

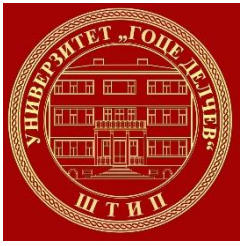
University "Goce Delchev" – Shtip
Faculty of Medical science

Legalization of cannabis for medical purposes **– legislation in Republic of Macedonia and public health–**

Assistant professor

Marija Darkovska-Serafimovska



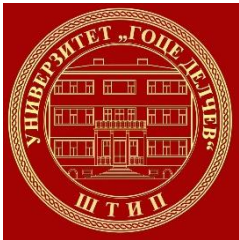


FROM IDEA TO REALISATION

- **Why changes in the legal regulations was important?**

- ✓ **The fact that more patients in the Republic of Macedonia are buying them on black market**
- ✓ **The need for regulation in order to help people was necessary**

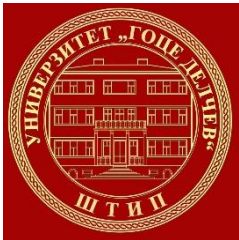




FROM IDEA TO REALIZATION

- **Why changes in the legal regulations was important?**
 - ✓ **Article 39 of the Constitution of the Republic of Macedonia: "Every citizen has a duty to promote his own health"**
 - ✓ **Article 215 of the Criminal code of the Republic of Macedonia “the one who unauthorized produces, sale or buy.....narcotic drugs, psychotropic substances and precursors, shall be punished with imprisonment of three to ten years.”**





FROM IDEA TO REALISATION

- **Why changes in the legal regulations was important?**
- **Changes to the existing law:**
 - ✓ in order to allow the use of the cannabis-based preparations
 - ✓ to have strictly controlled cannabis products on the market in R. Macedonia
 - ✓ at the same time to preventing abuse





STATUS OF CANNABIS BASED MEDICINES IN AMERICA

- Two medicines that contain cannabis are approved by the FDA
 - **Dronabinol** (Marinol®) capsules - Solvay Pharmaceuticals
 - ✓ contains synthetic dronabinol (tetrahydrocannabinol)
 - ✓ approved for treatment of nausea and vomiting induced by chemotherapy in patients who do not respond to conventional antiemetic drugs and for the treatment of anorexia associated with extreme weight loss in patients with AIDS
 - ✓ available on a prescription in a large number of countries outside the US
 - ✓ is also produced by two German companies, THC Pharm and Delta 9 Pharma

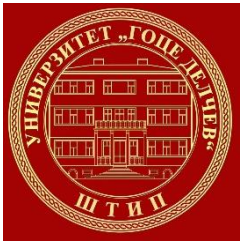




STATUS OF CANNABIS BASED MEDICINES IN AMERICA

- **Nabilone (Cesamet®)** capsules - Valeant Pharmaceuticals International
 - ✓ has obtained a FDA approval as level II controlled substance
 - ✓ contains synthetic cannabinoids similar to tetrahydrocannabinol
 - ✓ approved for treatment of chemotherapy induced nausea and vomiting in patients who do not respond to the conventional antiemetic medicines

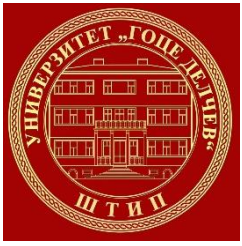




STATUS OF CANNABIS BASED MEDICINES IN AMERICA

- At the beginning of 2014 - FDA grants a special status on the preparation:
Epidiolex™- GW Pharmaceuticals from United Kingdom
 - ✓ the active ingredient in this preparation is a purified liquid extract of cannabis
 - ✓ the medicine is intended for the treatment of a particularly severe form of childhood epilepsy
 - ✓ this status allows to Epidiolex™ to be included in a shortened clinical trial procedure, with one goal - obtaining an approval for marketing authorisation in the United States
 - ✓ at the moment this product is used by several pediatric clinics in the US, who are included in clinical trials



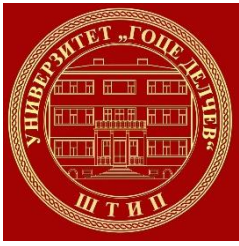


STATUS OF CANNABIS BASED MEDICINES IN EU

At the site of the European Medicines Agency (EMA), stands that the cannabidiol is approved for two indications:

- 1) treatment of Dravet's syndrome as a rare disease (epileptic seizures occurring in the first year of life and associated with high temperature) - approved on 15.10.2014
- 2) treatment of perinatal asphyxia (occurs in babies as a result of a lack of oxygen in the blood, also a rare disease) - approved on July 28, 2015

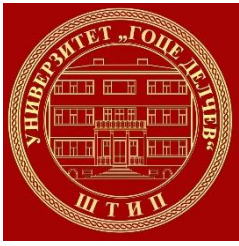




STATUS OF CANNABIS BASED MEDICINES IN EU

- Also, EMA has approved clinical studies (which are ongoing):
 - 1) for the treatment of pain (approval number P/0298/2014) - the study ends in July 2026
 - 2) for the treatment of spasticity in multiple sclerosis, approval number P/0290/2012 - the study is completed in December 2017 (Sativex is examined)

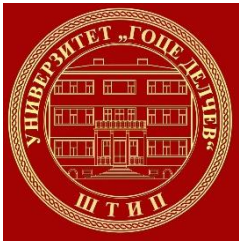




STATUS OF SATIVEX

- The first European product containing natural cannabinoids is being marketed for the first time in 2005. in Canada and from 2010 in the United Kingdom
- **Sativex**[®] oral spray - GW Pharmaceuticals from United Kingdom
 - ✓ the world's first medicine based on natural extracts of cannabis
 - ✓ contains delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)
 - ✓ is produced in a complete standardized formulation
 - ✓ it is on the market in Germany, Austria, England, Denmark, Canada and Switzerland - it has been registered with an MRP procedure (the procedure of mutual recognition)





STATUS OF SATIVEX

- ✓ it is approved for the treatment of spasticity in patients with multiple sclerosis
- ✓ approved for use in the treatment of neuropathic pain in patients with medium to severe spasticity who did not respond adequately to standard antispastic treatment
- ✓ GW Pharmaceuticals also collaborate with Bayer and Novartis to sell the product
- ✓ GW Pharmaceuticals also signed an agreement with the Japanese pharmaceutical company Otsuka with one goal- marketing authorisation of this medicine in the United States, where currently is in Phase III of the clinical trial for this indication





STATUS OF SATIVEX

The positive clinical experience of Sativex in the treatment of chronic pain has been described in a number of studies :

Blake DR, Robson P, Ho M, Jubb RW, McCabe C. A randomised, double-blind, placebo-controlled study of the efficacy, tolerability and safety of Sativex in patients with advanced cancer. *ClinicalTrials.gov*, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Moran J, Haines D. Sativex successfully treats neuropathic pain in patients with advanced cancer: A randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, tolerability and safety of Sativex and Tetranabinex in patients with advanced cancer. *ClinicalTrials.gov*, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

Johnson JR, Potts R. Cannabis-based medicines in the treatment of cancer pain: A randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, tolerability and safety of Sativex and Tetranabinex in patients with advanced cancer. *ClinicalTrials.gov*, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

A study of Sativex_ for relieving persistent pain in patients with advanced cancer. *ClinicalTrials.gov*, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

<http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

ex+malignancy&rank=8&show_locs=Y#locn. Accessed 2012.

Sativex_ for relieving persistent pain in patients with advanced cancer (SPRAY III). *ClinicalTrials.gov*, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

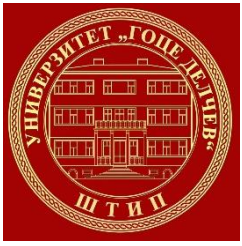
Effects of sativex and oral THC on attention, affect, working memory, reversal learning, physiology and brain activation. *ClinicalTrials.gov*, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

ClinicalTrials.gov, 2011. Available from <http://clinicaltrials.gov/ct2/show/study/NCT01262651>.

Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex [R], as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2010;16:707–14.

Novotna A, Mares J, Ratcliffe S, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex [R], as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2010;16:707–14.

Wade DT, Collin C, Stott C, Duncombe P. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. *Mult Scler* 2010;16:707–14.

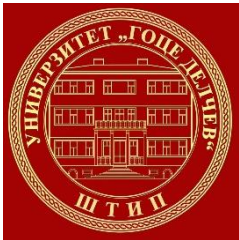


FROM IDEA TO REALISATION

➤ In this direction it was necessary:

- 1) to make changes in the Law on Narcotic Drugs and Psychotropic Substances
- 2) to make changes in the Lists for the classification of drugs and psychotropic substances

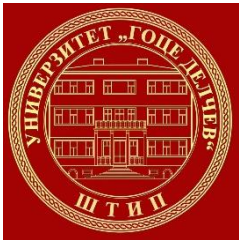




CLASSIFICATION OF NARCOTICS AND PSYCHOTROPIC SUBSTANCES

Schedules	Harmfulness	Degree of control	Examples of listed drugs
I	Substances presenting a high risk of abuse, posing a particularly, serious threat to public health which are of very little or no therapeutic value	Very strict; use is prohibited except for scientific or limited medical purposes	LSD, MDMA (ecstasy), mescaline, psilocybine, tetrahydrocannabinol
II	Substances presenting a risk of abuse, posing a serious threat to public health which are of low or moderate therapeutic value	Less strict	Amphetamines and amphetamine-type stimulants
III	Substances presenting a risk of abuse, posing a serious threat to public health which are of moderate or high therapeutic value	These substances are available for medical purposes	Barbiturates, including amobarbital, buprenorphine
IV	Substances presenting a risk of abuse, posing a minor threat to public health with a high therapeutic value	These substances are available for medical purposes	Tranquillisers, analgesics, narcotics, including allobarbital, diazepam, lorazepam, phenobarbital, temazepam

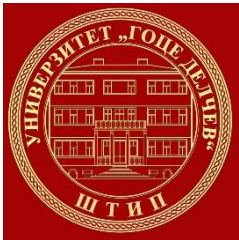




CLASSIFICATION OF NARCOTICS AND PSYCHOTROPIC SUBSTANCES

According to the valid drug regulation (NN 156/2014), the cannabis is in schedule I which means: "use of drugs in vary limited medical purposes" - treatment is only available for experimental purposes.

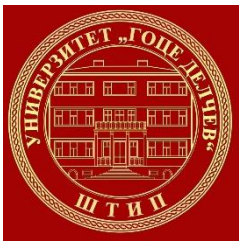




FROM IDEA TO REALISATION

**CANNABIS PRODUCTS TO BE MOVED FROM SCHEDULE I
- AVAILABLE ONLY FOR EXPERIMENTAL PURPOSES
TO SCHEDULES II OR III - SOLD/ISSUED TO INDIVIDUALS WITH
A MEDICAL PRESCRIPTION ONLY**





CHANGES TO THE LAW ON NARCOTICS AND PSYCHOTROPIC SUBSTANCES

- permitted growing, extraction and production of cannabis based medicines
- a permit for growing is issued by the Ministry of Health
- a permit for extraction is issued by the Agency for medicines and medical devices





PUBLIC HEALTH

- What about the public health?
- Do we have more medicine based evidence for use of cannabis based medicines?
- For which indications we have enough positive medicine based experience?





PUBLIC HEALTH

For the first time, a cannabis extract was approved for clinical use in Germany in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis

German Medical Association issued the following statement:

“The benefit of treatment with cannabinoids for a number of medical indications has been shown in controlled trials in which predominantly standardized and/or synthetic cannabinoid preparations were used. The use of such preparations may therefore **be reasonable for patients in whom conventional treatment does not achieve adequate relief of symptoms such as spasticity, pain, nausea, vomiting, or loss of appetite”**





PUBLIC HEALTH

An electronic search of all literature published until June 2017, was made in Medline/Pubmed, Embase, The Cochrane Controlled Trials Register and specific web pages devoted to cannabis





Cannabinoids for relieve pain in patients with malignant diseases

Double-blind, 2-week, multicenter RCT, placebo control study

Johnson JR, Burnell-Nugent M, Lossignol D et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010; 39:167-179.

Extension of the main Double-blind, 2-week, multicenter RCT, placebo control study

Johnson JR, Lossignol D, Burnell-Nugent M et al. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Sympt Manage 2013; 46:207-218.

Multicentre, double blind, placebo-controlled RCT, 3 different doses of Sativex

Portenoy RK, Banae-Motan ED, Allende S et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized placebo-controlled dose-graded trial. J Pain 2012; 13:438-449.





Cannabinoids for relieve pain in patients with malignant diseases

Results:

This trials demonstrated a significant analgesic effect of cannabinoid as compared to placebo.

The most commonly reported adverse effects (drowsiness, nausea, vomiting and dry mouth) were generally well tolerated, mild to moderate.

The proportion of “responders” (patients who at the end of 2 weeks of treatment reported $\geq 30\%$ reduction in pain intensity on a scale of 0-10, which is considered to be clinically important) was 43% in comparison to placebo (21%).





Cannabinoids for relieve symptoms of nausea and vomiting induced by chemotherapy

30 RCTs that compare **efficacy of cannabis** (oral nabilone in 16 trials, oral drobaninol in 13 trials and intramuscular levonantradol in one trial) for this indications (nausea and vomiting) **to placebo and to other antiemetics** (prochlorperazine in 12 trials, metoclopramide in 4 trials, chlorpromazine in 2 trials, thiethylperazine in one trial, haloperidol in one trail, domperidone in 2 trials and alizapride in one trial) which involvs 1366 chemotherapy patients analysed.





Cannabinoids for relieve symptoms of nausea and vomiting induced by chemotherapy

A pilot, randomized, double blind, placebo controlled phase II clinical trial

Duran M, Perez E, Abanades S, Vidal X et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol 2010; 70:656-663.

Dronabinol versus ondansetron in preventing delayed CINV

Solvay Pharmaceuticals Dronabinol versus standard ondansetron antiemetic therapy in preventing delayed-onset chemotherapy-induced nausea and vomiting. [Accessed April 13, 2016]. NLM identifier: NCT00642512. Available from:

<https://clinicaltrials.gov/ct2/show/NCT00642512>.



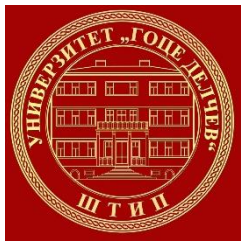


Cannabinoids for relieve symptoms of nausea and vomiting induced by chemotherapy

Conclusion:

- there is justification for use of cannabinoids to relieve symptoms of nausea and vomiting induced by cytotoxic therapy
- cannabis has antiemetic effects when given at the same time with emetogenic chemotherapy
- but with safe and effective available antiemetics (5HT₃ and NK₁ antagonists), cannabinoids cannot be recommended as first or second line therapy to relieve symptoms of nausea and vomiting induced by cytotoxic therapy
- in the case where the standard therapy for the treatment of nausea and vomiting in malignant patients who receive chemotherapy does not work, oral synthetic cannabinoid (e.g. dronabinol) could be recommended as the third or fourth line of therapy

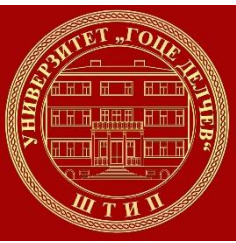




Cannabis based preparations

- On the market in RM 4 different formulations (for 4 indications) of cannabis based preparations for medical purposes are available:
 - ✓ for treatment of pain in malignant diseases - **(2.5 mg CBD + 2.5 mg THC)/ 1 ml**
 - ✓ for treatment of MS - **(1 mg CBD + 2 mg THC)/ 1 ml**
 - ✓ for stimulation of appetite in the treatment of anorexia in AIDS patients - **(1 mg CBD + 2.5 mg THC)/ 1 ml**
 - ✓ for treatment of severe epileptic syndromes in childhood - **(15 mg CBD + 1 mg THC)/1 ml**



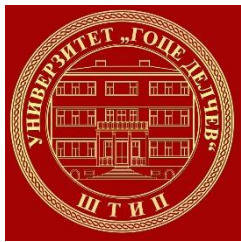


Disdistribution on market

- Article 11, paragraph 2 - Law on medicines and medical devices

"It is possible the medicine which does not have a marketing authorization, to be available for a group of patients with chronic or severe illness, as well as for those patients who can not be successfully treated with another drug that has a marketing authorization, only if documentation for marketing authorisation is submitted to the Agency or clinical trials of that medicine is ongoing"

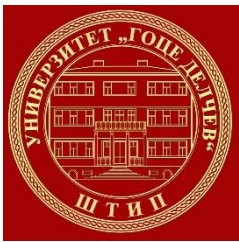




MEANING OF LEGAL REGULATION

**ACCESS TO CANNABIS BASED PRODUCTS
WITH STRICTLY CONTROLLED QUALITY**

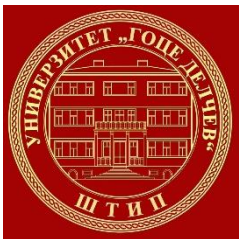




NOTE: INSTEAD OF CONCLUSION

**MEDICAL USE OF CANNABIS BASED
MEDICATIONS IT SHOULD NOT BE A SUBSTITUTE
FOR CONVENTIONAL MEDICAL THERAPY**





THANK YOU

