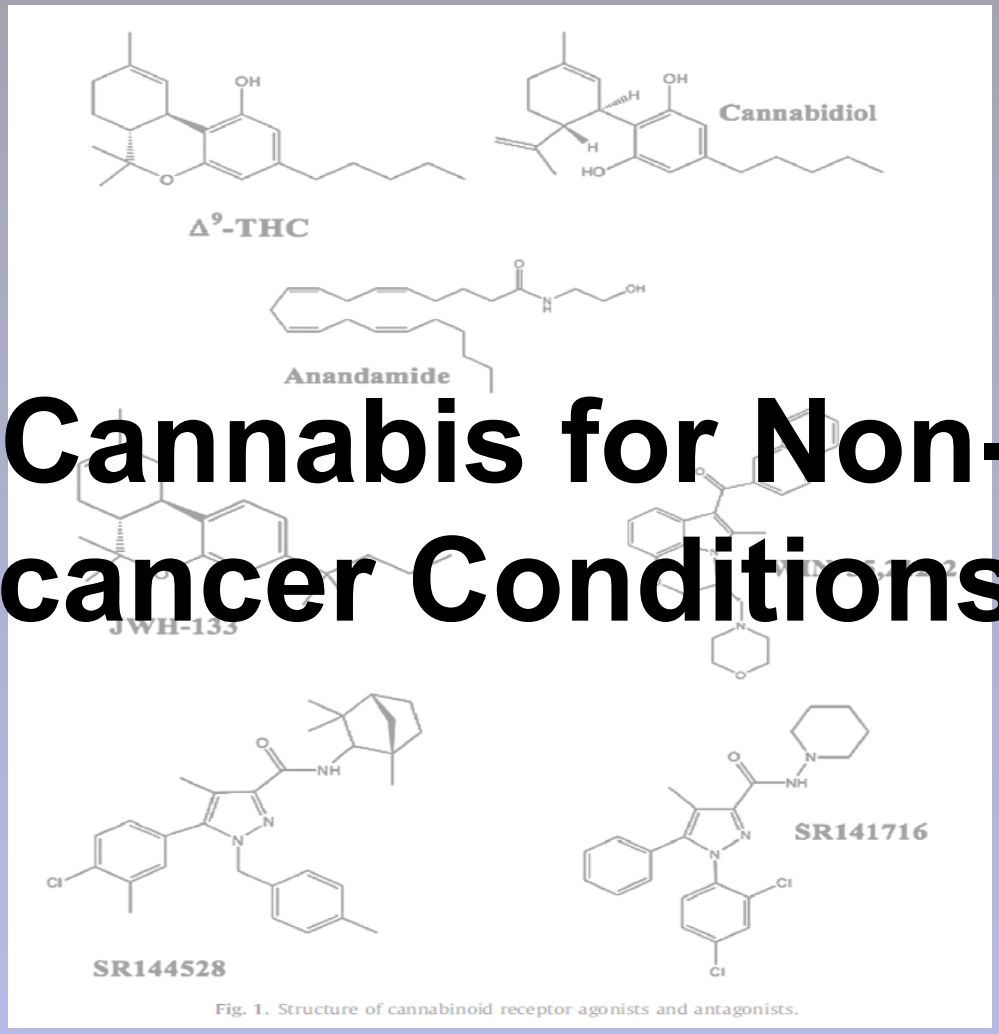
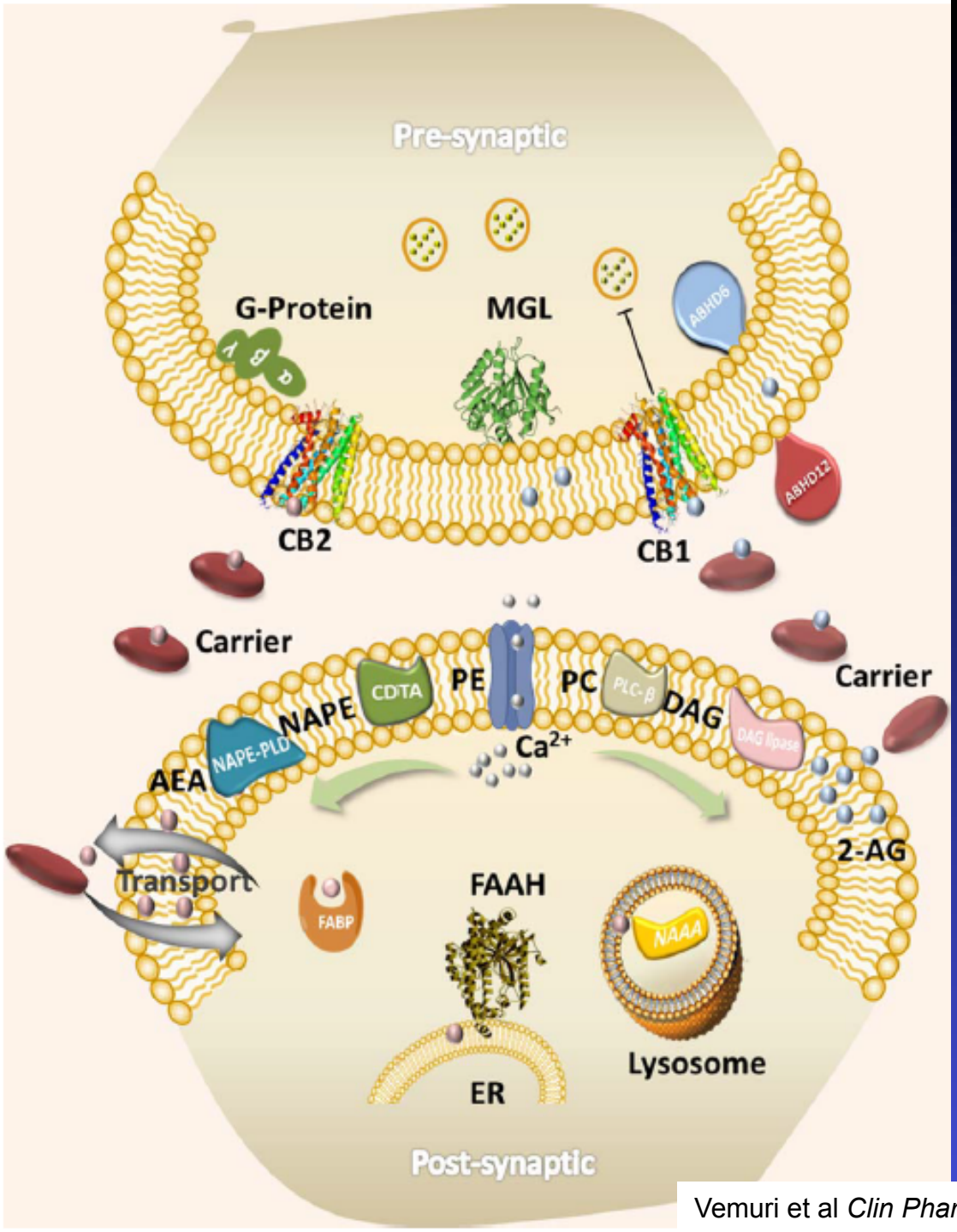


Fig. 1. Structure of cannabinoid receptor agonists and antagonists.

Cannabis for Non-cancer Conditions



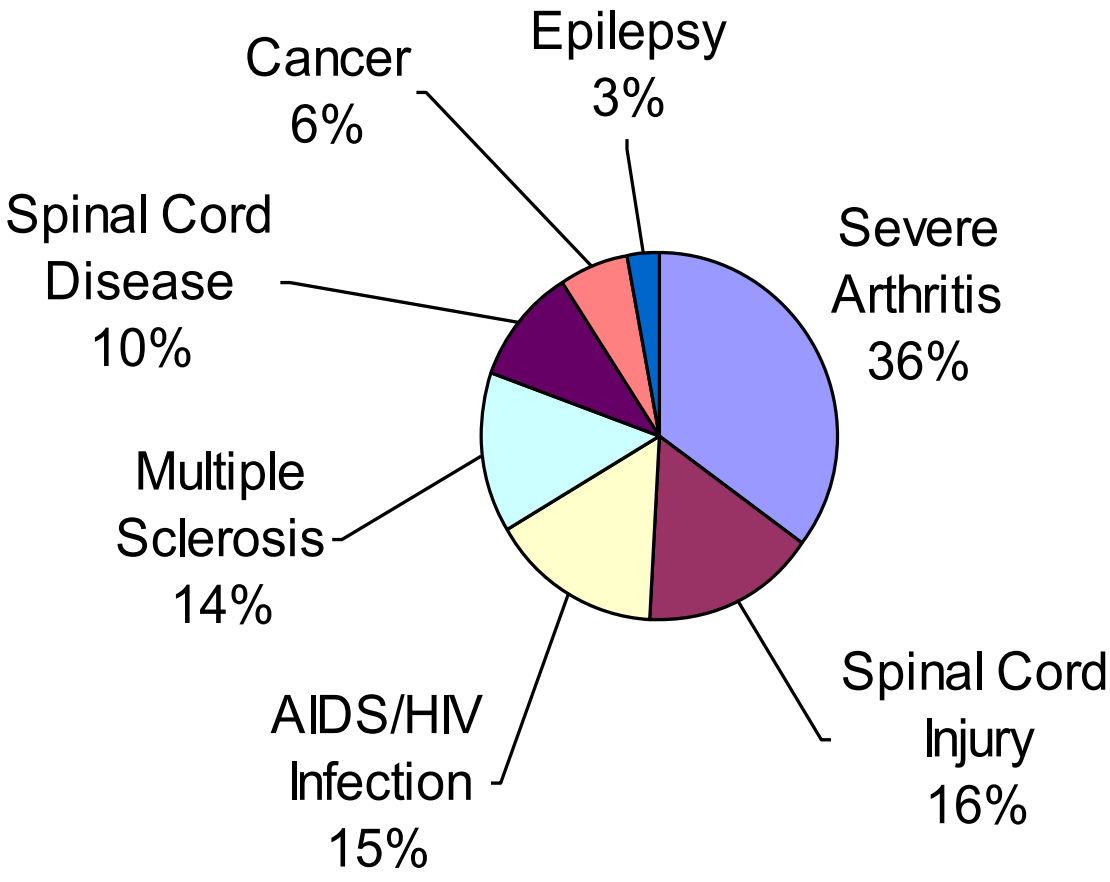
Vemuri et al *Clin Pharmacol Therapeutics* 2015

Endocannabinoids

Evidence supports the role of endocannabinoids in:

- Immune function
- Inflammation
- Appetite
- Metabolism and energy homeostasis
- Cardiovascular function
- Digestion
- Bone development and bone density
- Pain
- Reproduction
- Psychiatric disease
- Psychomotor behavior
- Memory
- Wake/sleep cycles
- Regulation of stress and emotional state
- Learning

Disease Distribution of 2604 Patients with MMAR Category 1 Approvals (Up to Feb 6, 2009)



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)
Lower urinary tract symptoms (MS)
Dementia-related symptoms

Neuropathic/nociceptive/ mixed pain
Chronic daily headache
Fibromyalgia
Anorexia and cachexia
Neurodegenerative diseases
Epilepsy
Inflammatory Bowel Disease

What is the evidence?

Pain	**Evidence**
Pre-clinical	**++**
Clinical	**+++**
-neuropathic-	

Pre-clinical data: chronic pain

- Robust *in vitro* evidence pain responds to cannabinoid treatment
- Neuropathic pain has strongest evidence
- Direct use of agonists/antagonists and prevention of FAAH degradation
- Peripheral application effective, few A/E

Clinical data: Pain

- RCT evidence supports oral use, smoking/vaporization, oral extracts
- None using edibles or oils
- Opioid sparing noted in many studies
- Few A/E noted

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.03970.x

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

Correspondence
Dr Mary E. Lynch, MD, FRCPC, Pain Management Unit, Queen Elizabeth II Health Sciences Centre, 4th Floor Dickson Centre, Room 4086, Halifax, Nova Scotia, B3H 1V7, Canada.
Tel.: +1 902 473 6428
Fax: +1 902 473 4126
E-mail: mary.lynch@dal.ca

Keywords
cannabinoids, chronic non-cancer pain, neuropathic pain, systematic review

J Neuroimmune Pharmacol
DOI 10.1007/s11481-015-9600-6

INVITED REVIEW

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

M. E. Lynch[1,3] · Mark A. Ware[2]

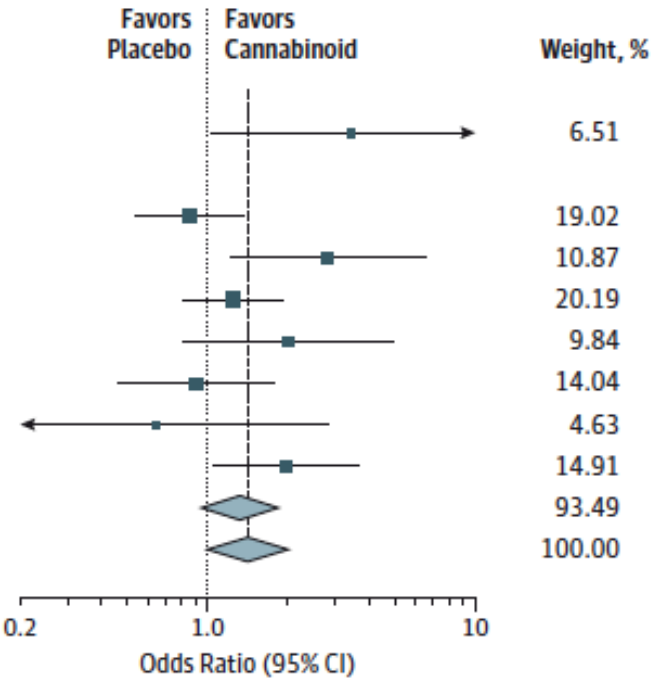
Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

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)

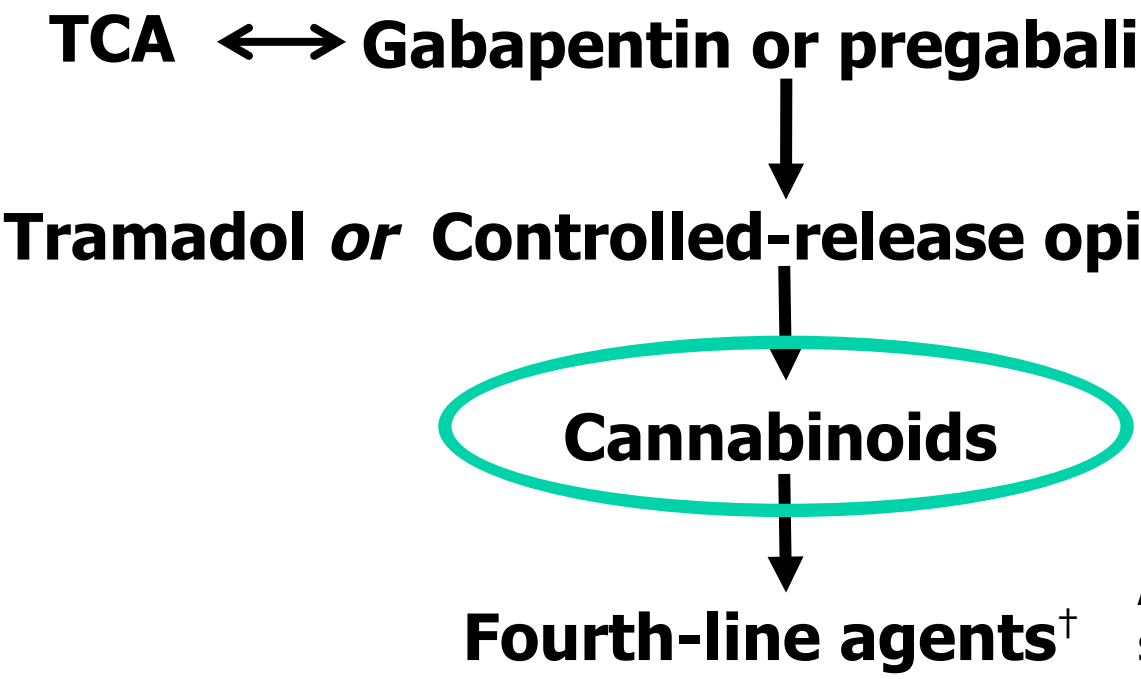


Conclusions of reviews

Studies small, short in duration, modest effect size

“cannabinoids are safe, demonstrate a modest analgesic effect and provide a reasonable treatment option for chronic pain”

CPS Neuropathic Pain guideline



Add additional agents sequentially if partial but inadequate pain relief

†methadone, lamotrigine, topiramate, valproic acid, lidocaine.
‡Do not add SNRIs to TCAs

Pain Res Manage 2014;19(6):328-335

What is the evidence?

MS	Evidence
Pre-clinical	+++
Observations	++
Clinical trials	+++

Cannabinoids in spasticity

Publication	Indication	Medication	N	Results
Zajicek et al. MUSEC. ECTRIMS 2009	Muscle stiffness and other symptoms in MS	Oral cannabis extract versus placebo	279	• Patients' assessment of change from baseline: Significant for muscle stiffness, body pain, spasms and sleep quality
Vaney et al. Mult Scler. 2004	Spasticity in MS	Cannabis extract versus placebo	57	• Ashworth: Not significant • Spasm frequency and mobility: Significant in per-protocol set
Hagenbach et al. Spinal Cord. 2007	Spasticity in spinal cord injury	Oral and rectal cannabinoids	25	• Spasticity sum score using Ashworth and self-ratings of spasticity: Significant
Pooyania et al. Arch Phys Med Rehabil. 2010	Spasticity in spinal cord injury	Nabilone versus placebo	12	• Ashworth of Selected Muscle group: Significant •Overall Ashworth: Significant
Corey-Bloom J et al. CMAJ 2012	Spasticity in MS	Smoked cannabis vs placebo	37	•Ashworth improved vs placebo: significant; VAS for pain improved

Cannabinoids in spasticity

nabiximols

Study	Study Details	Endpoints
Collin et al., 2007	MS, Spasticity (N=189)	Improvement in Spasticity (NRS)
Collin et al., 2010	MS, Spasticity (N=337)	Improvement in Spasticity (NRS)
Novotna et al., 2011	MS, Spasticity (N= [A] 572, [B] 241)	Improvement in Spasticity (NRS)

Multiple sclerosis

CMAJ RESEARCH

Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial

Jody Corey-Bloom MD PhD, Tanya Wolfson MA, Anthony Gamst PhD, Shelia Jin MD MPH, Thomas D. Marcotte PhD, Heather Bentley BA, Ben Gouaux BA

CMAJ 2012, 184:1143-50

RCT, crossover design
37 cannabis naïve or exposed MS patients with moderate + spasticity
Average of 4 puffs of 4% THC or placebo cigarettes

Multiple sclerosis

Table 2: Changes in spasticity, pain and cognitive performance, by treatment

Performance measure	Placebo		Cannabis		Mean difference		
	Before treatment	After treatment	Before treatment	After treatment	Cannabis	Placebo	Effect
Spasticity, modified Ashworth score, mean (95% CI)*	8.92 (8.03 to 9.79)	8.71 (7.57 to 9.71)	9.13 (8.21 to 10.07)	6.18 (5.13 to 7.21)	2.95 (2.49 to 3.38)	0.21 (–0.09 to 0.51)	2.74 (2.20 to 3.14)
Pain, visual analogue score, mean (95% CI)†	14.51 (9.16 to 21.75)	11.52 (7.21 to 18.32)	16.61 (10.79 to 24.93)	8.34 (4.89 to 14.39)	8.27 (4.51 to 13.49)	2.99 (0.04 to 6.55)	5.28 (2.48 to 10.01)
Physical performance, timed walk, s, mean (95% CI)‡	11.68 (8.87 to 16.41)	11.70 (8.81 to 16.98)	11.66 (8.90 to 16.69)	12.89 (9.55 to 17.94)	1.23 (0.33 to 2.63)	0.03 (–0.95 to 1.63)	1.20 (0.15 to 4.31)
Cognitive function, PASAT score, mean (95% CI)§	138.08 (123.76 to 149.74)	138.43 (123.37 to 150.38)	140.78 (127.31 to 151.52)	132.46 (116.38 to 144.07)	8.32 (4.95 to 14.16)	–0.35 (–2.92 to 2.47)	8.67 (4.10 to 14.31)

Note: CI = confidence interval, PASAT = paced auditory serial addition test.
*Scores range from 0 to 24, with higher scores suggesting greater spasticity.
†Scores range from 0 to 100, with higher scores suggesting more severe pain.
‡Times range from 0 to 66 s, with higher scores suggesting a slower pace.
§Scores range from 0 to 196, with higher scores suggesting better cognitive performance.

Significant improvement in spasticity ($p < 0.001$)
Better pain control ($p<0.01$)
Reduction in cognitive function ($p=0.003$)
No significant change in physical function

Corey-Bloom et al *CMAJ* 2012, 184:1143-50

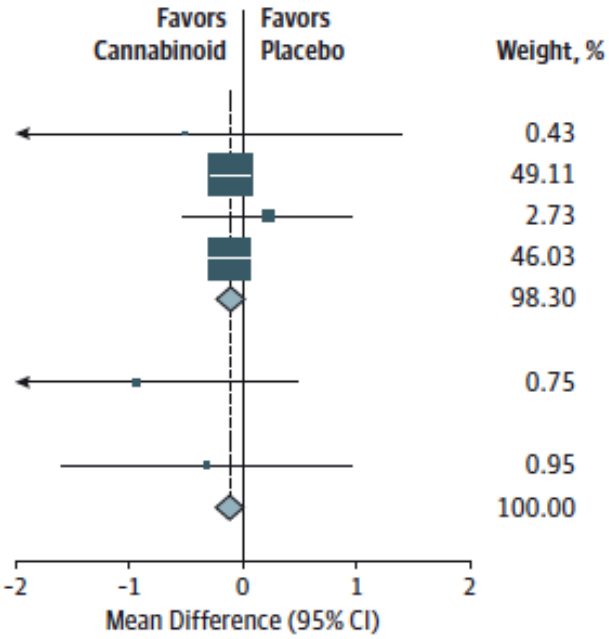
Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

Figure 3. Change in Ashworth Score for Cannabinoid Compared With Placebo, Stratified According to Cannabinoid

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid: No. of Patients	Cannabinoid: Mean (SD) Score Change	Placebo: No. of Patients	Placebo: Mean (SD) Score Change	Mean Difference (95% CI)	Weight, %
Nabiximols						
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)	0.43
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)	49.11
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)	2.73
Berman,[87] 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)	46.03
Subtotal I^2 = 0.0%, (P = .0.82)	383		337		-0.11 (-0.23 to 0.02)	98.30
Dronabinol						
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)	0.75
Tetrahydrocannabinol/cannabidiol						
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)	0.95
Overall I^2 = 0.0%, (P = .80)	590		544		-0.12 (-0.24 to 0.01)	100.00



What is the evidence?

Seizures	Evidence
Pre-clinical	+
Clinical	++

Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders

*Orrin Devinsky, †Maria Roberta Cilio, ‡Helen Cross, §Javier Fernandez-Ruiz, *Jacqueline French, ¶Charlotte Hill, Russell Katz, Independent Consultant, **Vincenzo Di Marzo, ††Didier Jutras-Aswad, ‡‡§§William George Notcutt, ##Jose Martinez-Orgado, ***Philip J. Robson, †††Brian G. Rohrback, ‡‡‡Elizabeth Thiele, ¶Benjamin Whalley, and *Daniel Friedman

Epilepsia, 55(6):791–802, 2014
doi: 10.1111/epi.12631

Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Orrin Devinsky, Eric Marsh*, Daniel Friedman*, Elizabeth Thiele, Linda Laux, Joseph Sullivan, Ian Miller, Robert Flamini, Angus Wilfong, Francis Filloux, Matthew Wong, Nicole Tilton, Patricia Bruno, Judith Bluvstein, Julie Hedlund, Rebecca Kamens, Jane Maclean, Srishti Nangia, Nilika Shah Singhal, Carey A Wilson, Anup Patel, Maria Roberta Cilio*

Lancet Neurol 2016; 15: 270–78

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D.,

EDITORIALS

Cannabinoids for Epilepsy — Real Data, at Last

Samuel F. Berkovic, M.D.

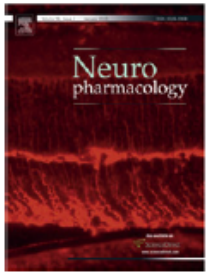
What is the evidence?

Neuroprotection	**Evidence**
Pre-clinical	**++/-**
Clinical	**+**

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

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



Neuropharmacology 63 (2012) 776–783

Cannabidiol administration after hypoxia–ischemia to newborn rats reduces long-term brain injury and restores neurobehavioral function

M.R. Pazos [a], V. Cinquina [f], A. Gómez [a], R. Layunta [a], M. Santos [a], J. Fernández-Ruiz [c,d,e], José Martínez-Orgado [a,b,*]

BJP British Journal of Pharmacology

Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Endocannabinoids and traumatic brain injury

Esther Shohami, Ayelet Cohen-Yeshurun, Lital Magid, Merav Algali and [illegible]lechoulam

BJP British Journal of Pharmacology

Themed Issue: Cannabinoids in Biology and Medicine, Part I

RESEARCH PAPER

Symptom-relieving and neuroprotective effects of the phytocannabinoid Δ^9-THCV in animal models of Parkinson's disease

C García[1,2,3], C Palomo-Garo[1,2,3], M García-Arencibia[1,2], JA Ramos[1,2,3], RG Pertwee[4] and J Fernández-Ruiz[1,2,3]

Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study

Itay Lotan, MD, Therese A. Treves, MD, Yaniv Roditi, MD, and Ruth Djaldetti, MD

Pharmacology Biochemistry & Behavior, Vol. 40, pp. 701–708. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/9

Controlled Clinical Trial of Cannabidiol in Huntington's Disease

Survey of cannabis use in patients with amyotrophic lateral sclerosis

What is the evidence?

Anxiety	**Evidence**
Pre-clinical	**++**
Clinical	**+**
PTSD	**++**

Cannabinoids and anxiety

Oral cannabinoids used for nausea produces sedation and reduced anxiety

Very low dose cannabis can produce sedation, diminish anxiety independent of psychoactivity

Cannabidiol can exert anti-anxiety effects, although only demonstrated in acute, experimentally-induced anxiety

Tramer et al, *BMJ* 2001; 323:1-8
Graham and Li, Cannabis and Health, 1976
Bergamaschi et al, *Neuropsychopharmcol* 2011; 36: 1219-26

A role for cannabinoid CB_1 receptors in mood and anxiety disorders

J. M. Witkin[a], E. T. Tzavara[b] and G. G. Nomikos[a]

Behavioural Pharmacology 2005, 16:353–362

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Neuropharmacology 47 (2004) 1170–1179

NEURO PHARMACOLOGY

www.elsevier.com/locate/neuropharm

Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats

Paola Fadda [a,b], Lianne Robinson [a], Walter Fratta [b], Roger G. Pertwee [a], Gernot Riedel [a,*]

SHORT COMMUNICATION

CNS Neuroscience & Therapeutics

The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD)

George A. Fraser

Psychoneuroendocrinology (2015) 51, 577—584

Translational evidence for a role of endocannabinoids in the etiology and treatment of posttraumatic stress disorder

Alexander Neumeister[a,b,*], Jordan Seidel[a], Benjamin J. Ragen[a], Robert H. Pietrzak[c,d]

What is the evidence?

Depression	**Evidence**
Pre-clinical	**+**
Clinical	**?**
Psychiatric Disorders	
Pre-clinical	**++**
Clinical	**+**

Serum Endocannabinoid Content is Altered in Females with Depressive Disorders: A Preliminary Report

Matthew N. Hill, M.A.[1], Gregory E. Miller, Ph.D[1], W.-S. Vanessa Ho, Ph.D[2], Boris B. Gorzalka, Ph.D[1,*], and Cecilia J. Hillard, Ph.D[2]

Review

Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential

Psychopharm

Journal of Psychopharmacology
19(3) (2005) 293–300

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10.1177/0269881105051541

frontiers in Pharmacology

REVIEW
published: 23 May 2017
doi: 10.3389/fphar.2017.00269

Plastic and Neuroprotective Mechanisms Involved in the Therapeutic Effects of Cannabidiol in Psychiatric Disorders

Alline C. Campos[1], Manoela V. Fogaça[1], Franciele F. Scarante[1], Sâmia R. L. Joca[2], Amanda J. Sales[2], Felipe V. Gomes[3], Andreza B. Sonego[1], Naielly S. Rodrigues[1], Ismael Galve-Roperh[4,5] and Francisco S. Guimarães[1]*

Pharmacology & Therapeutics xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

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

ELSEVIER

Endocannabinoid system and mood disorders: Priming a target for new therapies

Vincenzo Micale [a,b,c,*], Vincenzo Di Marzo [d], Alexandra Sulcova [a], Carsten T. Wotjak [b], Filippo Drago [c]

What is the evidence?

Inflammation	Evidence
Pre-clinical	+++
Observations	++
Clinical trial	+

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:1276–1280

Cannabis Induces a Clinical Response in Patients With Crohn's Disease: A Prospective Placebo-Controlled Study

Published in final edited form as:
Inflamm Bowel Dis. 2013 December : 19(13): 2809–2814. doi:10.1097/01.MIB.0000435851.94391.37.

Marijuana Use Patterns Among Patients with Inflammatory Bowel Disease

High Hope for Medical Marijuana in Digestive Disorders

Robert W. Isfort, MD[1] and Mark E. Gerich, MD[1]

Am J Gastroenterol 2016; 111:159–160; doi:10.1038/ajg.2016.3; published online 2 February 2016

Dig Dis Sci (2017) 62:1615–1620
DOI 10.1007/s10620-017-4540-z

ORIGINAL ARTICLE

Low-Dose Cannabidiol Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial

Timna Naftali[1,2] · Refael Mechulam[3,4] · Amir Marii[5] · Gila Gabay[1,2] · Asaf Stein[1,2] · Miriam Bronshtain[1,2] · Ido Laish[1,2] · Fabiana Benjaminov[1,2] · Fred M. Konikoff[1,2]

Arthritis Care & Research
Vol. 66, No. 6, June 2014, pp 797–801
DOI 10.1002/acr.22267

REVIEW ARTICLE

The Dilemma of Medical Marijuana Use by Rheumatology Patients

MARY-ANN FITZCHARLES,[1] DANIEL J. CLAUW,[2] PETER A. STE-MARIE,[1] AND YORAM SHIR[1]

Diabetes

- Observation: cannabis users better glucose control
- Useful in diabetic neuropathy
- Small study-use of CBD and THCV
  - reduced glucose, improved pancreatic f'n
- New isolate with clinical benefit

EDITORIAL

THE AMERICAN JOURNAL of MEDICINE®

Marijuana for Diabetic Control

The Impact of Marijuana Use on Glucose, Insulin, and Insulin Resistance among US Adults

Elizabeth A. Penner, MD, MPH,[a,b] Hannah Buettner, BA,[c] Murray A. Mittleman, MD, DrPH[b,c]

Efficacy and Safety of Cannabidiol and Tetrahydrocannabivarin on Glycemic and Lipid Parameters in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Pilot Study

Diabetes Care 2016;39:1777–1786 | DOI: 10.2337/dc16-0650

Glaucoma

Preclinical evidence supportive

Little clinical evidence to support use

Amer Glaucoma Society-recommends against its use

Ideal format for administration not found

Editorial

Cardiovascular Effects of Marijuana

Shereif Rezkalla, MD, FACP, FACC[1], Rachel Stankowski, PhD[2], and Robert A. Kloner, MD, PhD, FACC[3,4]

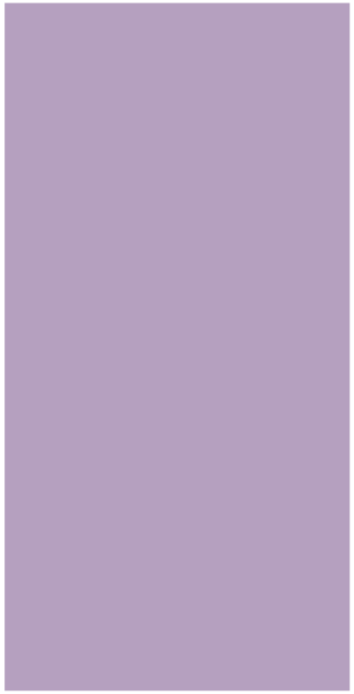
Journal of Cardiovascular Pharmacology and Therapeutics
2016, Vol. 21(5) 452-455

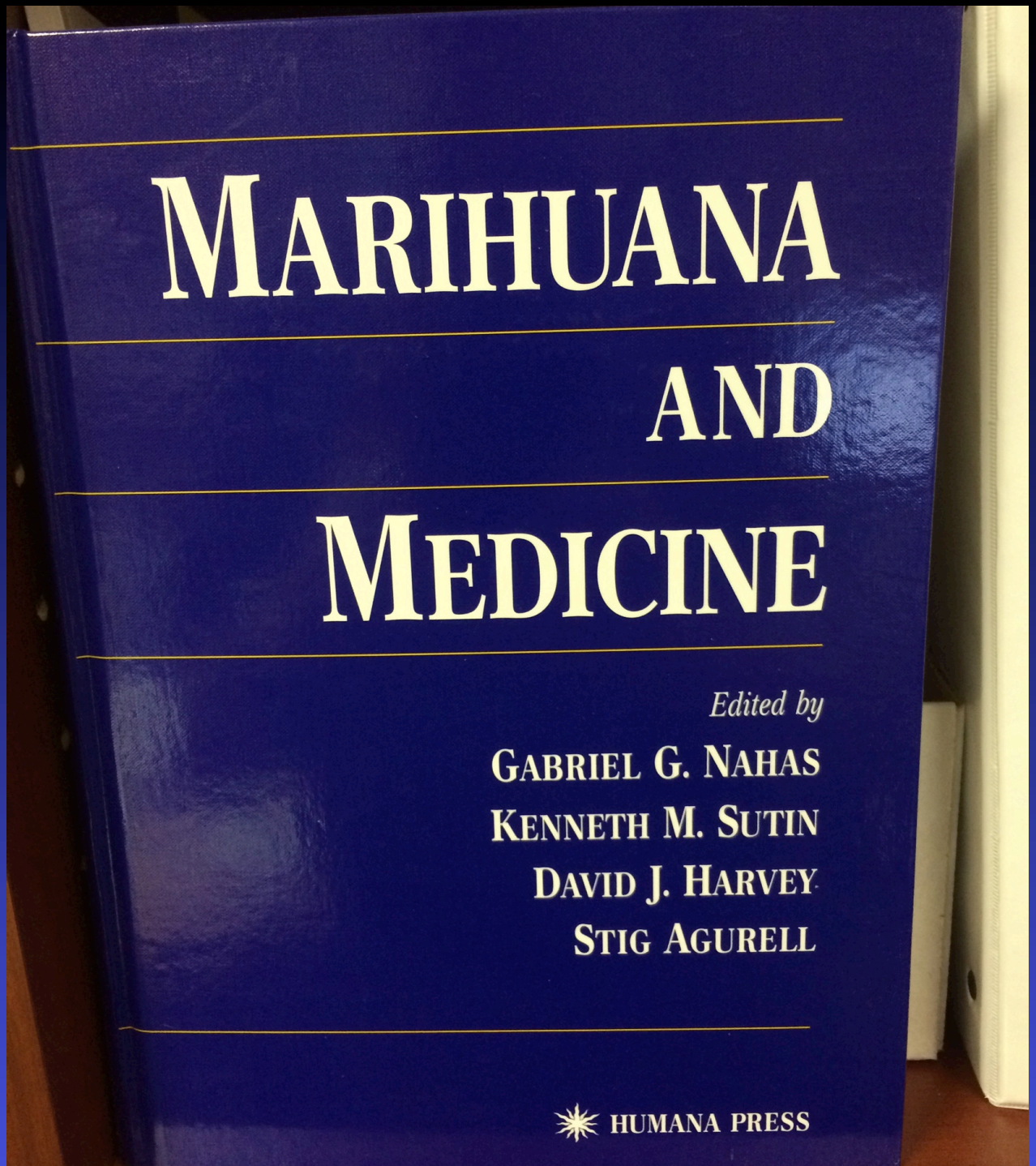
DOI: 10.1177/1074248415627874
cpt.sagepub.com
SAGE

Mostly deleterious effects upon coronary and cerebral arteries, vascular endothelium leading to MI and CVA
Arrhythmia more common in users
Advocating for national reporting system

Information for Health Care Professionals

Cannabis (marihuana, marijuana) and the cannabinoids

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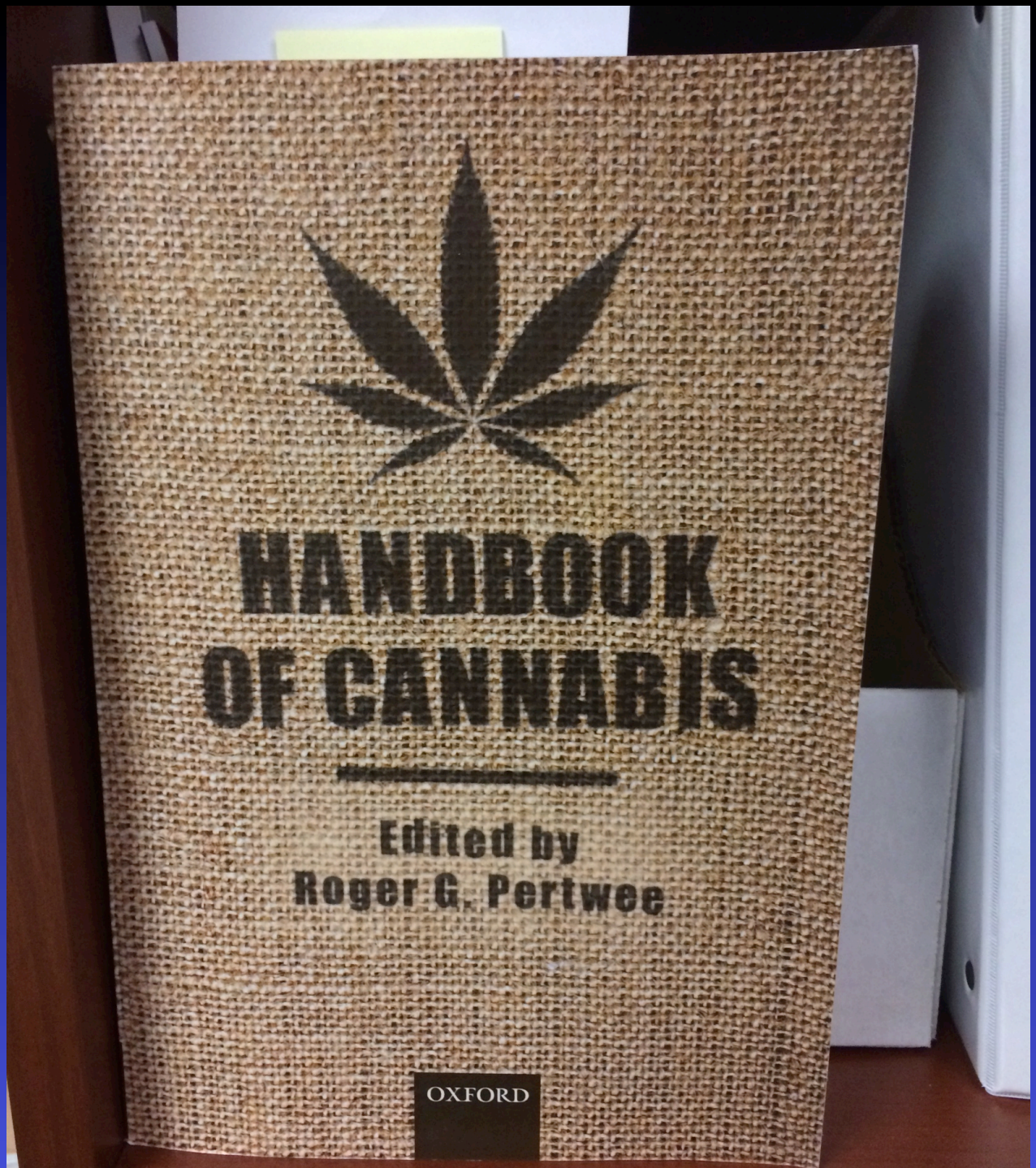
HANDBOOK
OF CANNABIS
Edited by
Roger G. Pertwee
OXFORD

Summary

- Cannabis & cannabinoids active in disease models
- Pre-clinical work evolving quickly
- Clinical benefits in a variety of diseases and conditions
- Not a panacea