Systematic review and meta-analysis seem to indicate that Cannabinoids for Chronic Primary Pain treatment have limited benefit.

Authors:
Riccardo Giossi[1,2,3]*, Federica Carrara[1]*, Matteo Padroni[1], Maria Concetta Bilancio[1], Martina Mazzari[1], Silvia Enisci[1], Maria Silvia Romio[1], Gloria Boni[1], Federica Corrù[1], Veronica Andrea Fittipaldo[4], Irene Tramacere[2], Arianna Pani[5], Francesco Scaglione[5], Diego Fornasari[1]

*These authors equally contributed to this study.

Affiliations:
[1]Department of Medical Biotechnology and Translational Medicine, Postgraduate School of Clinical Pharmacology and Toxicology, Università degli Studi di Milano, Milan, Italy
[2]Department of Research and Clinical Development, Scientific Directorate, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy
[3]Neuroimmunology and Neuromuscular Diseases Unit, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Milan, Italy
[4]Oncology Department, Mario Negri Institute for Pharmacological Research IRCCS, Milan, Italy
[5]Department of Oncology and Hemato-oncology, Postgraduate School of Clinical Pharmacology and Toxicology, Università degli Studi di Milano, Milan, Italy

Corresponding Author: Riccardo Giossi, MD; Department of Medical Biotechnology and Translational Medicine, Postgraduate School of Clinical Pharmacology and Toxicology, Università degli Studi di Milano, Milan, Italy. Department of Research and Clinical Development, Scientific Directorate, Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, Via Celoria 11, 20133, Milan, Italy. Email: riccardo.giossi@unimi.it

SUPPLEMENTARY MATERIAL

Supplement S1. Search strategy

MEDLINE (Pubmed) (1946 to 30 October 2021)

((((((((((((("Fibromyalgia"[Mesh]) OR "Causalgia"[Mesh]) OR "Reflex Sympathetic Dystrophy"[Mesh] OR "Headache Disorders"[Mesh] OR "Cluster Headache"[Mesh]) OR "Mandibular Diseases"[Mesh] OR "Trigeminal Neuralgia"[Mesh] OR "Irritable Bowel Syndrome"[Mesh]) OR "Prostatitis"[Mesh]) OR "Neck Pain"[Mesh]) OR "Burning Mouth Syndrome"[Mesh]) OR "Facial Pain"[Mesh]) OR "Chest Pain"[Mesh]) OR "Abdominal Pain"[Mesh] OR "Low Back Pain"[Mesh]) OR "Phantom Limb"[Mesh])))) OR ((((((Fibromyalgia*[Title/Abstract] OR "Fibromyalgia-Fibromyositis Syndrome"[Title/Abstract] OR "Fibromyalgia Fibromyositis Syndrome"[Title/Abstract] OR "Fibromyalgia-Fibromyositis Syndromes"[Title/Abstract] OR "Muscular Rheumatism"[Title/Abstract] OR Fibrositis[Title/Abstract] OR Fibrositides[Title/Abstract] OR "Diffuse Myofascial Pain Syndrome"[Title/Abstract] OR "Fibromyositis-Fibromyalgia Syndrome"[Title/Abstract] OR "Fibromyositis Fibromyalgia Syndrome"[Title/Abstract] OR "Fibromyositis-Fibromyalgia Syndromes"[Title/Abstract] OR (Secondary[Title/Abstract] OR Primary[Title/Abstract] AND Fibromyalgia)[Title/Abstract] OR Causalgia[Title/Abstract] OR "Type II Complex Regional Pain Syndrome"[Title/Abstract] OR "CRPS Type II"[Title/Abstract] OR "Deafferentation Pain"[Title/Abstract] OR "Causalgia Syndrome"[Title/Abstract] OR "Causalgia Syndromes"[Title/Abstract]) OR ("Complex Regional Pain Syndrome Type II"[Title/Abstract] OR "Reflex Sympathetic Dystrophies"[Title/Abstract] OR "Sudek Atrophy"[Title/Abstract] OR "RSD (Reflex Sympathetic Dystrophy)"[Title/Abstract] OR "RSDs (Reflex Sympathetic Dystrophy)"[Title/Abstract] OR "Sympathetic Reflex Dystrophia"[Title/Abstract] OR "Sympathetic Reflex Dystrophias"[Title/Abstract] OR "Type I Complex Regional Pain Syndrome"[Title/Abstract] OR "Sudek's Atrophy"[Title/Abstract] OR "Sudek's Atrophies"[Title/Abstract] OR "Sudeks Atrophy"[Title/Abstract] OR "Reflex Sympathetic Dystrophy Syndrome"[Title/Abstract] OR "Cervical Sympathetic Dystrophy"[Title/Abstract] OR "Cervical Sympathetic Dystrophies"[Title/Abstract])) OR (("Shoulder-Hand Syndrome"[Title/Abstract] OR "Shoulder Hand Syndrome"[Title/Abstract] OR "Shoulder-Hand Syndromes"[Title/Abstract] OR "Algodystrophic Syndrome"[Title/Abstract] OR Algodystrophy[Title/Abstract] OR Algodystrophies[Title/Abstract] OR "Cluster Headaches"[Title/Abstract] OR "Ciliary Neuralgia"[Title/Abstract] OR "Ciliary Neuralgias"[Title/Abstract] OR "Cluster Headache Syndrome"[Title/Abstract] OR "Cluster Headache Syndromes"[Title/Abstract] OR "Neuralgic Migraine"[Title/Abstract] OR "Neuralgic Migraines"[Title/Abstract] OR "Histamine Cephalgia"[Title/Abstract] OR "Histamine Cephalgias"[Title/Abstract] OR "Horton Syndrome"[Title/Abstract]) OR ("Horton's Syndrome"[Title/Abstract] OR "Hortons Syndrome"[Title/Abstract] OR "Chronic migraine"[Title/Abstract] OR "Chronic tension headache"[Title/Abstract] OR "Chronic tension type headache"[Title/Abstract] OR "Chronic tension-type headache"[Title/Abstract] OR "chronic headache"[Title/Abstract] OR "trigeminal-autonomic cephalalgias"[Title/Abstract])))) OR ((("trigeminal autonomic cephalalgias"[Title/Abstract] OR "Chronic temporomandibular disorder pains"[Title/Abstract] OR "temporomandibular joint disorder"[Title/Abstract] OR "temporomandibular joint disorders"[Title/Abstract] OR "temporomandibular joint pain"[Title/Abstract]) OR ("Chronic idiopathic orolingual pain"[Title/Abstract] OR "burning mouth"[Title/Abstract] OR "Chronic burning tongue syndrome[Title/Abstract])) OR ("Chronic temporomandibular disorder pains"[Title/Abstract] OR "chronic orofacial pain"[Title/Abstract] OR "orofacial pain"[Title/Abstract])))) OR (("oro-facial pain"[Title/Abstract] OR "oro facial pain"[Title/Abstract] OR "facial pain"[Title/Abstract] OR "chest pain"[Title/Abstract] OR "Chronic primary chest pain syndrome"[Title/Abstract] OR "epigastric pain syndrome"[Title/Abstract]) OR ("epigastric pain"[Title/Abstract] OR "Irritable Bowel Syndromes"[Title/Abstract] OR "Irritable Bowel Syndrome"[Title/Abstract] OR "Irritable Colon"[Title/Abstract] OR "Mucous Colitides"[Title/Abstract] OR "Mucous Colitis"[Title/Abstract] OR "abdominal pain syndrome"[Title/Abstract])))) OR ((("abdominal pain"[Title/Abstract] OR "interstitial cystitis"[Title/Abstract] OR "bladder pain"[Title/Abstract] OR cystitis[Title/Abstract] OR "pelvic sympathetic syndrome"[Title/Abstract] OR "uterine pain"[Title/Abstract] OR "pelvic pain"[Title/Abstract] OR "Neck Pain" OR "Neck Ache"[Title/Abstract] OR Cervicalgia*[Title/Abstract] OR Cervicodynia*[Title/Abstract] OR Neckache*[Title/Abstract] OR "Cervical Pain"[Title/Abstract] OR "Cervical Pains"[Title/Abstract]) OR (("posterior cervical"[Title/Abstract] OR "anterior cervical"[Title/Abstract]) AND (pain[Title/Abstract])))) OR ("thoracic pain"[Title/Abstract] OR "chest pain"[Title/Abstract] OR "Precordial Catch Syndrome"[Title/Abstract] OR "Precordial Catch"[Title/Abstract] OR "Texidor's Twinge"[Title/Abstract] OR "Texidor Twinge"[Title/Abstract] OR "Low Back Pain"[Title/Abstract] OR Lumbago[Title/Abstract] OR "Lower Back Pain"[Title/Abstract] OR "Lower Back Pain"[Title/Abstract] OR "Low Back Ache"[Title/Abstract] OR "Low

Backaches"[Title/Abstract] OR "Phantom limb pain"[Title/Abstract] OR "limb pain"[Title/Abstract])))) AND ((("Cannabinoids"[Mesh])) OR (Nabilone[Title/Abstract] OR Dronabinol[Title/Abstract] OR Nabiximols[Title/Abstract] OR Epidiolex[Title/Abstract] OR bedrosian[Title/Abstract] OR Bediol[Title/Abstract] OR Bedrobinol[Title/Abstract] OR "THC (tetrahydrocannabinol)"[Title/Abstract] OR tetrahydrocannabinol[Title/Abstract] OR "CBD (cannabidiol)"[Title/Abstract] OR cannabidiol[Title/Abstract] OR Cannabis[Title/Abstract] OR Cannabinoid*[Title/Abstract] OR Marinol[Title/Abstract])

Embase (1974 to 30 October 2021)

#1 'fibromyalgia'/exp/mj OR 'complex regional pain syndrome type ii'/exp/mj OR 'complex regional pain syndrome type i'/exp/mj OR 'headache and facial pain'/exp/mj OR 'cluster headache'/exp/mj OR 'jaw disease'/exp/mj

#2 'trigeminus neuralgia'/exp/mj OR 'irritable colon'/exp/mj OR 'prostatitis'/exp/mj OR 'neck pain'/exp/mj OR 'burning mouth syndrome'/exp/mj

#3 'face pain'/exp/mj OR 'thorax pain'/exp/mj OR 'abdominal pain'/exp/mj OR 'low back pain'/exp/mj OR 'phantom limb'/exp/mj

#4 #1 OR #2 OR #3

#5 fibromyalgia* OR 'fibromyalgia-fibromyositis syndrome' OR 'fibromyalgia fibromyositis syndrome' OR 'fibromyalgia-fibromyositis syndromes' OR 'muscular rheumatism' OR fibrositis OR fibrositides OR 'diffuse myofascial pain syndrome' OR 'fibromyositis-fibromyalgia syndrome' OR 'fibromyositis fibromyalgia syndrome' OR 'fibromyositis-fibromyalgia syndromes' OR ((secondary OR primary) AND fibromyalgia) OR causalgia OR 'type ii complex regional pain syndrome' OR 'crps type ii' OR 'deafferentation pain' OR 'causalgia syndrome' OR 'causalgia syndromes' OR 'complex regional pain syndrome type ii' OR 'reflex sympathetic dystrophies' OR 'rsd (reflex sympathetic dystrophy)' OR 'rsds (reflex sympathetic dystrophy)' OR 'sympathetic reflex dystrophia' OR 'sympathetic reflex dystrophias' OR 'type i complex regional pain syndrome' OR 'sudek atrophy' OR 'sudek atrophies' OR 'sudeks atrophy' OR 'reflex sympathetic dystrophy syndrome' OR 'cervical sympathetic dystrophy' OR 'cervical sympathetic dystrophies' OR 'shoulder-hand syndrome' OR 'shoulder hand syndrome' OR 'shoulder-hand syndromes' OR 'algodystrophic syndrome':ti,ab

#6 algodystrophy OR algodystrophies OR 'cluster headaches' OR 'ciliary neuralgia' OR 'ciliary neuralgias' OR 'cluster headache syndrome' OR 'cluster headache syndromes' OR 'neuralgic migraine' OR 'neuralgic migraines' OR 'histamine cephalgia' OR 'histamine cephalgias' OR 'horton syndrome' OR 'hortons syndrome' OR 'chronic migraine' OR 'chronic tension headache' OR 'chronic tension type headache' OR 'chronic tension-type headache' OR 'chronic headache' OR 'trigeminal-autonomic cephalalgias' OR 'trigeminal autonomic cephalalgias' OR 'chronic temporomandibular disorder pains' OR 'temporomandibular joint disorder' OR 'temporomandibular joint disorders' OR 'temporomandibular joint pain' OR 'burning mouth syndrome' OR 'chronic idiopathic orolingual pain' OR 'burning mouth' OR 'chronic burning tongue syndrome':ti,ab

#7 'chronic temporomandibular disorder pains' OR 'chronic orofacial pain' OR 'orofacial pain' OR 'oro-facial pain' OR 'oro facial pain' OR 'facial pain' OR 'chest pain' OR 'chronic primary chest pain syndrome' OR 'epigastric pain syndrome' OR 'epigastric pain' OR 'irritable bowel syndromes' OR 'irritable bowel syndrome' OR 'irritable colon' OR 'mucous colitides' OR 'mucous colitis' OR 'abdominal pain syndrome':ti,ab

#8 ('abdominal pain' OR 'interstitial cystitis' OR 'bladder pain' OR cystitis OR 'pelvic sympathetic syndrome' OR 'uterine pain' OR 'pelvic pain' OR 'neck pain') AND oe AND 'neck ache' OR cervicalgia* OR cervicodynia* OR neckache* OR 'cervical pain' OR 'cervical pains':ti,ab

#9 'thoracic pain' OR 'chest pain' OR 'precordial catch syndrome' OR 'precordial catch' OR 'texidor twinge' OR 'low back pain' OR lumbago OR 'lower back pain' OR 'low back ache' OR 'low backaches' OR 'phantom limb pain' OR 'limb pain':ti,ab

#10 #5 OR #6 OR #7 OR #8 OR #9

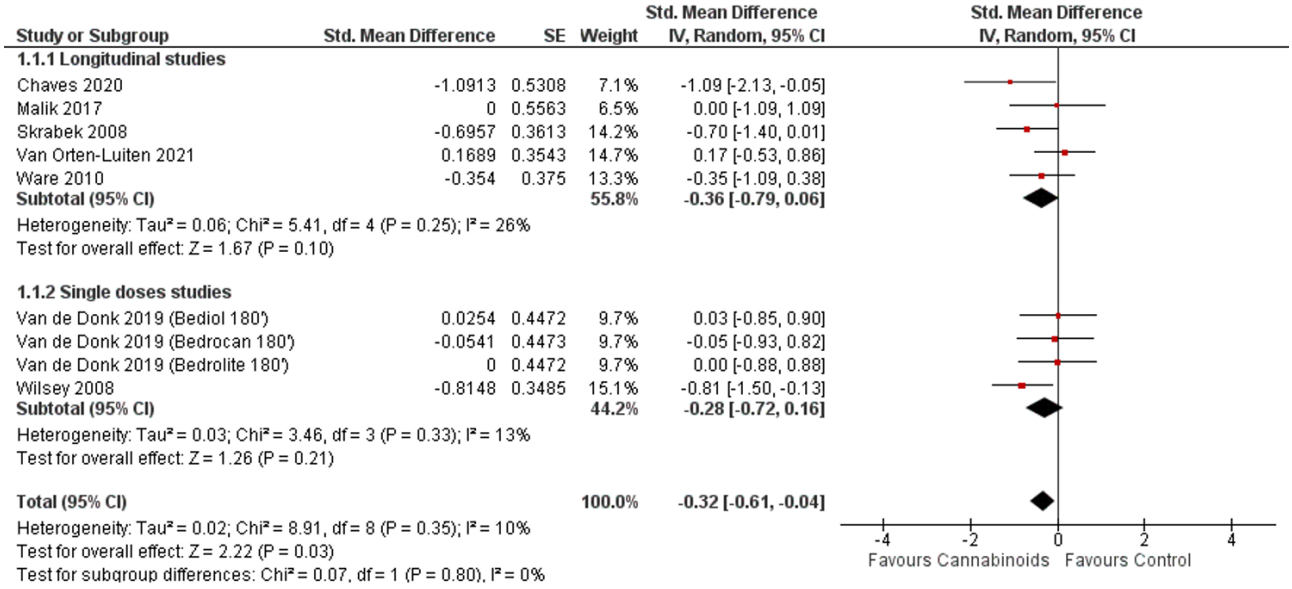
#11 #4 OR #10

#12 'cannabinoid'/exp/mj

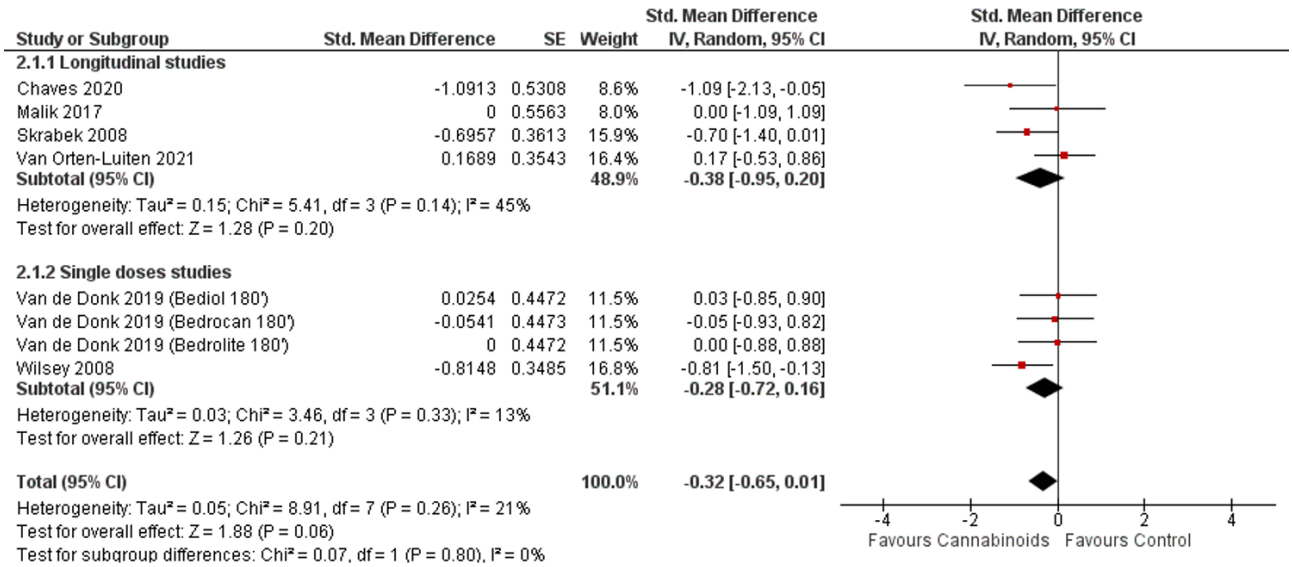
#13 nabilone OR dronabinol OR nabiximols OR epidiolex OR bedrocan OR bediol OR bedrobinol OR 'thc (tetrahydrocannabinol)' OR tetrahydrocannabinol OR 'cbd (cannabidiol)' OR cannabidiol OR cannabis OR cannabinoid* OR marinol:ti,ab

#14 #12 OR #13

A.



B.



C.

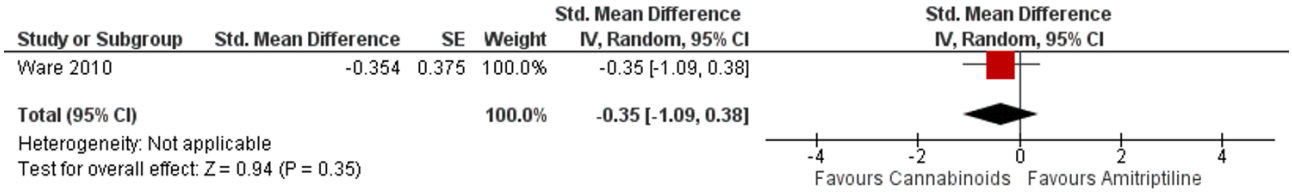
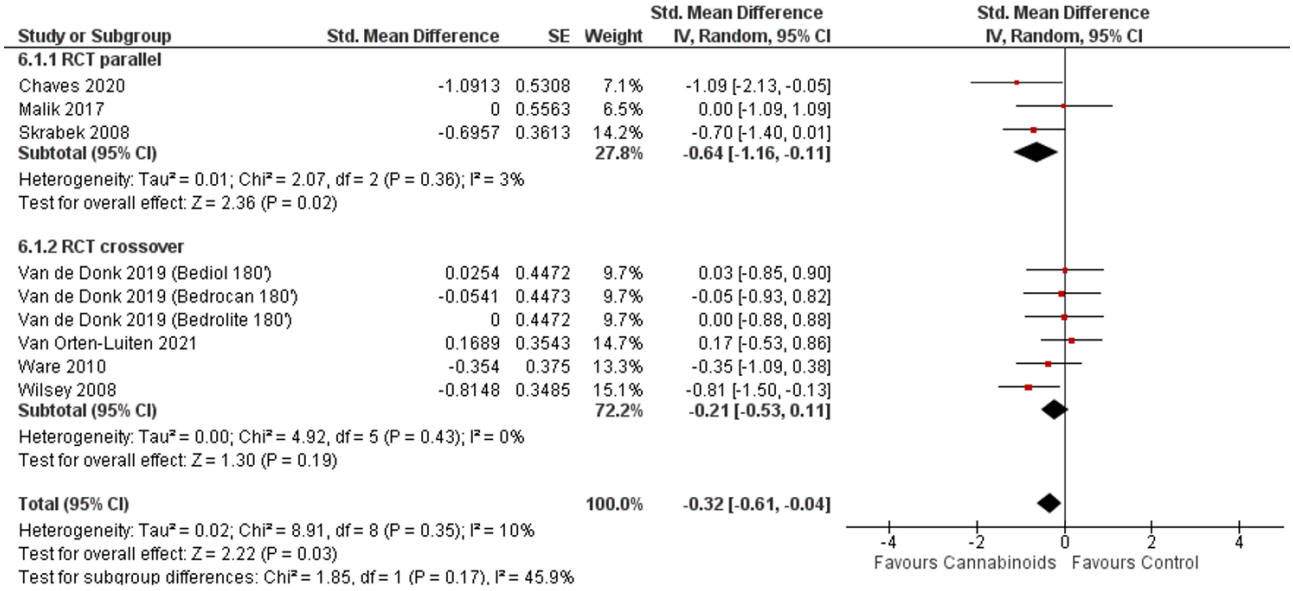


Figure S1. Pain reduction

Forest plots for pain reduction comparing (A) cannabinoids against any treatment, (B) cannabinoids against placebo, and (C) nabilone against amitriptyline. Subgroups indentify studies by different product administration schedule.

A.



B.

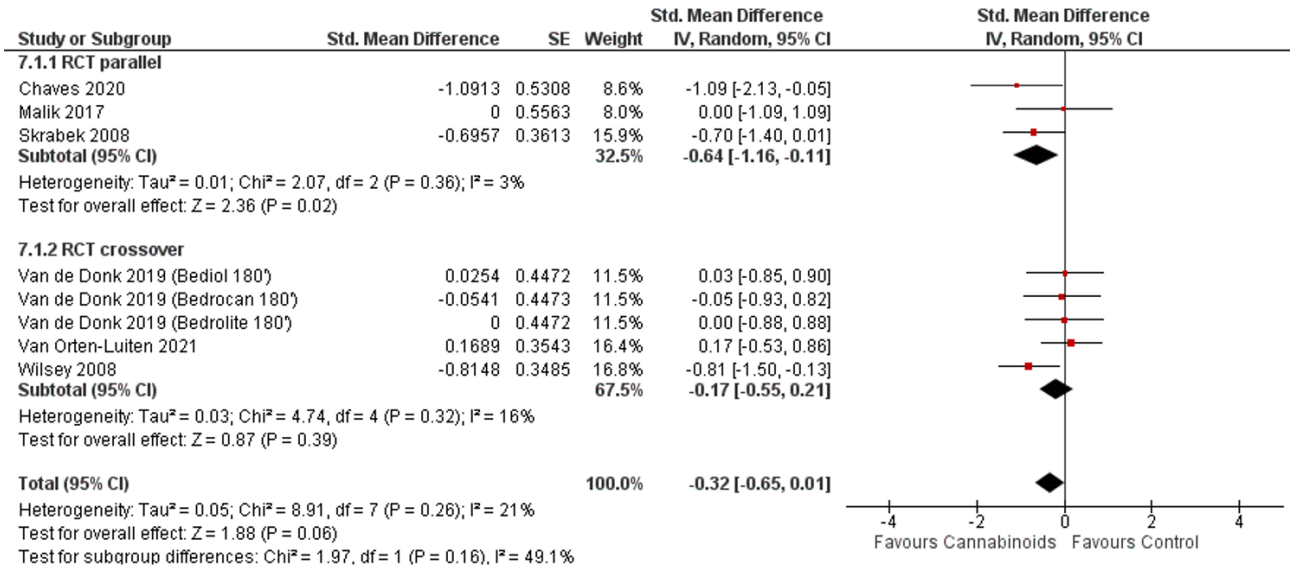
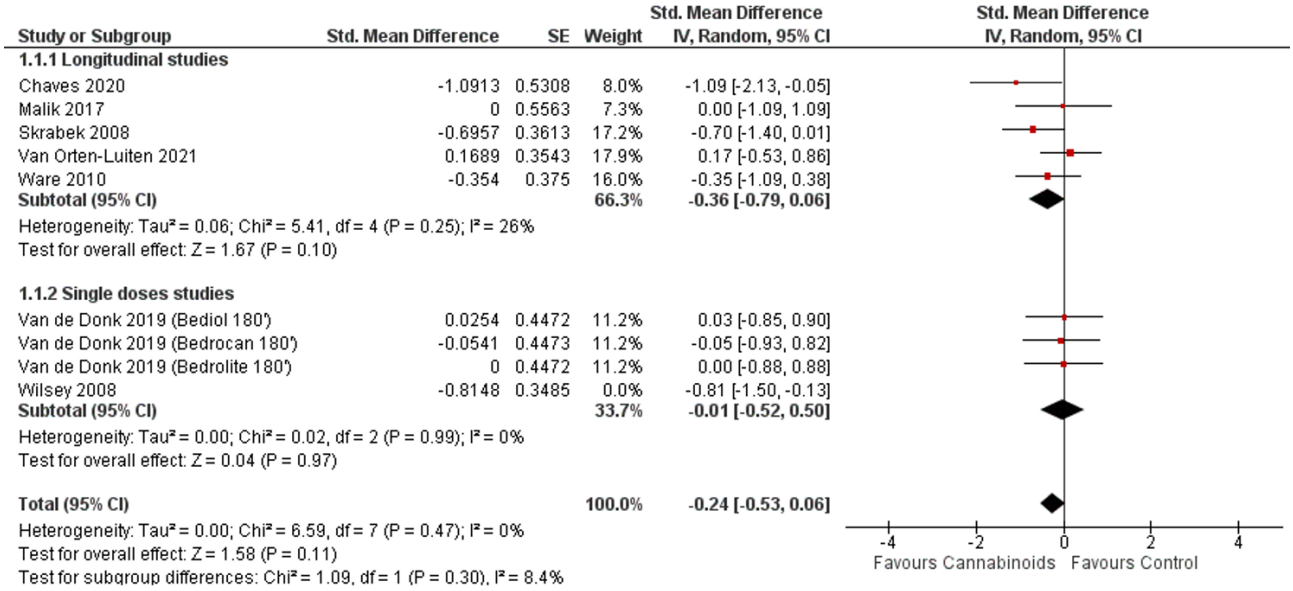


Figure S2. Pain reduction by study design and treatment duration

Subgroup analysis for pain grouping included studies by study design, parallel arm or crossover RCTs. The same subgroups correspond to a treatment duration of at least 4 weeks or less than for weeks, respectively. (A) Cannabinoids against any comparator and (B) Cannabinoids against placebo.

A.



B.

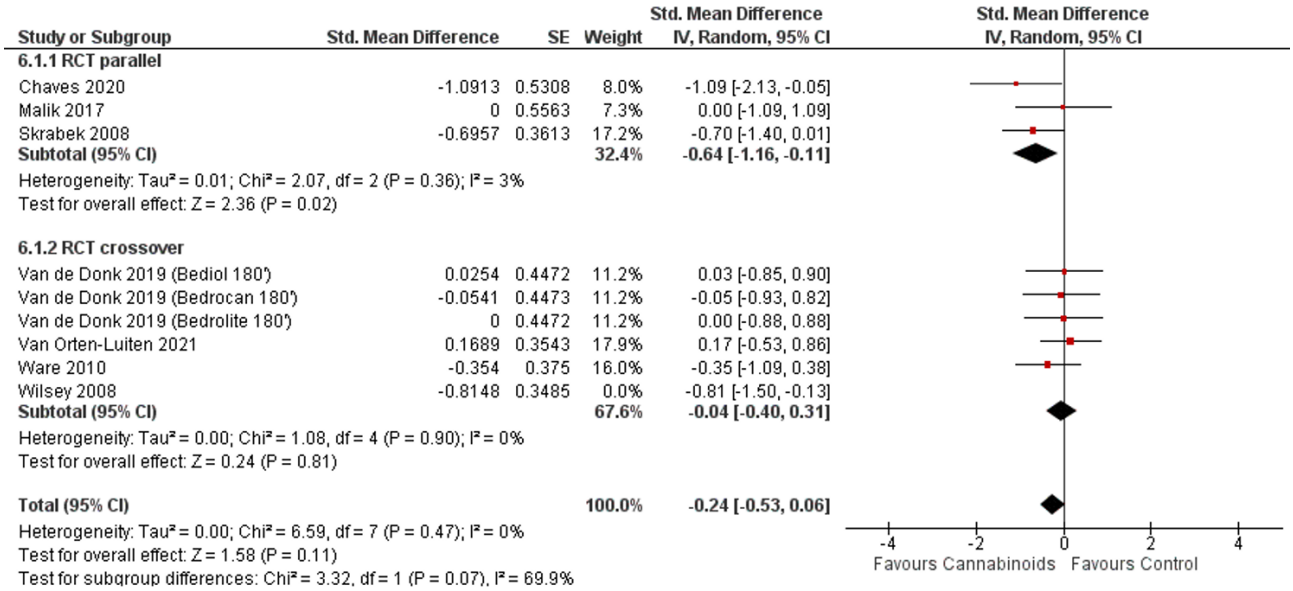
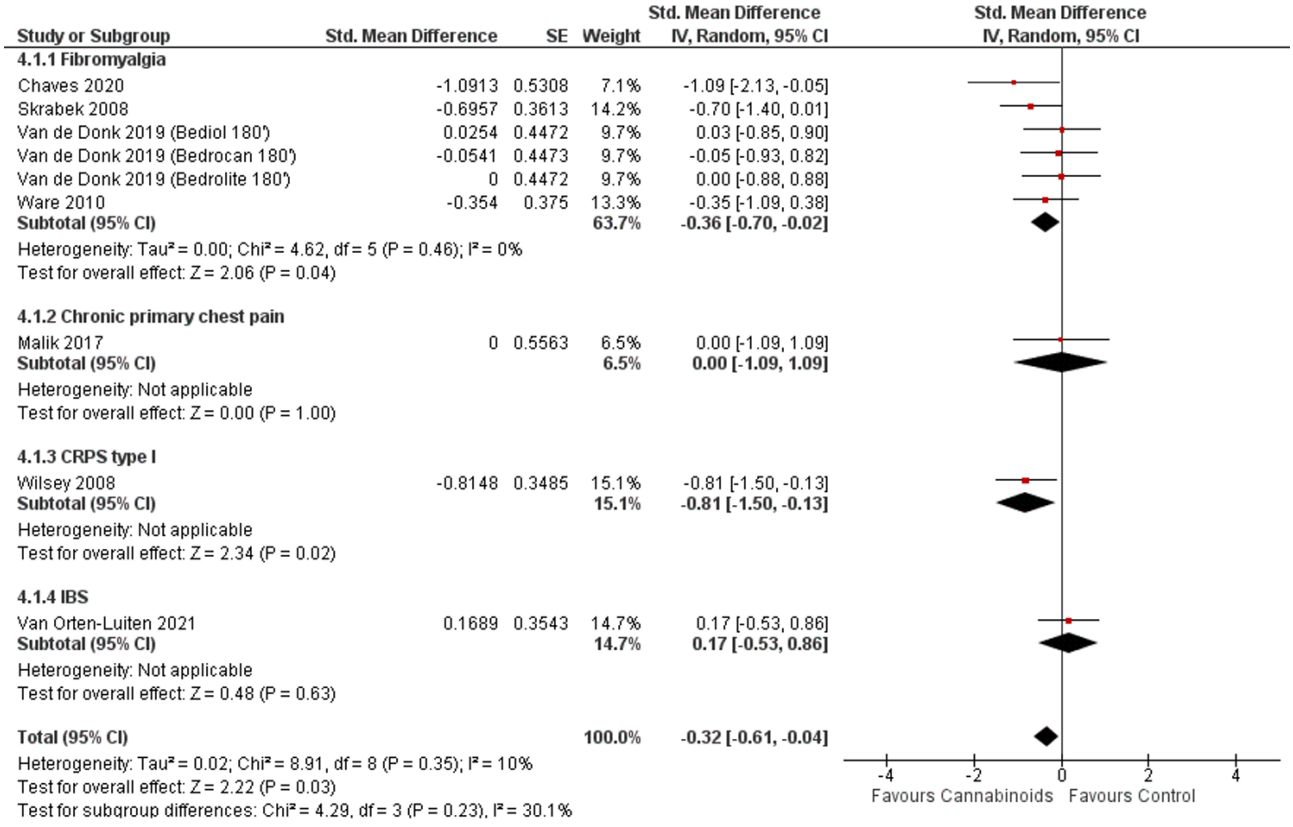


Figure S3. Sensitivity analysis

Sensitivity analysis for the pain outcome excluding the study enrolling also secondary chronic pain. Forest plots present results for (A) Cannabinoids compared to any treatment grouped by product administration schedule and (B) Cannabinoids compared to any treatment grouped by study design.

A.



B.

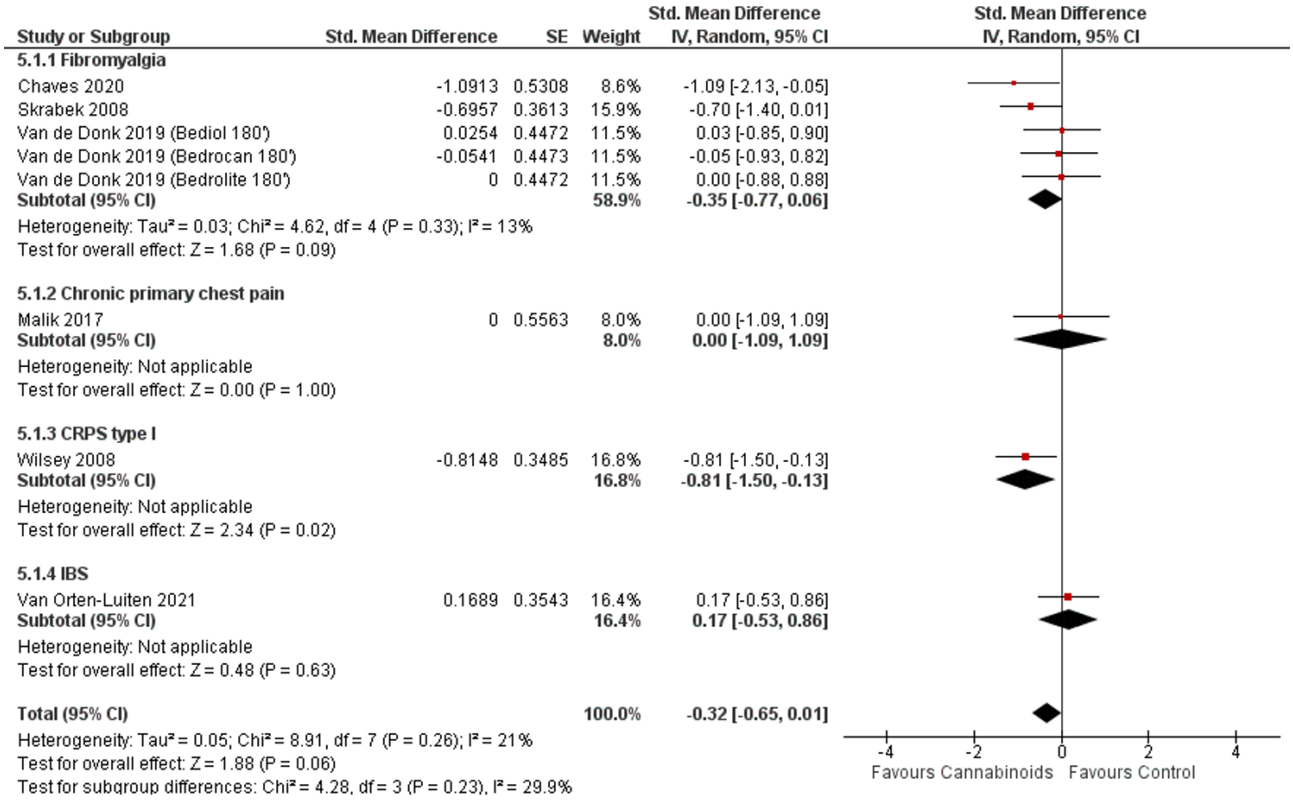
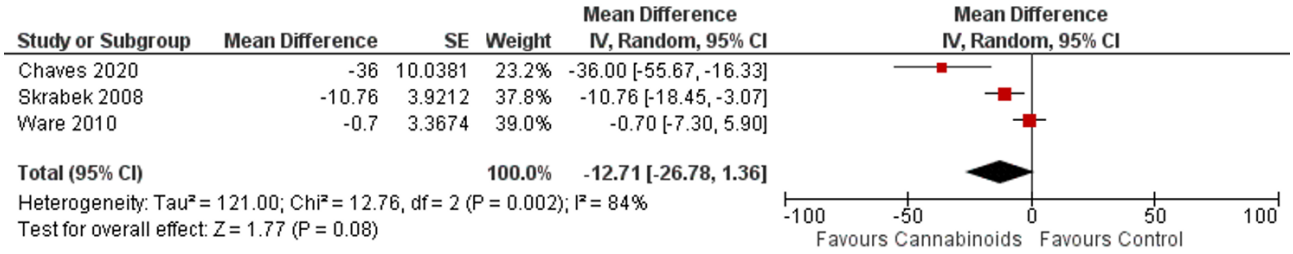


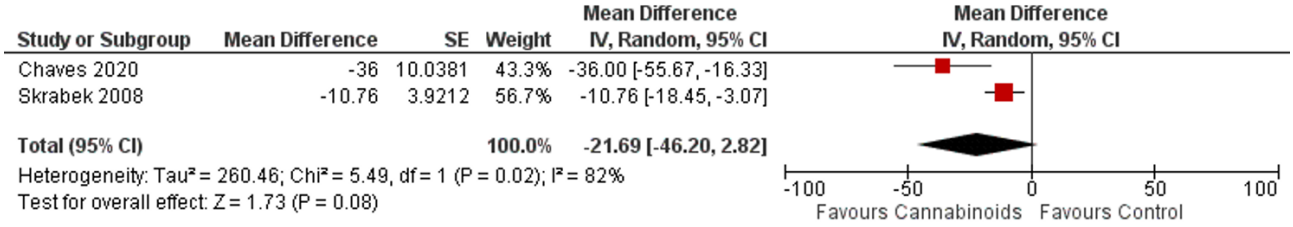
Figure S4. Pain reduction by condition

Subgroup analysis for pain grouping included studies by condition, parallel arm or crossover RCTs. (A) Cannabinoids against any comparator and (B) Cannabinoids against placebo.

A.



B.



C.

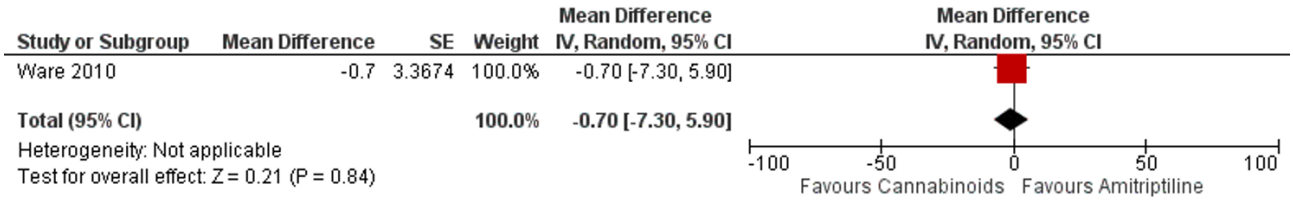
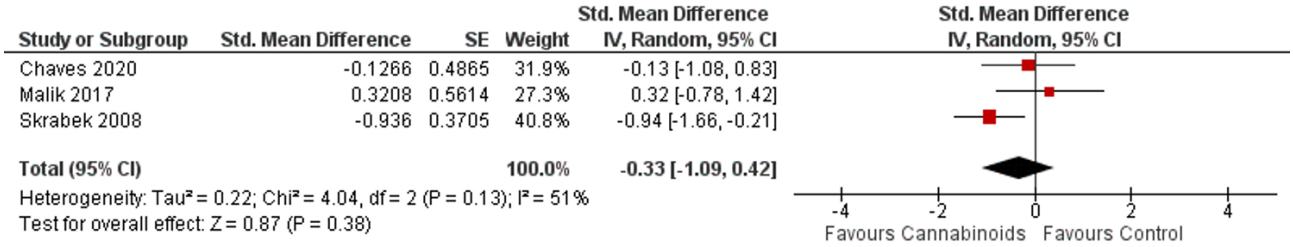
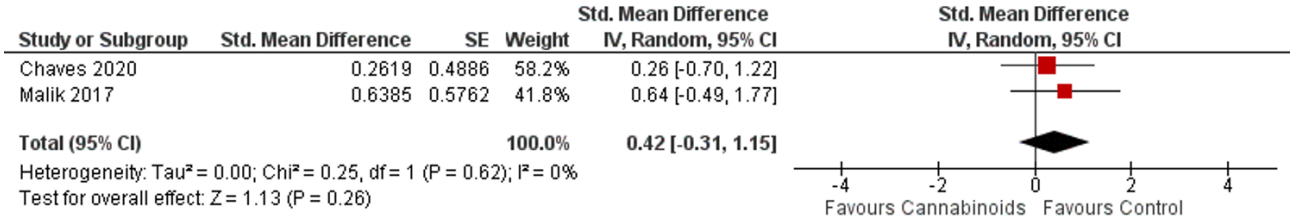


Figure S5. Fibromyalgia Impact Questionnaire
Forest plots for the Fibromyalgia Impact Questionnaire comparing (A) cannabinoids against any treatment, (B) cannabinoids against placebo, and (C) nabilone against amitriptyline.

A.



B.



C.

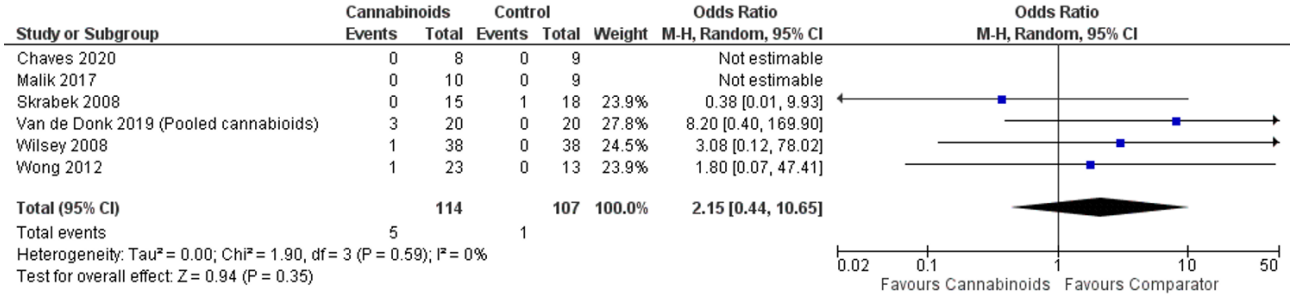


Figure S6. Anxiety, depression, and discontinuation due to AEs
Forest plots presenting the comparison between cannabinoids and placebo for (A) anxiety reduction (B) depression reduction, and (C) discontinuation due to AEs.

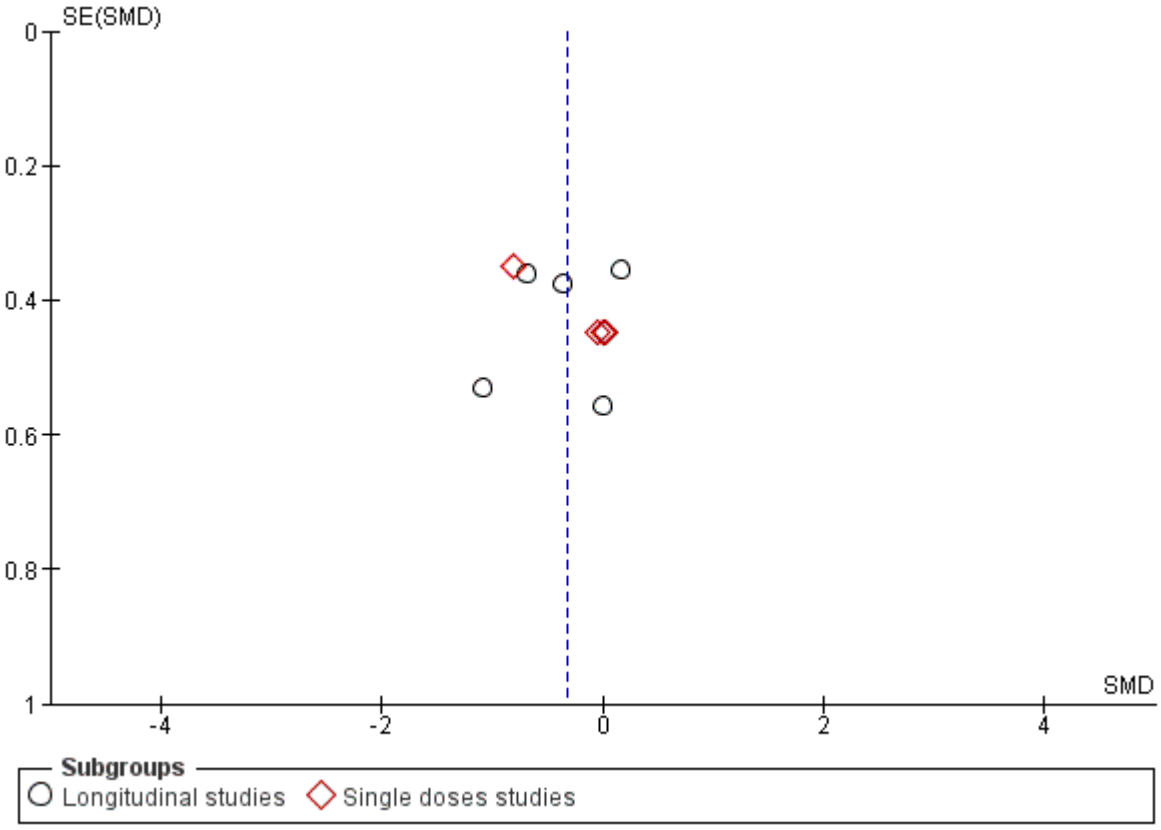


Figure S7. Funnel plot
Funnel plot presenting all studies included in the primary outcome analysis.

Supplement S2. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	S 2-3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7-8

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8; 19
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	8-9; 21
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9; 20
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9-11; S 4-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11; 20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-11; 22; S 4-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-10; S 4-8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9; 22
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	22
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-14
	23b	Discuss any limitations of the evidence included in the review.	13-14
	23c	Discuss any limitations of the review processes used.	13-14
	23d	Discuss implications of the results for practice, policy, and future research.	13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.8;	8; 15
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA