Cannabinoid Analgesia:
What Is The Real Evidence For Benefit And Harm?

Andrew SC Rice

Chair - IASP Presidential Taskforce on Cannabis & Cannabinoid Analgesia

Imperial College London

IASP
INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN

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DISCLOSURES

- Employee of Imperial College London
- IASP:
  - President-Elect
  - Chair - Presidential Task Force on Cannabis and Cannabinoid Analgesia
- Inventor on patents (not being pursued): WO2013 110945; WO2005 079771
- Consultancy and advisory board work for Imperial College Consultants- in the last 24 months this has included remunerated work for: Confo, CombiGene & Lateral

- Member: Neurology, Pain & Psychiatry Expert Advisory Group, Commission on Human Medicines, Medicines & Healthcare Products Regulatory Agency (MHRA)

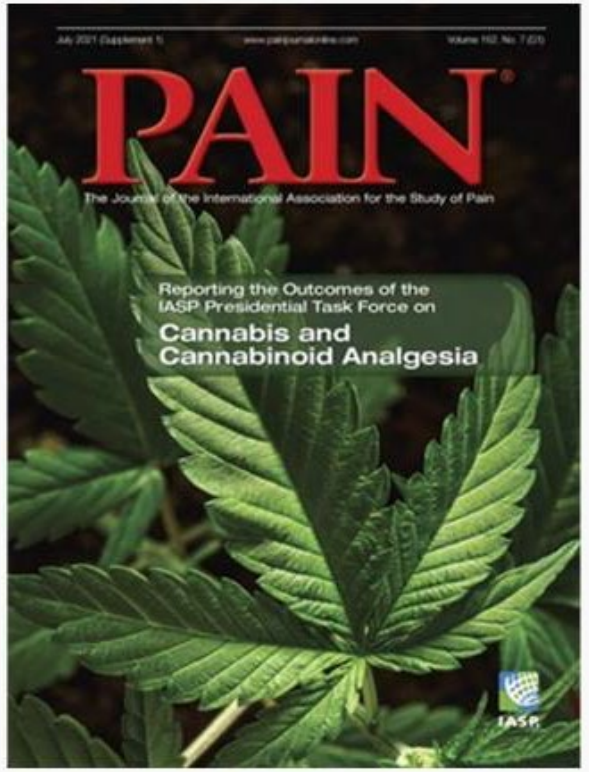
Task Force Membership

- Andrew Rice, United Kingdom (Chair)
- Joletta Belton, USA (Lived Experience Expert)
- Lars Arendt Nielsen, Denmark (President, ex officio)
- Fiona Blyth, Australia
- Louisa Degenhardt, Australia
- Marta Di Forti, United Kingdom
- Chris Eccleston, United Kingdom
- David Finn, Ireland
- Nanna Finnerup, Denmark
- Emma Fisher, United Kingdom
- Ian Gilron, Canada
- Simon Haroutounian, USA
- Andrea Hohmann, USA
- Eija Kalso, Finland
- Elliot Krane, USA
- Andrew Moore, United Kingdom
- Mike Rowbotham, USA
- Nadia Soliman, United Kingdom
- Mark Wallace, USA
- Nantthasorn Zinboonyahgooon, Thailand

Many thanks to IASP and PAIN Staff

TASKFORCE REMIT

- To prepare IASP's position statement on cannabis and cannabinoid analgesia.
  - Rigorously and transparently appraise the relevant preclinical and clinical evidence for benefit and harm
  - Publish outputs of the evidence appraisal and a research agenda required to fill knowledge gaps
  - Reach consensus on the Position Statement
- We did not consider:
  - "Recreational" use and laws
  - Medical use for indications other than pain
  - Clinical guidelines on prescribing etc



2021:162:supplement

IASP
INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN

Cannabinoids Are Broadly Defined As Constituents Of Cannabis Or Synthetic Compounds With Pharmacological Activity On The Endocannabinoid System

- **"Medical or medicinal cannabis"** - cannabis plants, plant material, or full plant extracts when used for medical purposes, but which do not have regulatory approval for marketing as a therapeutic.

- **"Medicinal cannabis extracts"** (also known as licensed cannabis-based medicines) - preparations derived from cannabis plants and which have regulatory approval for marketing as a therapeutic.

- **Synthetic cannabinoids** - pharmacologically active compounds, usually having affinity for and activity at cannabinoid receptors, which may have regulatory approval for marketing as a therapeutic.

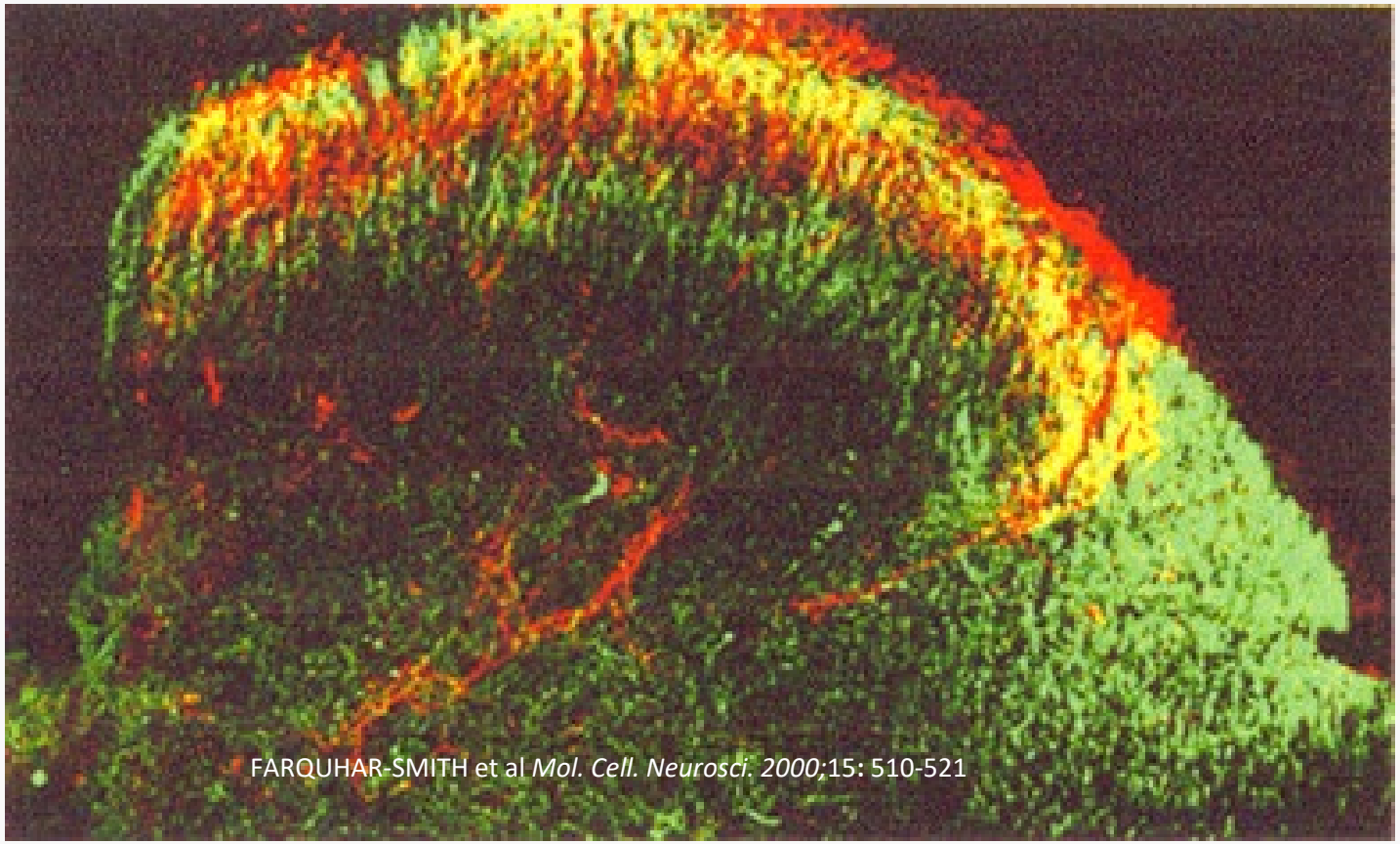
Narrative Review

PAIN

2021:162:S5-25

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]



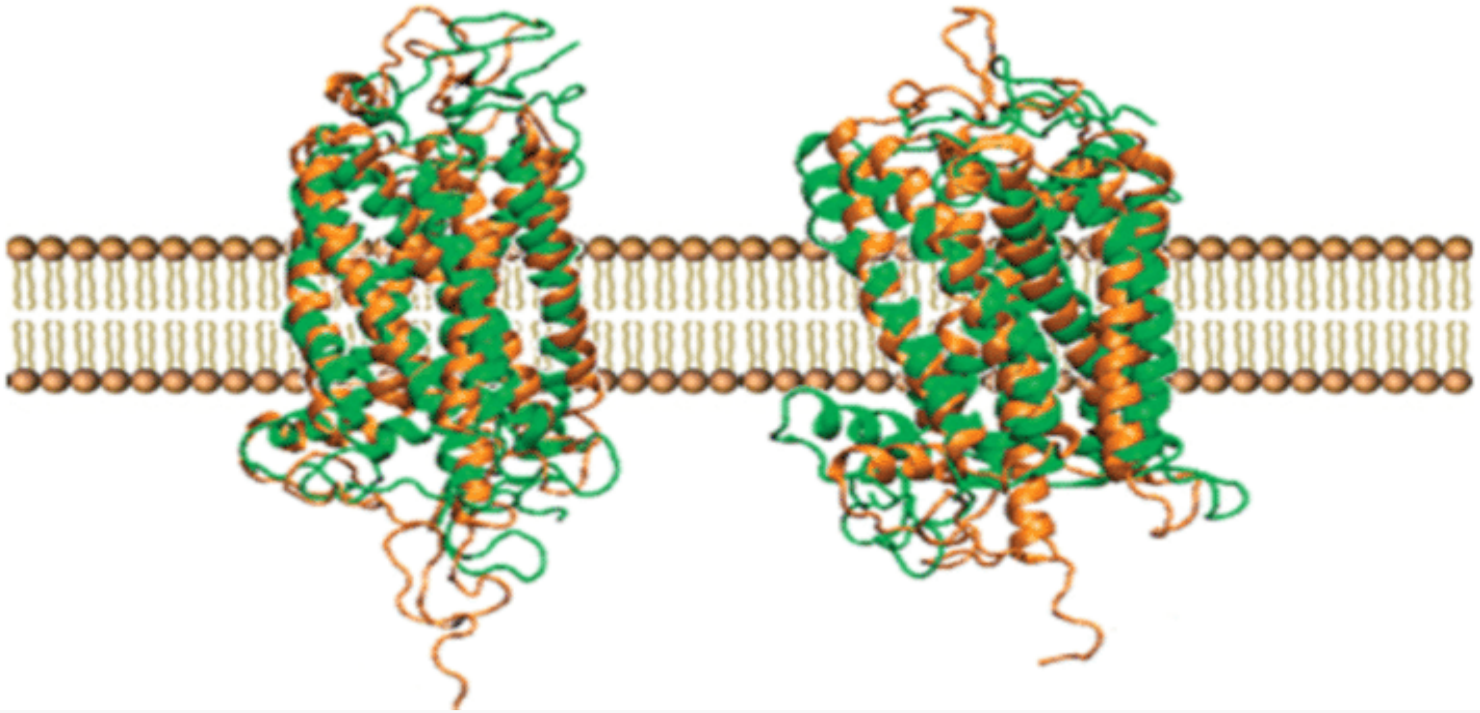
Cannabinoid Receptors

CB_1

Neurones

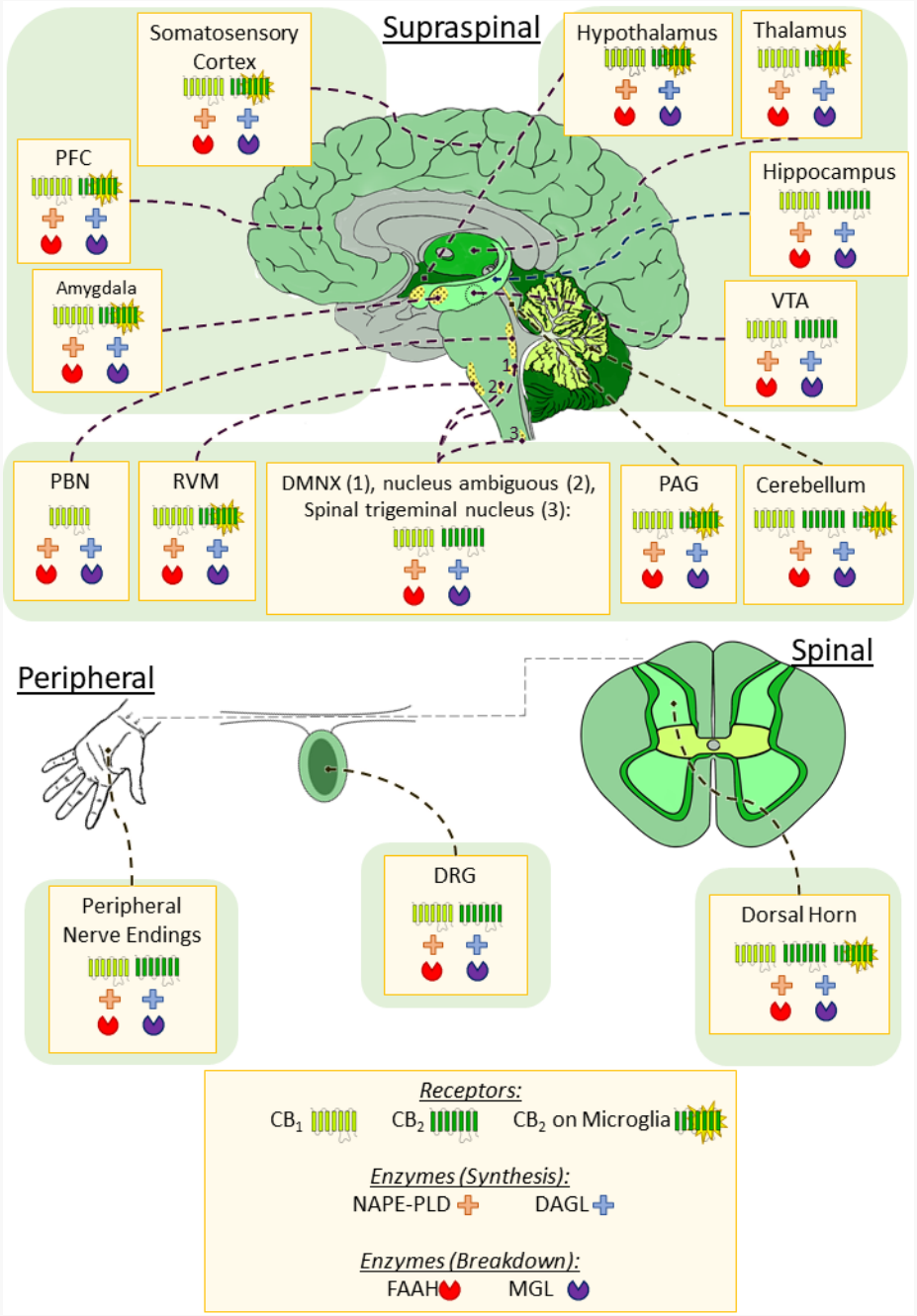
CB_2

Immune Cells



Sites Of Potential Analgesia Action Of Cannabinoids

Finn et al PAIN 2021;162:S5-25



Slide courtesy of Prof David Finn, U. Galway

Nadia Soliman PhD

Systematic Review and Meta-Analysis

PAIN 2021:162:S26-44 OPEN

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

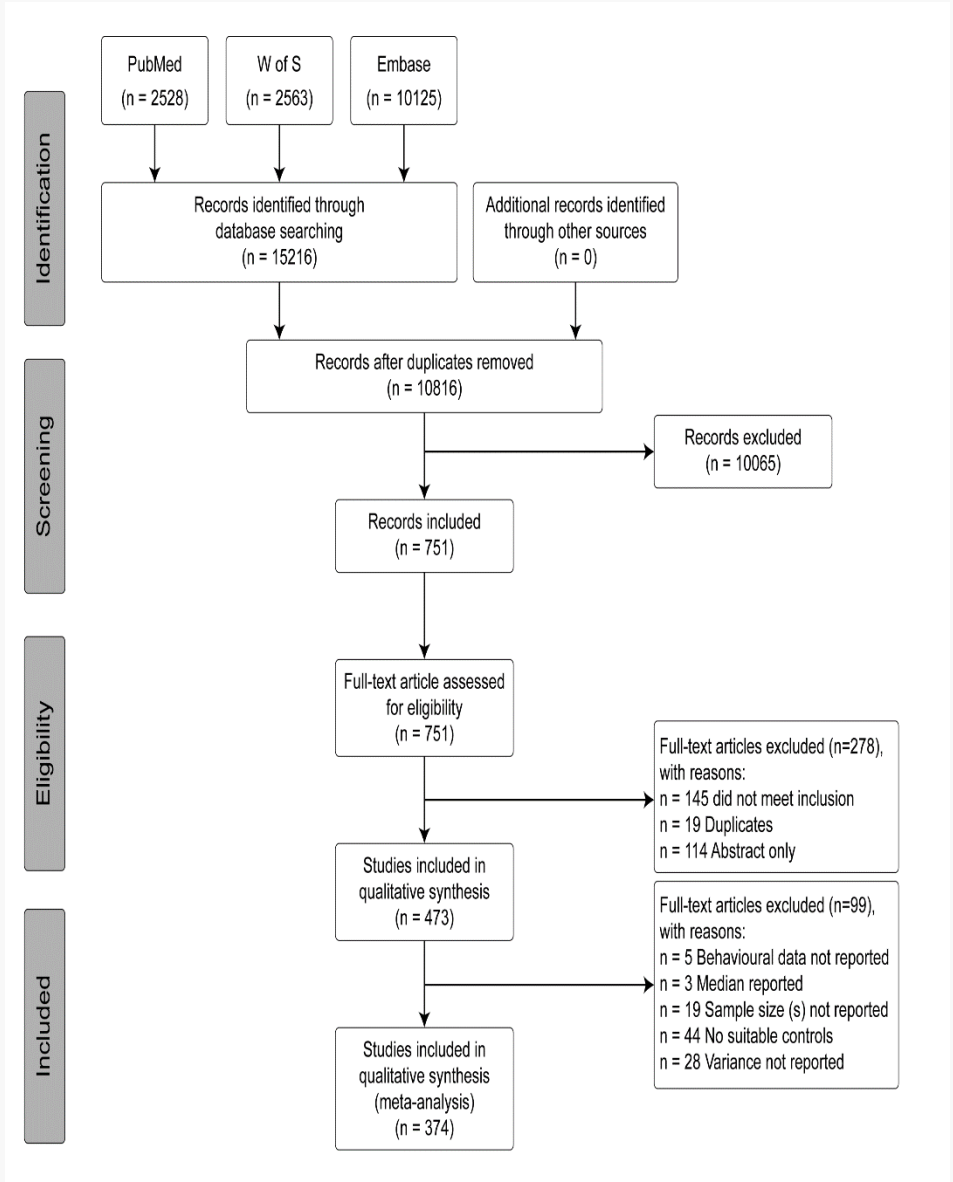
Nadia Soliman[a,*], Simon Haroutounian[b], Andrea G. Hohmann[c], Elliot Krane[d], Jing Liao[e], Malcolm Macleod[e], Daniel Segelcke[f], Christopher Sena[e], James Thomas[g], Jan Vollert[a], Kimberley Wever[h], Harutyun Alaverdyan[b], Ahmed Barakat[i,j], Tyler Barthlow[i], Amber L. Harris Bozer[k], Alexander Davidson[i], Marta Diaz-delCastillo[i], Antonina Dolgorukova[m], Mehnaz I. Ferdousi[n], Catherine Healy[n], Simon Hong[o], Mary Hopkins[n], Arul James[p], Hayley B. Leake[q,r], Nathalie M. Malewicz[s], Michael Mansfield[t], Amelia K. Mardon[q], Darragh Mattimoe[n], Daniel P. McLoone[n], Gith Noes-Holt[u], Esther M. Pogatzki-Zahn[f], Emer Power[n], Bruno Pradier[f], Eleny Romanos-Sirakis[v,w], Astra Segelcke[x], Rafael Vinagre[y], Julio A. Yanes[z], Jingwen Zhang[aa], Xue Ying Zhang[a], David P. Finn[n], Andrew S.C. Rice[a]

- **P**opulation: any injury-related or pathological persistent pain model. Persistent pain was described as typically studied over a period of hours, days, weeks, or months, and therefore for inclusion, a minimum experiment length of 1 h.

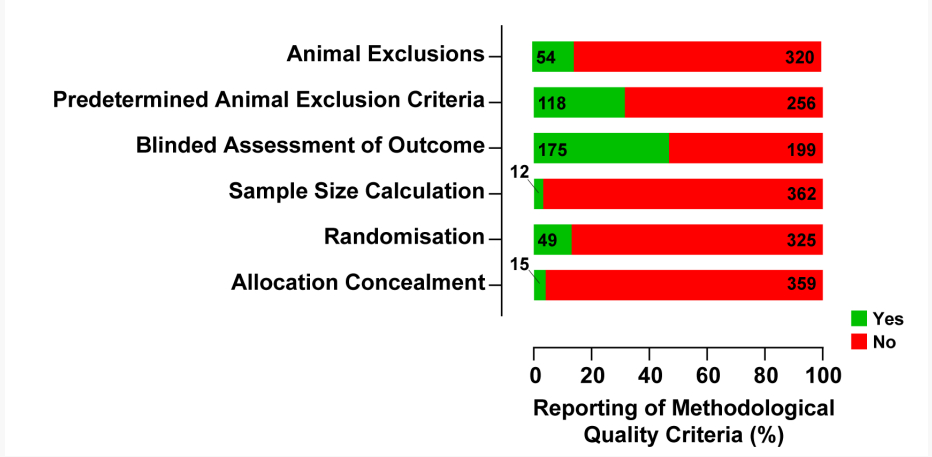
- **I**ntervention: any cannabinoid, cannabis-based medicine or endocannabinoid system modulator administered to assess antinociceptive effect.

- **C**omparison: a separate cohort of animals in which the model was induced and was given a vehicle control treatment.

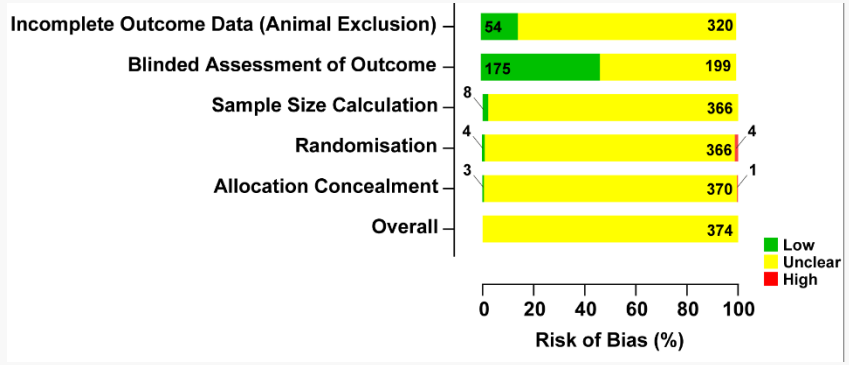
- **O**utcome: any pain-associated behavioural outcome measures



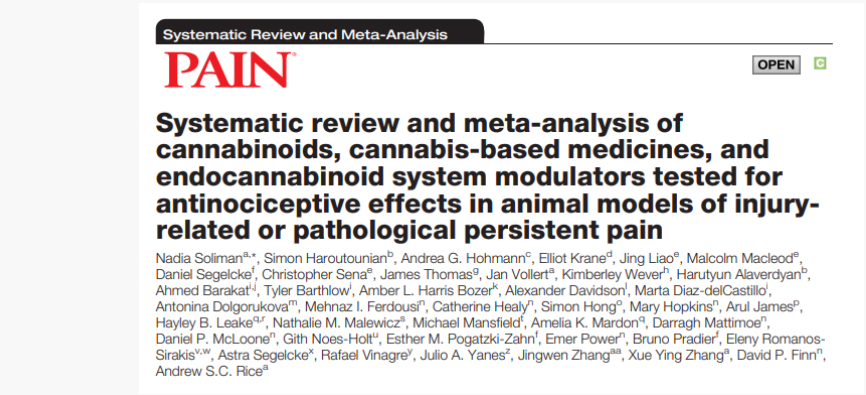
Reporting Quality
(CAMARADES)

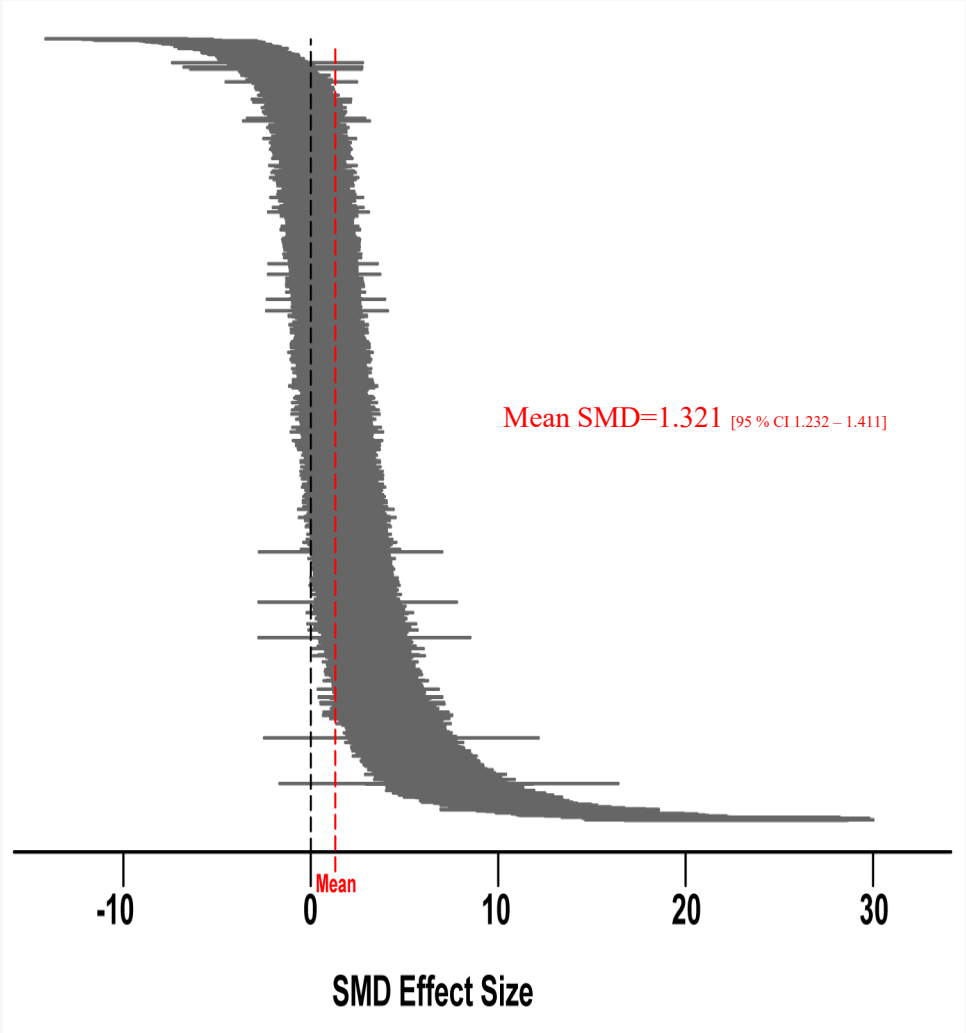


Risk of Bias
(SYRCLE)

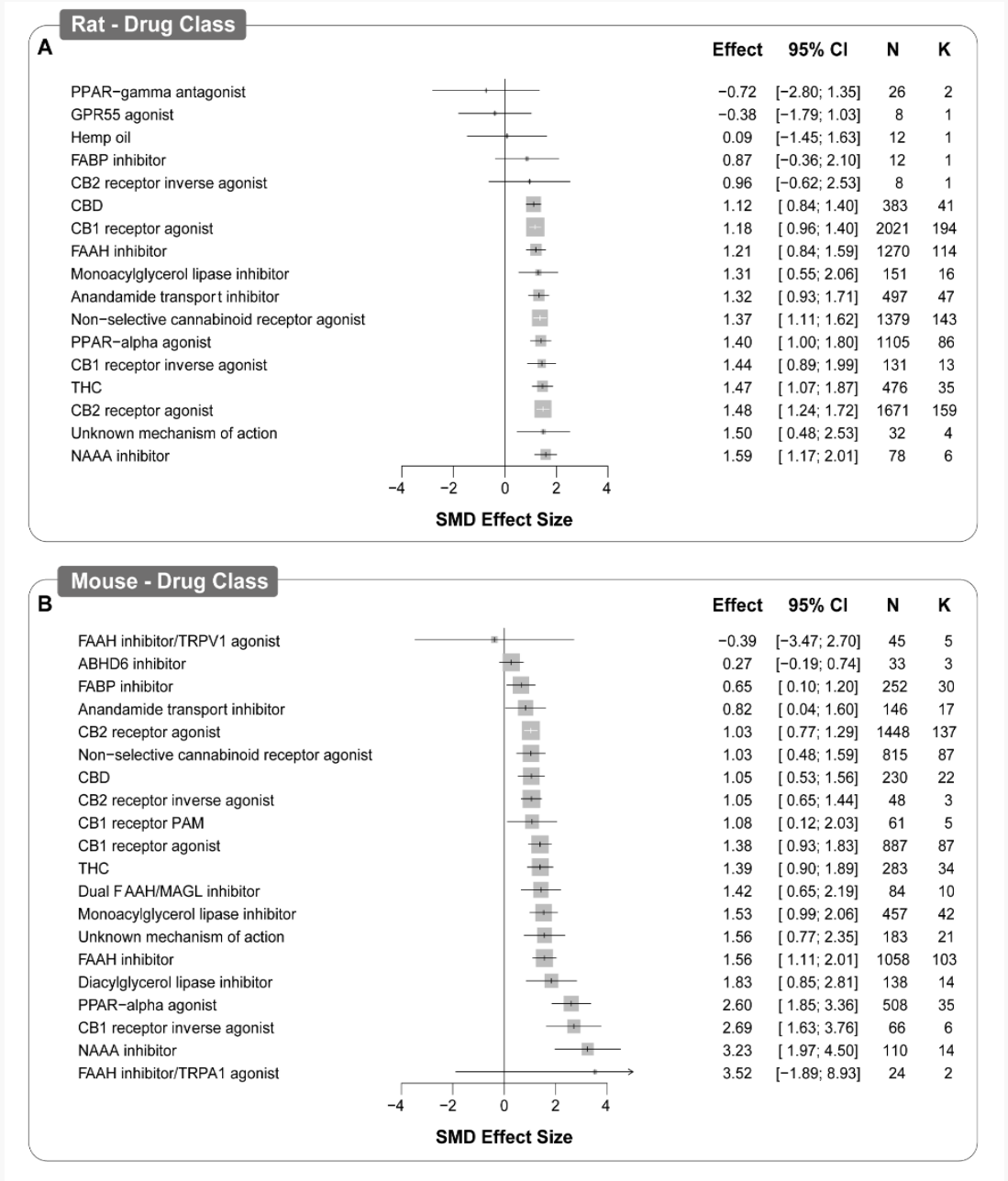


Model Type	Number of Studies	Number of Nested Comparisons
Inflammation	434	467
Nerve injury	348	413
Formalin	223	235
Chemotherapy	112	128
Diabetes	63	74
Cancer	57	65
Post-operative	27	52
Visceral inflammation	20	31
Chemical cauterization	1	16
Migraine	9	13
HIV	4	11
Capsaicin	5	9
Heat injury	2	7
Multiple sclerosis	6	7
Musculoskeletal	2	4
Antiretroviral	1	3
Burn injury	1	3
Mustard-oil	3	3
Sickle cell disease	2	2





Drug Class	Number of Studies	Number of Nested Comparisons
CB2 receptor agonist	75	299
CB1 receptor agonist	88	281
Non-selective cannabinoid receptor agonist	71	230
FAAH inhibitor	57	217
PPAR-alpha agonist	40	121
THC	16	69
Anandamide transport inhibitor	18	64
CBD	17	63
Monoacylglycerol lipase inhibitor	23	58
FABP inhibitor	3	31
Unknown mechanism of action	6	25
NAAA inhibitor	4	20
CB1 receptor inverse agonist	7	19
Diacylglycerol lipase inhibitor	3	14
Dual FAAH/MAGL inhibitor	4	10
CB1 receptor PAM	1	5
FAAH inhibitor/TRPV1 agonist	1	5
CB2 receptor inverse agonist	2	4
ABHD6 inhibitor	1	3
FAAH inhibitor/TRPA1 agonist	1	2
PPAR-gamma antagonist	1	2
GPR55 agonist	1	1
Hemp oil	1	1



Clinical Evidence of Efficacy?

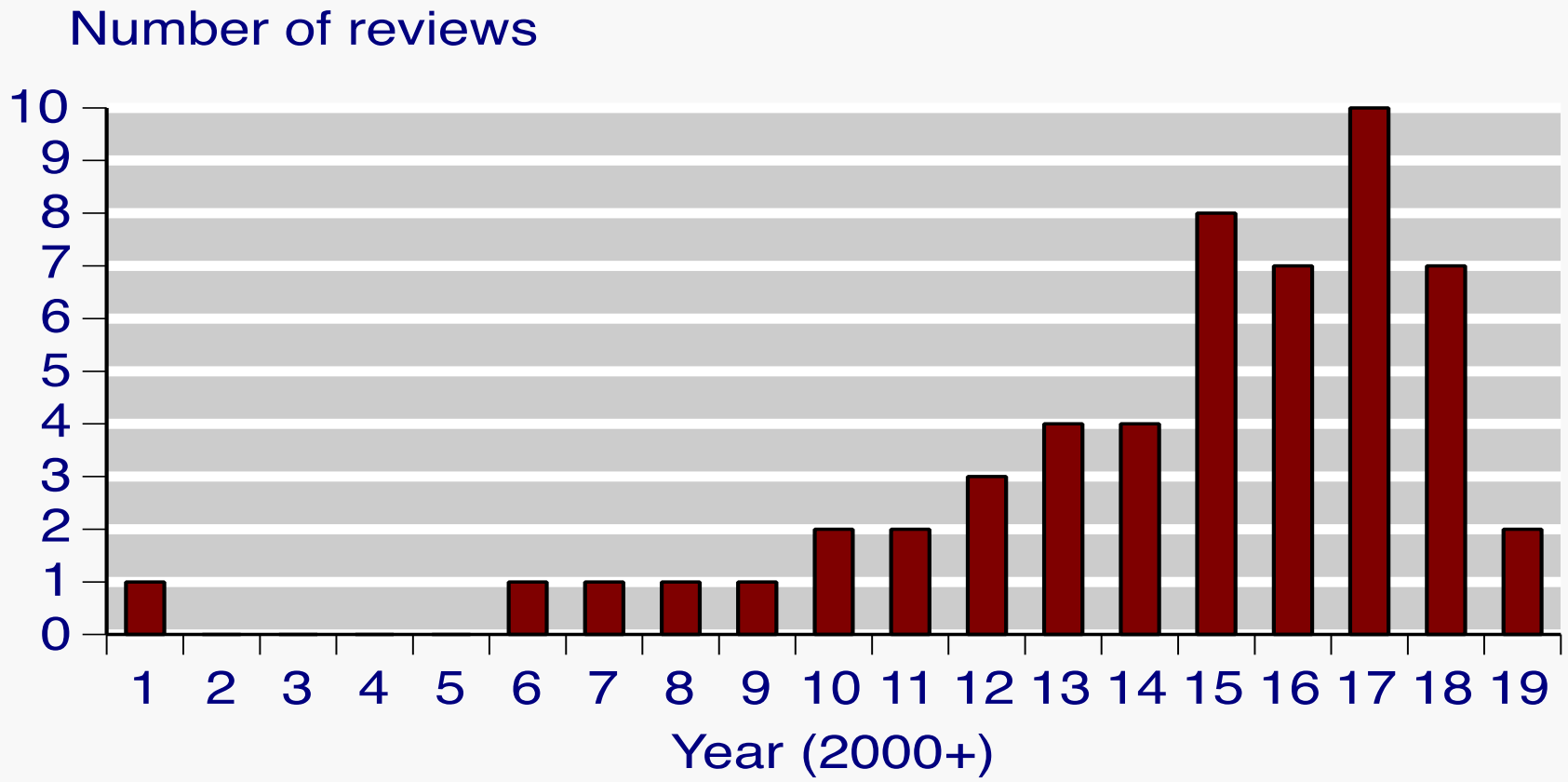
Comprehensive Review

PAIN

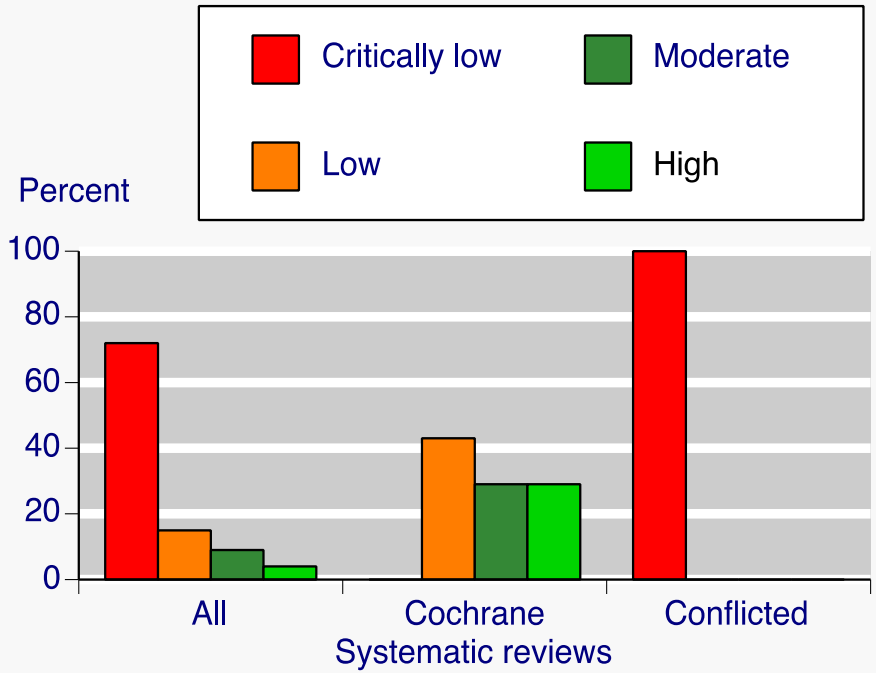
2021:162:S69-79

Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews

R. Andrew Moore[a,*], Emma Fisher[b,c], David P. Finn[d], Nanna B. Finnerup[e,f], Ian Gilron[g,h,i], Simon Haroutounian[j,k], Elliot Krane[l], Andrew S.C. Rice[m], Michael Rowbotham[n,o], Mark Wallace[p], Christopher Eccleston[b,c,q]

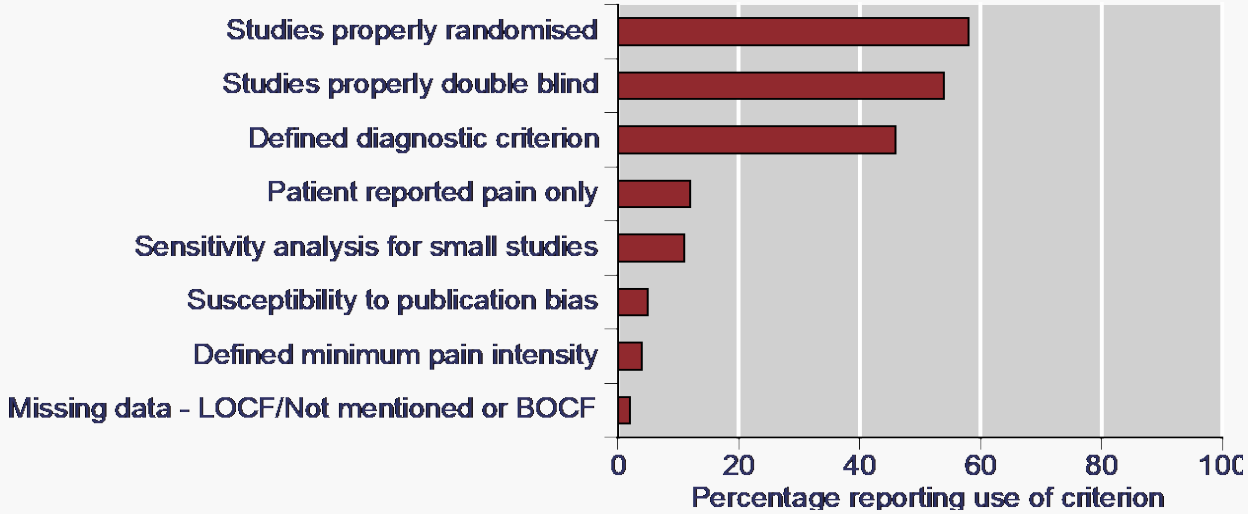


57 Reviews published before January 2020



AMSTAR-2

86% = low or critically low confidence



Pain-specific quality metrics

Moore, Fisher at al for IASP Taskforce

PAIN 2021:162:S45-66

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]

Inclusion criteria

- Randomised, double blind trial
- Any type /dose of medicinal cannabis, medicinal cannabis extracts or synthetic cannabinoid.
- Adults or children with any type pain, but excluding experimental pain
- Excluded studies <30 participants

Primary outcomes

- 30% and 50% pain reduction

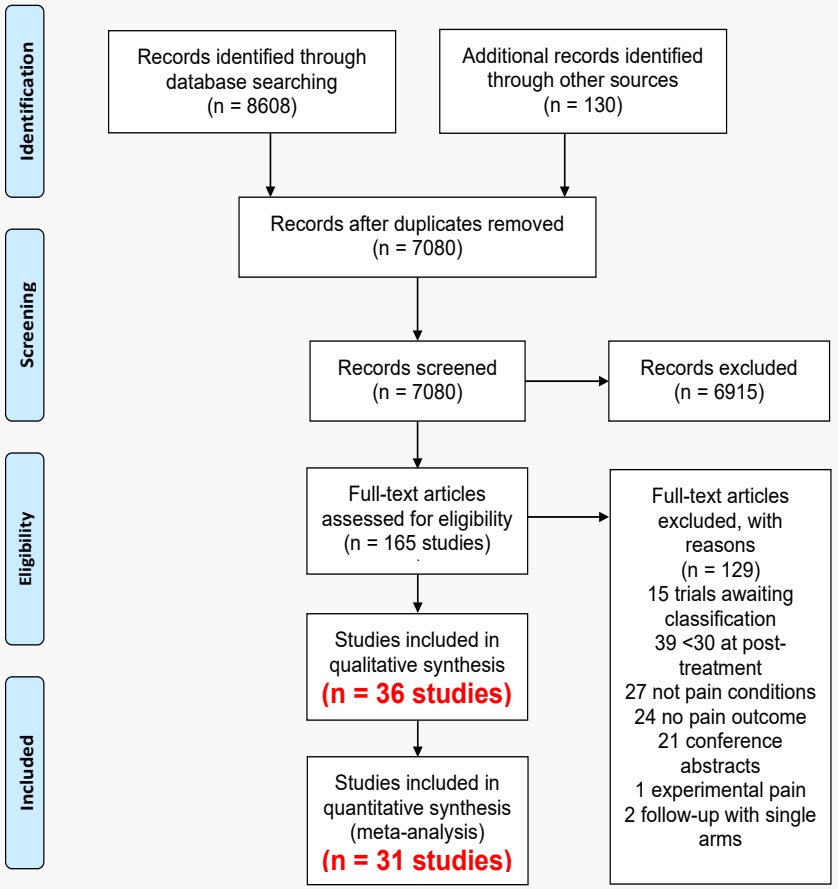
Secondary outcomes

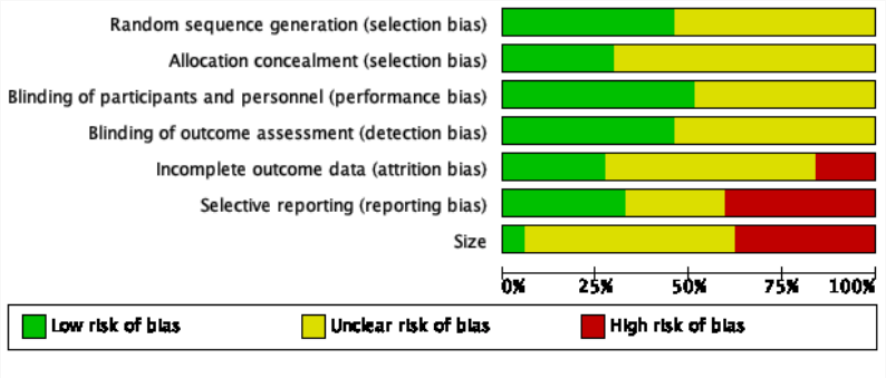
- Pain intensity difference (continuous scale)
- Disability
- Emotional functioning
- Carer Global Impression of Change
- Quality of life
- Adverse events
- Requirement for rescue analgesia
- Sleep duration and quality
- Onset and duration of analgesic effect

Study quality

- Cochrane Risk of Bias Tool
- GRADE quality of evidence
- Pain specific criteria monitored

any pain condition

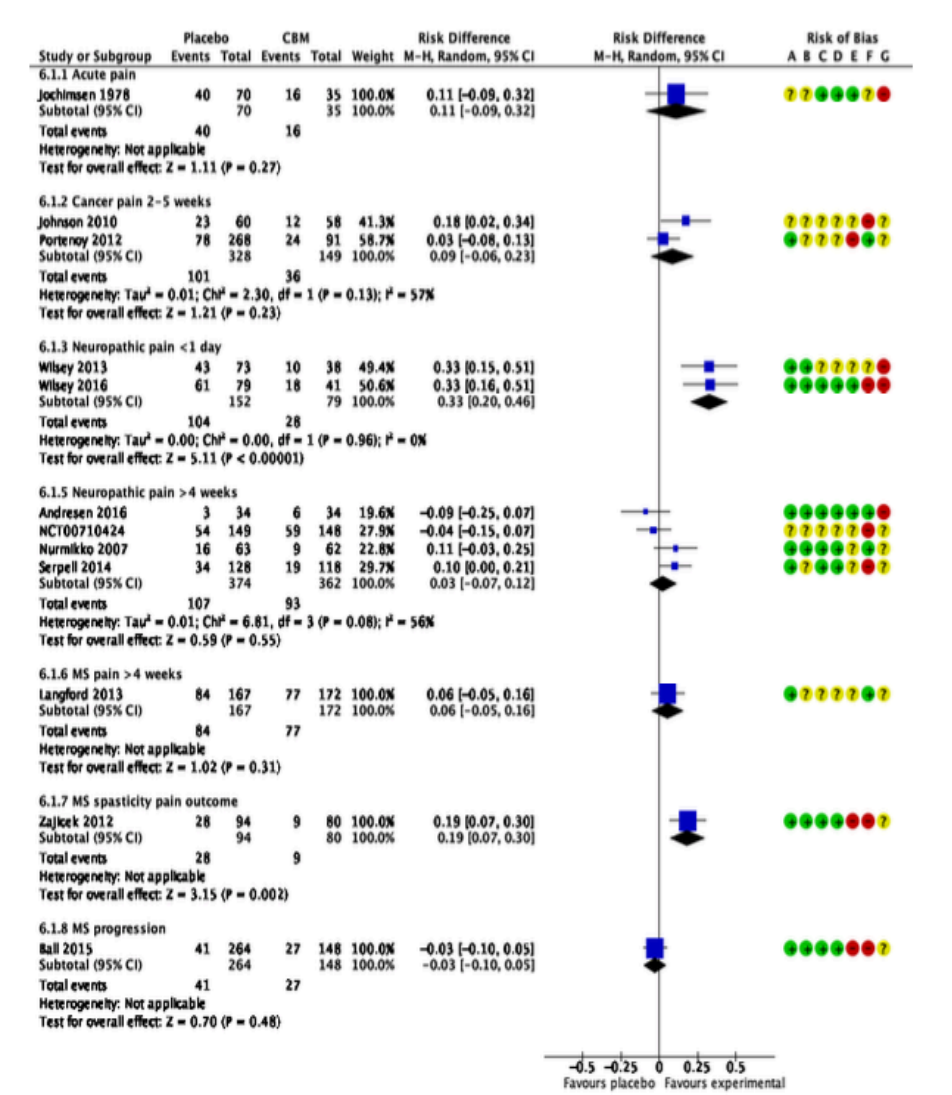




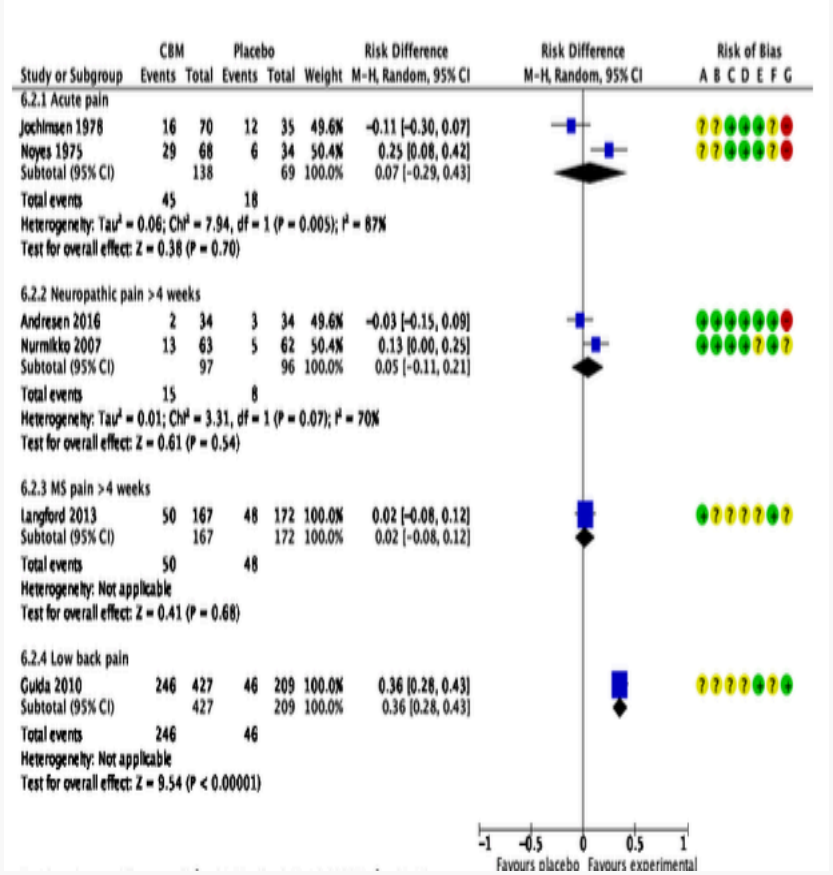
Characteristics of studies	
Number of participants	7217
Average attrition	14.4% (0-33%)
% Female	54%
Age	51 years
Pain condition	
Neuropathic pain	13 studies
Cancer	6 studies
Acute pain after surgery	4 studies
Multiple sclerosis	10 studies
Other	3 studies

Cannabis and CBMs delivered	Number of arms
Nabiximols	17
Cannabis	6
Palmitoylethanolamide	4
Fatty acid amide hydrolase inhibitors	3
Dronabinol	2
Nabilone	2
Cannabinoid receptor agonist (AZD1940, GW842166)	2
THC congener (benzopyran peridine)	1

≥30% Reduction In Pain Intensity

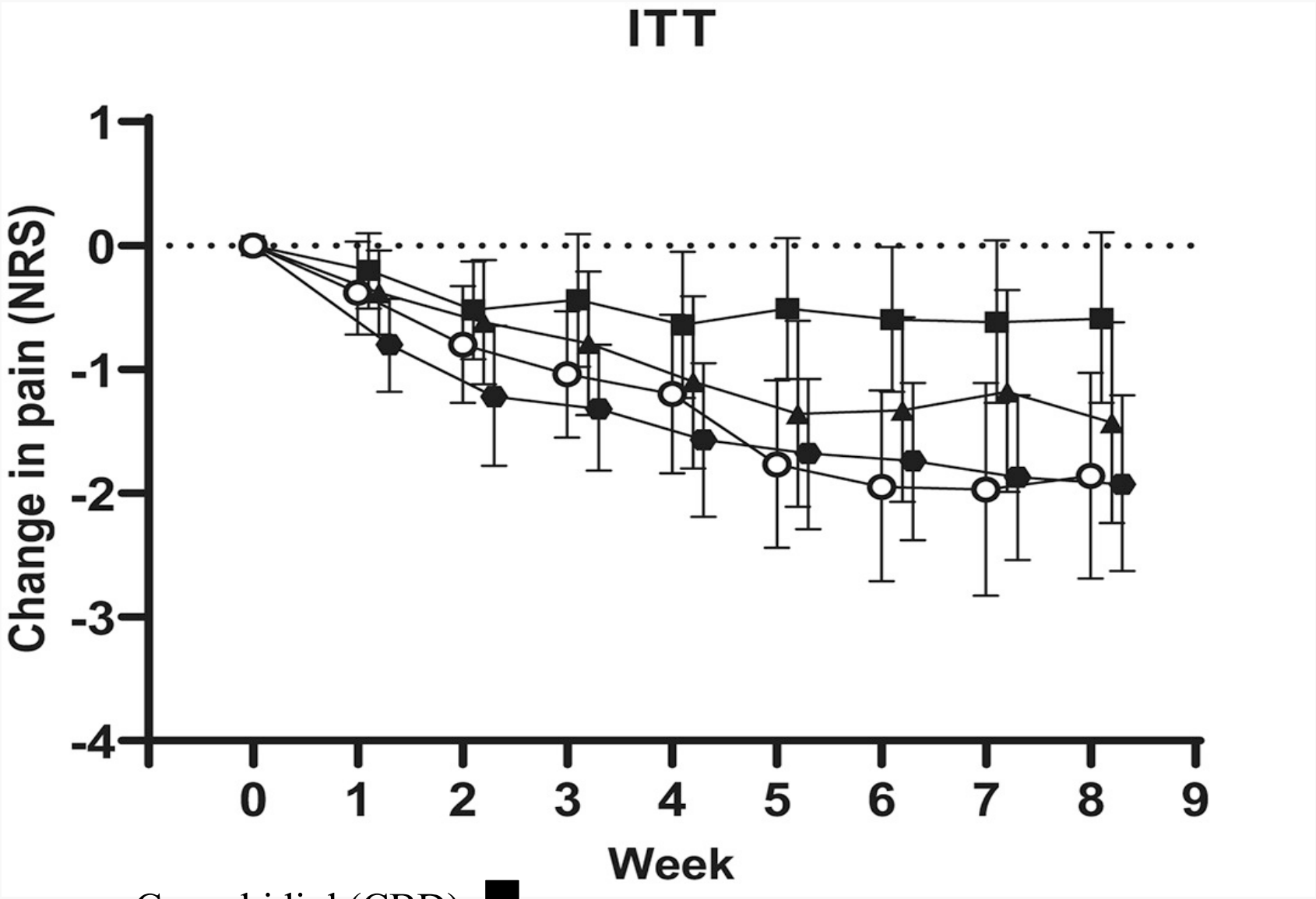


>50% Reduction In Pain Intensity



Neuropathic Pain Trials
Author Reported Outcomes

	Condition	Tx period	N	Design	Intervention	Control	Outcome
< 4 weeks							
Berman 2004	Brach Plex. Avul.	2 wk	45	X-over	Nabix THC:CBD 1:1	PBO	No benefit over PBO
"	"	"	"	"	Nabix THC	PBO	No benefit over PBO
NCT01606176	MS	3 wk	63	Para	Nabix	PBO	No benefit over PBO



Cannabidiol (CBD): ■
9-delta-tetra-hydro-cannabinol (THC): ▲
Combination CBD/THC: ⬣

Placebo: ○

DOI: 10.1002/ejp.2072

ORIGINAL ARTICLE

Eur J Pain. 2023;27:492–506

Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment

Kanita Zubcevic[1,2] | Merete Petersen[3] | Flemming Winther Bach[4,5] | Aksel Heinesen[6] | Thomas Peter Enggaard[7] | Thomas Peter Almdal[8] | Jakob Vormstrup Holbech[1,2] | Lene Vase[9] | Troels Stahelin Jensen[4,5] | Christian Stevns Hansen[6] | Nanna Brix Finnerup[4,5] | Søren H. Sindrup[1,2]

Evidence of Harm

Evidence of Harm?

Clin J Pain 2020;36:302-319

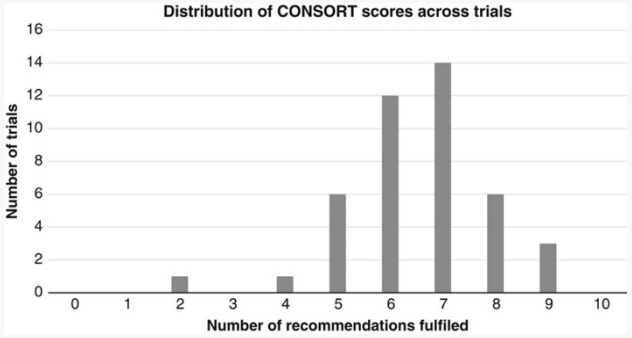
Adherence to Consolidated Standards of Reporting Trials (CONSORT) Guidelines for Reporting Safety Outcomes in Trials of Medical Cannabis and Cannabis-based Medicines for Chronic Noncancer Pain

A Systematic Review

Mohammed M. Mohiuddin, BSc, Glenio B. Mizubuti, MD, MSc,**
Simon Haroutounian, MSc, PhD,† Shannon M. Smith, BA, PhD,‡
Andrew S.C. Rice, MD, FRCP, FRCA FFPMRCA, FFPMCAI,§
*Fiona Campbell, BSc, MD, FRCA,‖ Rex Park, BHSc,**
and Ian Gilron, MD, MSc, FRCPC¶#*

1. If the study collected data on harms and benefits, the title or abstract should so state
2. If the trial addresses both harms and benefits, the introduction should so state
3. List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs. unexpected events, reference to standardized and validated definitions, and description of new definitions
4. Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent)
5. Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses
6. Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment
7. Provide the denominators for analyses on harms
8. Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent
9. Describe any subgroup analyses and exploratory analyses for harms
10. Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms

The CONSORT harms guidelines are publicly available guidelines created by Ioannidis et al.[24] This table was created in order to display these guidelines.



- 43 studies (4436 participants) included.
- Median CONSORT score = 7.
  - On average, 3 to 4 recommendations of the CONSORT guidelines were not being met in trials
  - 4 trials did not report on serious AEs
  - Seventeen trials did not provide their method of AE assessment
  - 7 trials provided no quantitative data about Aes

- Interventions reported: Nabiximols (12 studies), dronabinol (8), nabilone (7), oral cannabis extract (5), smoked tetrahydrocannabinol (5), vaporized tetrahydrocannabinol (3), novel synthetic cannabinoids (2), sublingual cannabis extract preparations (1).

Clin J Pain 2020;36:302-319

Harms Evidence From Clinical *Pain* Trials Of Cannabinoids

Mohiuddin et al, Clin J Pain 2020

• Systematic review of placebo-controlled chronic pain treatment RCTs of cannabinoids

Common adverse effects (≥10%) reported in ≥2 trials:

Dizziness, drowsiness, fatigue: smoked cannabis, nabiximols, nabilone dronabinol, oral THC/CBD

Weakness: nabixomols, nabilone, dronabinol, oral THC/CBD

Nausea: nabiximols, dronabinol

Euphoria: sublingual/vaporized cannabinoid, dronabinol

Dissociation: nabilone

Dry mouth: nabilone

All cannabinoids – **All-cause withdrawals: Tx = 8-17%; Placebo = 0-17%**

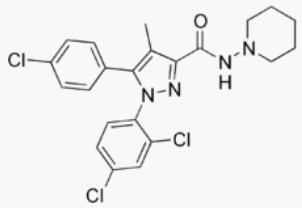
Similar results reported in Stockings et al, Pain 2018; Fisher et al, Pain 2020

• **Limitations of RCT harms evidence**: small n, short duration, highly selected patient population, controlled clinical setting

Slide courtesy Mohammed Mohiuddin & Ian Gilron

Lessons from Rimonabant (SR141617a)

Christensen et al Lancet 2007;370:1706



- CB_1 antagonist (inverse agonist)
- Developed for obesity & smoking cessation
- EMEA & FDA approval for obesity 2006
- Withdrawn 2009
  - Suicidality, depression and other psychiatric AEs

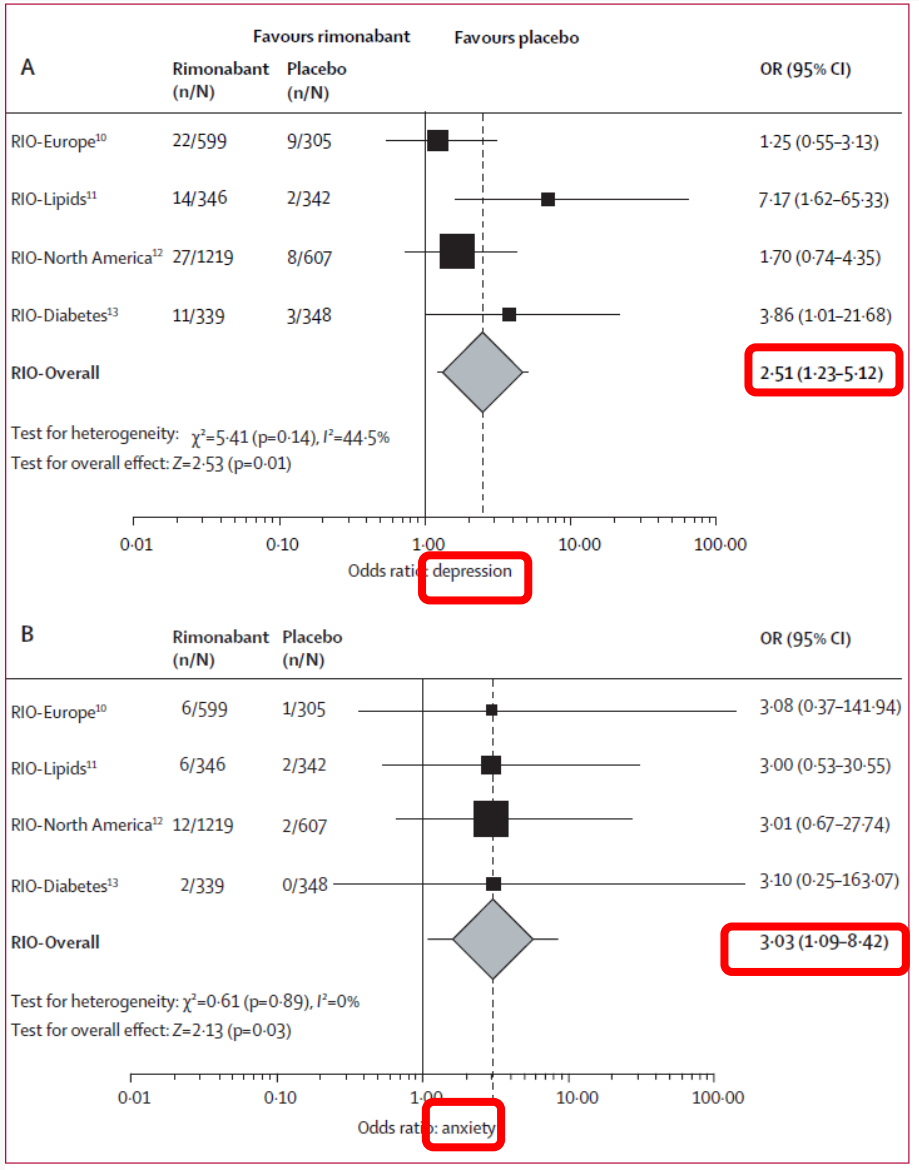


Figure 4: Number of individuals who discontinued treatment because of adverse psychiatric events

Evidence of Harm?

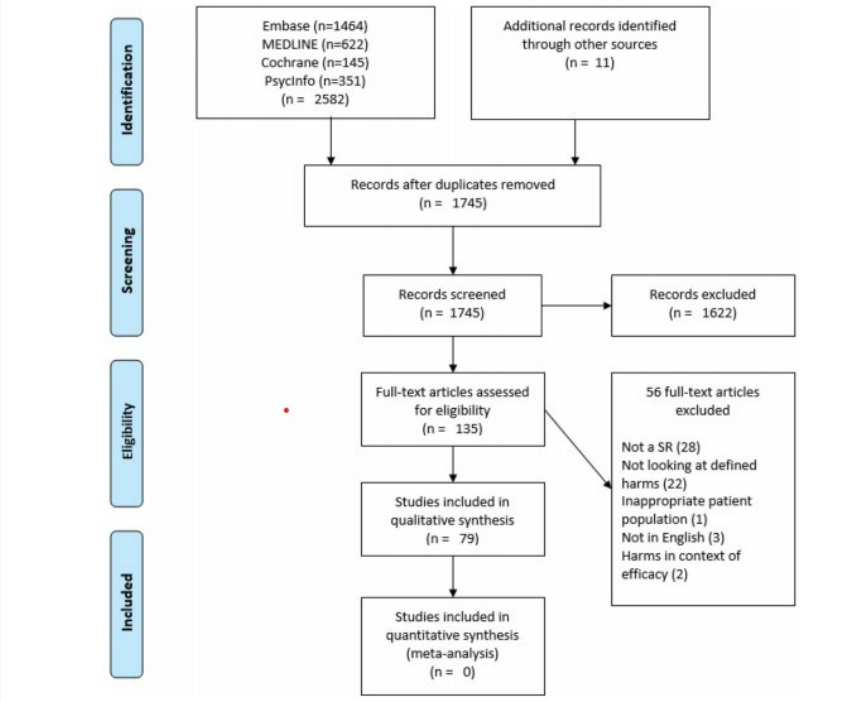
Systematic Review and Meta-Analysis

PAIN

2021:162:S80-96

General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews

Mohammed Mohiuddin[a], Fiona M. Blyth[b], Louisa Degenhardt[c], Marta Di Forti[d,e,f], Christopher Eccleston[g], Simon Haroutounian[h], Andrew Moore[i], Andrew S.C. Rice[j], Mark Wallace[k], Rex Park[a], Ian Gilron[a,l,m,n,*]



79 reviews of 2200 studies/reports each involving a wide range of participants (single case reports to cohort study of 172,718)

PSYCHIATRIC HARMS

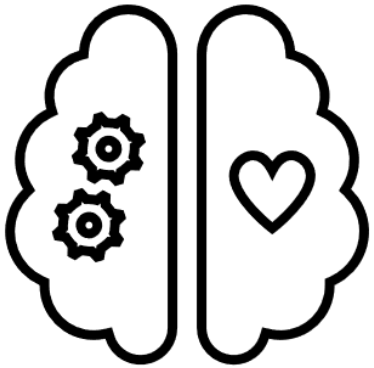
Anxiety
OR=1.28 [1.06, 1.54]

Depression
OR=1.33 [1.19, 1.49]

Co-Morbid OR=1.68 [1.17, 2.40]

Suicide:

- Ideation OR=1.50 [1.11, 2.03]
- Attempt OR=2.23 [1.24, 4.00]
- Death OR=2.56 [1.25, 5.27]



Mania OR=2.97 [1.80, 4.90]

Psychosis:

- Symptoms: OR=3.59 [2.42, 5.32]
- Onset: OR=2.58 [1.08, 6.13]
- Age at onset <2.7y

Slide courtesy Mohammed Mohiuddin & Ian Gilron

Public health implications of legalising the production and sale of cannabis for medicinal and recreational use

Lancet 2019; 394: 1580–90

Wayne Hall, Daniel Stjepanović, Jonathan Caulkins, Michael Lynskey, Janni Leung, Gabrielle Campbell, Louisa Degenhardt

	Size of effect (95% CI)	Level of evidence
Motor vehicle injuries*		
Use 1–3 h before driving	Small risk: RR 1·37 (1·2–1·5) to 2·7 (2·1–3·4)	B
Low birthweight†		
Maternal use in pregnancy	Small increase in risk: OR 1·8 (1·0–3·0)	B
Dependence syndrome†		
Lifetime use	Small to moderate risk: 7·2% (6·6–7·7) to 28·3% (22·0–34·6)	B
Daily use	Large risk: 40·9% (29·0–52·8)	B
Psychosis or schizophrenia*		
Ever used	Small increase: OR 1·4 (1·2–1·7)	B
Daily use	Doubling: OR 2·1 (1·5–2·8)	B
Depression*		
Ever used	Very small increase: OR 1·2 (1·1–1·3)	B
Daily use	Small increase: OR 1·6 (1·2–2·2)	
Bronchitis*		
Cannabis smoking	Large increase: RR 7·48 (no CIs)	D
Regular cannabis smoking	Large increase‡	B
Lung cancer		
Regular cannabis smoking	No significant increase: OR 0·95 (0·66–1·38)	B

Evidence of Psychiatric Harm?

Topical Review

PAIN

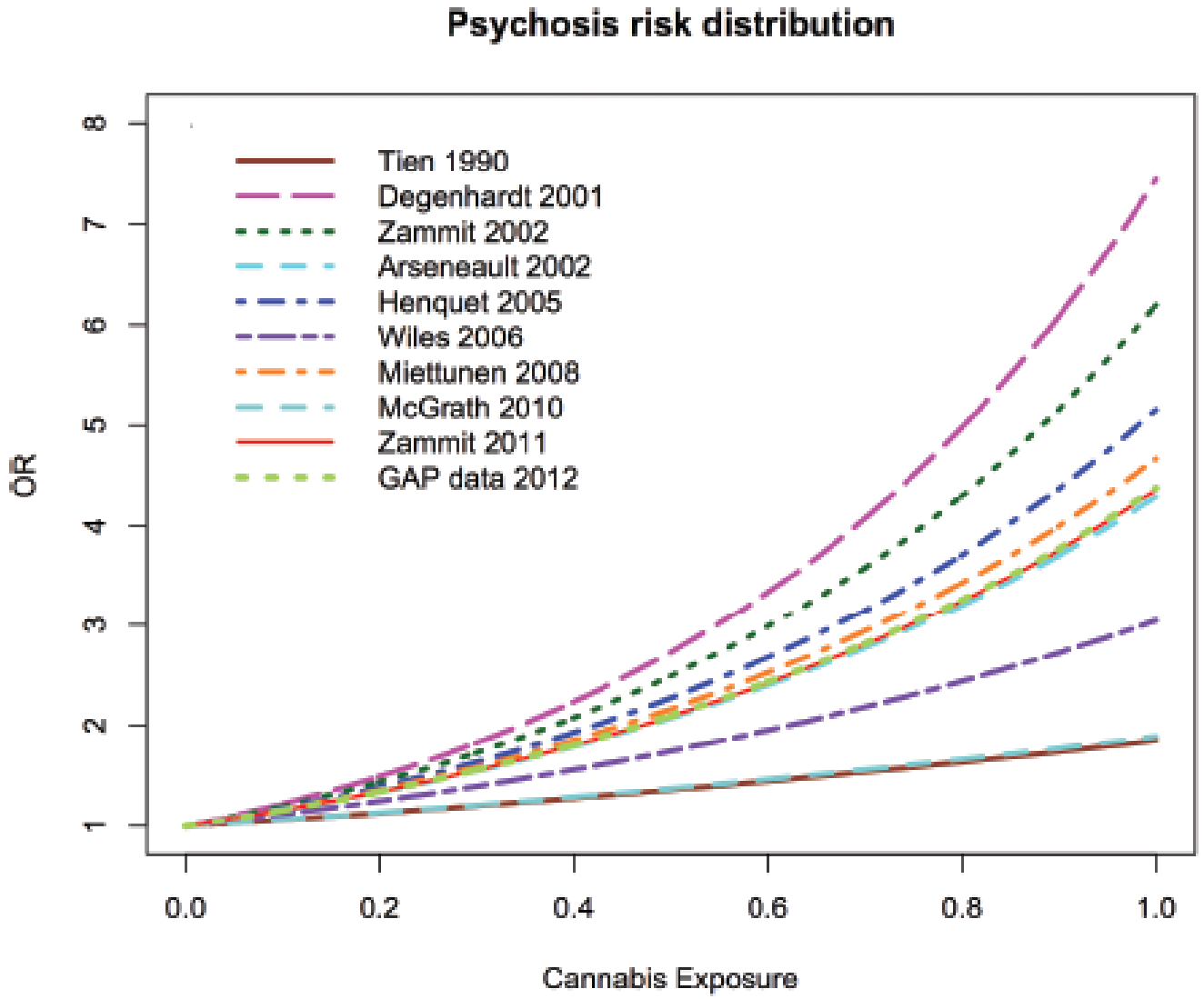
2021:162:S97-104

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,*]

Association Between Cannabis Use and Psychosis

Marconi Schizophr Bull 2016;42:1262



Cannabis Dose and Psychosis Risk

di Forti et al Br. J. Pysch.2009;195:488–491

- Resin (hashish)
  - 2000: 70% of abuse market
  - 2–4% Δ9-THC
- Sinsemilla (skunk)
  - 2008: >70% of abuse market
  - 12–18% Δ 9-THC with virtually no cannabidiol

Table 3 Patterns of cannabis use

	Cases, $n = 159$ n (%)	Controls, $n = 109$ n (%)	Odds ratio (95% CI) Unadjusted	Odds ratio (95% CI) Adjusted[a]
Duration of use				
0–5 years	65 (40.8)	68 (62.5)	1.0	1.0
Over 5 years	94 (59.2)	41 (37.5)	2.4 (1.2–4.7)	2.1 (0.9–8.4)*
Frequency of use				
Less than every day	37 (23.1)	73 (66.7)	1.0	1.0
Every day	122 (76.9)	36 (33.3)	6.7 (2.0–11.5)	6.4 (3.2–28.6)*
Type used				
Resin (hash) and traditional imported herbal cannabis (Δ9-THC and CBD both 1%)	34 (21.6)	68 (62.6)	1.0	1.0
Sinsemilla (skunk) (Δ9-THC 12–18%; CBD 0%)	125 (78.4)	41 (37.4)	8.1 (4.6–13.5)	6.8 (2.6–25.4)*

CBD, cannabidiol; Δ9-THC, Δ9-tetrahydrocannabinol.
a. Adjusted for age, gender, ethnicity, other stimulant use, level of education achieved and employment status.
*$P<0.05$.

Baseline Psychosis Predisposition & Risk of Cannabis-Associated Psychosis

Henquet et al BMJ 2005;330:11-16

2436 Adolescents Followed for 4 Years

Table 4 Interactions between any cannabis use and predisposition for psychosis

Cannabis use at baseline	No with psychosis outcome*	No without psychosis outcome*	Risk of psychotic symptoms at follow up	Difference in risk	
				Unadjusted	Adjusted† (95% CI)
No predisposition for psychosis at baseline					
None	294	1642	15%	6%	5.6% (0.4 to 10.8) P=0.033
Any (≥5 times)	59	216	21%		
Predisposition for psychosis at baseline‡					
None	47	133	26%	25%	23.8% (7.9 to 39.7) P=0.003
Any (≥5 times)	23	22	51%		

*Numbers total 2436 because of one missing value on predisposition for psychosis at baseline.
†Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at follow up. Test for additive interaction 18.2% adjusted difference in risk (95% confidence interval 1.6 to 34.8), P=0.032 (tests whether risk difference in "predisposition" group is significantly greater than risk difference in "no predisposition" group).

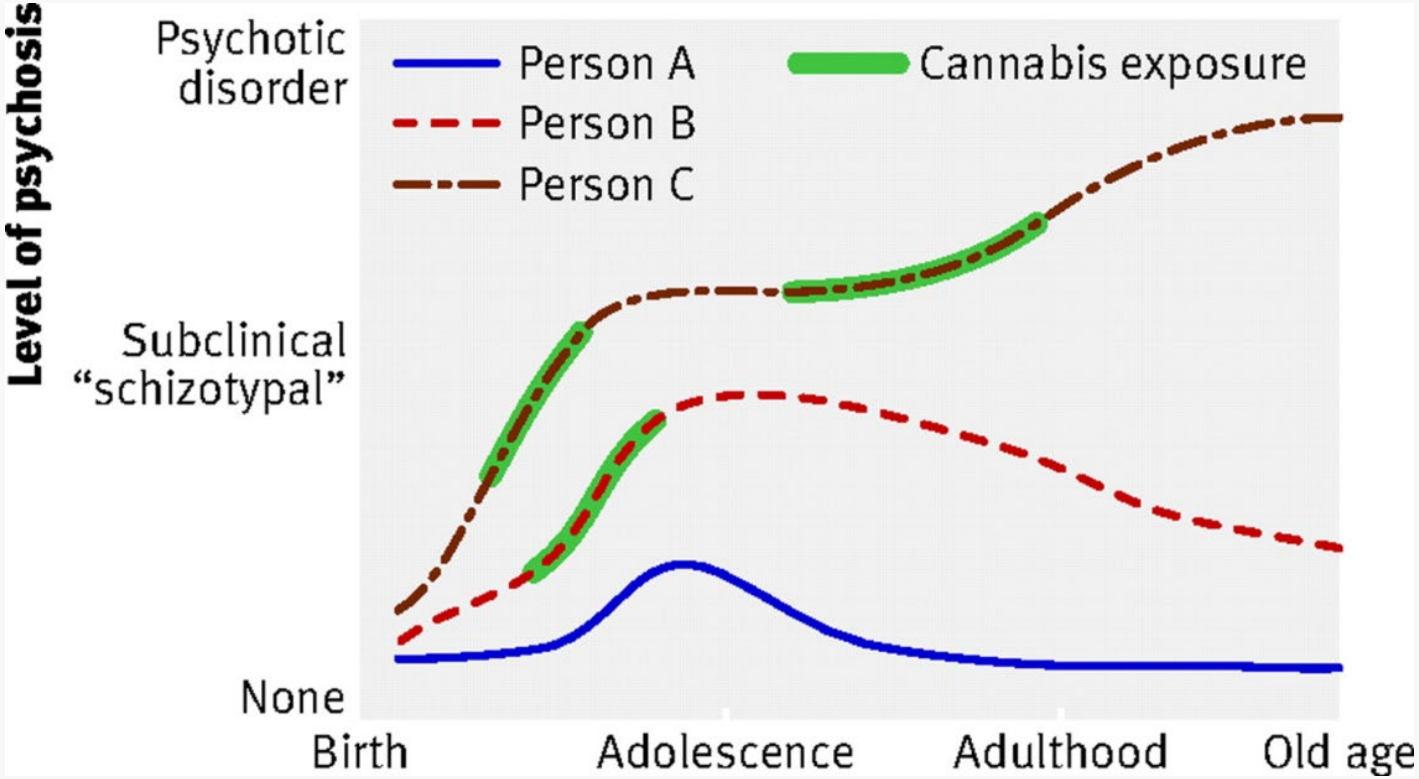
Nb. predisposition to psychosis at baseline does not predict cannabis use, thus refuting self-medication hypothesis

BMJ 2011;342:d738

RESEARCH

Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study

Rebecca Kuepper, research psychologist,[1] Jim van Os, professor,[1] visiting professor,[2] Roselind Lieb, professor,[3,4] Hans-Ulrich Wittchen, professor,[4,5] Michael Höfler, research statistician,[5] Cécile Henquet, lecturer[1]



Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

- Dunedin cohort (n=1,037) followed from birth (1972/1973) to age 38
- Cannabis use ascertained by interview at 5 points ages 18-38
- Neuropsychological testing conducted at:
  - 13 yr before initiation of cannabis use
  - 38 yr after a pattern of persistent cannabis use had developed

Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

- Persistent cannabis use associated with broad neuropsychological decline across domains, even after controlling for years of education
- Informants also reported noticing more cognitive problems for persistent cannabis users
- Persistent cannabis use associated with greater decline
- Impairment concentrated among adolescent-onset cannabis users
- Cessation of cannabis use did not fully restore neuropsychological function in adolescent-onset cannabis users

Topical Review
PAIN
2021:162:S110 - 106

Societal issues and policy implications related to the use of cannabinoids, cannabis, and cannabis-based medicines for pain management

Simon Haroutounian[a,b,*], Ian Gilron[c,d,e], Joletta Belton[f,g], Louisa Degenhardt[h], Marta DiForti[i,j,k], David P. Finn[l], Alexandra Fogarty[m], Eija Kalso[n,o], Elliot Krane[p], R. Andrew Moore[q], Michael Rowbotham[r], Mark Wallace[s], Andrew S.C. Rice[t]

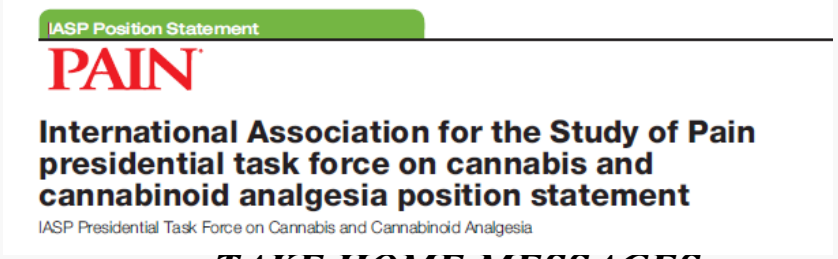
Table 1

Key societal issues and policy implications related to the use of cannabinoids, cannabis, and cannabis-based medicines in the context of pain management.

Area of risk	Examples and implications	Area of need
Regulation of cannabis cultivation	Inconsistent and unregulated supply Lack of standardization of allowable chemical and microbial contaminants, posing particular risks to vulnerable populations (eg, immunocompromised patients) Labeling often not reflecting composition Lack of regulated allowable THC content, resulting in extremely high-potency products Use of natural resources (eg, soil and water) and carbon footprint of cannabis cultivation is not accounted for	Adoption of strict policies on cannabis cultivation and quality control, to minimize harm Environmental implications need to be considered and mitigated
Testing for cannabis and cannabinoid safety and efficacy	Paucity of large, high-quality studies with cannabinoids in pain The freedom of manufacturers to sell cannabis without a proof of efficacy and safety minimizes their responsibility and motivation to conduct large, rigorous studies	Use taxation of recreational and unregulated medicinal cannabis, to fund large-scale rigorous studies on efficacy and safety of cannabis and cannabinoids in conditions such as chronic pain
Marketing and advertising of cannabis and cannabinoids	Cannabis and cannabinoid-containing products are widely advertised on a variety of platforms, including social media Little regulation exists over cannabis advertising; exposure to advertising of potentially addictive substances increases use and misuse, particularly among adolescents. Unregulated marketing and advertising of cannabis has increased adolescent cannabis use, and fueled the false perception that cannabis use is safe	Banning of advertising and promoting cannabis, to mitigate societal harms (particularly in children and adolescents) Tight regulation of health claims made for marketing Mandatory demonstration of efficacy in high-quality efficacy studies, to allow supporting health claims
Cannabis legalization and its effects on medicinal cannabis use	Availability of nonmedicinal cannabis (potentially at lower price and higher potency) will likely cause diversion to use cannabis without careful medical supervision, increasing the likelihood of adverse outcomes	Careful control of supply, quality, access, and pricing of medicinal cannabis to prevent adverse outcomes
Cannabis policy and opioid use	Possibility that opioid doses can be reduced by initiating cannabis Cannabis is being promoted as a solution for opioid overdose crisis The possible opioid-sparing effects of cannabinoids are unclear, and the safety of opioid and cannabinoid combination is not established	Careful experiments required to determine opioid-sparing properties of cannabis Safety of cannabinoid and opioid combinations needs to be determined in rigorous trials
Driving and operating aircraft and machinery	Cannabis impairs cognitive skills and reaction time, and doubles the risk of motor vehicle collision Consistent regulations on allowable use of cannabis (or blood levels of THC) compatible with driving are lacking	Clear and consistent guidelines need to be set regarding driving under cannabinoid influence, as well as fast and reliable methods of testing cannabis exposure
Cannabis legalization and its effects on vulnerable populations	Daily or almost daily use of cannabis, particularly high-potency, is linked with substantial increase in cognitive and psychiatric problems, particularly among younger adults and adolescents, and people with preexisting mental health problems Immunosuppressed patients are at higher risk of toxicity from potential chemical and microbial impurities and contaminants found in cannabis Edible cannabis products increase risk of accidental poisoning in children Cannabis use during pregnancy has been associated with adverse maternal and neonatal outcomes	Introduce strict regulation for adult-only use of cannabis (unless specifically prescribed by an expert clinician for a childhood disorder such as epilepsy) Properly educate and implement programs for minimizing exposure and use in high-risk populations

Political Issues and Societal Harm

- Justification for bypassing of well established regulatory systems for assessing efficacy, safety, manufacture and marketing of medicines?
- Risk of diversion of potent medicinal cannabinoids to abuse market?
- Bypassing of medical oversight and protections where “recreational” cannabis is now legal.
- Influence of votes, tax revenues and new business opportunities on political decisions vs duty of HCPs to protect public health?
  - *The government of Canada will launch a national, uncontrolled experiment in which the profits of cannabis producers and tax revenues are squarely pitched against the health of Canadians.* *Kelsall CMAJ 2018;190:E1218*



TAKE HOME MESSAGES:

- **Due to the lack of high-quality clinical evidence for efficacy and harm, IASP does not endorse general use of cannabis and cannabinoids for pain relief.**

- **There are concerns about the potential for harms of cannabis and cannabinoids; the relevance of which to the (chronic pain) therapeutic setting needs clarification (dose/duration).**

- **Reviews of preclinical research and clinical safety and efficacy of cannabis and cannabinoids for pain relief have identified important knowledge gaps. Research agenda of priorities to fill those gaps published.**

- **Concerns regarding jurisdictions where permissive "medicinal" and "recreational" cannabis use opens routes which bypass well-established regulatory processes and safeguards for the licensing, manufacturing quality, marketing and evidence-based prescribing, of medicines.**

- **The considerable business and tax implications from the rapidly evolving recreational and medicinal cannabis industries are conflicts in political decision making.**

- **While IASP cannot endorse general use of cannabis or cannabinoids for pain, we do not dismiss the lived experiences of people with pain who have found benefit from their use.**