Cannabis et la douleur: est-ce qu'on peut apprendre de l'autre

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3 Novembre 2017

Centre universitaire de santé McGill
McGill University Health Centre

Faculty/Presenter Disclosure

- **Faculty:** Mark Ware

- **Relationships with commercial interests:**
  - **Grants/Research Support:** CanniMed, GSL
  - **Consulting Fees:** CHI Inc, Zynerba, CanniMed
  - **Other:** Executive Director of CCIC (non-profit)

Objectives

- Overview of cannabis and its constituents
- Introduction to the endocannabinoid system
- Review of existing cannabinoid preparations
- Pharmacology of cannabinoids
- Considerations of clinical trial evidence
- Cannabinoid and opioids
- Cannabis and palliative care

Cannabis and palliative care

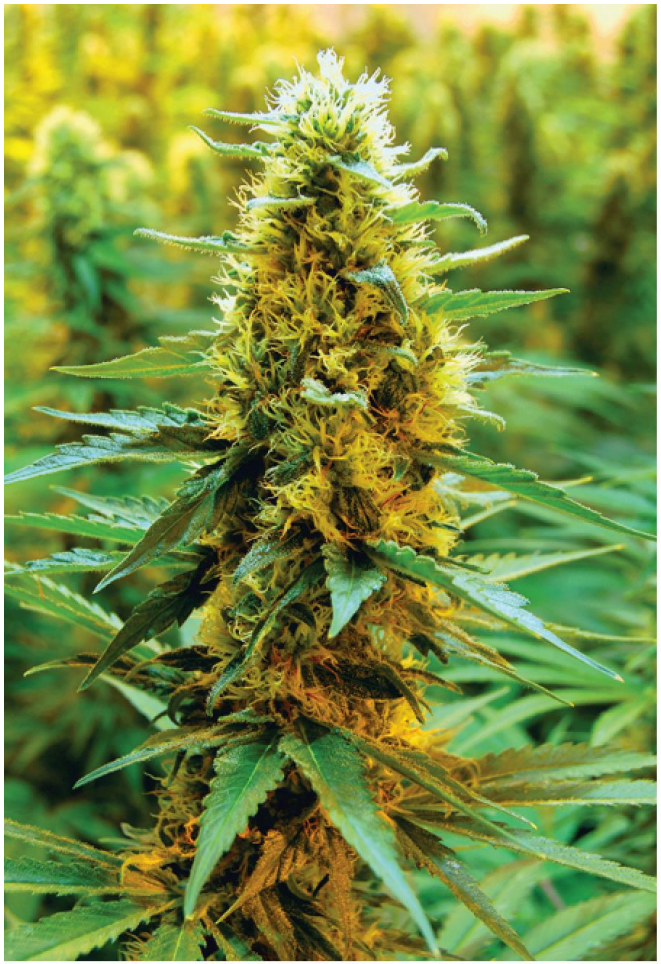
- All purpose (Hall 2005, Carter 2011; McCarberg 2007)
- Anorexia
- Anticancer effects (esp Prostate) (Guzman 2003, Fowler 2010; Pacher 2013 – CBD; McAllister 2015-CBD; Velasco 2016)
- Cancer pain (Portenoy 2013- Sativex)
- Metastatic bone pain (Maida 2008, Coluzzi 2011)
- Nausea & vomiting (Glare 2011; Gupta 2013 – Cleveland Clinic protocol)
- Refractory breathlessness (Booth 2009)
- The role of the nurse (Peat 2010; Green 2010)

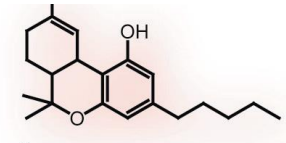
van Bakel *et al. Genome Biology* 2011, **12**:R102
http://genomebiology.com/2011/12/10/R102

Genome Biology

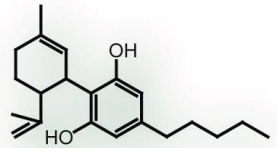
RESEARCH Open Access

The draft genome and transcriptome of *Cannabis sativa*

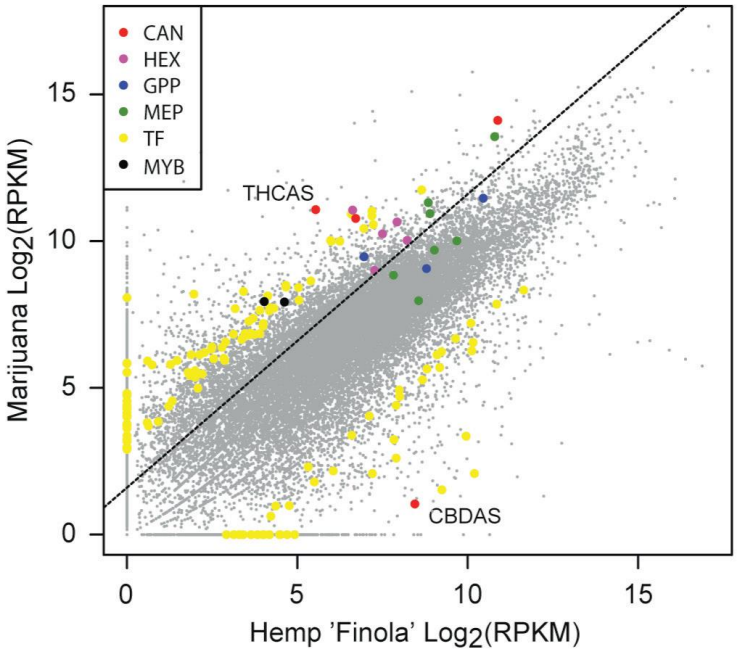




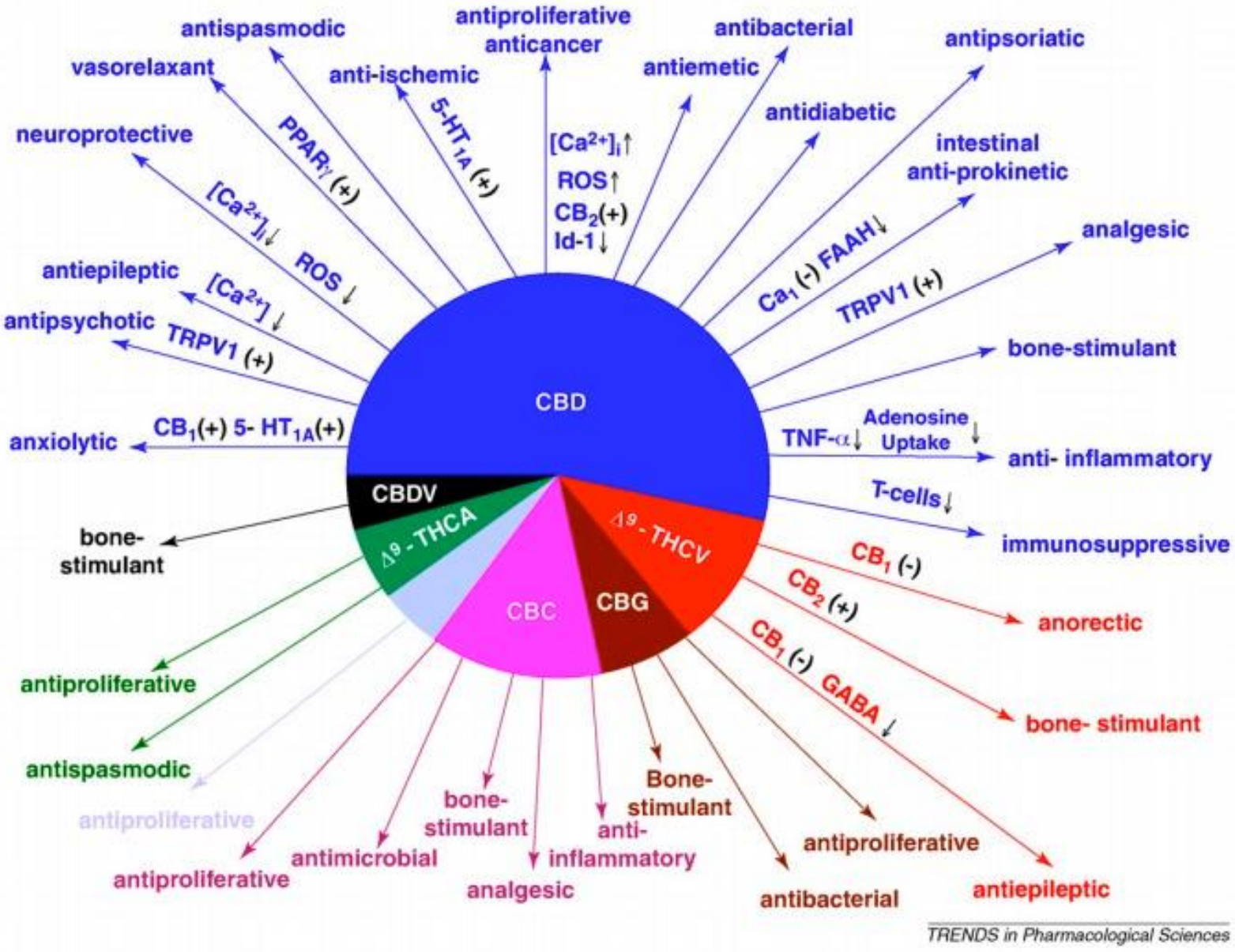
Δ^9-Tetrahydrocannabinol



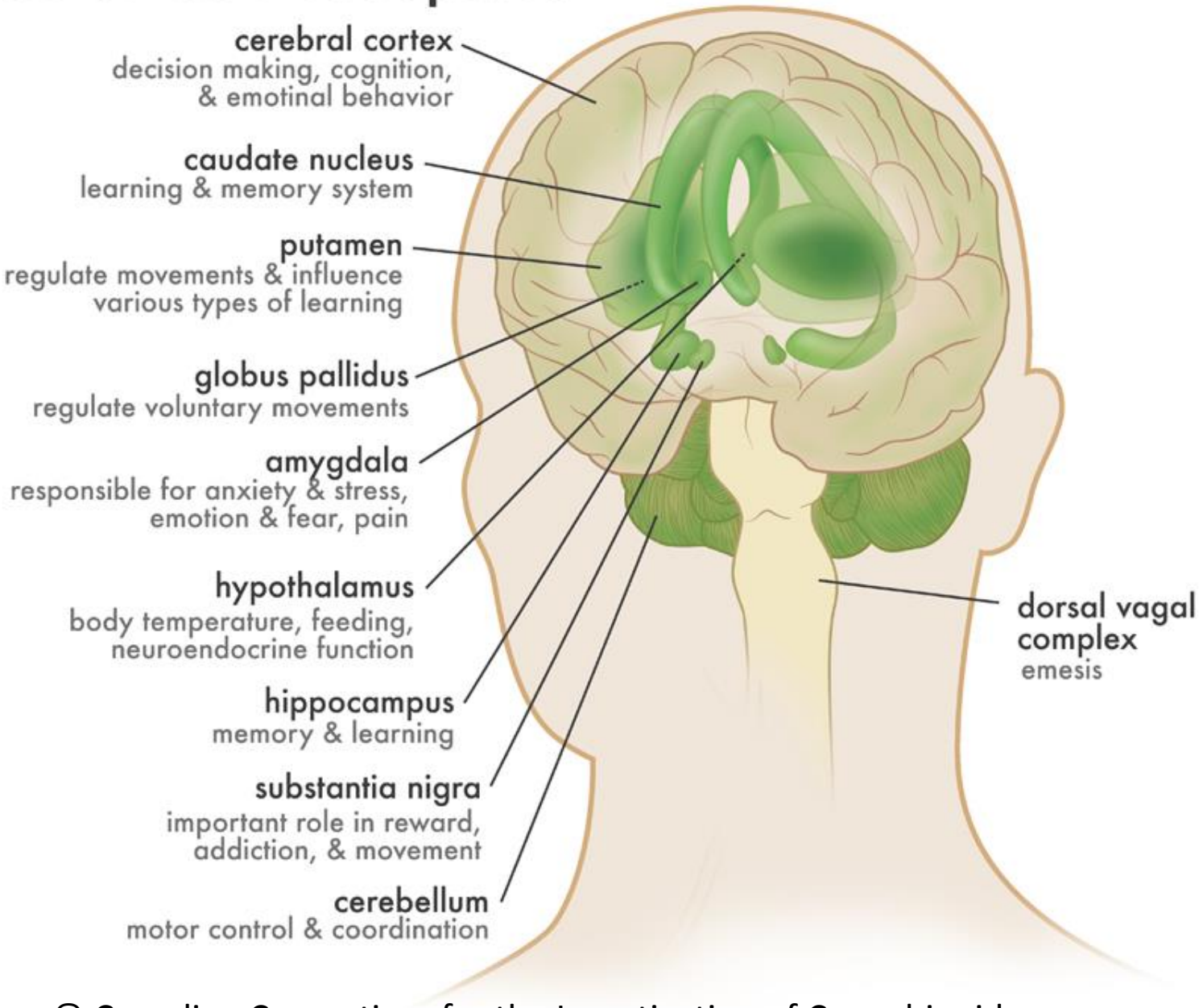
Cannabidiol



Non-psychoactive phytocannabinoids

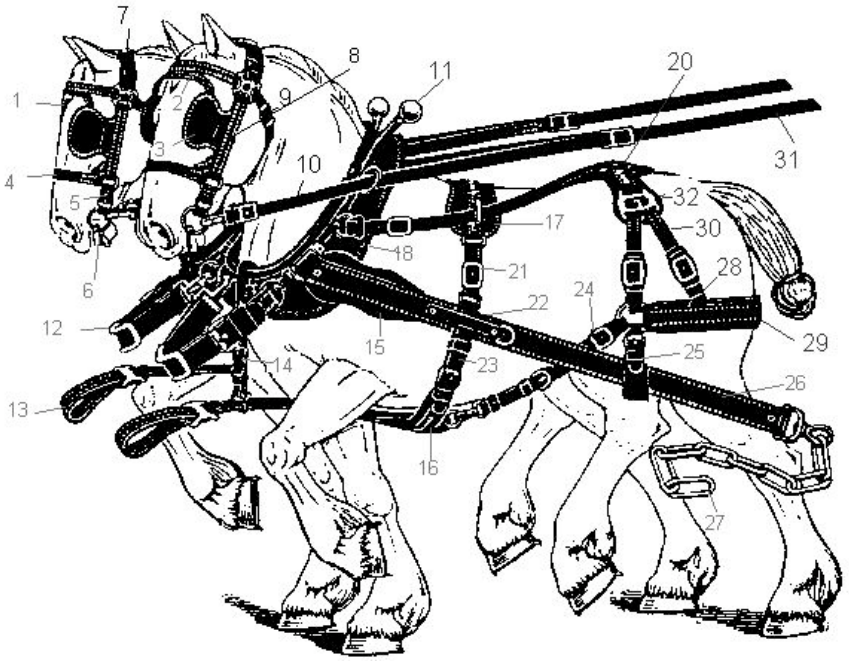


Distribution of CB1 receptors



Defining the cannabinoid system

- Exogenous compounds
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Nabilone, dronabinol
    - K2, “spice”
- Endogenous cannabinoids
  - Anandamide
  - 2-arachidonyl glycerol
- Receptor targets
  - CB1, CB2, TRPV1, PPAR, 5-HT, other…



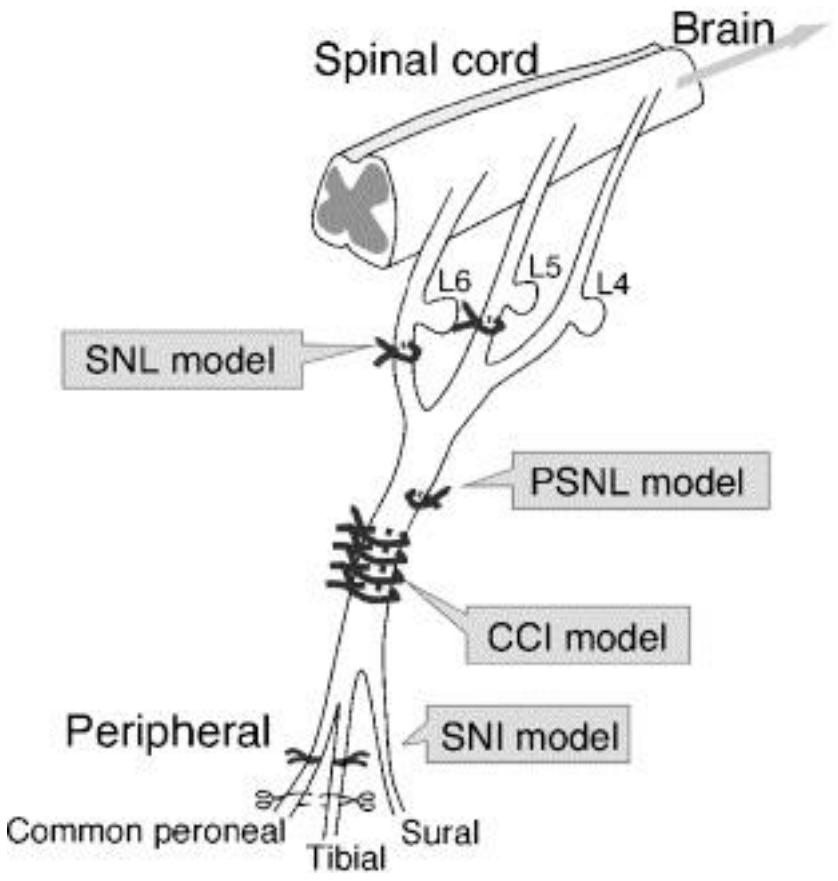
Cannabinoids are effective in all peripheral neuropathic pain models

Nerve injury
- Chronic constriction injury
- Sciatic nerve ligation
- Brachial plexus avulsion
- Trigeminal neuralgia

Diabetes
- Streptozotocin

Chemotherapy
- Paclitaxel
- Cisplatin
- Vincristine

HIV neuropathy



Pharmacology & Therapeutics
Volume 109, Issues 1–2, January 2006, Pages 57–77

…and in other pain models

- Spinal cord injury
- Multiple sclerosis
- Cancer pain
- Osteoarthritis
- Visceral pain
- Inflammatory, nociceptive pain
- Muscle pain

Prescription cannabinoids

Dronabinol (Δ-9 tetrahydrocannabinol – THC) (2.5 - 10mg)

- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting and anorexia associated with HIV/AIDS**

Nabilone (0.25 - 1.0mg)

- Oral capsule
- Approved for **chemotherapy-induced nausea and vomiting**

Nabiximols (2.7mg THC + 2.5mg CBD)

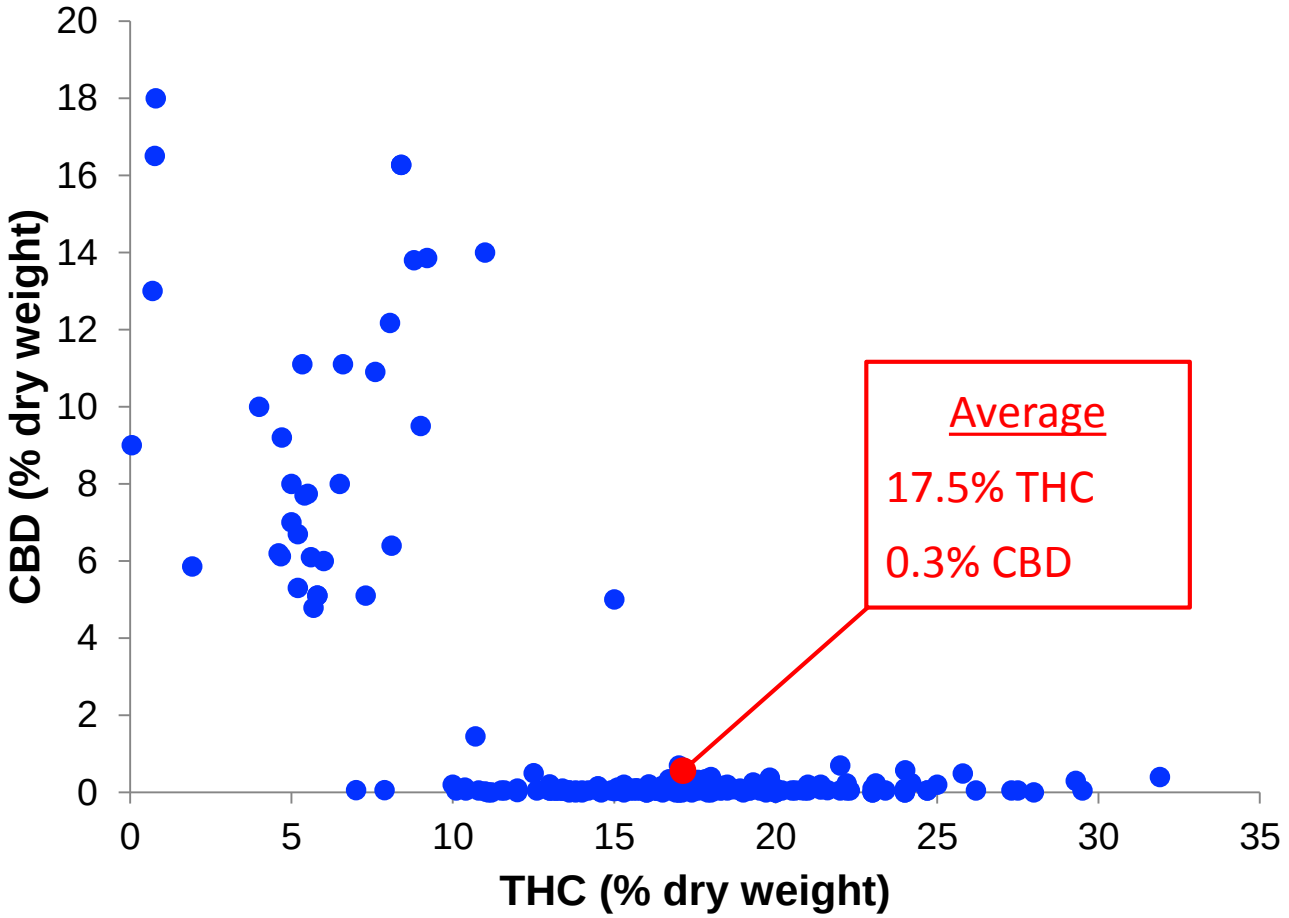
- Oromucosal spray
- Approved in Canada for **multiple sclerosis-associated neuropathic pain, spasticity and advanced cancer pain**

Herbal cannabis (varying THC levels)

- State programs (USA)
- Federal programs (Canada, Holland, Israel)
- **No formal 'approval'**

THC and CBD levels in cannabis strains (2015)

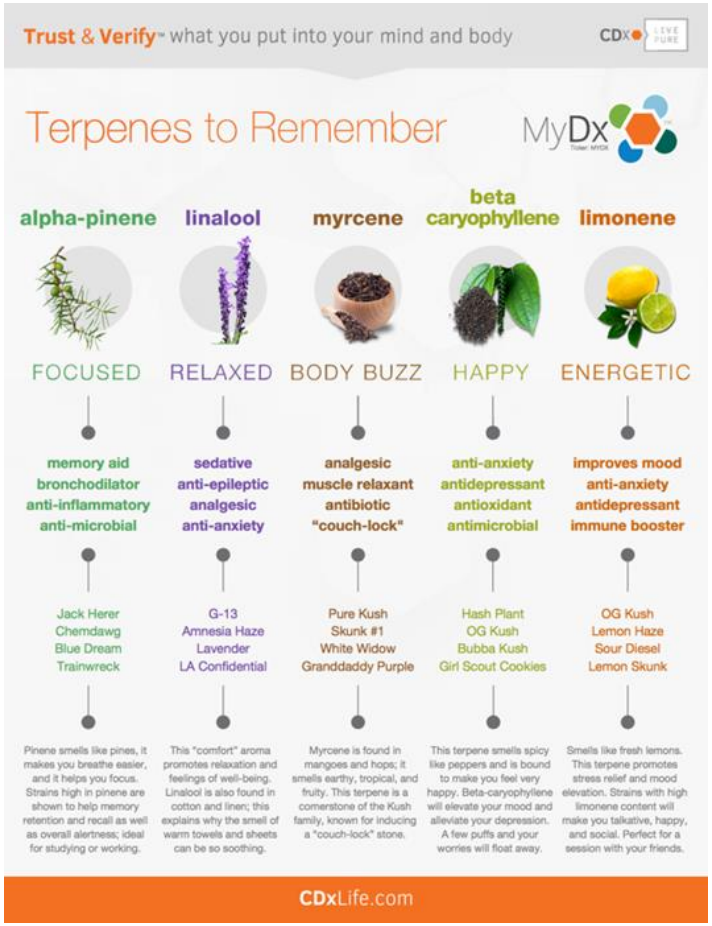
- Data from March 2015
- ~210 strains available for 15 MMPR LPs



Slide courtesy of Jon Page

Cannabis ‘strains’

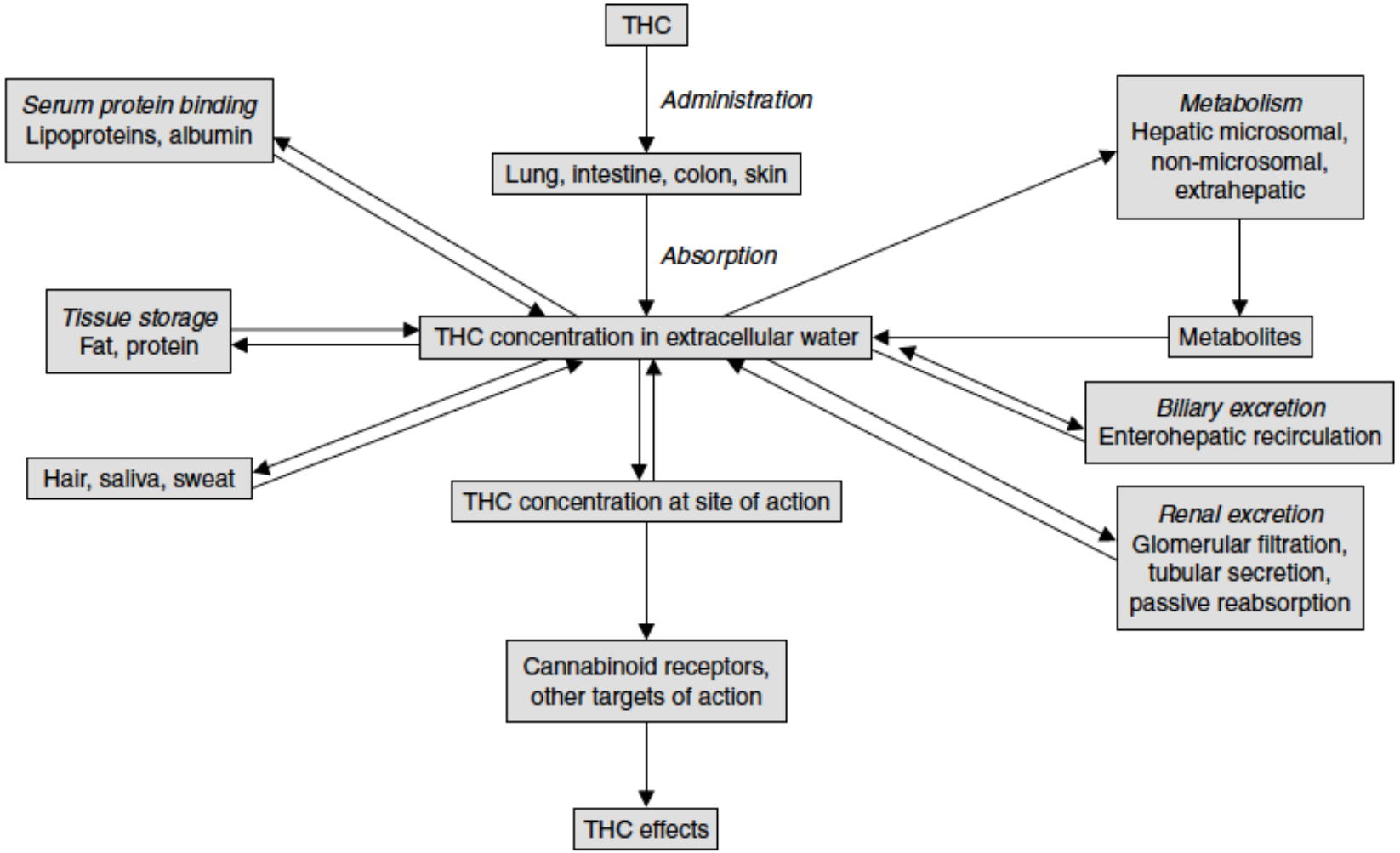
Leafly



Pharmacokinetics and Pharmacodynamics of Cannabinoids

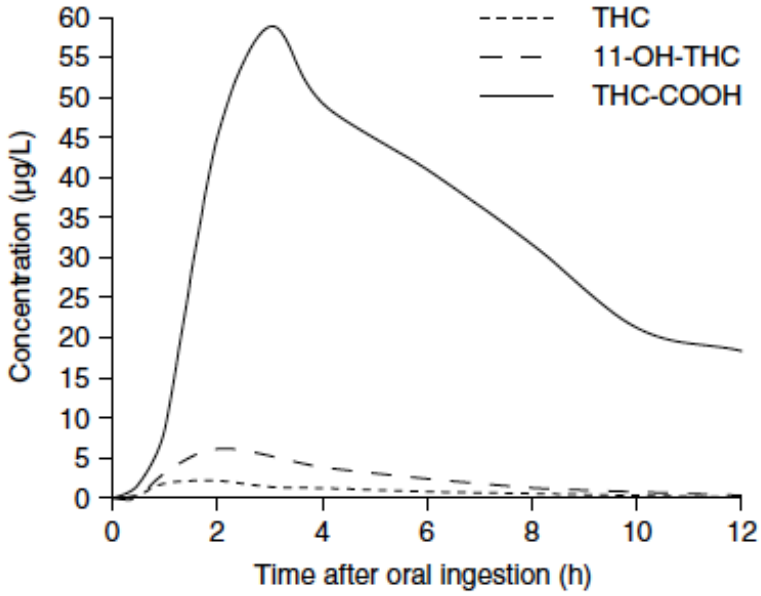
Franjo Grotenhermen

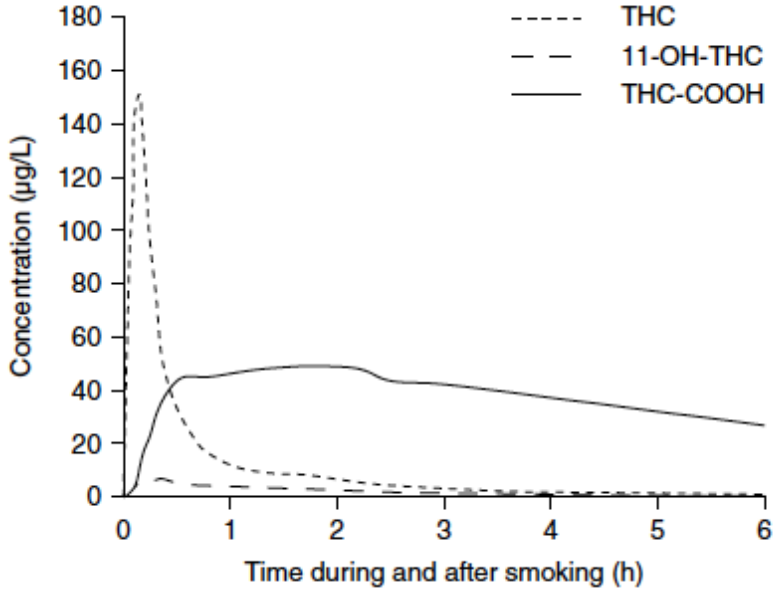
Nova-Institut, Hürth, Germany

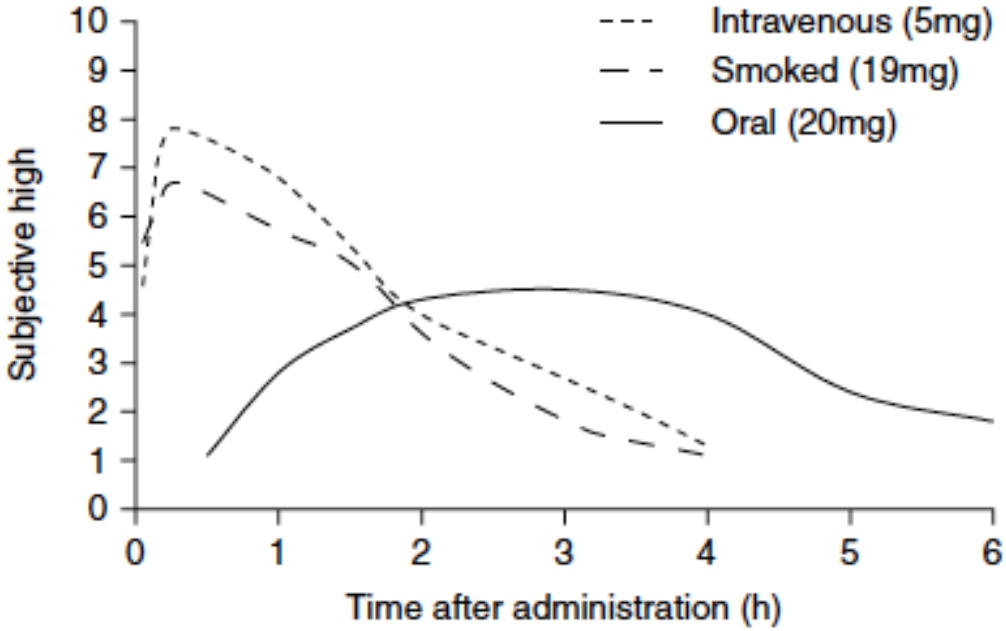


DRUG DISPOSITION

Clin Pharmacokinet 2003; 42 (4): 327-360
0312-5963/03/0004-0327/$30.00/0


THC
11-OH-THC
THC-COOH
Concentration (µg/L)
Time after oral ingestion (h)


THC
11-OH-THC
THC-COOH
Concentration (µg/L)
Time during and after smoking (h)

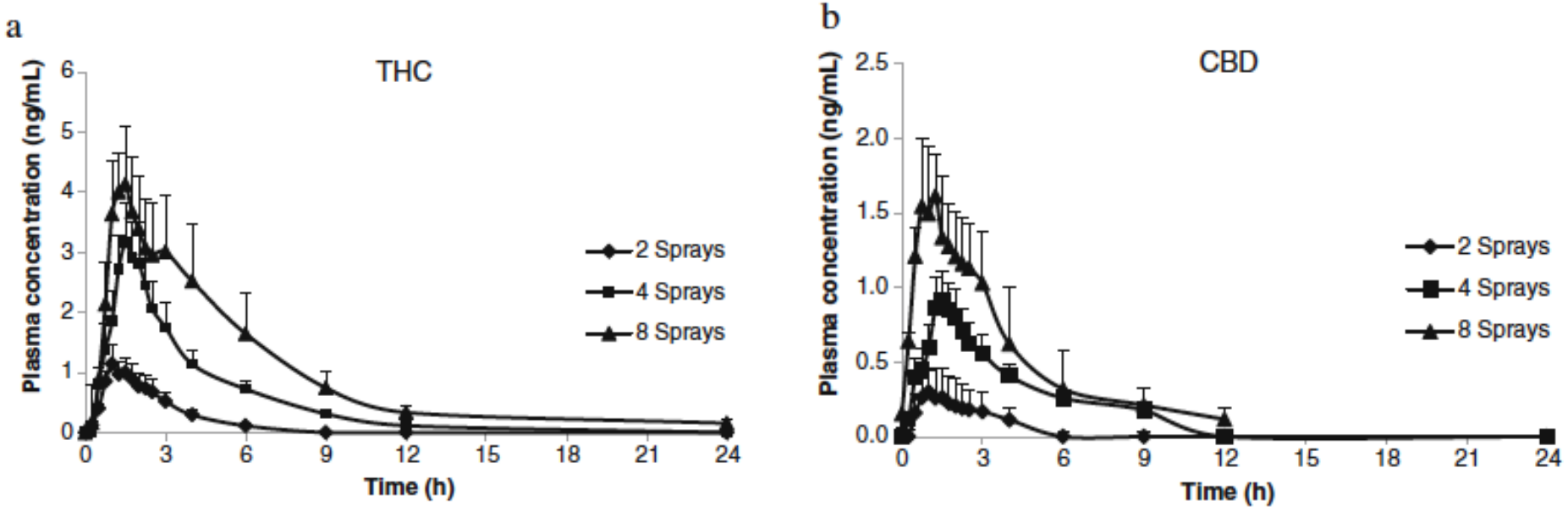

Intravenous (5mg)
Smoked (19mg)
Oral (20mg)
Subjective high
Time after administration (h)

Eur J Clin Pharmacol (2013) 69:1135–1147
DOI 10.1007/s00228-012-1441-0

PHARMACOKINETICS AND DISPOSITION

A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray

C. G. Stott · L. White · S. Wright · D. Wilbraham · G. W. Guy

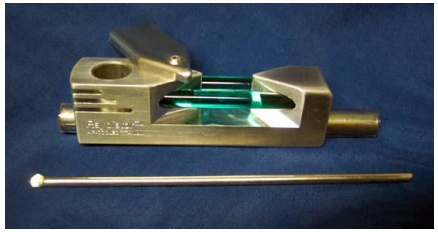


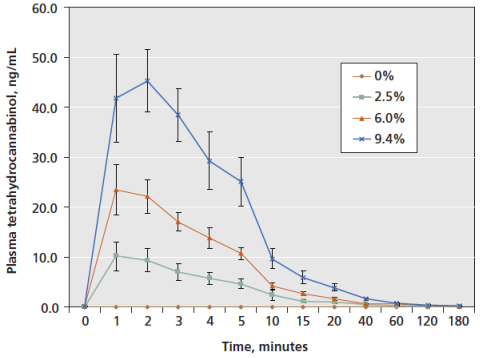
CMAJ RESEARCH

Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

25 mg herbal cannabis; 0, 2.5, 6, 9.4% THC
Single inhalation using pipe, 3 times daily
N=23 neuropathic pain patients





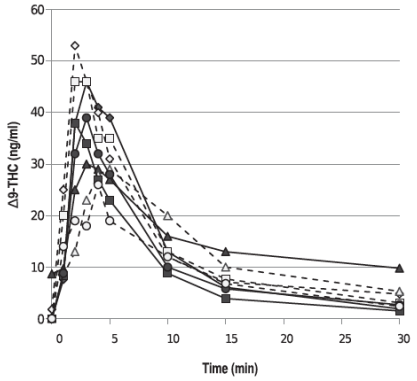
Journal of Pain & Palliative Care Pharmacotherapy. 2014;28:216–225.
Copyright © 2014 Informa Healthcare USA, Inc.
ISSN: 1536-0288 print / 1536-0539 online
DOI: 10.3109/15360288.2014.941130

informa
healthcare

REPORT

The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable Metered-Dose Cannabis Inhaler in Patients With Chronic Neuropathic Pain: A Phase 1a Study

15 mg herbal cannabis; 19% THC
Single inhalation using inhaler
N=10 neuropathic pain patients



Clin Pharmacokinet (2016) 55:807–812
DOI 10.1007/s40262-015-0363-2

REVIEW ARTICLE

Pharmacokinetics of Cannabis in Cancer Cachexia-Anorexia Syndrome

Stephanie E. Reuter[1,2,3] · Jennifer H. Martin[3]

A high-quality, rigorous, phase I/II study to elicit pharmacokinetic dose–concentration and concentration–response data, with a clinically acceptable mode of delivery to reduce intrapatient variability and enable more consistent bioavailability is needed in this population.

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

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

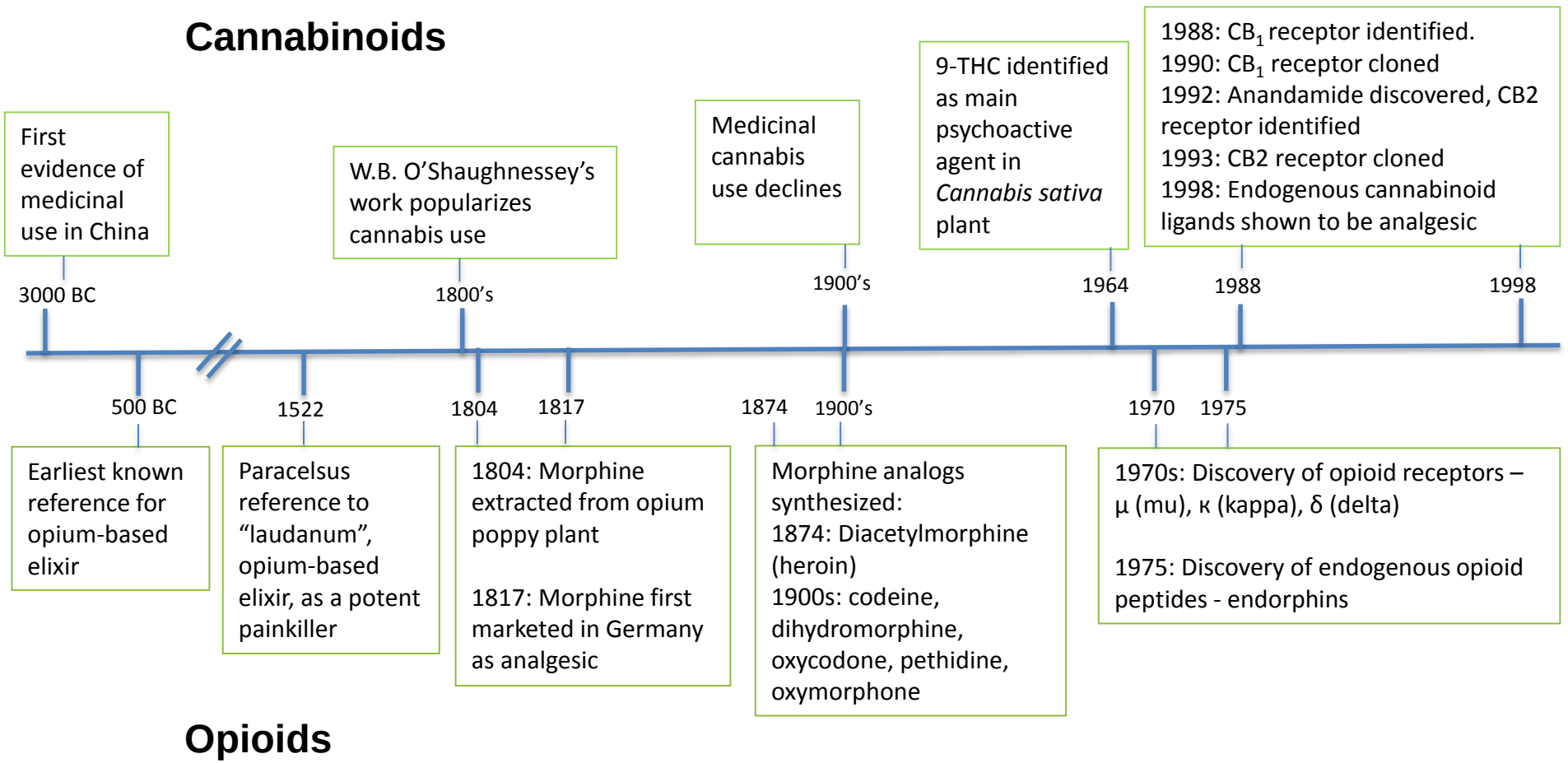
Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research.* Washington, DC: The National Academies Press.

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Safety concerns

- Brain development
- Psychosis
- Cannabis use disorder
- Cognitive function
- Driving
- Drug interactions
- Anxiety/depression
- Cardiovascular effects
- Pregnancy/lactation
- Bronchitis
- Cannabinoid hyperemesis syndrome
- …

Cannabinoids and Opioids: A Historical Perspective



1. Mack A & Joy J., 2001.
2. Notcutt W., 2004.

Opioid Sparing Effects of Cannabis

- Three case studies* where patients used small doses of smoked marijuana in combination with an opioid
- Patients were able to decrease the dose of opioid by 60–100% as compared to before the regular use of smoked marijuana
- With the introduction of smoked marijuana, each patient reported better pain control

***Uncontrolled data**

Lynch ME & Clark AJ., 2003.

Neuropsychopharmacology (2017), 1–14

www.neuropsychopharmacology.org

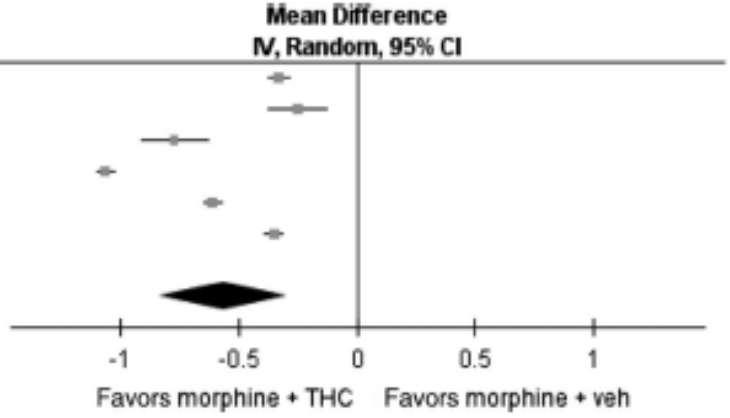
Review Article

Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

Suzanne Nielsen[*,1,2], Pamela Sabioni[3], Jose M Trigo[3], Mark A Ware[4], Brigid D Betz-Stablein[5], Bridin Murnion[6,7], Nicholas Lintzeris[2,6], Kok Eng Khor[8], Michael Farrell[1], Andrew Smith[9] and Bernard Le Foll[3]

Study or Subgroup	Morphine + THC Mean	SD	Total	Morphine + Vehicle Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cichewicz 1999	1.12	0.09	30	1.45	0.08	30	16.9%	-0.33 [-0.37, -0.29]
Cichewicz 2003	1.13	0.18	12	1.38	0.18	30	16.4%	-0.25 [-0.37, -0.13]
Cox 2007	-0.39	0.17	7	0.38	0.17	28	16.2%	-0.77 [-0.91, -0.63]
Smith 1998	0.44	0.07	30	1.5	0.08	30	16.9%	-1.06 [-1.10, -1.02]
Welch 1992	-0.82	0.07	96	-0.21	0.19	120	16.9%	-0.61 [-0.65, -0.57]
Williams 2008	0.39	0.07	24	0.74	0.06	24	16.9%	-0.35 [-0.39, -0.31]
Total (95% CI)			**199**			**262**	**100.0%**	**-0.56 [-0.83, -0.29]**

Heterogeneity: Tau² = 0.11; Chi² = 926.85, df = 5 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.10 (P < 0.0001)



Original Investigation

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
Independent Variable[a]	Estimate (95% CI)[b]	Estimate (95% CI)[c]	Estimate (95% CI)[d]
Medical cannabis law	−24.8 (−37.5 to −9.5)[e]	−31.0 (−42.2 to −17.6)[f]	−23.1 (−37.1 to −5.9)[e]
Prescription drug monitoring program	3.7 (−12.7 to 23.3)	3.5 (−13.4 to 23.7)	7.7 (−11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (−10.4 to 23.1)	4.1 (−11.4 to 22.5)	2.3 (−15.4 to 23.7)
Increased state oversight of pain management clinics	−7.6 (−19.1 to 5.6)	−11.7 (−20.7 to −1.7)[e]	−3.9 (−21.7 to 18.0)
Annual state unemployment rate[g]	4.4 (−0.3 to 9.3)	5.2 (0.1 to 10.6)[e]	2.5 (−2.3 to 7.5)

JAMA Intern Med. doi:10.1001/jamainternmed.2014.4005
Published online August 25, 2014.

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 17, No 6 (June), 2016: pp 739-744
Available online at www.jpain.org and www.sciencedirect.com

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

Kevin F. Boehnke,* Evangelos Litinas,† and Daniel J. Clauw‡,§

Medication Type	Use Before Initiation of Cannabis, n/N (%)	Use After Initiation of Cannabis, n/N (%)
Opioids	119/184 (65)	33/184 (18)
Nonsteroidal anti-inflammatory drugs	115/184 (62)	38/184 (21)
Disease-modifying antirheumatic drugs	15/184 (8)	3/184 (2)
Antidepressants	72/184 (39)	25/184 (14)
Serotonin–norepinephrine reuptake inhibitors	13/184 (7)	3/184 (2)
Selective serotonin reuptake inhibitors	34/184 (18)	8/184 (4)
Other	69/184 (38)	40/184 (22)

Sample Medical Document for the Access to Cannabis for Medical Purposes Regulations

This document may be completed by the applicant's health care practitioner as defined in the Access to Cannabis for Medical Purposes Regulations (ACMPR). A health care practitioner includes medical practitioners and nurse practitioners. In order to be eligible to provide a medical document, the health care practitioner must have the applicant for the medical document under their professional treatment. Regardless of whether or not this form is used, the medical document must contain all of the required information, (see in particular s. 8 of the ACMPR).

Patient's Given Name and Surname _____

Patient's Date of Birth (DD/MM/YYYY) _____

Daily quantity of dried marihuana to be used by the patient: _____ g/day

The period of use is _____ day(s) _____ week(s) _____ month(s).

NOTE: The period of use cannot exceed one year

Health care practitioner's given name and surname: _____

Profession: _____

Health care practitioner's business address: _____

Full business address of the location at which the patient

consulted the health care practitioner (if different that above): _____

Phone Number: _____

Fax Number (if applicable): _____

Email Address (if applicable): _____

Province(s) Authorized to Practice in: _____

Health Care Practitioner's Licence number: _____

By signing this document, the health care practitioner is attesting that the information contained in this document is correct and complete.

Health Care Practitioner's Signature: _____

Date Signed (DD/MM/YYYY): _____

Canada

www.registrecannabisquebec.com

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

QCR Objectives

1. To establish an **infrastructure for research** aimed at producing new knowledge on medical cannabis use, and specifically studies on its potential risks and benefits
2. To implement a mechanism to **generate new research question**s on the subject
3. To foster **collaboration** among researchers conducting projects on cannabinoid use, from Quebec, and possibly other provinces, the US and elsewhere, by giving them a means to share research data

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

QCR oversight

- Scientific committee
  - William Barakett
  - Yola Moride
  - Pierre Beaulieu
  - Andrée Néron
  - Antonio Vigano
- Ethics committee
  - CCER (MSSS)
- Steering committee
  - FMOQ
  - FMSQ
  - MSSS
  - AAQ
  - AQDC
  - CMQ

RI-MUHC Centre for Innovative Medicine

Registry coordination

Data management

Investigator training

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Data collection

- Clinical data
  - Diagnosis/es
  - Symptom/s
  - Cannabis producer
  - Strain/THC:CBD profile
  - Concomitant medications
- Patient reported outcomes
  - Global cannabis questionnaire
  - BPI
  - ESAS
  - EQ5D
- Adverse events

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Population

- Adults 18y and older
- Able to consent
- Authorized to possess cannabis for medical purposes
- May also consent to longer term follow up and to be contacted for additional studies

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Recruitment of collaborators

- Submit request www.registrecannabisquebec.com
- Confidentiality Agreement
  - Receive and review study documents
- Inter-institutional Agreement
  - May need DPS for public institutions
- Online training modules
  - I h on GCP, data collection, consent, adverse event reporting

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Collaborator's responsibilities

- Complete and send medical document to LP
- Assign study number (e.g. 005-104) to subject
- Maintain log of enrollment and study visits
- Maintain CRFs in secure files
- Collect and report AEs

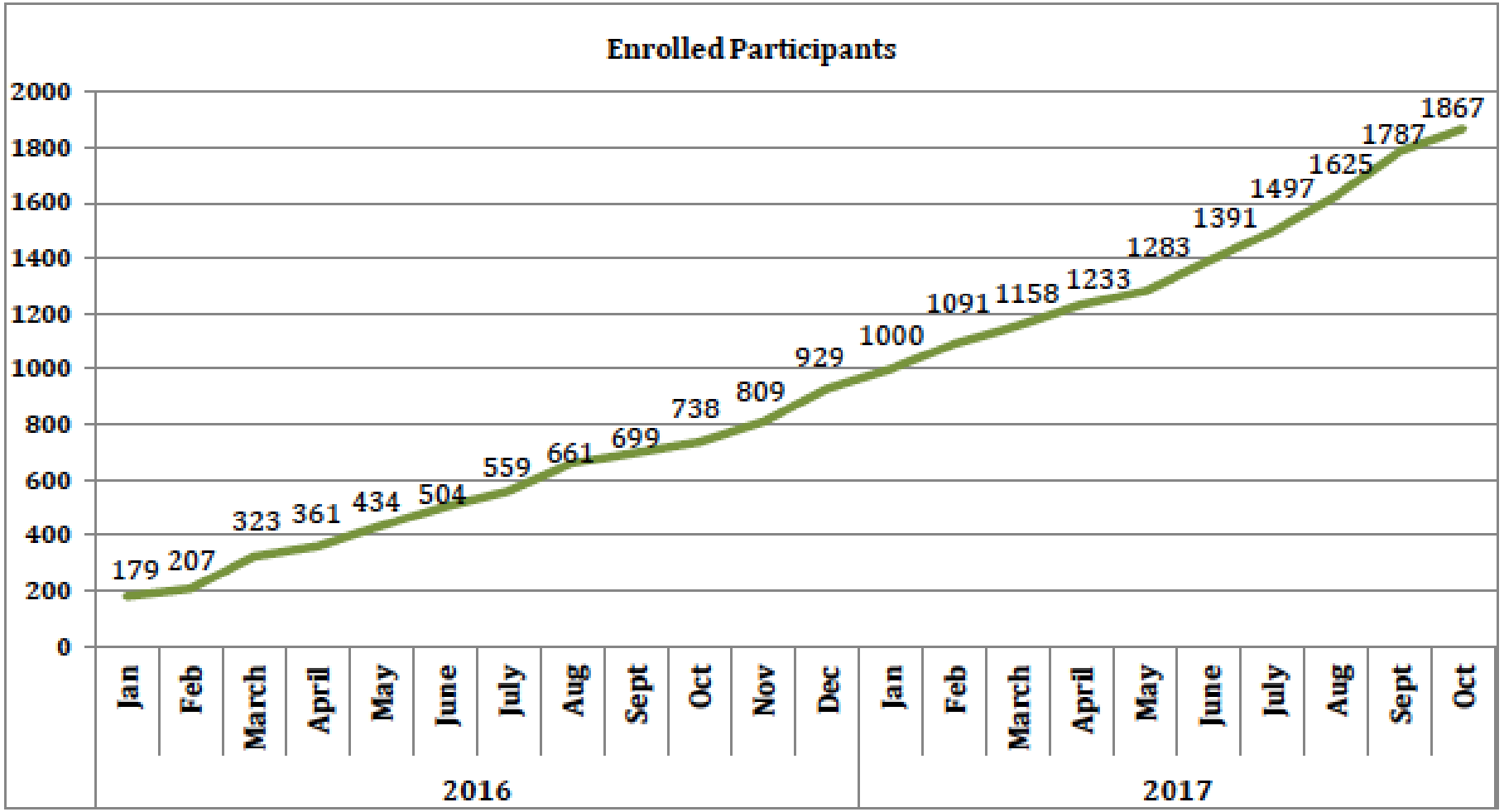
REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Data collection

- Every three months for two years
- Annually for two years
- Total time in study: 4y
- Total duration of study: 10y
- Data collected by fax (patient questionnaires) and/or online (MD questionnaires)
- QCR team performs quality control on CRFs and monitors sites

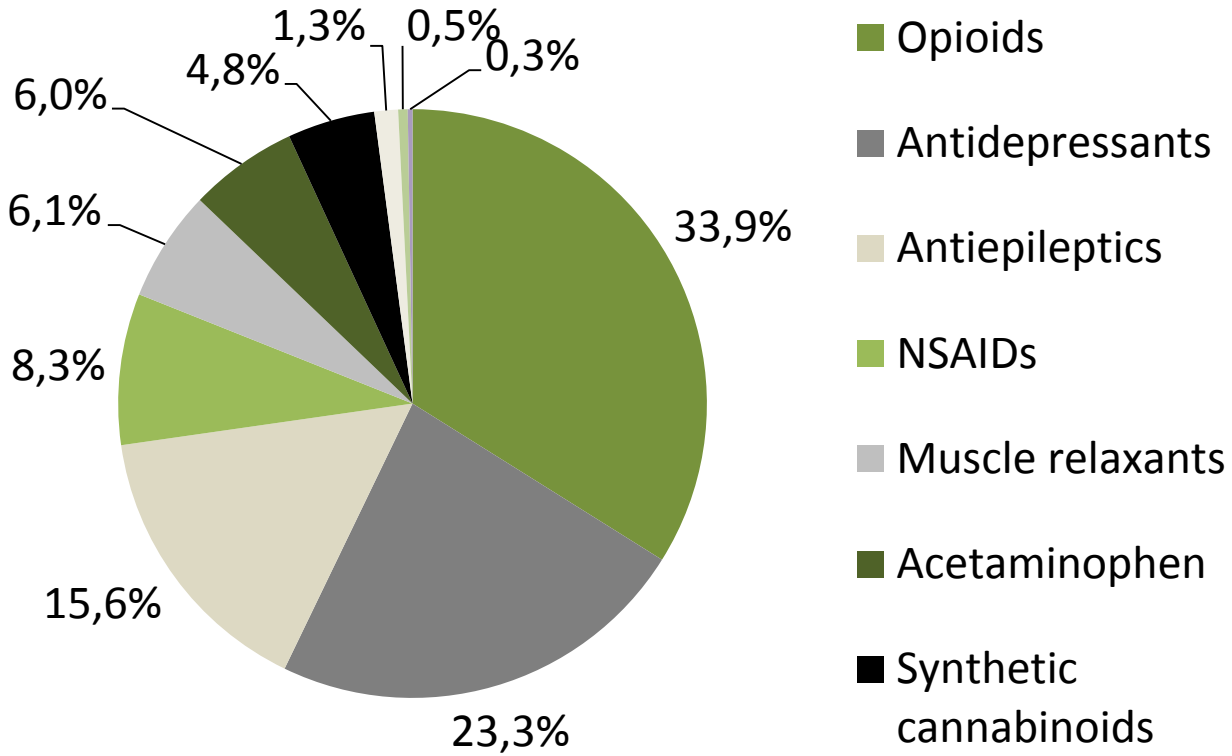
REGISTRE CANNABIS QUÉBEC
CANNABIS REGISTRY

Recruitment



REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

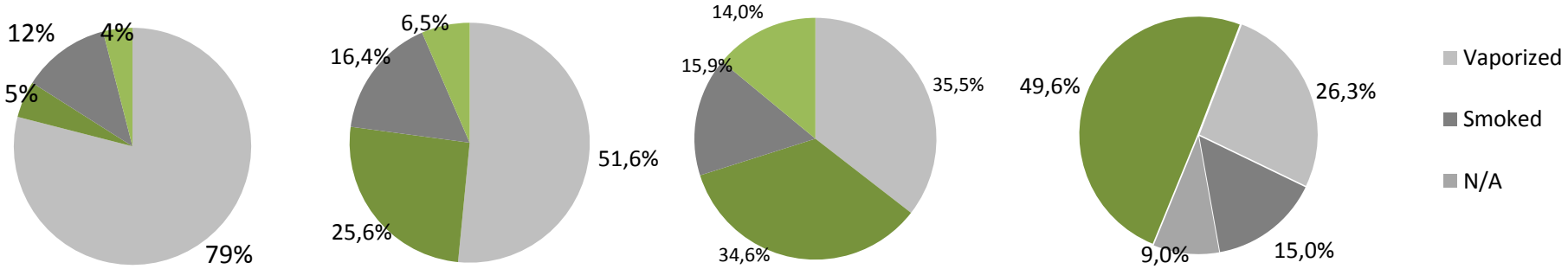
Concomitant medications



Unpublished data

REGISTRE CANNABIS QUÉBEC CANNABIS REGISTRY

Modes of administration



November 2015

May 2016

November 2016

May 2017

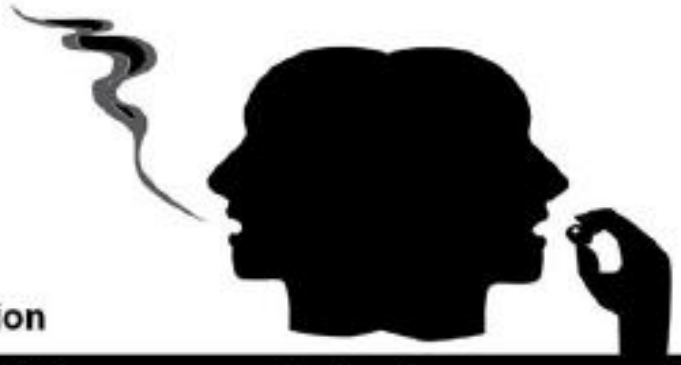
Unpublished data

Patterns of cannabis use in palliative care

- Australian experience
  - Prevalence: 13% (n=204) (Luckett 2016)
  - Preference for tablets and sprays over vapourizers
- Israel experience
  - “Improvement in pain, general well-being, appetite, and nausea were reported by 70%, 70%, 60%, and 50%, respectively” (Waissengrin 2015)

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

Steven A. Pergam, MD, MPH [1,2,3,4]; Maresa C. Woodfield, BS[1]; Christine M. Lee, PhD[5,6]; Guang-Shing Cheng, MD[2,3]; Kelsey K. Baker, MS[2]; Sara R. Marquis, MPH[1]; and Jesse R. Fann, MD, MPH[2,5]



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)

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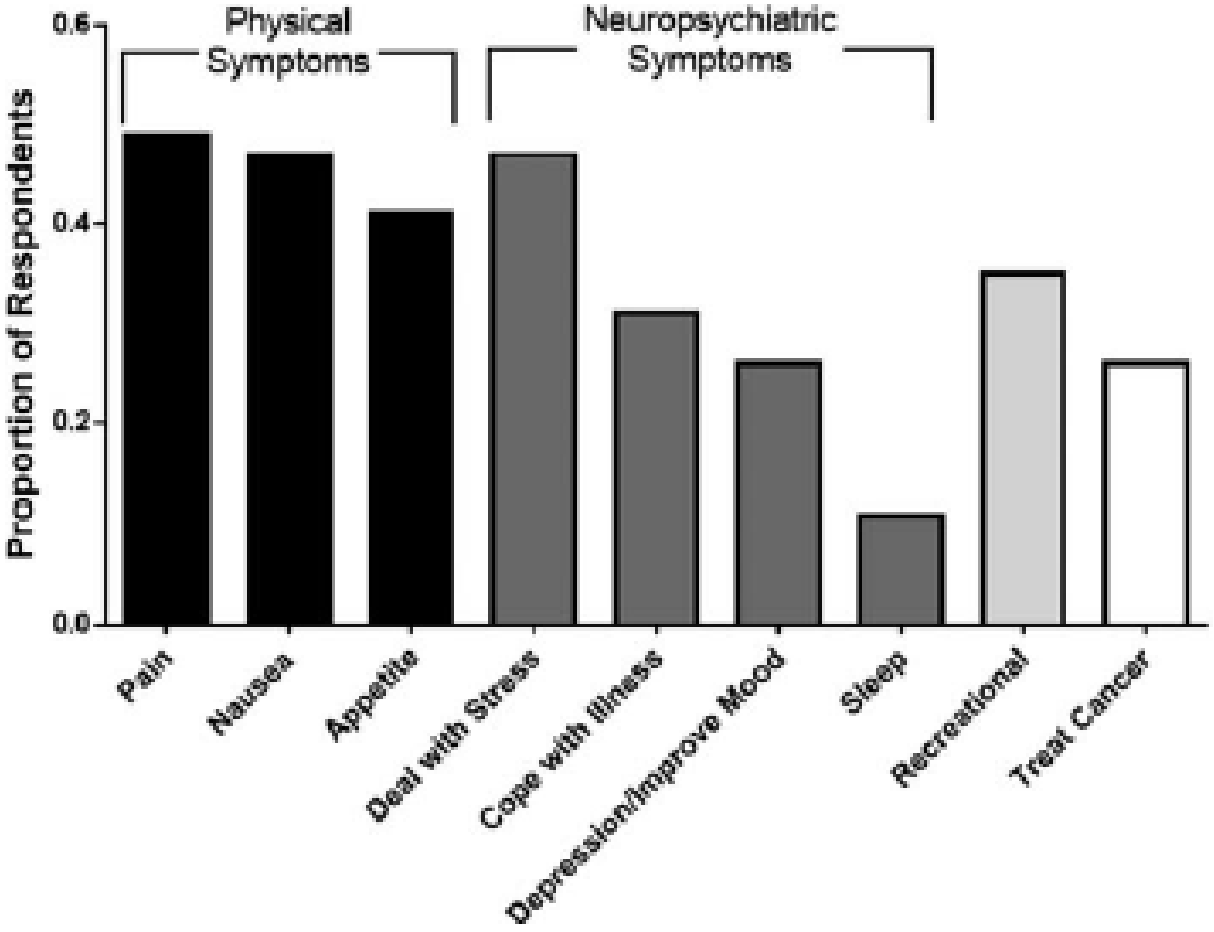
Cannabis Use Among Patients at a Comprehensive Cancer Center in a State With Legalized Medicinal and Recreational Use

Steven A. Pergam, MD, MPH [1,2,3,4]; Maresa C. Woodfield, BS[1]; Christine M. Lee, PhD[5,6]; Guang-Shing Cheng, MD[2,3]; Kelsey K. Baker, MS[2]; Sara R. Marquis, MPH[1]; and Jesse R. Fann, MD, MPH[2,5]



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Adjunctive Nabilone in Cancer Pain and Symptom Management: A Prospective Observational Study Using Propensity Scoring

Vincent Maida, MD, BSc, ABHPM, Marguerite Ennis, PhD, Shiraz Irani, RN,MSN,FNP, Mario Corbo, BHSc, and Michael Dolzhykov, BSc

Baseline Symptoms and Medication Use

	ESAS SYMPTOM SCORE		
	NABILONE-TREATED (n = 47) MEAN (SD)	UNTREATED (n = 65) MEAN (SD)	P VALUE
Symptom			
Pain	7.1 (2.4)	5.6 (2.7)	0.0029
Tiredness	5.7 (1.8)	4.8 (1.9)	0.0109
Nausea	4.7 (2.7)	3.4 (2.0)	0.0024
Depression	5.1 (2.5)	3.5 (1.9)	0.0003
Anxiety	5.2 (2.5)	4.0 (1.9)	0.0038
Drowsiness	4.4 (2.1)	3.4 (1.7)	0.0041
Appetite loss	6.0 (2.4)	4.8 (2.2)	0.0113
Lack of well-being	5.7 (2.3)	4.3 (1.9)	0.0010
Shortness of breath	2.8 (2.4)	3.2 (2.2)	0.2765
Total score	46.7 (15.6)	37.1 (11.2)	0.0002
Medication use			
Total MSE	60.3 (64.6)	67.3 (101.0)	0.8259
NSAIDs	19 (40.4)	20 (30.8)	0.3198
TCAs	10 (21.3)	15 (23.1)	1.0000
Gabapentin	9 (19.1)	7 (10.8)	0.2757
Dexamethasone	19 (40.4)	16 (24.6)	0.0987
Metoclopramide	27 (57.4)	40 (61.5)	0.6993
Ondansetron	4 (8.5)	5 (7.7)	1.0000

Dronabinol Versus Megestrol Acetate Versus Combination Therapy for Cancer-Associated Anorexia: A North Central Cancer Treatment Group Study

By Aminah Jatoi, Harold E. Windschitl, Charles L. Loprinzi, Jeff A. Sloan, Shaker R. Dakhil, James A. Mailliard, Sarode Pundaleeka, Carl G. Kardinal, Tom R. Fitch, James E. Krook, Paul J. Novotny, and Brad Christensen

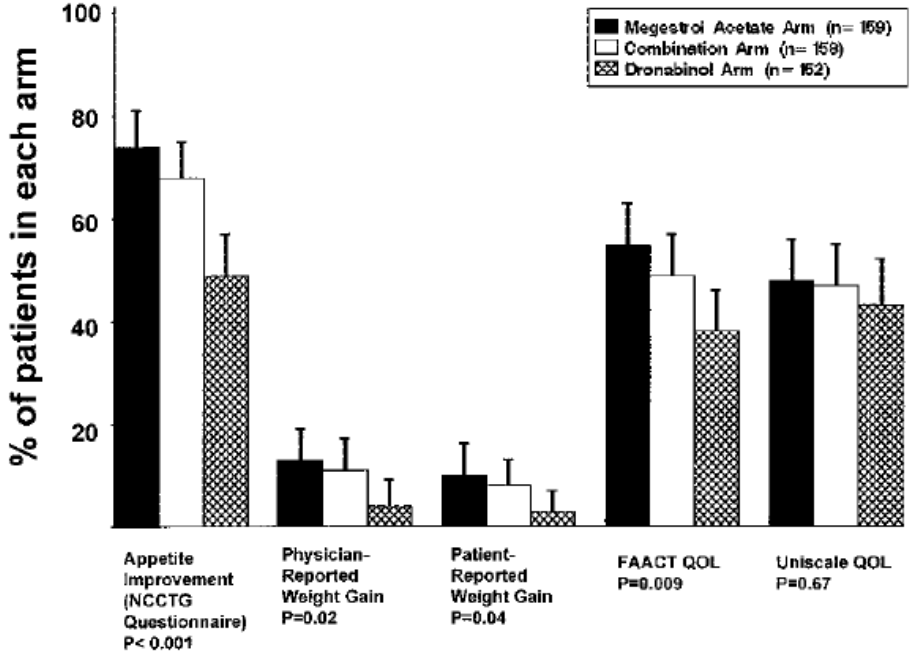
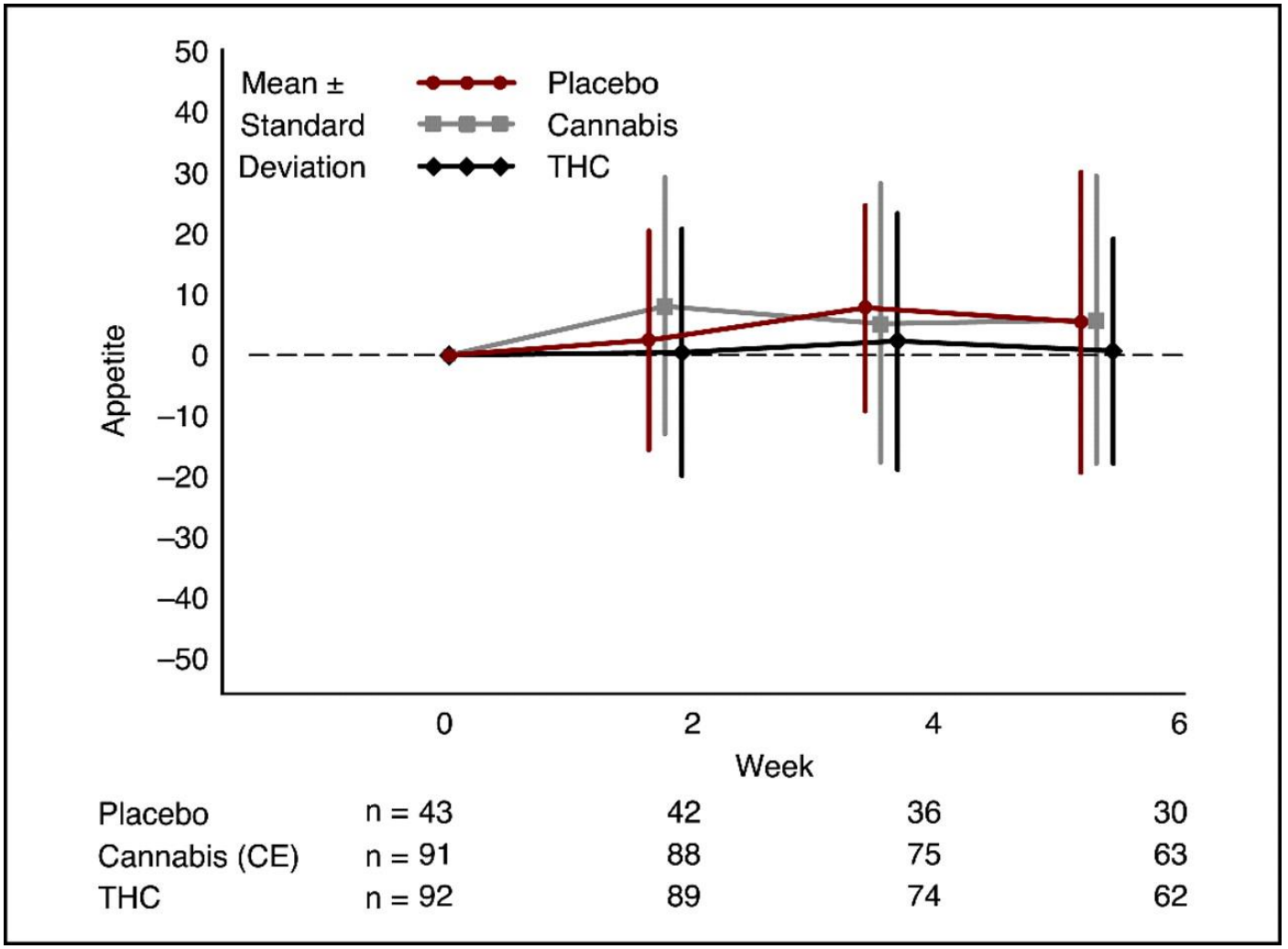


Fig 1. Megestrol acetate improved (1) appetite, (2) physician-reported weight, (3) patient-reported weight, and (4) FAACT QOL score (Fisher's exact test, $P < .001$, .02, .04, and .009, respectively). The UNISCALE found no significant differences in QOL. Bars represent 95% confidence intervals.

J Clin Oncol 20:567-573.

Changes in visual analog scale (VAS) scores from baseline for appetite in the intent-to-treat population.



Florian Strasser et al. JCO 2006;24:3394-3400

Discussion

- Can we harness the cannabinoid system to reduce opioid use and its consequences?
- Improvements in cannabinoid administration and quality may lead to more acceptable therapies
- Will legalization of cannabis allow for more open and thorough evaluation of the potential for cannabinoids in pain and symptom management?

CURRENT ONCOLOGY COMMENTARY

Use of cannabinoids in cancer care: palliative care

S.K. Aggarwal MD PhD*

> It seems evident that at least one advantage was gained from the use of the remedy—the awful malady was stripped of its horrors; if not less fatal than before, it was reduced to less than the scale of suffering which precedes death from most ordinary diseases.... Next to cure, the physician will perhaps esteem the means which enable him "to strew the path to the tomb with flowers," and to divest of its specific terrors the most dreadful malady to which mankind is exposed.
>
> O'Shaughnessy WB. On the preparations of the Indian hemp, or gunjah—*Cannabis indica* their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Prov Med J Retrosp Med Sci* 1843;5:363–9.