JAMA Network Open

Research Letter | Pharmacy and Clinical Pharmacology

Evaluation of THC-Related Neuropsychiatric Symptoms Among Adults Aged 50 Years and Older

A Systematic Review and Metaregression Analysis

Latha Velayudhan, MD; Katie Louise McGoohan, PhD; Sagnik Bhattacharyya, MD, PhD

Introduction

Experimental administration of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, but not cannabidiol (CBD), a nonaddictive component, induces transient psychotic symptoms,[1] and regular use of cannabis high in THC is associated with increased risk of psychotic symptoms or disorders and poor outcomes in those with an established psychotic disorder.[2,3] This association is well recognized among young people, the age group most often affected by psychosis. Although use of cannabinoid-based medicines (CBMs) is increasing across all age groups, it remains unclear whether THC-containing CBMs also increase the risk of psychotic symptoms in older adults.[4,5] Hence, we used metaregression analyses to examine any association between THC dose and self-reported neuropsychiatric adverse events (AEs) using data from double-masked, randomized clinical trials (RCTs) investigating CBMs in people aged 50 years or older. We hypothesized that there would be a significant association between THC dose and incidence of neuropsychiatric AEs.

Methods

We conducted a systematic review of RCTs published until October 31, 2020, undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (eAppendix, eTable, and eFigure in the Supplement), reporting the safety and tolerability of different CBMs (CBD and THC combinations, THC, or its analogues). All-cause and treatment-related AEs were coded according to the Medical Dictionary for Regulatory Activities system organ classes.

Pooled effect sizes (incident rate ratios [IRRs]) were estimated for each AE, and the association of AEs with THC dose (for THC studies) as well as with CBD and THC dose (for CBD and THC combination studies) was examined separately using metaregression analyses under the random-effects model using the restricted maximum-likelihood estimator (metafor package in R version 3.6.3 [R Project for Statistical Computing]), with 2-tailed significance set at $P < .05$. For each broad category of intervention, we combined both parallel-group and crossover RCTs, with the latter treated as parallel-group design.[6] Studies with more than 1 active treatment group were treated as independent studies.

Results

Thirty RCTs using THC-only CBMs (15 [50.0%] crossover; 15 [50.0%] parallel-group) analyzed 1417 patients (median [interquartile range {IQR}] age, 59.5 [52.4-67.0] years; median [IQR] percentage men, 52.5% [40.5%-67.8%]; total person-years of THC exposure, 1252.83) in intervention groups and 1210 patients (median [IQR] age, 58.9 [52.0-65.4] years; median [IQR] percentage men, 53.0% [41.3%-71.5%]) in control groups. A total of 24 studies using CBD and THC combinations (5 [20.8%] crossover; 19 [79.2%] parallel-group) analyzed a total of 1917 patients (median [IQR] age, 58.2 [52.3-59.8] years; median [IQR] percentage men, 49.5% [36.0%-56.0%]; total person-years of THC

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY License.

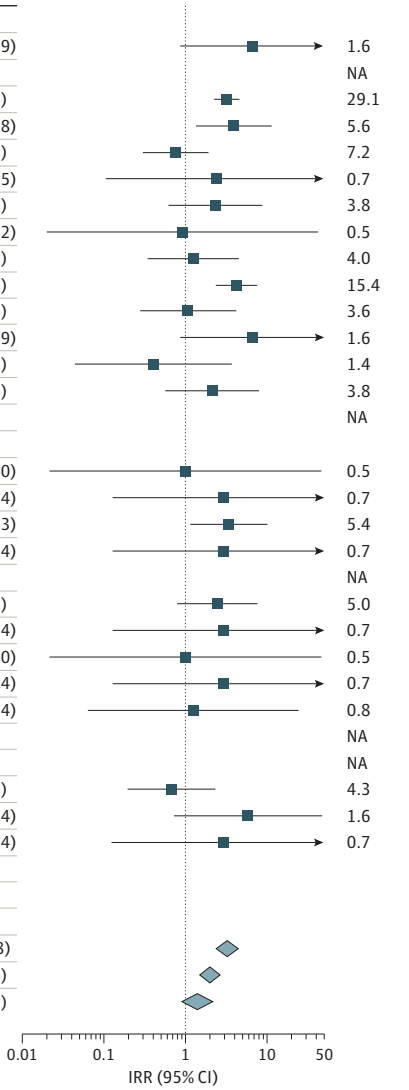
Downloaded From: https://jamanetwork.com/ by Dale Quigley on 03/05/2021

and CBD exposure, 388.56) in intervention groups and 1835 patients (median [IQR] age, 56.0 [53.7-60.3] years; median [IQR] percentage men, 48.0% [35.0%-52.0%]) receiving placebo.

There was a significant positive association between THC dose and IRR for dizziness or lightheadedness (estimate, 0.05; 95% CI, 0.02-0.08; P = .001) (**Figure 1**) and thinking or perception disorder (estimate, 0.07; 95% CI, 0.03-0.11; P < .001) (**Figure 2**) for THC studies, but no association was found with other neuropsychiatric AEs for THC or THC and CBD combination studies. The association with thinking or perception disorder results were associated mainly with 2 studies (eAppendix in the Supplement).

Figure 1. Forest Plot From Metaregression Analysis of Pooled Incident Rate Ratio (IRR) of Dizziness or Lightheadedness Associated With Treatment With Cannabinoid-Based Medicines, With Delta-9-Tetrahydrocannabinol (THC) Dose as a Moderator

Authors and year	Active/ control, No.	Condition	Drug	THC dose (mg/d)	IRR (95% CI)	Weight, %
Parallel-group RCTs						
Lane et al,[15] 1991	21/21	Cancer	Dronabinol	40	7.00 (0.86-56.89)	1.6
Jatoi et al,[17] 2002	152/159	Cancer	Dronabinol	5	NA	NA
Zajicek et al,[8] 2003	206/213	MS	Marinol	14	3.29 (2.29-4.74)	29.1
Zajicek et al,[9] 2005	117/111	MS	Dronabinol	25	4.03 (1.36-11.98)	5.6
Strasser et al,[10] 2006	100/48	Cancer	THC	5	0.75 (0.29-1.95)	7.2
Meiri et al,[20] 2007	17/14	Cancer	Dronabinol	10	2.47 (0.10-60.65)	0.7
Johnson et al,[11] 2010	58/59	Pain	THC	23	2.37 (0.61-9.18)	3.8
Brisbois et al,[24] 2011	11/10	Cancer	Dronabinol	7.5	0.91 (0.02-45.82)	0.5
Toth et al,[26] 2012	13/13	Pain	Nabilone	4	1.25 (0.34-4.65)	4.0
Zaijicek et al,[27] 2013	329/164	MS	Dronabinol	28	4.36 (2.40-7.93)	15.4
Van den Elsen et al,[29] 2015	24/26	ND	Namisol	4.5	1.08 (0.27-4.33)	3.6
Van Amerongen et al,[12] 2017	12/12	MS	THC	24	7.00 (0.86-56.89)	1.6
Carley et al,[14] 2018	21/25	Other	Dronabinol	2.5	0.40 (0.04-3.81)	1.4
Carley et al,[14] 2018	27/25	Other	Dronabinol	10	2.16 (0.56-8.35)	3.8
Peball et al,[33] 2020	19/19	ND	Nabilone	1	NA	NA
Crossover RCTs						
Volicer et al,[4] 1997	12/12	ND	Dronabinol	5	1.00 (0.02-50.40)	0.5
Sieradzan et al,[16] 2001	9/9	ND	Nabilone	2	3.00 (0.12-73.64)	0.7
Svendsen et al,[18] 2004	24/24	MS	Dronabinol	10	3.50 (1.15-10.63)	5.4
Tomida et al,[19] 2006	6/6	Other	THC	5	3.00 (0.12-73.64)	0.7
Curtis et al,[21] 2009	37/37	ND	Nabilone	2	NA	NA
Ware et al,[22] 2010	32/32	Other	Nabilone	1	2.50 (0.78-7.97)	5.0
Weber et al,[23] 2010	22/22	ND	Dronabinol	5	3.00 (0.12-73.64)	0.7
Walther et al,[7] 2011	2/2	ND	Dronabinol	2.5	1.00 (0.02-50.40)	0.5
Zadikoff et al,[25] 2011	9/9	Other	Dronabinol	15	3.00 (0.12-73.64)	0.7
Ahmed et al,[5] 2014	11/11	Other	Namisol	6.5	1.25 (0.06-26.04)	0.8
Ahmed et al,[28] 2015	10/10	ND	Namisol	3	NA	NA
Van den Elsen et al,[32] 2015	22/22	ND	Namisol	3	NA	NA
de Vries et al,[30] 2016	24/24	Other	Namisol	8	0.67 (0.19-2.36)	4.3
Van Amerongen et al,[12] 2017	24/24	MS	THC	16	6.00 (0.72-49.84)	1.6
Herrmann et al,[31] 2019	38/38	ND	Nabilone	1.6	3.00 (0.12-73.64)	0.7
Random-effects model (Q = 13.26, df = 23, P = .95; I^2 = 6.5%)						
Estimate (intercept) = 0.219, P = .40; estimate (THC) = 0.049, P = .001						
Model–based estimates of IRR (at different THC doses)						
At 20 mg/d					3.33 (2.43-4.58)	
At 10 mg/d					2.04 (1.51-2.75)	
At 2.5 mg/d					1.41 (0.90-2.20)	



The disease conditions investigated are listed under the Condition column and were classified into broader subgroups for reporting purposes as neurodegenerative (ND) (ie, Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis), multiple sclerosis (MS), pain (ie, neuropathic pain), cancer (ie, cancer- or chemotherapy-related anorexia, pain, or nausea/vomiting), and other (type 2 diabetes, chronic obstructive pulmonary disease, fibromyalgia, raised intraocular pressure, cervical dystonia, healthy, pancreatitis, obstructive sleep apnea, and Levodopa-induced dyskinesia in Parkinson disease). References appear in eReferences in the Supplement. NA indicates not available; RCT, randomized clinical trial.

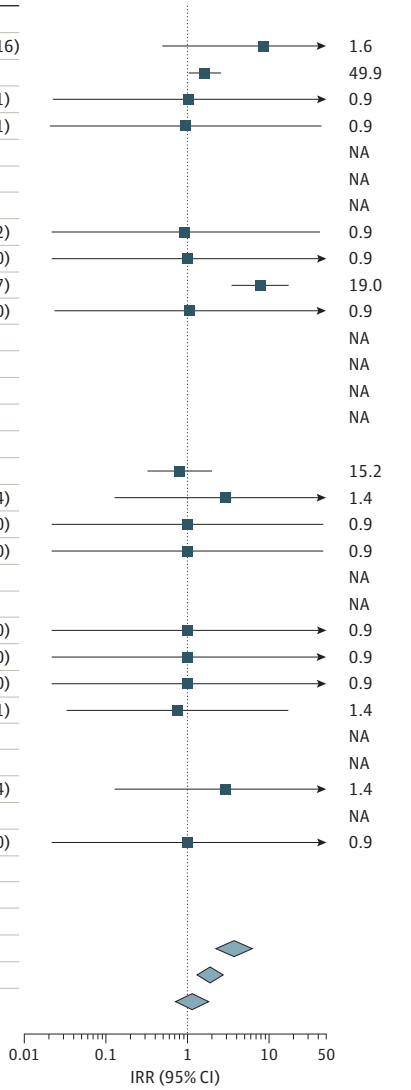
Downloaded From: https://jamanetwork.com/ by Dale Quigley on 03/05/2021

Discussion

Consistent with our hypothesis, higher THC dose was associated with a higher incidence of thinking or perception disorder and dizziness or light-headedness, but no other neuropsychiatric AEs in RCTs using THC but not THC and CBD combination for a range of nonpsychiatric indications in older adults. Although not diagnosed using standardized assessments, self-reported thinking or perception disorders reflect alterations in thinking and perception typically described under psychotic symptoms and suggest that older adults may also be at risk of psychotomimetic effects from THC. However, this association may be considered tentative based on influence diagnostics. Key limitations of the present analyses are the inability to exclusively focus on older adults or conduct

Figure 2. Forest Plot From Metaregression Analysis of Pooled Incident Rate Ratio (IRR) of Thinking/Perception Disorder Associated With Treatment With Cannabinoid-Based Medicines, With Delta-9-Tetrahydrocannabinol (THC) Dose as a Moderator

Authors and year	Active/ control, No.	Condition	Drug	THC dose (mg/d)	IRR (95% CI)	Weight, %
Parallel-group RCTs						
Lane et al,[15] 1991	21/21	Cancer	Dronabinol	40	9.00 (0.48-167.16)	1.6
Jatoi et al,[17] 2002	152/159	Cancer	Dronabinol	5	1.65 (1.03-2.64)	49.9
Zajicek et al,[8] 2003	206/213	MS	Marinol	14	1.03 (0.02-52.11)	0.9
Zajicek et al,[9] 2005	117/111	MS	Dronabinol	25	0.95 (0.02-47.81)	0.9
Strasser et al,[10] 2006	100/48	Cancer	THC	5	NA	NA
Meiri et al,[20] 2007	17/14	Cancer	Dronabinol	10	NA	NA
Johnson et al,[11] 2010	58/59	Pain	THC	23	NA	NA
Brisbois et al,[24] 2011	11/10	Cancer	Dronabinol	7.5	0.91 (0.02-45.82)	0.9
Toth et al,[26] 2012	13/13	Pain	Nabilone	4	1.00 (0.02-50.40)	0.9
Zaijicek et al,[27] 2013	329/164	MS	Dronabinol	28	8.14 (3.57-18.57)	19.0
Van den Elsen et al,[29] 2015	24/26	ND	Namisol	4.5	1.08 (0.02-54.60)	0.9
Van Amerongen et al,[12] 2017	12/12	MS	THC	24	NA	NA
Carley et al,[14] 2018	21/25	Other	Dronabinol	2.5	NA	NA
Carley et al,[14] 2018	27/25	Other	Dronabinol	10	NA	NA
Peball et al,[33] 2020	19/19	ND	Nabilone	1	NA	NA
Crossover RCTs						
Volicer et al,[4] 1997	12/12	ND	Dronabinol	5	0.80 (0.32-2.03)	15.2
Sieradzan et al,[16] 2001	9/9	ND	Nabilone	2	3.00 (0.12-73.64)	1.4
Svendsen et al,[18] 2004	24/24	MS	Dronabinol	10	1.00 (0.02-50.40)	0.9
Tomida et al,[19] 2006	6/6	Other	THC	5	1.00 (0.02-50.40)	0.9
Curtis et al,[21] 2009	37/37	ND	Nabilone	2	NA	NA
Ware et al,[22] 2010	32/32	Other	Nabilone	1	NA	NA
Weber et al,[23] 2010	22/22	ND	Dronabinol	5	1.00 (0.02-50.40)	0.9
Walther et al,[7] 2011	2/2	ND	Dronabinol	2.5	1.00 (0.02-50.40)	0.9
Zadikoff et al,[25] 2011	9/9	Other	Dronabinol	15	1.00 (0.02-50.40)	0.9
Ahmed et al,[5] 2014	11/11	Other	Namisol	6.5	0.75 (0.03-18.41)	1.4
Ahmed et al,[28] 2015	10/10	ND	Namisol	3	NA	NA
Van den Elsen et al,[32] 2015	22/22	ND	Namisol	3	NA	NA
de Vries et al,[30] 2016	24/24	Other	Namisol	8	3.00 (0.12-73.64)	1.4
Van Amerongen et al,[12] 2017	24/24	MS	THC	16	NA	NA
Herrmann et al,[31] 2019	38/38	ND	Nabilone	1.6	1.00 (0.02-50.40)	0.9
Random-effects model (Q = 4.40, df = 16, P <.99; I^2 = 1.5%)						
Estimate (intercept) = -0.038, P =.90; estimate (THC) = 0.069, P <.001						
Model–based estimates of IRR (at different THC doses)						
At 20 mg/d					3.84 (2.27-6.50)	
At 10 mg/d					1.92 (1.32-2.80)	
At 2.5 mg/d					1.14 (0.71-1.85)	



The disease conditions investigated are listed under the Condition column and were classified into broader subgroups for reporting purpose as neurodegenerative (ND) (ie, Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis), multiple sclerosis (MS), pain (ie, neuropathic pain), cancer (ie, cancer- or chemotherapy related anorexia, pain, or nausea/vomiting), and other (ie, type 2 diabetes, chronic obstructive pulmonary disease, fibromyalgia, raised intraocular pressure, cervical dystonia, healthy, pancreatitis, obstructive sleep apnea, and Levodopa-induced dyskinesia in Parkinson disease). References appear in eReferences in the Supplement. NA indicates not available; RCT indicates randomized clinical trial.

Downloaded From: https://jamanetwork.com/ by Dale Quigley on 03/05/2021

sensitivity analyses in those aged 65 years or older because of limited studies (n = 4); use of self-report rather than structured questionnaires, potentially resulting in underreporting of psychotomimetic effects; and incomplete tolerability reporting in included studies. Given the lack of studies in the population aged 65 years or older, the lack of further AEs in that age group cannot be inferred from our findings. Thus, these results indicate that THC-containing CBMs should be used cautiously in those aged 50 years or older, especially considering that dizziness or light-headedness may increase the risk of falls among older adults.

ARTICLE INFORMATION

Accepted for Publication: December 13, 2020.

Published: February 2, 2021. doi:10.1001/jamanetworkopen.2020.35913

Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2021 Velayudhan L et al. *JAMA Network Open*.

Corresponding Author: Sagnik Bhattacharyya, MD, PhD, Department of Psychosis, Institute of Psychiatry, Psychology, and Neuroscience, Division of Academic Psychiatry, King's College London, M6.01.04, De Crespigny Park, PO Box P067, London SE5 8AF, United Kingdom (sagnik.2.bhattacharyya@kcl.ac.uk).

Author Affiliations: Department of Old Age Psychiatry, Institute of Psychiatry, Psychology, and Neuroscience, Division of Academic Psychiatry, King's College London, London, United Kingdom (Velayudhan, McGoohan); Department of Psychosis, Institute of Psychiatry, Psychology, and Neuroscience, Division of Academic Psychiatry, King's College London, London, United Kingdom (Bhattacharyya).

Author Contributions: Drs Velayudhan and Bhattacharyya had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Velayudhan, Bhattacharyya.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Velayudhan, Bhattacharyya.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Bhattacharyya.

Obtained funding: Bhattacharyya.

Supervision: Velayudhan, Bhattacharyya.

Conflict of Interest Disclosures: Dr Velayudhan reported receiving grants from Parkinson's UK. Dr Bhattacharyya reported receiving grants from the National Institute of Health Research Efficacy and Mechanism Evaluation scheme and Parkinson's UK; receiving honoraria for serving on the advisory board or as a speaker for Reckitt Benckiser, EmpowerPharm/SanteCannabis, and Britannia Pharmaceuticals, paid through King's College London into a research support account; and receiving a study drug from Canopy Growth for investigator-initiated research. No other disclosures were reported.

Disclaimer: The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute of Health Research, or the Department of Health.

REFERENCES

1. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*. 2010;35(3):764-774. doi:10.1038/npp.2009.184

2. Schoeler T, Petros N, Di Forti M, et al. Association between continued cannabis use and risk of relapse in first-episode psychosis: a quasi-experimental investigation within an observational study. *JAMA Psychiatry*. 2016;73(11):1173-1179. doi:10.1001/jamapsychiatry.2016.2427

3. Di Forti M, Quattrone D, Freeman TP, et al; EU-GEI WP2 Group. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry*. 2019;6(5):427-436. doi:10.1016/S2215-0366(19)30048-3

4. Fraguas-Sánchez AI, Torres-Suárez AI. Medical use of cannabinoids. *Drugs*. 2018;78(16):1665-1703. doi:10.1007/s40265-018-0996-1

5. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

Downloaded From: https://jamanetwork.com/ by Dale Quigley on 03/05/2021

6. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-149. doi:10.1093/ije/31.1.140

SUPPLEMENT.

eAppendix. Supplementary Methods
eReferences.
eTable. Characteristics of Included Randomized Clinical Trials
eFigure. Study Flow Diagram

Downloaded From: https://jamanetwork.com/ by Dale Quigley on 03/05/2021