Dr Graham Gulbransen

General Practitioner

Kingsland Family Health Centre

Auckland

Saturday, August 12, 2017 (Room 2)

14:00 - 14:55 WS #114: Medicinal Cannabis for GPs

15:05 - 16:00 WS #125: Medicinal Cannabis for GPs (Repeated)

Case History, 2005 presentation

- Science writer Professor Stephen Jay Gould, who was treated for a mesothelioma.

- *I had surgery, followed by a month of radiation, chemotherapy, more surgery, and a subsequent year of additional chemotherapy. I found that I could control the less severe nausea of radiation by conventional medicines. But when I started intravenous chemotherapy (Adriamycin), absolutely nothing in the available arsenal of antiemetics worked at all. I was miserable and came to dread the frequent treatments with an almost perverse intensity.*

- *[Smoking] marihuana worked like a charm. I disliked the "side effect" of mental blurring (the "main effect" for recreational users), but the sheer bliss of not experiencing nausea -and then not having to fear it for all the days intervening between treatments -was the greatest boost I received in all my year of treatment, and surely had a most important effect upon my eventual cure.* (Brit Med Assn, 1997, p. 90)

Cannabis as Medicine in Australia

Presented at

International Medicine in Addiction Conference, Sydney 26/3/17

Prof Nicholas Lintzeris MBBS, PhD, FAChAM

Director D&A Services, SESLHD

University of Sydney, Division Addiction Medicine

HEMP Health & innovation

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2017 HHI EXPO & SYMPOSIUM

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2017 Symposium | Donate

Medical Practitioners

2017 Medicinal Cannabis Course

22 June 2017 Melbourne Crowne Plaza

australian medical cannabis observatory

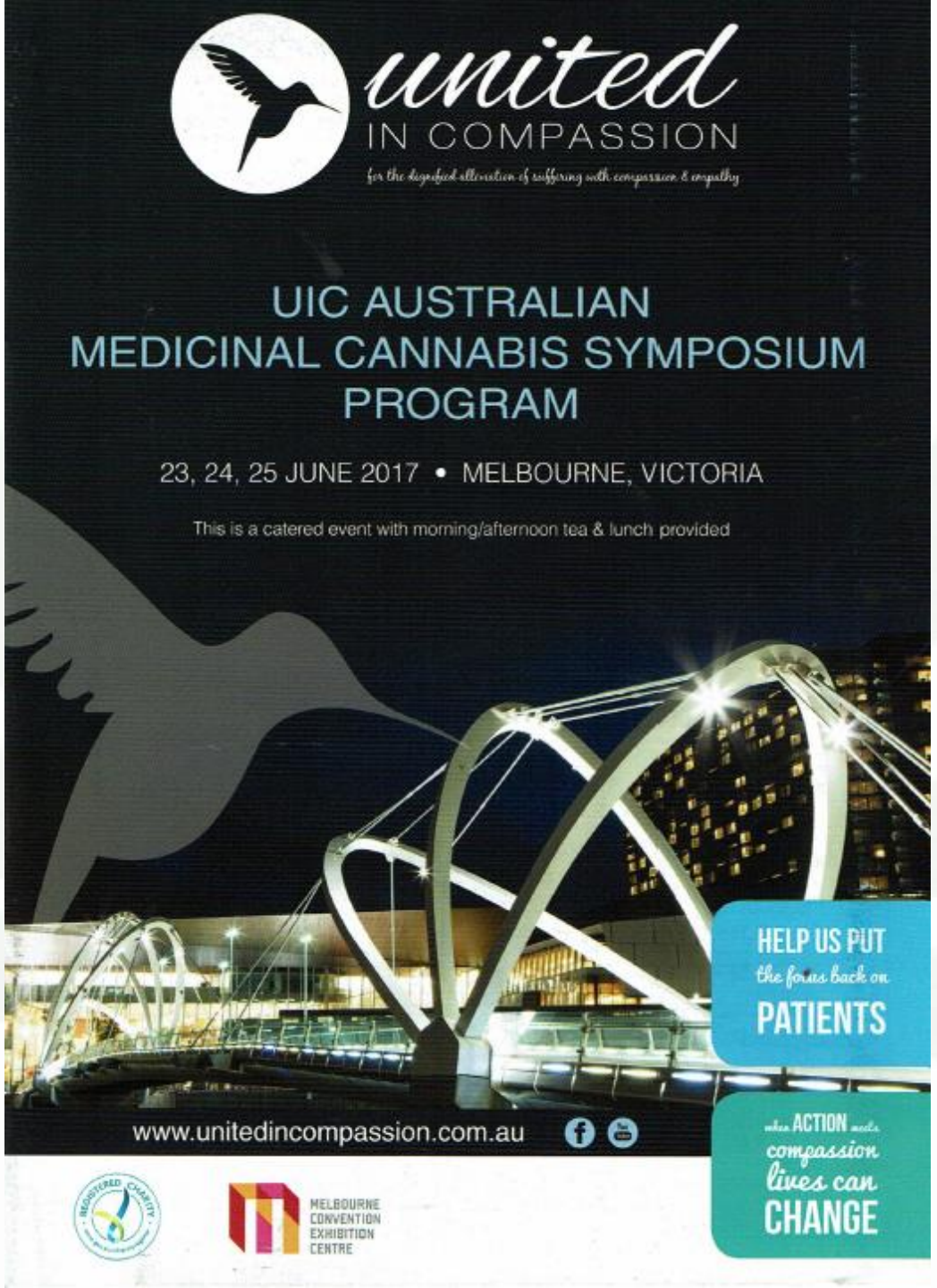
The First Australian Medicinal Cannabis Course designed for health care practitioners for health care practitioners.

A comprehensive introduction to:

- The Australian history of medicinal cannabis
- The endocannabinoid system
- The pharmacology of cannabinoid medicine
- The practicalities of dosing
- Conditions amenable to treatment
- Up to date literature
- International perspectives

...& much more!

Assoc Prof
David Caldicott
Canberra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MEDICINAL CANNABIS SYMPOSIUM
PROGRAM
23, 24, 25 JUNE 2017 • MELBOURNE, VICTORIA
This is a catered event with morning/afternoon tea & lunch provided
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EXHIBITION
CENTRE
when ACTION meets
compassion
lives can
CHANGE

‘…almost everybody knows

that cannabis is either essentially harmless

or else necessarily toxic.

Yet, like most arguments,

the truth is between these extremes, depending on the ages of use,

and frequency and chronicity of use.’

Richard P Mattick,

Drug and Alcohol Review,

July 2017

You may find this presentation challenging…

1. Is it safe?
2. Is it legal?
3. Is it snake oil?
4. Why haven’t we been taught about ECS?
5. Should GPs be recommending herbs?
6. How do GPs recommend/prescribe?
7. Remember medicinal cannabis is here now!

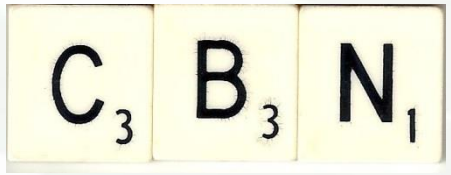
Summary

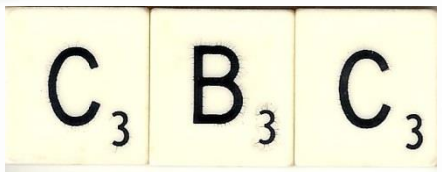
- Recreational vs medicinal cannabis
- Case histories
- Mechanism of Action: EndoCannabinoid System ~ Biological Plausibility
- Medicinal uses

- How to prescribe

Cannabis plant

- Thousands of strains – like tomatoes!
- THC & CBD main active compounds
- Continuum from
  - THC dominant
  - Balanced
  - CBD dominant





Phytocannabinoids

>100 cannabinoids in cannabis plant. Most non-psychoactive.

Each cannabinoid has its own pharmacological actions and therapeutic potential.

Plus … terpenes

“Entourage” effects: whole plant vs single molecules

BEDROCAN®

Bedrocan is featuring 22% THC, with a CBD-level below 1%.

BEDROBINOL®

Its THC-level is standardised at 13.5%, with a CBD-level below 1 %.

BEDIOL®

Bediol has a balanced ratio of THC 6.3% and CBD 8%.

BEDICA®

Bedica contains 14% THC with less than 1% CBD.

BEDROLITE®

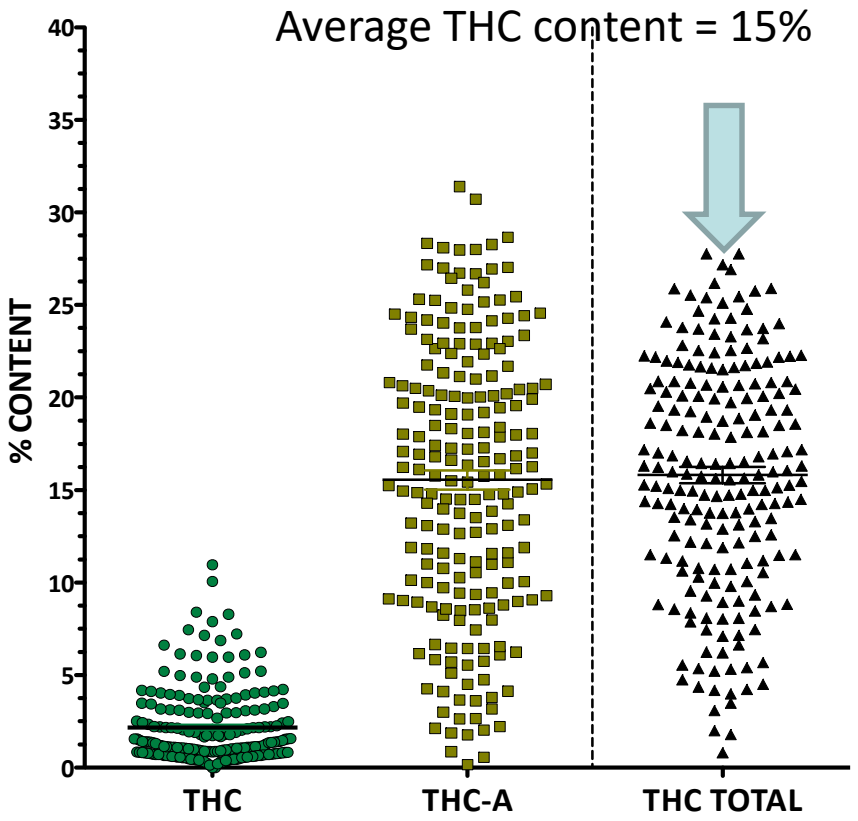
Bedrolite is a CBD-only product, with less than 1% THC and 9% CBD.

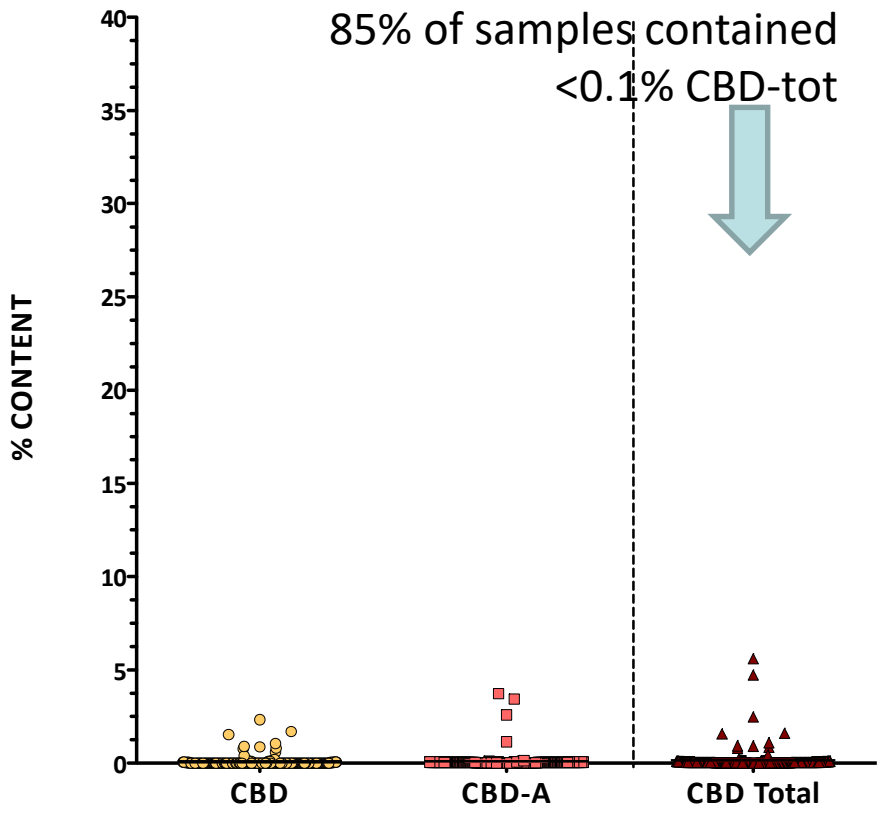
Definitions

- Recreational
- Therapeutic
- Medicinal

Potency of NSW police seized cannabis: high THC and low CBD

Swift et al PLoS One 2013





THC: psychoactive, sedation, analgesia, antiemesis, antispasmodic

CBD: anxiolytic, antipsychotic, anticonvulsant, protective against memory loss

Sativex

Each spray THC 2.7mg, CBD 2.5mg, ethanol, peppermint oil

Peter 58 (MS)

- MULTIPLE SCLEROSIS
- Left hemiparesis
- Disease modifying therapy: tecfidera
- Muscle spasms: baclofen inadequate.

- Prescribe Sativex with neurologist recommendation.

Prescription pathways at the end of this

Lynda 67 (Palliative care)

- Terminal pancreatic cancer
- Palliative care; chemotherapy nothing more to offer
- Smoked cannabis during chemo
  - Less nausea
  - Better appetite, but lost weight
  - Less pain
  - But – hated smoking, illegal

- Sativex approved – easy to take, control dose, no choking, eases abdo discomfort, huge appetite stimulant, regained weight!

Barbara 35 (Chronic pain)

- Severe endometriosis, 18 surgeries, full pelvic clearance
- Chronic pain, central sensitisation disorder
- Past misuse of prescription and illicit drugs to manage chronic endometriosis pain (pseudoaddiction)
- Was using cannabis most evenings for analgesia.

- Sativex approved. 1-2 sprays per week effective.

Nick 20 (Knobloch Syndrome)

- Autism spectrum disorder, global development delay, blind, epilepsy with uncontrolled prolonged seizures about twice a week.

Anticonvulsants ineffective with intolerable adverse effects.

- Hemp extract drops taken with unbroken sleep for the first time in his life and calmer during the day! Rapid recovery from seizures.

Jo 61 (MSA)

- Multiple systems atrophy, cerebellar type
- (chronic progressive debilitating neurological condition)
- Quadraparesis, confined to bed, dystonia, muscle spasms, contractures, depressed
- Clonazepam, levodopa/benserazide: minimal relief

- Sativex approved, difficult to use, short trial ineffective.

Eddie 30 (Chronic pain)

- Unexplained chronic facial pain 10 years
- Several surgeries without benefit

- 3 weeks after taking 10 drops of hemp extract tid:
  - Reduced oxycodone from 70mg → 40mg daily
  - Stopped gabapentin 600mg daily
  - Stopped nitrazepam 10mg nocte for sleep

- Continues hemp extract, feels hope for the first time.

Introduction

Jeffrey Y. Hergenrather, MD
General practice physician
Solo private practice
Cannabis consultations since 1997
Sebastopol, California

SOCIETY of CANNABIS CLINICIANS

President and founding member of
The Society of Cannabis Clinicians

I have no financial relationships to disclose.

Developing the Treatment Plan

Jeffrey Y. Hergenrather MD
Cannabis consultant
Sebastopol, CA, USA

United In Compassion
Melbourne Convention & Exhibition Centre
June 23 - 25, 2017

Conditions in Clinical Practice

Rank order - Hergenrather 2017

- Pain (acute pain, chronic inflammatory, neuropathic)
- Mental disorders (all kinds)
- Cancers
- Gastrointestinal disorders
- Insomnia
- Migraine headaches
- Harm reduction, alternative to opioids . . .
- Spastic disorders
- Autoimmune disorders
- Neurodegenerative disorders
- Glaucoma
- Skin diseases
- Epilepsy, Autism, Tourettes, ADD, Dystonia, Dementia
- AIDS and other infections

Have you any patients
who are ‘stuck’?

Conventional medicines
just not working?

Sativex

Each spray THC 2.7mg, CBD 2.5mg, ethanol, peppermint oil

What is Sativex®?

Sativex® is a cannabis-based product classified as a Schedule 2, Part 1 (Class B1) controlled drug product under the Misuse of Drugs Act 1975.

Sativex® is an oromucosal (mouth) spray administering a metered, actuated dose containing the cannabis extracts delta-9-tetrahydrocannabinol (THC) (2.7 mg/spray) and cannabidiol (CBD) (2.5 mg/spray)

[+ traces of terpenes and other cannabinoids].

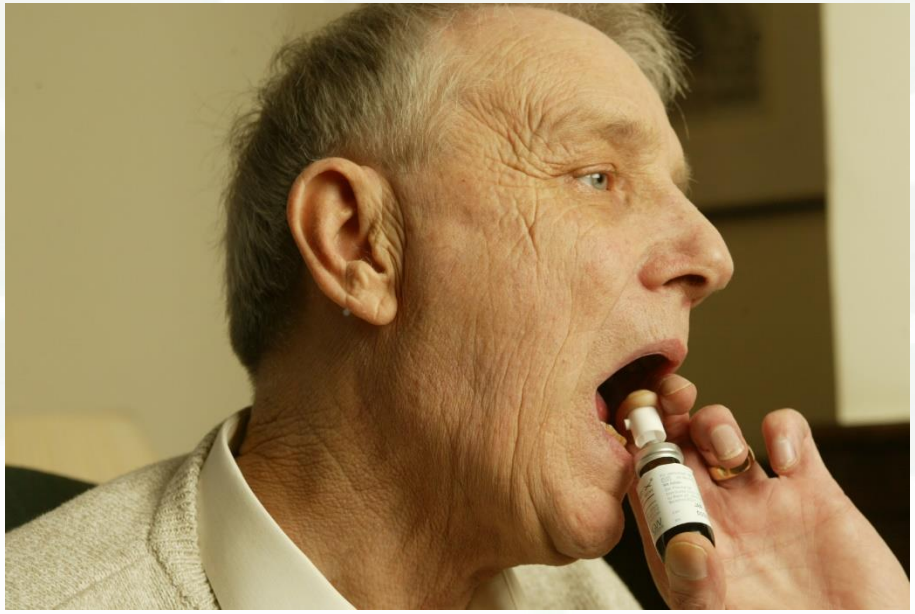
What is Sativex® approved for?

- In New Zealand Sativex® is approved for use as an add-on treatment for symptom improvement in patients with moderate to severe spasticity due to Multiple Sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

Sativex dosing

Day	Number of sprays in the morning	Number of sprays in the evening	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

Five Pathways to medicinal cannabis



1. Restriction on the Supply of Sativex—Approval to Prescribe, Supply and Administer (Approval No. 2016/AP305)

- MS: spasms not managed by conventional medicine
- Medical practitioners… acting on the written recommendation… of a Neurologist may prescribe Sativex
- The prescriber is required to state **multiple sclerosis** & Neurologist name on the prescription form.

1. Restriction on the Supply of Sativex—Approval to Prescribe, Supply and Administer (Approval No. 2016/AP305)

- Medical practitioners with a vocational scope of practice of Internal Medicine (specialising in neurology), registered with the Medical Council of New Zealand under the Health Practitioners Competence Assurance Act 2003, for the treatment of multiple sclerosis; or
- any other medical practitioner registered with the Medical Council of New Zealand when acting on the written recommendation of one of the medical practitioners with the vocational scope described above, for the condition specified. The name of the recommending medical practitioner with the appropriate vocational scope must be endorsed on the prescription form.
- The prescriber is required to state the condition being treated (ie "**multiple sclerosis**") on the prescription form.

2. Sativex ‘unapproved use’

- Form 2
- 6 pages
- GP & Specialist signatures
- Process time 1 – 4 weeks.

- SPECIAL AUTHORITY FORM – My proposal for an efficient approval system!!!

- However, as GPs we know that evidence based medicine doesn’t work for everyone, we work in ‘zones of therapeutic uncertainty’

Form 2

FORM 2

Application for
APPROVAL TO PRESCRIBE SATIVEX® FOR AN UNAPPROVED USE under Regulation 22 of the Misuse of Drugs Regulations 1977

A completed and signed copy of this form must be submitted for each application for Ministerial approval to prescribe Sativex® for an **unapproved use** in a specified patient.

Please refer to the current New Zealand Sativex® data sheet when completing this form (see http://www.medsafe.govt.nz/profs/Datasheet/s/sativexspray.pdf)

Please note that Sativex® is currently **not** funded by PHARMAC.

Form 2

4. SPECIALIST ENDORSEMENT

NOTE: SPECIALIST ELIGIBILTY CRITERIA
Specialist assessment and endorsement of the proposal to use Sativex®, and the proposed patient management plan, **must** be issued by a practitioner who is registered with the New Zealand Medical Council as being competent in the scope of practice appropriate to the management of the *specified condition* to be treated. For example, treatment for cachexia related to cancer should be endorsed by a registered oncologist or palliative care specialist.

Specialist endorsement is limited to oncologists, neurologists, anaesthetists and palliative care specialists.

NOTE: PROPOSED USE
To be eligible for approval to prescribe Sativex® for an unapproved use the patient **must** have a *specified condition* as follows:

- nausea, anorexia and wasting (cachexia) associated to cancer and AIDS; or
- chronic pain (including cancer pain) for which other pain relief treatments are ineffective or have significant/severe adverse side-effects; or
- neuropathic pain (associated with conditions including multiple-sclerosis, stroke, cancer, spinal cord injury, severe physical trauma, and peripheral neuropathy resulting from diabetes); or
- muscle spasm and spasticity associated with spinal cord injury.

NOTE: FAILURE OF OTHER PRESCRIPTION MEDICINES OR CURRENTLY AVAILABLE TREATMENTS
To be eligible for approval to prescribe Sativex® for an unapproved use the patient **must** have trialled adequate doses of standard treatments for the *specified condition* for appropriate periods of time without sufficient therapeutic benefit, or the standard treatments are not tolerated by the patient, or are contraindicated in the patient.

3. Application for Ministerial approval to prescribe a pharmaceutical grade cannabis-based product without consent for distribution in New Zealand under Regulation 22 of the Misuse of Drugs Regulations 1977

Please note that the Government does not support the use of unprocessed or partially processed cannabis leaf or flower preparations for medicinal use.

http://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/prescribing-cannabis-based-products

a.application from an appropriate specialist
b.a manufacturer has demonstrated a commitment to the development of the product as a pharmaceutical or
c.the product has been prepared pharmaceutically and the characteristics and formulation are clearly described and defined
d.the product has completed animal studies demonstrating proof of concept and potential clinical benefit
e.the product is undergoing an appropriately designed Phase II clinical study or
f.the product has completed clinical trials and is marketed overseas but is not approved for distribution in New Zealand
g.the product is available for use
h.the following are met where relevant:

i. evidence that there will be close follow up of patient by a prescriber
ii. evidence that a wide range of conventional treatments have been trialled and symptoms are still poorly controlled
iii. condition is an approved condition for use or
iv. condition is one for which there is some evidence of efficacy, preferably in clinical trials
v. Ministry clinicians assess application is appropriate if for non-approved use
vi. no history of abuse or diversion of controlled drugs
vii. the patient has no known contraindication to the use of the product
viii. initial approvals usually for 6 months
ix. baseline clinical indicators generally required and evidence of improvement before a new approval is given.

MINISTRY OF HEALTH
MANATŪ HAUORA

Application for Ministerial approval to prescribe a pharmaceutical grade cannabis-based product without consent for distribution in New Zealand under Regulation 22 of the Misuse of Drugs Regulations 1977

A completed and signed copy of this form must be submitted for each application for Ministerial approval to prescribe a pharmaceutical grade cannabis-based product without consent for distribution in New Zealand for a specified patient.

IMPORTANT INFORMATION FOR APPLICANTS
Applications to prescribe pharmaceutical grade cannabis-based products without consent for distribution in New Zealand are considered on a case by case basis. Please review the guidelines used for assessing applications listed on the Medicines Control section of the Ministry of Health website.

1. PRODUCT

Name of the product:

Do you have a Certificate of Analysis?

- ☐ No
- ☐ Yes – please attach details

Please attach any evidence of potential benefits of the use in the product in the condition(s) to be treated and known adverse effects.

2. PATIENT INFORMED CONSENT

"I, the patient named above, am willing to use the product named in the application and I am aware that it is a pharmaceutical grade cannabis-based product without consent for distribution in New Zealand. I have been fully informed of the potential dangers associated with its use. I am aware that if the product is abused or diverted then this application and approval is no longer valid and that future applications will be declined."

Signature of above named patient *Date*

3. APPLICANT DETAILS

NOTE: APPLICANT ELIGIBILTY AND POTENTIAL EXCLUSION CRITERIA

The application must be completed by a specialist who is managing the condition that the product is to treat. The specialist must be registered with the New Zealand Medical Council as being competent in the scope of practice appropriate to the management of the condition to be treated, for example oncologists, neurologists, anaesthetists and palliative care specialists.

Health professionals with a documented history of abuse or diversion of controlled drugs, or who have had their rights to prescribe controlled drugs limited under the Misuse of Drugs Act 1975 may be ineligible to prescribe. The applicant should not have any previous complaints against them for drug or alcohol abuse, and Medicines Control (Ministry of Health) should have no outstanding investigations or concerns about their prescribing pattern of Drugs of Misuse.

4. Alternatives to Sativex

‘In practical terms the changes mean CBD would be able to be prescribed by a doctor to their patient and supplied in a manner similar to other prescription medicine.’

Peter Dunne, Associate Minister of Health, 2/6/17.

5. Compassionate Cannabis

- Medical Cannabis Awareness NZ, http://mcawarenessnz.org/
- Patients could go to

Auckland Patients Group on

and write a post introducing themselves, their condition and request support.

- Several licenced NZ hemp farms may have animal remedies eg for stressed dogs.

Hikurangi Hemp, coming soon…

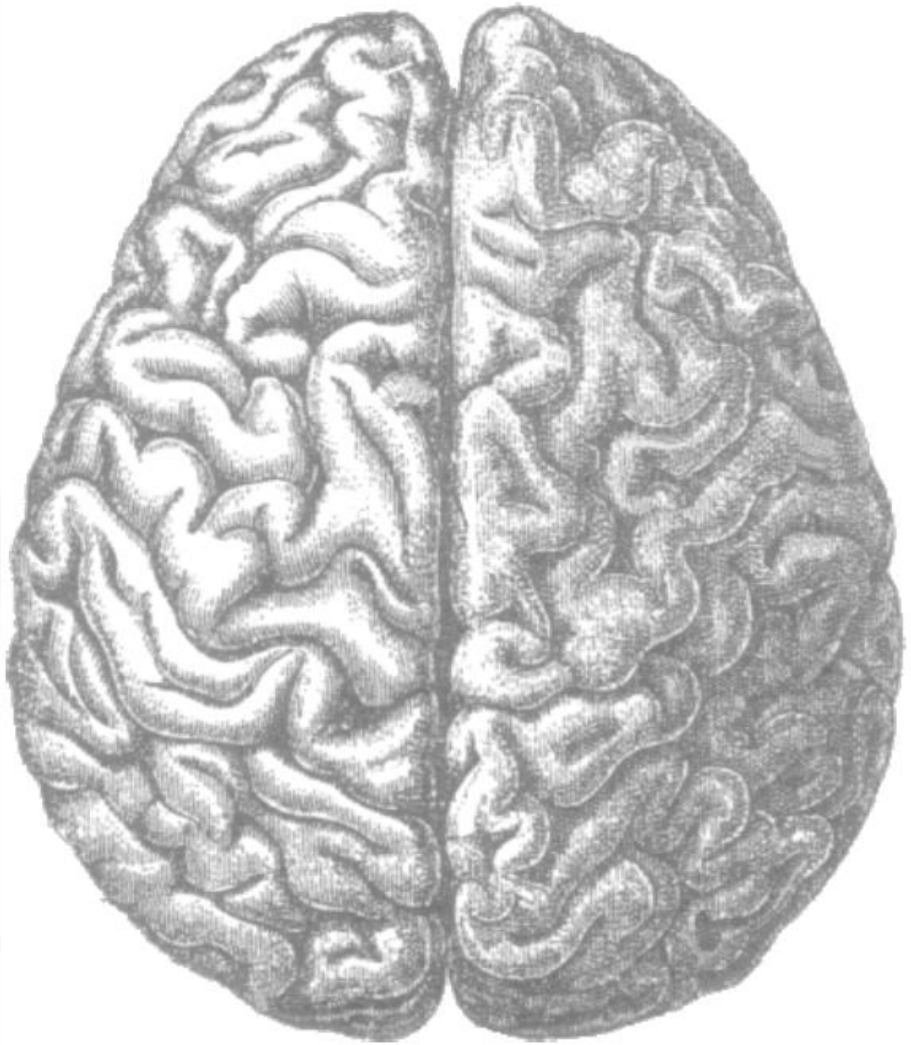
HikuHemp

10ml	10:1	CBD	THC
500mg	$59	0.5g (5%)	0.05g (0.5%)
1000mg	$119	1.0g (10%)	0.10g (1.0%)
1500mg	$189	1.5g (15%)	0.15g (1.5%)

Varieties of Cannabinoids

Endocannabinoids	Phytocannabinoids	Synthetic cannabinoids
In our brain and body	In plants	From the lab
Anandamide (AEA), 2-AG, Noladin ether etc.	*THC, CBD, CBG, CBDV, THCV, CBC, CBN, THCVA etc.*	*Nabilone, HU-210, AB-PINACA, JWH-018, Includes K2, Kronik etc*

The Endocannabinoid System (ECS)



- ✓ The ECS has evolved over 500 million years in mammals, birds & fish
  (McGeeney 2013; Grotenhermen 2006; McPartland *et al.* 2007; Elphick *et al.* 2003; McPartland *et al.* 2006).
- ✓ It is a major neuromodulatory system involved in the regulation of homeostasis.
- ✓ The ECS was originally found by researchers investigating how Cannabis interacted with human physiology
  (Herkenham et al. 1990; Pertwee 1997; Devane et al. 1992; Galiegue et al. 1995).
- ✓ The ECS is not a focus of teaching in current medical or health science curriculums.

Biological Plausibility: ECS

- There's a reason cannabis works:
  - The Endocannabinoid System
- 'Neuro-immuno homeostasis signalling system'
- Present in all vertebrates, in most animals from sea squirts to humans
- **Cannabinoid receptors are present throughout the body, embedded in cell membranes, and are believed to be more numerous than any other receptor system.**

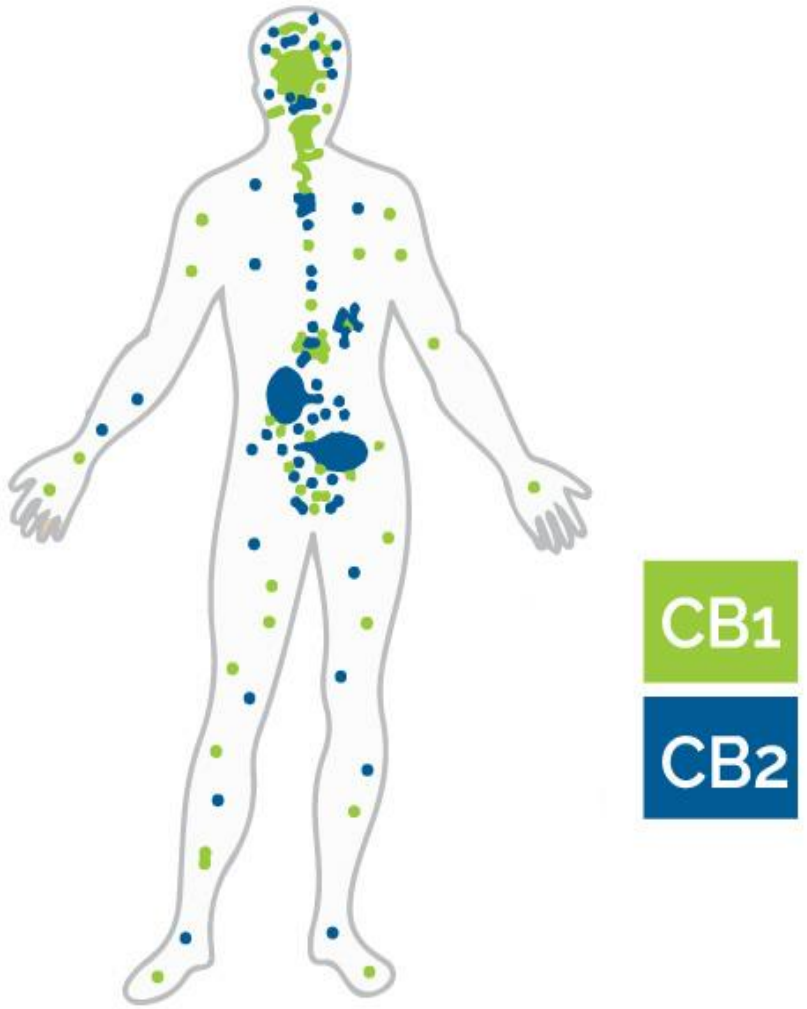
Viola Brugnatelli - Neuroscientist

Hemp Expo Sydney May 2017 & https://naturegoingsmart.com/understanding-endocannabinoid-system/

Endocannabinoid System - ECS

Homeostasis

- CB1 receptors:
  - Brain: cortex, basal ganglia, hippocampus, cerebellum
  - Modulate: memory, mood, executive function, cognition, analgesia, movement
  - GI: appetite, lipolysis
  - Respiratory
- CB2 receptors
  - Immune system: regulate inflammation, neuropathic pain
- CB3 & other receptors under investigation



THE ENDOCANNABINOID SYSTEM GUARDS LIFE'S MOST CRITICAL FUNCTIONS

CELL CYCLE

Repair / Pro-apoptotic

METABOLISM

Sleeping / eating

CANNABINOIDS PROMOTE BALANCE

IMMUNE SYSTEM

Anti-inflammatory

BRAIN ACTIVITY

Neuromodulators / analgesia

Slide by Viola Brugnatelli

In each tissue, the cannabinoid system performs different tasks, but the goal is always the same: homeostasis.

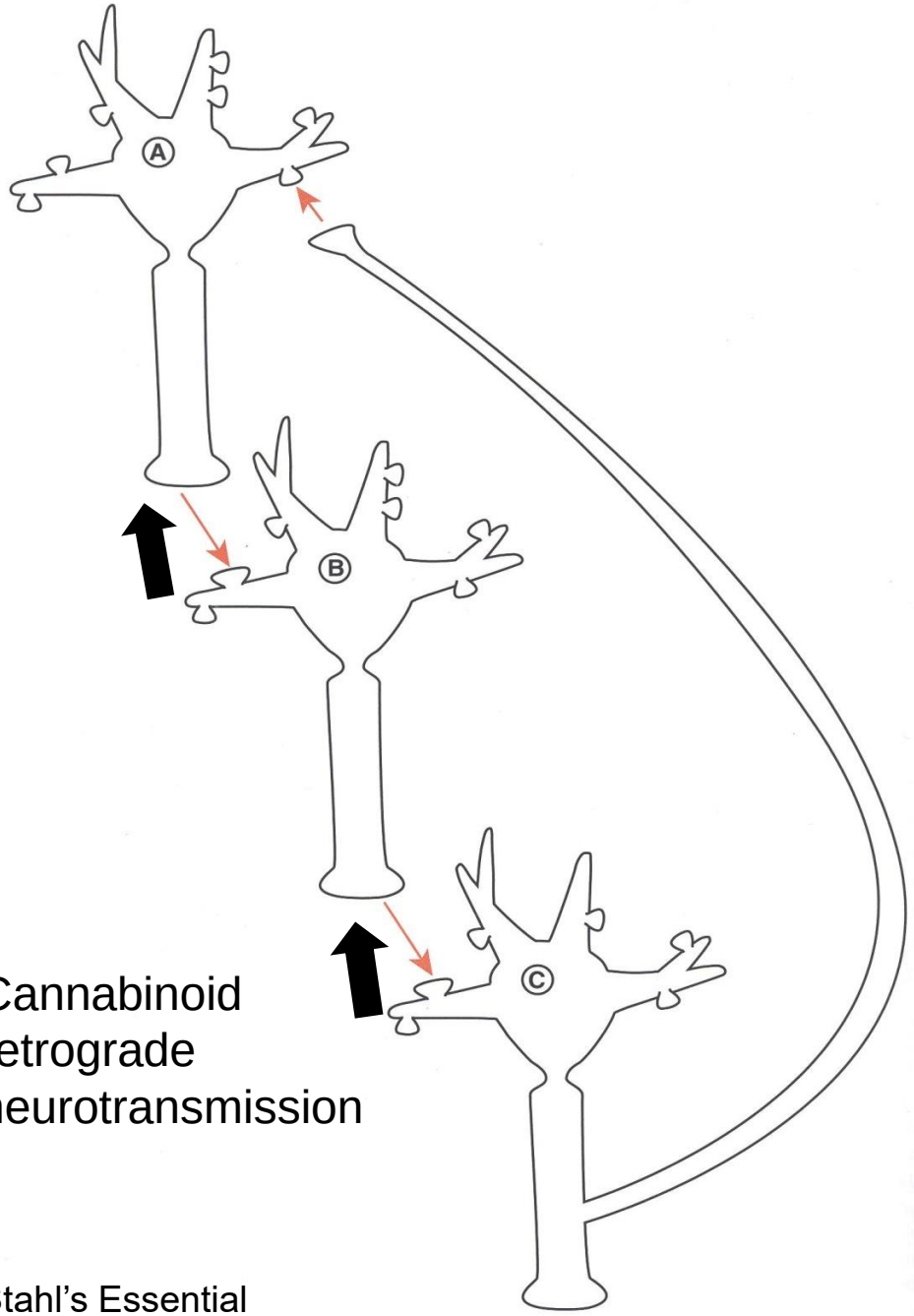
At the site of an injury, for example, cannabinoids can be found

- **decreasing the release of activators and sensitizers from the injured tissue**
- **stabilizing the nerve cell to prevent excessive firing**
- **calming nearby immune cells to prevent release of pro-inflammatory substances**

Cannabinoid receptors are present throughout the body, embedded in cell membranes, and are believed to be more numerous than any other receptor system.

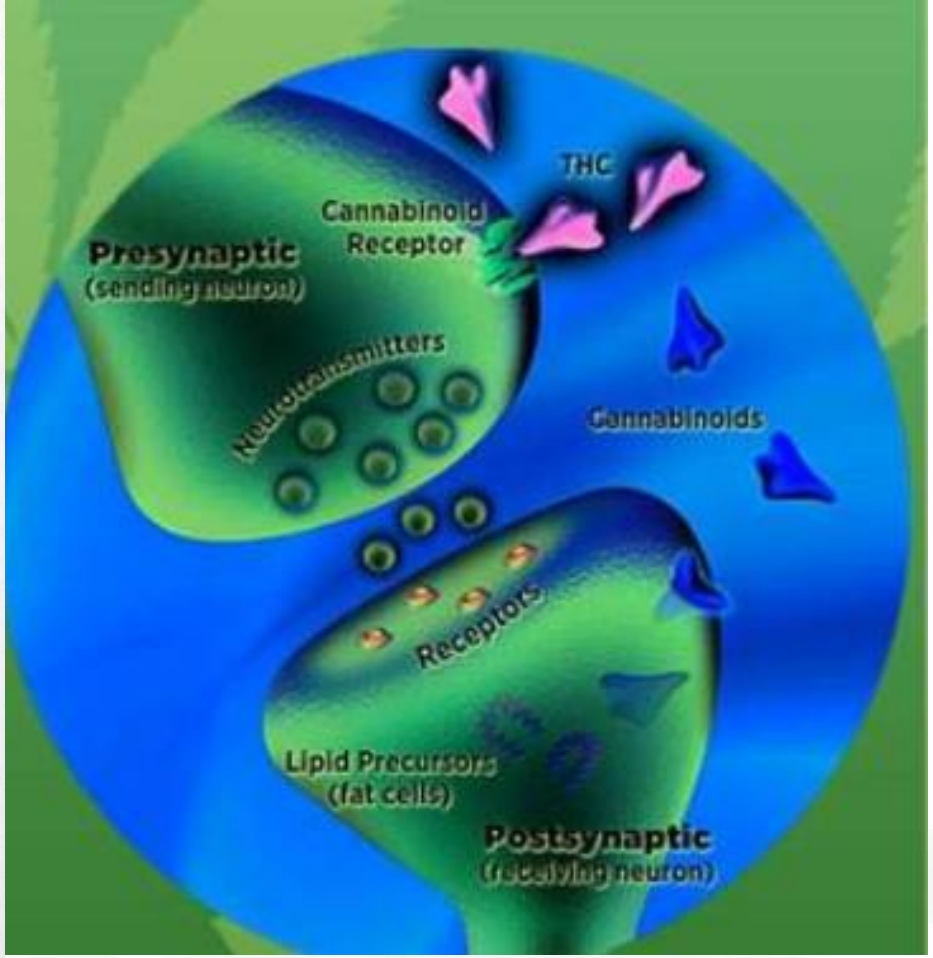
Endocannabinoids are synthesised on-demand from cell membrane arachidonic acid derivatives, have a local effect and short half-life before being degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)

Modified from https://naturegoingsmart.com/understanding-endocannabinoid-system/ by Viola Brugnatelli.



Cannabinoid retrograde neurotransmission

Stahl's Essential Psychopharmacology, 2008, p56



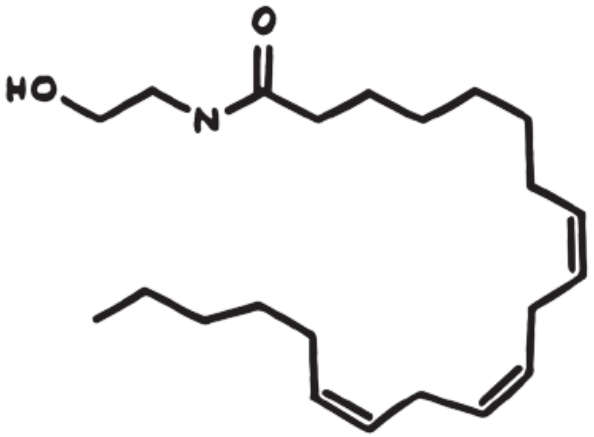
Viola Brugnatelli, neuroscientist, https://naturegoingsmart.com/understanding-endocannabinoid-system/ 2017

Cannabinoids regulate neurotransmission

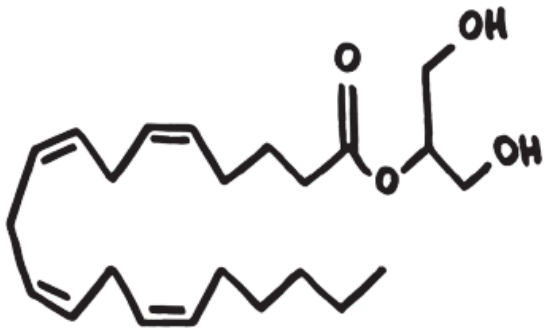
- Pain
- Epilepsy
- Anxiety, PTSD

The Endocannabinoid System (ECS)

2. Endogenous ligands

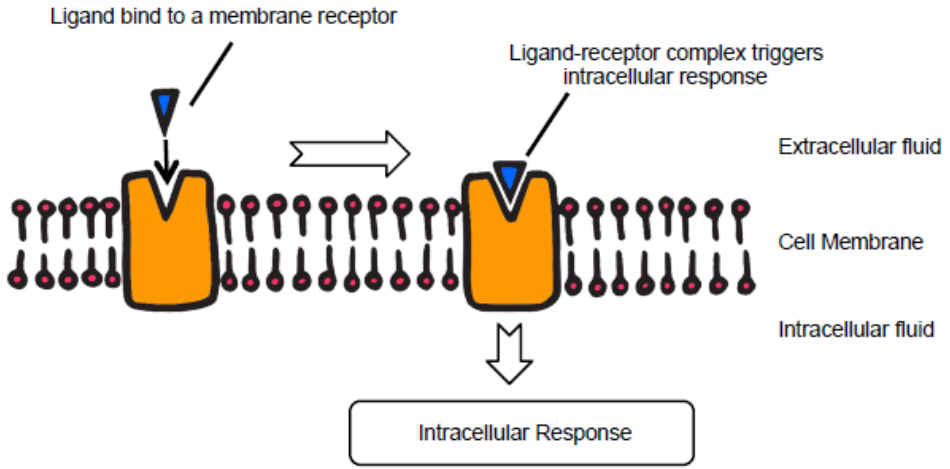


Anandamide
(N-arachidonoylethanolamine).

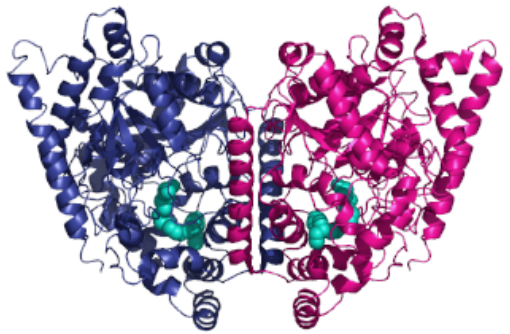


2-AG (2-arachidonoyl glycerol).

1. Cannabinoid Receptors *



3. Enzymes

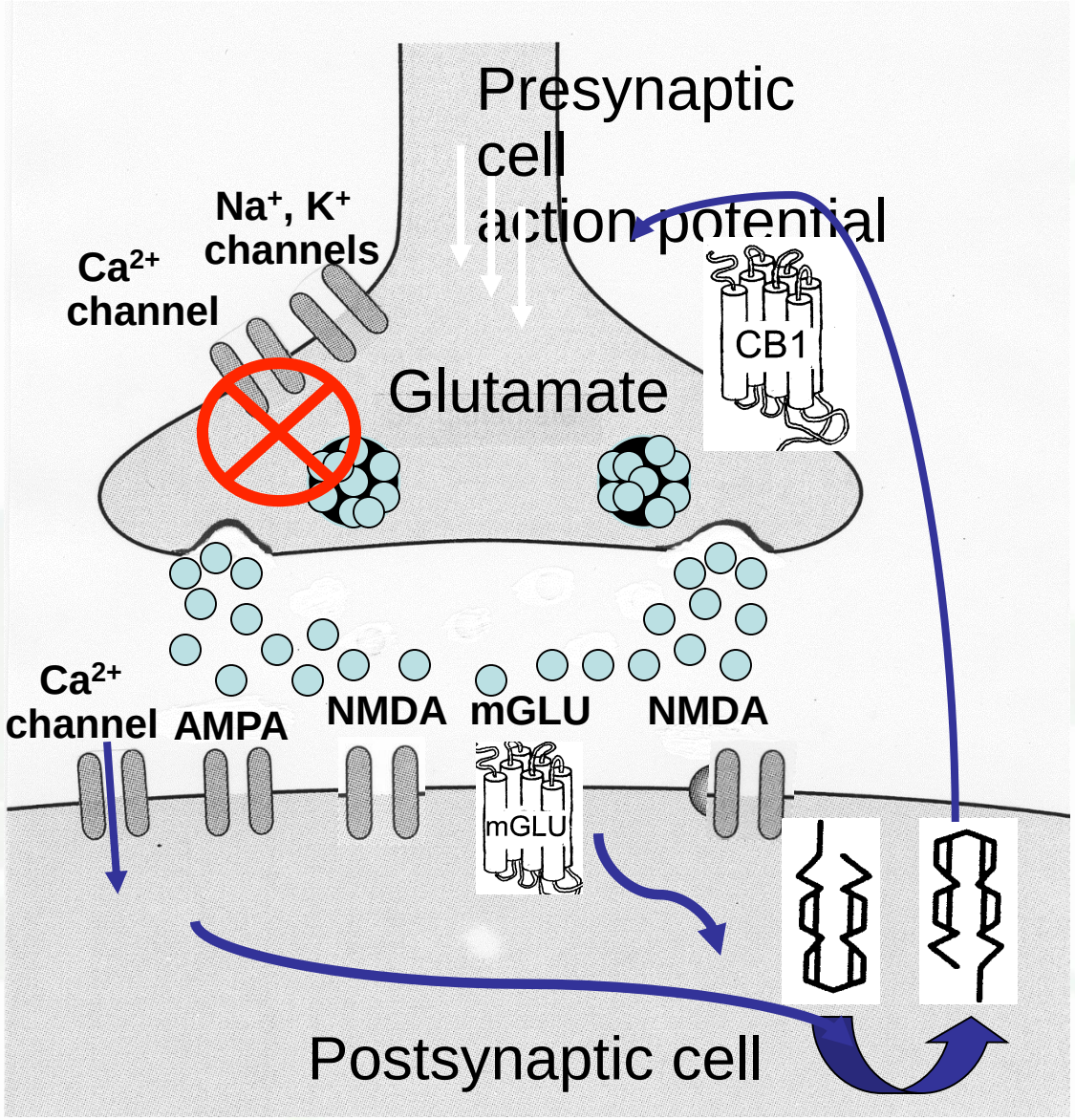


Fatty Acid Amide Hydrolase (FAAH)

* for educational purposes only. Not an accurate reflection of cannabinoid receptor activity.

Depolarization-Induced Suppression of Excitation

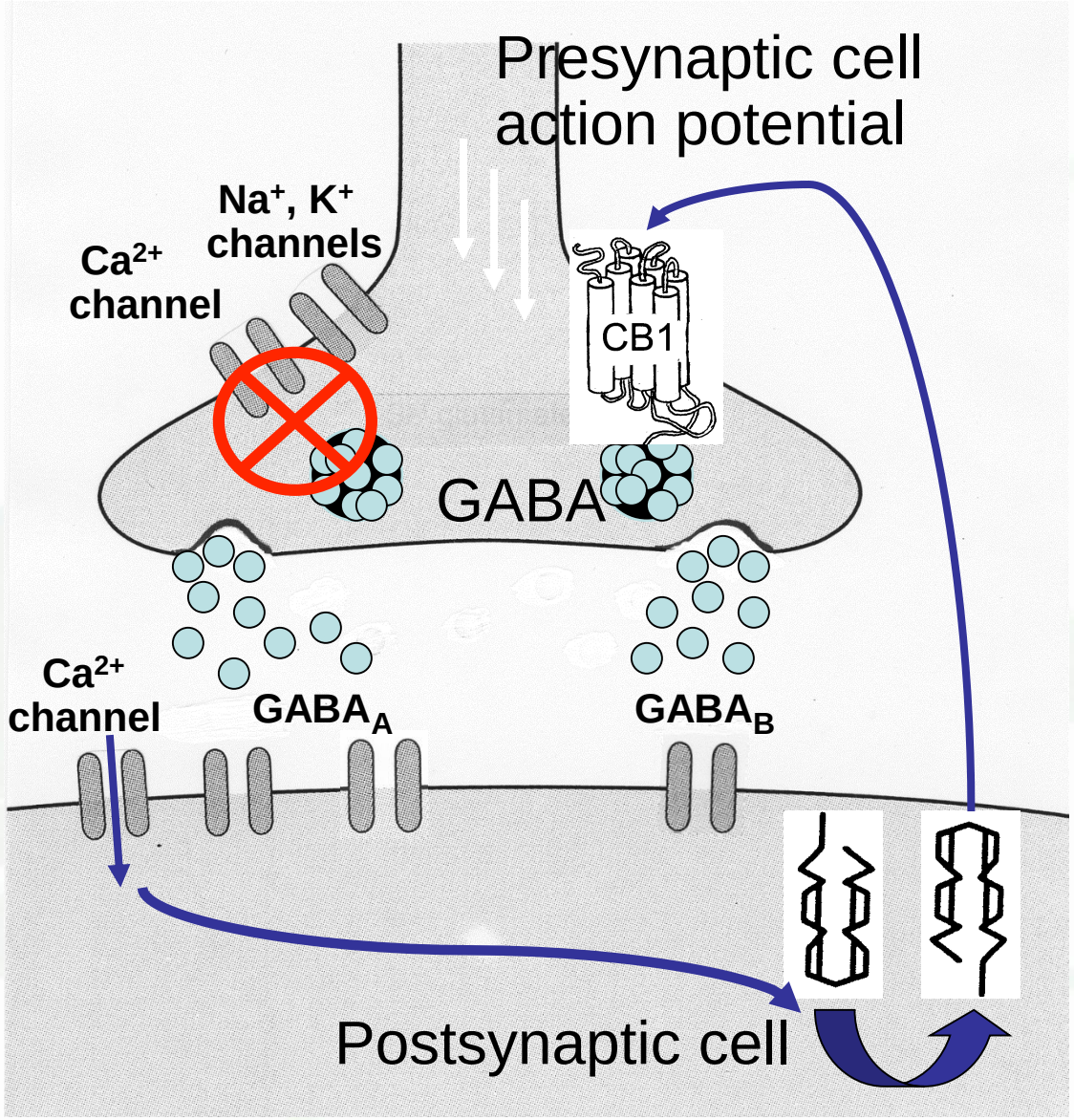
- Ca^{2+} influx into post-synaptic cell stimulates the synthesis and release of 2-AG.
- 2-AG diffuses retrograde to presynaptic CB1, which closes pre-synaptic Ca^{2+} channels and stops vesicle release.



(Wilson & Nicholl, 2002)

Depolarization-Induced Suppression of *Inhibition*

- Ca^{2+} influx into post-synaptic cell stimulates the synthesis and release of 2-AG.
- 2-AG diffuses retrograde to presynaptic CB1, which closes pre-synaptic Ca^{2+} channels and stops vesicle release



(Wilson & Nicholl, 2002)

Cannabinoids play immunomodulatory role

Abundant evidence indicates that cannabinoids modulate immune responses. Activation effectively down-regulates immune activity without compromising efficacy of the immune system.

Δ⁹-THC attenuates allogenic host-versus-graft response indicating possible role in transplant rejection.

Nagarkatti et al 2015
In a Simian monkey study chronic Δ-9-THC administration prior to and during simian immunodeficiency virus (SIV) infection ameliorates disease progression, attenuates viral load and tissue inflammation, significantly reducing morbidity and mortality of SIV-infected macaques. Winsauer et al, 2011

Physiology of the ECS: Neurological

- ✓ Elevated anandamide levels have been observed in both normal and abnormal ECS function.
- ✓ Increased anandamide plasma levels have been observed during and after moderate intensity aerobic workouts in healthy individuals (Sparling *et al.* 2003; Raichlen *et al.* 2012)
- ✓ Markedly increased levels of anandamide has been found in both plasma and CSF of schizophrenic patients in contrast to healthy controls (Desfosses *et al.* 2010; De Marchi *et al.* 2003)
- ✓ The CNR1 gene may be a susceptibility locus for schizophrenia (Cao *et al.* 1997)
- ✓ Susceptibility for schizophrenia may be increased by a genetically predetermined decrease in CB_2 receptor functioning. (Desfosses *et al.* 2010; Ishiguru *et al.* 2010)

Physiology of the ECS: Cardiovascular

- ✓ CB_2 receptors appear to be protective within the CVS
- ✓ Activation of CB_2 decreases pro-inflammatory and fibrotic responses and initiates protective mechanisms in cardiac myocytes (Steffens & Pacher 2012)
- ✓ CB_2 activation reduces immune cell chemotaxis, cellular activation and inflammatory cell adhesion (Steffens & Pacher 2012)
- ✓ These actions appear to be the reason for the protective effects shown in preclinical models of MI, restenosis, stroke and atherosclerosis
- ✓ CB_1 antagonists and CB_2 agonists are of particular clinical interest pharmacologically for specific CVS disorders (Maccarrone et al. 2015)

Neuro Endocrinol Lett. 2014;35(3):198-201.

Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

Smith SC, Wagner MS.

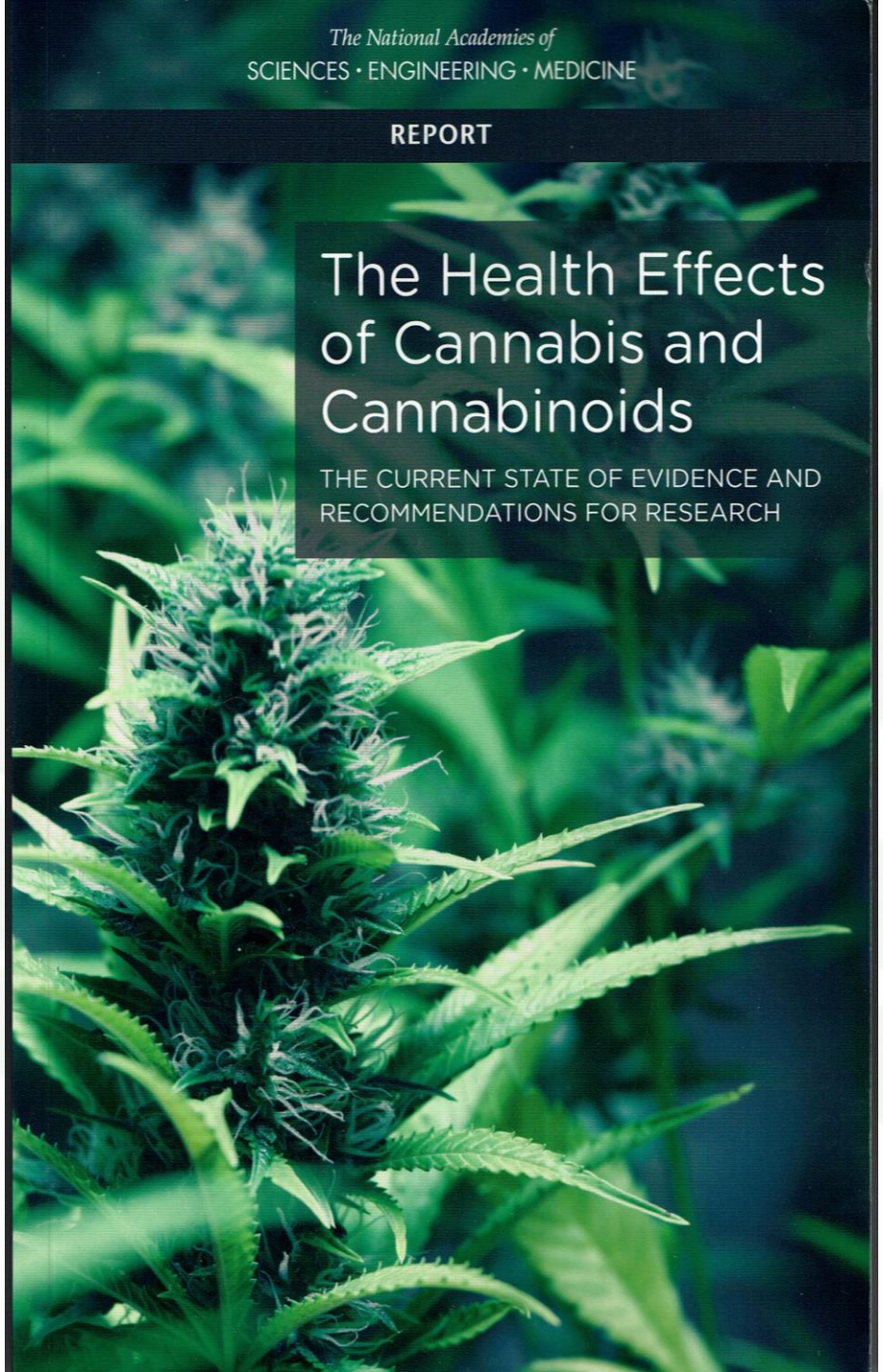
Abstract

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.

RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestional mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.

CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.


The National Academies of
SCIENCES • ENGINEERING • MEDICINE
REPORT
The Health Effects of Cannabis and Cannabinoids
THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

Evidence of Benefit

- 2017 National Academies of Science, Engineering, Medicine, USA reviewed 10,700 clinical studies
- Few high quality RCTs available:
  - Prohibition restricts supply and standardisation of cannabis
  - Cannabis plant has hundreds of compounds to study separately and individually, different ratios
  - Plants cant be patented, reduces funding sources
- EBM vs Personalised Medicine: GPs know RCTs are a guide but not real-world, we personalise Rx
- Neuroscientists have huge research data-base
- Patients' experience of illicit cannabis useful guide.

Systematic review Cannabinoids

Whiting et al JAMA June 2015

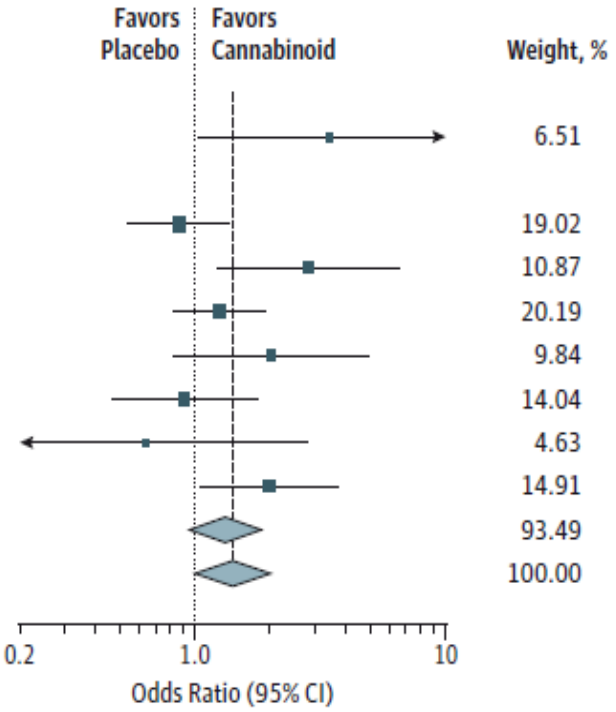
Condition	# studies	Strength of evidence	Conclusion
Nausea & vomiting	3 RCTs	Low	THC or THC/CBD > placebo
Weight gain in HIV/AIDS	1 RCT	Low	THC > placebo
Spasticity in MS / paraplegia	14 RCTs	Moderate	THC/CBD > placebo
Depression	3 RCTs	Low	Placebo > THC/CBD
Anxiety	1 RCT	Low	CBD>placebo
Sleep	12 RCTs	Low	THC/CBD, THC > Placebo
Psychosis	1 RCT	Low	CBD = amisulpiride
Tourette Syndrome	1 RCT	Low	THC > placebo
Glaucoma	1 RCT	Low	THC=CBD=placebo
Epilepsy	Not completed	N/A	CBD

Cannabinoids in chronic pain

Systematic review: Whiting et al JAMA June 2015

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)



Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Compared to other medicines we use to treat pain

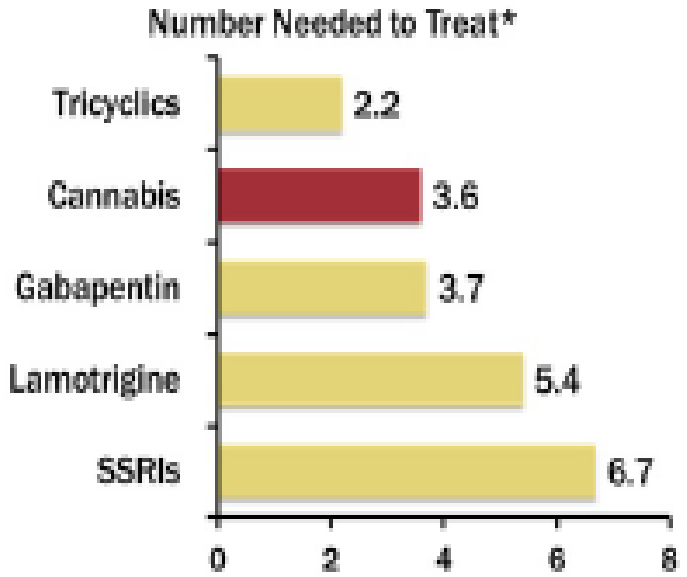


Figure 1. Common analgesics for neuropathic pain.
*to achieve a 30% reduction in pain.
Number needed to treat (NNT) = 1/(E-P), where E is the proportion improved in experimental condition and P is the proportion improved on placebo. Example: If 60% "improve" (according to a given definition) in the experimental condition, while 30% "improve" in the placebo condition, then NNT = 1/(.6-.3) = 3.3. Data adapted from Abrams et al. [3] and Ellis et al. [4].

Grant I, AMA Journal Ethics. 2013

Targeting cannabinoids for people with CNCP

- Pain, substance use, mood and sleep disorders often co-occur, and individually difficult to address
- Childhood trauma is a common link

- Role of cannabinoids for this population?
  - Cannabinoids target the ‘distress’ of pain > pain ‘severity’
  - Cannabinoids involved with mood, sleep, substance use
  - Safer profile than many other medicines used by pain patients

- Could cannabinoids be a useful strategy in addressing ‘high risk’ medication in pain patients - or will they contribute to the problem?
  - All CB RCTs for pain to date have excluded ‘addiction comorbidities’

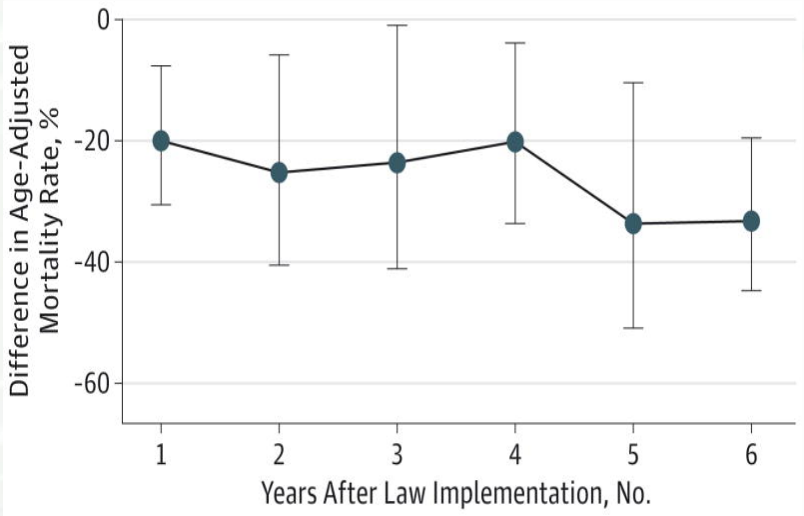
Medical cannabis & opioid related deaths

Bachhuber et al 2014. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Int Med 174:1668-73.

- "Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to …"

Review of opioid-sparing role of cannabinoids – animal and clinical studies: suggestive but not conclusive

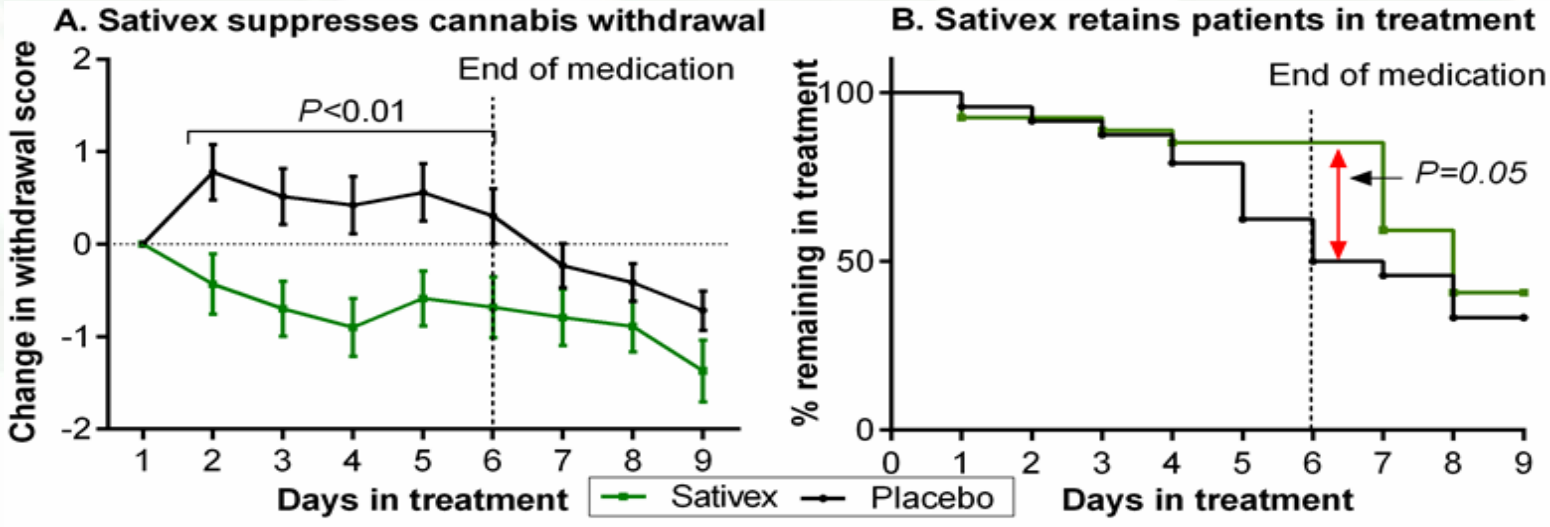
(Nielsen et al Neuropsychopharmacology accepted)



CBs for cannabis withdrawal

- Nabiximols (Sativex) effective in treating cannabis withdrawal

(Allsop *JAMA Psychiatry* 2015)



- Similar positive findings with synthetic THC (dronabinol, nabilone)
- BUT … withdrawal alone rarely results in better long term outcomes …

Cannabinoid agonist substitution treatment

- **Nabiximols vs placebo RCT** underway in NSW

  (49% THC, 49% CBD, 1% other CBs)

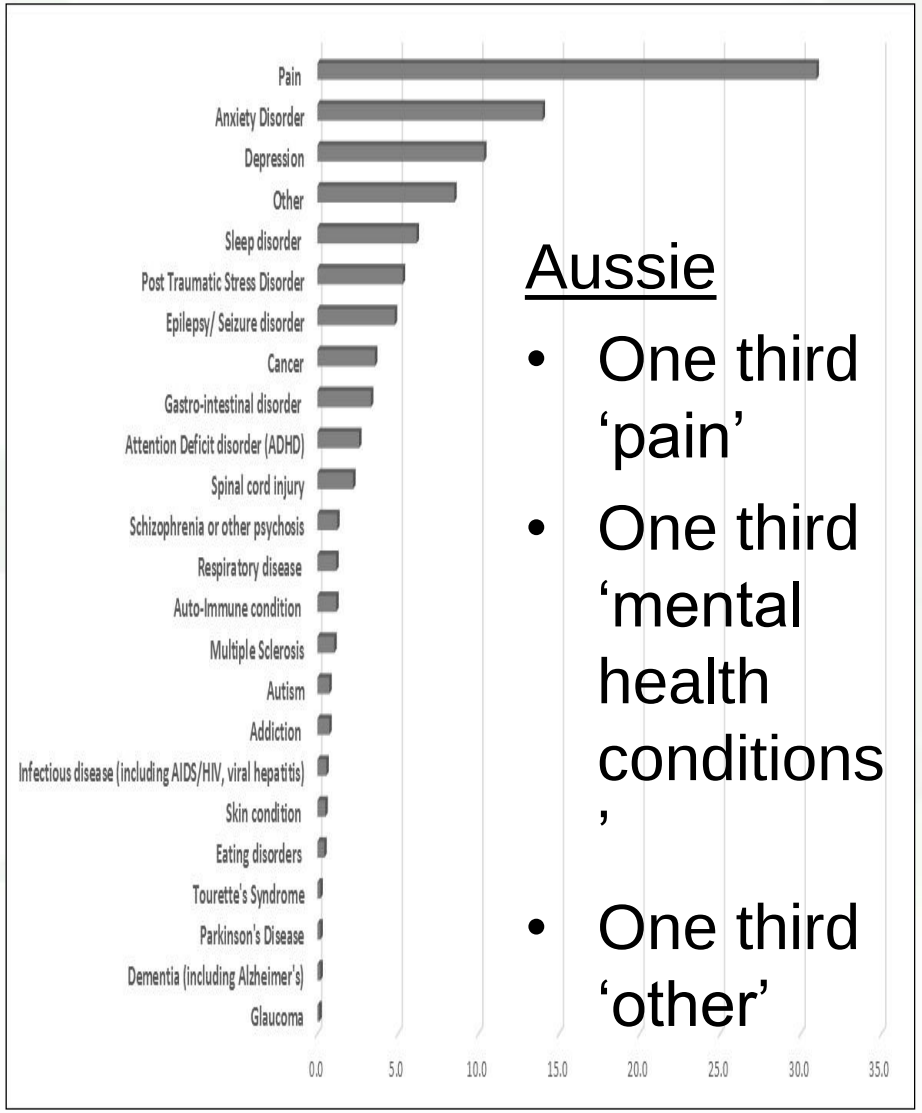
  - University Sydney, NHMRC funded
  - SESLHD, WSLHD, HNELHD

- Target n=142, ~100 enrolled thus far …
- Interventions:
  - Weekly review & medication supply
  - Nabiximols dose: up to 32 sprays / day (~80mg THC / CBD)
  - Manualised CBT both groups
- 1° Outcomes: cannabis use, safety, cost effectiveness

Cannabinoids for other addictions: ‘exit drug’

- Alcohol
  - CBD (and other CBs) for alcohol withdrawal, relapse prevention, cravings
- Opioids
  - CBs (THC) for opioid withdrawal
  - Opioid sparing in pain management
- Amphetamines
  - Promising animal research re: CBD

CAMS-16:
Reason for use (n=1624)



Aussie

- One third ‘pain’
- One third ‘mental health conditions’
- One third ‘other’

NZ Health Survey
2012/13 (n=13,009)

NZ

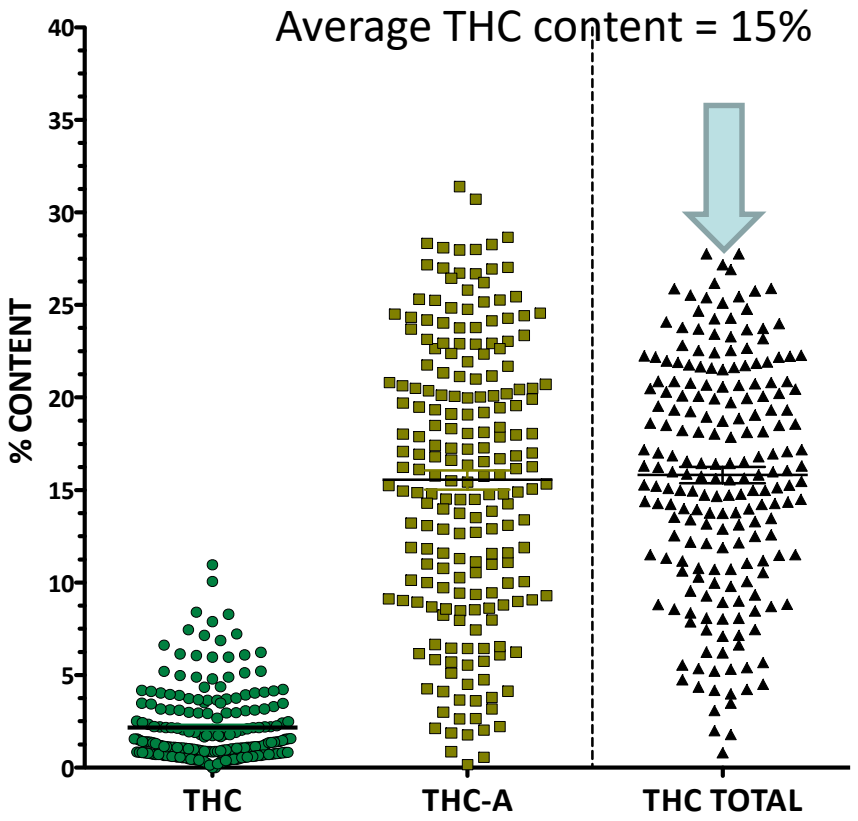
- 11% used cannabis in past year
- 5% used cannabis medicinally
- Of those
  - 40% for pain
  - 27% for anxiety
  - 26% for depression
  - 11% for nausea

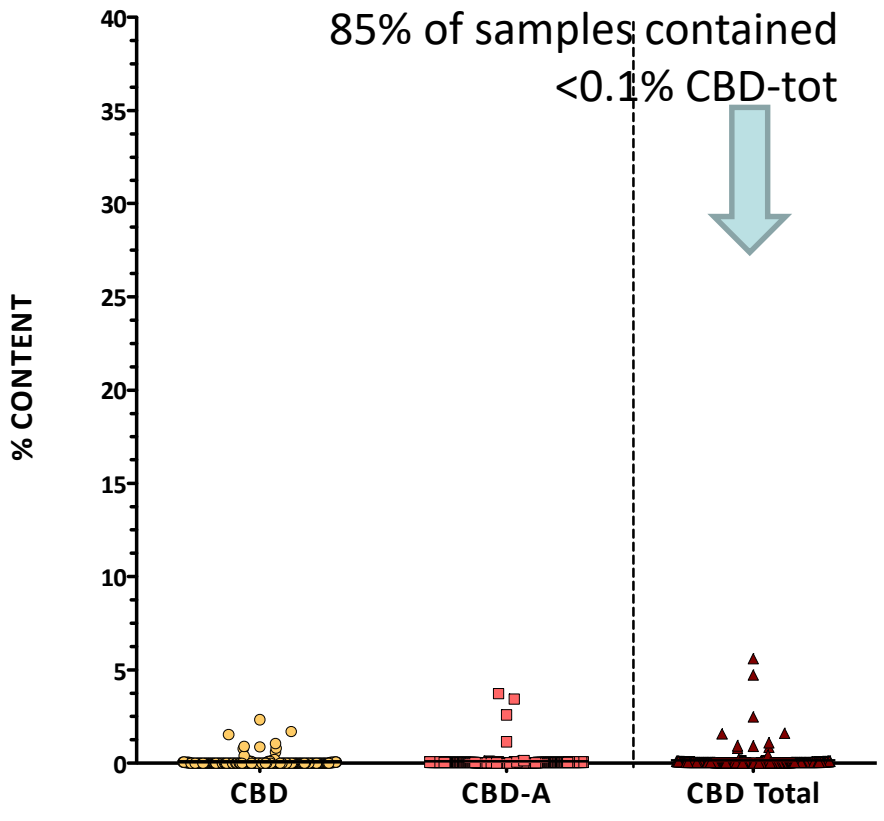
CAMS:16 (preliminary data only)

- Male 68%, Mean age: 38; 62% employed / student
- Using CAM for 10 yrs (mean)
  - ~ half using cannabis for other reasons before ‘medical’ use
  - ~ half not using cannabis (2/3^{rds} any prior use, 1/3rd never used)
- Median levels of use: 20/28 days; 3gm/day, $72 / week
- Source:
  - Recreational dealer: 42%; Friends/family 33%; grow own 13%; medical cannabis supplier 10%
- Route:
  - Smoked 63% (“Bong”/ pipe 43%; “joint” 19%; “dabbing” 1%)
  - Vaporiser: 14%
  - Oral: 21%

Potency of NSW police seized cannabis: high THC and low CBD

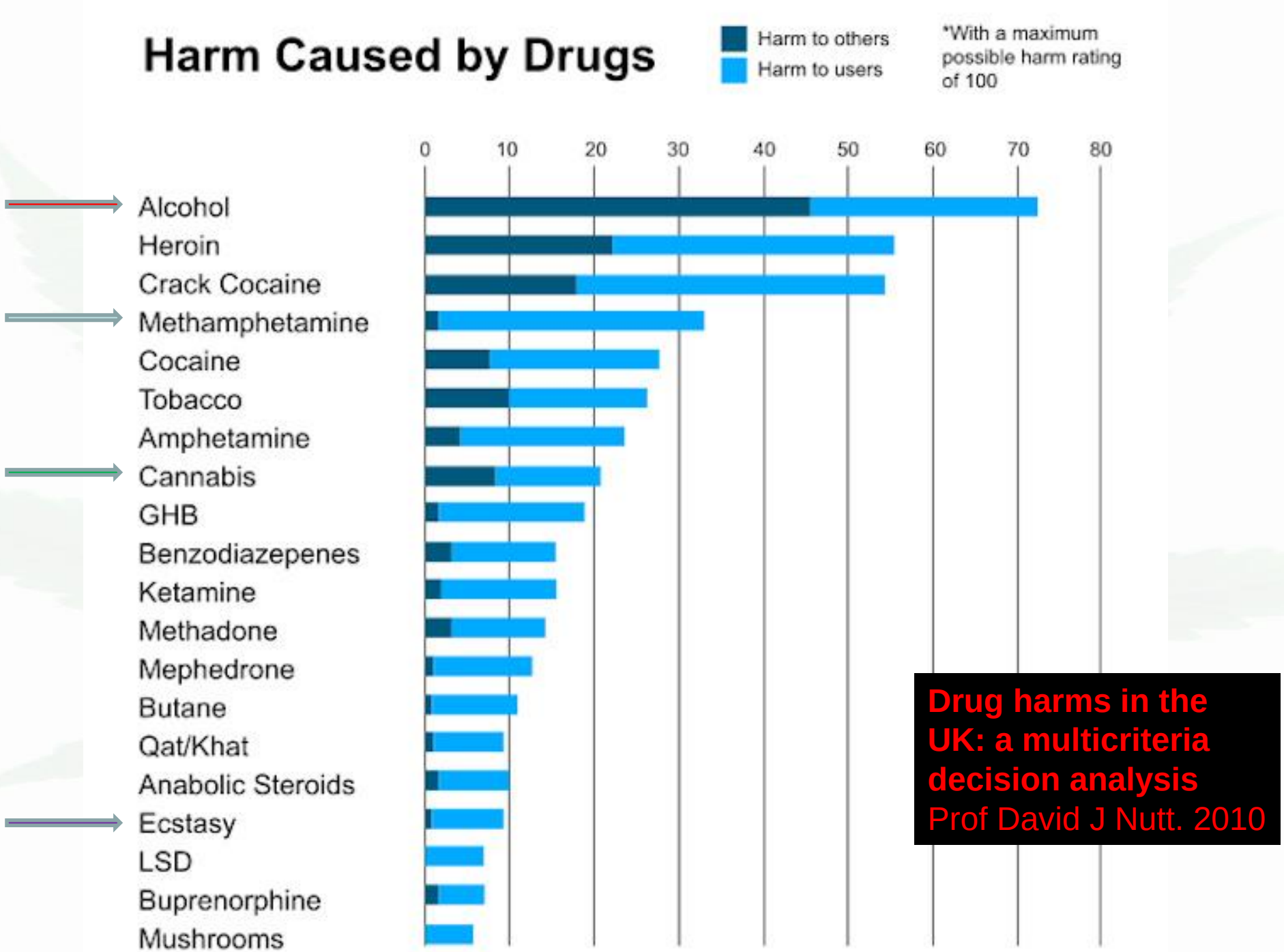
Swift et al PLoS One 2013





THC: psychoactive, sedation, analgesia, antiemesis, antispasmodic

CBD: not psychoactive, anxiolytic, antipsychotic, anticonvulsant, protective against memory loss


Harm Caused by Drugs
Harm to others
Harm to users
*With a maximum possible harm rating of 100
0
10
20
30
40
50
60
70
80
Alcohol
Heroin
Crack Cocaine
Methamphetamine
Cocaine
Tobacco
Amphetamine
Cannabis
GHB
Benzodiazepenes
Ketamine
Methadone
Mephedrone
Butane
Qat/Khat
Anabolic Steroids
Ecstasy
LSD
Buprenorphine
Mushrooms
Drug harms in the UK: a multicriteria decision analysis
Prof David J Nutt. 2010

Potential harms / AEs of cannabis

(high THC)

- Cognition & performance
  - Sedation and mild cognitive impairments in attention, memory, learning, psychomotor functions. Most effects reversible with abstinence, although may persist in heavy adolescent users
  - Intoxication related injuries (e.g. driving, falls)
- Mental health
  - Increased risk of psychoses OR = 2.09 (95%CI 1.54 to 2.84) & linked to genetic predisposition
  - Adolescent cannabis use associated with increased anxiety
- Dependence: estimated at 1 to 10% illicit users
- Physical effects
  - Hypotension, tachycardia, dizziness, dry mouth, respiratory
- Drug-drug interactions: CBD (THC) is CYP_{450} inhibitor

Sativex Adverse Effects

See New Zealand Data Sheet for full list

- Very common ≥ 10%: dizziness & fatigue during titration

- Common: 1 – 10%: appetite changes, depression, disorientation, dissociation, euphoria, asthenia, feeling drunk, malaise, blurred vision, vertigo, constipation, diarrhoea, dry mouth, mouth ulcers, nausea, vomiting

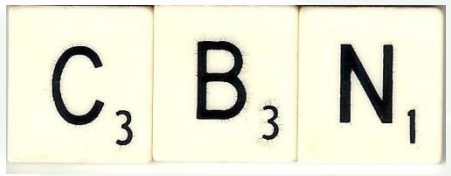
- Uncommon: 0.1 – 1%: hallucination, paranoia, suicidal thoughts, syncope, tachycardia, abdo pain etc

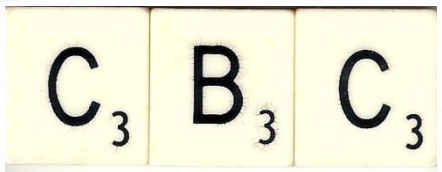
Sativex Drug-Drug Interactions (DDIs)

- Unlikely with usual doses of Sativex
- Cytochrome P450 metabolism,
- CYP3A4 inhibitors may increase THC levels
    - Ketoconazole, itraconazole, ritonavir, clarithromycin
- CYP3A4 inducers may reduce THC levels
  - Rifampicin, carbamazepine, phenytoin, St Johns Wort
- Care with sedatives, alcohol
- Anti-spasticity agents may increase risk of falls.

Key points

- ✓ Cannabis is not a panacea. Cannabis and cannabinoid based medications will not work for everyone
- ✓ The endocannabinoid system will be expressed differently in each individual, particularly when genetic polymorphisms are taken into consideration
- ✓ More research into the ECS could uncover as yet unknown causes to disease and revolutionise our understanding of human health and homeostasis





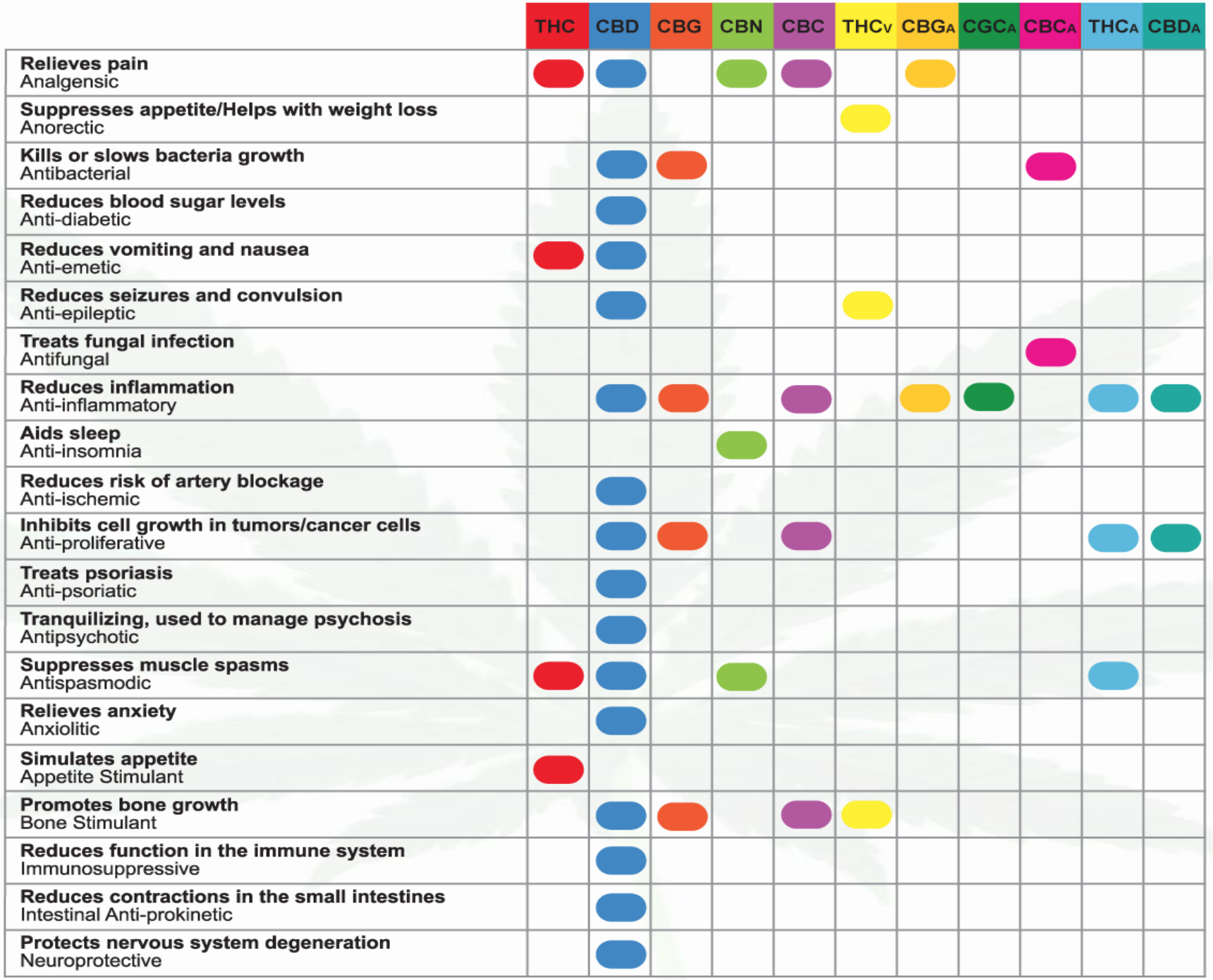
Phytocannabinoids

>100 cannabinoids in cannabis plant. Most non-psychoactive.

Each cannabinoid has its own pharmacological actions and therapeutic potential.

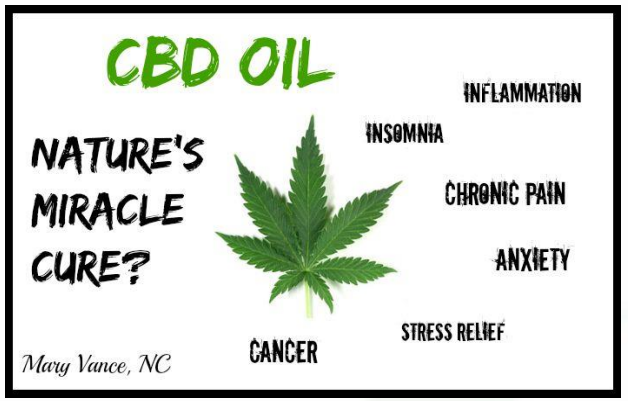
Plus … terpenes

“Entourage” effects: whole plant vs single molecules


THC
CBD
CBG
CBN
CBC
THCV
CBGA
CGCA
CBCA
THCA
CBDA
Relieves pain
Analgensic
Suppresses appetite/Helps with weight loss
Anorectic
Kills or slows bacteria growth
Antibacterial
Reduces blood sugar levels
Anti-diabetic
Reduces vomiting and nausea
Anti-emetic
Reduces seizures and convulsion
Anti-epileptic
Treats fungal infection
Antifungal
Reduces inflammation
Anti-inflammatory
Aids sleep
Anti-insomnia
Reduces risk of artery blockage
Anti-ischemic
Inhibits cell growth in tumors/cancer cells
Anti-proliferative
Treats psoriasis
Anti-psoriatic
Tranquilizing, used to manage psychosis
Antipsychotic
Suppresses muscle spasms
Antispasmodic
Relieves anxiety
Anxiolitic
Simulates appetite
Appetite Stimulant
Promotes bone growth
Bone Stimulant
Reduces function in the immune system
Immunosuppressive
Reduces contractions in the small intestines
Intestinal Anti-prokinetic
Protects nervous system degeneration
Neuroprotective

Cannabidiol (CBD)

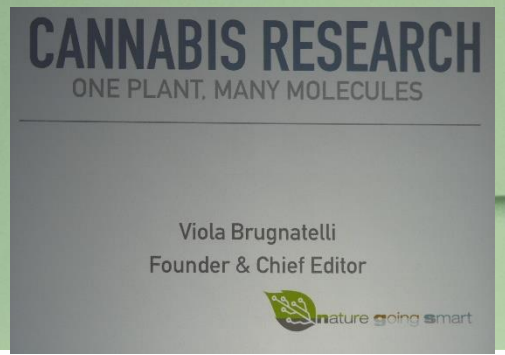
- A non-intoxicating cannabinoid
  - Anticonvulsant effects
  - Anxiolytic, antipsychotic
  - Neuroprotective: ?dementia
  - Analgesia: THC+CBD > THC or CBD alone; synergistic
- Hepatic metabolism:
  - CYP 3A4, 2D9 inhibition: ?clinically relevant
- Doses:
  - ?200-1200mg oral / day prescribed
  - 10-50mg oral / day OTC for ‘wellness’



OTHER COMPONENTS

- 120 terpenes
- 50 hydrocarbons
- 34 sugars
- 20 alkaloids
- 19 flavonoid-glycosides
- 16 phenols
- 13 ketones
- 12 aldehydes
- 11 steroids
- 7 alcohols
- 2 pigments

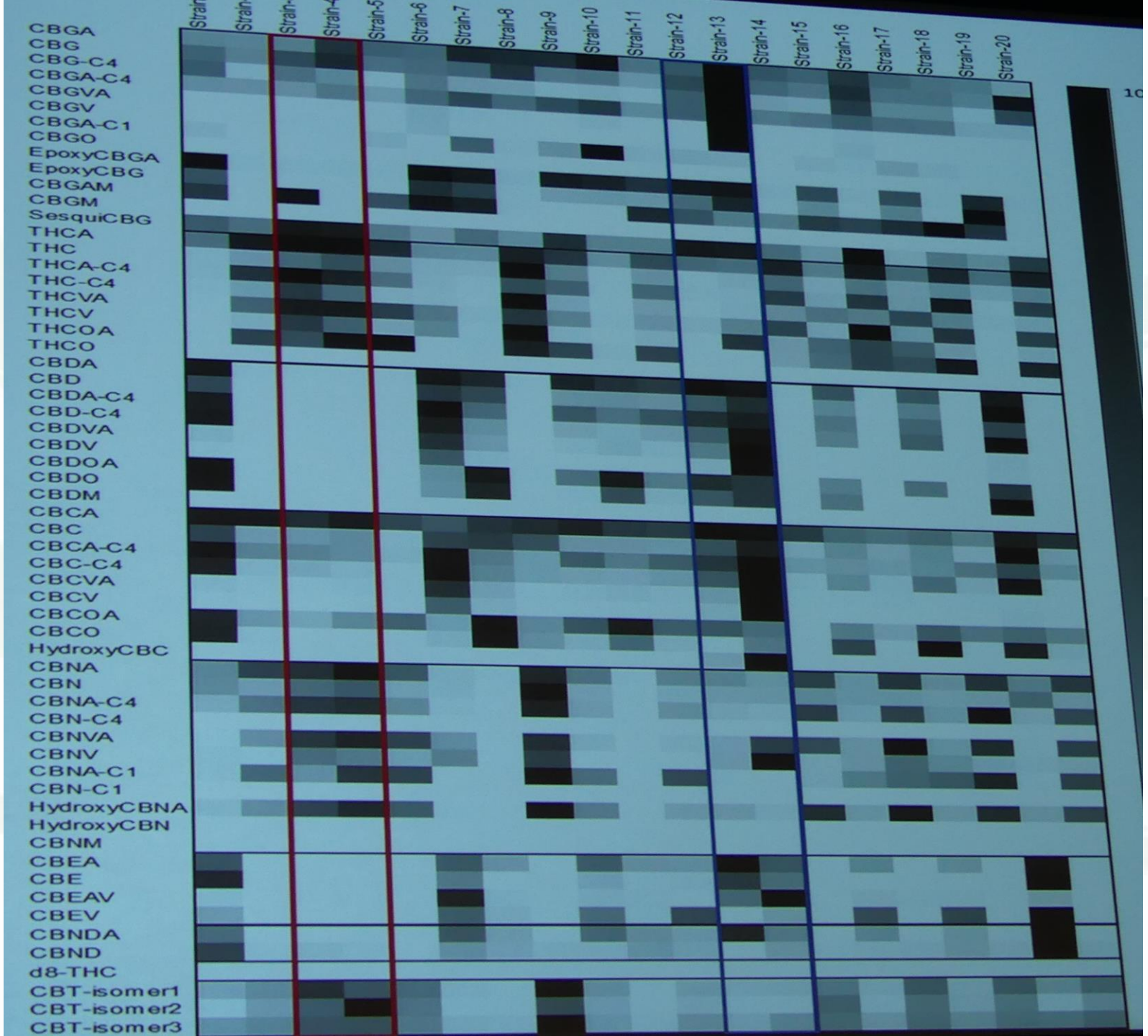
> 500



From Epilepsy Action Australia
www.epilepsy.org.au

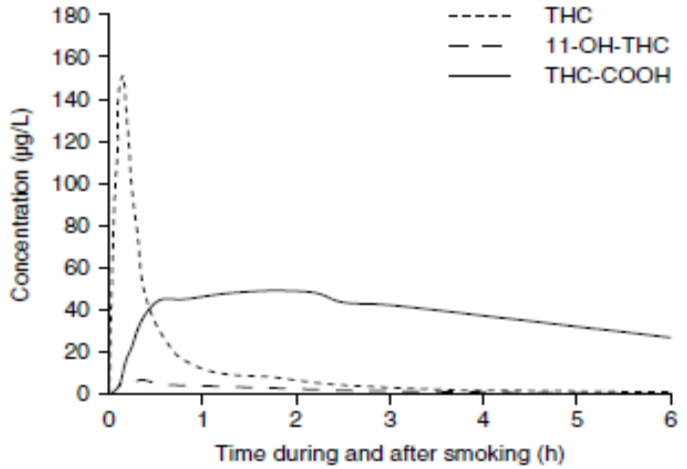
Terpenes

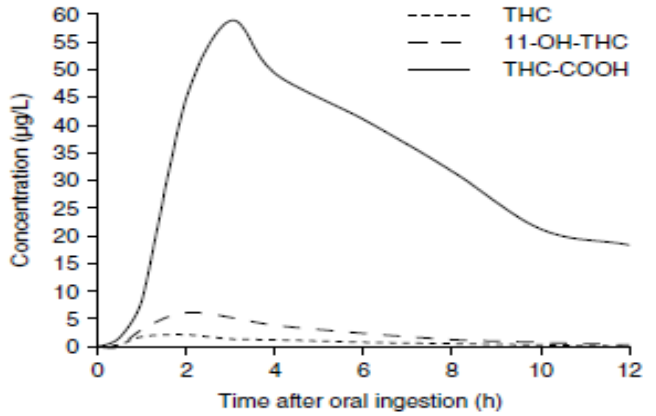
α-PINENE	Pine Needles	Anti-bacterial Anti-fungal Anti-inflammatory Bronchodilator Aids short term memory
B-CARYOPHYLLENE	Black Pepper Clove Hops	Anti-bacterial Anti-cancer Anti-fungal Anti-inflammatory Anti-septic
BORNEOL	Camphor	Analgesic Anti-insomnia Anti-septic Bronchodilator
CARYOPHYLLENE OXIDE	Eucalyptus	Anti-fungal Anti-ischemic
CINEOL	Tea tree	Anti-bacterial Anti-depressant Anti-inflammatory Anti-ischemic Bronchodilator
CITRONELLOL	Rose	Anti-cancer Anti-inflammatory Anti-insomnia Anti-spasmotic
HUMULENE	Hops	Anoretic Anti-cancer Anti-bacterial Anti-inflammatory
LIMONENE	Citrus	Anti-anxiety Anti-bacterial Anti-cancer Anti-depressant Anti-fungal
LINALOOL	Lavender	Anti-anxiety Anti-bacterial Anti-depressant Anti-insomnia
MYRCENE	Lemongrass Mango	Analgesic Anti-cancer Anti-inflammatory Anti-insomnia Anti-spasmotic
NEROLODOL	Wood Citrus rind	Anti-fungal Anti-insomnia
PHYTOL	Green tea	Anti-insomnia
TERPINOLENE	Lilac Apple	Anti-bacterial Anti-fungal Anti-insomnia Anti-septic


CBGA
CBG
CBG-C4
CBGA-C4
CBGVA
CBGV
CBGA-C1
CBGO
EpoxyCBGA
EpoxyCBG
CBGAM
CBGM
SesquiCBG
THCA
THC
THCA-C4
THC-C4
THCVA
THCV
THCOA
THCO
CBDA
CBD
CBDA-C4
CBD-C4
CBDVA
CBDV
CBDOA
CBDO
CBDM
CBCA
CBC
CBCA-C4
CBC-C4
CBCVA
CBCV
CBCOA
CBCO
HydroxyCBC
CBNA
CBN
CBNA-C4
CBN-C4
CBNVA
CBNV
CBNA-C1
CBN-C1
HydroxyCBNA
HydroxyCBN
CBNM
CBEA
CBE
CBEAV
CBEV
CBNDA
CBND
d8-THC
CBT-isomer1
CBT-isomer2
CBT-isomer3
Strain-5
Strain-6
Strain-7
Strain-8
Strain-9
Strain-10
Strain-11
Strain-12
Strain-13
Strain-14
Strain-15
Strain-16
Strain-17
Strain-18
Strain-19
Strain-20

Using Plant Cannabis

- Higher bioavailability inhaled
  - 10-35% inhaled
  - 5-15% oral (hepatic CYP 2C8/9/19)
- Peak effects:
  - Inhaled:10-90 minutes after use
  - Oral: 60- 240 minutes after use
- Vaporising: similar to ‘e-cigarettes’
  - heats cannabis at lower temperature
  - fewer ‘toxins’, higher bioavailability
  - no side stream smoke (fewer concerns re: passive smoking)
  - TGA-compliant devices: Volcano, Mighty Medic





Vaporisers: The Hemp Store

www.hempstore.co.nz

Vaporite digital desktop

Herb chamber

mouthpiece

Arizer Air handheld

Focus handheld

BEDROCAN®

Bedrocan is featuring 22% THC, with a CBD-level below 1%.

BEDROBINOL®

Its THC-level is standardised at 13.5%, with a CBD-level below 1 %.

BEDIOL®

Bediol has a balanced ratio of THC 6.3% and CBD 8%.

BEDICA®

Bedica contains 14% THC with less than 1% CBD.

BEDROLITE®

Bedrolite is a CBD-only product, with less than 1% THC and 9% CBD.

LIQUID CAPSULES

Available in Sativa, Indica, Hybrid and two varieties of CBD for easy ingestion and precise dosage.

DROPS

Available in Sativa, Indica, Hybrid and two varieties of CBD for convenient ingestion. These products also give patients the option of infusing cannabis into many foods of their choice.

VAPORIZER OIL

Available in two varieties of CBD for inhalation and ease of use via vaporization, which is an alternative to smoking.

ORAL SPRAY

Available in Sativa, Indica, Hybrid and two varieties of CBD for quick onset of relief; both convenient and fast-acting.

TOPICAL OIL

Available in Hybrid and two varieties of CBD for direct skin application and localized use.

50+ STRAINS

Tilray has sourced 50+ strains of high quality medical cannabis from British Columbia and around the world, with some of the highest concentrations of THC and CBD available on the market.

Acknowledgements

- Presenters at the United in Compassion Australian Medicinal Cannabis Course & Symposium, Melbourne June 2017
- Assoc Prof David Caldicott
- Prof Nick Lintzeris
- Dr Jeffrey Hergenrather
- Dr Viola Brugnatelli
- Justin Sinclair

~NGA MIHI NUI~

Figure 3: Distribution of THC in the body. Graph from Nahas GG. (1975) after Kreutz and Axelrod (1973)