LUCIAN M. MACREA, 15.02.2023

BEHANDLUNG VON NEUROPATHISCHEN SCHMERZEN: DIE ROLLE VON CANNABIS – KLINISCHE UND PRAKTISCHE ASPEKTE DER MAGISTRALEN REZEPTUR





https://pharmadavos.ch/

ISSAGES AND THE STATES OF THE

PANISA GOMPLEX PHENOMENA

NEUROPATHICPAIN

PHARMAGEUTICAL QUAL TYCAN BE A VALUABLE THERAPEUTIC OPTION

DOSAGE: "START LOW AND GO SLOW"

RISKS OF GANKABIS

RETIRED BOARD MEMBER OF THE SWISS SOCIETY OF CANNABIS IN MEDICINE



TRAVEL SUPPORT FOR CONSULTING OR LECTURING FROM THE FOLLOWING COMPANIES: ALMIRALL AG, 8304 WALLISELLEN; BOSTON SCIENTIFIC AG, SOLOTHURN, SWITZERLAND; GRÜNENTHAL PHARMA SCHWEIZ, MITLÖDI; SWIT-ZERLAND; MEDTRONIC, BERN, SWITZERLAND; MUNDIPHARMA MEDICAL. COMPANY, BASEL, SWITZERLAND; NEVRO MEDICAL LLC REINACH; ST. JUDE MEDICAL AG, ZURICH.



Burden of disease / & Pain

Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators*

oa OPEN ACCESS

Background The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017) includes a Lancet 2018; 392: 1789-858

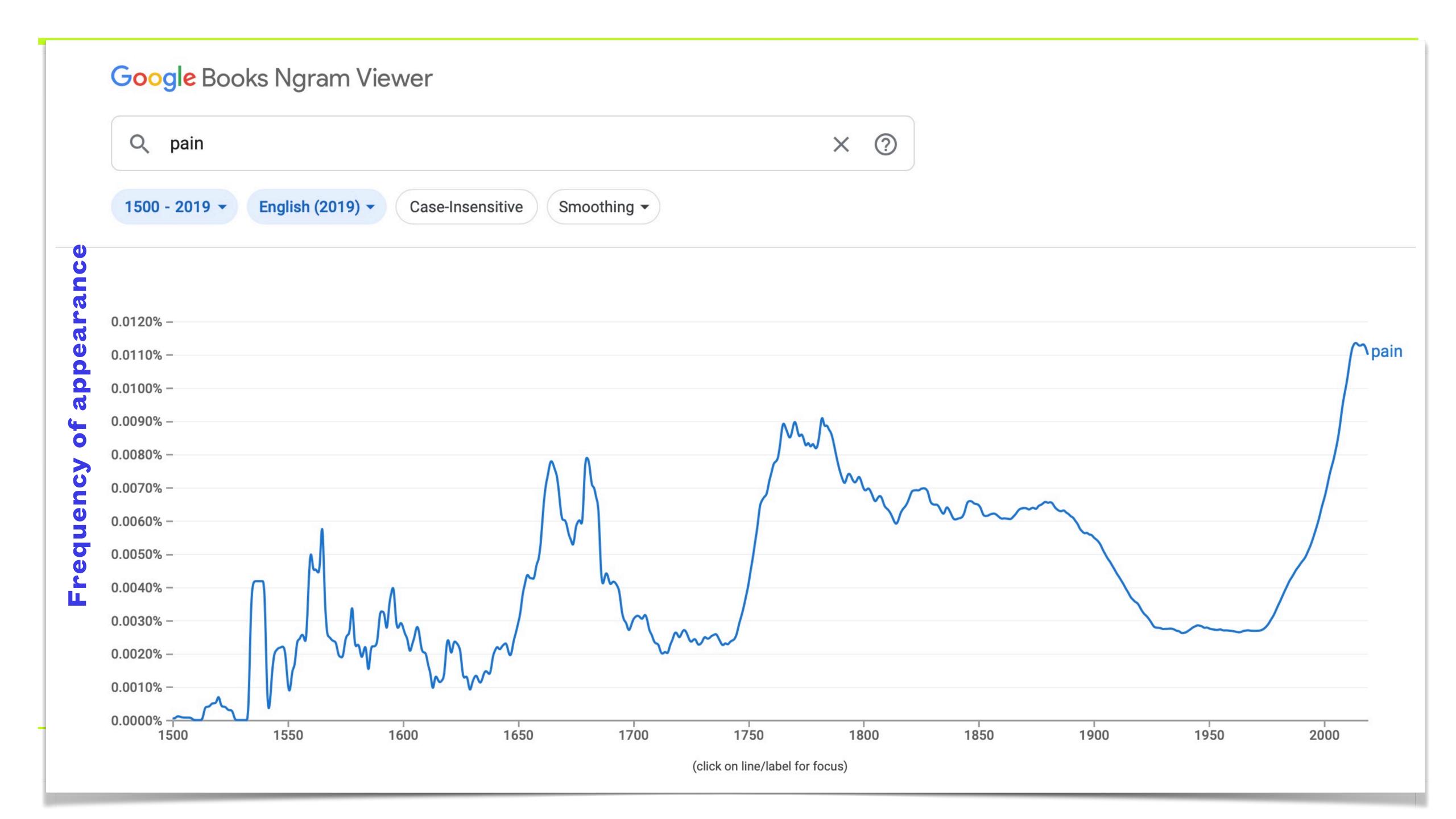
Males							- Section of the sect	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
1 Low back pain	1 Low back pain	30-2	3.9	-6.8	[1 Low back pain	17.8	4.6	-1.3
2 Headache disorders	2 Headache disorders	34.1	7.0	1.1		2 Headache disorders	15.5	2.6	1.5
3 Dietary iron deficiency	3 Diabetes	79.0	42.9	21.9		3 Diabetes	30.1	15.5	4.2
4 Depressive disorders	4 Depressive disorders	35.5	8.1	-0.1		4 Age-related hearing loss	24.2	10.2	-0.7
5 Age-related hearing loss	5 Age-related hearing loss	44.0	14.9	-0.1	/``··	5 Depressive disorders	14.8	1.9	-1.9
6 Diabetes	6 Neonatal disorders	51.5	20-9	27.3		6 Neonatal disorders	22.1	8.4	11.4
7 COPD	7 Dietary iron deficiency	-1.1	-21.1	-15·1		7 Drug use disorders	21.5	7.9	7.9
8 Drug use disorders	8 COPD	32.6	5⋅8	-9.5		8 Blindness and vision impairment	23.6	9.7	-1.5
9 Blindness and vision impairment	9 Drug use disorders	34.8	7.6	4.5		9 COPD	17-9	4.7	-8.2
10 Other musculoskeletal	10 Blindness and vision impairment	36⋅2	8.7	-5·3		10 Other musculoskeletal	16.4	3.3	-2.9
11 Neonatal disorders	11 Other musculoskeletal	41.5	12.9	1.0	-	11 Neck pain	22.3	8.5	0.4
12 Neck pain	12 Neck pain	42.6	13.8	-0.9	\\	12 Dietary iron deficiency	-5.6	-16-2	-13.7
13 Anxiety disorders	13 Anxiety disorders	31.2	4.7	0.1		13 Anxiety disorders	13.6	0.8	0.0
14 Falls	14 Falls	23.1	-1.7	-11.4		14 Falls	25.0	11.0	3.1
15 Vitamin A deficiency	15 Alcohol use disorders	39-2	11.1	3.8		15 Stroke	46.0	29.6	13.1
16 Alcohol use disorders	16 Oral disorders	38.7	10.8	-2.4		16 Oral disorders	20.5	7.0	-1.8
17 Congenital anomalies	17 Congenital anomalies	22.5	-2.2	-0.5	./ ``\	17 Alcohol use disorders	7.9	-4.2	-6.3
18 Oral disorders	18 Stroke	44.4	15.3	-2.4	X	18 Other mental disorders	17.2	4.1	-0.1
19 Other mental disorders	19 Other mental disorders	36.8	9.2	-0.2		19 Schizophrenia	16.7	3⋅6	-0.4
20 Schizophrenia	20 Schizophrenia	37.7	9.9	-0.1	``	20 Congenital anomalies	12.0	-0.6	0.3
21 Stroke Leading causes 1990	24 Vitamin A deficiency Leading causes 2007	Mean percentage change in number of	Mean percentage change in all-age	Mean percentage change in age standardised		30 Vitamin A deficiency eading causes 2017	and n	nunicable, mate utritional diseas communicable o	ses

YLD rate,

1990-2007 1990-2007 1990-2007

YLDs,

YLD rate,





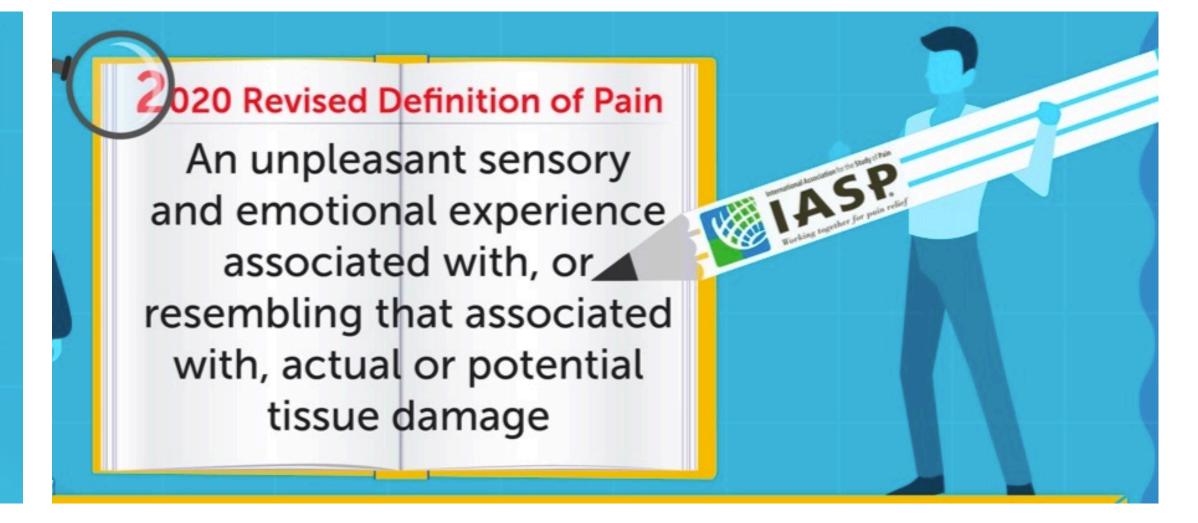
Content

- Medical Pain definition
- Neurobiology of pain
- Cannabis Evidence Risks and Hazard
- Pain Treatments
- Treatment in CH/Personal experience

Pain Definition

1979 Definition of Pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage



- Schmerz ist ein unangenehmes Sinnes- und Gefühlserlebnis, das mit einer tatsächlichen oder drohenden Gewebeschädigung verknüpft ist oder mit Begriffen einer solchen Schädigung beschrieben wird.
- Une expérience sensorielle et émotionnelle désagréable associée ou ressemblant à celle associée à une lésion tissulaire réelle ou potentielle



Pain Types

Table 1

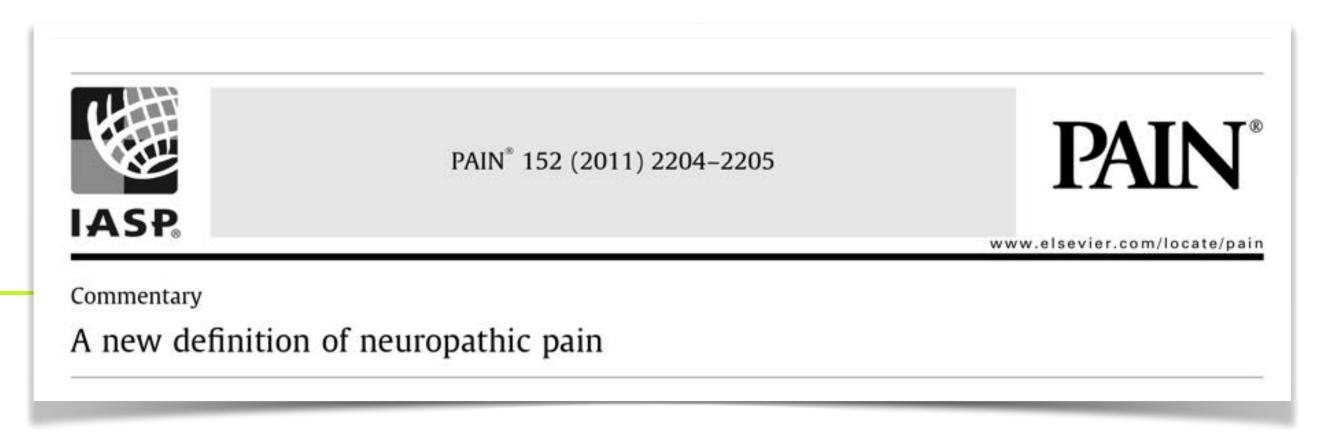
Historical overview of mechanistic pain terminology.

	Nociceptive	Neuropathic
1994*	Not defined	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
2005*	Pain due to stimulation of primary nociceptive nerve endings	Pain due to lesion or dysfunction of the nervous system
2007-2010	Pain due to activation of primary nociceptors	
	Pain arising from activation of nociceptors	
	Pain resulting from noxious stimulation of normal tissue with	
	a normal somatosensory nervous system	
2011*	Pain that arises from actual or threatened damage to non- neural tissue and is due to the activation of nociceptors	Pain caused by a lesion or disease of the somatosensory nervous system

^{*} Adopted by IASP council in those years.

Neuropatic pain - Definition

- Pain caused by a lesion or disease of the somatosensory nervous system.
- lesion is commonly used when diagnostic investigations (e.g. imaging, neurophysiology, biopsies, lab tests) reveal an abnormality or when there was obvious trauma.
- disease is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, diabetes mellitus, genetic abnormality)
- Somatosensory refers to information about the body per se including visceral organs, rather than information about the external world (e.g., vision, hearing, or olfaction).



Epidemiology of neuropathic pain

• 8% der Bevölkerung (9.3% für Diabetes) mit neuropathische Schmerzen

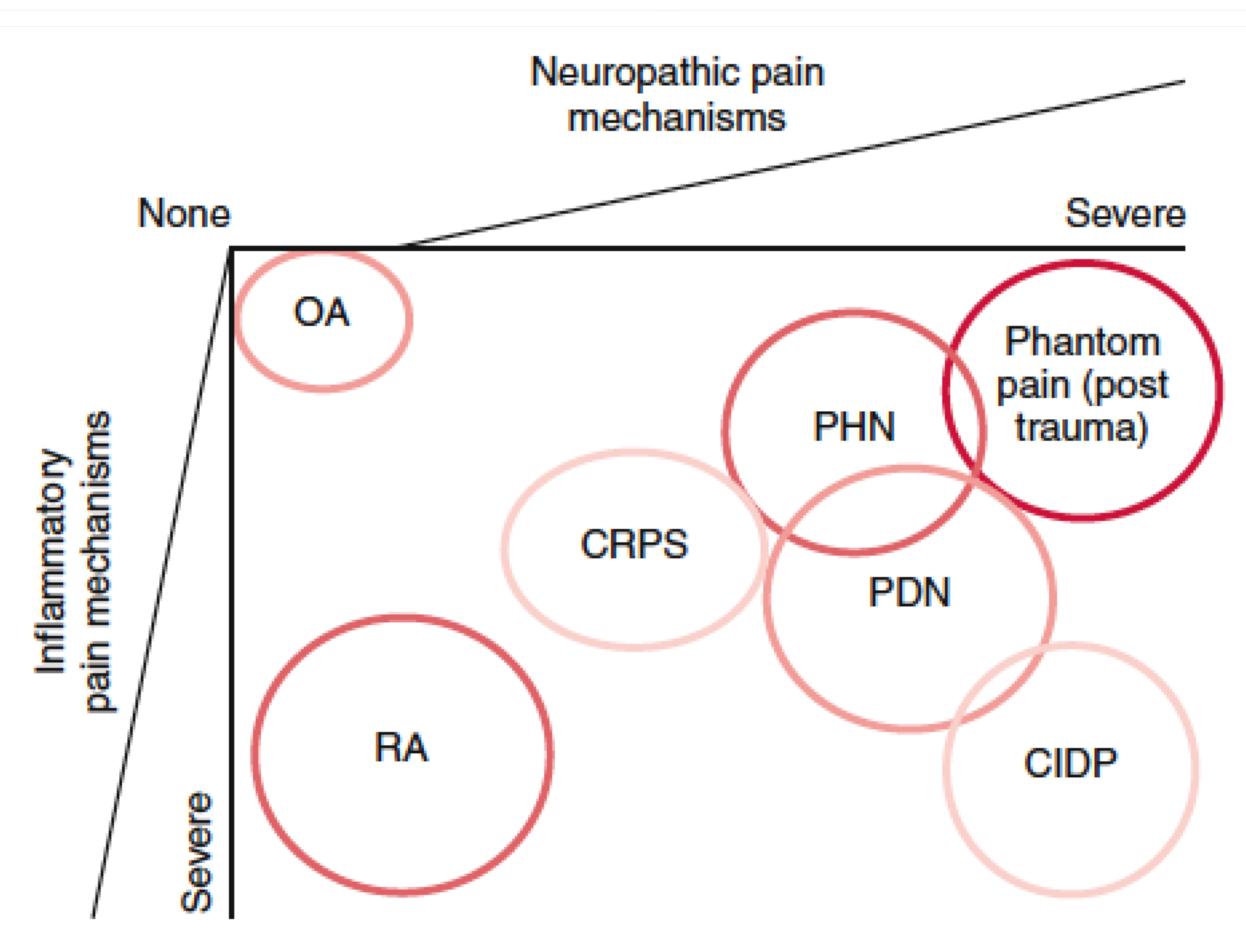


Figure 6-1. Spectrum of pathophysiologic mechanisms, neuropathic and inflammatory, and their influence on common painful disorders. CIDP, chronic inflammatory diabetic polyneuropathy; CRPS, complex regional pain syndrome; OA, osteoarthritis; PDN, painful diabetic neuropathy; PHN, postherpetic neuralgia; RA, rheumatoid arthritis.

Pathophysiology

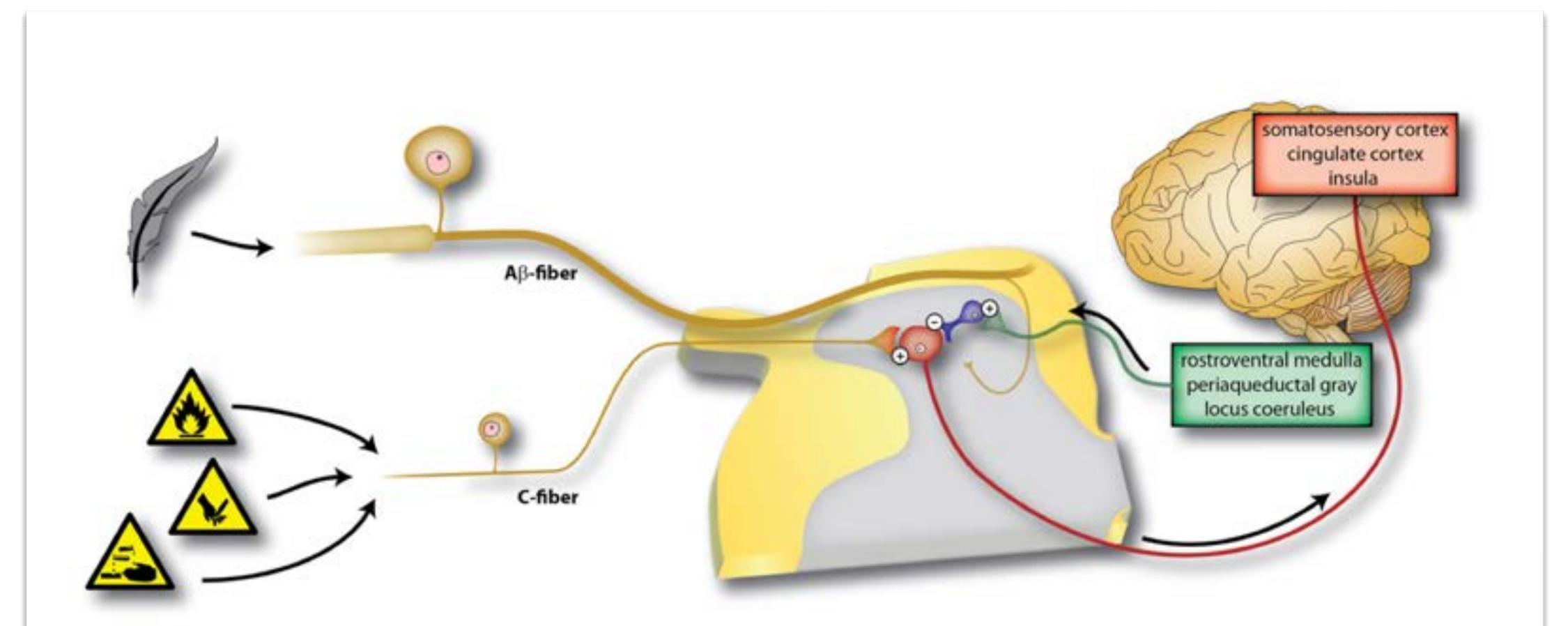


Figure 1. The Nociceptive Pain Circuit

High-threshold nociceptors are activated by intense mechanical, thermal, or chemical stimuli and feed this information to nociceptive neurons in the spinal cord, which project via the thalamus to cortical areas generating the sensory and emotional qualities of pain. These spinal cord pathways are subject to descending inhibitory and facilitatory influences from the brainstem. Normally, activity in low-threshold afferents is carried by independent peripheral and central pathways and only generates innocuous sensations.

Nociplastic Pain







Do we need a third mechanistic descriptor for chronic pain states?

Eva Kosek^{a,*}, Milton Cohen^b, Ralf Baron^c, Gerald F. Gebhart^d, Juan-Antonio Mico^e, Andrew S.C. Rice^f, Winfried Rief^g, A. Kathleen Sluka^h

Definition:

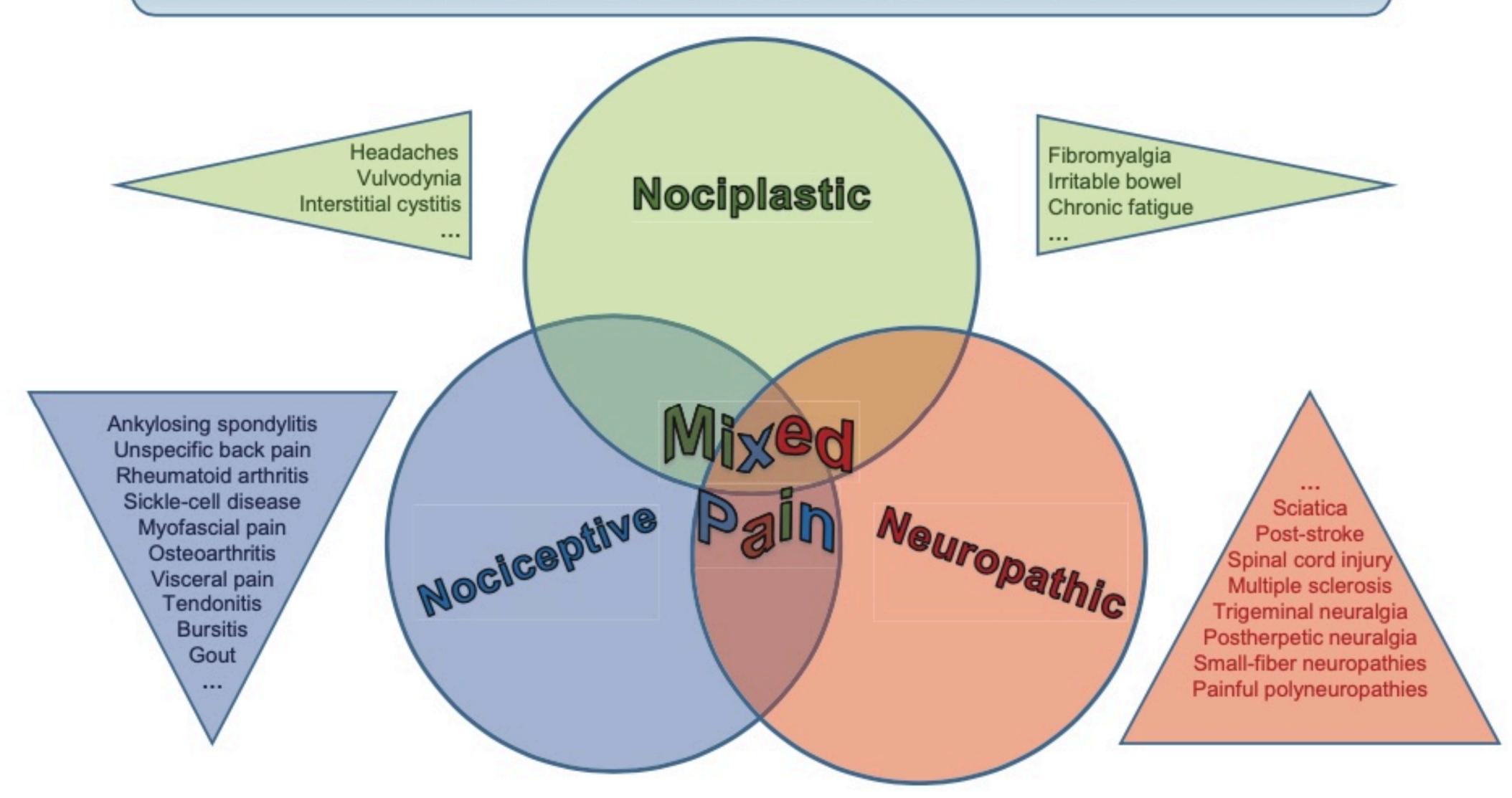
• Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

https://www.iasp-pain.org/resources/terminology/#pain

- Pain that arises from altered nociceptive function.
 - **IF** there is <u>no clear evidence of actual or threatened tissue damage</u> causing the activation of peripheral nociceptors
 - AND there is no evidence for disease or lesion of the somatosensory system causing the pain
 - THEN \square the pain is nociplastic **IF, AND ONLY IF**, it arises from $\alpha ltered$ nociception.

Potential mixed pain states

Sciatica, Low back pain, Neck pain, Cancer pain, Osteoathritis pain, Chronic postsurgical pain,
Musculoskeletal disorders, Chronic Temporomandibular disorders, Lumbar spinal stenosis, Pain in Fabry Disease,
Chronic joint pain, Painful ankylosing spondylitis, Leprosy, Burning mouth syndrome, ...



Chronic Primary Pain - Definition

- Chronic primary pain is chronic pain in:
 - one or more anatomical regions
 - that persists or recurs for longer than 3 months,
 - and that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) or
 - functional disability (interference in daily life activities and reduced participation in social roles)
- is multifactorial: biological psychological and social factors contribute to the pain syndrome.

Chronic Primary Pain - Diagnostic criteria

Conditions A to C are fulfilled

- A. Chronic pain (persistent or recurrent for longer than 3 months) is present
- B. The pain is associated with at least one of the following:
 - B.1. Emotional distress due to pain is present.
 - B.2. The pain interferes with daily life activities and social participation.
- C. The pain is not better accounted for by another chronic pain condition.



Nicholas et al., 2019

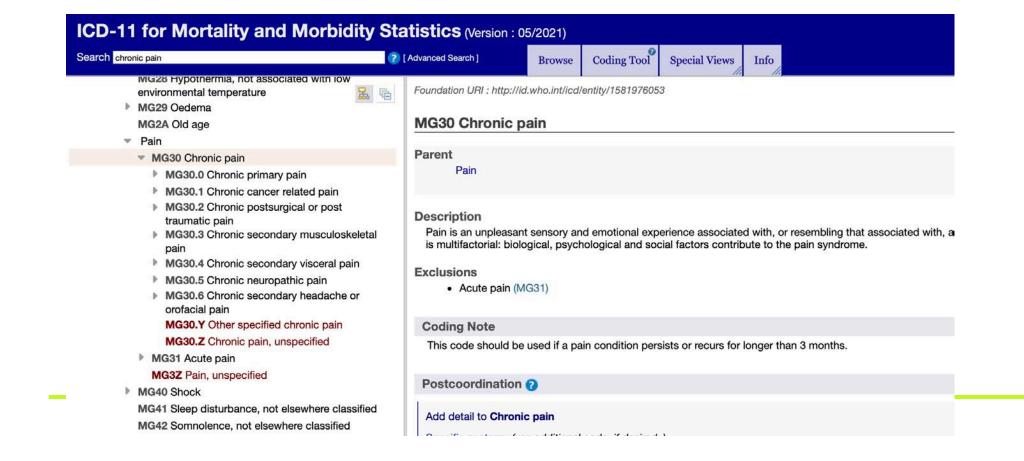
Advantages for GP/Pharmacist - red flags

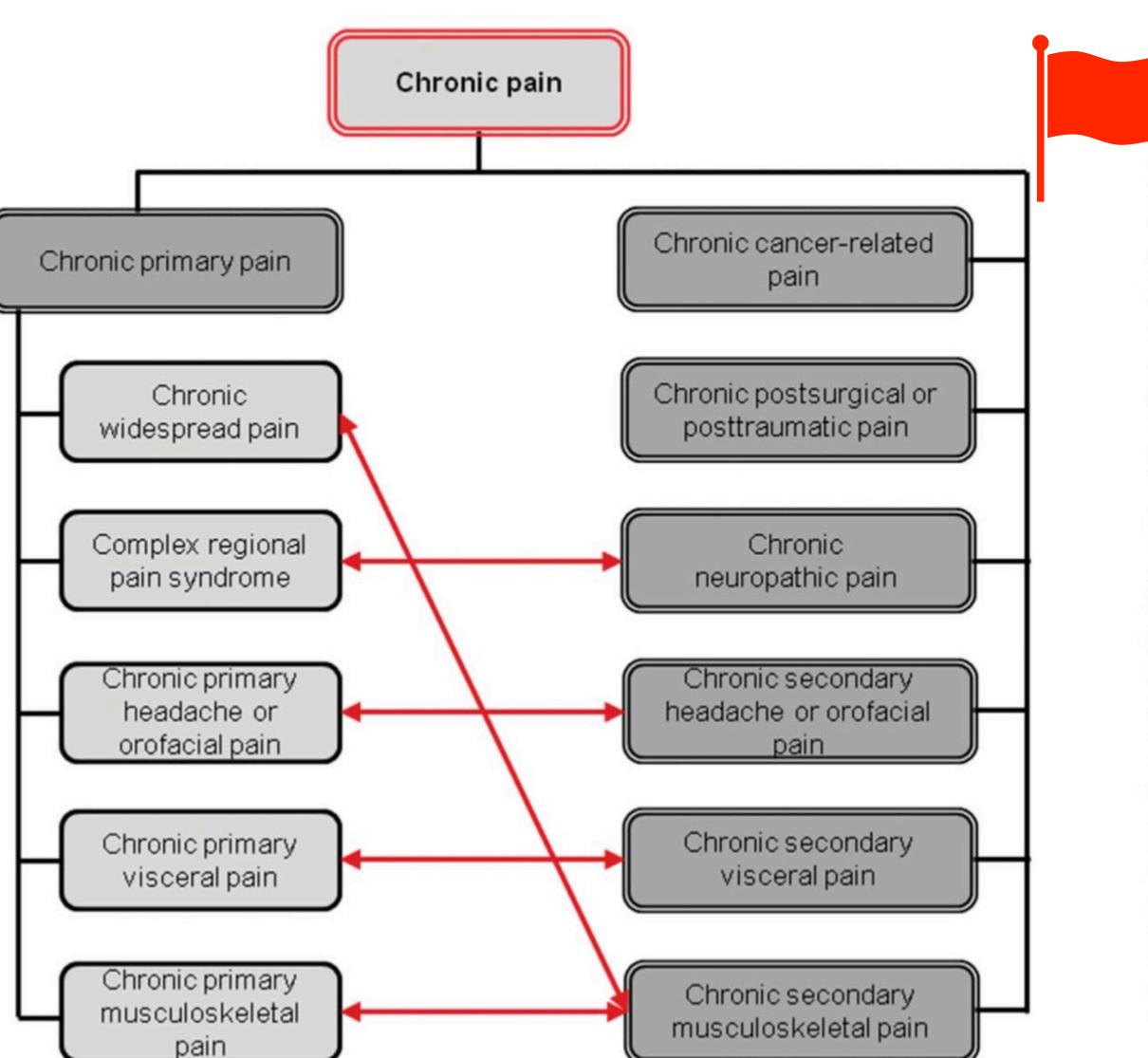


Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the *International Classification of Diseases* (ICD-11)

Rolf-Detlef Treede^{a,*}, Winfried Rief^b, Antonia Barke^b, Qasim Aziz^c, Michael I. Bennett^d, Rafael Benoliel^e, Milton Cohen^f, Stefan Evers^g, Nanna B. Finnerup^{h,i}, Michael B. First^j, Maria Adele Giamberardino^k, Stein Kaasa^{l,m,n}, Beatrice Korwisi^b, Eva Kosek^o, Patricia Lavand'homme^p, Michael Nicholas^q, Serge Perrot^r, Joachim Scholz^s, Stephan Schug^{t,u}, Blair H. Smith^v, Peter Svensson^{w,x}, Johan W.S. Vlaeyen^{y,z,aa}, Shuu-Jiun Wang^{bb,cc}

7 diagnostic groups





secondary pain

Content

- Medical Pain definition
- Neurobiology of pain
- Cannabis Evidence Risks and Hazard
- Pain Treatments
- Treatment in CH/Personal experience

I. Definition

HISTOIRE



Platon et Aristote
La douleur est une «Passion de l'âme »

(une émotion)

17° siècle



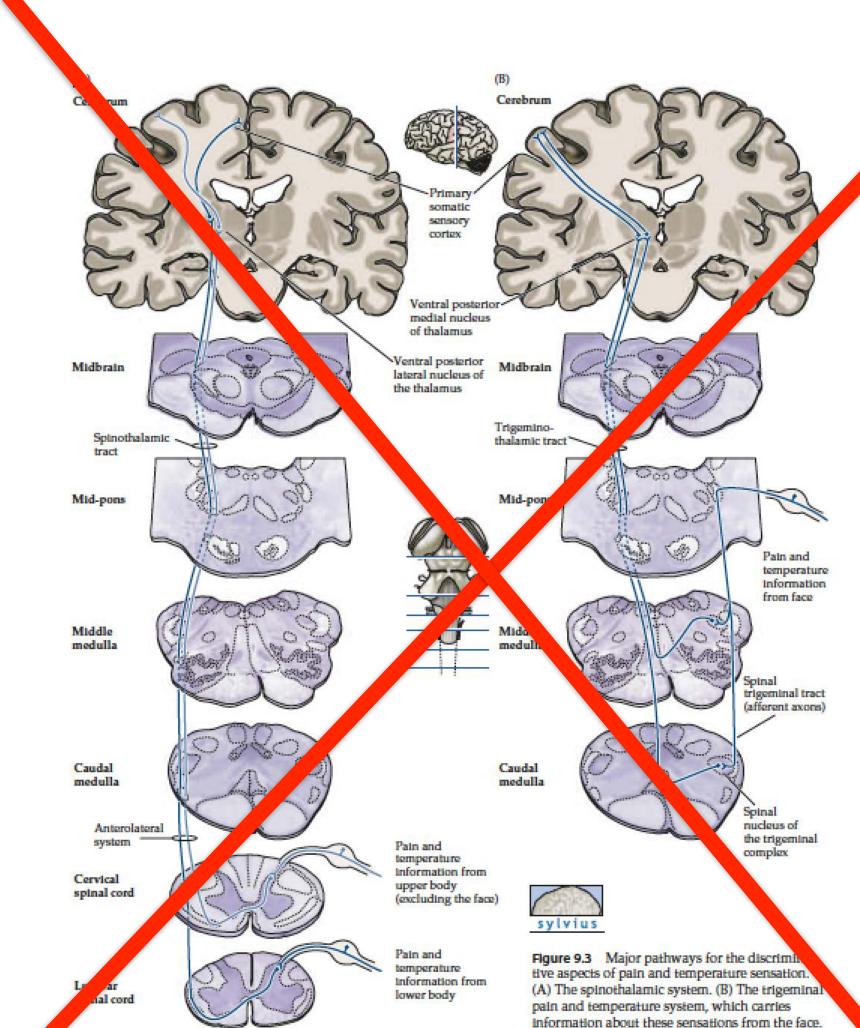
René Descartes



(une sensation)

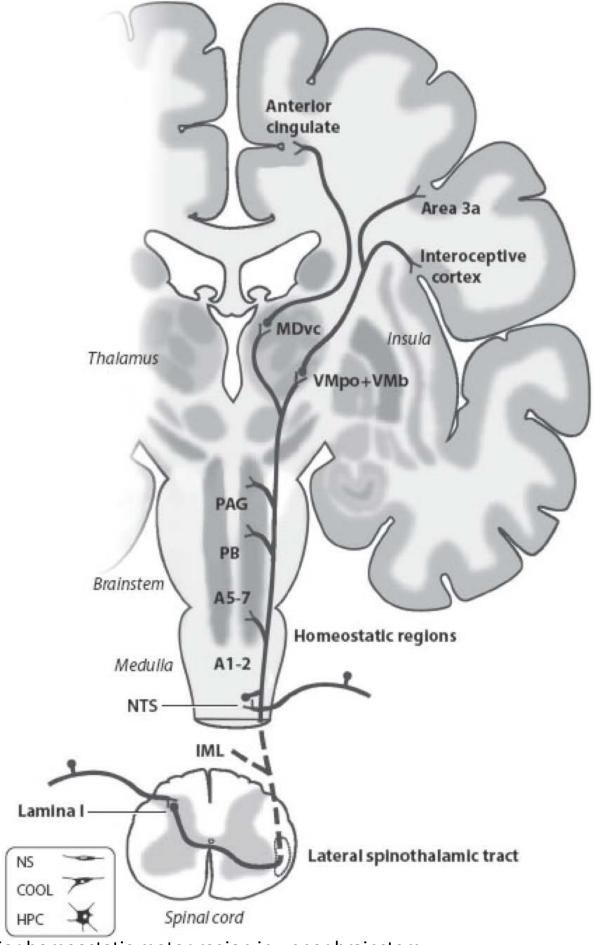
les particules de ce feu qui comme on le sait peuvent se mobiliser à grande vitesse, ont le pouvoir de mobiliser le point de la peau qu'elles touchent......

II. Anatomie of nociception (acute)



≠ Pain

corresponds to nociception



PAG - periaqueductal gray; major homeostatic motor region in upper brainstem

PB - parbrachial nucleus, major homeostatic sensory region in mi d/upper brain

NTS - nucleus tractus solitarius

MDvc - ventral caudal part of the medial dorsal nucleus of the thalamus

VMpo posterior part of the ventral medial nucleus of the thalamus

VMb basal part of the ventral medial nucleus of the thalamus

IML - intermediolateral cell column; lateral horn T1-T4 spinal segments; contains sympathetic preganglionic motro output neurons

NS - nocicieptive specific lamina I neuron.

COOL cooling-sensitive thermoreceptive specific lamina I neuron

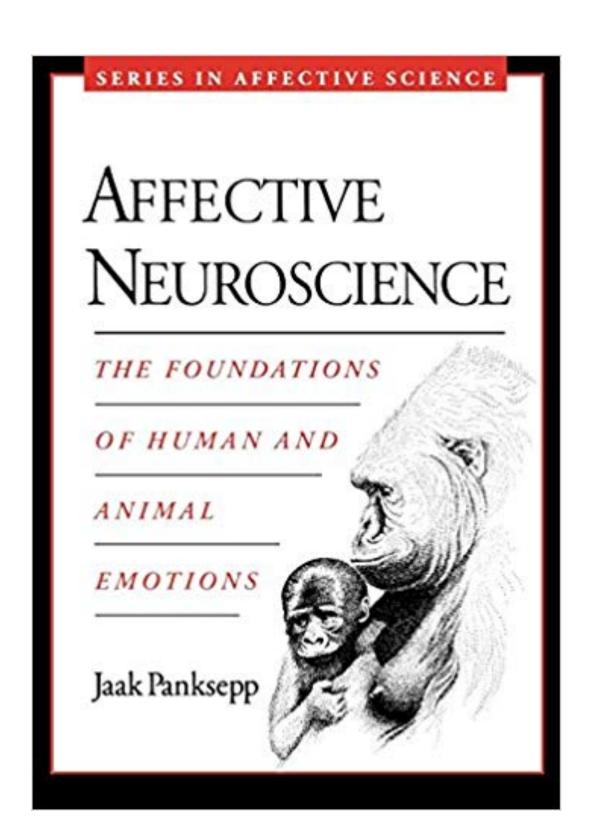
HPS - Heat, pinch and cold ; polymodal nociceptive lamina I neuron

I. Definition

How Emotions are Made a sort of pattern theory of emotions

"Fascinating . . . a thought-provoking journey into emotion science." - Wall Street Journal HOW EMOTIONS ARE MADE The Secret Life of the Brain "A singular book, remarkable for the freshness of its ideas and the boldness and clarity with which they are presented." - Scientific American LISA FELDMAN BARRETT

Primal emotions of 'PLAY', 'PANIC/ GRIEF', 'FEAR', 'RAGE', 'SEEKING', 'LUST' and 'CARE'



Pattern theory

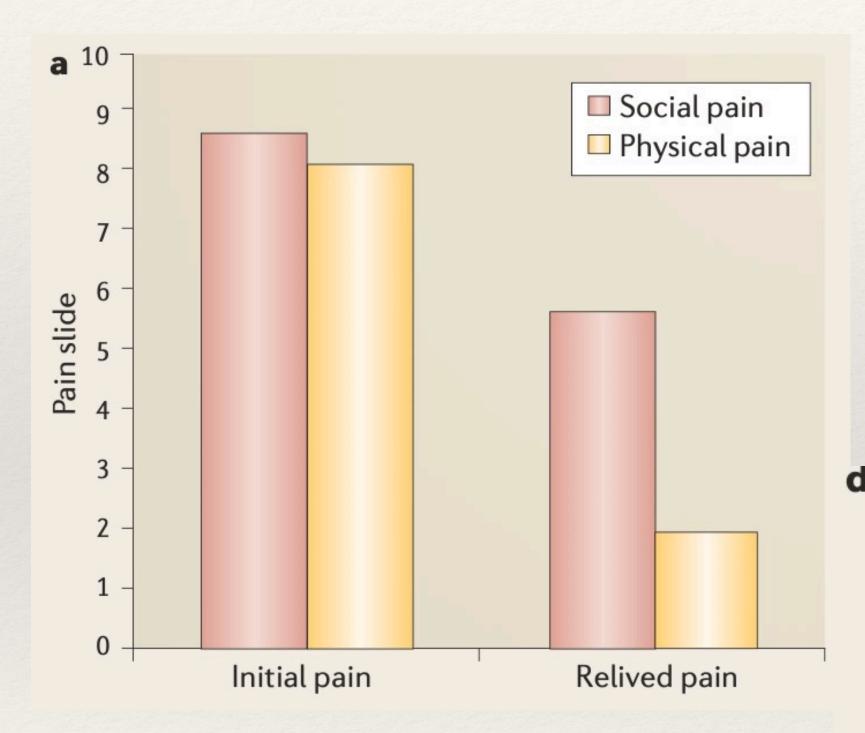
Specificity theory

Both are right!!!

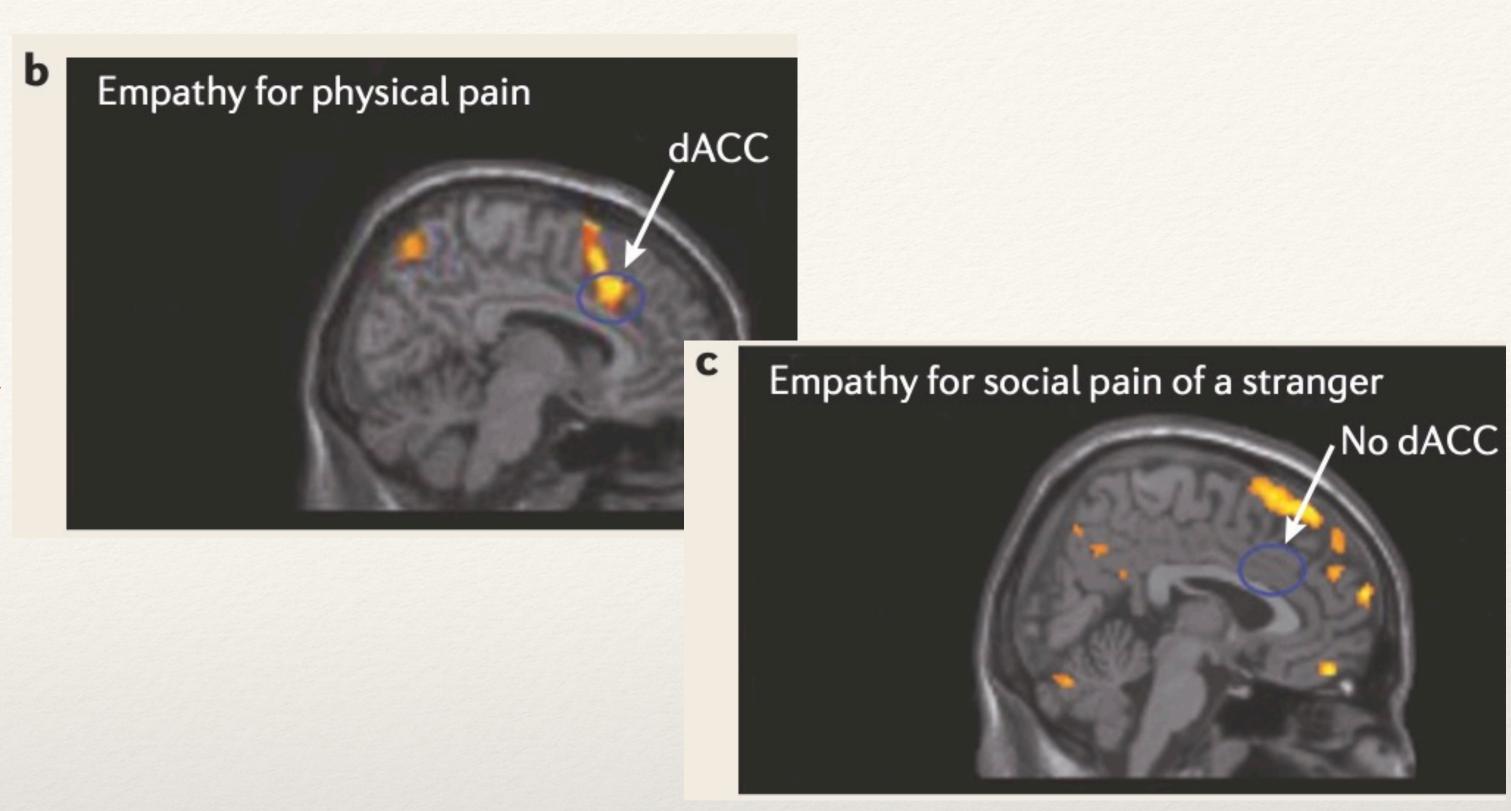
We speak of pains and not of pain!!!

It depends on the type of pain

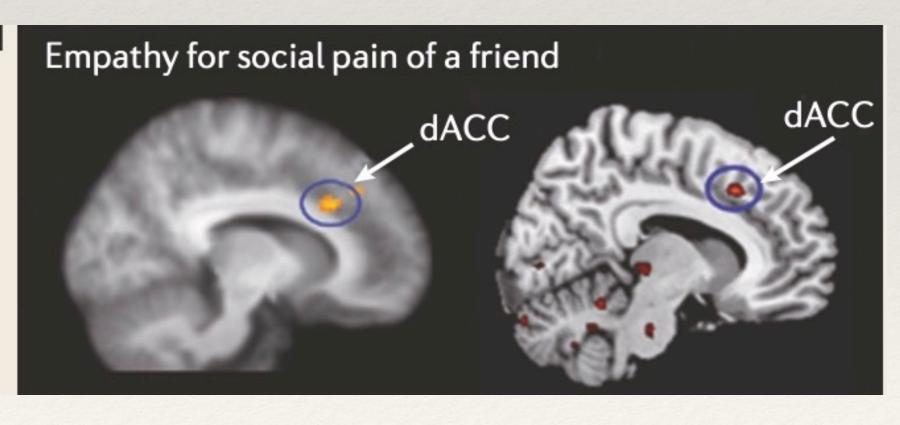
Differences between physical and social pain



observing the pain of others (empathy)

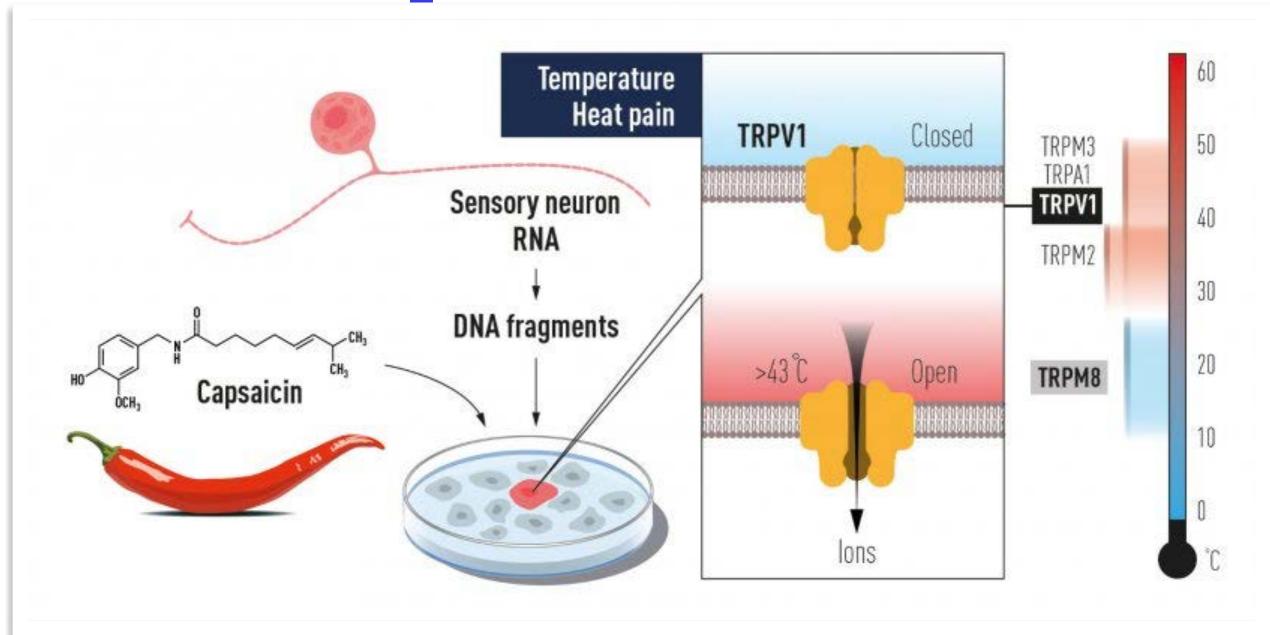


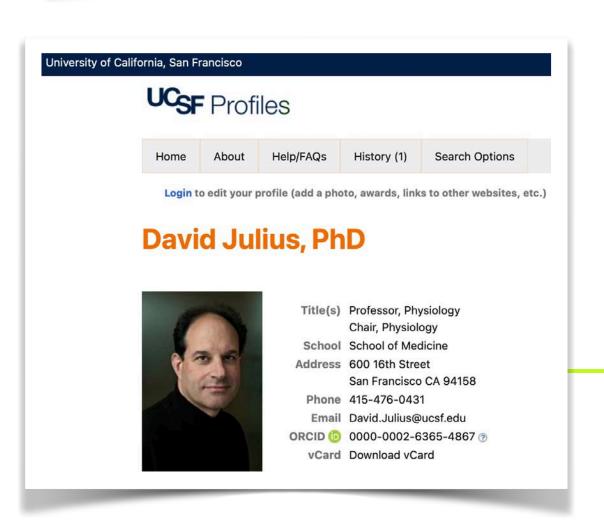
An avoidable tragedy

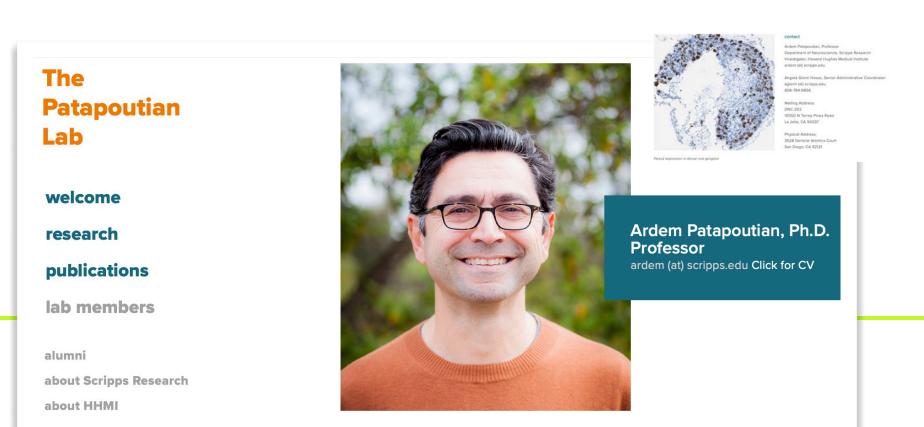


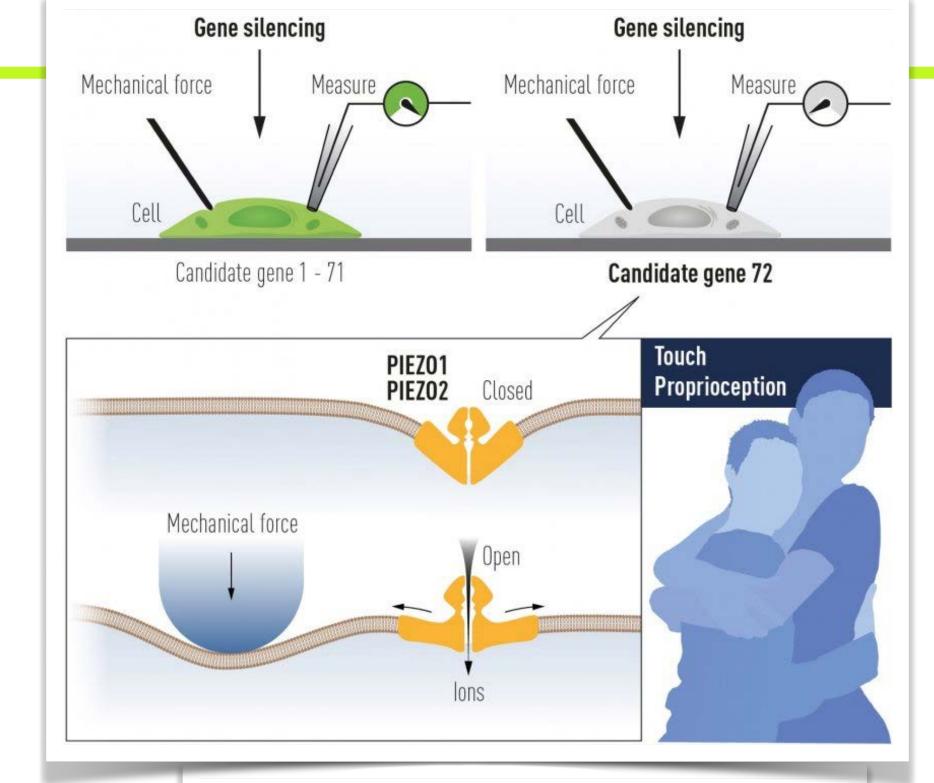


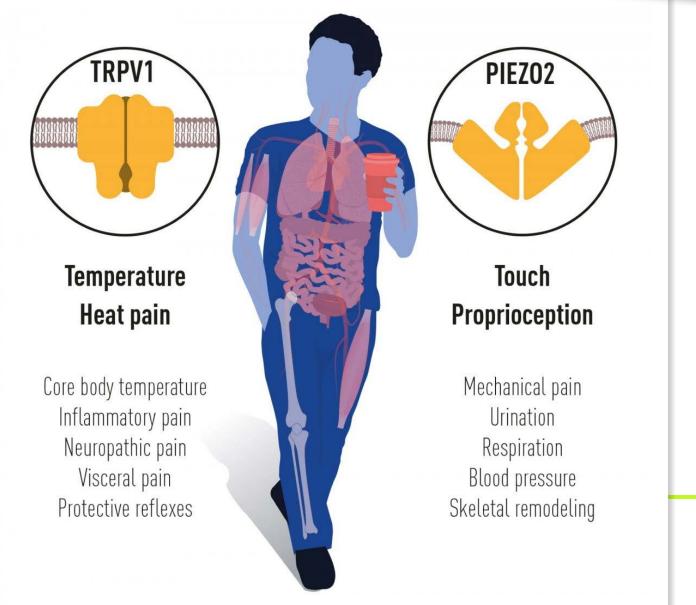
Nobelpreis 2021











Complicated

Complex





Content

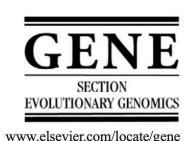
- Medical Pain definition
- Neurobiology of pain
- Cannabis Evidence Risks and Hazard
- Pain Treatments
- Treatment in CH/Personal experience

ENDOGANNABINOD SYSTEM

- Plants they do not have CBRs, nor do endocannabinoids, yet plants produce & entourage compounds, and these compounds receptors
- Insects can synthesize 2-AG despite the
- Ticks expressed endocannabinoids in t them elude detection by mammalian ho



Available online at www.sciencedirect.com SCIENCE DIRECT

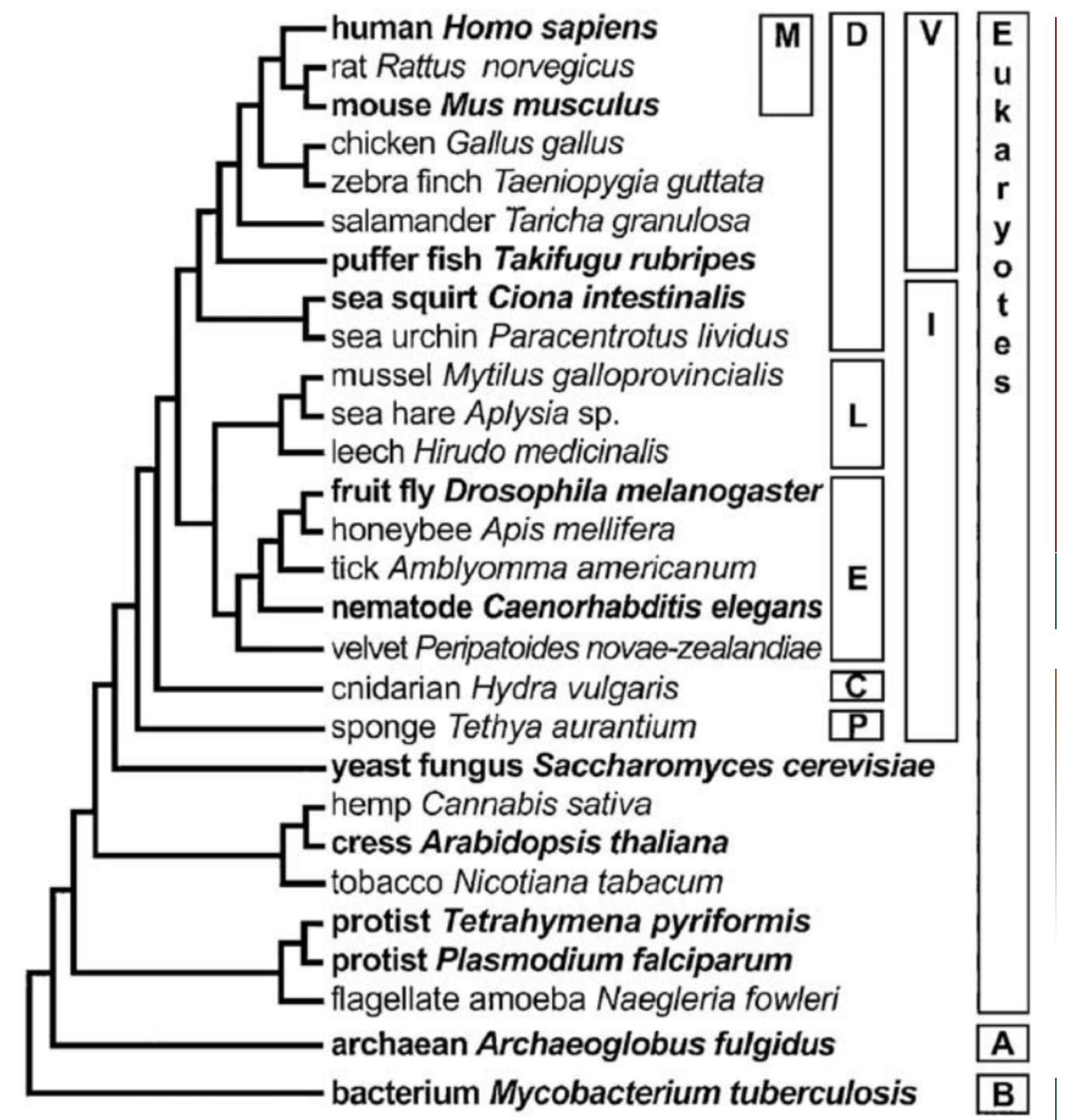


Evolutionary origins of the endocannabinoid system

John M. McPartland a,*, Isabel Matias b, Vincenzo DiMarzo b, Michelle Glass c

^a GW Pharmaceuticals, 53 Washington Street Ext., Middlebury, VT, 05753, USA

^b Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, 80078 Pozzuoli (Napoli), Italy ^c Department of Pharmacology, University of Auckland, Private Bag 92019, New Zealand



PAIN

Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies

David P. Finn^{a,*}, Simon Haroutounian^b, Andrea G. Hohmann^c, Elliot Krane^d, Nadia Soliman^e, Andrew S.C. Rice^e

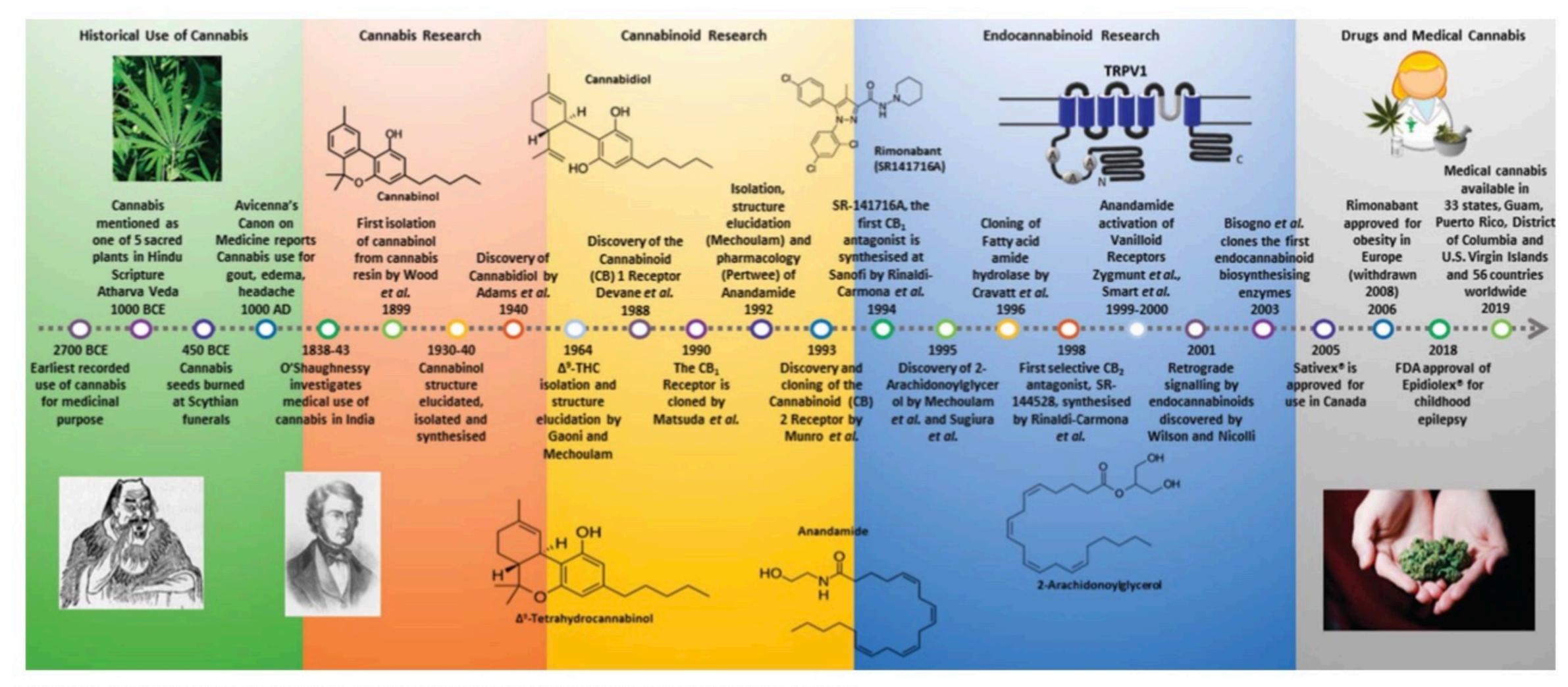


Figure 1. A historical timeline of key milestones in cannabis and cannabinoid research.



Systematic review and meta-analysis of cannabinoids, cannabis-based medicines, and endocannabinoid system modulators tested for antinociceptive effects in animal models of injury-related or pathological persistent pain

- meta-analysed 374 studies
- with 171 interventions for antinociceptive efficacy
- male animals (86%)

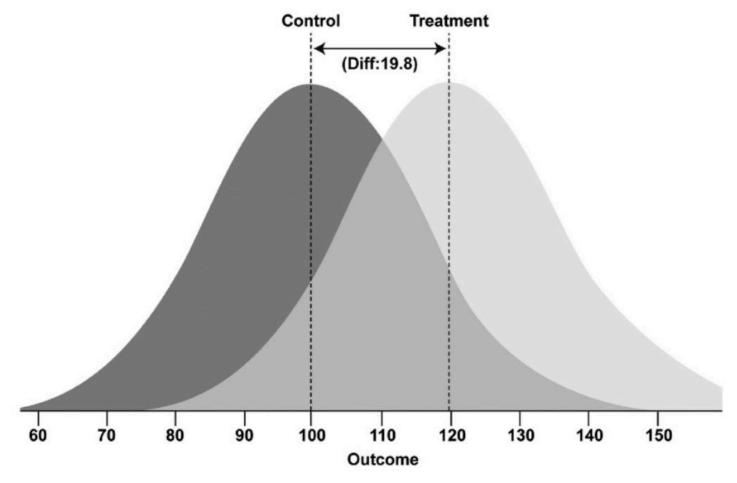


Figure 4. Visualisation of the overlap between control and treatment group distributions of the overall SMD effect size of 1.32.³⁴ The darker distribution curve represents the control group and the lighter distribution curve represents the treatment group. Animals within each group can fall anywhere within their respective curves, with increasing likelihood towards the peak; imagine each curve a hill of animals with single animals at the tail-ends of the distribution curve. SMD, standardised mean difference.

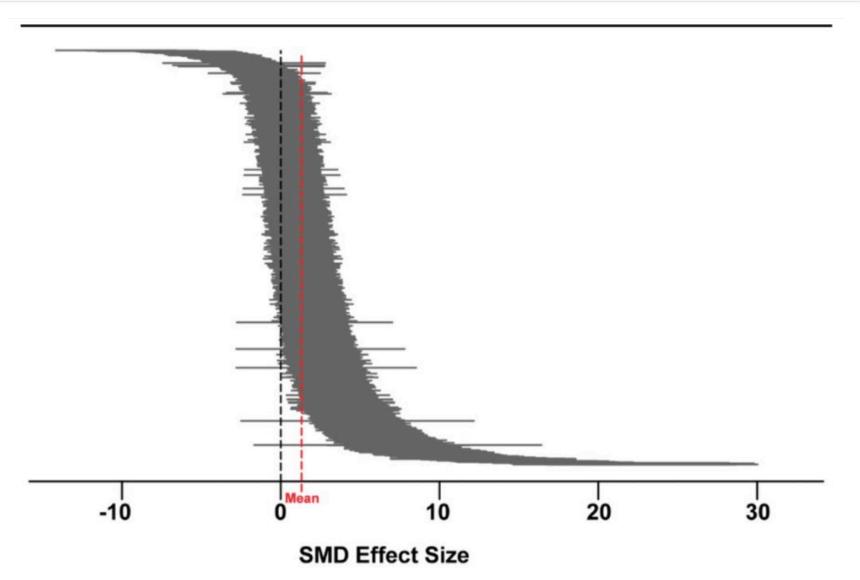
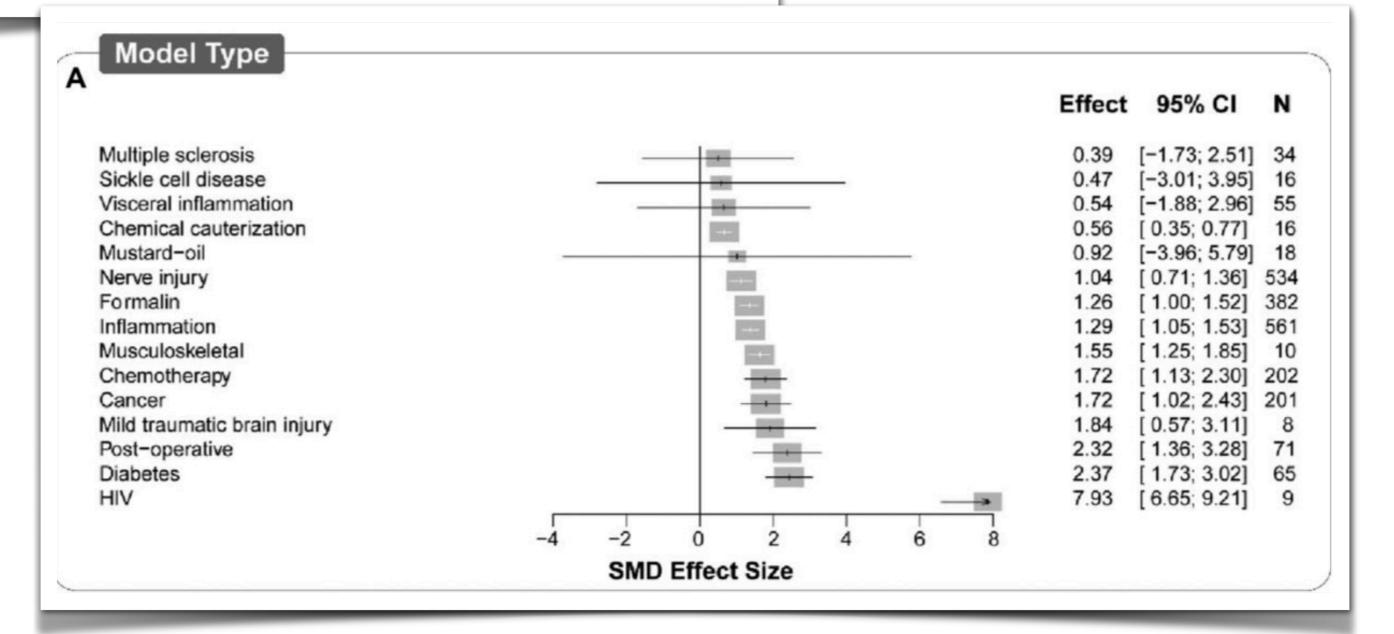
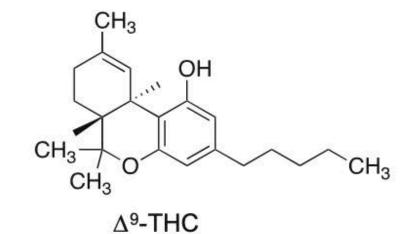


Figure 2. A caterpillar plot of the 1544 nested comparisons extracted from the 374 studies included in the meta-analysis. Hedges' g standardised mean differences (SMD) were calculated for each comparison. Effect sizes were pooled using the random-effects model and heterogeneity estimated with the restricted maximum-likelihood model (red dashed line indicates overall mean). Overall effect size = 1.321. Q = 4101.26, df 1543, P < 0.0001, $I^2 = 61.58\%$.

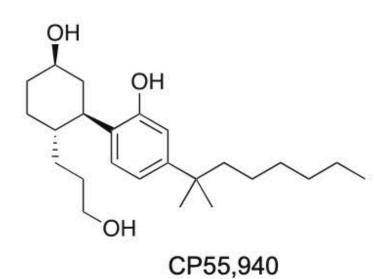


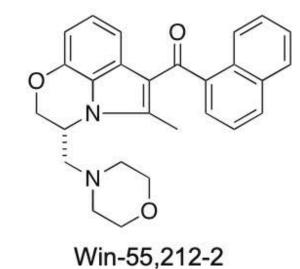
ENDOCANNABINOID SYSTEM - LIGANDS

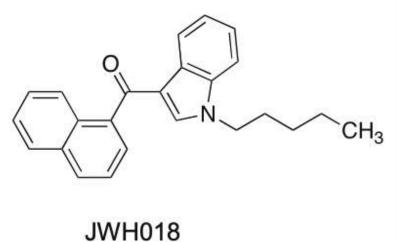
A. Phytocannabinoids



B. Synthetic Cannabinoids

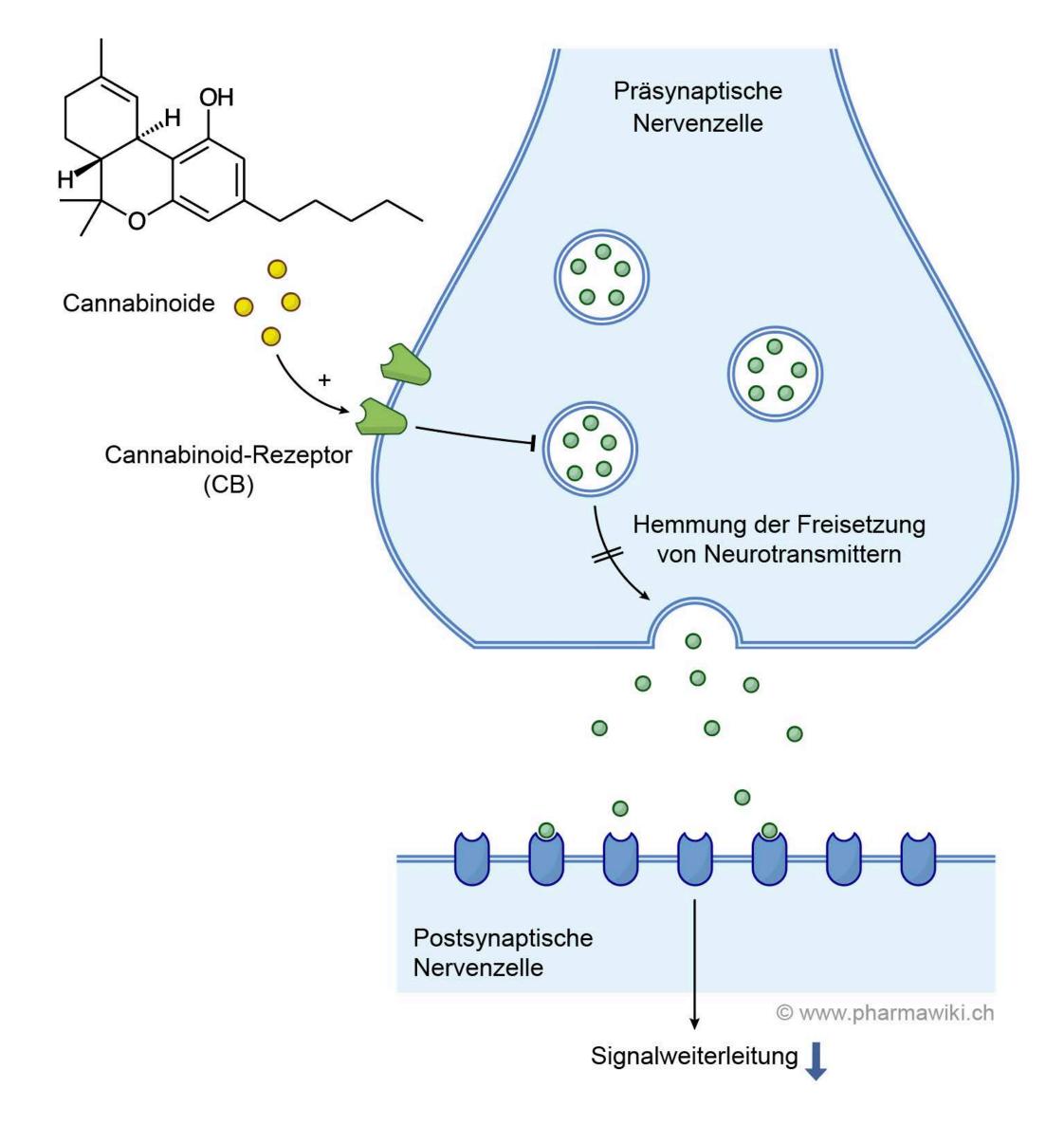






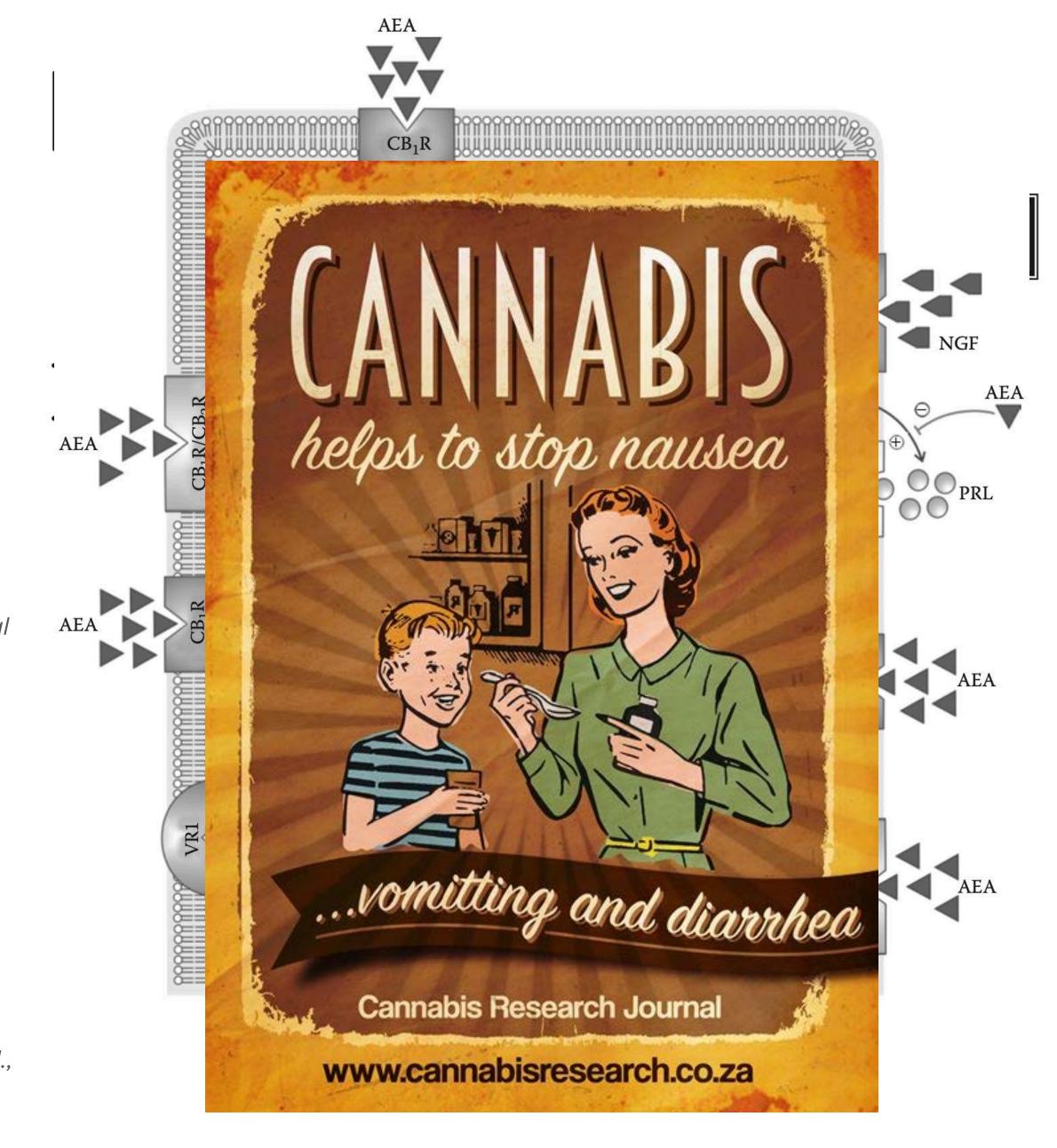
C. Endocannabinoids

Anandamide



ENDOCANNABINOID SYSTEM IN PERIPHERAL ORGAN SYSTEMS

- Modulation of the inflammation and immune response
- Involvement in Cancer
- Endocrine Function
 - tonic inhibition of the HPA axis (hypothalamic-pituitary-adrenal axis) at the hypothalamic level increased anxiety
 - steroid hormones corticosterone, estrogen, and progesterone modulate the expression of CB1 receptors in the hypothalamus and CNS (Rodríguez de Fonseca et al., 1994; González et al., 2000; Paria et al., 2001)
- Fertilization, Pregnancy, and Development
 - chronic heavy marijuana smokers may experience fertility problems, but this view remains controversial (Chopra and Jandu, 1976; Smith and Asch, 1984; Mueller et al., 1990; Grotenhermen, 1999)



ENDOCANNABINOID SYSTEM IN PERIPHERAL ORGAN SYSTEMS

Gastrointestinal Function

- Antimotility effects of cannabinoids are thought to be due to inhibition of evoked acetylcholine release, substance P
- 2-AG is a potent emetogen that produces vomiting
- models of GI pathological states exhibit an overexpression of enteric intestinal cannabinoid CB1 receptors

Cardiovascular System

- Vasorelaxant effect in Vitro
- in Vivo observed appear dependent on the prevailing conditions, e.g., the absence or presence of anesthetic



Abb. 2 Holzschnitt aus dem "New Kreüterbuch" des Leonhardt Fuchs, 1543.

ENDOCANNABINOID SYSTEM - MODULTATION OF PAIN

CENTRALLY MEDIATED ANALGESIA

 Descending pain modulation network the rostral ventro- lateral medulla, the amygdala, and the periacqueductal gray (PAG), is densely populated with CB1 receptors

ANXIETY-RELATED BEHAVIOR

- low doses of cannabinoid agonists usually induce an anxiolytic-like effect, whereas higher doses cause the opposite response
- CB1 basolateral amygdala, the anterior cingulated cortex, the prefrontal cortex, and the paraventicular nucleus (PVN) of the hypothalamus (Mailleux and Vanderhaeghen, 1992; Tsou et al., 1998)
- DEPRESSION
- AGGRESSIVE BEHAVIOR
- APPETITE AND FEEDING BEHAVIOR

ENDOCANNABINOID SYSTEM - MODULTATION OF PAIN



SPINAL ANALGESIA

- CB1 receptors are located on cell bodies of primary afferent neurons and in the laminae of the dorsal horn that are associated with nociceptive transmission.
- CB1 receptors are colocalized, in different cell populations or interneurons, with a number of molecular markers like GABA, μ-opioid receptors, substance P, calcitonin-gene-related peptide (CGRP), glutamate, tyrosine kinase A (trkA), NO synthase

PERIPHERAL ANALGESIA

- Palmitoylethanolamide (PEA) exhibits cannabinomimetic properties, including analgesic effects, which are blocked by SR144528, a selective CB2 receptor antagonist
 - PEA attenuated the bladder hyperreflexia induced by intravesical administration of nerve growth factor (NGF)

STRESS-INDUCED ANALGESIA

 Reduction of SIA, but not of opiate- induced analgesia, has been demonstrated in mice lacking CB1 receptors (Valverde et al., 2000)

FINANCIAL ASPECTS

- 6 Billion products in 2016 in USA
 - $== 10^9 == 1.000 Millions == 1.000.000.000$
- **Cannabis Industry Association**
 - follow the Alcohol Industry
 - 80% of the Poduct ist cor
 - And how can they achiev



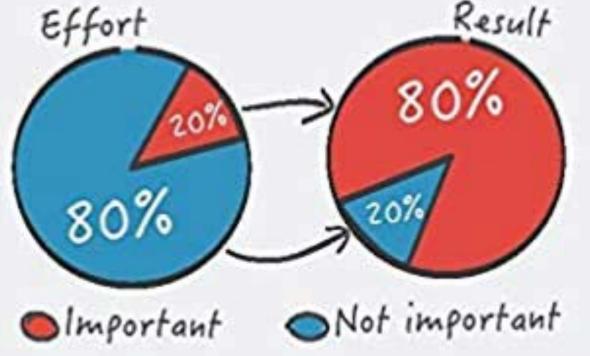
The cannabis space Market value \$47.3B is powering ahead. With U.S. and Canada leading the charge, consumer spending trends are shooting up. Source: Arcview Research and BDS Analytics \$30B

As more investors come

PARETO'S PRINCIPLE

Copyrighted Material

Expand your business with the 80/20 rule





Business 50MINUTES.com

Copyrighted Material

Content

- Medical Pain definition
- Neurobiology of pain
- Cannabis Evidence Risks and Hazard
- Pain Treatments
- Treatment in CH/Personal experience

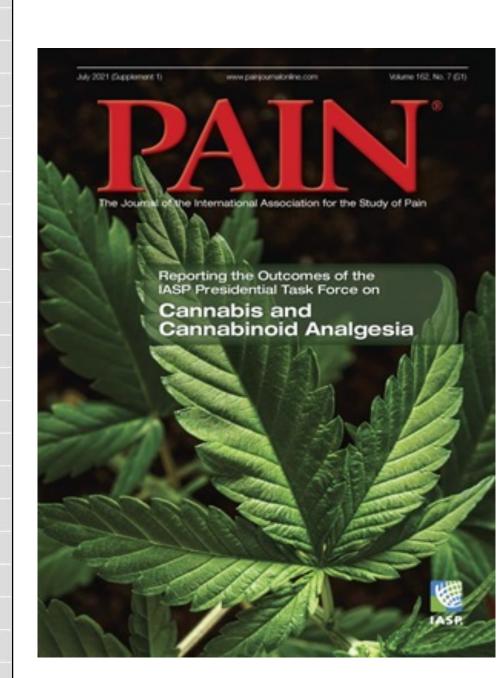
CANNABIS & PAIN

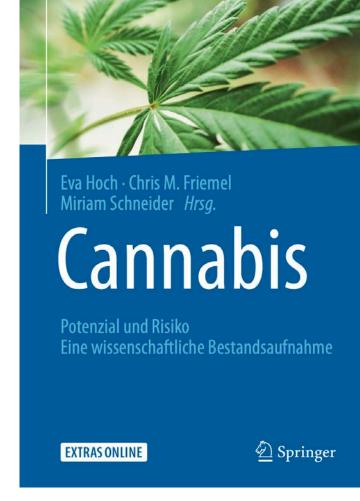
Systematic Reviews (8)

Chronischer Schmer	z							
	Whiting (2015)	Petzke (2016)	Fritzcharles (2016)	Mücke (2016)	Deshpande (2015)	Jawar (2013)	Martin- Sanchez (2009)	Iskedijan (2007)
Abrams (2007)	Х				х			
Berman (2004)	х	Х					Х	Х
Berman (2006)	х							
Blake (2006)	х		Х				х	
Breuer (2007)						Х		
Chitsaz (2009)						Х		
Corey-Bloom (2012)					Х			
Cree (2010)						Х		
Demster								X
Ellis (2009)	х	х			х			
Falah (2007)								
Frank (2008)	х	Х						
GW Pharma- ceuticals (2005)	х			Incl	uded .	Jour	nals	
GW Pharma- ceuticals (2012)	х							
Houtchens (1997)						Х		
Johinsem (1978)							X	
Johnson (2010)	х	K		Х				
Johnaon (2005)							х	
Karst (2003)	Х							X
Kalman (2002)						Х		
Killestein (2002)							х	
Langford (2013 a)	Х	Х						
Langford (2013 b)		Х						
Lynch (2014)	Х	Х						
Narang (2008)	Х							
NCT00391079						X		
NCT00755807						X		
NCT00710424		Х						

Chronischer Schmerz	2							
	Whiting (2015)	Petzke (2016)	Fritzcharles (2016)	Mücke (2016)	Deshpande (2015)	Jawar (2013)	Martin- Sanchez (2009)	Iskedijan (2007)
NCT01606202		х						
NCT01606176		Х						
Notcutt (2004)							х	
Noyes (1975a)	Х						Х	
Noyes (1975b)							х	
Nurmikko (2007)	х	X					х	
Panitch et al. (2006)						х		
Pinsger (2006)	х		x				х	
Portenoy (2012)	х			Х				
Rog (2005)	х	Х				Х	х	х
Selvarajah (2010)	х	X				Х		
Solaro (2007)						Х		
Solaro (2009)						Х		
Rossi (2009)						Х		
Serpell (2014)	Х	Х						
Skrabek (2008)	Х		X.				Х	
Staquet (1978a)							х	
Staquet (1978b)							х	
Svendsen (2004)	х	Х				Х	х	Х
Toth (2012)		X						
Turcotte (2015)	Х	Х						
Wallace (2015)	Х							
Wade (2003)						Х	Х	Х
Wade (2004)							х	х
Ware (2010)	х	X	Х					
Ware (2010)	x				Х			
Wisley (2008)					Х			
Wilsey (2013)	Х				Х			
Wilsey (2011)	x							
Wissel (2006)							Х	

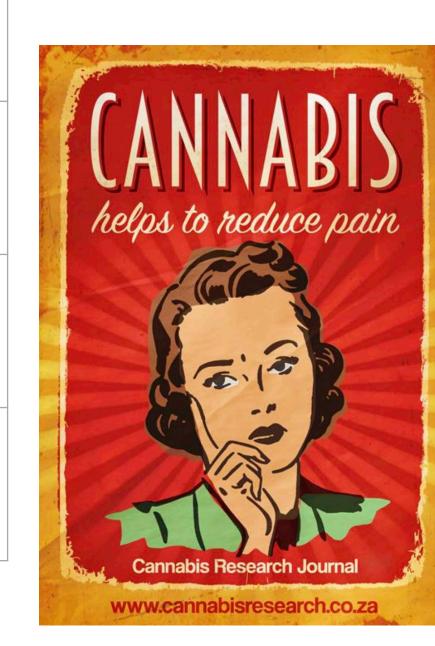






CANNABIS IN CHRONIC PAIN - EFFECTIVE, TOLERABLE AND SAFE?

	NNH
Euphoria; Changes in perception	4x higher than controls
Motor dysfunction	5
Dysphoric change in mood	NS
Change in perception, mood and cognition	7-8



PAIN OPEN Adverse effects of heavy cannabis use: even plants can harm the brain Lucia Sideli^a, Giulia Trotta^a, Edoardo Spinazzola^{a,b}, Caterina La Cascia^c, Marta Di Forti^{d,e,f,*}

THC

- Its % determines the potency of a type of cannabis
- Gives the "High"
- Drives dependence
- Impairment of cognition
- Psychosis: Hallucinations and paranoid ideas
- Affects the outcome of Psychotic Disorders

No association with Psychosis Might have antipsychotic properties Not associated with dependence No adverse effect on cognition Does not reduce the "high" associated with THC Delta-9-Tetrahydrocannabinol (THC) Cannabidiol (CBD) **Cannabigerol**

CBD



Adverse effects of heavy canr can harm the brain

Lucia Sideli^a, Giulia Trotta^a, Edoardo Spinazzola^{a,b}, Caterina La C

Summary of meta-analyses reporting adverse effects associated with cannabis use.

Adverse effect	Participants	Studies	Main findings	Estimate
Psychosis				
Marconi et al. ¹⁸	66,816 individuals from 10 studies	Random-effects meta-analysis on risk of psychosis	the risk of psychotic outcomes with	OR = 3.9, 95% CI [2.84-5.34]
Large et al. ⁷⁷ Schoeler et al. ¹⁰³	8167 substance using patients from 83 studies 16,565 individuals from 24 studies	Random-effects meta-analysis on age at onset of psychosis Random-effects meta-analysis on clinical outcomes of psychosis	a dose–response relationship Relationship between cannabis use and earlier onset of psychotic illness Continued cannabis use after onset of psychosis predicts adverse outcome than for nonusers	ES = -2.70 , 95% CI [-0.53 to -0.30] d = 0.31, 95% CI [$0.04-0.57$]
Bipolar				
Gibbs et al. ⁴²	2391 individuals from 6 studies	Random-effects meta-analysis	Association between cannabis use and both the exacerbation of manic	OR = 2.97, 95% CI [1.8-4.9]
			symptoms in those with previously diagnosed bipolar disorder and new- onset manic symptoms	
Depression				
Gobbi et al. ⁴⁴	22,317 individuals from 11 studies	Random-effects meta-analysis	Cannabis consumption in adolescence is associated with	OR = 1.37, 95% CI [1.16-1.62]
			increased risk of developing depression in young adulthood	
Lev-Ran et al. ⁷⁸	76,058 individuals from 14 studies	Random-effects meta-analysis	Heavy cannabis use may be associated with an increased risk for	OR = 1.62, 95% CI [1.21-2.16]
			developing depressive disorders	
Anxiety				
Gobbi et al. ⁴⁴	22,317 individuals from 11 studies	Random-effects meta-analysis	No evidence of an association with anxiety	OR = 1.18, 95% CI [0.84-1.67]
Twomey et al. ¹¹³	58,538 individuals from 10 studies	Random-effects meta-analysis	Cannabis use is no more than a minor risk factor for the development of elevated anxiety symptoms in the general population	aOR = 1.08, 95% CI [0.94-1.23]

Cannabis Risks

Society Risks

- Adolescent (early and frequent) cannabis use:
- may influence neurodevelopment¹
- risk $\widehat{\Omega}$ for depression and suicidality in adulthood²
- risk û for psychotic experiences (individuals genetically predisposed to schizophrenia may be especially vulnerable³
- Synthetic cannabinoids: life-threatening toxic effects describeds⁴

- We check our phones every 12 minutes1
- An interruption every eight minutes or about seven or eight per hour
- Continuous partial attention





- 1) Albaugh et al. JAMA Psychiatry 2021, Burggren et al. Am J Drug Alcohol Abuse 2019;
- 2) Hengartner et al. J Affect Disord 2020
- 3) Wainberg et al. Trans Psychiatry 2021. Robinson et al. Psychol Med 2022
- 4) 5Cooper Ziva D. Curr Psvchiatry Rep 2016; curtesy from Eigenmann Daniela

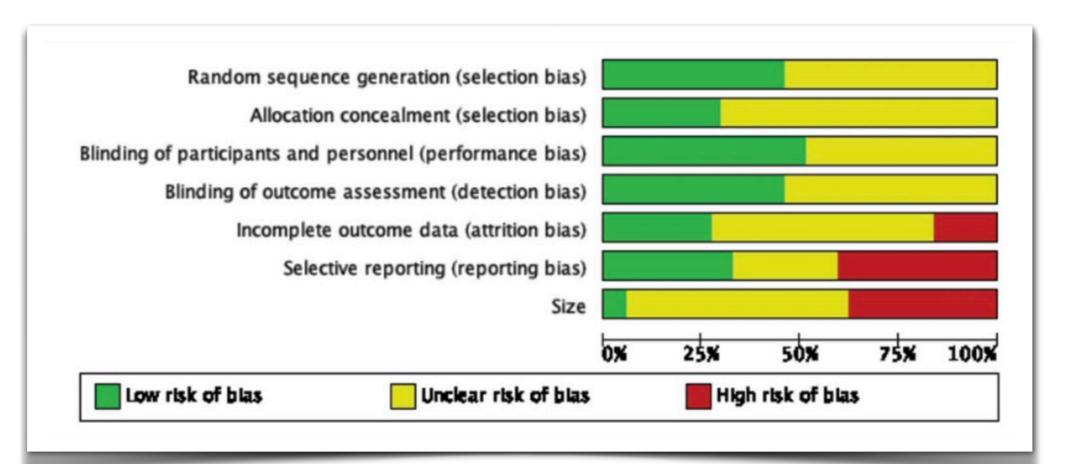
PAIN

Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

Emma Fisher^{a,b,*}, R. Andrew Moore^c, Alexandra E. Fogarty^d, David P. Finn^e, Nanna B. Finnerup^{f,g}, Ian Gilron^{h,i,j}, Simon Haroutounian^k, Elliot Krane^{l,m}, Andrew S.C. Riceⁿ, Michael Rowbotham^{o,p}, Mark Wallace^q,

CANNABIS IN CHRONIC NEUROPATHIC PAIN?

36 studies (7217 participants) !!!



ıdy	Posttreatment N	Trial arms	Cannabis type Contr	rol group	Treatment lengti (wk)
Carpal tunnel					
Faig-Marti and Martinez- Catassus ¹⁶	61	2	PEA	Placebo	8.5
Multiple sclerosis, >4 weeks					
Langford et al.35	297	2	Nabiximols	Placebo	14
Rog et al. 59	64	2	Nabiximols	Placebo	5
Schimrigk et al.62	169	2	Dronabinol	Placebo	16
Multiple sclerosis, progression					
Ball et al. ²	415	2	Dronabinol	Placebo	144
Multiple sclerosis, spasticity					
Collins, 2010 ⁵	305	2	Nabiximols	Placebo	14
Corey-Bloom et al.6	30	2	Cannabis (with THC)	Placebo	0.4
Leocani et al.37	38	2	Nabiximols	Placebo	4
Markova, 2019 ⁴⁰	96	2	Nabiximols	Placebo	4
Zajicek et al.82	224	2	Cannabis	Placebo	15
Zajicek et al. ⁸¹	611	3	Cannabis and THC/CBD		12
Neuropathic pain <1 day					
Wilsey et al. 78	32	3	Cannabis	Placebo	0.14
Wilsey et al. ⁷⁷	36	3	Cannabis	Placebo	0.14
Wilsey et al. 79	42	3	Cannabis	Placebo	0.14
Neuropathic pain <4 weeks					
Berman et al. ³	45	3	CBD+THC (1:1) and THC	Placebo	2
NCT01606176 ⁴⁸	63	2	Nabiximols	Placebo	3
Neuropathic pain >4 week			10-00		
Andresen et al.1	63	2	PEA	Placebo	12
Bradford et al.4	63	2	FAAH	Placebo	6
EUCTR2004-002530-20 ²⁶	230	2	Nabiximols	Placebo	14
Frank et al. ²¹	64	2	Nabilone	30 mg dihydrocodeine	14
NCT00710424 ²⁷	230	2	Nabiximols	Placebo	14
NCT01606202 ⁴⁹	106	2	Nabiximols	Placebo	7
Nurmikko et al. ⁵³	105	2	Nabiximols	Placebo	5
Serpell et al. 64	173	2	Nabiximols	Placebo	14



Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

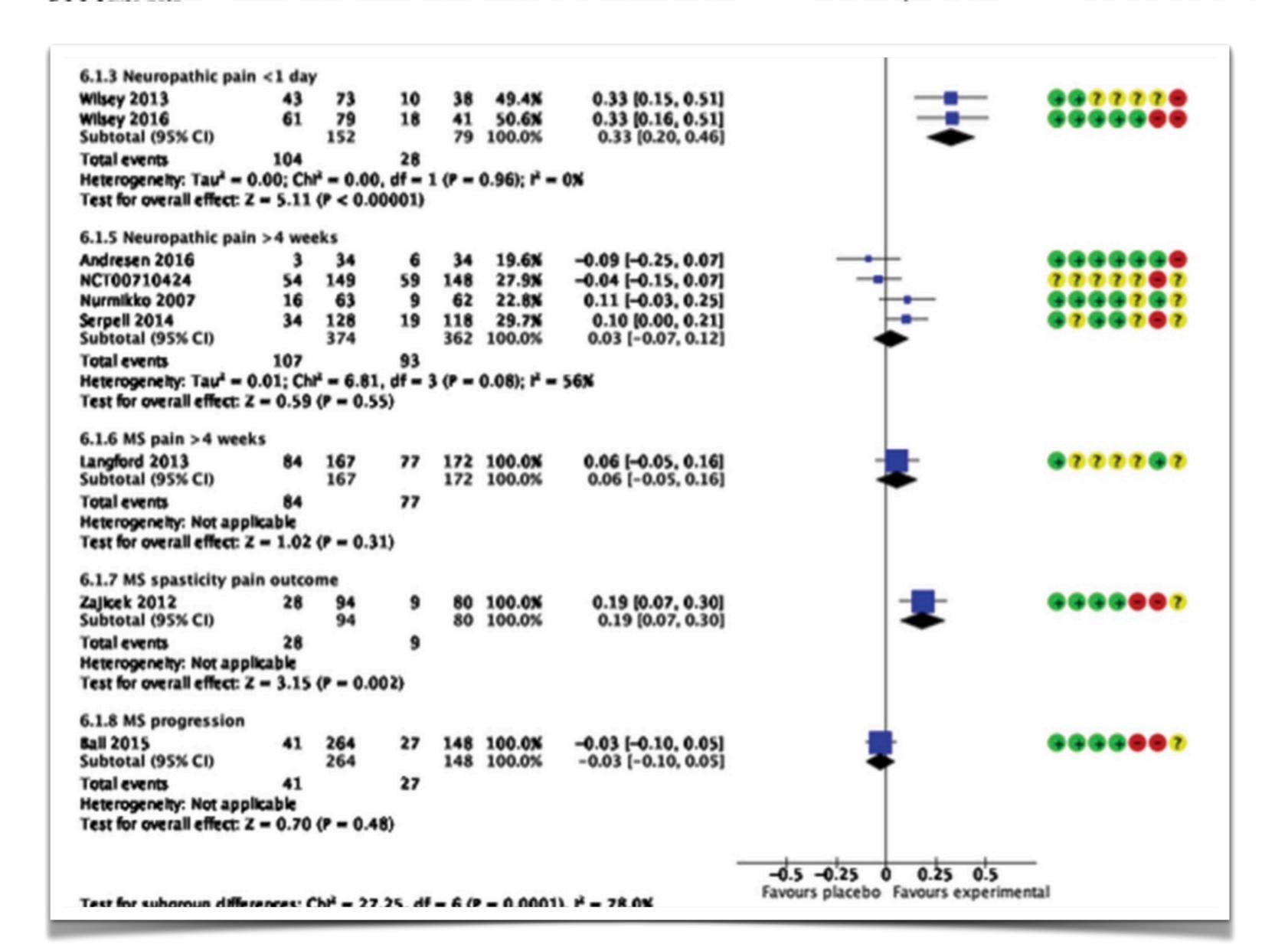
Emma Fisher^{a,b,*}, R. Andrew Moore^c, Alexandra E. Fogarty^d, David P. Finn^e, Nanna B. Finnerup^{f,g}, Ian Gilron^{h,i,j}, Simon Haroutounian^k, Elliot Krane^{l,m}, Andrew S.C. Riceⁿ, Michael Rowbotham^{o,p}, Mark Wallace^q, Christopher Eccleston^{a,b,r}



30% pain reduction

Placebo CBM Risk Difference Risk Difference Risk Difference Risk of Bias

Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI A B C D E F G

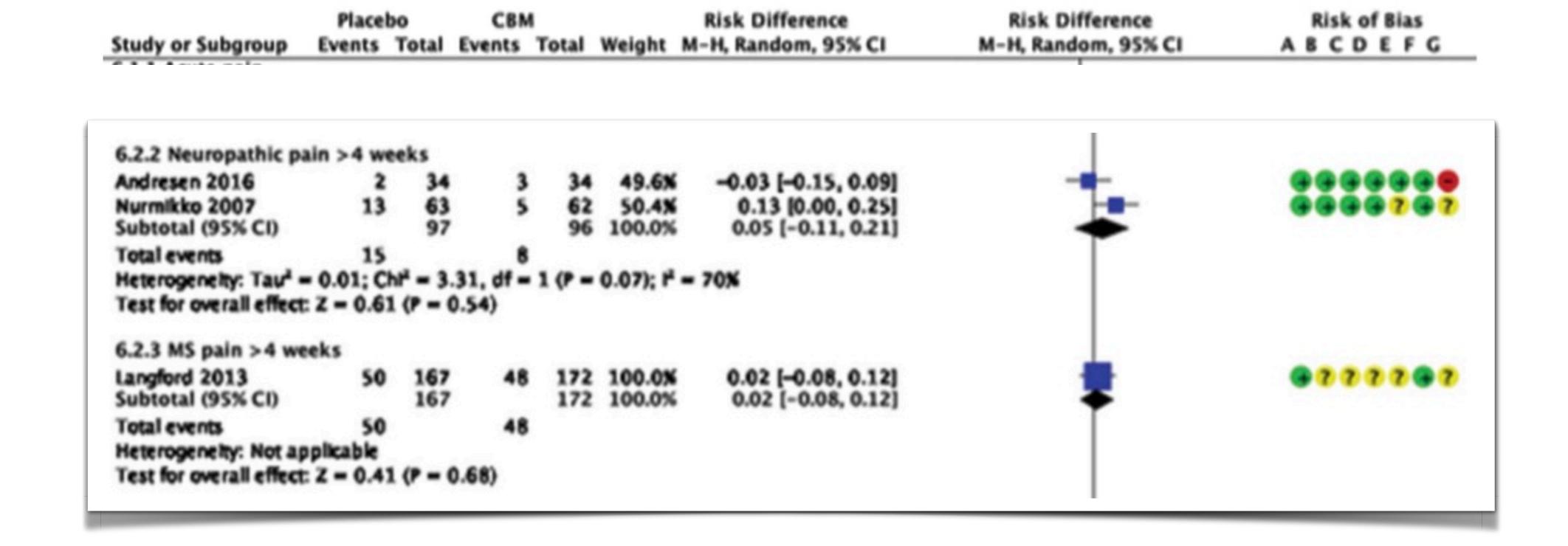


PAIN

Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

Emma Fisher^{a,b,*}, R. Andrew Moore^c, Alexandra E. Fogarty^d, David P. Finn^e, Nanna B. Finnerup^{f,g}, Ian Gilron^{h,i,j}, Simon Haroutounian^k, Elliot Krane^{l,m}, Andrew S.C. Riceⁿ, Michael Rowbotham^{o,p}, Mark Wallace^q,

50% pain reduction



CANNABIS IN CHRONIC MULTIPLE SCLEROSIS PAIN

6 systematic reviews 3 RCTs 565 examined patients	NNT 30% Reduction	NNT 50% Reduction
Pain reduction	NS	NS

Table 3. The CERQual approach—Definitions of levels of confidence in a review finding.

Level	Definition
High confidence	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest
Moderate confidence	It is likely that the review finding is a reasonable representation of the phenomenon of interest
Low confidence	It is possible that the review finding is a reasonable representation of the phenomenon of interest
Very low confidence	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest.

doi:10.1371/journal.pmed.1001895.t003

Medizinalcannabis gegen Spastik bei MS

Studienlage und Praxis

Studienlage (vgl. Literaturübersicht): In den letzten 30 Jahren wurde zur Wirksamkeit von Cannabis in der Behandlung von spastischen Bewegungsstörungen bei Multipler Sklerose (MS) eine breite Palette von Arbeiten publiziert, ausgehend von Fallberichten bis hin zu grossen Metaanalysen. Auch wenn in den randomisierten, Placebo-kontrollierten Studien nicht immer ein signifikanter Wirkungsnachweis bezüglich Linderung von Spastik und Schmerzen durch die Einnahme von Cannabis besteht, so kommen die Metaanalysen in der Gesamtschau doch zum Schluss, dass Cannabispräparate bei fast 50% der sie einnehmenden Patienten einen positiven Gesamteindruck hinterlässt.

SGCM-SSCM Empfehlung

Bei fehlender oder ungenügender Wirksamkeit konventioneller medikamentöser und nicht-medikamentöser Behandlungen oder damit verbundenen, nicht-tolerierbaren Nebenwirkungen kann eine Cannabistherapie eine mögliche Option im Sinne eines individuellen Therapieversuches sein (mit oder ohne konventionelle Begleittherapie) bei RLS-Patienten über 18 Jahren ohne Kontraindikationen.

NEUROPATHIC PAIN

Wrap-up

Medizinalcannabis bei Trigeminusneuralgie

Studienlage und Praxis (vgl. Literaturübersicht)

Studienlage: Insgesamt existieren aktuell nur drei qualitativ wenig hochwertige Studien mit kleinen Fallzahlen. Die aktuelle Studienlage erlaubt keine Empfehlung als Firstoder Second-Line-Therapie.

SGCM-SSCM Empfehlung

Cannabispräparate können bei fehlender oder ungenügender Wirksamkeit konventioneller medikamentöser und nicht-medikamentöser Behandlungen eine valable, individuelle Therapieoption (mit oder ohne konventionelle Begleittherapie) bei Trigeminusneuralgie-Patienten über 18 Jahren und keinen Kontraindikationen aufgrund des hohen Leidensdruckes darstellen, auch wenn die Evidenz dafür fehlt.

Medizinalcannabis gegen Spastik bei MS

Studienlage und Praxis

Studienlage (vgl. Literaturübersicht): In den letzten 30 Jahren wurde zur Wirksamkeit von Cannabis in der Behandlung von spastischen Bewegungsstörungen bei Multipler Sklerose (MS) eine breite Palette von Arbeiten publiziert, ausgehend von Fallberichten bis hin zu grossen Metaanalysen. Auch wenn in den randomisierten, Placebo-kontrollierten Studien nicht immer ein signifikanter Wirkungsnachweis bezüglich Linderung von Spastik und Schmerzen durch die Einnahme von Cannabis besteht, so kommen die Metaanalysen in der Gesamtschau doch zum Schluss, dass Cannabispräparate bei fast 50% der sie einnehmenden Patienten einen positiven Gesamteindruck hinterlässt.

SGCM-SSCM Empfehlung

Bei fehlender oder ungenügender Wirksamkeit konventioneller medikamentöser und nicht-medikamentöser Behandlungen oder damit verbundenen, nicht-tolerierbaren Nebenwirkungen kann eine Cannabistherapie eine valable, individuelle Therapieoption sein (mit oder ohne konventionelle Begleittherapie) zur Behandlung der Spastik bei MS-Patienten über 18 Jahren ohne Kontraindikationen.

Medizinalcannabis bei Fibromyalgie

Studienlage und Praxis

Studienlage: Einige Studien sind vorhanden, wenn auch qualitativ wenig hochwertig mit meistens kleinen Fallzahlen, einer sehr grossen Bandbreite der verwendeten Produkte, Applikationsformen, Dosen, Co-Medikation und untersuchten Endpunkten resp. erfassten Parametern. Resultate weisen jedoch auf eine mögliche Wirksamkeit – insbesondere gegen Schmerzen, Erschöpfung, Angst, Depression und Schlafstörungen – von Cannabinoiden bzw. Medizinalcannabis bei Fibromyalgie-Patienten hin.

SGCM-SSCM Empfehlung

Bei fehlender oder ungenügender Wirksamkeit konventioneller medikamentöser und nicht-medikamentöser Behandlungen oder damit verbundenen, nicht-tolerierbaren Nebenwirkungen kann eine Cannabistherapie eine valable, individuelle Therapieoption sein (mit oder ohne konventionelle Begleittherapie) bei Fibromyalgie-Patienten über 18 Jahren und keinen Kontraindikationen.

Content

- Medical Pain definition
- Neurobiology of pain
- Cannabis Evidence Risks and Hazard
- Pain Treatments
- Treatment in CH/Personal experience

Drug interactions

	CYP-Substrat	CYP-Inhibitor	CYP-Induktor
THC Dronabinol	3A4, 2C9, 2C19.	?	Tala a a a a
CBD Canabidiol	3A4, 2C9, 2C19.	2C9, 2C19, 3A4	Tobacco: CYP1A2

CYP inhibitors may increase plasma levels of THC/CBD ketoconazole, ritonavir, clarithromycin, grapefruit, etc.

CYP inducers may decrease plasma levels of THC/CBD rifampicin, carbamazepine.

CBD may decrease the degradation of CYP substrates and thus increase their plasma levels

- Antiepileptic drugs: clobazam, rufinamide, topiramate toxicity 1
- Anticoagulants: phenprocoumon, acenocoumarol bleeding hazard +
- Immunosuppressants: tacrolimus3, everolimus4 > plasma levels +
- Others: tamoxifen45 (active metabolie endoxifen 1)... (?)

Contraindications

Severe psychiatric diseases

- Severe cardiovascular diseases
- Addictive disorders? Morphine for pain?
- Active road users
- Children and adolescents under 18

european Journal of Pediatrics (2022) 181:335–347 https://doi.org/10.1007/s00431-021-04202-z

ORIGINAL ARTICLE



Use and caregiver-reported efficacy of medical cannabis in children and adolescents in Switzerland

Kathrin Zürcher¹ · Carole Dupont¹ · Peter Weber² · Sebastian Grunt³ · Ilca Wilhelm⁴ · Daniela E. Eigenmann⁵ · Martina L. Reichmuth¹ · Manfred Fankhauser⁵ · Matthias Egger^{1,6} · Lukas Fenner¹

- 205 contacted families, 90 agreed
- CBD in 57% & THC in 43% patients
- Indications for THC: spasticity, pain, lack of weight gain, vomiting, or nausea
- Indications for CBD seizures
- Improvements in 66%
- 43% treatment interruption
 - lack of improvement (56%), side effects (46%), the need for a gastric tube (44%), cost considerations (23%)

Cannabis and Road Traffic

- Participation is prohibited (Art. 2 para. 2 VRV*)
 - ZERO TOLERANCE analytical limit of 1.5ng/ml THC in blood
- Not applied if a there is a medical prescription **BUT**
 - driving ability (at the time of accident)
 - driving fitness (can be assessed in advanced)
 - possible criminal, insurance consequences



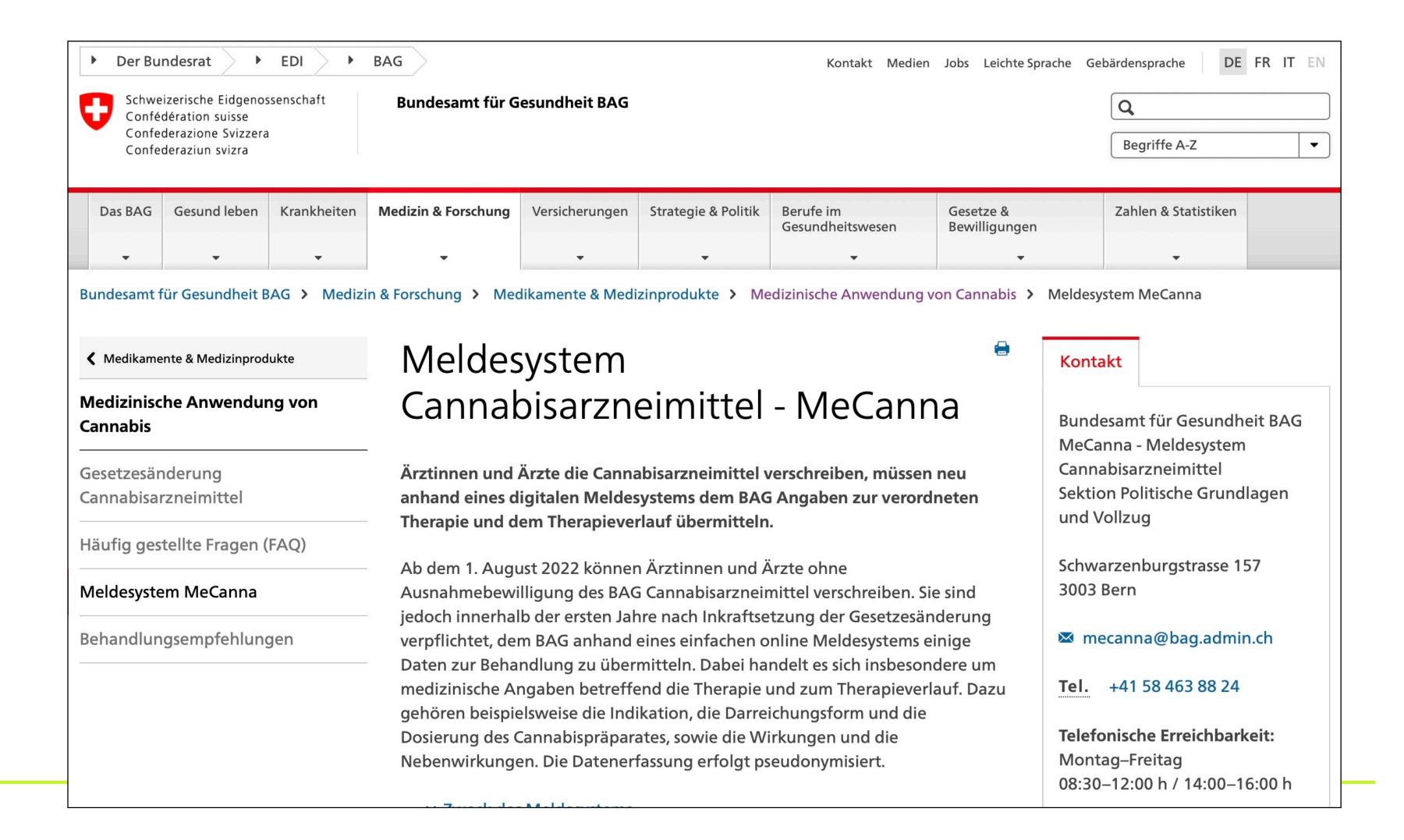
https://www.forbes.com/sites/chrisroberts/2021/06/29/study-marijuanas-impact-on



https://www.bestgastromd.com/blog/how-medical-marijuana-is-helping

Legal issues in CH





Legal issues in CH THC <1%



Chemicals NO MEDICATION no medicines





HEIDAK SPAGYRIK Cannabis sativa FI 500 ml

Nur gegen Rezept versendbar



HEIDAK SPAGYRIK Cannabis sativa Fl 250 ml

Nur gegen Rezept versendbar



SN Cannabis indica Glob MK 1 g

Nur gegen Rezept versendbar



Spagyros Cannabis indiGlob MCF Easyclick 1 Dos

Nur gegen Rezept versendbar



Amavita, zurRose

Practical a

- 1. Patients willing to try
- 2. No other recommended
- 3. Patient can afford to pa (10ml Cannabis 10mg/m
- 4. Pain diary
- 5. Improvement of Mir
- 6. Demand of reimbursem



											L.	
schmerzen n	ach	Beh	nanc	llun	g: n	ris	2	on	me	alu	sel	normient (10 MG THC/ML 10.
Datum	schme	zfrei	= 0				sch	nlimms	ter Sc	chmerz	z = 10	Bernerkungen
10.7.20	0			3		5	6	7	8	X	10	7 Troplen THC fruit Aloud 7 Troples 7 Troplen THC mittag
11.7.20						5				9/	10	7 Tropper THE from misse Tropper
12:7.20								7			X	7 Tropfee THE fruit miltag Hropfes
13.7.20	0	1						7		450	0	7 Tropfer TOK fruh-mittog 7 Tropfer
14.7.20	0	1						7.				7 Tropper THC frish - milliog 7 Troppler
15.7.20	0	1	2	3	4	5	6	7	X	X	10	7 Tropper TH (frish - mittop 7 Tropper
16.7.20	0	1	2	3	4	5	6	7	8	X	10	7 Tropper THC finh mittage 7 Tropper
17.7.20	0	1	2	3	4	5	6	7	8	9	X	7 Tropfer THC fruh mittog 7 Trople oblids Tropper fruh 10 mittog 15 Trolleuch Horphum Sulek. St. Ama
18.7.20	0	1	2	3	4	5	6	7	8	9	X	Horphuin Sulek. St. Ama
19.7.20	0	1	2	3	4	5	6	7	8	9	10	7 1 m pen pour 10 mm pag 113 beteches
20.7.20	0	1	2	3	4	5	6	7×	8	9	10	10 Troppenfuh :7 mfag-15 alceeds
21.7.20	0	1	2	3	4	5	6	7	8	9	X	Horshium Sidebulon St. Anna
22,7.20	0	1	2	3	4	5	6	7	8	9	X	10 Troplen fruh 10 miles 15 orle
23.7.20	0	1	2	3	4	5	6	7	8	9	10	mikros kopische Fluertration L5/51 und Dekompiersvon Gelenkrezessus der Wurzel S1
24.7.20	0'	1	2	3	4	5	6	7	8	9	10	5 chulthen klimk
25.7-20	0	1	2	3	4	5	6	7	8	9	10"	Schulthenklink
26.7.20	0	1	2	3	4	5	6	×	×	g	10	7 TV. The fruit - 7 TM. Files 7 Tp. Alexands
277.20	0							X			10	Troppen relevant 15Tr. Nacht Troppen relevant 15Tr. Nacht
28720	0	1	2	3	4	5	6	X	X	9	10	Foroppen nochts
alle ?	376	Co	ref	FE	H	for	ol	fly	ele	200	der	Temes 2,5 mg

Praxis für invasive Schmerztherapie / Dr. med. Lucian M. Macrea/ Seehofstrasse 7 / CH-6004 Luzern Telefon 041 418 80 80 / Fax 041 418 80 81 / inva-schmerz@hin.ch

ois treatment

Bisherige Therapien.

Medikamente: -

- siehe auf Liste mit Unverträglichkeiten bezüglich Morphinpräparate
- Valoron Tropfen ohne Wirkung
- Palladon ohne Wirkung und bei höheren Dosen mit starker Müdigkeit, gereizt
- einzige wirksame Mittel sind i.v. Titration von Fentanyl oder Alfentanil
- intranasales Ketamin mit leichter Besserung der Schmerzen
- Fentanylpflaster 12 μg/h gestoppt wegen Hautausschlägen November 2020
- Palexia nicht möglich wegen Lactoseintoleranz

Medikamenten-Entzug:

- von Pethidin subkutan
- Temesta Einzug 01.2022

Infusionen: - Ketamininfusionen mit übergangsweise Verbesserung der Schmerzen. Serie Nr. 2. ab März 21

<u>Interventionen:</u> - keine seit 2020, seitdem die Patientin in unserer Betreuung ist. <u>Krankengymnastik:</u> - keine.

TENS: keine Wirkung

Massagen, Bäder, Kälte-/Wärmetherapie: - keine.

Akupunktur: - keine.

Chiropraktik: - keine.

Psychotherapie: - Mitbetreuung zusammen mit psychiatrische Praxis.

Entspannungsverfahren, Hypnose, Biofeedback: - keine.

Kur-/Reha-Behandlung: - keine.

Sonden- (SCS) oder Pumpensysteme: - keine.

Andere Therapien: - keine.

Allergien und Unverträglichkeiten:

- Salicylate, Novalgin, Irfen (NSAR generell), Bupivacain,
- Tramal, Buprenorphin (Transtec), Oxycontin, Targin, Pethidin Überdosis 1100mg/die
- Palexia nicht möglich wegen Lactoseintoleranz
- Jod, Pflaster,
- Clamoxyl, Augmentin, Garamycin (Aminoglykoside generell wegen Ototoxizität)
- Lactose Intoleranz

ve

First systematic experiences with the use of cannabis treatment in a pain practice.





SWISS PAIN INSTITUTE
INSTITUT SUISSE DE LA DOULEUR

LM. Macrea, P. Koutsotheodorou, V. Mouthon, V. Bocherens, P. Mavrocordatos



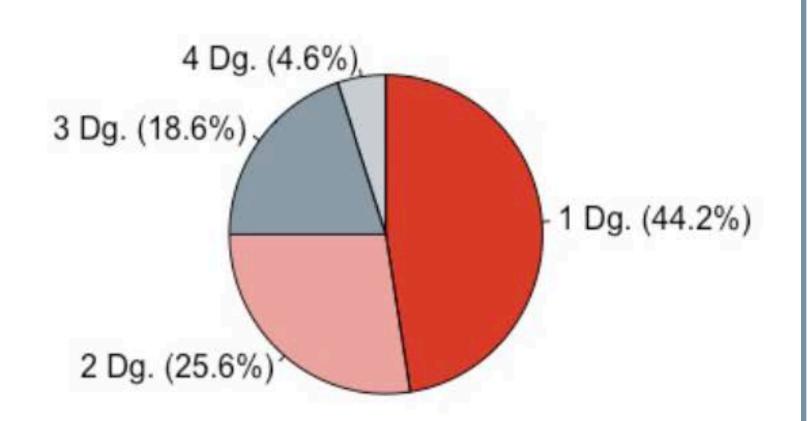
We report on 40 treatments in 37 patients 55% were female; mean age was 62 years (SD=17.5; min 22ans, max 96ans).

. 32% of patients had only one pain diagnosis, with a median of 2 diagnoses for a patient (mean 1.8, SD=0.9, max=4); there were 73 pain diagnosis in total.

Patients had a median of 5 medical diagnoses (mean = 6.4, SD = 4.1, max = 18) and used a median of 8 medical treatments (mean = 7.9, SD = 4.2, max = 16).

The most frequently used diagnostic pain codes are depicted in the following table.

Number of pain diagnosis



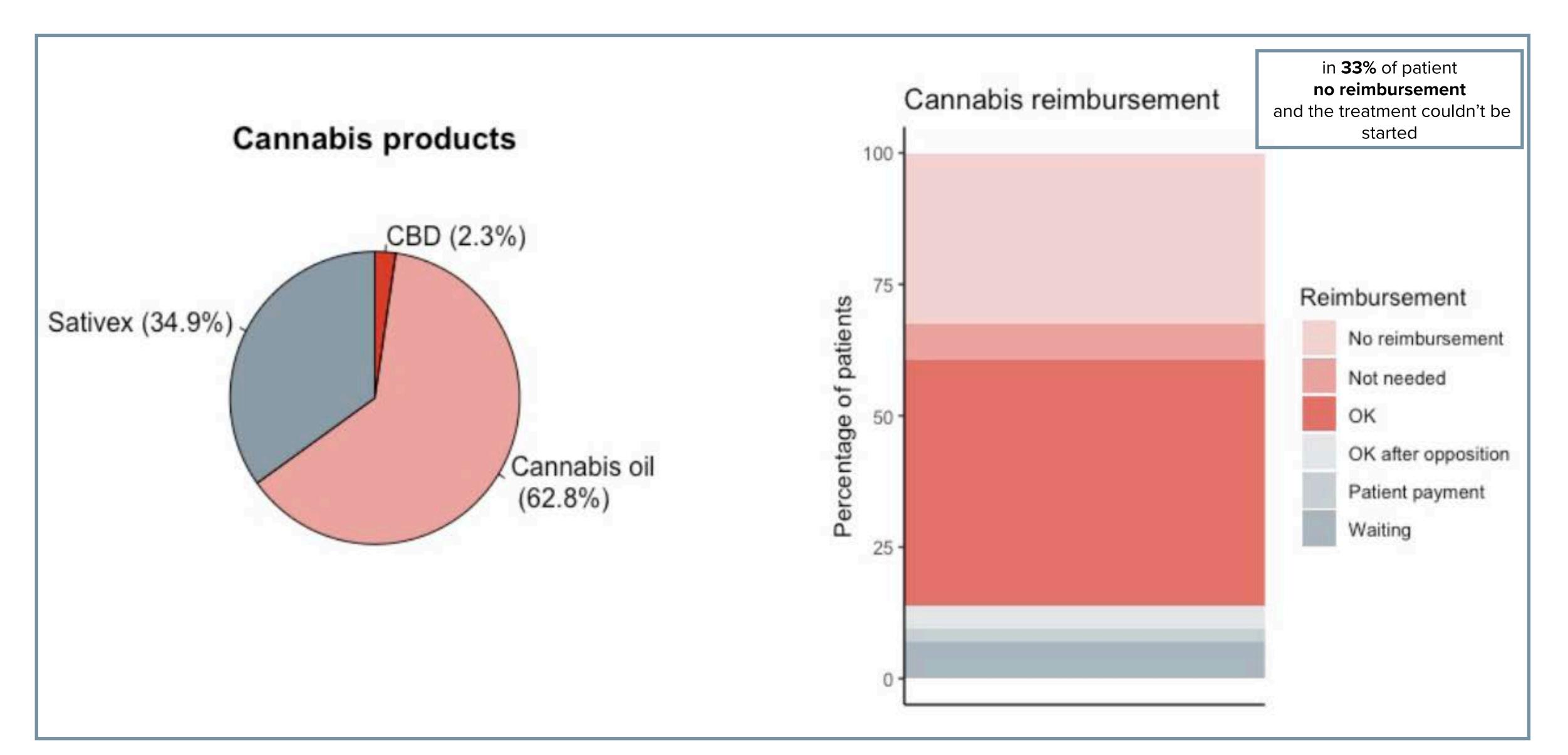
ICD code	First pain diagnosis (40 diagnoses, 40 patients)	All pain diagnosis (73 diagnoses, 40 patients)
Diseases of the musculoskeletal system (M54.5, M54.4, M54.2, M96.1, M48.06)	15	21
Unspecified pain diagnosis generalized pain (R52.2, R10.2)	11	14
Diseases of the nervous system M54.2 (G62, G57,)	9	18
Postsurgical pain (Z98.89)	2	6
Opioid dependence (F.11.2)	1	2
Headache (ICHD-3 11.2.1)	1	8
Cancer pain (C.50)	1	1
Other (Y42.6, 197.2, N94.4)	*	3



LM. Macrea, P. Koutsotheodorou, V. Mouthon, V. Bocherens, P. Mavrocordatos



Poster # 9.



First systematic experiences with the use of cannabis treatment in a pain practice.



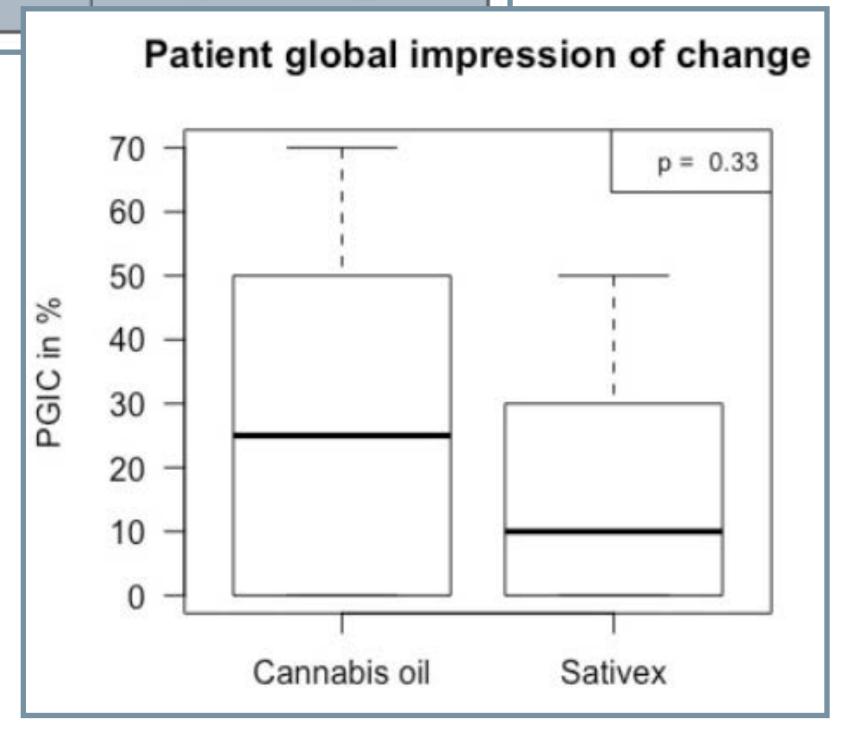
LM. Macrea, P. Koutsotheodorou, V. Mouthon, V. Bocherens, P. Mavrocordatos



Poster Presentation Congress 2018



	Sativex		Cannabis oil			
	Treatment stopped	Treatment	Treatment stopped	d Treatment		
Number of patients	7	4	2	7		
Dosage	12.5 mg	11.1 mg	7.5 mg	6.5 mg		
PGIC	5.8%	38.7	0	36.4%		
Side effects	Cognitive side effects, Dizziness, Difficulty with the oral application	0	Cognitive side effects, Bad taste	1 patient euphoria 1 patient fatigue		

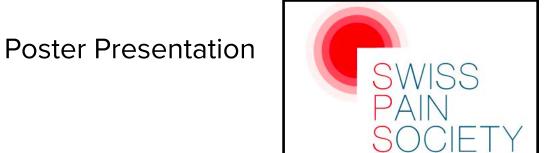


First systematic experiences with the use of cannabis treatment in a pain practice.



LM. Macrea, P. Koutsotheodorou, V. Mouthon, V. Bocherens, P. Mavrocordatos







Conclusions

- Cannabis treatment seems to induce a 20-30% improvement in the pain symptoms.
- We did not observe the development of tolerance or pharmacological interference with other medications.
- The therapeutic index of cannabis is low small difference between the dosages in patients where the treatment was discontinued.
- Sativex seems inferior to the cannabis oil treatment. The application form permits is difficult and titration is not possible.
- This data must be confirmed by a large prospective observational study to permit the identification of specific pain diagnosis especially suitable for the cannabis treatment.



https://www.sgcm-sscm.ch/





"You have a lot of boring health issues, so I'm prescribing medical marijuana for myself."



Mitgliedskategorien

- ☐ CH- Einzelmitglieder ausgebildet CHF 100
- ☐ CH-Einzelmitglieder in Ausbildung CHF 50
- ☐ CH-Fachgesellschaften/CH-Berufsverbände/CH- Akademien CHF 600
- ☐ CH-Industrieorganisationen CHF 3000
- ☐ CH- Patientenorganisationen CHF 300
- ☐ Ehrenmitglieder (Aufnahme nach Antrag an Vorstand) CHF 0.00
- ☐ Korrespondierende Mitglieder (Aufnahme nach Antrag an Vorstand) individuell
- ☐ Gönnerschaft/Patronat individuell



ICEN MESSAGES

1.Pain is a complex phenomena



2. Neuropathic pain





CAUSED BY A LESION OR DISEASE OF THE SOMATOSENSORY NERVOUS SYSTEM

3. Cannabis preparations in controlled and pharmaceutical quality can be a valuable therapeutic option

IN: SPASTICITY, NEUROPATHIC PAIN, NAUSEA, ANOREXIA, EPILEPSY, ETC

4. Cannabis dosage: "start low and go slow"

3 X 3-7DROPS (1DROP = 0.4MG THC = 10MG/ML)

5.Risk of Cannabis

FOR MEDICAL USE ????

© RECREATIONAL !!! < 18YEARS

DANKE; MERCI, THANK YOU!!!!

QUESTIONS @

LUCIAN.MACREA@ICLOUD.COM