CANNABIS AS A POSSIBLE TREATMENT FOR SPASTICITY IN MULTIPLE SCLEROSIS

Katarina Vesic [1,2], Slavica Djukic Dejanovic [3,4], Milica Borovcanin [5,4], Janko Samardzic [6] and Gordana Toncev [1,2]
[1] Clinic of Neurology, Clinical Centre Kragujevac, Kragujevac, Serbia
[2] Department of Neurology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[3] Clinic for Psychiatric Illnesses "Dr Laza Lazarevic", Belgrade, Serbia
[4] Department of Psychiatry, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[5] Psychiatric Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia
[6] Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Belgrade, Belgrade, Serbia

KANABIS KAO MOGUĆI TRETMAN U LEČENJU SPASTIČNOSTI KOD MULTIPLE SKLEROZE

Katarina Vesić [1,2], Slavica Đukic Dejanović [3,4], Milica Borovčanin [4,5], Janko Samardzić [6] i Gordana Tončev [1,2]
[1] Klinika za neurologiju, Klinički centar Kragujevac, Kragujevac, Srbija
[2] Katedra za neurologiju, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija
[3] Klinika za psihijatrijske bolesti "Dr Laza Lazarevic", Beograd, Srbija
[4] Katedra za psihijatriju, Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija
[5] Klinika za psihijatriju, Klinički Centar Kragujevac, Srbija
[6] Institut za farmakologiju, kliničku farmakologiju i toksikologiju, Medicinski fakultet, Univerzitet u Beogradu, Srbija

Received / Primljen: 04.03.2015 Accepted / Prihvaćen: 14.05.2015

ABSTRACT

The therapeutic potential of cannabis has been known for centuries. Cannabinoids express their effects through two types of receptors, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). Present studies indicate that cannabis-based drugs can make a positive impact in the treatment of different diseases. For many years, multiple sclerosis patients have self-medicated with illegal street cannabis to alleviate spasticity, a common and debilitating symptom that impairs quality of life.

Nabiximols is the cannabis-based medicine approved in many countries as an add-on therapy for symptom improvement in patients with spasticity who have not responded adequately to other medications. Adverse events such as dizziness, diarrhoea, fatigue, nausea, headache and somnolence occur quite frequently with nabiximols, but they are generally of mild-to-moderate intensity and their incidence can be markedly reduced by gradual uptitration. The prerequisite for the therapeutic use of cannabis in Serbia arerequires legal clarification for the use of the drug in a clinical environment.

Keywords: *cannabis, multiple sclerosis, spasticity, nabiximols*

SAŽETAK

Vekovima unazad je poznato da kanabis ima terapijski potencijal. Kanabinoidi ispoljavaju svoje efekte vezujući se za dve vrste receptora, kanabinoid receptor 1 (CB1) i kanabinoid receptor 2 (CB2). Dosadašnje studije su pokazale da lekovi bazirani na kanabisu mogu imati značajnu ulogu u lečenju mnogih bolesti. Godinama unazad, oboleli od multiple skleroze samoinicijativno, ilegalno koriste kanabis za ublažavanje spastičnosti. Spasticitet je jedan od najčešćih simptoma bolesti koji dovodi do nastanka invaliditeta i može značajno uticati na kvalitet života.

Nabiximol je lek od kanabinoida biljnog porekla koji je danas u mnogim zemljama, zvanično odobren za lečenje spastičnosti kod multiple skleroze. Indikovan je kod pacijenata kod kojih druge terapijske opcije nisu dale zadovoljavajuće rezultate.

Neželjeni efekti nabiximola kao što su vrtoglavica, dijareja, umor, mučnina, glavobolja i pospanost su česti, ali blagog do umerenog intenziteta, a njihova učestalost se smanjuje postepenom titracijom doze leka. Osnovni preduslov za terapijsku upotrebu kanabisa u našoj zemlji je promena postojećih zakonskih okvira.

Ključne reči: *kanabis, multipla skleroza, spasticitet, nabiximol.*

ABBREVIATIONS

CB1-Cannabinoid receptor 1
CB2-Cannabinoid receptor 2
CBD-Cannabidiol
FDA-Food and Drug Administration
HIV-Human immunodeficiency virus
THC-Tetrahydrocannabinol

DE GRUYTER OPEN

UDK: 615.212.7.076 / Ser J Exp Clin Res 2016; 17 (1): 61-66
DOI: 10.1515/SJECR-2015-0047

Corresponding author: Katarina Vesić, MD
Clinic of Neurology, Clinical Center Kragujevac, Zmaj Jovina 30, 34 000 Kragujevac
Tel: 0607129294; Fax: 034370166; E mail: stojanovick@yahoo.

Cannabis consumption throughout the centuries

Medications derived from cannabis have been used for therapeutic purposes for centuries. In ancient Greece, Rome, China and India, cannabis was used to ameliorate muscle spasms, cramps and pain (1). At the end of the 19th century in Europe, cannabis was used for the treatment of pain, asthma, sleep disorders, depression, and loss of appetite (2). UntilBefore 1964, scientists were unable to establish the chemical structure of the essential ingredient of the cannabis plant, but after the principal active ingredient of cannabis was defined as trans-delta-9-tetrahydrocannabinol (THC) (3), an Currentlyextensive literature on the effects of cannabis-based compounds in clinical studies and animal models has been developed.

Cannabinoid receptors and endocannabinoids

Cannabis-based medications have been the subject of intense research since the endogenous cannabinoid system was discovered more than twenty years ago (4, 5). Two principal types of receptors have been found to be part of the endocannabinoid system. Cannabinoid receptor 1 (CB1), predominantly located in the terminals of nerve cells (central and peripheral neurons and glial cells), the reproductive system, some glandular systems and the microcirculation, was identified in 1990 (4). Three years later, cannabinoid receptor 2 (CB2) was found initially in multiple lymphoid organs with the highest expression detected in B lymphocytes, moderate expression in monocytes and polymorph nuclear neutrophils and the lowest expression in T lymphocytes; subsequent studies have identified them in microglial cells (5, 6). The highest distribution of cannabinoid receptors was found in the hippocampus, the basal ganglia, and the cerebellum, areas associated predominantly with memory and motor coordination (7). Cannabinoid receptors also occur in high density in many areas related to pain, such as the periaqueductal grey mass, the rostral ventrolateral medulla, and superficial layers of the spinal dorsal horn. They are also found in the dorsal root ganglion, from which they are transported to both central and peripheral terminals of primary afferent neurons (8, 9, 10). These discoveries consequently lead to the identification of natural ligands for the CB1 receptor: arachidonoylethanolamide, named anandamide, and 2- arachidonoylglycerol (11).

As reviewed by Wegener and Koch in 2009 (12), CB1 receptors are expressed in the presynaptic membrane of neurons, and they utilize a negative feedback mechanism to regulate transmitter release at GABAergic, glutamatergic and dopaminergic synapses. Cellular activity of the postsynaptic neuron promotes continuous synthesis and release of the endocannabinoids from phospholipids of the cell membrane, which then bind to the CB1 receptors in the presynaptic membrane. Stimulation of the CB1 receptors blocks the activity of the presynaptic neurons through activation of A-type potassium channels and potassium inward rectifiers and through the inhibition of voltage-dependent calcium channels and adenylate cyclase. The outcomes are reduced transmitter release in the presynaptic terminals and reduced cellular excitability.

The endocannabinoid effect is regulated through the transport of endocannabinoids into the cell via specific transporters and subsequent degradation through the membrane-bound enzyme fatty acid hydrolase. (13).

Therapeutic potential of cannabis

Cannabis preparations exerts numerous therapeutic effects, and the augmentation of cannabinergic tone is therapeutically beneficial in the treatment of multiple disease states (14). Numerous studies, most of them carried out in the 1970s and 1980s, have demonstrated that cannabinoids are equally or more effective in treating chemotherapy-related nausea and vomiting as the standard antiemetics (15, 16, 17). Some studies have shown that cannabis is effective in the treatment of anorexia and cachexia in patients with human immunodeficiency virus (HIV) (18), tumours (19) and Alzheimer's disease (20), as well as in the treatment of chronic neuropathic pain and multiple sclerosis (21,22). However, cannabis may be ineffective in treating patients with acute pain (23). Small randomized controlled trials have shown a positive effect of cannabis preparations in the treatment of tics in Tourette syndrome (24) and levodopa-induced dyskinesia in Parkinson's disease (25).

Cannabis treatment of spasticity in multiple sclerosis

Spasticity is a consequence of a damaged corticospinal tract, which plays a role in controlling voluntary movements (26). Therefore, it is characterized by sudden involuntary movements, muscle stiffness, or muscle spasm sufficient to cause pain, particularly in the lower back and legs. Spasticity ,and itcan result in difficulty moving the limb at all. This condition is often associated with spinal cord injury, amyotrophic lateral sclerosis, cerebral palsy and brain damage (27).

Cannabis preparation has been discussed as a promising agent in multiple sclerosis treatment, particularly for spasticity. Spasticity is the most commonly reported symptom, occurring in 90% of patients, causing significant disability and quality of life impairment. Spasticity may also contribute, directly or indirectly, to hroughother symptoms of multiple sclerosis, such as bladder or bowel dysfunction (28), and it can be associated with pain, weakness, clonus, sleep disturbance, fatigue and loss of dexterity (29). At worst, severe spasticity can lead to complete immobility (30). Prolonged immobility may lead to pressure sores and thromboembolism (31).

Standard drugs used to treat spasticity include centrally acting agents, such as benzodiazepines, baclofen, tizanidine and gabapentin, and peripherally acting agents such as dantrolene (29, 32). There is a very limited evidence

base for these drugs, and they provide only moderate relief from spasticity (33). Because many patients are refractory to treatment with existing oral drugs (29, 32, 33), there is a clear need for new treatments for spasticity in multiple sclerosis.

Demographic evidence has shown that many people with multiple sclerosis use cannabis for self-medication (34). The antispastic effect of cannabis has been supported through a demonstration of the inhibitory properties in exogenous agonists for cannabis receptors found in the central nervous system (35). Stimulation of CB1 receptors by cannabis-based drugs have the potential to regulate aberrant levels of glutamatergic excitability during spasticity (36). The endocannabinoid system is upregulated in lesioned areas to provide further control of aberrant neurotransmission, suggestings that further enhancement of endocannabinoid tone by stimulating endocannabinoid synthesis or blockade of endocannabinoid degradation may exhibit anti-spastic activity. CB1 receptors in the basal ganglia are probably the target for cannabinoid control of tremor, spasticity, and painful muscle spasms in multiple sclerosis. CB1 is densely expressed in the output neurons of the substantia nigra, pars reticulata and globus pallidus (37). Activation of CB1 within these neurons can suppress excessive motor output and consequent muscle spasm (38). Cannabinoids can reduce chronic pain, one symptom of multiple sclerosis, but in this case, it is clinically important that cannabinoids can also reduce pain which is a consequence of muscle spasm (38).

Available cannabinoid-based medication for spasticity

For patients with multiple sclerosis, nabiximols is the first cannabis-based medicine to be licensed for the treatment of symptoms (39). The drug is a pharmaceutical product standardised in composition, formulation and dose. Nabiximols differs from all other pharmaceutically produced cannabinoids currently available because it is a mixture of compounds. Its principal active cannabinoid components are the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) (Figure 1).

Although there is considerable structural overlap between THC and CBD, their conformational structures differ significantly. As a result of this, CBD does not bind to or activate the CB1 receptor, which leads to a complete lack of psychoactivity by CBD, unlike THC, which is the psychoactive principle of cannabis. However, CBD shows significant pharmacological activity, such as anti-inflammatory and immunomodulatory effects, that appear to be mediated by the adenosine A2A receptors and could possibly influence the progression of the illness (40). Finally, it has been suggested that the combination of CBD and THC shows a better therapeutic profile than each cannabinoid component alone, with a lower predominance of unwanted, adverse side effects (41). Smoking cannabis achieves the fastest absorption, and the effects are manifested in a few minutes. Inhalation of 8 mg of THC results in a 24 times faster achievement of peak blood concentrations than 0 msublingual administration of 10 mg of THC. When inhaledAdditionally,This peak is achieved in 17 minutes when inhaled, and in 263 minutes when ingested sublingual (37).

Nabiximols is formulated as an oromuscular spray which is administered by spraying into the mouth. Each spray delivers a near 1:1 ratio of CBD to THC, with fixed a dose of 2.7 mg THC and 2.5 mg CBD (42). An essential part of the therapeutic use of the drug is that it is patient-directed and dose-optimized through self-titration. The titration period may take up to 2 weeks to find the optimal dose. On the first day of the titration period, one spray in the morning and one spray in the afternoon/evening should be administered. This dosage should be increased by one spray each day depending on efficacy and adverse effects. The average effective dose is 8-9 sprays per day, up to a maximum of 24 sprays per day (43).

Among all tested analogues, such as oral formulations Dronabinol and Nabilone, it has been concluded that only sublingual spray nabiximols hasve a sufficient evidence base to justify its theiruse in the treatment of spasticity to improve patient quality of life, particularly in patients who are refractory to current treatments (44).

Indications and contraindications for use of nabiximols

Nabiximols is registered for the relief of spasticity, tremor and pain in patients with multiple sclerosis who have not responded sufficiently to standard medication and who show a worthwhile degree of improvement during a 4-week trial period (44). It is contraindicated in patients with known or suspected allergies to cannabinoids or any of the other ingredients and for patients with severe psychiatric disorders other than illness-associated depression. Use is not advised for nursing mothers, they are adolescents or children under 18 or elderly patients (44).

Adverse effects of nabiximols

Because cannabis is a restricted drug, the use of cannabis for medical purposes inevitably raises a number of problems such as possible intoxication and neurotoxicity, the development of tolerance and dependence, as well as legal and ethical dilemmas. Using cannabis for medicinal purposes and the use of marijuana and hashish, which are derivatives of cannabis and are used as forbidden “soft” drugs, should not be equated. Many psychological effects of cannabis and THC are biphasic and bidirectional, depending upon the modality of administration, dosage, individual variability, the degree of tolerance, as well as other environmental factors (45). Acute effects can range from euphoria, relaxation, excitation, sharpened perception and increased motor activity to sedation, distortions of perception, ataxia, and loss of coordination (6). In larger doses,

cannabis can cause dysphoric reactions, anxiety, panic and hysteria (46). All of these central effects occur only after the activation of CB1 receptors (4).

The optimal doses of CB1 receptor agonism in motor control centres would invariably be associated with stimulation of CB1 receptors in cognitive centres, which could also be associated with some unwanted side effects. Acute exposure could also produce a full range of transient psychotomimetic symptoms that last only during the period of intoxication but also and acute psychosis that lasts longer (47). THC produces the full range of transient, positive psychotomimetic symptoms, negative symptoms and cognitive deficits observed in schizophrenia, while CBD has been shown to have anxiolytic properties and even to inhibit the psychotomimetic effects of THC. Cannabis also produces transient, dose-related cognitive impairments, especially in the domains of verbal learning, short-term memory, working memory, executive function, abstract ability, decision-making and attention. Variable duration to full recovery (absence of persistent neuropsychiatry deficits) has been demonstrated to last from a week to an average of 2 years of abstinence (47).

The safety profile of nabiximols, in randomized studies, conducted on patients suffering from multiple sclerosis, indicates that the drug is well tolerated and the most common side effects are dizziness, fatigue, nausea, diarrhoea, drowsiness, headache and somnolence (48).

There is no evidence that nabiximols causes intoxication, cognitive impairments or any of the other central side effects commonly associated with recreational use. T, he reason for this may beis the presence of cannabidiol in nabiximols, which is not psychotropic and may reduce THC levels in the brain and attenuate its psychotropic side effects (49, 50). All cannabinoids in current therapeutic use have a therapeutic index that is relatively narrow for most uses, with adverse effects limiting dose titration. Under everyday clinical practice conditions, nabiximols at a mean daily dose of <7 sprays in ehas been shown to relieve spasticity in approximately 70% of patients previously resistant to treatment. In large observational studies, >80% of patients reported no adverse events. Subjectivity of the spasticity assessment and coexistence of other symptoms in patients with multiple sclerosis must be taken into account as a serious obstacle when evaluations of drug efficacy are conducted. (51). Further limitations in designing adequate comparative studies that cannot be ignored are the legal aspects of psychotropic drug use and the possible influence of pharmacological companies.

Regulation of cannabis use in different countries

There is no unified position regarding the use of cannabis and its analogues, from full legalization and free traffic, through legislation or controlled traffic to a complete ban. In June 2010, the Medicines and Healthcare products Regulatory Agency of the United Kingdom licensed nabiximols as a prescription-only medicine for the treatment of spasticity due to multiple sclerosis (52). This regulatory authorization represents the world's first full regulatory approval for the medicine. Currently, the drug is available for medical use in the United Kingdom, Spain, the Czech Republic, Germany, Denmark, the Netherlands, Sweden, Italy, Austria, Norway, Iceland, Poland, Finland, Switzerland, France, and in some countries in Asia and in Israel (52). In the USA, nabiximols is not officially approved by the FDA for the treatment of spasticity in multiple sclerosis (53, 54). In countries where the medical use of cannabis is approved, there are legally defined conditions for the cultivation of cannabis. For example, in England and the Netherlands, cannabis is grown with the permission of the Government under strictly controlled conditions (55).

If it is in use, there are strictly defined indication areas in which it can be used, and cannabis can be obtained for medical use only by physician prescription. In Serbia, according to the existing legislation, possession, production and trade of marijuana is illegal (56). Laws provide for the strict distribution of cannabis for therapeutic use. C theannabis is availableonly issued by prescription andto doctors and specialists and only after a clear indication of how it will be used. Also it is necessary to define who can grow cannabis and under which conditions it can be produced and distributed. The eventual formation of a user registry is a priority. Regardless of the dilemmas that exist regarding the legislation of marijuana, patients have a right to all beneficial treatments and to deny them access to treatments violates their basic human rights. Therefore, it is necessary to harmonize the scientific, clinical knowledge and national legislative opinions to provide proper use of this psychotropic substance. Considering all of the positive findings, regulatory bodies and the Ministry of Health in Serbia are trying to initiate discussion and establish a legal environment for the use of this compound.

Concluding remarks

Cannabis preparations have been used to relieve nausea, improve appetite and reduce pain for thousands of years. The development of synthetic drugs in the 20th century supplanted these and herbal remedies, but in the past several decades there has been a resurgence of interest in using cannabis and cannabinoid preparations for medical purposes. There is evidence from controlled trials that cannabinoids are effective in relieving nausea and vomiting, alleviating acute pain and improving appetite in people with HIV-related disorders. The potential role of cannabinoids in the treatment of spasticity in multiple sclerosis was highly controversial following the publication of initial studies. Most of the clinical trials conducted in recent years have shown that nabiximols is a useful treatment option for its approved indication, treating spasticity in multiple sclerosis. Apart from reducing spasticity, nabiximols also offers moderate relief of pain associated with muscle spasm and also with centrally generated neuropathic pain. Quality of life, particularly with respect to

sleep, is improved for patients taking the drug, and urinary incontinence is moderately reduced (57). The pharmacoeconomical aspects also favour this therapeutic option because a lower severity of spasticity can lead to reduce resource consumption such as psychotherapy and medication. (58) All of the aspects of cannabis use as a treatment of spasticity in multiple sclerosis must be thoroughly discussed in Serbia.

REFERENCES

1. Zuardi AW. History of cannabis as a medicine:a review. Rev Bras Psiquiatr. 2006; 28 (2): 153-7.
2. Guy G, Whittle BA, Robson PJ. Medical Uses of Cannabis and Cannabinoids. London: Pharmaceutical Press. 2004.
3. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964; 86: 1646-1647.
4. Matsuda LA, Bonner TI and Lolait SJ. Localization of cannabinoid receptor mRNA in rat brain. J Comp Neurol.1993; 327: 535-550.
5. Munro S, Thomas KL and Abu-Sharr M. Molecular characterization of a peripheral receptor for cannabinoids. Nature.1993; 365: 61-65.
6. Iversen L.Cannabis and the brain: Review. Brain.2003 Jun; 126 (6): 1252-70.
7. Herkenham M, Lynn AB, Johnson MR, Melvin LS, De Costa BR and Rice KC. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci. 1991; 11: 563-583.
8. Hohmann AG, Walker JM. Cannabinoid suppression of noxious heat-evoked activity in wide dynamic range neurons in the lumbar dorsal horn of the rat. J Neurophysiol. 1999; (81): 575-583.
9. Sanudo-Pena MC, Strangman NM, Mackie K, Walker JM and Tsou K. CB1 receptor localization in spinal cord and roots, dorsal root ganglion and peripheral nerve. Acta Pharmacol Sin. 1999; (12): 1115-1120.
10. Vaughan VW, Connor M, Bagley EE and Christie MJ. Actions of cannabinoids on membrane properties and synaptic transmission in rat periaqueductal gray neurons in vitro. Mol Pharmacol. 2000; (57): 288-295.
11. Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. Alcohol Alchol. 2005; Vol.40 (1): 2-14.
12. Wegener N, Koch M. Neurobiology and systems physiology of the endocannabinoid system. Pharmacopsychiatry 2009; 42 (1): 79-86
13. Petrosino S., Di Marzo V. FAAH and MAGL inhibitors: therapeutic opportunities from regulating endocannabinoid levels. Curr Opin Investig Drugs 2010; 11: 51-62.
14. Matthew J. McFarland, Ekaterina A.Terebova and Eric L. Barker. Detergent-Resistant Membrane Microdomains in the Disposition of the Lipid Signaling Molecule Anandamide. 2005 AAPS National Biotechnology Conference Symposium on Lipidomics. 2006: 95-100.
15. Colls BM, Ferry DG, Gray AJ, Harvey VJ, McQueen EG. The antiemetic activity of tetrahydrocanabinol versus metoclopramide and thiethylperazine in patient undergoing cancer chemotherapy. N Z Med J.1980; (91): 449-451.
16. McCabe M, Smith FP, Goldberg D, Macdonald J, Wooley PV, Warren R. Efficacy of tetrahydrocannabinol in patient refractory to standard antiemetic therapy. Invest New Drugs. 1988; (6): 243-246.
17. Duran M, Perez E, Abanades S et al. Preliminary efficacy and safety of an oromuscular standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacology. 2010; (70): 656-663.
18. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Sympt Manag.1995; (10): 89-97.
19. Strasser F, Luftner D, et al. Canabis in cachexia study group.Comparasion of orally administreted canabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cnnabis in cachexia study group. J Clin Oncol. 2006; (24): 3394-3400.
20. Volicer L,Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patinets with Alzheimer's disease. Int J Geriatr Psychiatry.1997; (12): 913-919.
21. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomized, double-blind, placebo-controlled clinical trial. Pain. 2007; (133): 210-220.
22. Rog DJ, Nurmikko TJ, Friede T, Young CA.Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology.2005; (65): 812-819.
23. Seeling W,Kneer L, Buchele B, et al. Delta-9-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative paip. Anaesthesist. 2006; (55): 391-400.
24. Muller-Vahl KR, Schneider U, Prevedel H, et al. 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome:a 6-week randomized trial. J Clin Psychiatry. 2003; (64): 459-465.
25. Sieradzan KA, Fox SH,Dick J, Brotchie JM. The effects of the cannabinoid receptor agonist nabilone on L-dopa induced dyskinesia in patients with idiopathic Parkinon's disease. Movement disorders.1998; 13 (Suppl 2).
26. Nielsen JB, Crone C., Hultborn H. The spinal pathophysiology of spasticity-from a basic science point of view. Acta Physiologica 2007; 189: 171-180.
27. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL.Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler.2004; 10 (5): 589-595.

28. Crayton HJ, Rossman HS. Clinical Therapeutics 2006; 28 (4): 445-460.
29. Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technol Assess 2003; 7(40): 101-111.
30. Bhimani R, Anderson L. Clinical understanding of spasticity: implications for practice. Rehabil Res Pract. 2014; 2014:279175. doi: 10.1155/2014/279175.
31. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000; 160 (22): 415-420.
32. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev.2003; 4:CD001332.
33. Novotna A, Mares J, Ratcliffe S,et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. Eur J Neurol. 2011; 2-10.
34. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis.Nerurology.2004; 62:2098-2100.
35. Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG et al. Endocannabinoids control spasticity in a multiple sclerosis model. Faseb J.2011; 15:300-302.
36. Hohmann AG, Herkenham M. Localization of central cannabinoid CB1 receptor messenger RNA in neuronal subpopulations of rat dorsal root ganglia: a double-label in situ hybridization study. Neuroscience.1999; 90(3): 923-931.
37. Pertwee RG.Cannabinoid receptors and pain. Prog Neurobiology.2010; 63(5): 569-611.
38. Baker D., Pryce G., Jackson SJ., Bolton C., Giovannoni G. The biology that underpins the terapeutic potential of cannabis-based medicines for the control of spasticity in multiple sclerosis. Multiple sclerosis and Related Disordes 2012; 64: 64-75.
39. Kmietowicz Z. Cannabis based drug is licensed for spasticity in patients with MS. British Medical Journal 2010; 340: c 3363.
40. Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorg.Med.Chem. 2015; http://dx.doi.org/10.1016/ j.bmc 2015.01.059.
41. Russo E. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology. 2011; 163: 1344-1364.
42. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother. 2006; 7 (5): 607-15.
43. Collin C, Ehler E,Waberzinek G et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subject with symptoms of spasticity due to multiple sclerosis. Neurol Res.2010; 32(5): 451-459.
44. Ashton C John. Emerging treatment options for spasticity in multiple sclerosis-clinical utility of cannabinoids. Degenerative Neurological and Neuromuscular Disease. 2011; 15-23.
45. Tkaczyk M, Florek E, Piekoszewski W. Marihuana and cannabinoids as medicaments. Przegl Lek. 2012; 69 (10): 1095-97.
46. Iversen L. Long-termeffects of exposure to canabis. Curr Opin Pharmacol. 2005;5 (1):69-72 Radhakrishnan R., Wilkinson S. and D Souza DC. Gone to pot-a review of the association between cannabis and psychosis. Frontiers in psychiatry 2014; 54 (5): 1-24.
47. Radhakrishnan R., Wilkinson S. and D Souza DC. Gone to pot-a review of the association between cannabis and psychosis. Frontiers in psychiatry 2014; 54 (5): 1-24.
48. Wang T, Collet JP, Shapiro S, et al. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008; 178 (13): 1669-1678.
49. Perez J.Combined cannabinoid therapy via an oromuscular spray. Drugs of Today.2006; 42: 495-503.
50. Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders. CNS Neurosci Ther. 2009; 15: 65-75.
51. Pozzilli C. Advances in the management of multiple sclerosis spasticity: experiences from recent studies and everyday clinical practice. Expert Rev Neurother.2013; 12: 49-54).
52. www.mhra.gov.uk. Scheduling of the cannabis-based medicine 'Sativex' Accessed in April 2015. Published: 27 March 2013.
53. Barbara S. Koppel, John C.M. Brust, Terry F, Jeff Bronstein,Sarah Youssof, Gary Gronseth and David Gloss. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders. Neurology.2014; 82 (17): 1556-1563.
54. Wright S., Yadav V., Bever C Jr et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014; 83 (16):1484-1486.
55. Potter DJ. A rivew of the cultivation and processing of cannabis (Cannabis sativa L.) for production of prescription medicines in the UK. Drug Test Anal. 2014; 6 (1-2): 31-38.
56. www.zdravlje.gov.rs Zakon o psihoaktivnim kontrolisanim supstancama. Službeni glasnik Republike Srbije br.99/10. Accessed in April 2015.
57. Arroyo R, Vila C, Dechant KL. Impact of Sativex(®) on quality of life and activities of daily living in patients with multiple sclerosis spasticity.J Comp Eff Res. 2014; 3(4):435-44. doi: 10.2217/cer.14.30.
58. Slof J, Gras A. Sativex in multiple sclerosis spasticity: a cost-effectiveness model. Expert Rev Pharmacoecon Outcomes Res. 2012; 12 (4): 439-441