CANNABINOIDS: A NEW APPROACH FOR PAIN CONTROL?

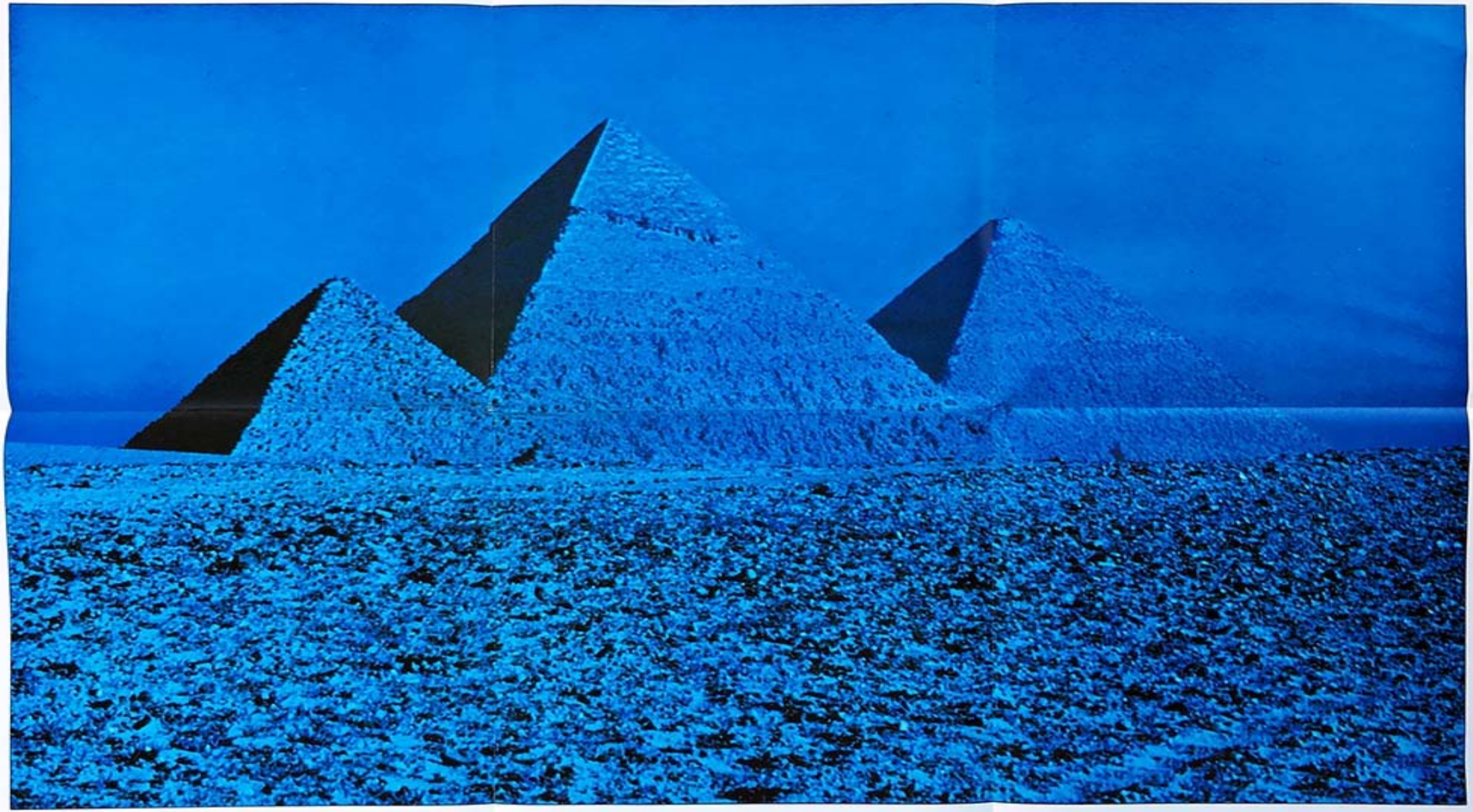
DOMINIQUE LOSSIGNOL, MD, PH D

INSTITUT JULES BORDET-ULB-UMONS

BELGIQUE

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



NATURAL CANNABINOIDS

- *Family: Cannabacées ou Cannabinacées*
- *Dioecic plant (female more interesting than male)*
- 2 types: *Cannabis* and *Humulus*
- *Genre Cannabis*
  - ***Cannabis sativa***
  - *Cannabis indica*
  - *Cannabis ruderalis*

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
- In humans:
- Location: Brain, Peripheral Nerves, Leukocytes, Coronary Arteries, Spleen, Heart, Digestive and Urinary System
- Brain: same distribution as injected THC - cerebral cortex, limbic areas (hypocampus and amygdala included), basal ganglia, cercellets, 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

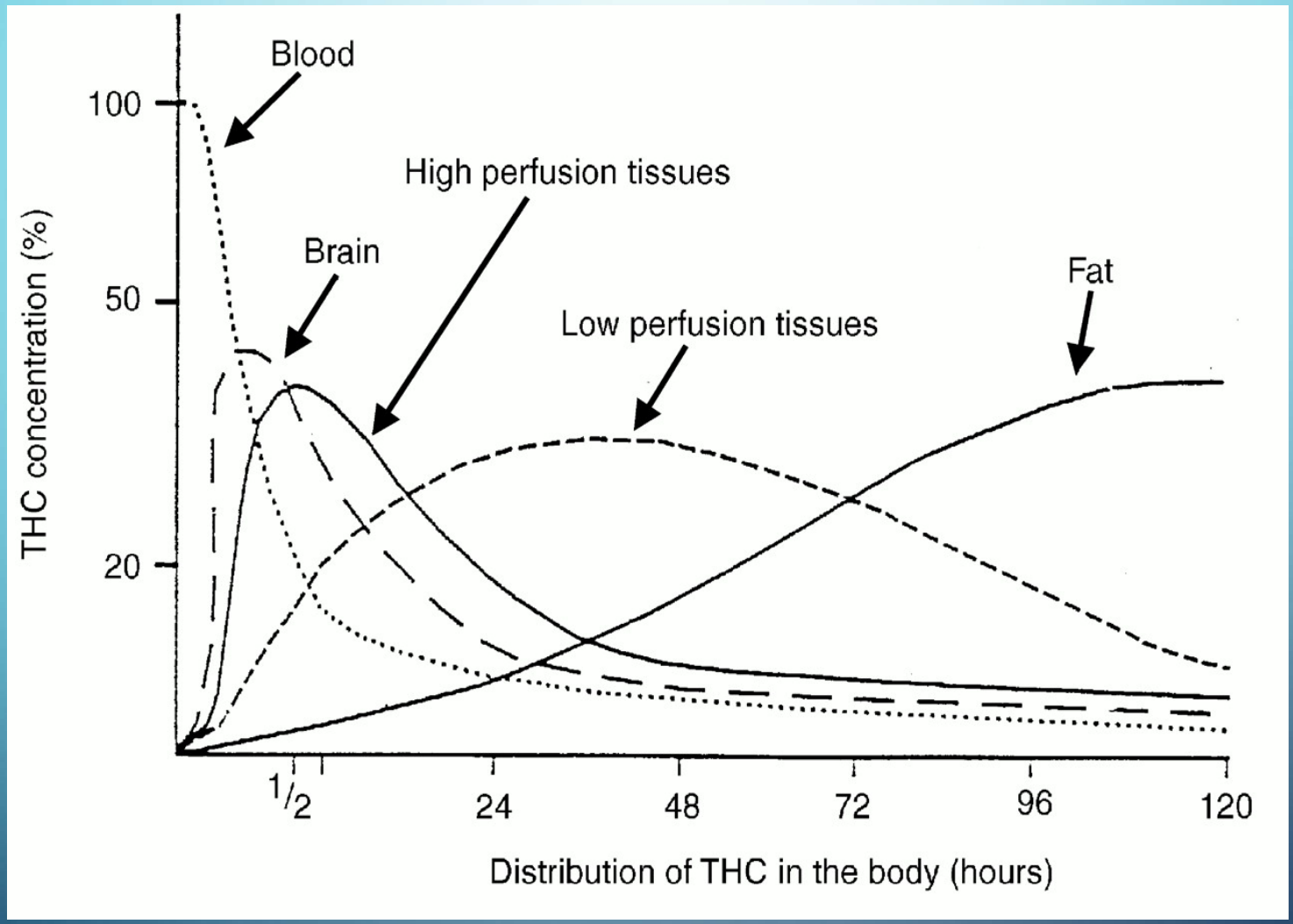
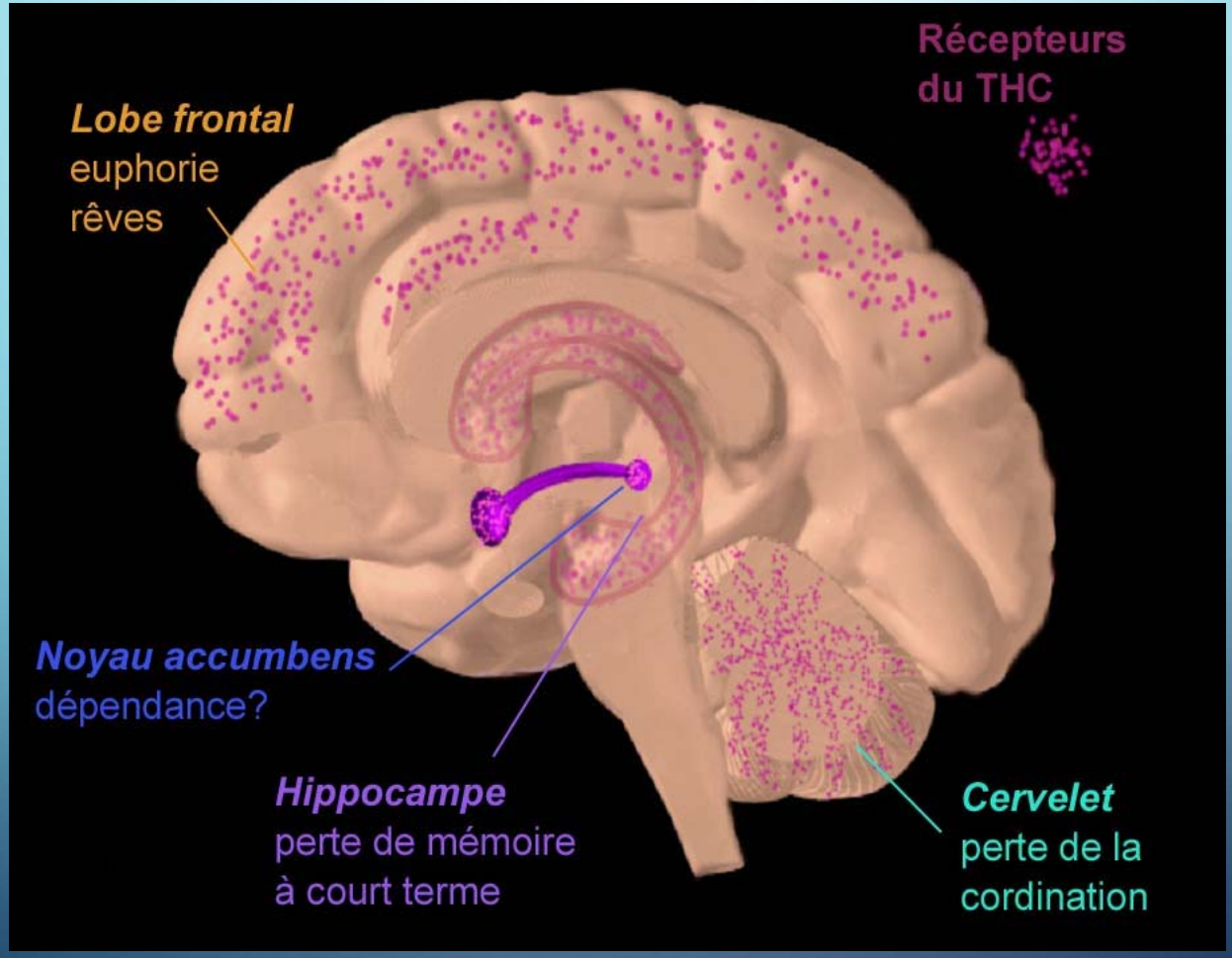
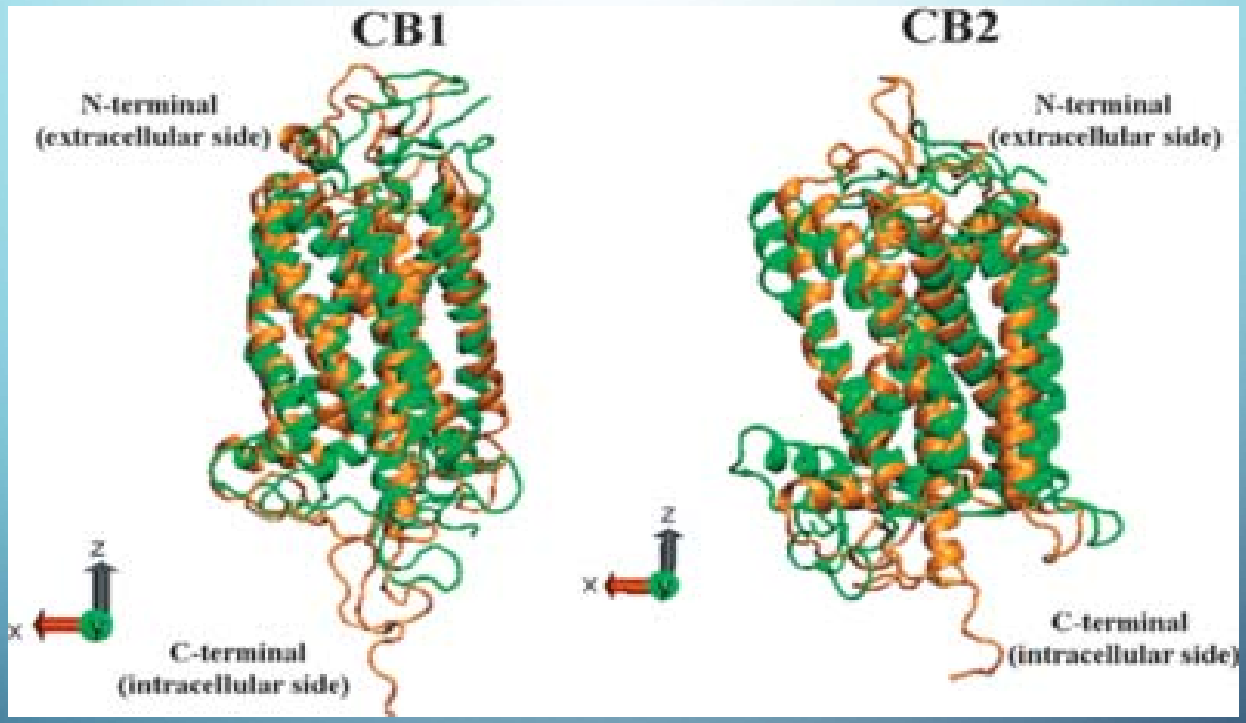


Figure: distribution of THC in the body. The distribution of THC after a single administration in plasma and body tissues. Note the 'biphasic' disappearance in plasma. The rapid phase (in minutes) indicates a rapid uptake of the drug by fat-containing tissues. The slow phase (in days) shows the release of THC by these tissues (Nahas, 1975). THC, tetrahydrocannabinol.

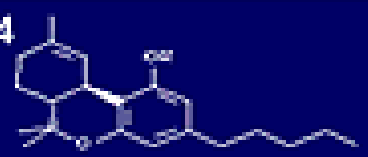
CB1 RECEPTORS
CENTRAL EFFECTS




CB1
N-terminal
(extracellular side)
C-terminal
(intracellular side)
Z
X
CB2
N-terminal
(extracellular side)
C-terminal
(intracellular side)
Z
X

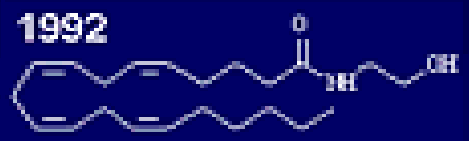
Cannabinoid Receptors

1964

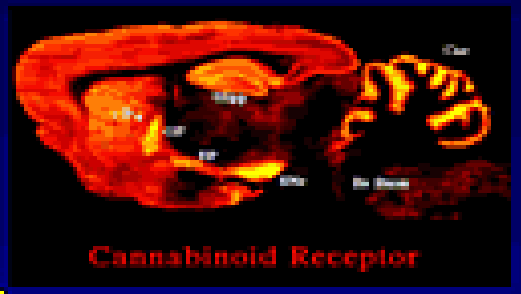


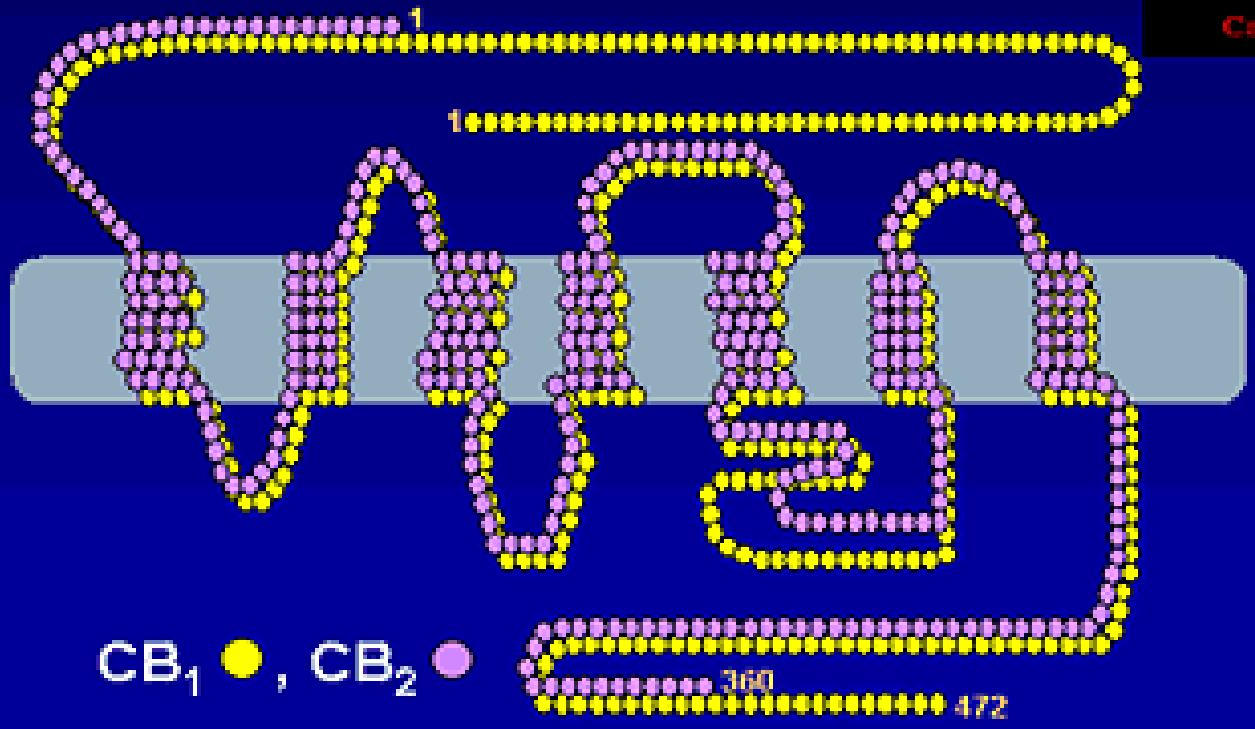
Δ^9-Tetrahydrocannabinol

1992



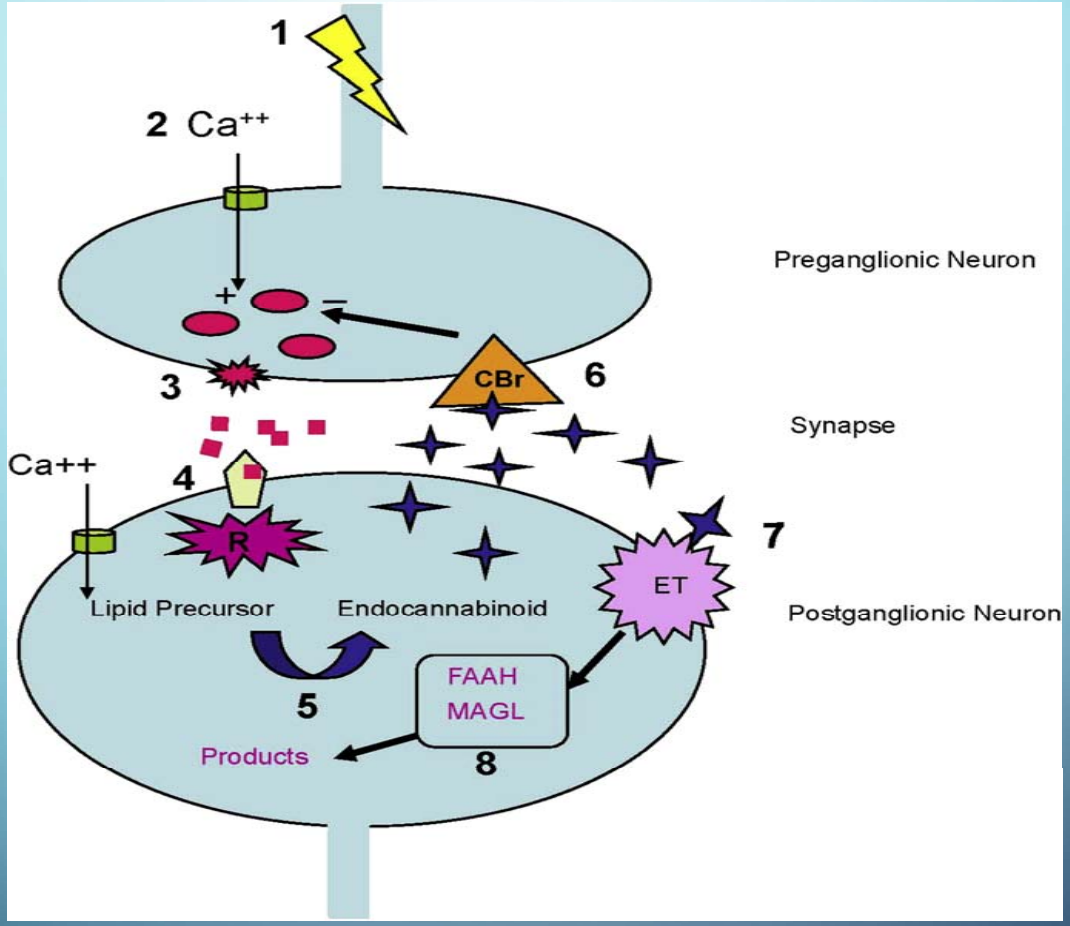
Anandamide



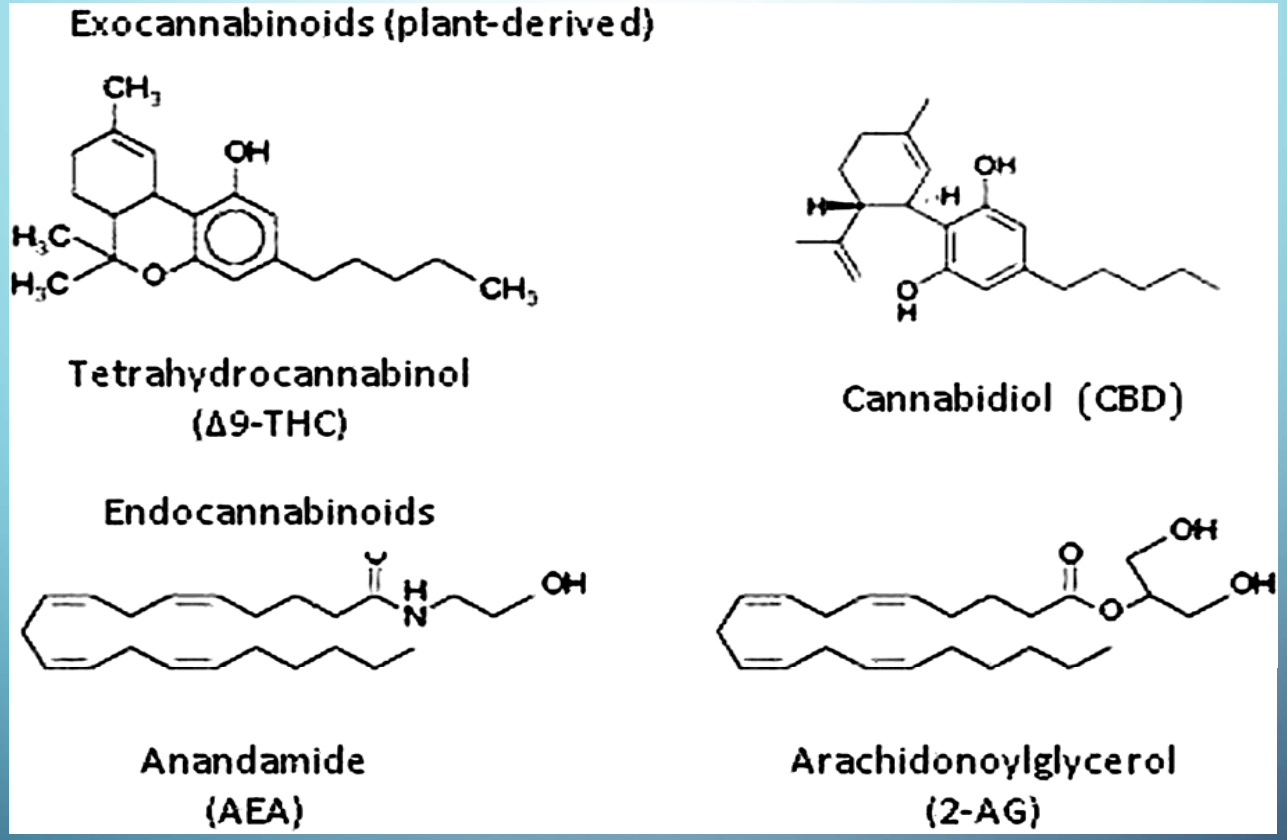


CB_1 ●, CB_2 ●

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



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



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

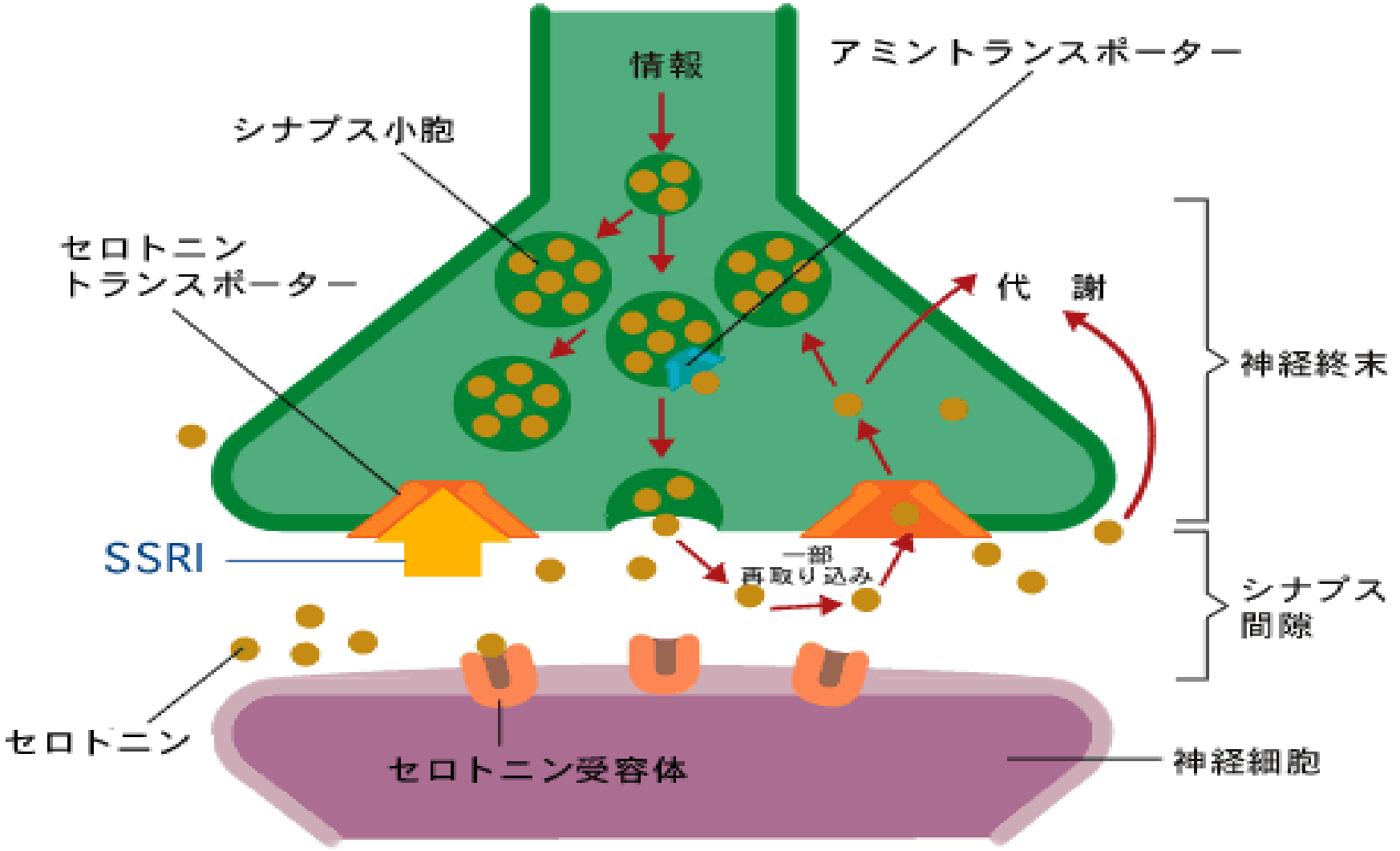
SIDE EFFECTS

- 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?

NEUROPATHIC PAIN

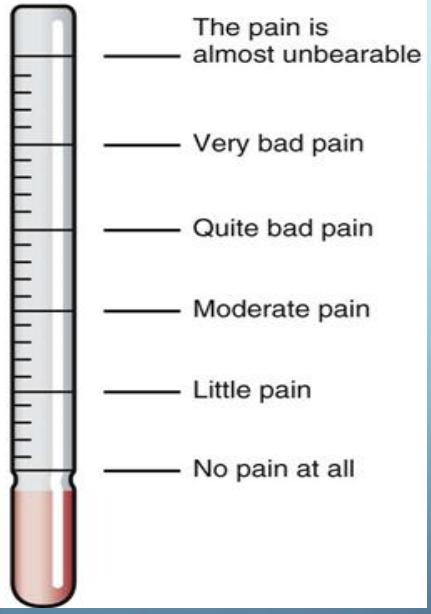
- Physiopathology
- Treatment

SSRIの作用のしくみ



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

- Oxycodone:
  - Métabolism P 450 2D6
  - Oxymorphone (15 % of the total dose)
- Fentanyl:
  - Métabolism CYP3A4
  - No interaction with cannabis derivated

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)

EFFECTS/ ACTIONS OF THC AND CBD

THC	Cannabidiol
CB1R/2R agonist Analgesia Muscle relaxation Antiemetic actions Appetite stimulation Psychotropic effects	Analgesia Muscle relaxation Anticonvulsant effects Anxiolytic effects Antipsychotic effects Neuroprotection Anti-inflammatory effects (e.g., antioxidant)

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

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 »

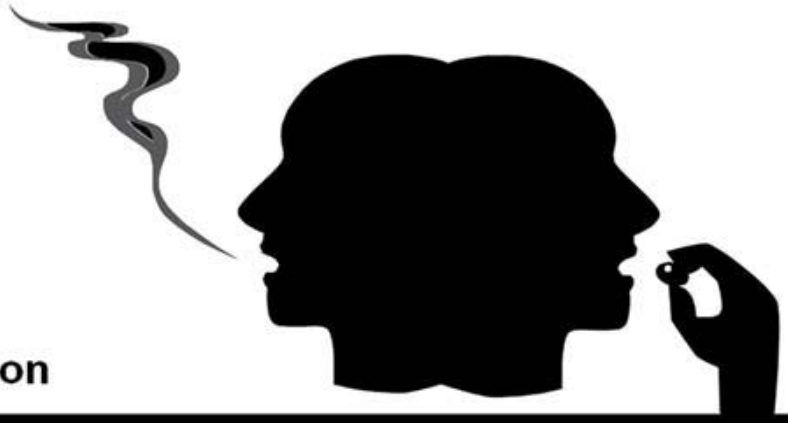
Davison S. .JPSM Volume 41, Issue 4, 2011, Pages 768–778

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)

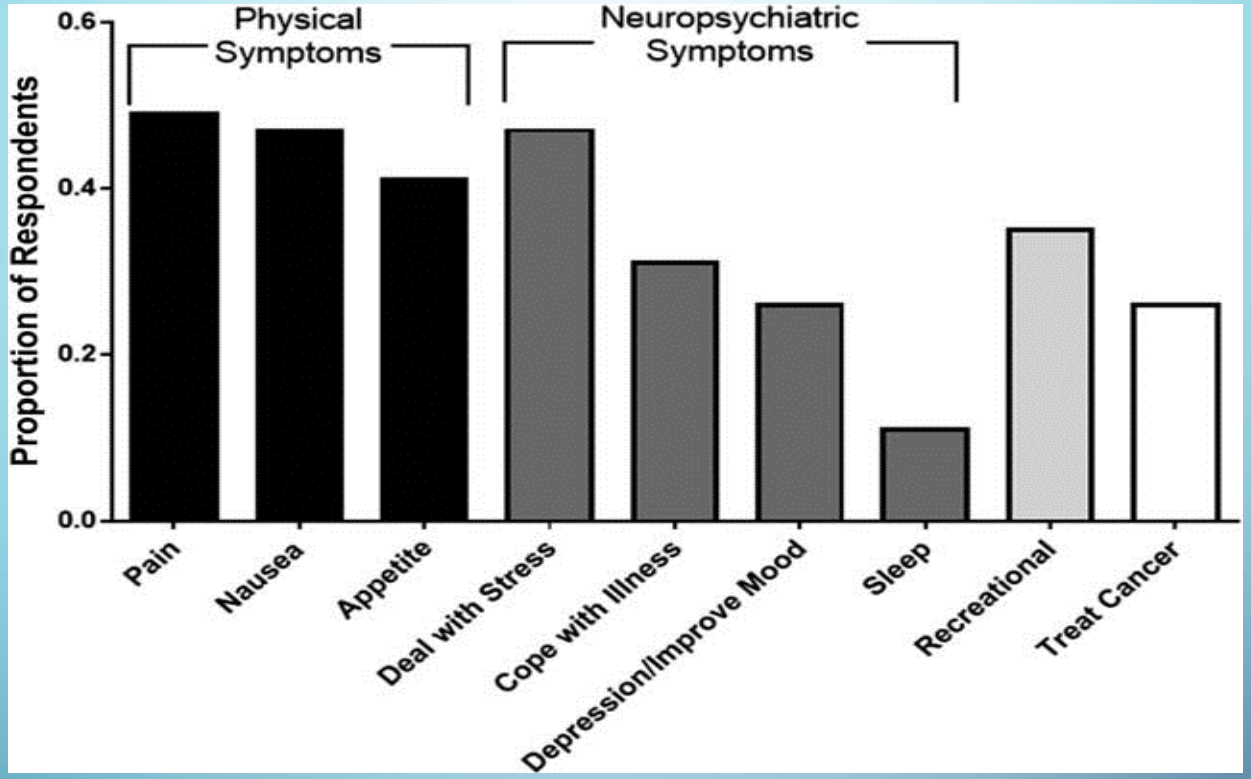


Figure 3. Reasons for cannabis use among the survey respondents.

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.

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)

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