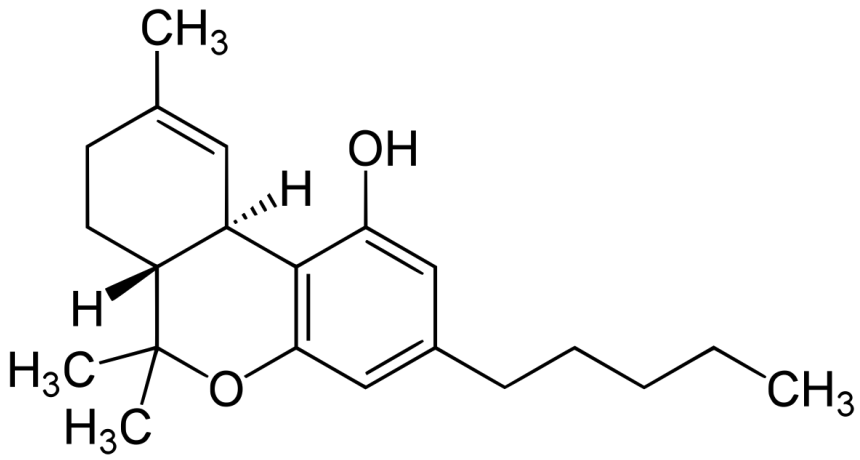


Universitätsspital Basel

Opioids and Cannabinoids in treatment of chronic pain

One? Both?- None?

Rehab Meets Pain Meets Rehab Congress Aarau 2025

PD Dr. med Tobias Schneider
Head of Pain medicine
University Hospital Basel

Conflict of interest

- None regarding cannabinoids and opioids (Research solely funded by the Dep. Anaesthesiology Basel)
- Pro Patient Stiftung Basel, Projekt Open label Placebo (FO145500) Main-Applicant; 2020-2025
- SNF «No Doubt Trail» (229722) Co-Applicant; 2025-2030

Content

Universitätsspital Basel

- Medical use of opioids and cannabis in the course of time
- Why cannabinoids and opioids are potential candidates to be pain killers!
- When evidence follows application…
- Resulting guidelines
- Supportive or complementary effects of combination?
- Responders

Medical use of opioids and cannabinoids in the course of time…

Swing of the pendulum: Opiophobia

At the beginning of the 20th Century:

- Morphinists and Cocainists “Elites”

Middle of the 20th Century:

- Opiates as “chemical Coping” everyday drug in the “working class”

Wars:

- 2nd World War: Pethidinisten
- Vietnam War (Heroine)
- Afghanistan (Heroine)
- Gaza War (2000): Tramadol kids at the Gaza-Strip

Herbert Volkmann

…the pendulum swings…

AMERICAN ACADEMY OF PAIN MEDICINE
Physicians Dedicated to Relieving Pain
aapm

The Use of Opioids for the Treatment of Chronic Pain

American Pain

A consensus statement from the American Aca

IV. Current information and need modifi

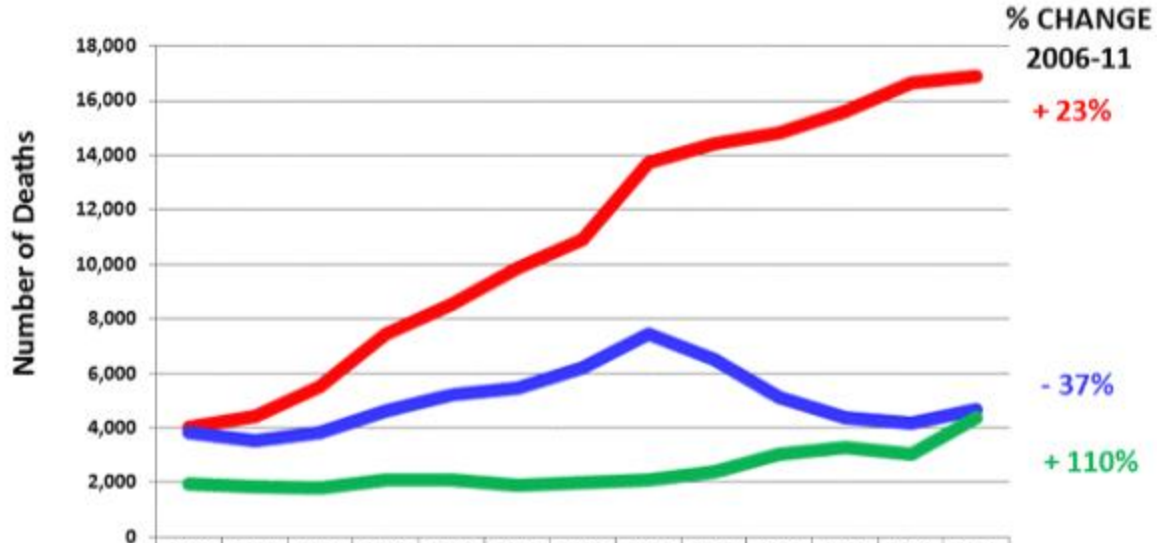
Fentanyl buccal tablet (F
pain in opioid-treated p
pain: a randomized

Portenoy RK, Messina

attention to di
nausea, possible early si

Tolerance: It was previously thoug
ability to use opioids efficaciously on
decreasing pain relief with the same
to long-term opioid use. Experience
appears to be tolerance is usually pro
does not appear to be an arbitrary up

Drug Poisoning Deaths Involving Opioid Analgesics, Cocaine and Heroin: United States, 1999–2011



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
opioid analgesic	4,030	4,400	5,528	7,456	8,517	9,857	10,928	13,723	14,408	14,800	15,597	16,651	16,917
cocaine	3,822	3,544	3,833	4,599	5,199	5,443	6,208	7,448	6,512	5,129	4,350	4,183	4,681
heroin*	1,963	1,843	1,784	2,092	2,084	1,879	2,010	2,089	2,402	3,041	3,279	3,038	4,397

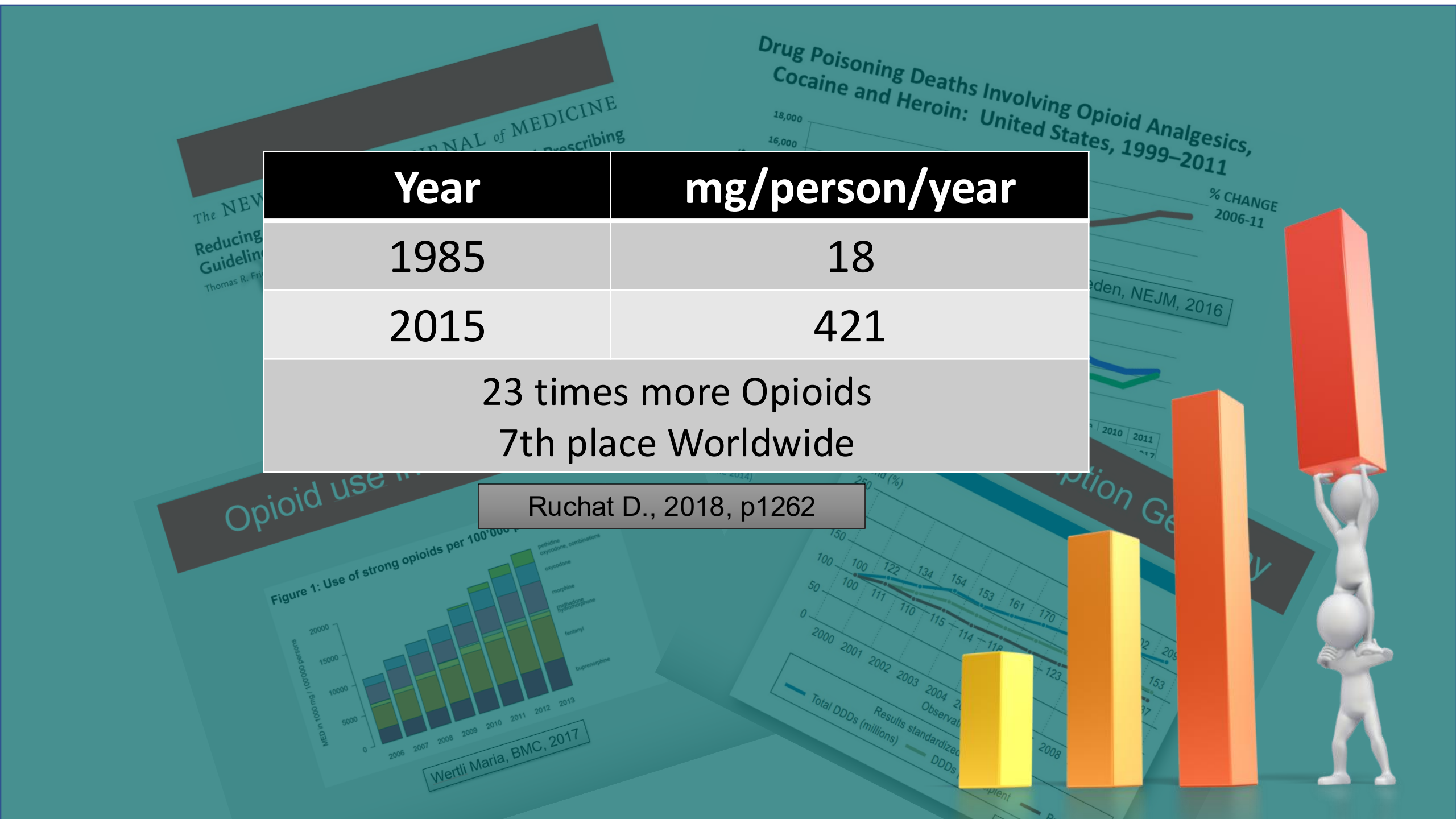
Note: Not all drug poisoning deaths specify the drug(s) involved, and a death may involve more than one specific substance. The rise in 2005-2006 in opioid deaths is related to non-pharmaceutical fentanyl (see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5729a1.htm). *Heroin includes opium.

Source: National Center for Health Statistics/CDC, *National Vital Statistics Report*, Final death data for each calendar year (June 2014).

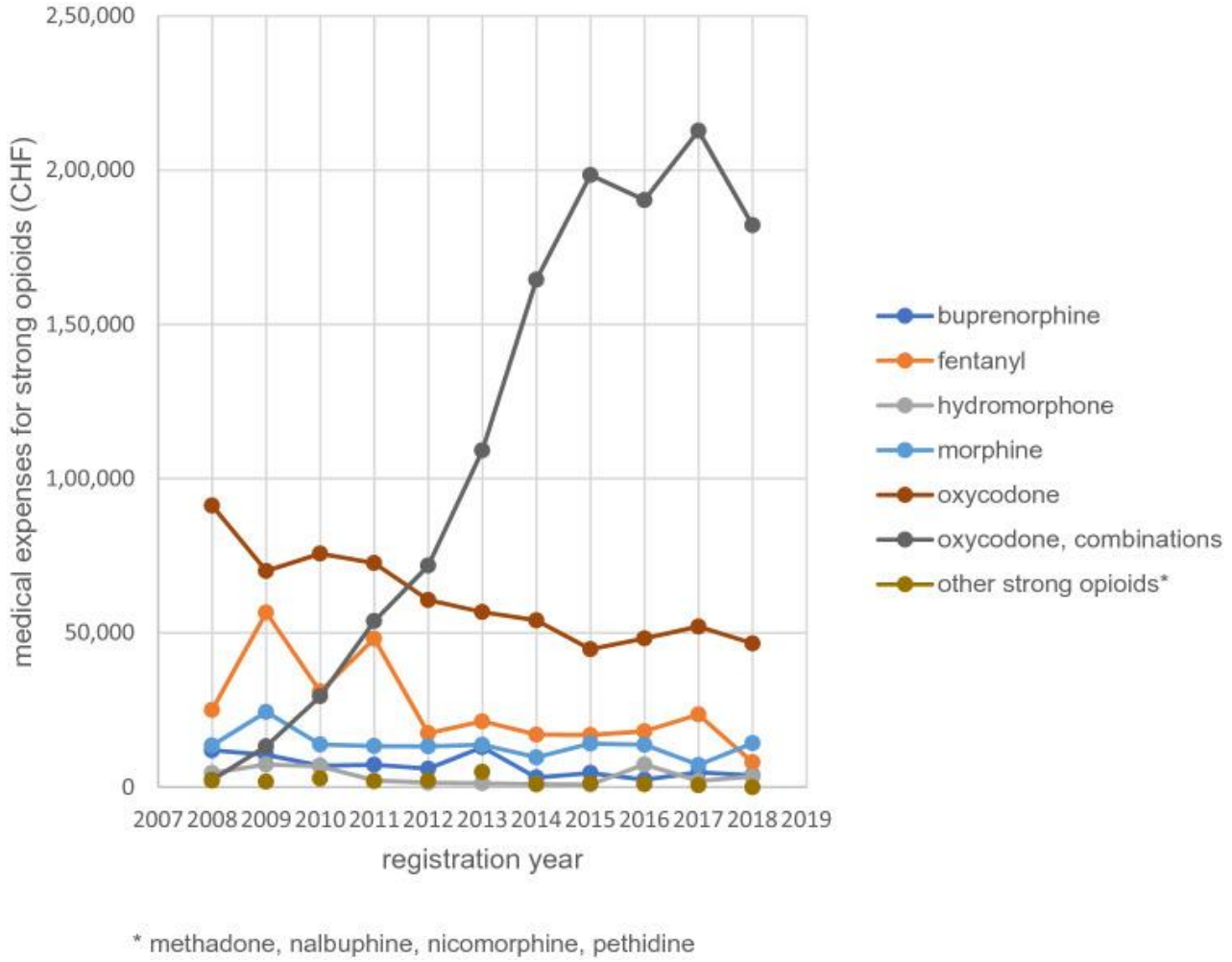
6/2014

Year	mg/person/year
1985	18
2015	421
23 times more Opioids 7th place Worldwide	

Ruchat D., 2018, p1262



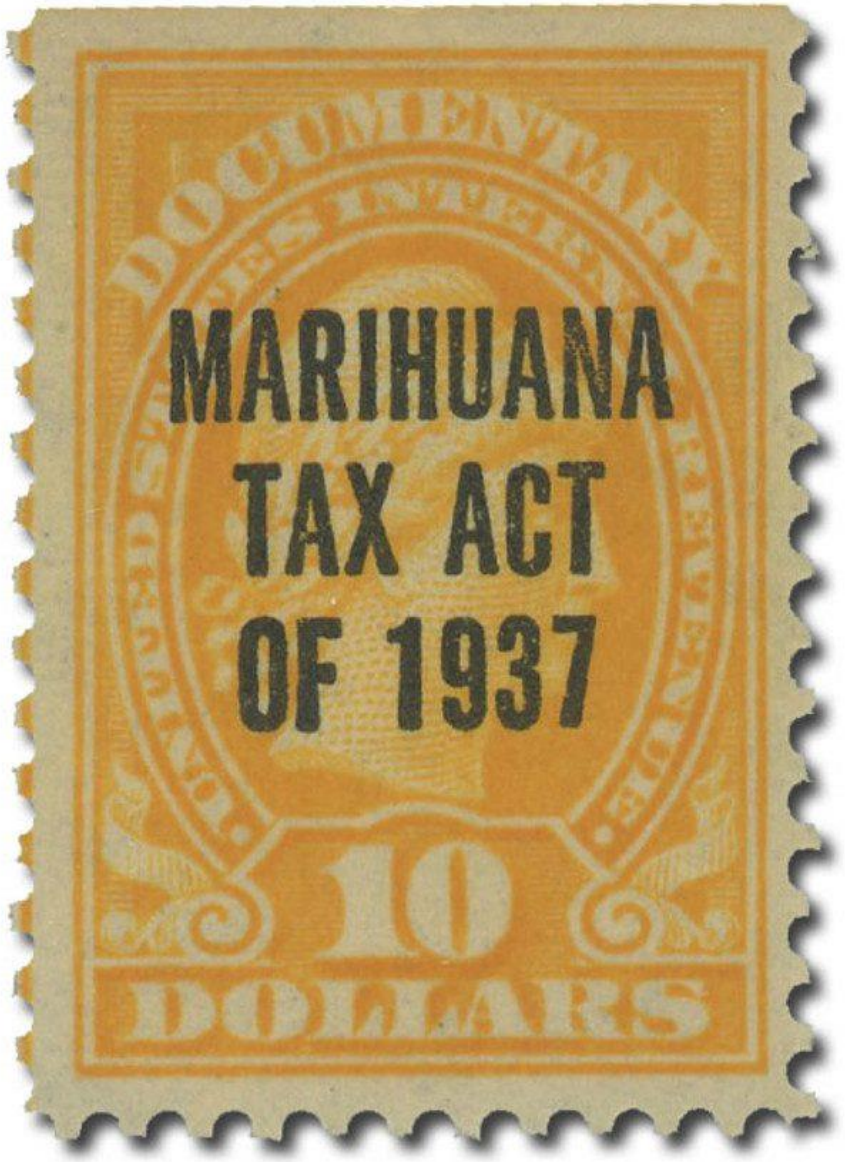
Different Opioids in Switzerland (SUVA Cases) after injuries (2024):



* methadone, nalbuphine, nicomorphine, pethidine

Increased Use and Large Variation in Strong Opioids and Metamizole (Dipyrone) for Minor and Major Musculoskeletal Injuries Between 2008 and 2018: An Analysis of a Representative Sample of Swiss Workers

Swing of the cannabinoid pendulum…



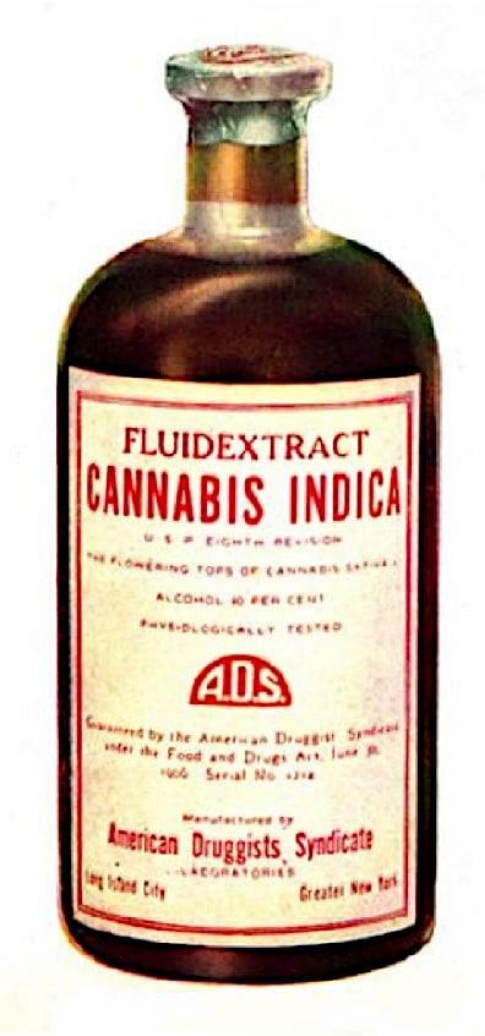
rmacopedia (1850–1930):

Government:

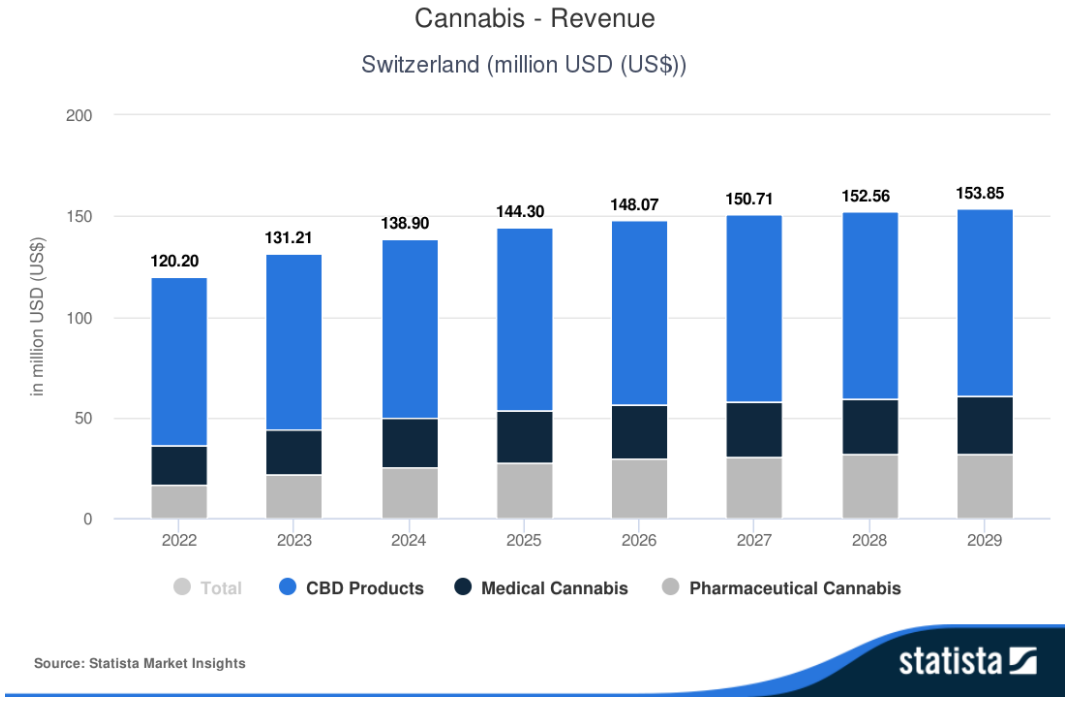
- Official:
  - Argumentation of health and safety issues:
    - Addiction
    - Criminal and immoral behavior

900–1930):

- In-official:
  - Concurence synthetic fibers (Nylon, DuPont) and paper industry
  - Campaign against Mexicans



Cannabis needs long time to get into the swing again…



1970: Controlled Substance act: Harmful substance without medical benefit

1990: Discovery of opioid receptors

1992 Endogenous cannabinoid Anandamide

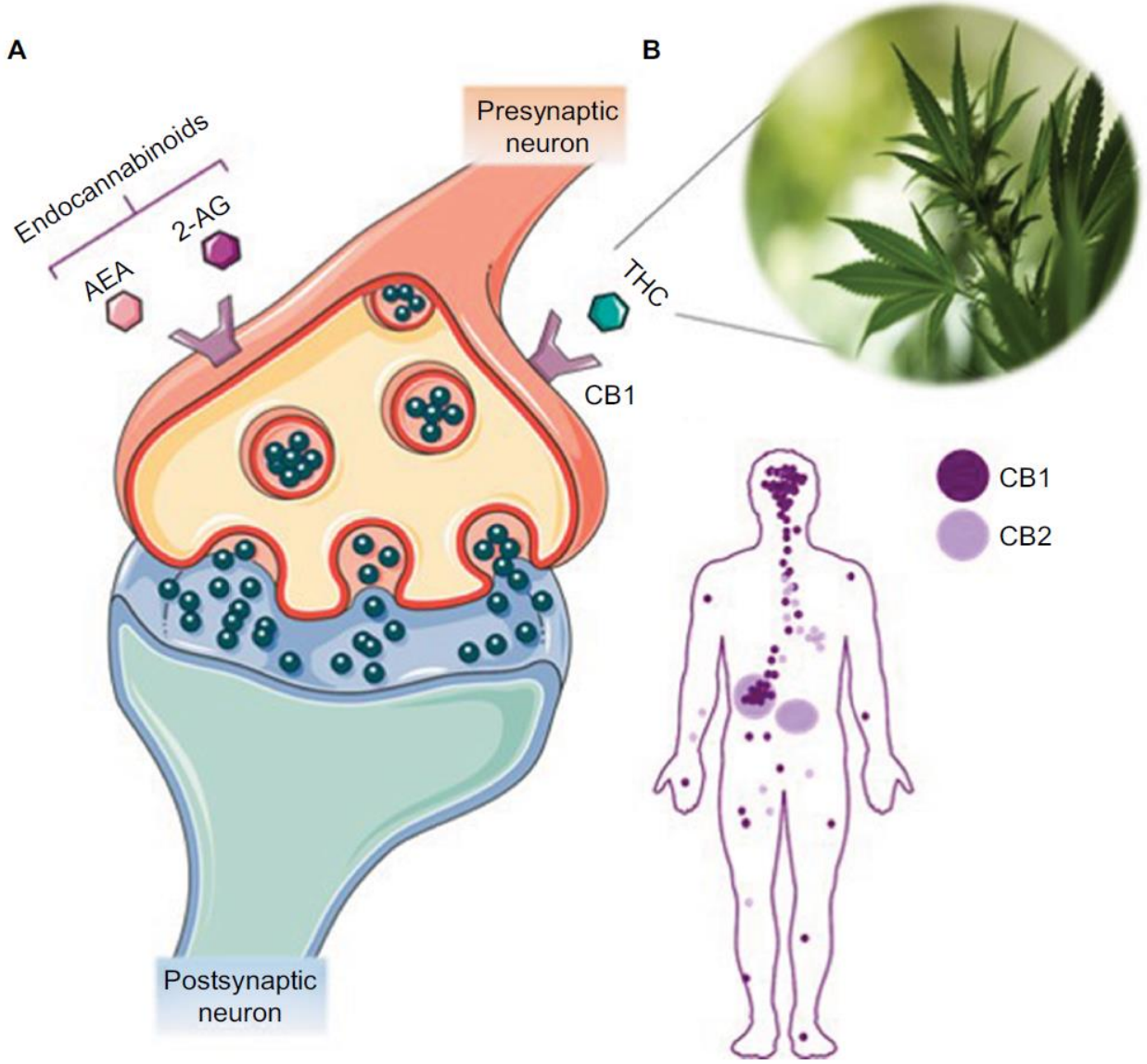
Compassion Clubs

Standardized Products enable research

02

Why cannabinoids and opioids are potential candidates to be pain killers!

The Endocannabinoid-System



AEA = Amandamide
2-AG = 2-Arachidonylglycerol

FAAH = Fatty acid amide hydrolase
MAGL = Monoacylglycerol lipase

Extracted from: Drug, Healthcare and Patient Safety 2018:10

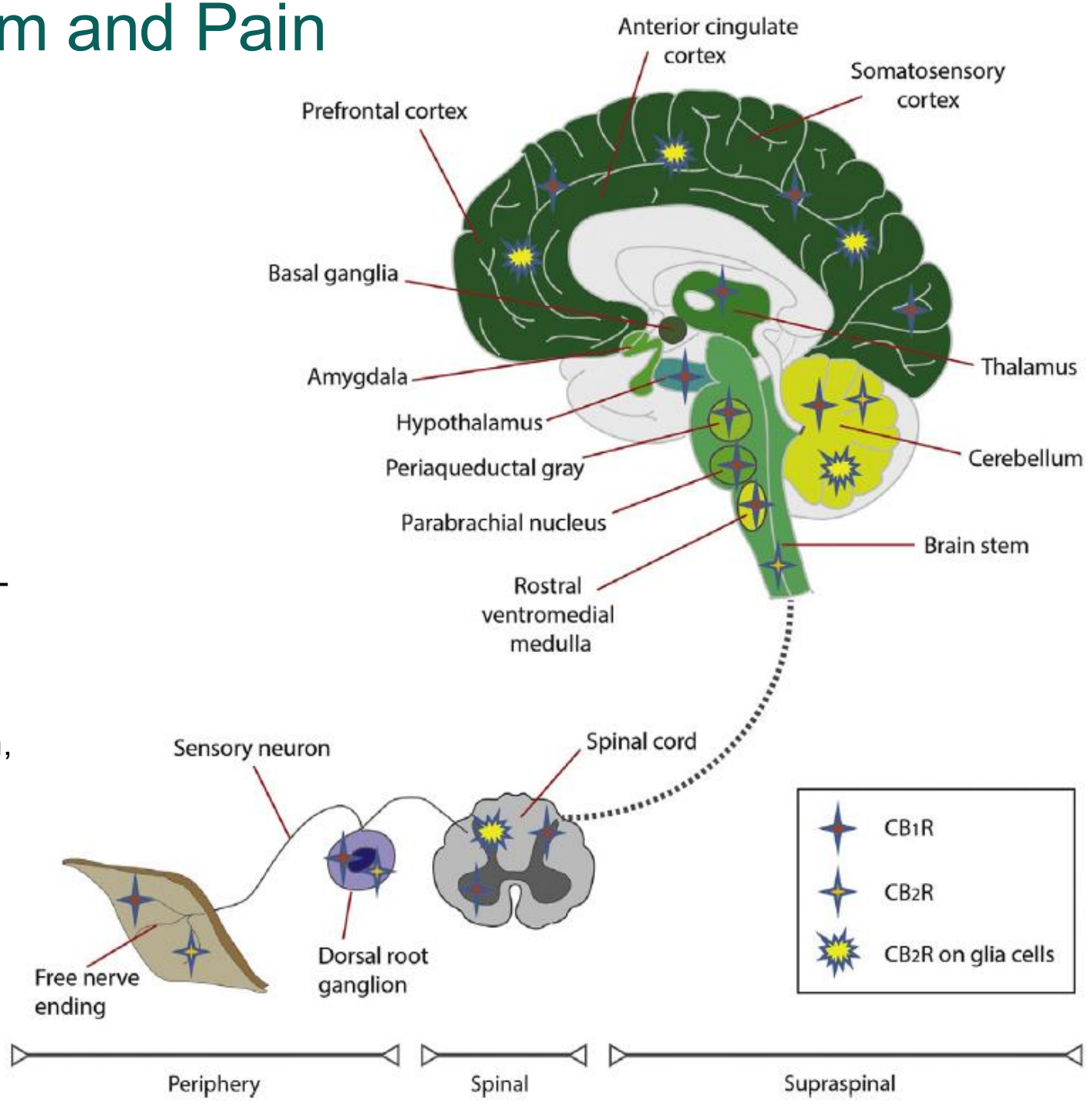
The Endocannabinoid-System and Pain

CB1-Rezeptor:

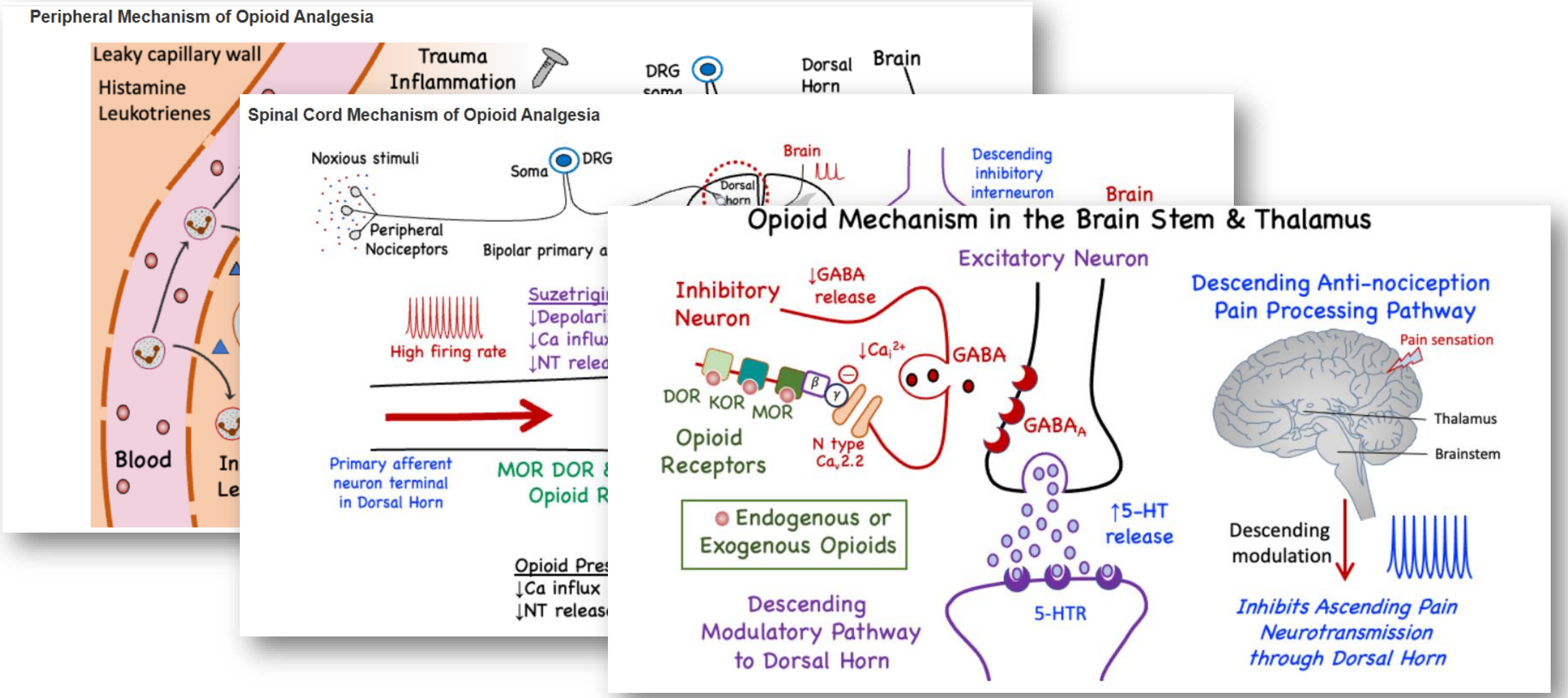
- Gate transduction of Pain singaling on terminal afferents
- CB1-R Bloc: Fireing of WDR-Neurons
  -> sekundary Hyperalgesia
- Higher Brain centers: Disinhibition of excitatory Neurons to off-cells
- Mediate the ACC's involvement in stress- or anxiety-linked analgesia.

CB2- Receptor:

- Stimulation affects: astrogliosis, microglial activation, pro-inflammatory cytokines
- Expression is not limited to the immune syste
- Expression in the spinal cord during persistent pain states



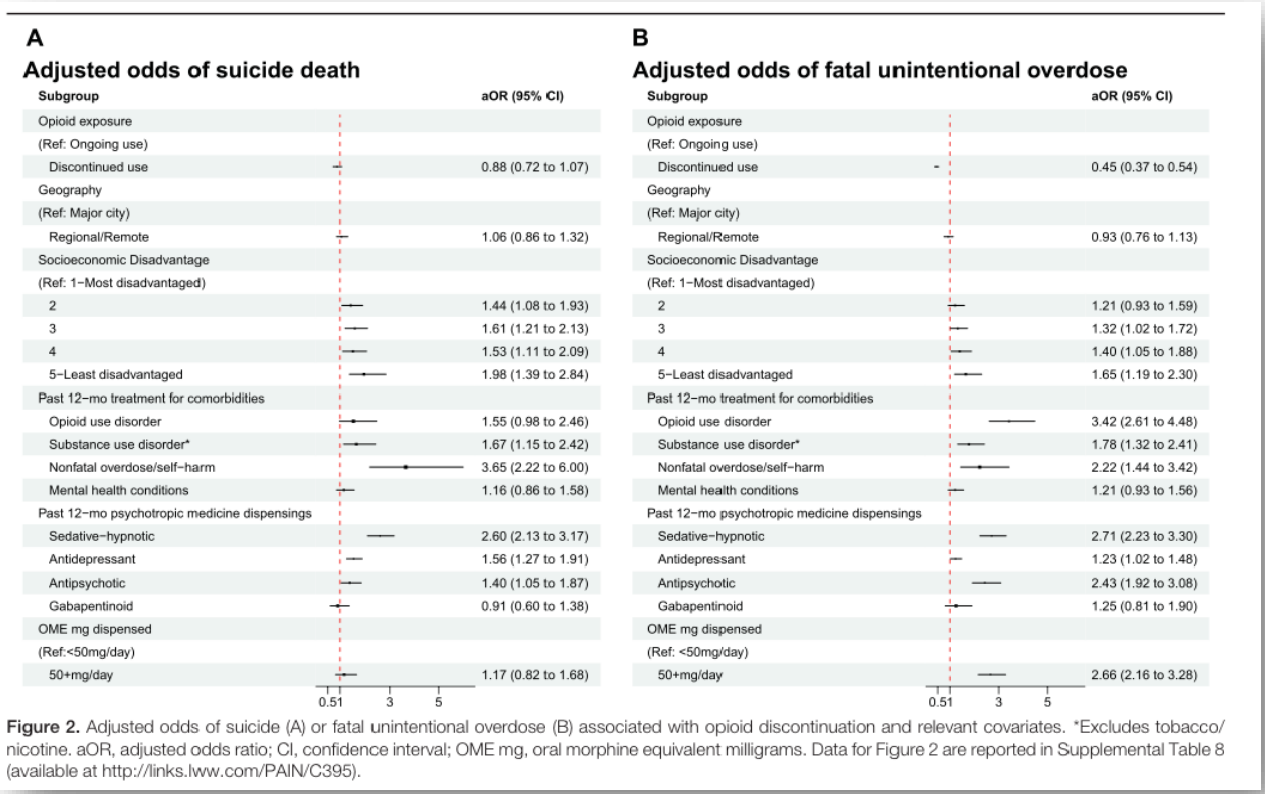
Opioid targets from the periphery to the center…



03

First try, then Error…

When evidence follows application…



A

Adjusted odds of suicide death

Subgroup	aOR (95% CI)
Opioid exposure	
(Ref: Ongoing use)	
Discontinued use	0.88 (0.72 to 1.07)
Geography	
(Ref: Major city)	
Regional/Remote	1.06 (0.86 to 1.32)
Socioeconomic Disadvantage	
(Ref: 1−Most disadvantaged)	
2	1.44 (1.08 to 1.93)
3	1.61 (1.21 to 2.13)
4	1.53 (1.11 to 2.09)
5−Least disadvantaged	1.98 (1.39 to 2.84)
Past 12−mo treatment for comorbidities	
Opioid use disorder	1.55 (0.98 to 2.46)
Substance use disorder*	1.67 (1.15 to 2.42)
Nonfatal overdose/self−harm	3.65 (2.22 to 6.00)
Mental health conditions	1.16 (0.86 to 1.58)
Past 12−mo psychotropic medicine dispensings	
Sedative−hypnotic	2.60 (2.13 to 3.17)
Antidepressant	1.56 (1.27 to 1.91)
Antipsychotic	1.40 (1.05 to 1.87)
Gabapentinoid	0.91 (0.60 to 1.38)
OME mg dispensed	
(Ref:<50mg/day)	
50+mg/day	1.17 (0.82 to 1.68)

0.51 3 5

B

Adjusted odds of fatal unintentional overdose

Subgroup	aOR (95% CI)
Opioid exposure	
(Ref: Ongoing use)	
Discontinued use	0.45 (0.37 to 0.54)
Geography	
(Ref: Major city)	
Regional/Remote	0.93 (0.76 to 1.13)
Socioeconomic Disadvantage	
(Ref: 1−Most disadvantaged)	
2	1.21 (0.93 to 1.59)
3	1.32 (1.02 to 1.72)
4	1.40 (1.05 to 1.88)
5−Least disadvantaged	1.65 (1.19 to 2.30)
Past 12−mo treatment for comorbidities	
Opioid use disorder	3.42 (2.61 to 4.48)
Substance use disorder*	1.78 (1.32 to 2.41)
Nonfatal overdose/self−harm	2.22 (1.44 to 3.42)
Mental health conditions	1.21 (0.93 to 1.56)
Past 12−mo psychotropic medicine dispensings	
Sedative−hypnotic	2.71 (2.23 to 3.30)
Antidepressant	1.23 (1.02 to 1.48)
Antipsychotic	2.43 (1.92 to 3.08)
Gabapentinoid	1.25 (0.81 to 1.90)
OME mg dispensed	
(Ref: <50mg/day)	
50+mg/day	2.66 (2.16 to 3.28)

0.51 3 5

Figure 2. Adjusted odds of suicide (A) or fatal unintentional overdose (B) associated with opioid discontinuation and relevant covariates. *Excludes tobacco/nicotine. aOR, adjusted odds ratio; CI, confidence interval; OME mg, oral morphine equivalent milligrams. Data for Figure 2 are reported in Supplemental Table 8 (available at http://links.lww.com/PAIN/C395).

Opioids: Efficacy?

Chronic back pain			
Studies (patients)	Variable	Opioid vs Placebo	Number needed to benefit / to harm (95%-CI)
6 (2869)	Pain intensity		11 (9-14)
2 (1492)	min. 50% reduction of pain intensity	26.2 vs 21.0	19 (10-107)
6 (2910)	Treatment stop due to side effects	21.2 vs 6.0	7 (6-8)

NNT 19 (50% pain relief)

Häuser, 2014; 732 – 40

Opioids: Tolerability?

chronic Osteoartritis			
Studies (Patients)	Variable	Opioid vs Placebo	Number needed to benefit / to harm (95%-CI)
16 (6743)	Pain intensity		13 (10-17)
2 (2709)	min. 50% reduction of pain intensity	25.1 vs. 25.7	8 (6-12)
6 (2910)	treatment stop due to side effects	25.6 vs. 7.0	5 (4-6)
5 (2509)	severe side effects	2.4 vs. 1.8	not calculated

NNH 5
(stop due to side effects)

Häuser, 2014; 732 – 40

JAMA

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Opioids for Chronic Noncancer Pain

A Systematic Review and Meta-analysis

Jason W. Busse, DC, PhD[1,2,3,4]; Li Wang, PhD[1,2,5]; Mostafa Kamaleldin, MB BCh[6]; et al

Author Affiliations | Article Information

JAMA
Published Online: December 18, 2018
2018;320;(23):2448-2460.
doi:10.1001/jama.2018.18472

RELATED ARTICLES MEDIA FIGURES SUPPLEMENTAL CONTENT

Opioids JAMA Review 2018

Figure 1. Diagram of the Study Selection Process for the Systematic Re

Table. GRADE Evidence Profile of Opioids vs Placebo for Patients With Chronic Noncancer Pain Included in Randomized Clinical Trials

Outcome Measure	No. of Trials (N = 96)	No. of Patients (N = 26 169)	Follow-up, mo	Serious Risk of Bias?[a]	I^2 (95% CI), %[b]	Serious Indirectness or Imprecision?[c]	*P* Value for Publicati… Bia…	…ed the MID	Risk Difference for Achieving the MID (95% CI), %	WMD (95% CI)	Quality of Evidence
Pain[e]	42	16 617	3-6[f]	No	70.4 (59.5 to 78.4)	No		…6)	11.9 (9.7 to 14.1)	−0.69 cm (−0.82 to −0.56)	High
Physical functioning[g]	51	15 754	1-6	No	65.7 (53.9 to 74.…			5058 (54.6)	8.5 (5.9 to 11.2)	2.04 points (1.41 to 2.68)	High
Emotional functioning[h]	23[i]	8962	1-4	No	47.2			…(35.0) 1899 (33.3)	−1.7 (−4.2 to 0.8)	−0.44 points (−1.09 to 0.20)	High
Role functioning[k]	16[i]	5329	1-4	No				1113 (48.0) 1475 (49.0)	1.0 (−0.7 to 2.6)	0.87 points (−0.54 to 2.28)	High
Social functioning[l]	29	7623	1-…				.84	1527 (43.8) 1920 (46.4)	2.6 (0.7 to 4.5)	1.58 points (0.45 to 2.70)	High
Sleep quality[m]	15	6585	3-6[f]		…5)	No	.06	1232 (47.2) 2111 (53.1)	5.9 (2.8 to 9.1)	3.42 mm (1.58 to 5.26)	High
Vomiting[n]											
Enrichment trials	18	5961	1.5-4		0 (0 to 41.3)	No	.65	68 (2.3)[o] 179 (5.9)[o]	3.6 (2.1 to 5.4)	RR, 2.50 (1.89 to 3.30)	High
Nonenrichment trials	33	11 268	1-6	No	0 (0 to 36.4)	No	.23	96 (2.3)[o] 667 (9.4)[o]	7.1 (5.4 to 9.3)	RR, 4.12 (3.34 to 5.07)	High

synthesis that reported the results from 96 trials

No follow up >6 month
Opioid effect decreases with time

Research Paper
PAIN 166 (2025) e555–e562

Mortality among patients with long-term prescription opioid use in Norway: a nationwide registry–based cohort study

Gabriela Rolova[a,b], Anders Engeland[c,d], Line Pedersen[e,f], Ingvild Odsbu[c,g], Aleksi Hamina[g,h], Svetlana Skurtveit[c,g,*]

Long term opioids Norway

- Register:
  - 116.000 Long term chronic pain
  - 18.800 cancer pain Patients
  - At least 2 prescriptions of opioids during the last 180days
- Indication for opioids:
  - Back pain
  - Arthritis
  - Pelvic pain
  - Abdominal pain
- Top 3 Opioids in Norway:
  - Codeine
  - Tramadol
  - Oxycodone

Table 1

Characteristics of patients with noncancer with long-term prescription opioid use by sex.

Characteristic (n, %)	Men N = 54,535	Women N = 61,471

Table 2

Crude mortality rates per 100,000 person-years for all-cause and cause-specific mortality in patients with noncancer with long-term prescription opioid use by sex.

	ICD-10	Men		Women	
		CMR	95% CI	CMR	95% CI
Person-time (y)		208,717.3		232,105.6	
All-cause mortality		1193.5	1146.6-1240.3	723.8	689.2-758.4
Natural causes of death	A00-R99	930.4	889.1-971.8	610.5	578.7-642.3
Unnatural causes of death	V01-Y98	220.9	200.7-241.0	100.8	87.9-113.7
Suicide	X60-X84; Y87.0	75.7	63.9-87.5	45.2	36.6-53.9
Accidents*	V01-X59; Y85-Y86	141.3	125.2-157.5	53.4	44.0-62.8
Accidental poisoning	X40-X49	91.5	78.5-104.5	35.8	28.1-43.5

* All accidents including accidental poisoning.
CI, confidence interval; CMR, crude mortality rate; ICD-10, International Classification of Diseases, 10th revision.

Single-person household 14,108 (25.9) 10,869 (17.7)

Table 3

Standardized mortality ratios for all-cause and cause-specific mortality in patients with noncancer with long-term prescription opioid use by sex and age groups.

	ICD-10	15–69 y			15–34 y			35–54 y			55–69 y		
		No. of death	SMR	95% CI	No. of death	SMR	95% CI	No. of death	SMR	95% CI	No. of death	SMR	95% CI
Men													
All-cause mortality		2491	3.8	3.6-3.9	107	8.2	6.8-10.0	562	4.6	4.2-5.0	1822	3.5	3.3-3.6
Natural causes of death	A00-R99	1942	3.8	3.7-4.0	26	7.5	5.1-11.0	313	4.2	3.7-4.6	1603	3.7	3.6-3.9
Unnatural causes of death	V01-Y98	461	5.0	4.6-5.5	77	8.9	7.1-11.1	231	5.8	5.1-6.6	153	3.6	3.0-4.2
Suicide	X60-X84; Y87.0	158	4.3	3.7-5.1	24	5.8	3.9-8.6	87	5.0	4.1-6.2	47	3.1	2.3-4.1
Accidents*	V01-X59; Y85-Y86	295	5.6	5.0-6.2	53	12.1	9.3-15.9	138	6.4	5.4-7.6	104	3.8	3.2-4.7
Accidental poisoning	X40-X49	191	9.1	7.9-10.5	47	17.7	13.3-23.6	101	9.0	7.4-10.9	43	6.1	4.5-8.2
Women													
All-cause mortality		1680	3.7	3.5-3.9	41	6.1	4.5-8.4	358	4.7	4.3-5.2	1253	3.5	3.3-3.7
Natural causes of death	A00-R99	1417	3.8	3.6-4.0	17	6.4	4.0-10.3	247	4.2	3.7-4.8	1153	3.7	3.5-3.9
Unnatural causes of death	V01-Y98	234	5.5	4.8-6.3	23	6.3	4.2-9.5	111	6.2	5.2-7.5	100	4.8	3.9-5.8
Suicide	X60-X84; Y87.0	105	5.5	4.5-6.6	13	6.0	3.5-10.4	54	5.6	4.3-7.3	38	5.2	3.8-7.1
Accidents*	V01-X59; Y85-Y86	124	5.7	4.8-6.8	10	7.3	3.9-13.5	55	7.4	5.6-9.6	59	4.6	3.5-4.7
Accidental poisoning	X40-X49	83	8.7	7.8-10.7	10	12.1	6.5-22.5	46	9.5	7.1-12.7	27	6.9	4.7-10.1

* All accidents including accidental poisoning.
CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; SMR, standardized mortality ratio.

Systematic Review and Meta-Analysis

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. Rice[n], Michael Rowbotham[o,p], Mark Wallace[q], Christopher Eccleston[a,b,r]

36 RCT:

- Neuropathic Pain(n=13)
- Cancer Pain(n=6)
- Acute postoperative pain (n=4)
- Multiple sclerosis (n=10)

Inclusion criteria:

- Any acute and chronic pain
- Cannabis, Cannabinoids, Receptor AG, AT
- Modulators of ECs
- Min. 30 patients per study arm

Pain; 2021; http://dx.doi.org/10.1097/j.pain.0000000000001929

Conclusions:

- (very) low level of evidence
- The authors lament that, especially due to companies, the provision of raw data was difficult.
- There is currently no evidence from RCTs for the use of cannabinoids or EC modulators in chronic pain patients for the treatment of:
  - Pain
  - Physical limiations
  - Emotional Stress
  - Insomnia

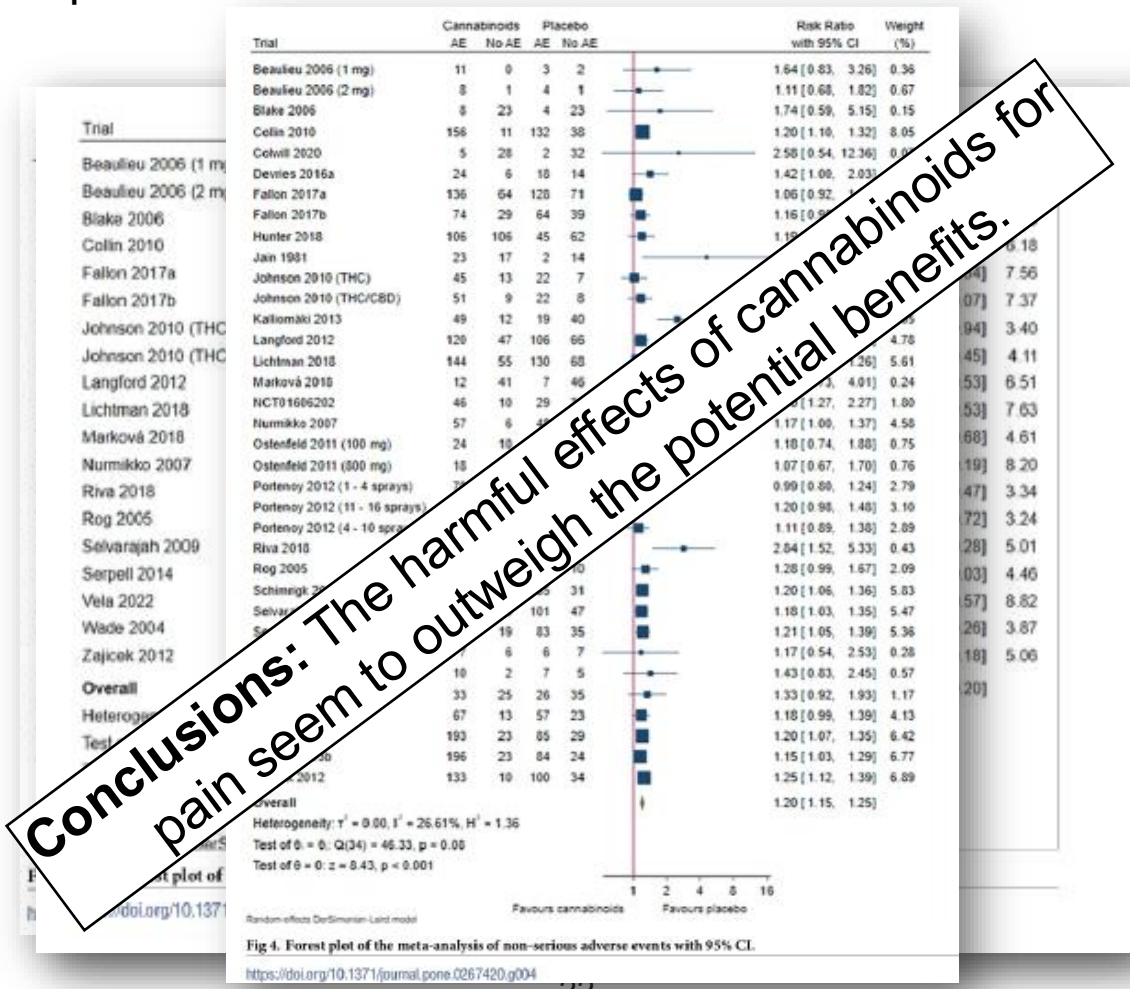
- There may be single responders who profit under supervision of pain specialists
- More high quality studies needed.

Cannabinoids versus placebo for pain: A systematic review with meta-analysis and Trial Sequential Analysis

Jehad Barakji[1]*, Steven Kwasi Korang[1], Joshua Feinberg[1,2], Mathias Maagaard[1,3], Ole Mathiesen[3,4], Christian Gluud[1,5], Janus Christian Jakobsen[1,5]

Cannabinoids VS Placebo Review 2023

- **2023:** 65 randomised placebo-controlled clinical trials; 7017 participants.
  - 59 at high risk of bias.
- **No** effect on:
  - **acute pain** (MD NRS: 0.52; 98% CI -0.40 to 1.43; P = 0.19)
  - **cancer pain** (MD NRS: -0.13; 98% CI -0.33 to 0.06; P = 0.1)
  - **quality of life** (MD: -1.38; 98% CI -11.81 to 9.04; P = 0.33)
  - **serious adverse events** (RR 1.18; 98% CI 0.95 to 1.45; P = 0.07)
  - **all-cause mortality** (RR 1.20; 98% CI 0.85 to 1.67; P = 0.22)
- **Positive** Effect on:
  - **chronic pain** (MD NRS -0.43; 98% CI -0.72 to -0.15; P = 0.0004)
  - **quality of sleep** (MD: -0.42; 95% CI -0.65 to -0.20; P = 0.0003).
  - both effect sizes were below minimal important differences.
- **Negative** Effect on:
  - **non-serious adverse events** (RR 1.20; 95% CI 1.15 to 1.25; P < 0.001)



Conclusions: The harmful effects of cannabinoids for pain seem to outweigh the potential benefits.

Chronic pain, cannabis legalisation, and cannabis use disorder among patients in the US Veterans Health Administration system, 2005 to 2019: a repeated, cross-sectional study

Deborah S Hasin, Melanie M Wall, Daniel M Alschuler, Zachary L Mannes, Carol Malte, Mark Olfson, Katherine M Keyes, Jaimie L Gradus, Magdalena Cerdá, Charles C Maynard, Salomeh Keyhani, Silvia S Martins, David S Fink, Ofir Livne, Yoanna McDowell, Scott Sherman, Andrew J Saxon

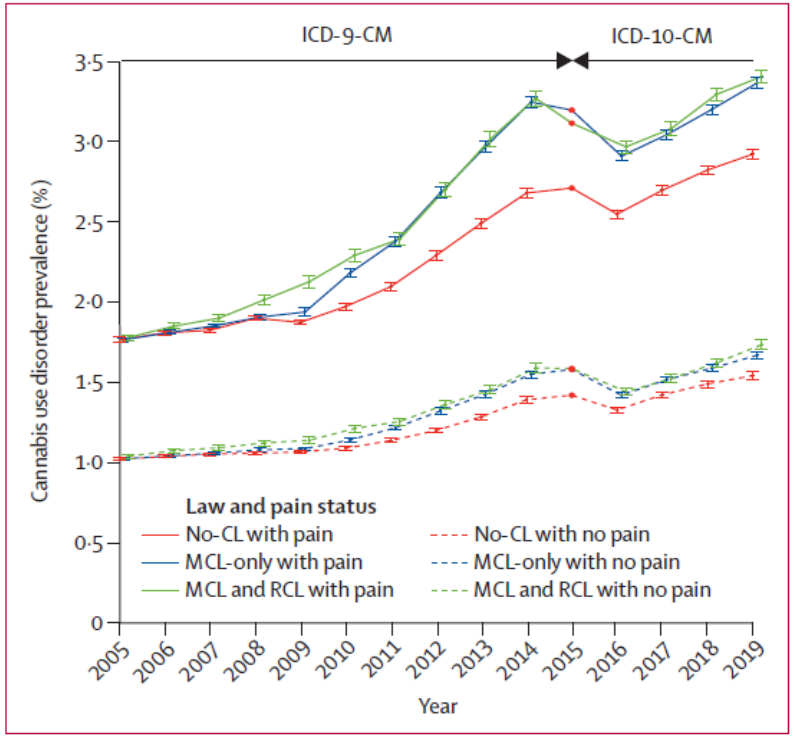


Figure 1: **Cannabis use disorder prevalence by state law status as of 2019, among patients with and without chronic pain**
No-CL=no cannabis law. MCL=medical cannabis law. RCL=recreational cannabis law.

Lancet Psychiatry 2023; 10:877-86

Universitätsspital Basel

04

Resulting Guidelines…

… From Trials and Errors

Guidelines: S3 LONTS 2. Edition 2020
updated by the DEGAM S1 Guidline 2023 of chronic pain treatment

Contraindications:

- Primary headaches
- Functional somatoform disorders
- Chronic pelvic pain in women
- Fibromyalgia (exeption Tramadol for 4-12 weeks)

- Chronic pain as leading symptom of psychiatric disorders:
  - Somatoform pain disorder
  - Generalized anxiety disorder
  - Postraumatic stress disorder

- Chronic inflammatory bowl disease (max. 4 weeks)
- Chronische pancreatitis (no long term effect)

Guidelines: S3 LONTS + S1 DEGAM Guidelines

Only in responders during a 4-12 week trial:

- Chronic back pain
- Chronic Osteoarthritis
- Chronic neuropathic pain

Successful Test:

- Is orianteted on functional outcomes
- No severe side-effects

Therapy limited to max. 12 weeks:

- Diabetic polyneuropathy
- Post-zoster neuralgia (2. line)
- Rheumatoid Arthritis (up to 6 weeks)

During pain exacerbations:

- First NOPA before increase opioids

Tapering attempt after 6 month

Regularly evaluation of therapy goals

Always stop (stepwise) if:

- Therapy goals reached through different therapy
- Therapy goals are not reached within 4-12 weeks
- Ongoing side-effects
- Misuse

Do not exceed 120mg ME

Research Paper

PAIN 00 (2025) 1–8

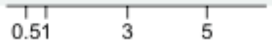
Presc
due t

Ria E. Hopk
Ramesh Wa

A

Adjusted odds of suicide death

Subgroup	aOR (95% CI)
Opioid exposure	
(Ref: Ongoing use)	
Discontinued use	0.88 (0.72 to 1.07)
Geography	
(Ref: Major city)	
Regional/Remote	1.06 (0.86 to 1.32)
Socioeconomic Disadvantage	
(Ref: 1–Most disadvantaged)	
2	1.44 (1.08 to 1.93)
3	1.61 (1.21 to 2.13)
4	1.53 (1.11 to 2.09)
5–Least disadvantaged	1.98 (1.39 to 2.84)
Past 12–mo treatment for comorbidities	
Opioid use disorder	1.55 (0.98 to 2.46)
Substance use disorder*	1.67 (1.15 to 2.42)
Nonfatal overdose/self–harm	3.65 (2.22 to 6.00)
Mental health conditions	1.16 (0.86 to 1.58)
Past 12–mo psychotropic medicine dispensings	
Sedative–hypnotic	2.60 (2.13 to 3.17)
Antidepressant	1.56 (1.27 to 1.91)
Antipsychotic	1.40 (1.05 to 1.87)
Gabapentinoid	0.91 (0.60 to 1.38)
OME mg dispensed	
(Ref:<50mg/day)	
50+mg/day	1.17 (0.82 to 1.68)



B

Adjusted odds of fatal unintentional overdose

Subgroup	aOR (95% CI)
Opioid exposure	
(Ref: Ongoing use)	
Discontinued use	0.45 (0.37 to 0.54)
Geography	
(Ref: Major city)	
Regional/Remote	0.93 (0.76 to 1.13)
Socioeconomic Disadvantage	
(Ref: 1–Most disadvantaged)	
2	1.21 (0.93 to 1.59)
3	1.32 (1.02 to 1.72)
4	1.40 (1.05 to 1.88)
5–Least disadvantaged	1.65 (1.19 to 2.30)
Past 12–mo treatment for comorbidities	
Opioid use disorder	3.42 (2.61 to 4.48)
Substance use disorder*	1.78 (1.32 to 2.41)
Nonfatal overdose/self–harm	2.22 (1.44 to 3.42)
Mental health conditions	1.21 (0.93 to 1.56)
Past 12–mo psychotropic medicine dispensings	
Sedative–hypnotic	2.71 (2.23 to 3.30)
Antidepressant	1.23 (1.02 to 1.48)
Antipsychotic	2.43 (1.92 to 3.08)
Gabapentinoid	1.25 (0.81 to 1.90)
OME mg dispensed	
(Ref: <50mg/day)	
50+mg/day	2.66 (2.16 to 3.28)

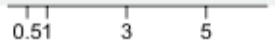


Figure 2. Adjusted odds of suicide (A) or fatal unintentional overdose (B) associated with opioid discontinuation and relevant covariates. *Excludes tobacco/nicotine. aOR, adjusted odds ratio; CI, confidence interval; OME mg, oral morphine equivalent milligrams. Data for Figure 2 are reported in Supplemental Table 8 (available at http://links.lww.com/PAIN/C395).

Figure 1. Study cohort formation. PBS, pharmaceutical benefits scheme.

Opioid Discontinuation

USB Vo

tsspital

CLINICAL GUIDELINE

ACP American College of Physicians® Leading Internal Medicine, Improving Lives

Cannabis or Cannabinoids for the Management of Chronic Noncancer Pain: Best Practice Advice From the American College of Physicians

Devan Kansagara, MD, MCR*; Kevin P. Hill, MD, MHS*; Jennifer Yost, PhD, RN; Linda L. Humphrey, MD, MPH; Beth Shaw, MSc; Adam J. Obley, MD; Ray Haeme; Elie A. Akl, MD, MPH, PhD; Amir Qaseem, MD, PhD, MHA; and the Population Health and Medical Science Committee of the American College of Physicians†

- Best Practice Advice 1a:
  - Clinicians should counsel patients ab … are considering whether to start or contir … r pain.
- Best Practice Advice 1b:
  - Clinicians should counsel the followir … e for chronic Noncancer pain are likely to outweigl
    - young adult and adolescent patients
    - patients with current or past substance
    - patients with Serious mental illness
    - frail patients and those at risk for falling
- Best Practice Advice 2:
  - Clinicians should advise Against starting … in patients Who are pregnant or breastfeeding or actively t…
- Best Practice Advice 3:
  - Clinicians should advise patients against t…

Figure 1. Summary of benefits and short-term harms of cannabis or cannabinoids for chronic noncancer pain (primarily neuropathic).

Product *Average Daily Dose*	Outcomes*							
	Benefits			Short-Term Harms				
	Pain Response†	Pain Severity‡	Function or Disability‡	Withdrawal due to AEs	SAEs	Dizziness	Nausea	Sedation
Comparable THC-CBD ratio§ vs. placebo or usual care								
Whole plant–derived, oral spray *23 mg of THC and 21 mg of CBD*	38% vs. 31% RR 1.18 (95% CI, 0.93 to 1.71) ●○○	MD −0.54 (CI, −0.95 to −0.19) ●●○	MD −0.42 (CI, −0.73 to −0.16) ●●○	12.5% vs. 10.2% RR 1.14 (CI, 0.65 to 3.02) ●○○	5.0% vs. 4.3% RR 1.18 (CI, 0.26 to 3.4) ●○○	31% vs. 8.0% RR 3.57 (CI, 2.42 to 5.60) ●○○	14% vs. 7.5% RR 1.79 (CI, 1.19 to 2.77) ●○○	8.0% vs. 1.2% RR 5.04 (CI, 2.10 to 11.89) ●○○
Interpretation	↑ May result in a small improvement	↓ Probably results in a small improvement	↓ Probably results in a small improvement ‖	↔ May be no difference	↔ May be no difference	↑ May result in a large increase	↑ May result in a medium increase	↑ May result in a large increase
High THC-CBD ratio¶ vs. placebo or usual care								
Synthetic or purified, oral *13 to 25 mg of THC*	Insufficient ○○○	MD −0.78 (CI, −1.59 to −0.08) ●○○	MD −0.18 (CI, −1.25 to 0.77) ●○○	14% vs. 7% RR 1.92 (CI, 1.10 to 4.80) ●○○	Insufficient ○○○	33% vs. 15% RR 2.30 (CI, 1.53 to 3.52) ●●○	12% vs. 6% RR 2.12 (CI, 1.09 to 3.96) ●○○	24% vs. 16% RR 1.57 (CI, 1.11 to 2.29) ●○○
Interpretation	? Uncertain	↓ May result in a small improvement	↔ May be no difference	↑ May result in a medium increase	? Uncertain	↑ Probably results in a large increase	↑ May result in a large increase	↑ May result in a medium increase
Whole plant–extracted, oral or sublingual *4.4 mg of THC and 0.08 mg of CBD or max daily THC dose of 25 mg*	No evidence ○○○	Insufficient ○○○	Insufficient ○○○	13.9% vs. 5.7% RR 3.12 (CI, 1.54 to 6.33) ●○○	Insufficient ○○○	62.2% vs. 7.5% RR 8.34 (CI, 4.53 to 15.34) ●○○	No evidence	No evidence
Interpretation	No evidence	? Uncertain	? Uncertain	↑ May result in a large increase	? Uncertain	↑ May result in a large increase	No evidence	No evidence

Practice Advice Cannabinoids

Abschlussbericht der Begleiterhebung nach § 31 Absatz 6 des Fünften Buches Sozialgesetzbuch zur Verschreibung und Anwendung von Cannabisarzneimitteln

Bundesinstitut für Arzneimittel und Medizinprodukte

Accompanying data collection of cannabis/cannabinoid prescriptions :

- Time period: 2017-2022 21.000

  (16.809 complete) Datasets

  1. Chronic pain (76.4%)
  2. Spasticity (9.6%)
  3. Anorexia/ Wasting (5.1%)
  4. Nausea/ Vometing (2.2%)

Good and bad news…

- Products: (Dronabinol, Sativex):
  - mean age: 57y
    median dose THC 15mg
- Reported:
  - Symptom improvement: 75%
  - Life quality improvement: 70%

- Medical Cannabis (Flowers):
- mean age: 47y; $^{2}/_{3}$ Männer
  median dose: THC: 249mg
- Therapy break up: 30%:
  - No effect; 38.5%
  - Side effects: 25.9%
  - death 20.2%

05

Both? Supportive or complementary effects of combination?

Opioid sparing effects of cannabinoids?

Rationale:

American College of Neuropsychopharmacology

www.nature.com/npp

ARTICLE OPEN

Check for updates

Opioid-sparing effect of cannabinoids for analgesia: an updated systematic review and meta-analysis of preclinical and clinical studies

Suzanne Nielsen[1,2✉], Louisa Picco[1], Bridin Murnion[3], Bryony Winters[4], Justin Matheson[5], Myfanwy Graham[6,7], Gabrielle Campbell[8], Laila Parvaresh[9,10], Kok-Eng Khor[11,12], Brigid Betz-Stablein[13], Michael Farrell[2], Nicholas Lintzeris[3,9] and Bernard Le Foll[5,14]

Opioid saving effects of Cannabinoids?

- 40 preclinical studies:
- Primary outcome: Dose of opioid required to give an equivalent antinociceptive effect in the presence and absence of cannabinoids

- 37 clinical studies (20 controlled; 17 observational; 5180 participants)
  - Outcomes of interest in clinical studies:
    - 1) reduction in total opioid doses
    - 2) reductions in pain through the addition of a cannabinoid
    - 3) adverse events
    - 4) evidence of abuse liability

Opioid sparing effects: Preclinical data

- Synergistic effects in all mixed CB1/CB2 agonists
- Mixed/conflicting Results in selective CB1-R and CB2-R AG
- Cannabinoids with complex Pharamakology (CBD), **No** synergistic effects

	Morphine + THC			Morphine + vehicle				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Cichewicz 1999	1.12	0.09	30	1.45	0.08	30	14.5%	-0.33 [-0.37, -0.29]
Cichewicz 2003	1.13	0.18	12	1.38	0.18	30	14.0%	-0.25 [-0.37, -0.13]
Cox 2007	-0.39	0.17	7	0.38	0.17	28	13.8%	-0.77 [-0.91, -0.63]
Maguire 2018	0.38	0.08	8	0.82	0.07	8	14.3%	-0.44 [-0.51, -0.37]
Smith 1998	0.44	0.07	30	1.5	0.08	30	14.5%	-1.06 [-1.10, -1.02]
Welch 1992	-0.82	0.07	96	-0.21	0.19	120	14.5%	-0.61 [-0.65, -0.57]
Williams 2008	0.39	0.07	24	0.74	0.06	24	14.5%	-0.35 [-0.39, -0.31]
Total (95% CI)			**207**			**270**	**100.0%**	**-0.54 [-0.78, -0.31]**

Heterogeneity: Tau² = 0.10; Chi² = 942.43, df = 6 (P < 0.00001); I² = 99%
Test for overall effect: Z = 4.46 (P < 0.00001)

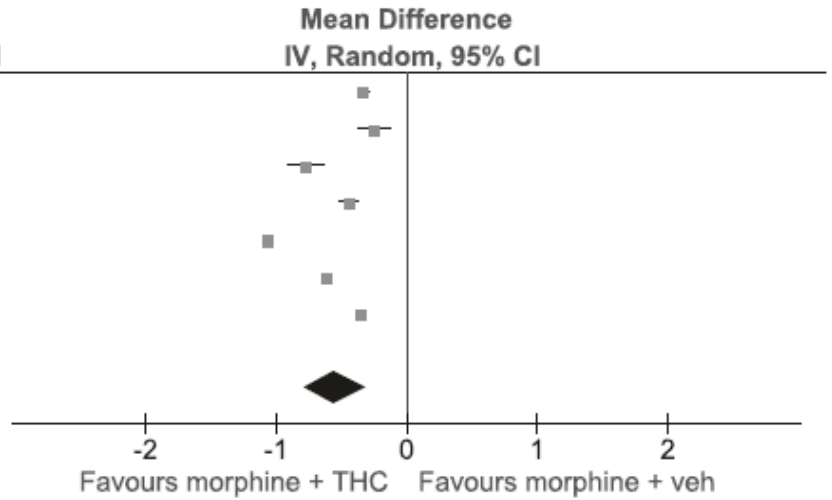


Fig. 1 Forrest plot for meta-analysis examining the opioid-sparing effect of delta-9-THC when co-administered with morphine. Note mean difference and standard deviation values are of $\log_{10} ED_{50}$.

Clinical data:

(a) Pain reduction:

Study or Subgroup	Nabiximols Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95
Fallon 2017a	12.46	21.96	198	14.94	25.76	199	26.7%	-2.48
Fallon 2017b	34.5	25.26	103	35.24	24.44	103	18.8%	
Johnson 2010	12	14.9	53	6.64	10.45	56	26.0%	
Lichtman 2018	13.7	22.4	199	9.34	21.36	198		
Total (95% CI)			**553**					

Heterogeneity: Tau² = 8.96; Chi² = 7.10, df = 3 (P

Test for overall effect: Z = 0.93 (P = 0.35)

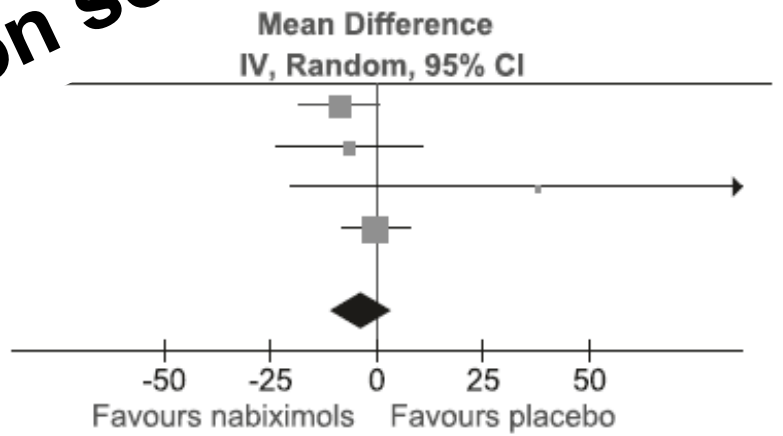
Authors conclusion: „While controlled studies showed a lack of robust analgesic effects, cannabis was nearly always associated with analgesia in open-label or retrospective reports, possibly indicating an effect on well-being or mood rather than on sensory pain“

(b) OMEDD:

Study or Sub			
Fallon 2017a			.0.60]
Fallon 2017b			
Johnson 2010			.0.33, 96.13]
Lichtman 2018			-0.30 [-8.19, 7.59]
Total (95% CI)		**100.0%**	**-3.80 [-10.97, 3.37]**

Heterogeneity: Tau² = 12 ... 23%

Test for overall effect: Z =



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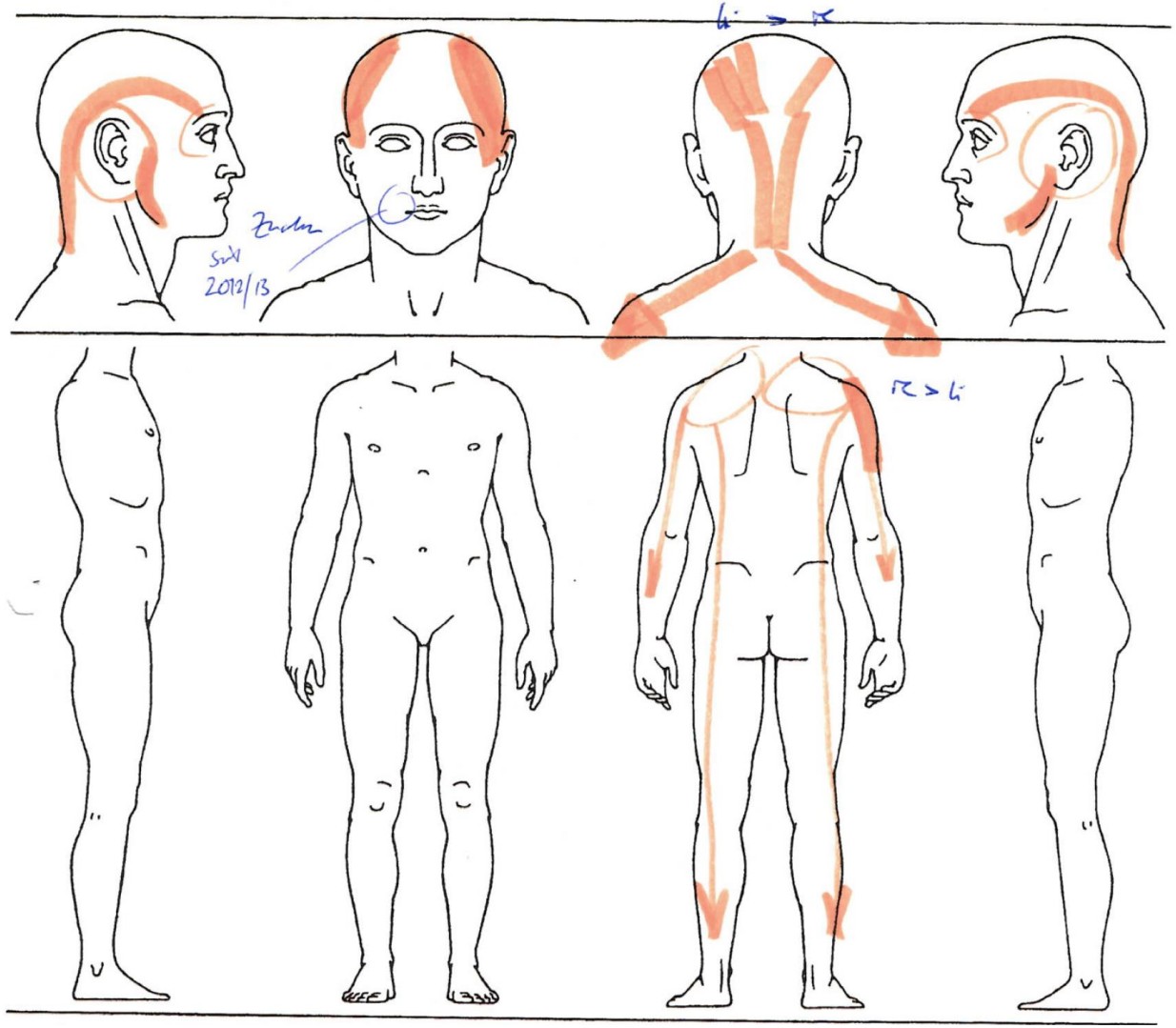
06

Responders



female 49y MD Immun… (50% pension)

1. Tension He…e and Migraine
2. Episod… Depression, Burnout 2012
3. B… Tinnitus Ohr links
4. …eloma … clinic)

Less inner and muscle tension

Pain does not hit me that direct anymore

Improved quality of sleep

Previou…
Johns Wort, Mitrazapine, Trimipramine

Accompan… …erapy: Qi-Gong, TENS, Akkupressur, reg… …chologic visits

Less rumination

Cannabis Oil 12mg T… CBD g/Lsg.
Stable on: 3x10 drp for 4 yea…

female, IV pensionist 53y

1. Chronic abdom… after multiple abdominal operations … shock in complex abdominal wall in… and necrosis)
2. More social interaction
3. Severe Lipoedema and Lymphoedema

Increased mobility

Less back pain

Previou… …ation: Metamizole …tosis); Acute kidney failure, CI, …aracetamol (no Effect); Pentinoids(Gain weig…

Less diarrhea

Stable on Targin 15/7.5mg 1-0-1 + Oxynorm 4mg i.R max. 3x daily for 3years

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Conclusions

In chronic pain both medication classes should be used with caution

And if a trial is made:

- according to available guidelines
- with regularly treatment goals and side effect evaluation.

Future research should :

- record and report PROMS
- report number of responders (e.g. pain reduction 50%)
- focus on responder profiling to prevent trial and error treatments
- for cannabinoids evaluate synthetic cannabinoid system modulators

Sind Cannabinoide die besseren Placebos?

JAMA Network | Open

Original Investigation | Pharmacy a

Placebo Response an … Clin
Cannabis-Based Ther…
A Systematic Review a…

Filip Gedin, PhD; Sebastian Blomé, MSc; Moa Pontén, PhD; Maria Lalouni, PhD; Jens Fust, PhD; Andreé Raquette, DC; Vikt…
William H. Thompson, PhD; Karin Jensen, PhD

- 20 Studien mit 1459 Probanden

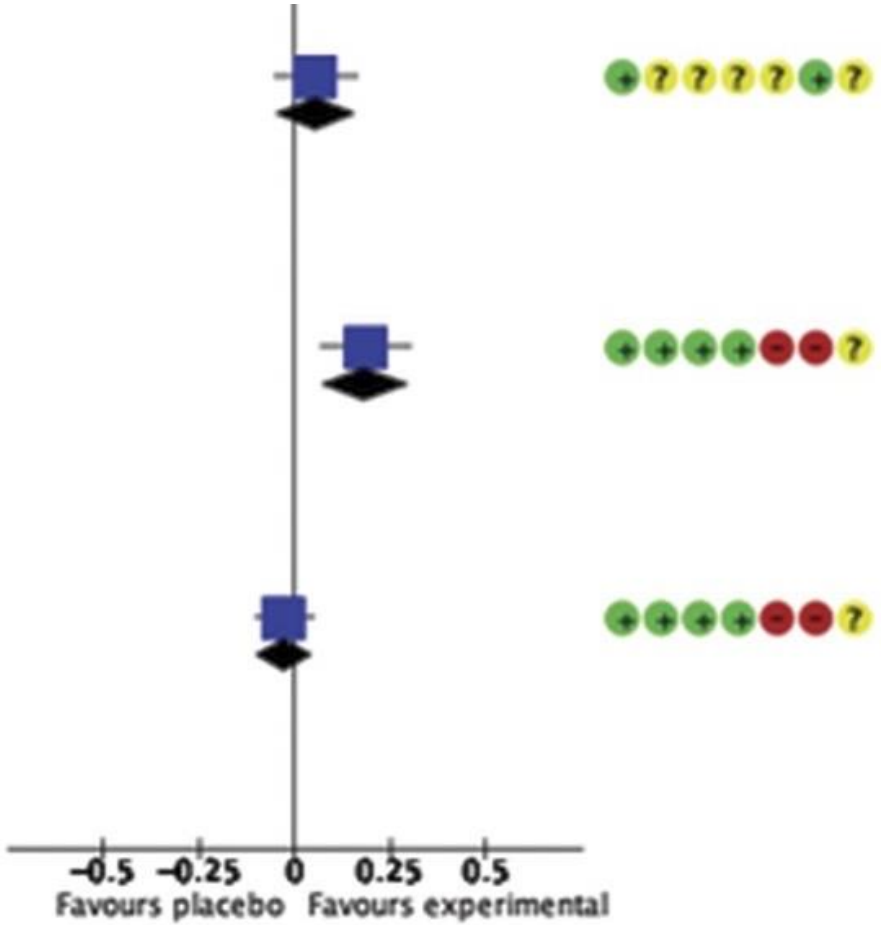
- …Effekte in RCTs: …-Stärken (…
- …ter Verblindung … die grösst…
- …erksamkeit für … hoch (88%…
- …arken positiven …

Conclusion: Der Placeboeffekt trä… …chteten Schmerzreduktion durch Cannabinoide in klinischen Studie…

Chronic low back pain
50% Schmerzreduktion nach 12-16 Wo Behandlung

Outcome: 30% Schmerzreduktion

6.1.6 MS pain >4 weeks							
Langford 2013	84	167	77	172	100.0%	0.06 [-0.05, 0.16]	
Subtotal (95% CI)		167		172	100.0%	0.06 [-0.05, 0.16]	
Total events	84		77				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
6.1.7 MS spasticity pain outcome							
Zajicek 2012	28	94	9	80	100.0%	0.19 [0.07, 0.30]	
Subtotal (95% CI)		94		80	100.0%	0.19 [0.07, 0.30]	
Total events	28		9				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.15 (P = 0.002)							
6.1.8 MS progression							
Ball 2015	41	264	27	148	100.0%	-0.03 [-0.10, 0.05]	
Subtotal (95% CI)		264		148	100.0%	-0.03 [-0.10, 0.05]	
Total events	41		27				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.70 (P = 0.48)							

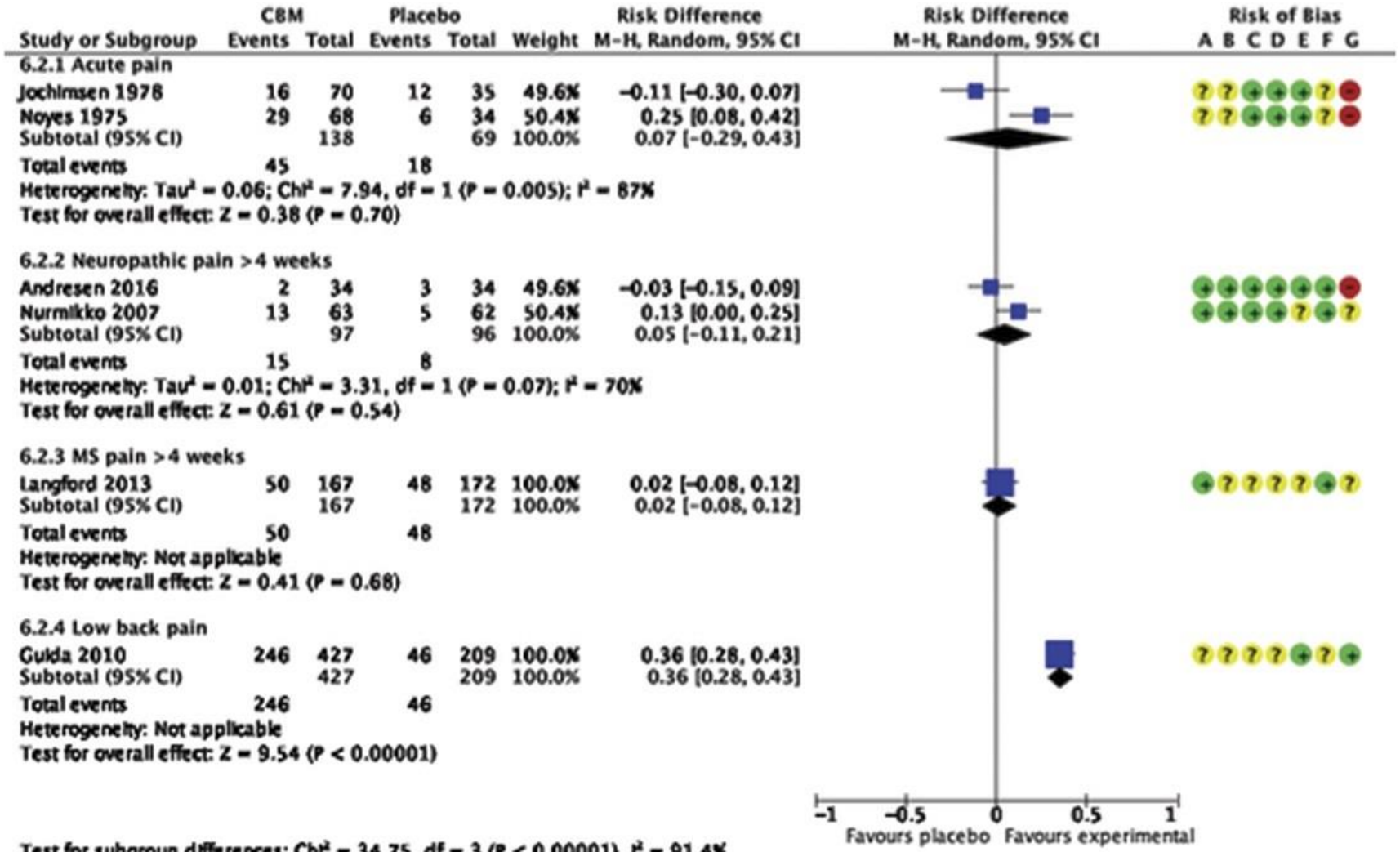


Test for subgroup differences: Chi^2 = 27.25, df = 6 (P = 0.0001), I^2 = 78.0%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Size

Outcome 50% Schmerzreduktion



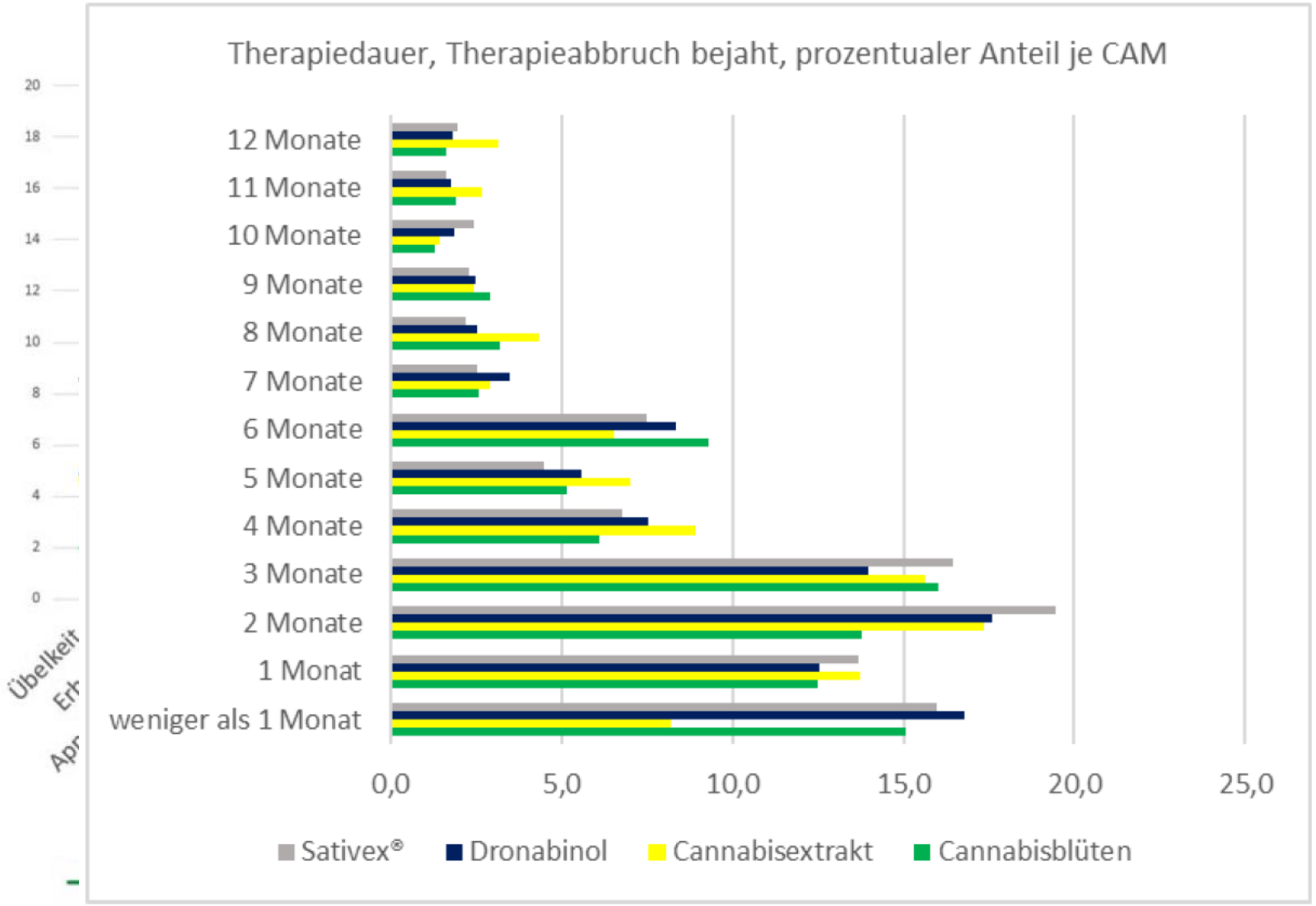
Test for subgroup differences: Chi² = 34.75, df = 3 (P < 0.00001), I² = 91.4%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Size

Patientenkollektiv chronischer Schmerz

Therapieabbru	N=674)
Kein ausreichende Effekt	.5%)
Nebenwirkung	.0%)
Interaktionen	%)
Keine Indikatic	%)
Tod	.%)
Weitere Gründ	3%)



ativex® (n=2188)

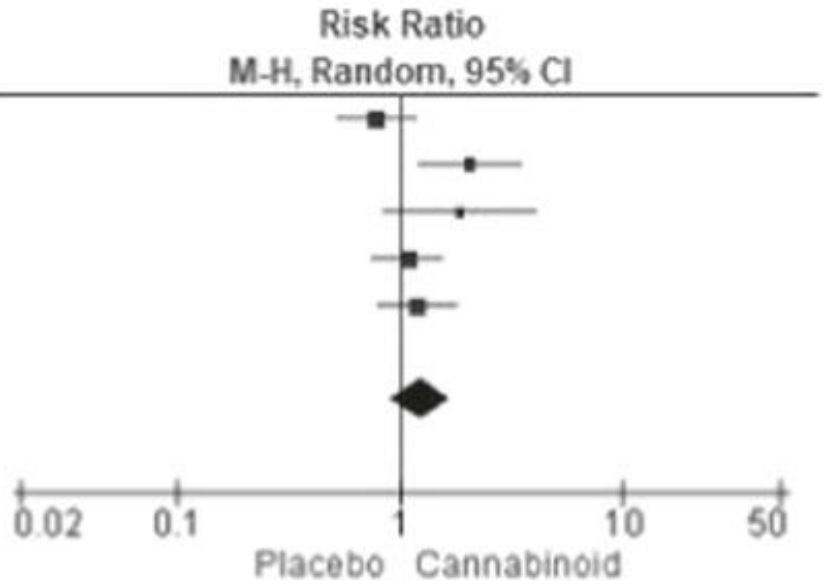
Opioid sparender Effekt Subgruppe: Tumorschmerz?

SAE:

(c)

Study or Subgroup	Cannabinoid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fallon 2017a	35	199	44	198	23.0%	0.79 [0.53, 1.18]
Fallon 2017b	33	103	16	103	18.0%	2.06 [1.21, 3.51]
Johnson 2010 (1)	26	118	7	59	11.6%	1.86 [0.86, 4.03]
Lichtman 2018	47	199	43	198	24.4%	1.09 [0.76, 1.56]
Portenoy 2012 (2)	81	268	23	91	23.0%	1.20 [0.80, 1.78]
Total (95% CI)		887		649	100.0%	1.23 [0.89, 1.70]
Total events	222		133			

Heterogeneity: Tau² = 0.08; Chi² = 9.63, df = 4 (P = 0.05); I² = 58%
Test for overall effect: Z = 1.28 (P = 0.20)

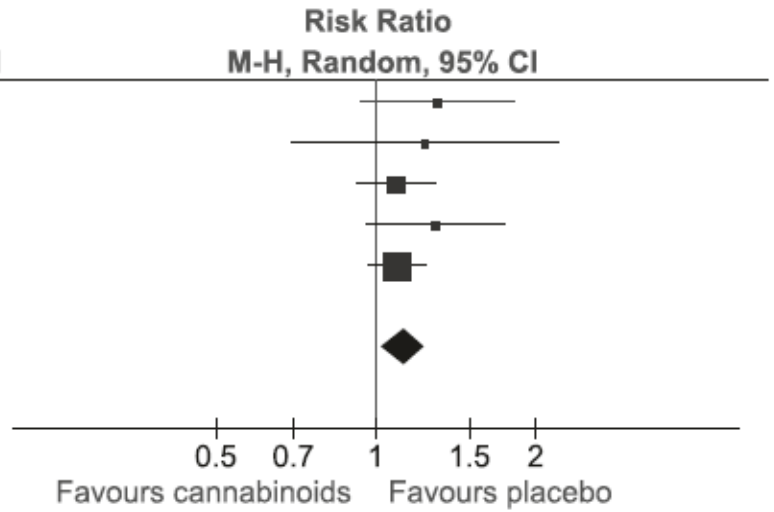


AE:

(d)

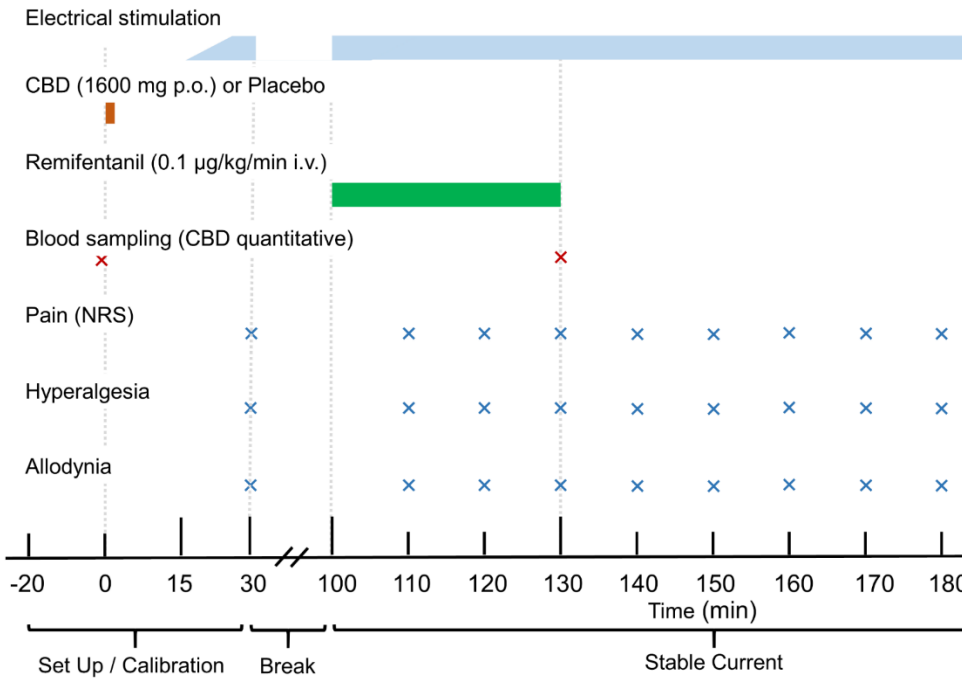
Study or Subgroup	Cannabinoids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fallon 2017a	59	199	45	198	7.6%	1.30 [0.93, 1.82]
Fallon 2017b	21	103	17	103	2.5%	1.24 [0.69, 2.20]
Johnson 2010	96	118	44	59	28.6%	1.09 [0.92, 1.30]
Lichtman 2018	69	199	53	198	9.5%	1.30 [0.96, 1.75]
Portenoy 2012	223	268	69	91	51.8%	1.10 [0.97, 1.25]
Total (95% CI)		**887**		**649**	**100.0%**	**1.13 [1.03, 1.24]**
Total events	468		228			

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)

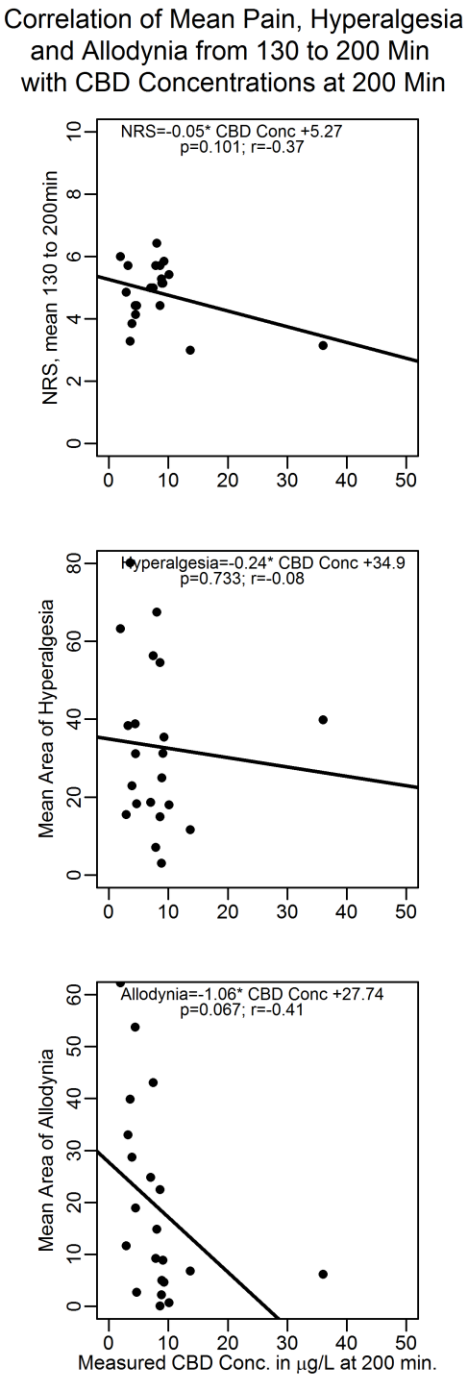


CANAB II:

- Cannabidiol 1600mg p.o
- Reduction of Opioid Induced Hyperalg



CANAB II; T. Schneider et al. Pain 2022;
http://dx.doi.org/10.1097/j.pain.0000000000002591



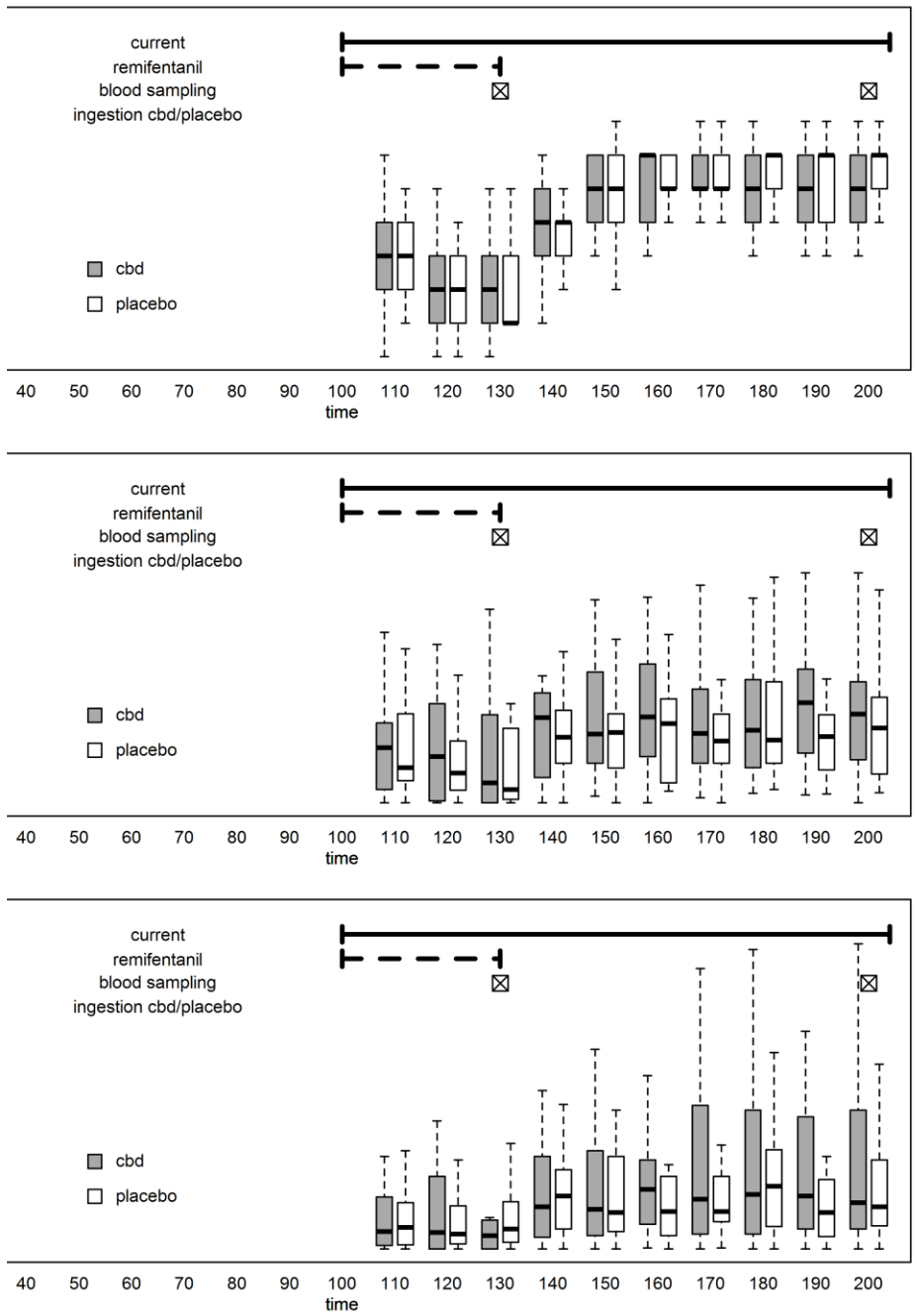


Table 2. Summary of Long-Term Harms of Cannabis and Cannabinoid Use

Long-Term Harm	Evidence Source	Finding
Cannabis use disorder	Systematic review (33) Cohort study (34) *Diagnostic and Statistical Manual of Mental Disorders* (35)	U.S. prevalence: 10% to 30% of those reporting past-year cannabis use (33) Symptoms: characterized by tolerance, withdrawal, and an increasing amount of time spent in activities related to cannabis use, often at the expense of fulfilling one's responsibilities in those with more severe cannabis use disorder (35) Risk factors: prevalence is higher among adolescents and young adults, males, those with a history of substance use disorder and/or psychiatric disorder, and those that use cannabis more frequently and over longer periods of time (33, 34)
Cannabis withdrawal syndrome	Systematic review (36)	U.S. prevalence: 17% to 87%, depending on setting (47% overall) (36) Symptoms: anxiety, irritability, and insomnia and start 24 to 48 h after stopping cannabis use, peaking during days 2 to 6 after cessation, and lasting up to 3 wk among those who use cannabis daily or near daily (36) Risk factors: concurrent tobacco or other substance use and daily cannabis use are associated with a higher prevalence (36)
Cognitive effects		
Acute effects	Systematic review (37) Narrative reviews (38, 39)	Acute cannabis intoxication is associated with mild to moderate effects on verbal learning, verbal memory, working memory, executive functioning, and processing speed (37, 39) There is likely a dose-response effect related to THC dose (38)
Chronic effects	Systematic reviews (40, 41) Narrative reviews (38, 39)	Adolescents who use cannabis regularly may experience small declines in IQ (38, 41) Clinically significant cognitive effects may largely resolve after abstinence, although the influence of factors such as duration of cannabis use and duration of abstinence is unclear (38–40)
Mental health effects		
Acute psychosis	Systematic review (42)	Large amounts of THC consumption can induce acute psychosis, which can sometimes be severe enough to require hospitalization (42)
Psychotic spectrum disorders	Case-control study (43) Cohort studies (44, 45) Cross-sectional study (46)	May be associated with long-term use of cannabis, particularly with use of high potency cannabis and with use starting at younger ages (43) Increased rates and earlier onset may be associated with early and heavy cannabis use in those with developing brains (44, 45) Association is particularly pronounced among those with a genetic predisposition to psychotic spectrum disorders (46)
Bipolar type 1 disorder	Systematic review (47)	Association of cannabis use with an increased incidence of mania in those with bipolar type I disorder (47)
Physical health effects		
Cancer	Systematic review (48) Cohort study (49)	Unclear whether cannabis increases risk for most types of cancer, including lung, head and neck, prostate, and colorectal cancer, although studies are limited by small populations of cannabis-only users (48) Low-certainty evidence of increased risk for testicular germ cell tumors with >10 y of cannabis use (48) One study found those with cannabis use disorder had a higher risk for head and neck cancer (49)
Cardiovascular	Narrative review (50) Case-crossover study (51) Cohort studies (52, 53) Cross-sectional study (54)	Cannabis use is associated with tachycardia, hypertension, and postural hypotension (50, 51) Cannabis can induce angina in high-risk persons, but unclear association with myocardial infarction, stroke, or atrial fibrillation particularly in lower-risk persons (52–54)
Gastrointestinal	Systematic review (55) Narrative review (56)	Cannabinoid hyperemesis syndrome (form of cyclical vomiting syndrome) occurs in some regular cannabis or cannabinoid users (55, 56)
Pregnancy	Systematic review (57)	Cannabis use during pregnancy has been associated with increased risk for adverse neonatal outcomes, including preterm birth, small for gestational age births, and perinatal mortality (57)
Pulmonary	Systematic review (58) Literature review (59) Cohort studies (60, 61)	Regular cannabis use is associated with bronchitis (58, 59) Unclear association between cannabis use and chronic obstructive pulmonary disease, particularly in lower-risk populations who do not use cannabis heavily (58–60) Unclear association between cannabis use and the risk for lung cancer (59, 61)

IQ = intelligence quotient; THC = delta-9-tetrahydrocannabinol.

Figure 2. Discussion points with patients who are considering cannabis or cannabinoids to manage their chronic noncancer pain.

The degree of benefit to ease chronic noncancer pain is, on average, small. We do not know how effective cannabis or cannabinoids are for pain over years of use. The potential benefits of cannabis for chronic noncancer pain should be weighed against the known short-term and long-term harms. Most people should try other treatment options before trying cannabis or cannabinoids for the management of chronic noncancer pain.

It is difficult to apply what we know from studies to practice in the United States because the potency (THC content) of products in dispensaries is typically far higher than that used in studies and because cannabis flower has not been well studied. Many of the harms associated with cannabis and cannabinoids are related to the total amount of THC used. It is best to use the least amount of THC necessary to achieve a beneficial effect.

The best studied form of cannabis is nabiximols, an oromucosal spray that delivers 2.7 mg of THC and 2.5 mg of CBD per spray and is not currently available in the United States. In studies, patients began with 1 spray and increased as needed to an average of 8 sprays per day over several weeks. The average effective daily dose of THC in these studies, and in studies of oral synthetic THC, was about 15–25 mg of THC per day.

If cannabis or cannabinoids are used for chronic noncancer pain, start at a low dose. There are several expert-based guidelines outlining titration strategies (77–79).

The goal of any treatment for chronic pain is to improve patients' ability to do the things they want and need to do. Establish and review functional goals at the outset. Stop using cannabis or cannabinoids if it is not helping to improve function or if it is causing adverse effects that outweigh the benefit experienced.

A patient should keep a record of their daily cannabis or cannabinoid use, including dose and timing, the effect on their chronic noncancer pain and their ability to do things, and any adverse effects.

Do not drive after using cannabis or cannabinoids. Be aware that some workplaces may test for drug use (including cannabis and cannabinoids) and that smoking cannabis can affect others through secondhand smoke.

Cannabis and cannabinoids can be addictive, even if it is being used to manage chronic noncancer pain. Some signals that show a patient may be developing problems with cannabis or cannabinoid use include the development of

- **tolerance (needing more cannabis to get the same effect);**
- **withdrawal (experiencing symptoms like irritability or insomnia when stopping or reducing cannabis use); or**
- **effects on social, professional, or mental well-being, such as relationship problems, forgoing activities in favor of using cannabis, failing to fulfill obligations, and continuing to use even if a patient feels it is causing physical or psychological problems.**

CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol.

Nebenwirkungen: Lebensqualität ↓