



Medical Cannabis for Palliative Care

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Health Sciences



CancerCare
MANITOBA



Medical Cannabis and Cancer

Panacea or Just Weed?



UNCERTAINTIES PAGE

Should doctors prescribe cannabinoids?

Michael Farrell *professor and director*¹, Rachelle Buchbinder *director and professor*², Wayne Hall *professor, National Health and Medical Research Council Australia fellow, and deputy director (policy)*³

Who uses cannabis as medicine?

2% use cannabis for medical purposes (2000)

>37,000 people registered with MMAR (Mar 2013)

approx 6% cancer Dx

>98,000 people registered with MMPR (Sept 2016)

>167,000 registrants with ACMPR (Mar 2017)

>5600 kg sold to clients (Jan –Mar 2017)

No epidemiology studies done in cancer or palliative care patients

The Medicinal Use of Cannabis and Cannabinoids—An International Cross-Sectional Survey on Administration Forms

Arno Hazekamp, Ph.D.^a; Mark A. Ware, M.D.^b; Kirsten R. Muller-Vahl, M.D.^c; Donald Abrams, M.D.^d
& Franjo Grotenhermen, M.D.^e

Journal of Psychoactive Drugs, 45 (3), 199–210, 2013

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DOI: 10.1080/02791072.2013.805976

FIGURE 1

Preferred Mode of Administration for Subjects in Each of the Top 5 Symptoms

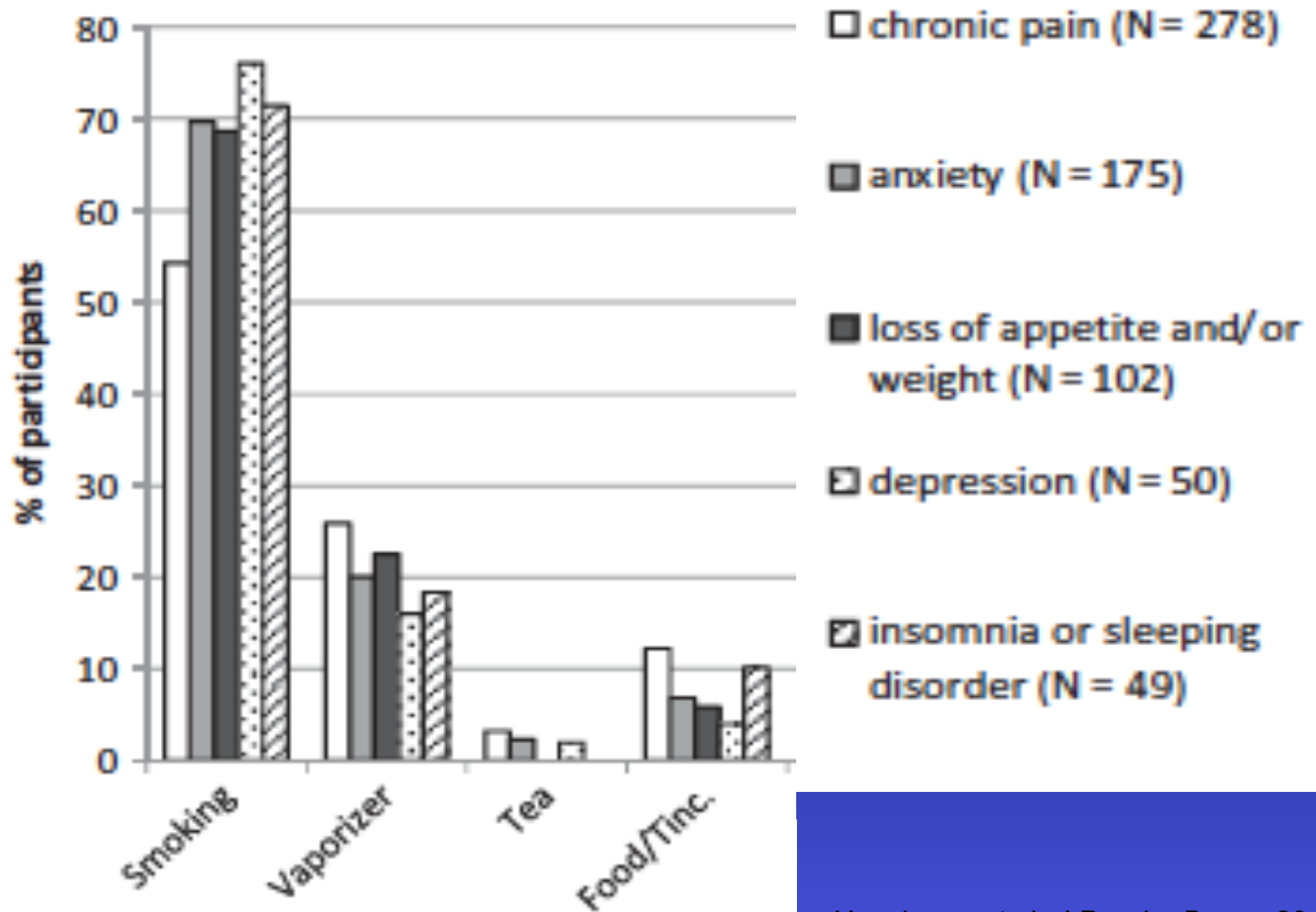


TABLE 2**Daily Dose, Daily Frequency, and Onset of Effects; Mean Values are Shown**

	<i>Smoking</i>	<i>Vaporizer</i>	<i>Tea</i>	<i>Food/Tinc</i>
<i>a) Daily use (units are indicated)</i>	3.0 <i>gram</i>	3.0 <i>gram</i>	2.4 <i>gram</i>	3.4 <i>gram</i>
<i>b) Daily frequency (times per day)</i>	6.0	5.2	1.9	1.8
<i>c) First onset of effects (minutes)</i>	7.0	6.5	28.9	45.5

Original Article

Patterns of Use of Medical Cannabis Among Israeli Cancer Patients: A Single Institution Experience

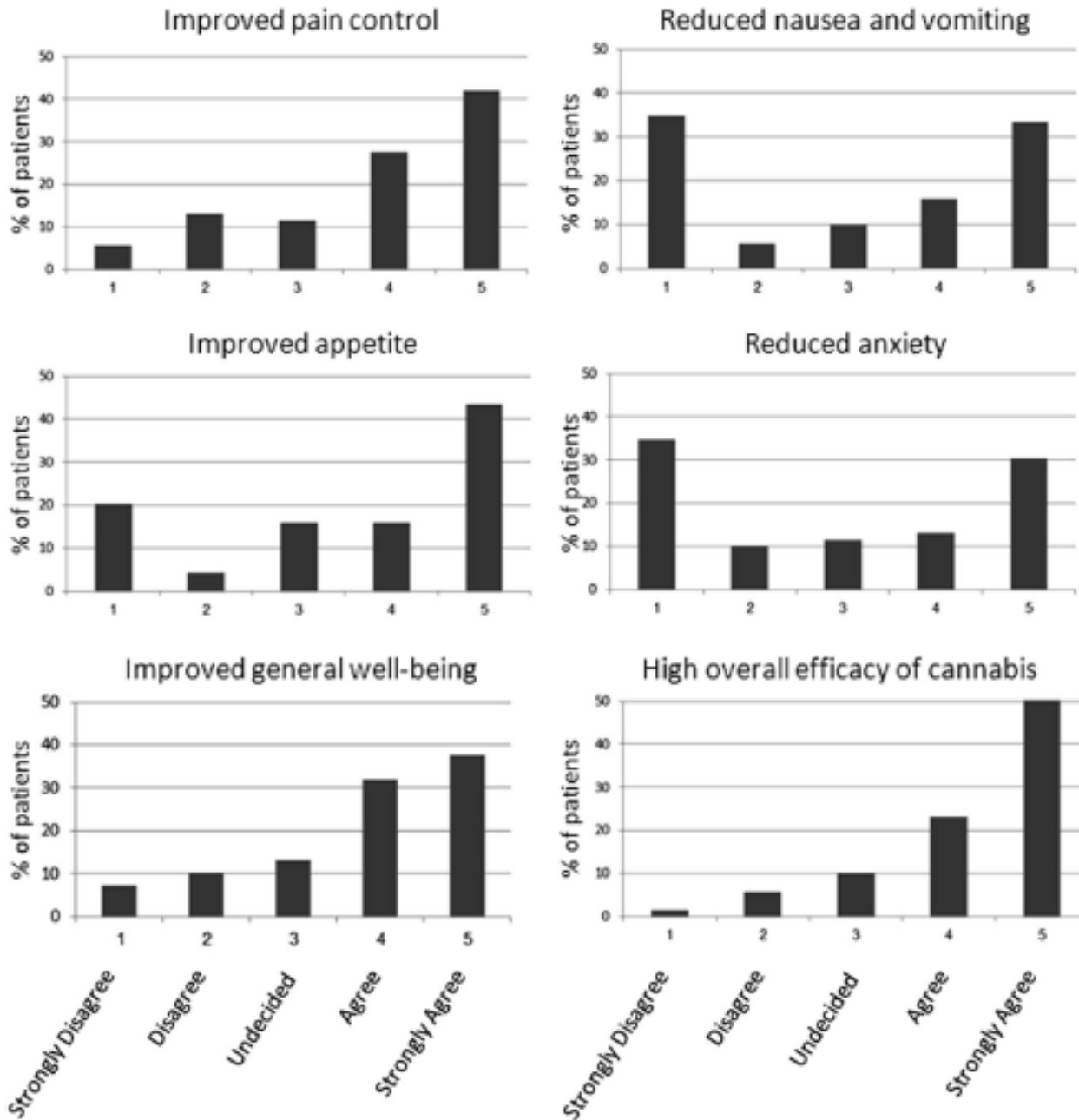
Barliz Waissengrin, MD, Damien Urban, MD, Yasmin Leshem, MD,
Meital Garty, BA, and Ido Wolf, MD

Review of 1 yr observational data, 5 oncologists
Approx 17,000 cancer pts
279 (1.7%) approved for cannabis use
Most w advanced cancer, >40% died within 6 mo
Improvement in symptoms in majority of pts

70%

60%

70%



50%

44%

83%

Fig. 1. Efficacy of cannabis use in patients, as perceived by patients who completed a detailed questionnaire (n = 69).



C U R R E N T

ONCOLOGY

VOLUME 23, SUPPLEMENT 2, MARCH 2016

USE OF CANNABINOIDS IN CANCER CARE

Guest Editor: Mark Ware, MD



Published by Multimed Inc.
www.multi-med.com

PubMed/PubMed Central
www.current-oncology.com



C U R R E N T

ONCOLOGY

Why I chose to use cannabis

L. Perrier*

Patient's tale of requesting, acquiring and benefits of cannabis to help symptoms associated with cancer and its treatment

How does cannabis work?



Cannabis: What's in it?

Cannabis sativa

Marijuana (dried leaves / flowering heads)

> 400 chemical compounds

Isolated pure compounds

> 80 types of cannabinoids

Non-cannabinoids

Cannabinoids

Most potent psychoactive ingredient

Psychoactive

Δ^9 -THC

Δ^8 -THC

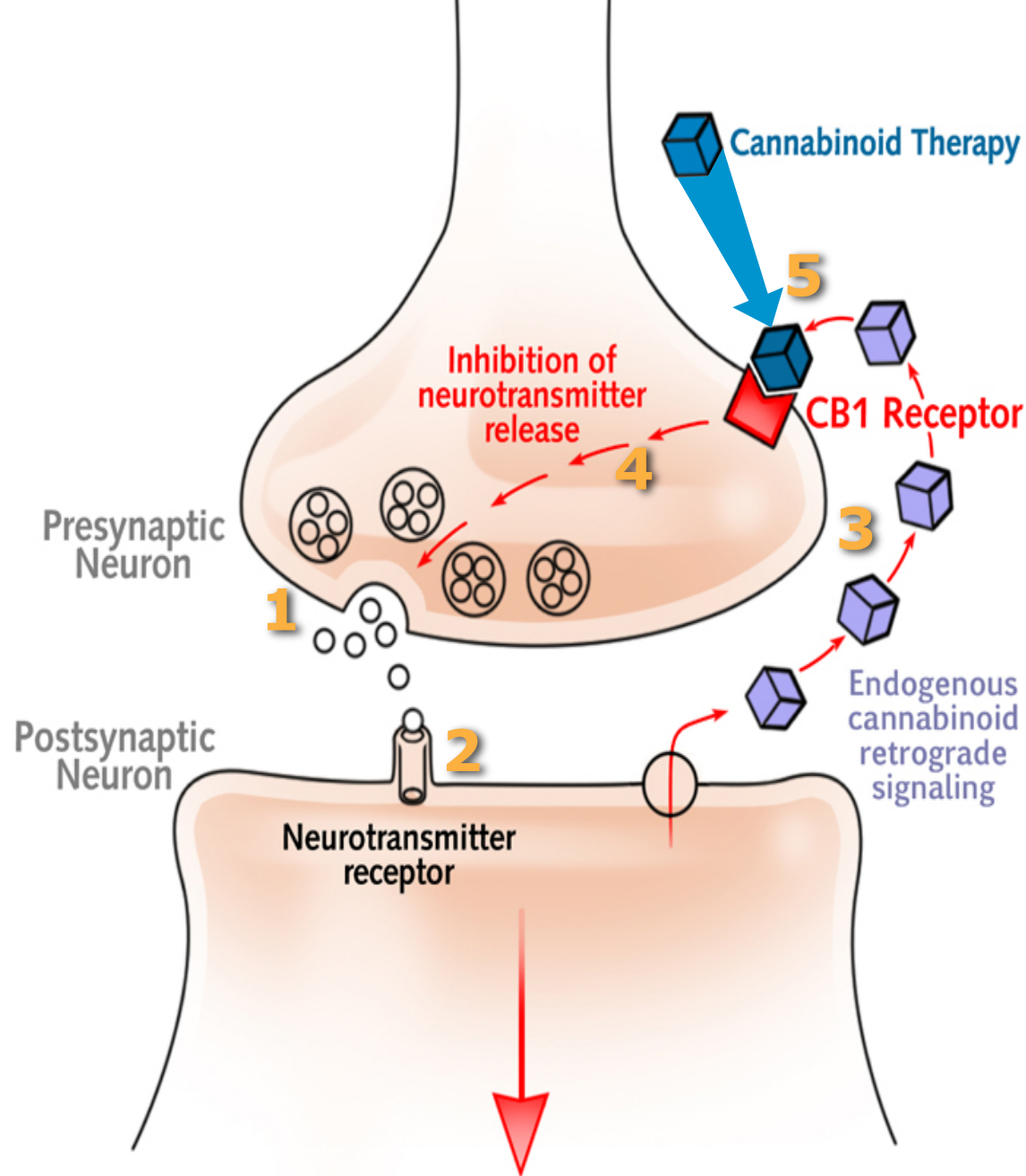
cannabinol (weak)

Active, not psychoactive
cannabidiol

Inactive?

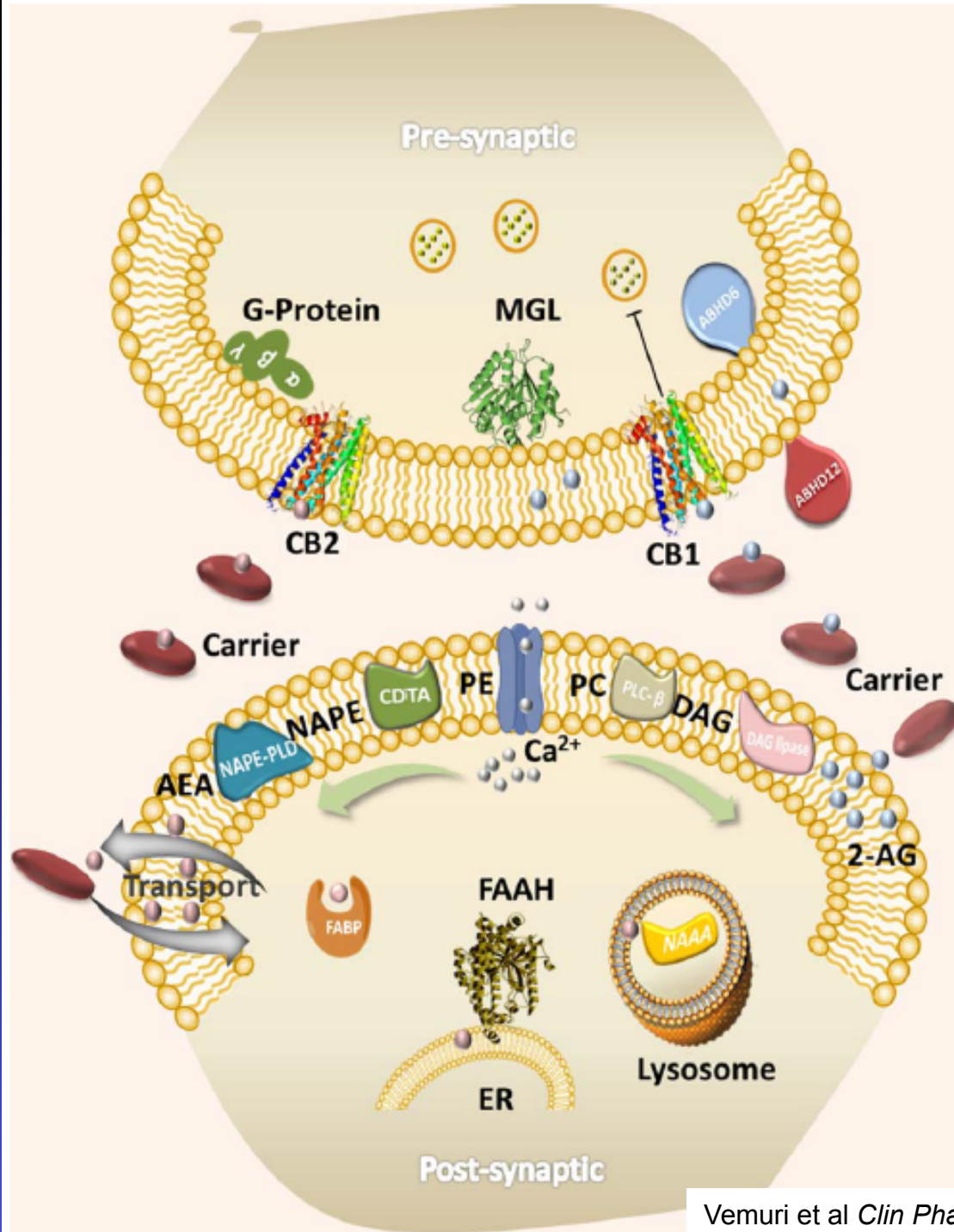
> 70 compounds

active in several conditions



Endogenous and exogenous cannabinoids reduce neuronal signaling

- 1) Neurotransmitter (NT) released from vesicles within the presynaptic neuron activates the postsynaptic neuron
- 2) Activation of postsynaptic neuron leads to synthesis and release of endocannabinoid
- 3) The endogenous CB1 ligand diffuses back to and binds to the presynaptic CB1 receptor
- 4) The CB1 receptor activates a G-protein, which lead to presynaptic events that result in inhibition of NT release
- 5) Exogenous drugs directly activate CB1 receptors to stimulate the endogenous cannabinoid system, enhancing its function





Why are
people
asking for
cannabis?
What is the
evidence?

Stoned

CAUTION: DO NOT USE WITH ALCOHOL OR NON-PRESCRIBED DRUGS WITHOUT CONSULTING THE PRESCRIBER.



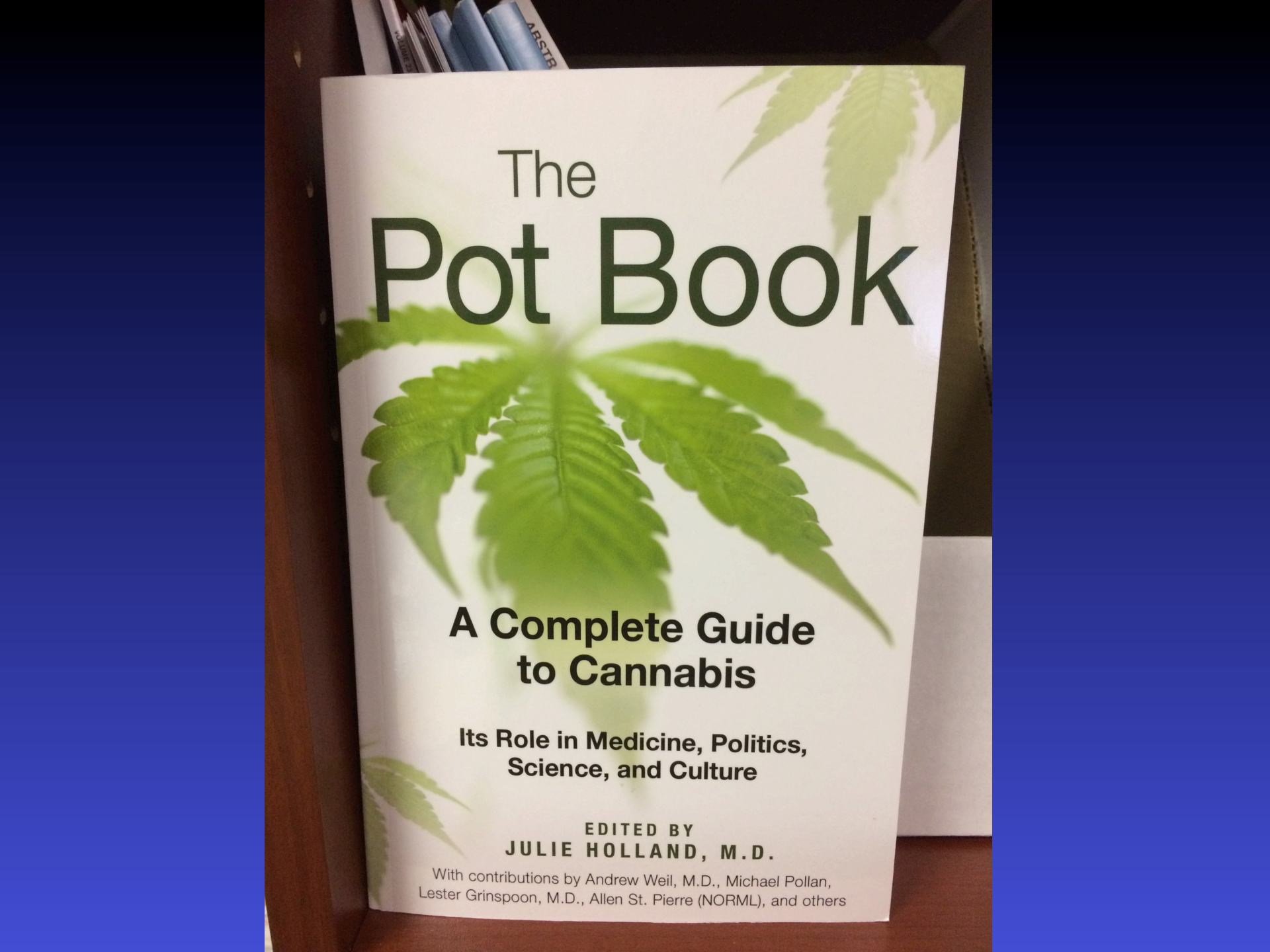
A DOCTOR'S
CASE FOR
MEDICAL
MARIJUANA

AVING, STATE FEDERAL LAW PROHIBITS THE TRANSFER OF THIS DRUG TO ANY PERSON OTHER THAN THE PERSON FOR WHOM IT WAS PRESCRIBED.

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David Casarett, M.D.



The
Pot Book

**A Complete Guide
to Cannabis**

**Its Role in Medicine, Politics,
Science, and Culture**

**EDITED BY
JULIE HOLLAND, M.D.**

With contributions by Andrew Weil, M.D., Michael Pollan,
Lester Grinspoon, M.D., Allen St. Pierre (NORML), and others

Cannabinoid indications

On-label indications:

Nausea and vomiting from chemotherapy

Chronic pain (neuropathic pain in MS and cancer)

Anorexia associated with HIV / AIDS

Off-label indications/emerging evidence for:

PTSD

Anxiety

Insomnia

Spasticity (MS)

Bladder spasms (MS)

Fibromyalgia

Neuropathic / mixed pain

Chronic daily headache

Anorexia / cachexia

Spasticity

Epilepsy

Symptom prevalence in cancer patients

Pain	35 - 96%
Depression	3 - 77%
Anxiety	13 - 79%
Confusion (delirium)	6 - 93%
Fatigue	32 - 90%
Breathlessness (dyspnea)	10 - 70%
Nausea	6 - 68%
Constipation	23 - 65%
Anorexia	30 - 92%

Symptoms responsive to cannabinoids

Pain

Depression

Anxiety

Confusion (delirium)

Fatigue

Breathlessness (dyspnea)

Nausea

Constipation

Anorexia

What is the evidence?

Pain

Pre-clinical

++

Clinical

+++

Pre-clinical data: cancer pain

Robust *in vitro* evidence cancer pain responds to cannabinoid treatment

Use in bone pain/neuropathic pain has strongest evidence

Direct use of agonists/antagonists



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Available online at www.sciencedirect.com

 ScienceDirect

Neuroscience Letters 433 (2008) 77–81

Neuroscience
Letters

www.elsevier.com/locate/neulet

Peripheral cannabinoids attenuate carcinoma-induced nociception in mice



ELSEVIER

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie



A cannabinoid 2 receptor agonist attenuates bone cancer-induced pain and bone loss

The Journal of Neuroscience, October 29, 2008 • 28(44):11141–11152 • 11141

Neurobiology of Disease

A Decrease in Anandamide Signaling Contributes to the Maintenance of Cutaneous Mechanical Hyperalgesia in a Model of Bone Cancer Pain



available at www.sciencedirect.com



www.elsevier.com/locate/brainres

**BRAIN
RESEARCH**

Research Report

The cannabinoid receptor agonist, WIN 55, 212-2, attenuates tumor-evoked hyperalgesia through peripheral mechanisms

Carl Potenziari^{a,b}, Catherine Harding-Rose^a, Donald A. Simone^{a,b,*}

Role of cannabinoid 2 receptor in the development of bone cancer pain

Zhonghua Yi Xue Za Zhi. 2012 Feb 21;92(7):440-3.

Wang D, Ren BX, Liu CL, Zhu J, Zhang J, Zhang W, Mei FM, Gu XP, Ma ZL.

doi: 10.3760/cma.j.issn.00376-2491-2012.07.003. [Article in Chinese]

Clinical data: Pain

Trial evidence supports oral use in cancer pain, in addition to usual therapy

Small studies using smoking/vaporization

None using edibles or oils

Reduction in use of pain meds noted

Few A/E

Original Article

Johnson et al *JPSM* 2010;39:167-79

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



RESEARCH
EDUCATION
TREATMENT
ADVOCACY



Journal of Pain 2012; 13:438-49

Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial

Russell K. Portenoy,^{*} Elena Doina Ganae-Motan,[†] Silvia Allende,[‡] Ronald Yanagihara,[§] Lauren Shaiova,[¶] Sharon Weinstein,[#] Robert McQuade,^{**} Stephen Wright,^{††} and Marie T. Fallon^{‡‡}

MEDICAL CANNABIS: DOES IT REDUCE THE AMOUNT OF OPIOID MEDICATION REQUIRED BY PATIENTS WITH CANCER PAIN?

Cudmore J¹ and Daeninck PJ^{1,2,3}

¹Department of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada

²Departments of Medical Oncology and Hematology CancerCare Manitoba, Winnipeg, MB, Canada

³WRHA Palliative Care Program, Winnipeg, MB, Canada

JOURNAL OF CLINICAL ONCOLOGY

..... Official Journal of the American Society of Clinical Oncology

The use of cannabinoids (CBs) for the treatment of chemotherapy-induced peripheral neuropathy (CIPN): A retrospective review

J. Gingerich, D. Wadhwa, L. Lemanski, M. Krahn, P. J. Daeninck

University of Manitoba, Winnipeg, MB, Canada; St. Boniface Hospital, Winnipeg, MB, Canada

Abstract e20743

What is the evidence?

Nausea

Evidence

Pre-clinical

++

Clinical

+++

Cannabinoids in nausea

Table 2

Clinical Trials With Cannabinoids: Emesis

DRUG(S)	SUBJECTS	OUTCOME	REFERENCES
Nabilone vs prochlorperazine	Pediatric chemotherapy patients	Nabilone more effective	56
Nabilone and prochlorperazine vs metoclopramide and dexamethasone	Chemotherapy patients	Better control of emesis with metoclopramide combination, but nabilone combination better tolerated	57
Nabilone vs metoclopramide	Patients undergoing irradiation	No difference in effectiveness; more adverse effects with nabilone	58
Nabilone vs alizapride	Chemotherapy patients	Nabilone more effective but with more adverse effects (especially at higher doses)	59
Nabilone vs domperidone	Chemotherapy patients	Nabilone more effective	60
Nabilone vs metoclopramide	Chemotherapy patients	No difference in efficacy	61
Oral THC vs prochlorperazine	Chemotherapy patients	No difference in efficacy	62
Oral THC vs prochlorperazine vs placebo	Chemotherapy patients	Oral THC more effective than prochlorperazine or placebo	63
Dronabinol and metoclopramide and prochlorperazine	Chemotherapy patients	No added benefit of dronabinol	64
Dronabinol and prochlorperazine	Chemotherapy patients	Dronabinol effective alone, but combination more effective	65, 53
Nabilone and prochlorperazine	Chemotherapy patients	Nabilone more effective	66
Oral THC vs prochlorperazine	Chemotherapy patients	Oral THC more effective	67

THC = Δ^9 -tetrahydrocannabinol

Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review

Martin R Tramèr, Dawn Carroll, Fiona A Campbell, D John M Reynolds, R Andrew Moore,
Henry J McQuay

BMJ 2001, 323:1-8

CBs may be superior to conventional therapies in low-medium emetogenic setting

Patient preference for CBs ranged from 38-90% (P 4-20%)

CBs produced significantly more A/E effects (good & bad), more pt withdrawals

“In selected patients, cannabinoids may be useful as mood enhancing adjuvants for the control of chemotherapy related sickness”

Inhaled cannabis

Three studies, associated with chemo administration

Some new users, many previous cannabis users

All studies showed benefit, but high incidence of side effects

25-35% pts prefer marijuana

What is the evidence?

Appetite/wt loss	Evidence
Pre-clinical	++
Clinical	+

Hypothalamic POMC neurons promote cannabinoid-induced feeding



Marijuana flips appetite switch in brain

Sudden attacks of 'the munchies' triggered by changes in hormone pro-opiomelanocortin (POMC) release by neurons

Appetite and weight loss

Table 1

Clinical Trials With Cannabinoids: Cachexia and Anorexia

DRUG(S)	SUBJECTS	OUTCOME	REFERENCE
Dronabinol and megestrol	Cancer patients	No effect of dronabinol or combination on appetite or body weight	37
Dronabinol	Cancer patients	Increased appetite	38
Dronabinol and megestrol	AIDS patients	No effect of dronabinol or combination on appetite	39
Dronabinol vs placebo	HIV-positive patients	Increased body fat and increased appetite	40
Dronabinol vs placebo	Alzheimer's patients with anorexia	Increased body weight and decrease in disturbed behavior	41
Dronabinol vs placebo	AIDS patients	Increased appetite; stabilized weight	42
Dronabinol vs placebo	Late-stage AIDS patients	Stable body weight for 7 months	43

Jatoi A et al. *J Clin Oncol* 2002;20:567-573

Nelson K et al. *J Pall Care* 1994;10:14-18

Timpone JG et al. *AIDS Res Hum Retroviruses* 1997;13:305-15

Struwe M et al. *Ann Pharmacother* 1993;27:827-31

Beal JE et al. *J Pain Symptom Manage* 1995;10:89-97

Beal JE et al. *J Pain Symptom Manage* 1997;14:7-14

Dronabinol: taste alterations

Pilot trial to improve taste, smell changes in advanced cancer patients

THC 2.5 mg BID or TID vs placebo x 18 days, n=21

Questionnaires / interviews revealed significant improvement in taste / smell, increased appetite and protein intake

QoL measures found improved relaxation, quality of sleep

Adverse effects same in both groups

What is the evidence?

Neuroprotection

Evidence

Pre-clinical

+/-

Clinical

+

Selective Activation of Cannabinoid CB₂ Receptors Suppresses Neuropathic Nociception Induced by Treatment with the Chemotherapeutic Agent Paclitaxel in Rats

Elizabeth J. Rahn, Alexander M. Zvonok, Ganesh A. Thakur, Atmaram D. Khanolkar, Alexandros Makriyannis, and Andrea G. Hohmann

British Journal of Pharmacology (2007), 1-13
© 2007 Nature Publishing Group All rights reserved 0007-1188/07 \$30.00
www.bjpharmacol.org



RESEARCH PAPER

Activation of cannabinoid CB₁ and CB₂ receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats

EJ Rahn¹, A Makriyannis² and AG Hohmann¹



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Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT™

American Society for Blood
and Marrow Transplantation

Cannabidiol for the Prevention of Graft-versus-Host-Disease after Allogeneic Hematopoietic Cell Transplantation: Results of a Phase II Study



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166 *Journal of Pain and Symptom Management*

Vol. 47 No. 1 January 2014

Brief Report

A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Using an Oral Mucosal Cannabinoid Extract for Treatment of Chemotherapy-Induced Neuropathic Pain

Mary E. Lynch, MD, FRCPC, Paula Cesar-Rittenberg, MD, FRCPS, and
Andrea G. Hohmann, PhD

What is the evidence?

Insomnia

Evidence

Pre-clinical

-

Clinical

++*

Anxiety

Pre-clinical

++

Clinical

In progress

*secondary finding

Epidemiologic review of marijuana use and cancer risk

Mia Hashibe^a, Kurt Straif^a, Donald P. Tashkin^b, Hal Morgenstern^c,
Sander Greenland^{d,e}, Zuo-Feng Zhang^{d,*}

Many epidemiologic studies

Older studies support increased risk of cancer

More recent studies, improved methodology

not clear if causative or protective effect

Smoked cannabis contributes to pulm damage

Vaporized cannabis oil may produce carcinogens¹

20 Medical Studies That Prove Cannabis Can Cure Cancer

<http://www.collective-evolution.com/2013/08/23/20-medical-studies-that-prove-cannabis-can-cure-cancer/#sthash.H5ypYS6a.dpuf>

Cannabis Cures Cancer

https://dl.dropboxusercontent.com/u/27713298/Web/cure/How_It_Works.html

Run From The Cure: How Cannabis Cures Cancer And Why No One Knows

Cannabis sativa hemp, the miracle plant, contains the cure for cancer and other ailments By Rick Simpson - Friday, March 7 2008

<http://www.cannabisculture.com/articles/5169.html>

Cannabis is not a cure for
cancer...

but can it be a cancer
therapy??

What is the evidence?

Cancer therapy

Evidence

Pre-clinical

+++

Clinical

Anecdote

Clinical trials

+

In Progress

Proposed mechanisms

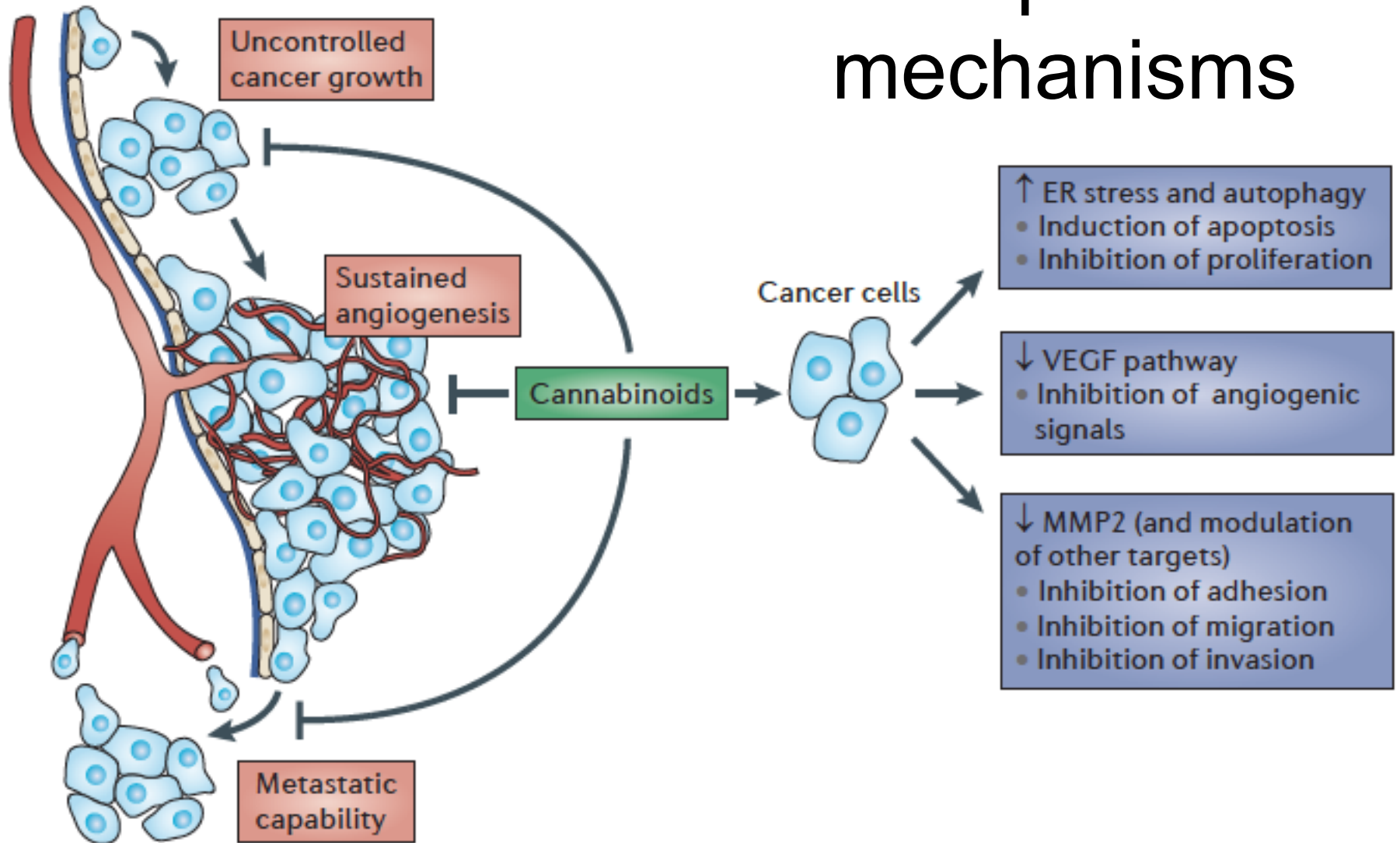


Figure 2 | **General mechanisms of cannabinoid antitumour action.** Cannabinoids block tumour

Cannabinoids as anticancer agents

Table 1 | **Cannabinoids activate a similar pro-apoptotic mechanism in different types of cancer cells***

Cancer cell	CB receptor involved	Ceramide synthesis	ER stress	p8-TRIB3 induction	AKT inhibition	Autophagy	Apoptosis	Refs
Glioma	CB1 and CB2	✓	✓	✓	✓	✓	✓	39
Pancreatic cancer	CB2	✓	✓	✓	✓	✓	✓	39,41
Hepatocellular carcinoma	CB2	✓	✓	✓	✓	✓	✓	40
Breast cancer	CB2	ND	ND	✓	✓	✓ (UO) [‡]	✓	94
Rhabdomyosarcoma	CB1	ND	✓	✓	✓	ND	✓	95
Mantle cell lymphoma	CB1 and CB2	✓	✓	ND	ND	✓ (WIN 55,212-2) [§]	✓ (WIN 55,212-2) [§]	96
Leukaemia	CB2	✓	ND	ND	✓	ND	✓	86,97,98
Prostate cancer	CB2	✓	ND	ND	✓	ND	✓	99,100
Melanoma	CB2	ND	ND	✓	✓	✓ (UO) [‡]	✓	42
Lung carcinoma	ND	ND	ND	ND	✓	ND	✓	56

CB, cannabinoid; ER, endoplasmic reticulum; ND, not determined; TRIB3, tribbles-homologue 3; UO, unpublished observations. *The existence of experimental evidence for the participation of CB receptors, *de novo*-synthesized ceramide, ER stress induction, upregulation of p8 and/or of TRIB3, autophagy induction or apoptosis in cannabinoid-induced death for each type of cancer cell is indicated by a tick. [‡]G.V., C.S. and M.G., unpublished observations. [§]WIN 55,212-2 produces a cytoplasmic vacuolization (autophagic-like) phenotype in mantle cell lymphoma, an effect that seems to be CB receptor-independent.

Pre-clinical work

CBs + gemcitabine act synergistically against pancreatic cancer cells

Adding THC to chemotherapy increased brain tumour sensitivity

Addition of CBD to THC enhanced anti-tumour activity using temozolamide

Similar synergism seen using radiation with THC and CBD in a murine model of glioma

“But again, mice and rats are not people, and what is observed *in vitro* does not necessarily translate into clinical medicine. The preclinical evidence that cannabinoids might have direct anticancer activity is provocative as well, but more research is warranted.”

Donald Abrams, 2016

Anecdotal reports

Childs Nerv Syst (2011) 27:671–679

DOI 10.1007/s00381-011-1410-4

CASE REPORT

Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas—possible role of *Cannabis* inhalation

Mansoor Foroughi • Glenda Hendson •
Michael A. Sargent • Paul Steinbok

Anecdotal reports

Case Reports in
Oncology

Case Rep Oncol 2013;6:585–592

DOI: 10.1159/000356446
Published online: November 28, 2013

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1662–6575/13/0063–0585\$38.00/0
www.karger.com/cro

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Cannabis Extract Treatment for Terminal Acute Lymphoblastic Leukemia with a Philadelphia Chromosome Mutation

Yadvinder Singh^a Chamandeep Bali^b

Cannabinoids and cancer treatment

British Journal of Cancer (2006) 95, 197–203

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www.bjcancer.com



A pilot clinical study of Δ^9 -tetrahydrocannabinol in patients with recurrent glioblastoma multiforme

M Guzmán^{*,1}, MJ Duarte², C Blázquez¹, J Ravina², MC Rosa², I Galve-Roperh¹, C Sánchez¹, G Velasco¹ and L González-Feria^{*,2}

THC delivered to tumour bed 3-6 days post-resection

cell growth effects noted in 8/9 pts

no survival benefit (mean 24 wks)

no psychoactive effects

Treatment was safe, set stage for further investigation

Current clinical trials

Israel: cannabis extracts (CBD) in patients resistant to usual chemotherapy protocols (NCT02255292)

US: Safety of dexanabinol in pts with advanced cancers (NCT01489826, NCT02423239)

Cannabis (high CBD concentration) for pain and inflammation in lung carcinomas (NCT02675842)

Medical marijuana in the pediatric CNS tumor population (NCT03052738)

A two-part safety and exploratory efficacy randomized double-blind, placebo-controlled study of a 1:1 ratio of the cannabinoids cannabidiol and delta-9-tetrahydrocannabinol (CBD:THC) plus dose-intense temozolomide in patients with recurrent glioblastoma multiforme (GBM).

Presented Monday, June 5, 2017 as a poster

J Clin Oncol 35, 2017 (suppl; abstr 2046)

n=21 pts, 12 temozolamide + CBD:THC vs 9 placebo

Median survival: >550 d experimental group vs 369 d placebo

1YS: 83% chemo + CBD:THC vs 53% placebo (p=0.042)

CBD:THC adverse events: dizziness and nausea

NCT01812603

Cannabis in Palliative Care?

Assessment of Hospice Health Professionals' Knowledge, Views, and Experience with Medical Marijuana

Tanya J. U

Pradel, Ph.D.²

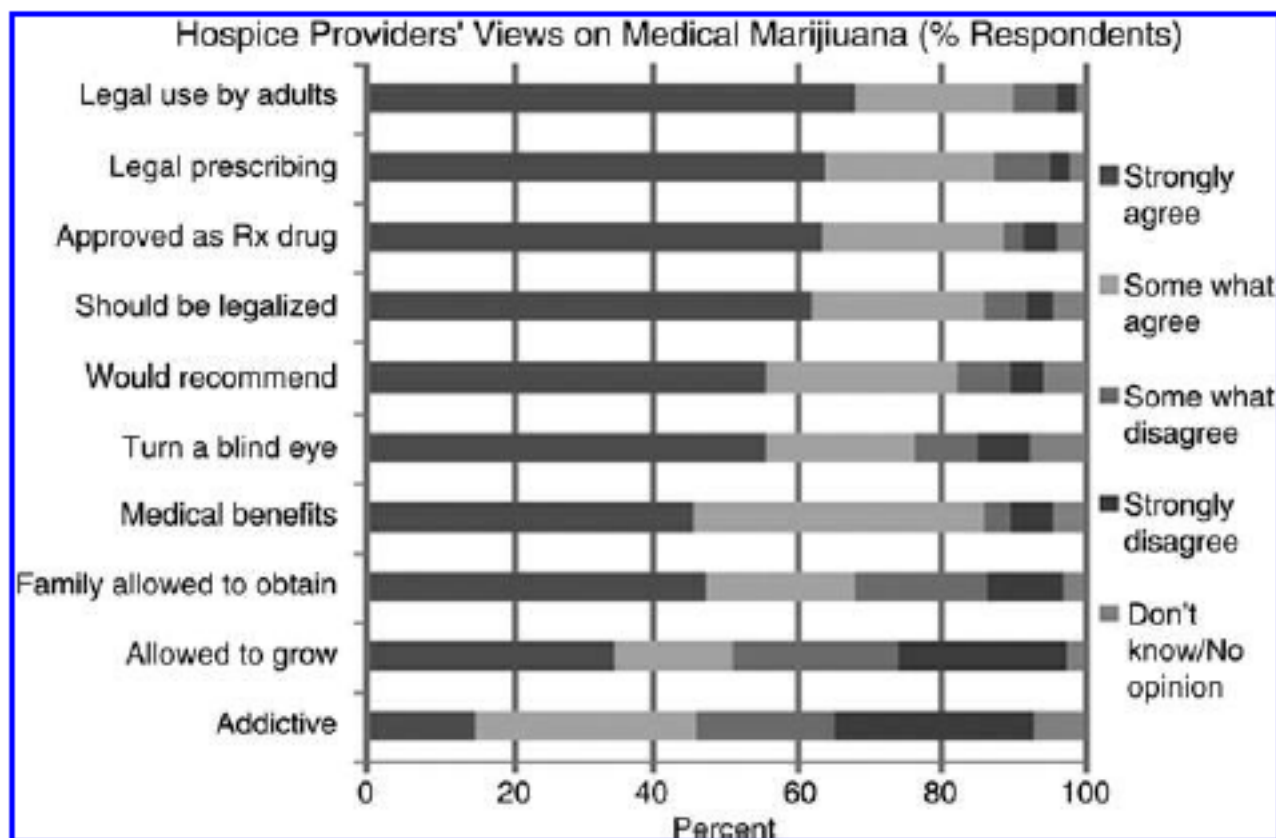


FIG. 1. Hospice providers' views on medical marijuana (% respondents).

Research Article

The Medical Necessity for Medicinal Cannabis: Prospective, Observational Study Evaluating the Treatment in Cancer Patients on Supportive or Palliative Care

**Gil Bar-Sela,^{1,2} Marina Vorobeichik,¹ Saher Drawsheh,¹ Anat Omer,¹
Victoria Goldberg,¹ and Ella Muller¹**

Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 510392, 8 pages
<http://dx.doi.org/10.1155/2013/510392>

Observational study, >100 pts cancer PC setting
Significant improvement in N/V, pain, mood disorders, fatigue, wt loss, anorexia, constipation, sexual function, sleep disorders, itching
43% reported dose reduction in pain meds
33% reduced anti-depression/anxiety meds

Bar-Sela et al

Significant adverse effects not noted in cannabis users

Reported reduction in memory in 20% - 40%

Improvement in symptom and distress scores

Limitations of the study:

- observational nature

- lack of a control group

- reliance on self-report



Use of cannabinoids in cancer care: palliative care

S.K. Aggarwal MD PhD*

Use for symptoms, but also integrate into holistic approach for overall well being and patient benefit

Medical cannabis use in an outpatient palliative care clinic: A retrospective chart review

Noah Spencer, BAsC(C), Erynn Shaw, MD,
and Marissa Slaven*, MD

J Pain Manage 2016;9(4):507-513

JOURNAL OF PALLIATIVE MEDICINE
Volume 20, Number 7, 2017
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DOI: 10.1089/jpm.2017.0197

Notes from the Editor

Cannabinoids in Palliative Medicine

Psychiatric Complications of Cannabis
Oil Use in Cancer Patients:
Whose Responsibility Is It To Manage?