years. Can J Psychitry, 2018 Oct 29:706743718809339. doi: 10.1177/0706743718809339.

[22] Khan M, Kabadi U. Vitamin D in Health and Disease,Primary care Reports, 2011 Volume17,no 8

[23] Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Clin Pharmacology; 2014;37(2):41-4. doi: 10.1097/WNF.0000000000000016.

[24] Abrams DI. The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report Eur J Intern Med. 2018;49:7-11. doi: 10.1016/j.ejim.2018.01.003. Epub 2018 Jan 9.

[25] Grotenhermen F, Müller-Vahl K. The therapeutic potential of cannabis and cannabinoids. Dtsch Arztebl Int. 2012 Jul;109(29-30):495-501. Epub 2012 Jul 23.

[26] Brunette M F, Borodovsky, J, Myers M., Budney A. Important Questions About the Impact of Medical Marijuana on People With Serious Mental Illness Psychiatric Services in Advance (doi: 10.1176/appi.ps.201800210)

[27] Nugent S M; Morasco B ; O'Neil M et al,;. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms A Systematic Review *Ann Intern Med.* 2017;167:319-331. doi:10.7326/M17-0155

[28] Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician. 2015;61(8):e372-81.

[29] E*lin C. Kondrad, MD, Alex J. Et al,* Lack of Communication about Medical Marijuana Use between Doctors and Their Patients
J Am Board Fam Med 2018;31:805–808

[30] Alan D. Kaye, MD,, Mark R. Jones, Adam M. Kaye et al,, Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1 Pain Physician 2017; 20: S93-S109• ISSN 1533-3159

[31] Hall W, Degenhardt L. The adverse health effects of chronic cannabis use. Drug Test Anal. 2014;6(1-2):39-45. doi: 10.1002/dta.1506. Epub 2013 Jul 8.

[32] Sorensen C J, DeSanto K, Borg L et al, Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review J. Med. Toxicol. (2017) 13:71–87 DOI 10.1007/s13181-016-0595-z

[33] Galli J, Sawaya, R, and. Friedenberg F. Cannabinoid Hyperemesis Syndrome Curr Drug Abuse Rev. 2011 ; 4(4): 241–249.

