CANNABINOÏDES: UN RÉVOLUTION VERTE?

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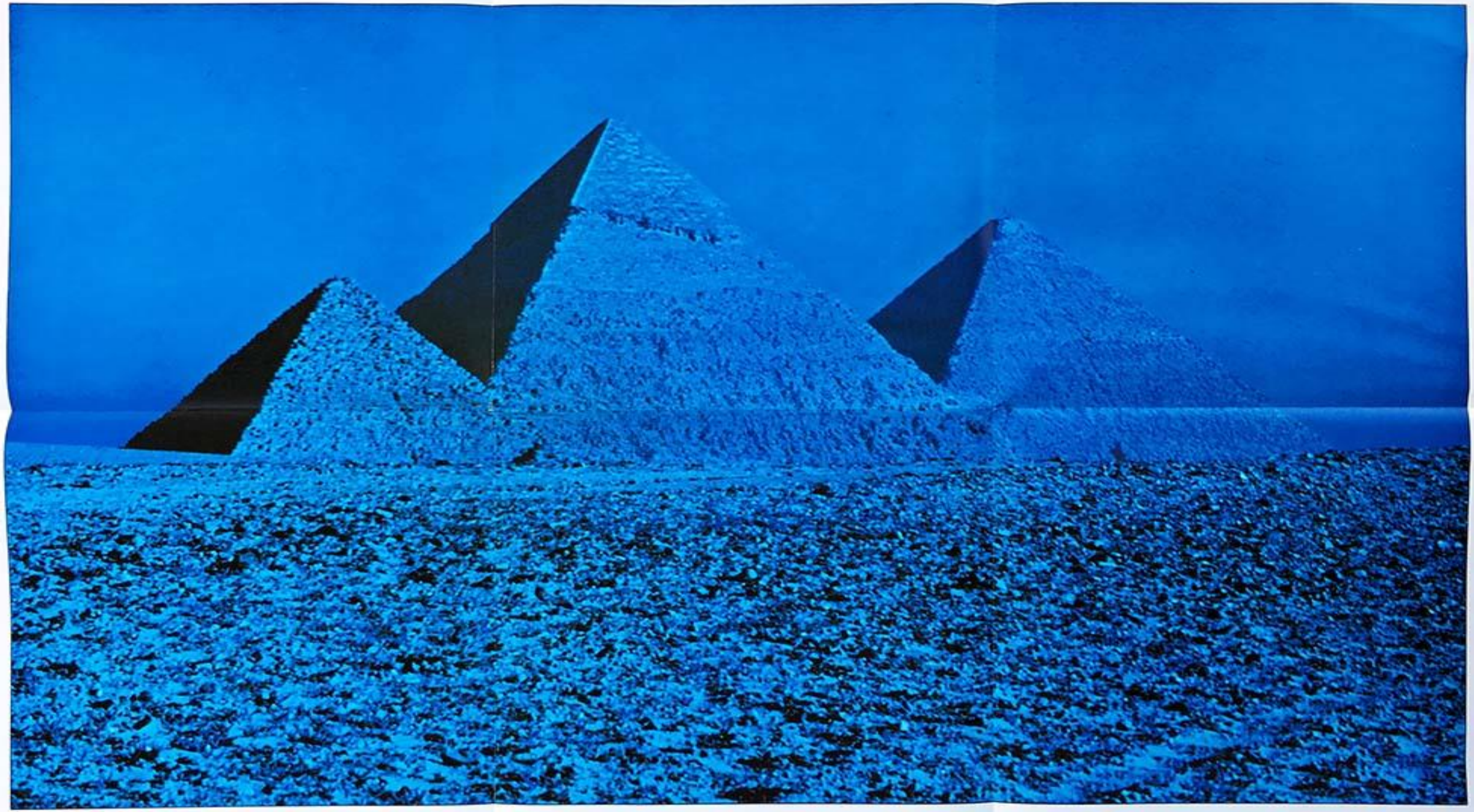
INTRODUCTION

- Beware of "normopathic monomaniacs"
- Medicine is not a science
- The "best medicine/drug" does not exist
- Knowledge is knowing how to measure ignorance of the other

QUESTIONS

- Cannabis, chanvre, drogues ou phyto-cannabinoïdes? Un peu d'histoire
- Utilité physiologique ou redondance? Un mot sur l'évolution
- Efficacité clinique? Les faits, « EBM » et autres
- Toxicité? Quelques précisions
- Développements? Evidemment
- Et en Belgique?...évidemment…



NATURAL CANNABINOIDS

- *Family: Cannabacées ou Cannabinacées*

- *Dioecic plant (female more useful, and interesting)*
- 2 types: *Cannabis* and *Humulus*
- *Genre Cannabis*
  - ***Cannabis sativa***
  - *Cannabis indica*
  - *Cannabis ruderalis*

CORNERSTONES

- Identification of active phytocannabinoids (THC, CBD, etc.)
- Identification of cannabinoids receptor in human
- Identification of terpenes and phenolic compounds (+myrcene-monoterpenoid)

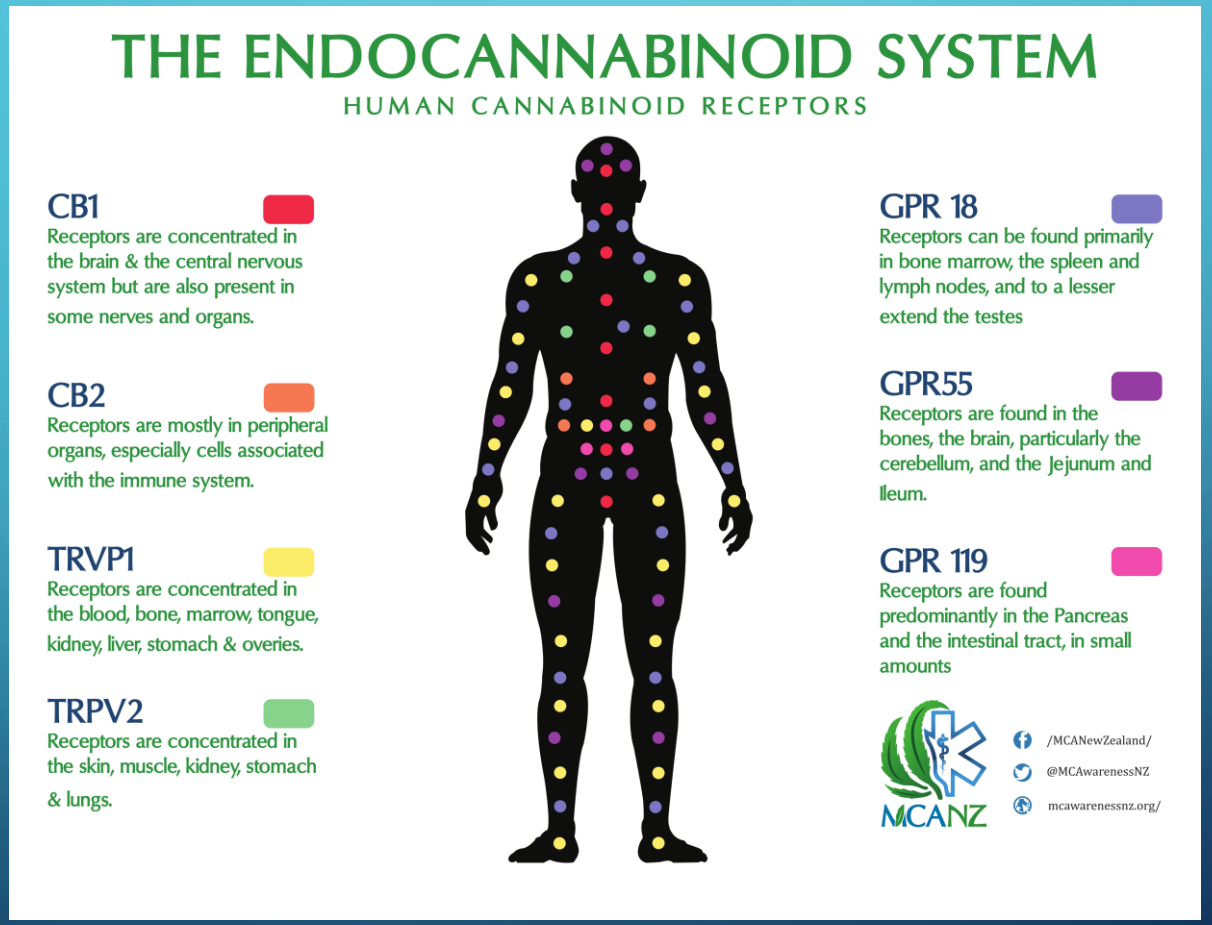
PHARMACOLOGY

- More than 5 identified endocannabinoids
- anandamide: "ananda" = "joy" or "inner happiness", "Internal Bliss"
- Affinity for the CB1 receptor
- Activity similar to THC
- + Arachydonyglycerol
- Blockade of neurotransmission by inhibition of Ca 2+ channels and adenyl cyclase
- Activation of K + channels and mitogen-activated protein kinase
- Interaction with neurotransmitters (Dopamine> state of wellbeing)

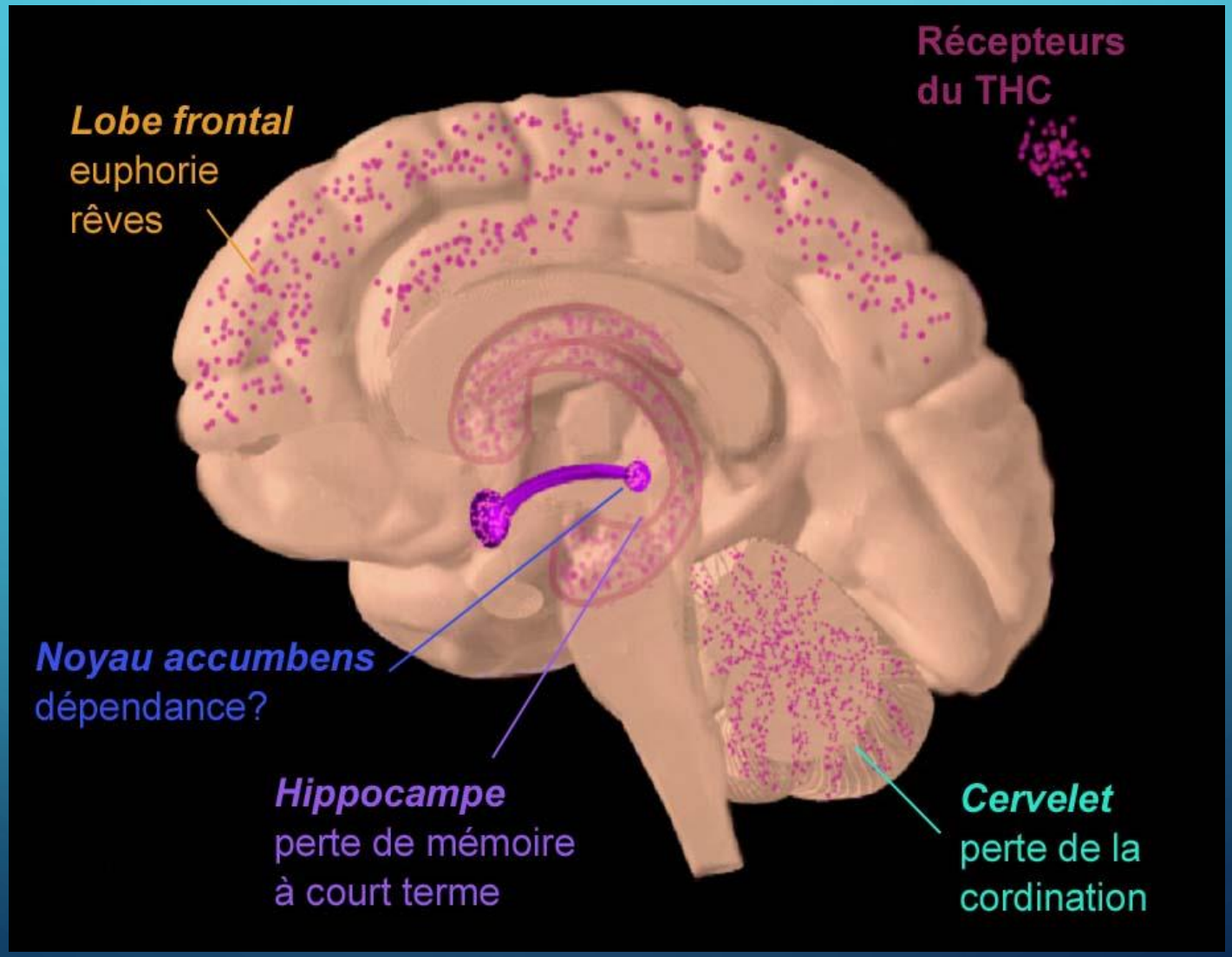
ENDOCANNABINOID RECEPTORS

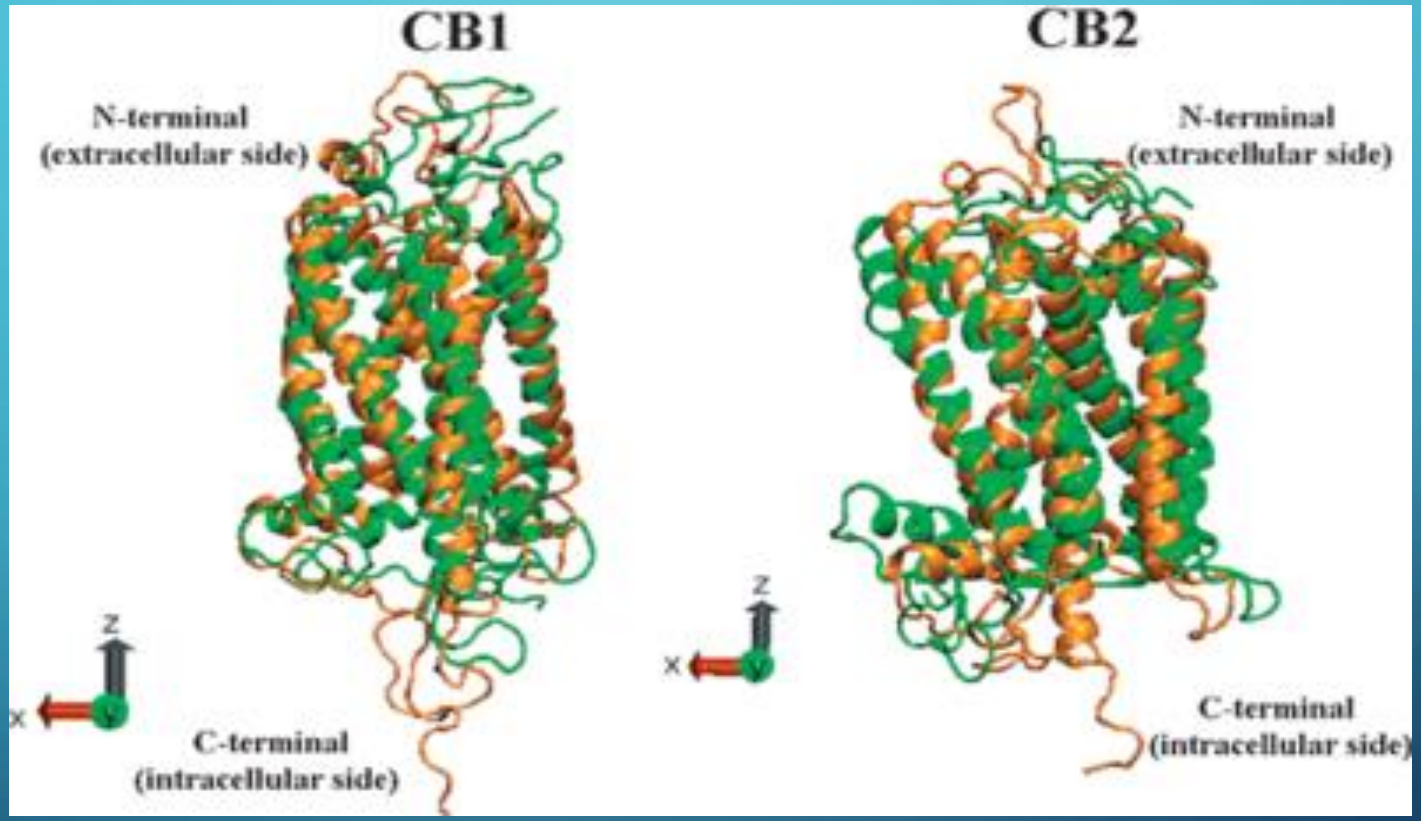
- Animals: rats, dog, pork, guinea pig, monkey, sea urchin , but not in sponges or cnidarians …
- In humans:
  - Location: Brain, Peripheral Nerves, Leukocytes, Coronary Arteries, Spleen, Heart, Digestive and Urinary System
- =>Ubiquitous but with different mechanisms of action
- Brain: same distribution as injected THC - cerebral cortex, limbic areas (hypocampus and amygdala included), basal ganglia, cerebellum, thalamus.
- Positive effects: reduction of nausea, increase of appetite, psychoactive effects, involved in the phenomena of addiction, withdrawal
- Adverse effects: tachycardia, vasodilation, cognitive and /or memory impairment

THE ECS AND RELATED RECEPTORS



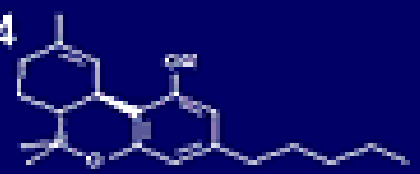
CB1 RECEPTORS
CENTRAL EFFECTS




CB1
N-terminal
(extracellular side)
C-terminal
(intracellular side)
z
x
CB2
N-terminal
(extracellular side)
C-terminal
(intracellular side)
z
x

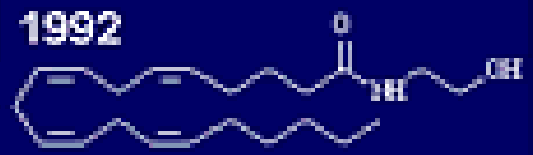
Cannabinoid Receptors

1964

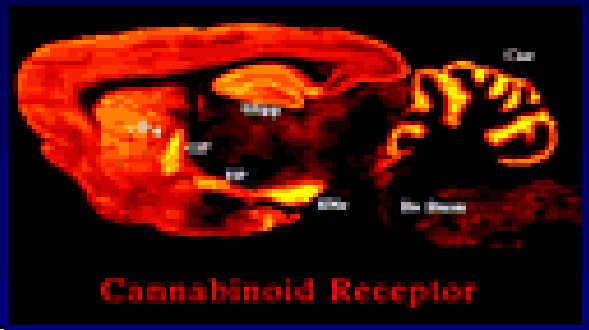


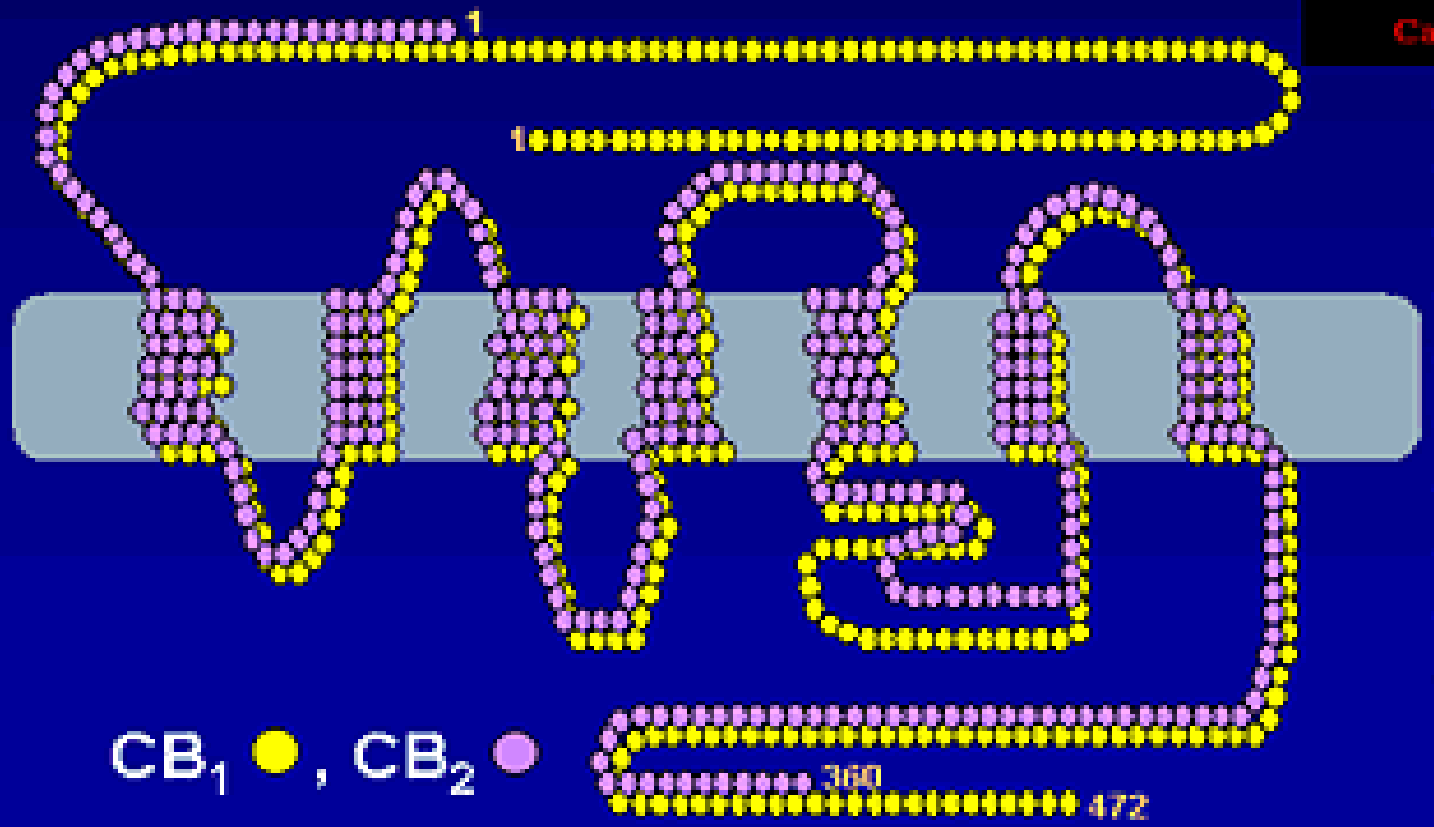
Δ^9-Tetrahydrocannabinol

1992



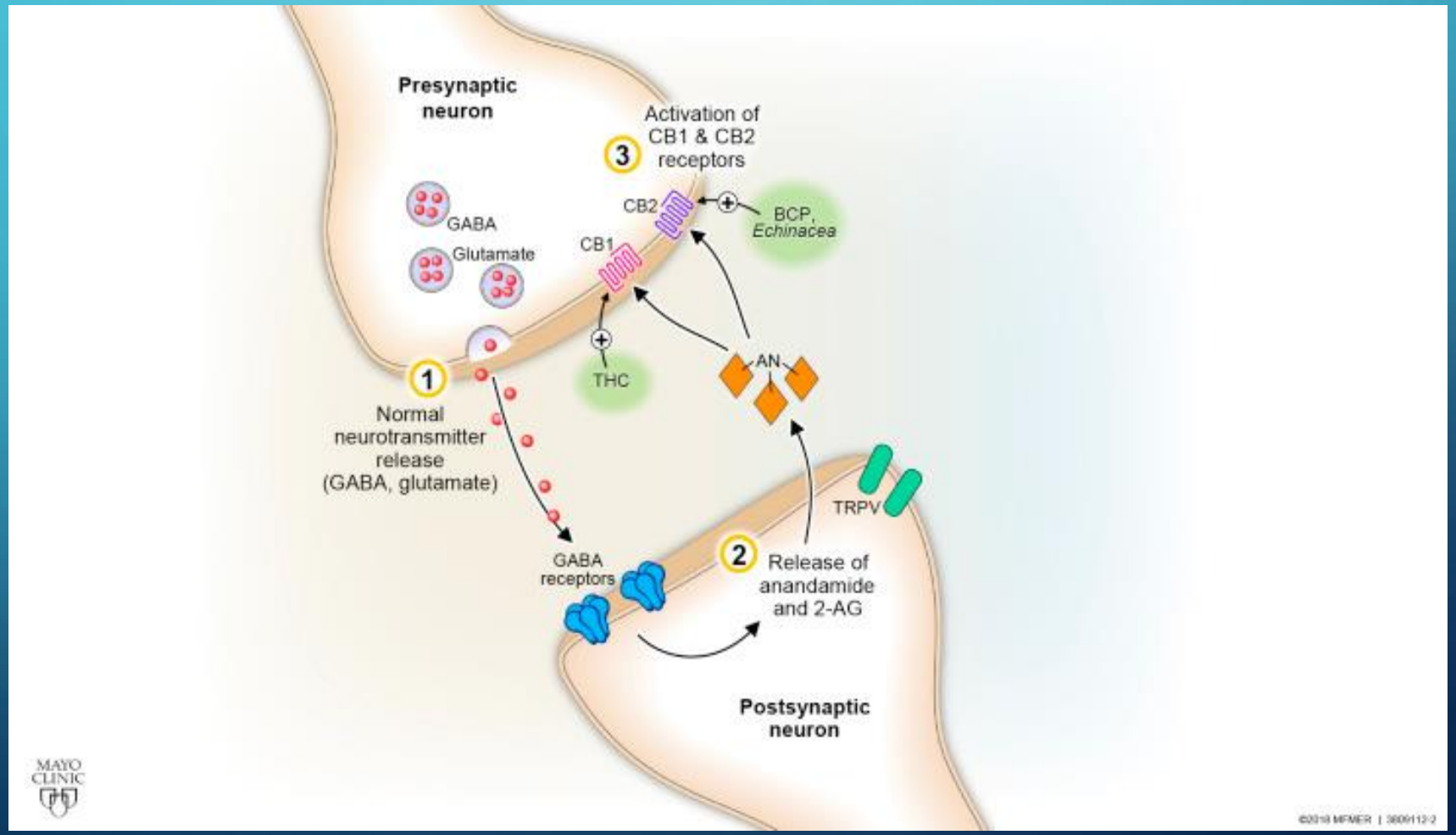
Anandamide



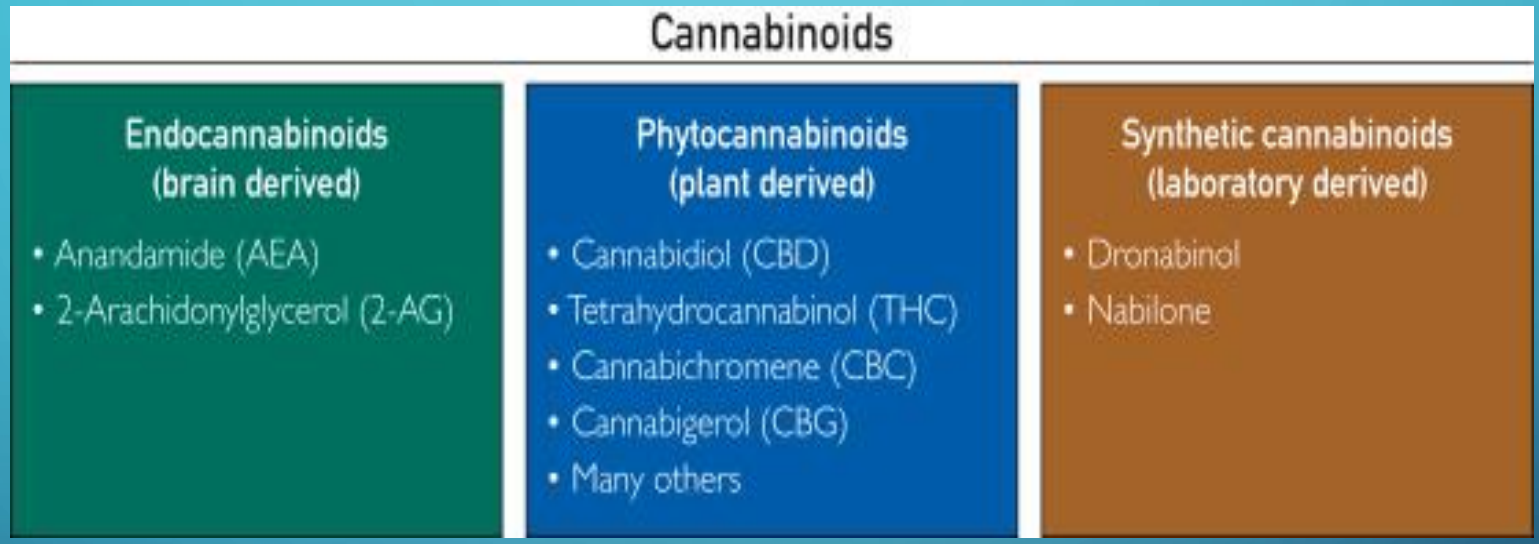


- Hippocampus
- Basal ganglia
- Cortex
- Cerebellum
- Hypothalamus
- Limbic structures
- [illegible]
- Adipocytes
- GI Tract
- Immune cells and tissues

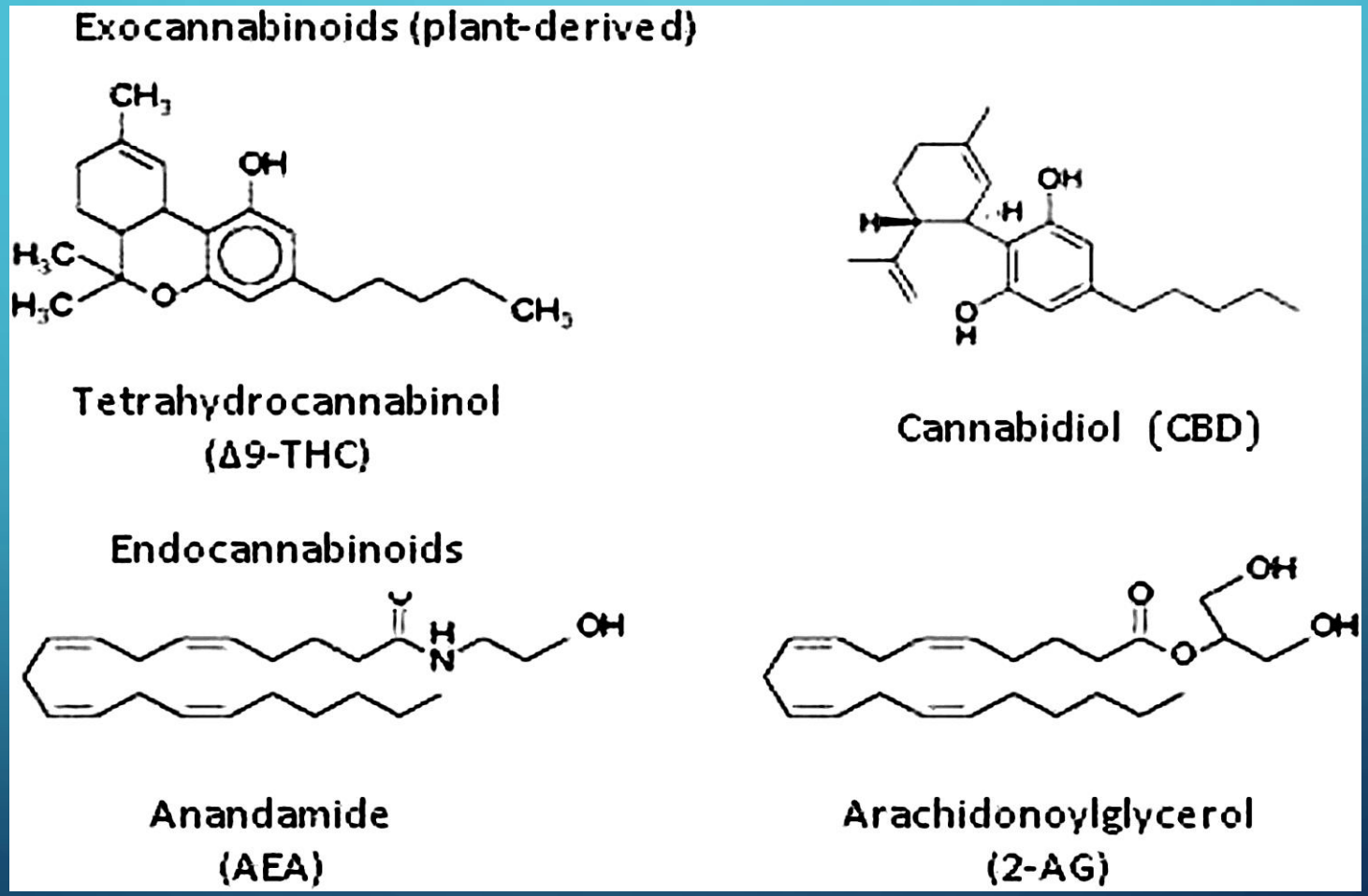
CB1/CB2 RECEPTORS



CANNABINOIDS

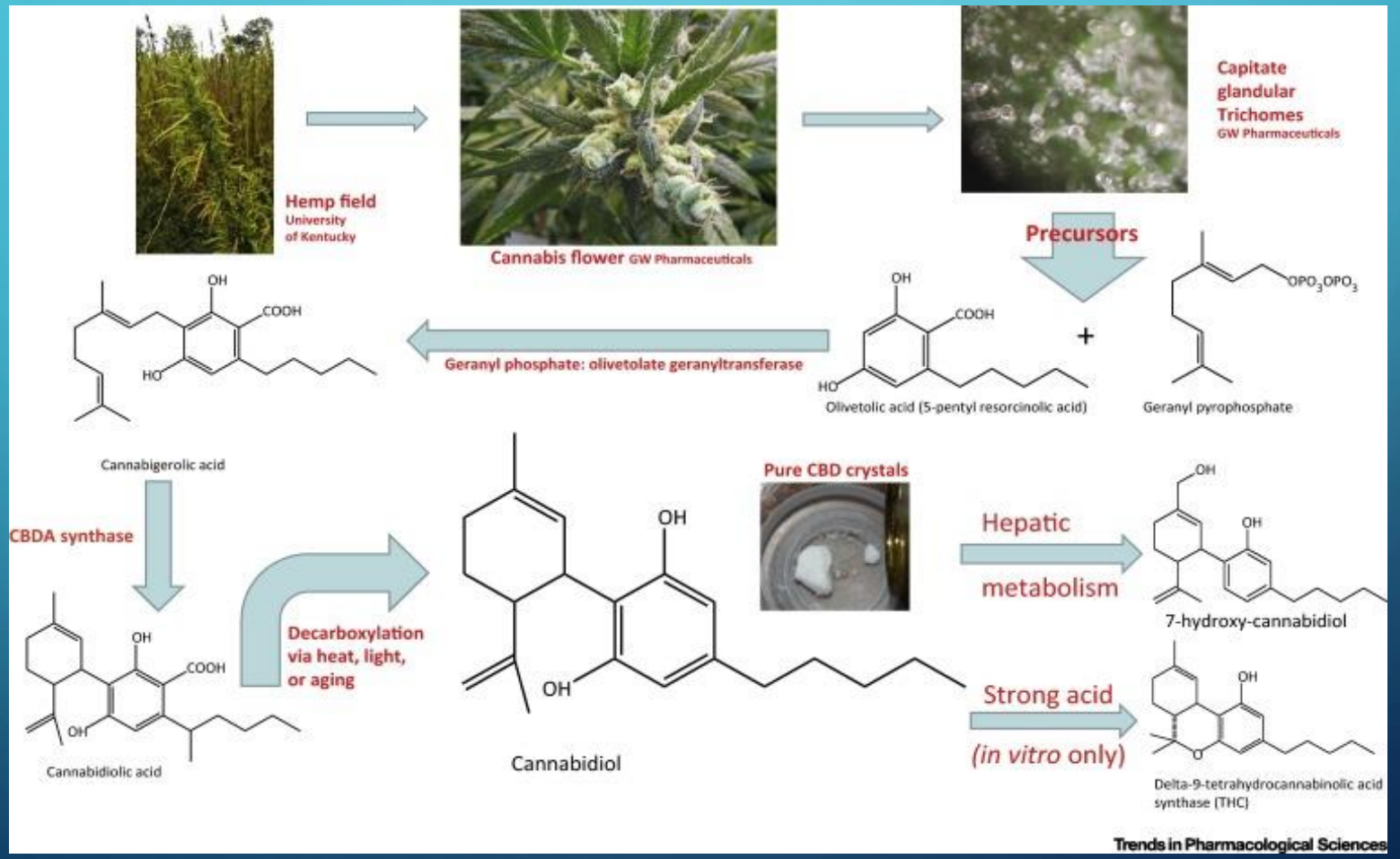


Biochemistry

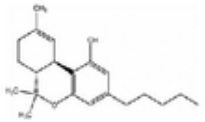
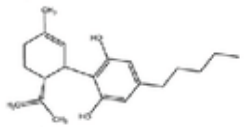
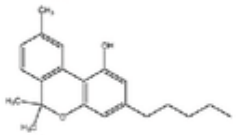
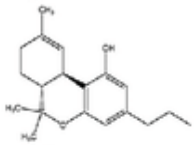
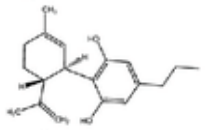
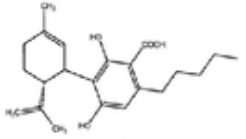
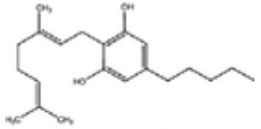


Journal of Pain and Symptom Management 2011 41, 768-778DOI: (10.1016/j.jpainsymman.2010.06.016)

EXTRACTION


Hemp field
University of Kentucky
Cannabis flower GW Pharmaceuticals
Capitate glandular Trichomes
GW Pharmaceuticals
Precursors
Geranyl phosphate: olivetolate geranyltransferase
Olivetolic acid (5-pentyl resorcinolic acid)
Geranyl pyrophosphate
Cannabigerolic acid
CBDA synthase
Cannabidiolic acid
Decarboxylation via heat, light, or aging
Cannabidiol
Pure CBD crystals
Hepatic metabolism
7-hydroxy-cannabidiol
Strong acid
(in vitro only)
Delta-9-tetrahydrocannabinolic acid synthase (THC)
Trends in Pharmacological Sciences

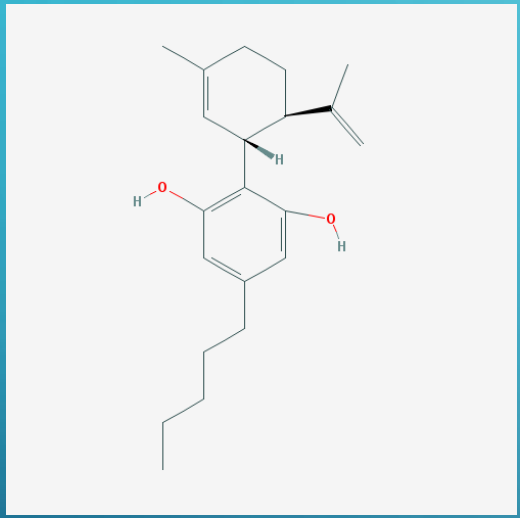
PHYTOCANNABINOIDS

Phytocannabinoids		
Δ^9-tetrahydrocannabinol (Δ^9-THC)		Psychoactive. Most abundant in drug-type plants Partial agonist CB1 ≈ CB2
Cannabidiol (CBD)		Non psychoactive. Most abundant in fiber-type plants. Not specific antagonist of CB1 e CB2 Inhibitor of AEA uptake and metabolism
Cannabinol (CBN)		Weak CB1 agonist, partial CB2 agonist
Δ^9-tetrahydrocannabivarin		Δ9-THCV antagonizes Δ9-THC at low doses (<3 mg/kg) CB1 agonist at greater doses (10 mg/kg)
Cannabidivarin (CBDV)		Mechanism of action unknown
Cannabidiolic acid		Selective inhibitor of COX2 TRPA1 and TRPV1 agonist
Cannabigerol		TRPA1 and TRPV1 agonist CB agonist; inhibitor of AEA reuptake
Cannabichromene		TRPA1 agonist Inhibitor of AEA reuptake

CANNABIDIOL/ CBD

- 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol
- Epidiolex® (in development)
- Arvisol® (in development)

CBD BIOCHEMISTRY



1.Molecular Formula: $C_{21}H_{30}O_2$

2.Molecular Weight: 314.469 g/mol

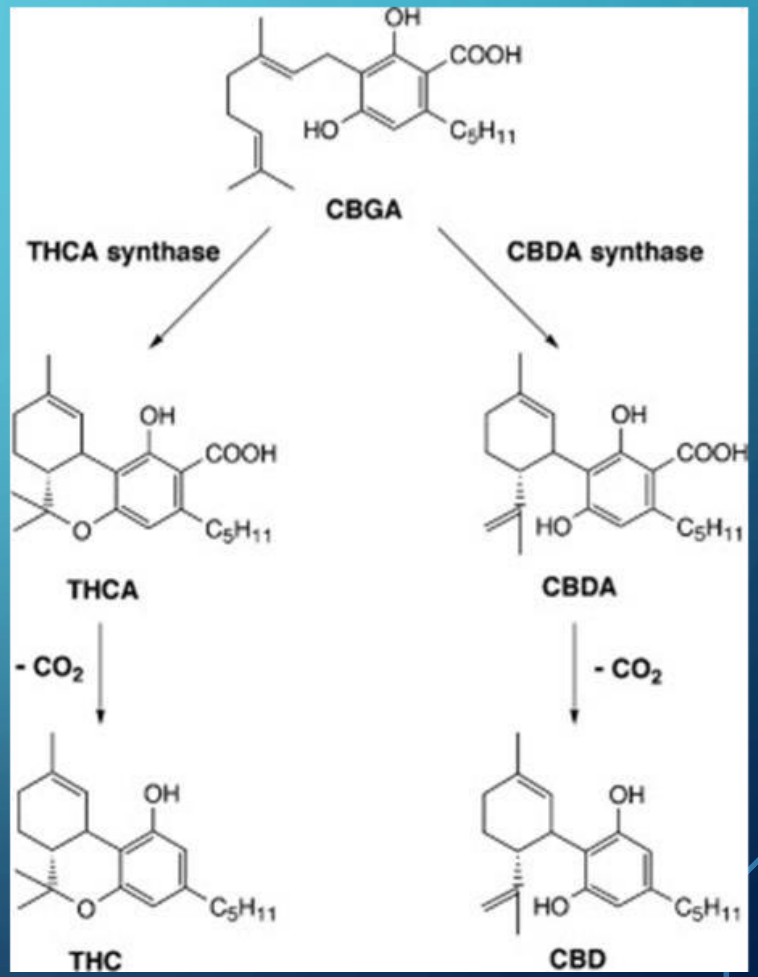
3.Metabolism: Seven recombinant human CYP enzymes were identified as capable of metabolising CBD: CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5

4.In a number of studies, CBD has been shown to inhibit CYP isozymes *in vitro*, but it is not clear that this occurs at concentrations achieved with doses used clinically.

CBD/PLANTS

Biogenesis of THC and CBD adapted from Taura et al. (2007)

THCA synthase and CBDA synthase catalyze oxidative cyclization of the monoterpene moiety of CBGA to form THCA and CBDA, respectively. THC and CBD are generated from THCA and CBDA by non-enzymatic decarboxylation.

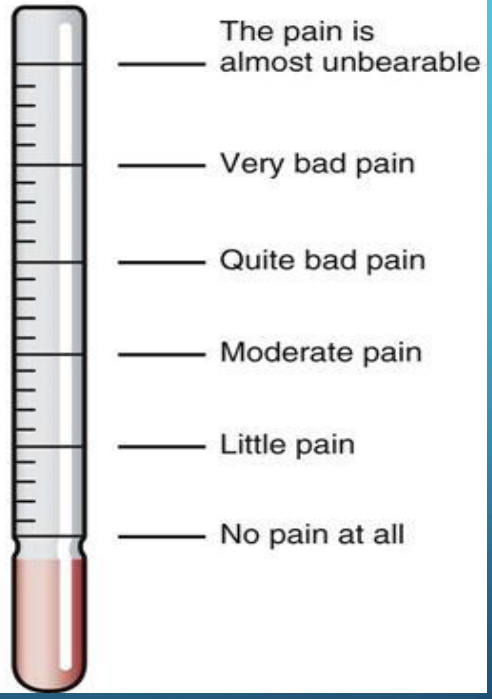


SIDE EFFECTS

- Cardiology: increased heart rate and blood pressure,
- Conjunctival erythema, xerostomia, appetite stimulation (orexigenic effect)
- Respiratory: very low brainstem density in terms of receptors - no respiratory depression (!)
- Cognitive and psychomotor: relaxation, moderate euphoria, hallucinations, disturbances of attention, drowsiness, decreased ability to drive vehicles, sometimes anhedonia, psychosis?

Pain Rating Scale

Instructions:
Below is a thermometer with various grades of pain on it from "No pain at all" to "The pain is almost unbearable." Put an X by the words that describe your pain best. Mark how bad your pain is **at this moment in time.**



INTERACTIONS (CBD)

- CBD, but not THC, is metabolized by CYP2C19
- Effects onCytochrome P450
- Oxycodone:
  - Métabolism P 450 Cyt 2D6
  - Oxymorphone (15 % of the total dose)
- Fentanyl:
  - Métabolism CYP3A4
  - No interaction with cannabis derivated
- Irinotecan, docitaxel: no interaction

- Pas d'implication clinique majeure

J Pain Symptom Manage. 2010 Feb;39(2):167-79. doi: 10.1016/j.jpainsymman.2009.06.008. Epub 2009 Nov 5.

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.

Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT.

Severn Hospice, Shrewsbury, Shropshire, United Kingdom.

- phase II – 177 patients 3 arms
  - THC:CBD 1:1
  - THC alone
  - Placebo

- *Résults* : THC:CBD is superior to placebo in cancer related pain

J Pain Symptom Manage. 2013 Aug;46(2):207-18. doi: 10.1016/j.jpainsymman.2012.07.014. Epub 2012 Nov 8.

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.

Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT.

Shropshire and Mid-Wales Hospice, Shrewsbury, Shropshire, United Kingdom. jeremyjohnson@severnhospice.org.uk

- Extension phase– 43 patients
  - 3 arms : THC:CBD; THC alone; Placebo
- Type of pain: bone, neuropathic, mixte
- Group THC:CBD
  - Doses/day: 5.4 ± 3.28
  - Duration : 2 – 579 d (25d)
  - AE: nausea, vomiting, fatigue
- Group THC
  - Doses/day: 14.5±16.84
  - Durée: 4 – 657d (151d)
  - AE: fatigue (!)

SATIVEX® STUDY

- Etude de phase III
  - GWCA 0958 : double blind, randomized, placebo controlled, parallel group
  - GWCA 0999: multicenter, non comparative, open-label extension study – long term safety of Sativex®

- 23 pays – Institut Jules Bordet en Belgique
- A partir du 1er janvier 2014 – Sativex® disponible en pharmacies, mais uniquement dans le cadre de la sclérose en plaques (+spasticité)

THC/CBD CLINICAL EFFECTS

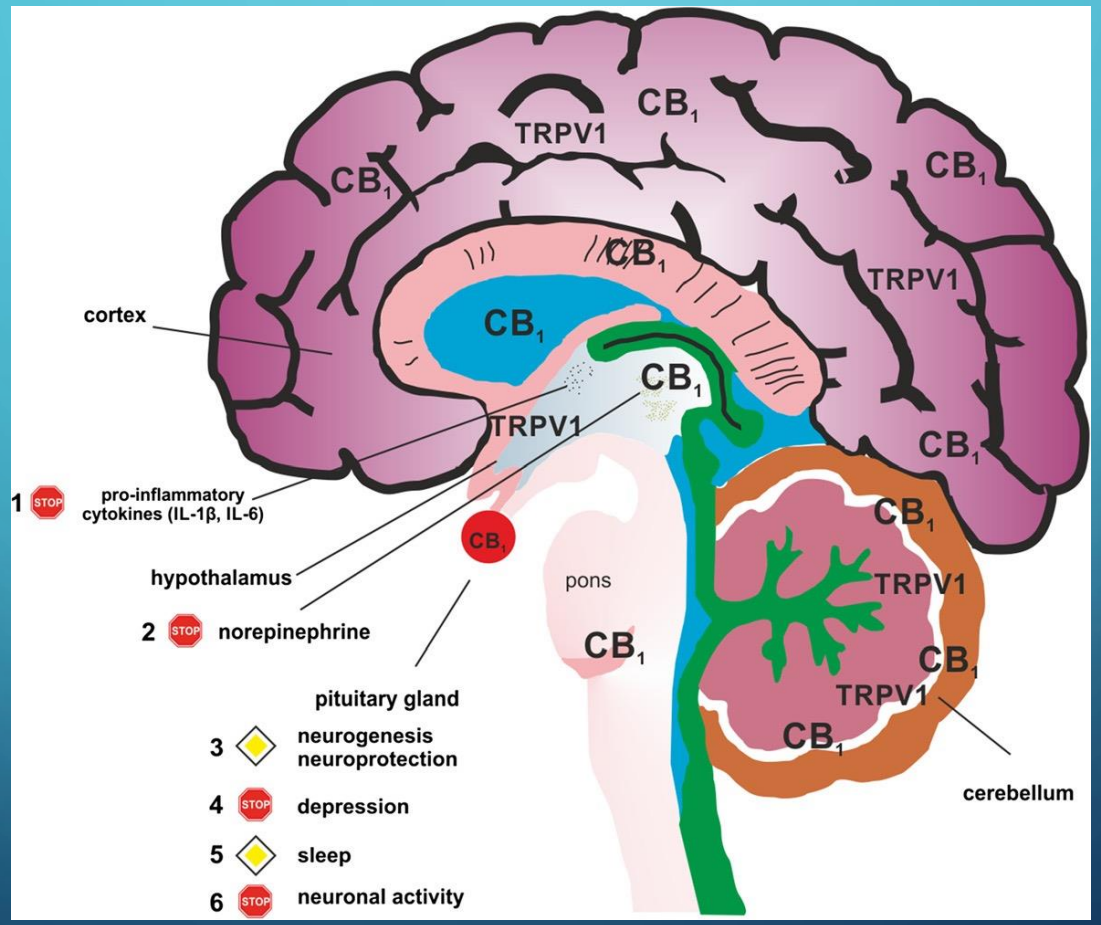
Δ^1 tetrahydrocannabinol (THC)	Cannabiniol (CBD)
Analgesia	Analgesia
Muscle relaxation	Muscle relaxation
Antiemetic	Anticonvulsant effects (refractory epilepsy)
Appetite stimulation	Anxiolytic
Psychotropic effect	Antipsychotic effects
Reduction of intra ocular pressure?	Neuroprotection
	Anti-inflammatory effects/Cardioprotection?
	Graft versus host disease prophylaxis?

CANNABINOIDS AND CKD OR ESRD

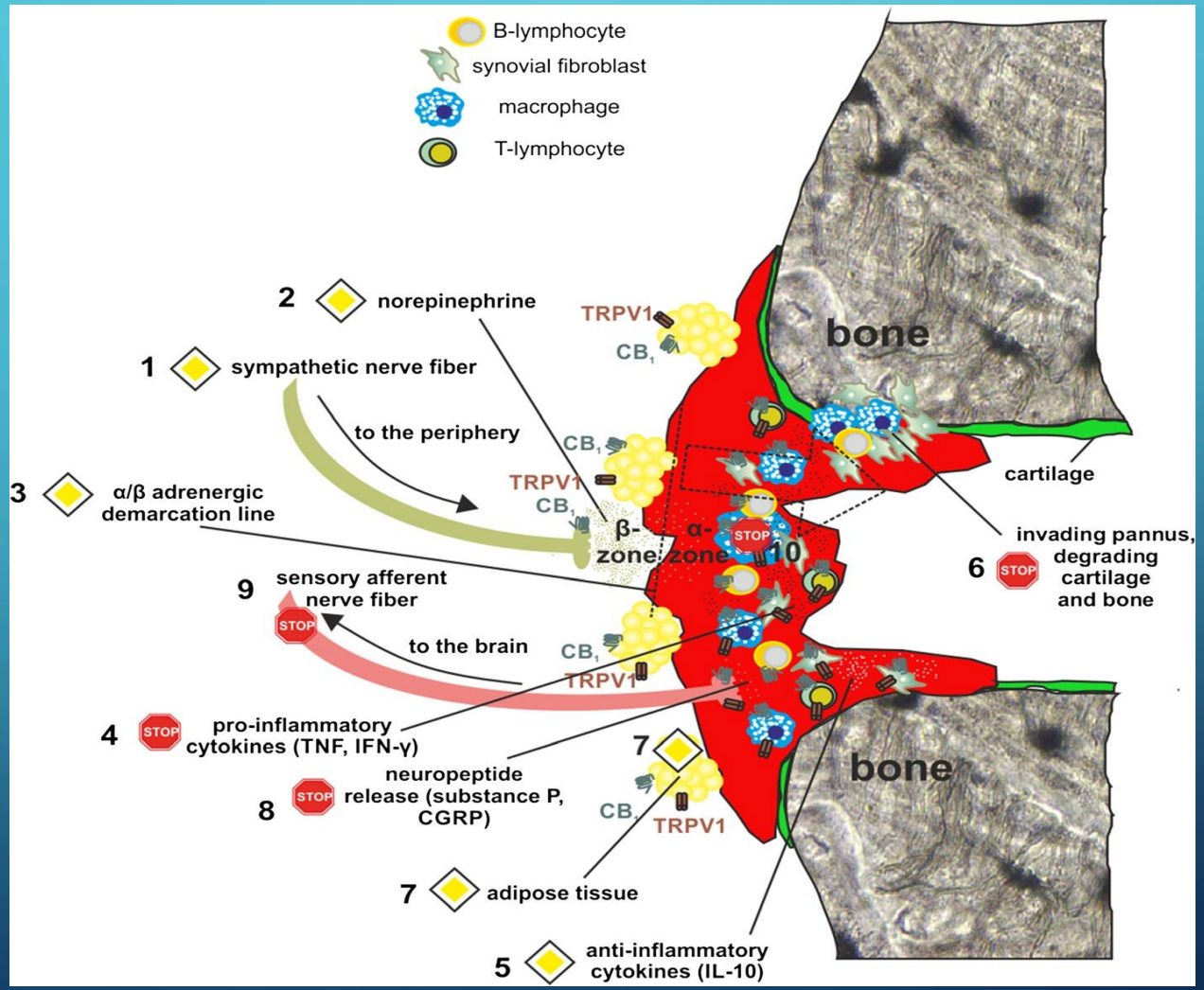
- « Even small improvements in symptoms with the use of THC:CBD in patients with difficult-to-treat symptoms may be clinically meaningful. This is particularly relevant for CKD patients where the second leading cause of death is withdrawal from dialysis, with most of these decisions reflecting poor HRQL. Moreover, given the prominence of adverse effects of opioids in CKD, which may exacerbate an already high symptom burden, CBs may present a reasonable alternative to pain and symptom management »

Davison S. .JPSM Volume 41, Issue 4, 2011, Pages 768–778

POSSIBLE EFFECTS OF FATTY ACID AMID HYDROLASE (FAAH) INHIBITION ON NEUROINFLAMMATION.



POSSIBLE EFFECTS OF CB1 ANTAGONISM AND FATTY ACID AMID HYDROLASE (FAAH) INHIBITION ON INFLAMMATION IN THE JOINT

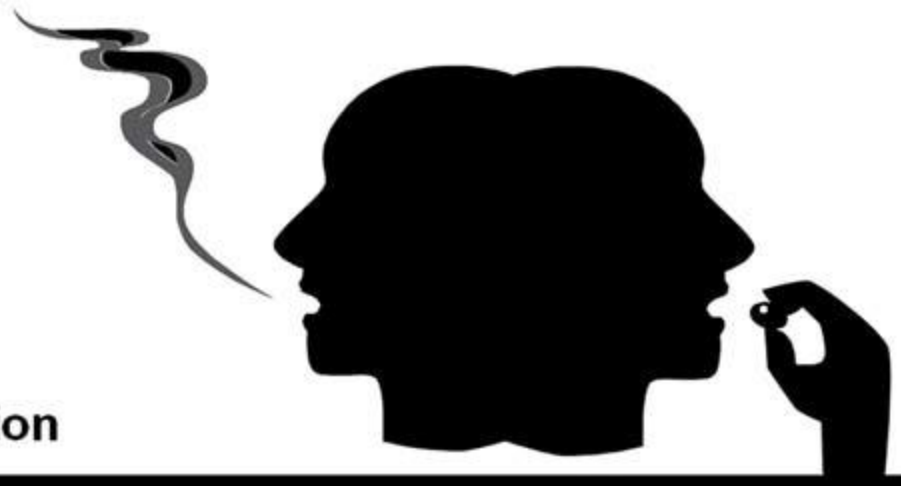


CONSUMPTION/USE

Cannabis Use Among Patients at a Comprehensive Cancer Center in a State With Legalized Medicinal and Recreational Use

Steven A. Pergam, MD, MPH, Maresa C. Woodfield, Christine M. Lee, PhD, Guang-Shing Cheng, MD, Kelsey K. Baker, Sara R. Marquis, and Jesse R. Fann, MD.

Cancer Nov 15, 2017



Methods of Inhalation

Method n=153*	n(%)
Pipe	95 (62)
Vaporizer	77 (50)
Joint	47 (31)
Water pipe/Bong	44 (29)
Other	5 (3)

Methods n=220*	n(%)
Both inhalation & ingestion	89 (40)
Ingestion only	65 (30)
Inhale/Smoke only	64 (29)
Topical	6 (3)
Other	2 (1)

Methods of Ingestion

Method n=154*	n(%)
Purchased candy/edibles	72 (47)
Butters/oils	64 (42)
Homemade baked goods	52 (34)
Purchased baked goods	40 (26)
Purchased beverages	21 (14)

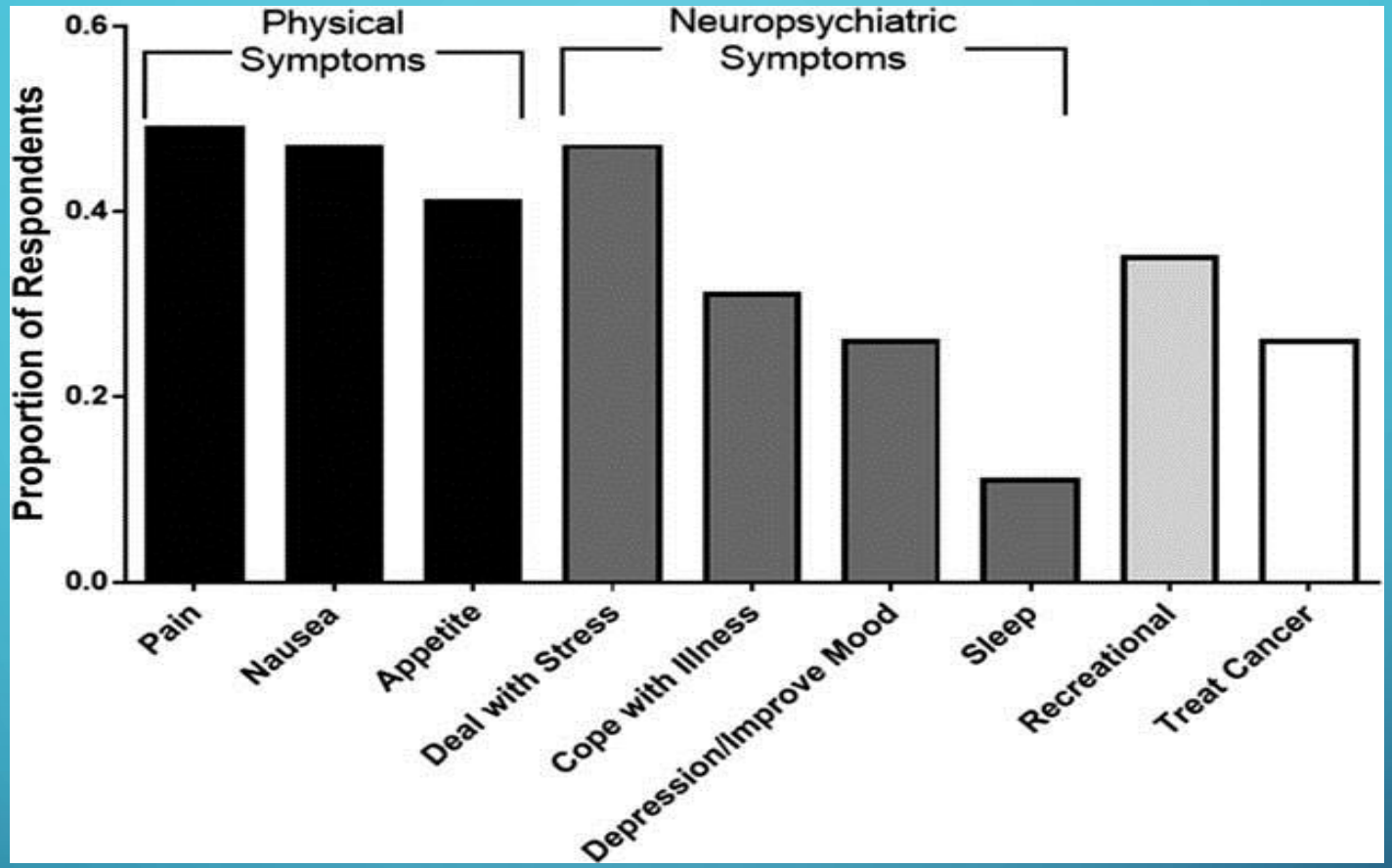


Figure 3. Reasons for cannabis use among the survey respondents.

The reasons for use were not mutually exclusive responses. Overall, the respondents used cannabis for physi- cal symptoms (165 of 219 [75%]), for neuropsychiatric symp- toms (139 of 219 [63%]), recreationally (76 of 219 [35%]), and to treat cancer (58 of 219 [26%]).

CANNABINOIDS

Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines [Internet].

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Sep.

The identified evidence based guideline recommends the use of THC:CBD buccal spray as third-line therapy in the management of chronic neuropathic pain. This applicability of this recommendation is limited in view of insufficient high-quality scientific evidence supporting the use of THC:CBD in chronic pain patients.

ENDOCANNABINOIDS

- **The Endogenous Cannabinoid System: A Budding Source of Targets for Treating Inflammatory and Neuropathic Pain.**
- Donvito G et al.Neuropsychopharmacology. 2018
- « Notably, cannabinoid receptor agonists as well as inhibitors of endocannabinoid-regulating enzymes fatty acid amide hydrolase and monoacylglycerol lipase produce reliable antinociceptive effects, and offer opioid-sparing antinociceptive effects in myriad preclinical inflammatory and neuropathic pain models. Emerging clinical studies show that 'medicinal' cannabis or cannabinoid-based medications relieve pain in human diseases such as cancer, multiple sclerosis, etc. »

ENDOCANNABINOIDS

- **The cannabinoid system and pain.**
- Woodhams SG et al. Neuropharmacology. 2017
- The EC system is a major endogenous pain control system, running in parallel to the opioid system and playing crucial roles the development and resolution of pain states, and the affective and cognitive aspects of pain. (…) greater understanding of the role of the EC system in non-opioid and opioid-dependent forms of endogenous pain suppression and exacerbation in response to stress, and the dysfunction of forebrain-limbic circuitry in pain states in humans will aid the development of future analgesic strategies, especially with respect to targeting particular populations of patients.

EBM

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003;327:1459–61

What is already known about this topic
Parachutes are widely used to prevent death and major injury after gravitational challenge Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury Studies of free fall do not show 100% mortality
What this study adds
No randomised controlled trials of parachute use have been undertaken The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a “healthy cohort” effect Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Conclusion

As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials.

Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data.

We think that everyone might benefit if the *most radical protagonists* of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

AIRPLANE STATISTICS

- In total, 523 people died in plane crashes in 2018, a sharp rise from 19 in 2017.
- Based on the data, on average, a passenger could take a flight every day for 241 years before experiencing an accident with one fatality on board.
- Questions:
  - Who wants to live 241 years to experiment an airplane crash?
  - What is the average age of victims?
  - Did they travel every day?

OPIOIDS

- **Opioids for cancer pain - an overview of Cochrane reviews. 2017**
- The amount and quality of evidence around the use of opioids for treating cancer pain is disappointingly low, although the evidence we have indicates that around 19 out of 20 people with moderate or severe pain who are given opioids and can tolerate them should have that pain reduced to mild or no pain within 14 days.
- This accords with the clinical experience in treating many people with cancer pain, but **overstates to some extent the effectiveness found for the WHO pain ladder**.
- Most people will experience adverse events, and help may be needed to manage the more common undesirable adverse effects such as constipation and nausea.
- Perhaps between 1 in 10 and 2 in 10 people treated with opioids will find these adverse events intolerable, leading to a change in treatment.

OPIOIDS

- **Methadone for cancer pain. Cochrane Data Base 2017**

- Based on low-quality evidence, methadone is a drug that has similar analgesic benefits to morphine and has a role in the management of cancer pain in adults. Other opioids such as morphine and fentanyl are easier to manage but may be more expensive than methadone in many economies.

SCHIZOPHRENIA

- Protective effect of anandamide?
  - Higher CSF rates, compared to "healthy" control, would be a response to the disease and not its cause
- Therapeutic role of cannabidiol?
  - "Moderate" inhibition of FAAH?
  - Effect superior to amisulpride (CBD 800 mg / D vs amisulpride 800 mg / D)

PSYCHOSIS

- Whether or not cannabis can cause psychosis is debated.
- Studies suggest that people at risk for schizophrenia run a higher risk of psychosis outcomes after cannabis use (Morrison et al 2015).
- A study of cannabis use in 1237 people with schizophrenia, who had ever used cannabis, found no additive effect of cannabis use on cognitive dysfunction (Power 2015).
- Smoking cannabis with a significant proportion of CBD may produce fewer psychotic symptoms (Morgan and Curran 2008, Schubart et al 2011).
- It has been suggested that cannabis has antipsychotic effects, but a Cochrane systematic review of cannabis and schizophrenia noted that studies were limited, and that “currently evidence is insufficient to show cannabidiol has an antipsychotic effect” (McLoughlin 2014).

CANNABIDIOL: STATE OF THE ART AND NEW CHALLENGES FOR THERAPEUTIC APPLICATIONS

SIMONA PISANTI A,□,1, ANNA MARIA MALFITANO A,1, ELENA CIAGLIA A, ANNA LAMBERTI A, ROBERTA RANIERI A, GAIA CUOMO A, MARIO ABATE A, GIORGIO FAGGIANA A, MARIA CHIARA PROTO B, DONATELLA FIORE B, CHIARA LAEZZA C, MAURIZIO BIFULCO

PHARMACOLOGY AND THERAPEUTICS, 2017

- This paper highlight the pharmacological activities of CBD, its cannabinoid receptor-dependent and -independent action, its biological effects focusing on immunomodulation, angiogenetic properties, and modulation of neuronal and cardiovascular function.
- Furthermore, the therapeutic potential of cannabidiol is also highlighted, in particular in neurological diseases and cancer.

CANNABIDIOL: STATE OF THE ART AND NEW CHALLENGES FOR THERAPEUTIC APPLICATIONS (FOLLOWING)

- **Alzheimer disease**: Results highlight the importance of CBD as a pharmacological tool, that lacking psychoactivity is able to mit- igate Aβ-evoked neuroinflammatory and neurodegenerative responses.
- **Multiple sclerosis:** Data suggest a significant therapeutic potential of this compound for the treatment of multiple sclerosis, in which the inflammatory component plays a key role for the onset and progression of the pathology.
- **Epilepsy:** CBD appears to be an excellent candidate among phytocannabinoids as an anti-epileptic drug, more randomized controlled trails are urgently needed and warranted to characterize its safety profile and true efficacy.

SAFETY AND EFFECTIVENESS OF CANNABINOIDS FOR THE TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA: A SYSTEMATIC REVIEW

JODIE BELINDA HILLEN, NATALIE SOULSBY, CHRIS ALDERMAN AND GILLIAN E. CAUGHEY

THERAPEUTIC ADVANCES IN DRUG SAFETY, 2019

While the efficacy of cannabinoids was not proven in a robust randomized control trial, observational studies showed promising results, especially for patients whose symptoms were refractory.

In addition, the safety profile is favourable as most of the ADEs reported were mild.

Future trials may want to consider dose escalation and formulations with improved bioavailability.

CANNABINOIDS IN EXPERIMENTAL STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

TIMOTHY J ENGLAND, WILLIAM H HIND, NADIAH A RASID AND SAOIRSE E O'SULLIVAN

JOURNAL OF CEREBRAL BLOOD FLOW & METABOLISM, 2015

The pleiotropic effects of CBs on the ischemic penumbra and cerebral vasculature after stroke, combined with their excellent tolerability, make them promising candidates for future treatment.

Overall, CBs significantly reduced infarct volume and improve functional outcome in experimental stroke. Further studies in aged, female and larger animals, with other co-morbidities are required.

Cannabis species and cannabinoid concentration preference among sleep-disturbed medicinal cannabis users.

Belendiuk KA[1], Babson KA[2], Vandrey R[3], Bonn-Miller MO[4].

Addict Behav. 2015 Nov;50:178-81.

« Associations between sleep characteristics and the type of cannabis used were observed in this convenience sample of individuals using cannabis for the management of sleep disturbances. Controlled prospective studies are needed to better characterize the impact that specific components of cannabis have on sleep ».

No Acute Effects of Cannabidiol (300 mg) on the Sleep-Wake Cycle of Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

Ila M. P. Linares[1,2], Francisco S. Guimaraes[3], Alan Eckeli[1,2], Ana C. S. Crippa[4], Antonio W. Zuardi[1,2], Jose D. S. Souza[1,2], Jaime E. Hallak[1,2] and José A. S. Crippa[1,2]*

1 Department of Neurosciences and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil, 2 Instituto Nacional de Ciência e Tecnologia Translacional em Medicina, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brasília, Brazil, 3 Department of Pharmacology, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil, 4 Department of Pediatrics, Neuropediatrics, Federal University of Paraná, Curitiba, Brazil

Front Pharmacol. 2018 Apr 5;9:315

The present findings support the proposal that CBD do not alter normal sleep architecture. Future studies should address the effects of CBD on the sleep-wake cycle of patient populations as well as in clinical trials with larger samples and chronic use of different doses of CBD. Such studies are desirable and opportune.

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Cannabis, Cannabinoids, and Sleep: a Review of the Literature.

Babson KA[1], Sottile J[2], Morabito D[3].

Curr Psychiatry Rep. 2017 Apr;19(4):23

CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while nabilone may reduce nightmares and may improve sleep among patients with chronic pain. Research on cannabis and sleep is in its infancy and has yielded mixed results. Additional controlled and longitudinal research is critical to advance our understanding of research and clinical implications.

Cannabis species and cannabinoid concentration preference among sleep-disturbed medicinal cannabis users

Katherine A. Belendiuk [a], Kimberly A. Babson [b], Ryan Vandrey [c], Marcel O. Bonn-Miller

Addictive Behaviors 50 (2015) 178–181

- Individuals using cannabis to manage nightmares preferred sativa to indica.
- Sativa users were less likely than indica users to endorse cannabis dependence.
- Insomnia and greater sleep latency are associated with using higher CBD cannabis.
- Weekly hypnotic medication use is associated with using cannabis with lower THC.

Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last?

Emilio Perucca1,2
[1]Division of Clinical and Experimental Pharmacology, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia; [2]C. Mondino National Neurological Institute, Pavia, Italy

« Based on currently available information, however, it is unclear whether the improved seizure control described in these trials was related to a direct action of CBD, or was mediated by drug interactions with concomitant medications, particularly a marked increased in plasma levels of N-desmethylclobazam, the active metabolite of clobazam.

Clarification of the relative contribution of CBD to improved seizure outcome requires re-assessment of trial data for the subgroup of patients not comedicated with clobazam, or the conduction of further studies controlling for the confounding effect of this interaction ».

SHOULD ONCOLOGISTS RECOMMEND CANNABIS?

DONALD I. ABRAMS

CURR. TREAT. OPTIONS IN ONCOL. (2019) 20: 59

- « (..) This is likely the reason that they report that the patient brings up the topic 78% of the time it is discussed. A survey of 153 oncology providers in Minnesota found that 65% supported the use of medical cannabis, but 85% desired more education on the topic »
- « Oncologists and palliative care providers should recommend this botanical remedy to their patients to gain first-hand evidence of its therapeutic potential despite the paucity of results from randomized placebo-controlled clinical trials to appreciate that it is both safe and effective and really does not require a package insert ».

CANCER?

- A pooled meta-analysis of 6 case-control studies in the US, Canada, UK, and New Zealand that included data on 2,159 lung cancer cases and 2,985 controls found **“little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers, although the possibility of potential adverse effects for heavy consumption cannot be excluded”** (Zhang et al 2015)

CANCER?

- « (…) the anti-proliferative effect of CBD was also reported on various glioma cell lines where it was shown that CBD actions were mediated by ROS production, release of cytochrome C and triggering autophagy and apoptosis cell death It has also been highlighted a beneficial effect of combined treatment of CBD with Δ9-THC that enhances inhibitory effect on cell growth in vitro and in vivo models »…

(Liu, Hu, Huang, Wey, & Jan, 2010; Scott, Shah, Dalgleish, & Liu, 2013)

(Marcu et al., 2010; Scott et al., 2014; Torres et al., 2011).

OFFICE EUROPÉEN DES DROGUES ET TOXICOMANIES (EMCDDA)

Un rapport de l'Office européen des drogues et toxicomanies souligne le manque d'études sur les effets réels du cannabis à usage médical.

Le rapport **souligne le manque de savoirs** sur les effets réels des produits aujourd'hui délivrés dans de nombreuses pharmacies du continent. Les chercheurs de l'EMCDDA ont compilé toutes les études connues sur leurs effets. Selon leurs conclusions, **les preuves** de ces effets sont – au mieux – « *modérées* » et – au pire – « *faibles* » ou « *insuffisantes* ».

Cherchez l'erreur…

NASEM (THE NATIONAL ACADEMIES OF SCIENCES ENGINEERING MEDICINE)

- **The Health Effects of Cannabis and Cannabinoids**
- The Current State of Evidence and Recommendations for Research

NASEM JANVIER 2017

- This report provides a broad set of evidence-based research conclusions on the health effects of cannabis and cannabinoids and puts forth recommendations to help advance the research field and better inform public health decisions.
- The committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health, organizing these into 5 categories: conclusive, substantial, moderate, limited, and no/insufficient evidence.

CBD, WHO, AND THE OLYMPIC GAMES

- CBD is not toxic
- CBD is not likely to be abused or create dependence
- CBD no longer fulfills two of the criteria to be considered for inclusion of the list of prohibited substances (*) (World Anti-Doping Association (WADA)

- (*) They enhance sports performance, they have potential health risks and violates the spirit of the sport

MEDICAL CANNABIS LAWS AND OPIOID ANALGESIC OVERDOSE MORTALITY IN THE UNITED STATES, 1999–2010

MARCUS A. BACHHUBER, BRENDAN SALONER, CHINAZO O. CUNNINGHAM, AND COLLEEN L. BARRY/

JAMA, 2014

- States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P = .003$) compared with states without medical cannabis laws.
- Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates.
- Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose.


CBD
Neuroprotective
Relieves pain
Relieves anxiety
Antidepressant
Causes vasorelaxation
Antioxidant
Reduces cancer cell growth
Reduces tumoral angiogenic process
Reduces inflammation

LA SITUATION EN BELGIQUE

- Loi de 1921
- CBD Shops
- Sativex
- CBD sur prescription (depuis août 2019)
- Normes GAP, GMP

LA SITUATION EN BELGIQUE

- Fagron Cannabidiol
- Exemple de prescription (10%)
- R/ Cannabidiol 1000 mg

  Triglycérides à chaîne moyenne (*) ad 94.9 gr ad 1O ml

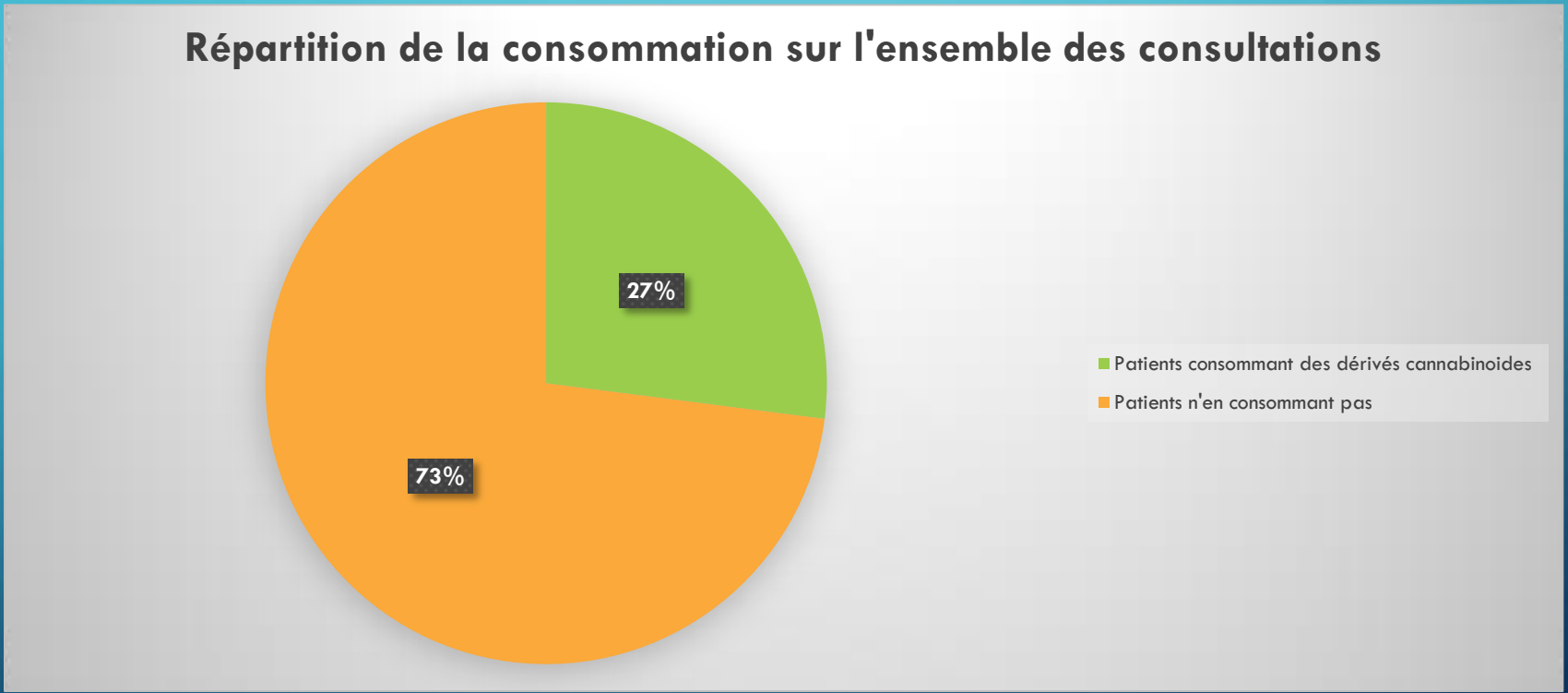
(chauffer légèrement si nécessaire…)

- Pas de posologie « standard » => 10-15 mg en Sublingual
- Coût
- (*) ou Miglyol (dispandieux), ou huile d'olive ou huile de sésame

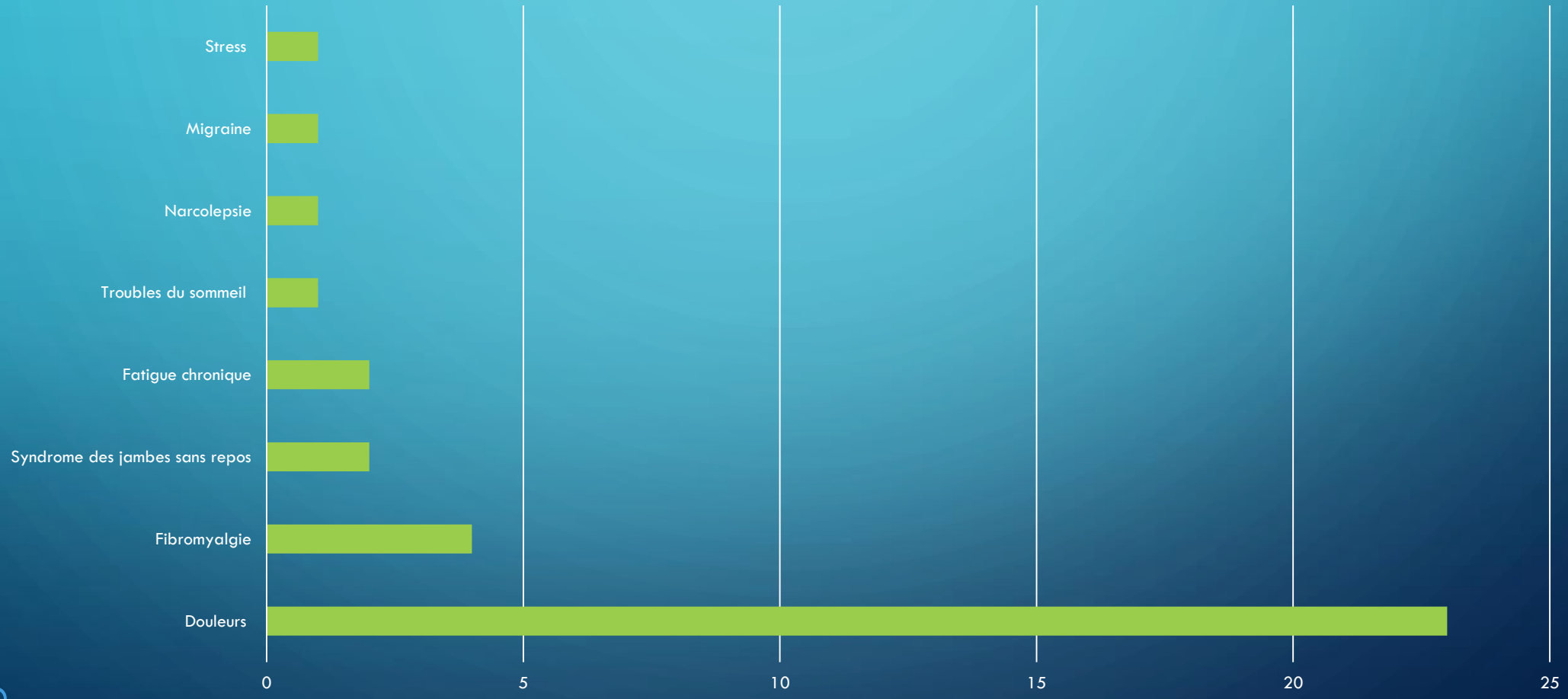
L'EXEMPLE DU LUXEMBOURG

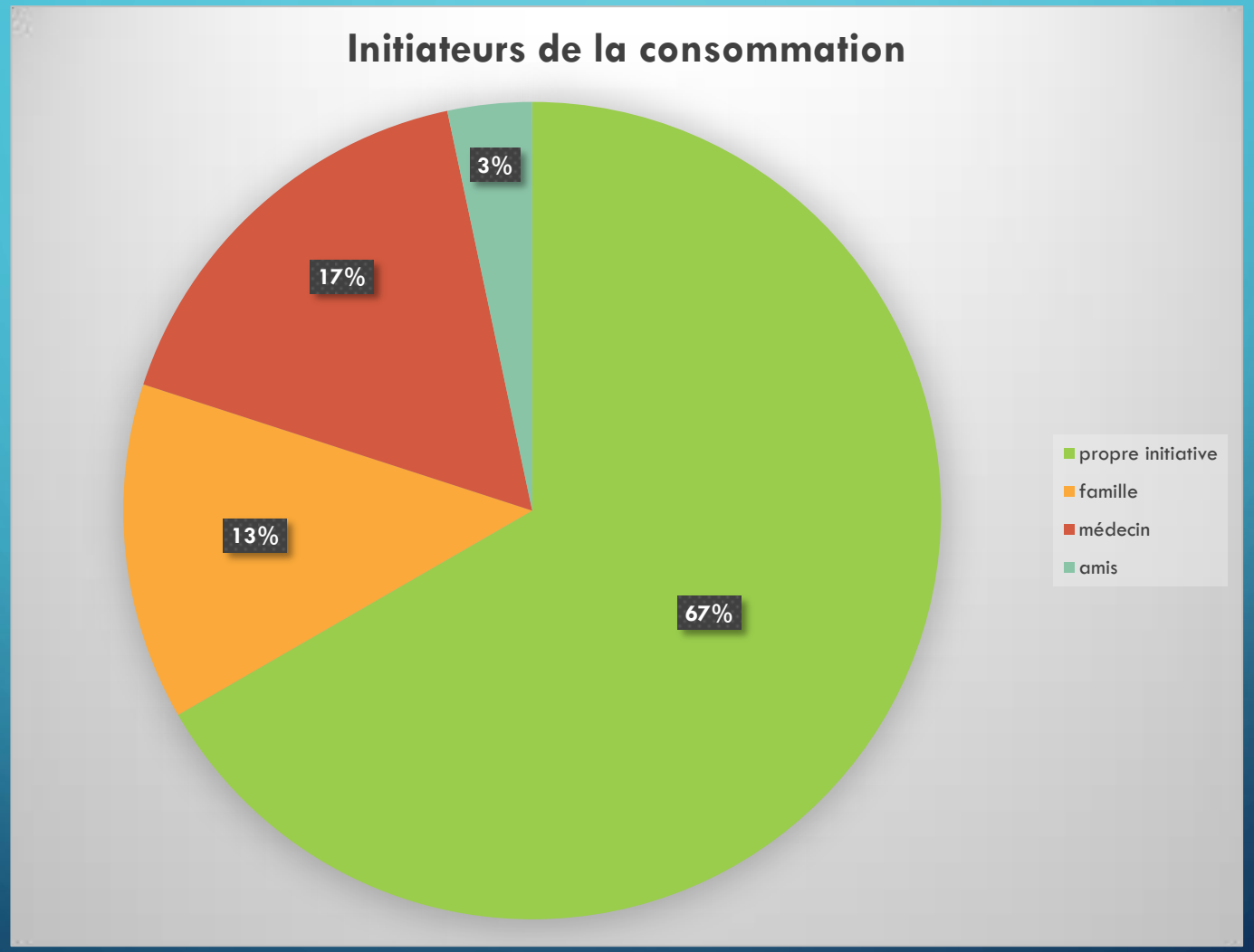
- Loi du 20 juillet 2018
- Concerne tous les médecins formés
- Elargissement des indications
- Elargissement à tous les patients?

CONSULTATION « DOULEUR »



Raisons de la consommation

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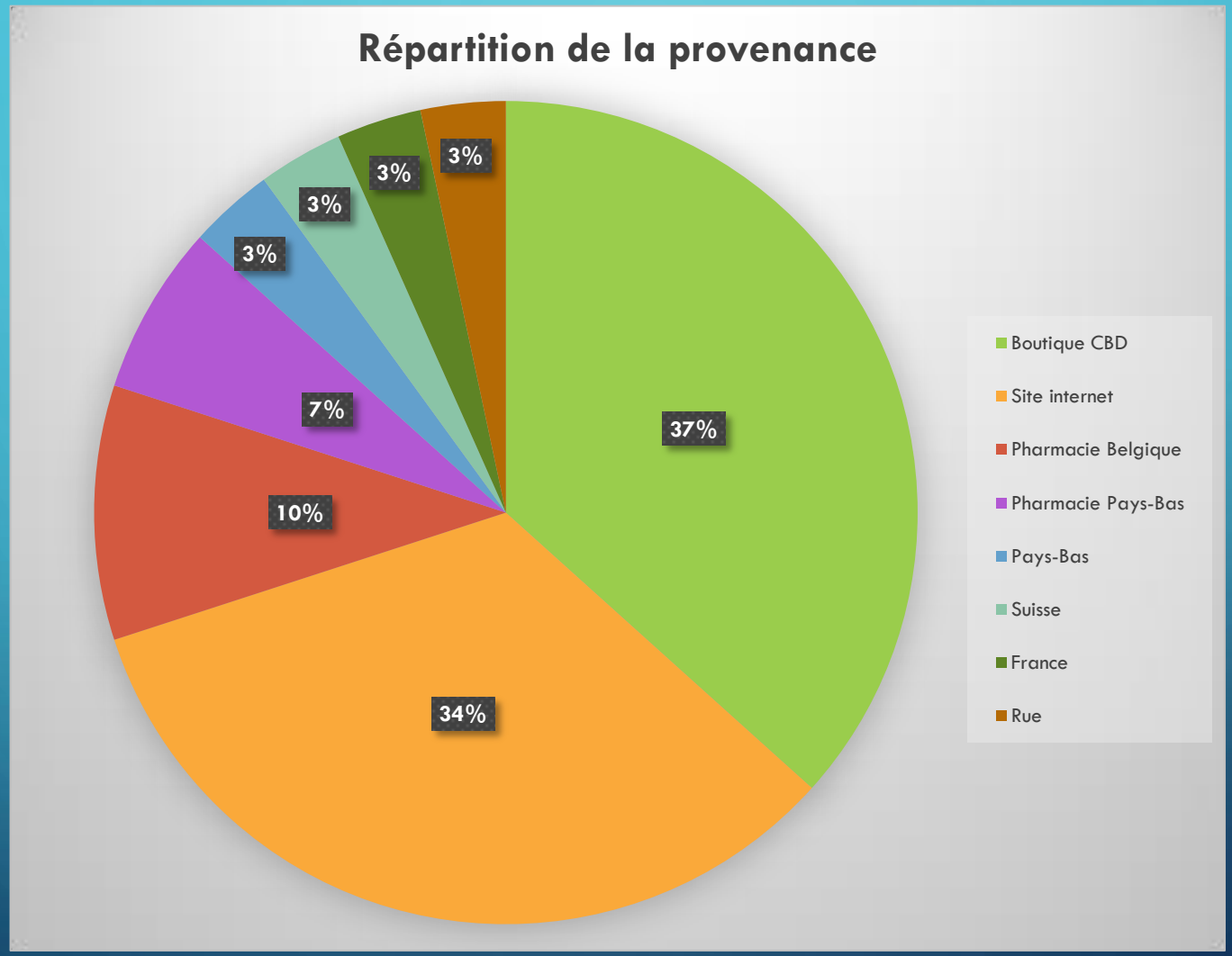
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Rue

CONCLUSION

- Given this current « nouvelle richesse » following its long history of obscurity, it is incumbent upon the scientific and medical communities to understand better the mechanisms of action of CBD, its limitations, and particularly the myths and misconceptions that its meteoric rise in popularity have engendered.

CONCLUSIONS

- Cannabinoid derivatives are an obvious therapeutic option in various fields of medicine: pain, sleep disorders, schizophrenia, Parkinson disease, epilepsy.
- Their use should be extended
- Additional controlled and longitudinal research is critical to advance our understanding of research and clinical implications.
- They must be available (therapeutic freedom)
- The various national laws could be harmonized.
- Natural plants vs specific molecules? (confusing data from medical literature)
- CBD > THC?
- Ignorance of some "decision-makers" needs to be corrected

« *L'un des grands services que chaque science peut rendre à nos recherches, c'est de nous inviter, en servant d'introduction, à la quitter pour sa voisine* »

"One of the great services that every science can render to our research is to invite us, as an introduction, to leave it for its neighbor."

Jules Bordet, Nobel Prize

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