Dr. Nicola Luigi Bragazzi

Are there enough scientific evidences to recommend psychotropic substances for medical use? Implications of a critical umbrella review

Some *biodata* on the speaker …

- **NOT** an expert in cannabis and cannabinoids
- My major expertise in biostatistics, systematic reviews and meta-analyses (**research methodology**)
- I have published so far up to 20 systematic reviews and meta-analyses (some of them in high/very high impact-journals, including Frontiers in physiology, Seizure, Epilepsy and behavior, Drugs, Human vaccines and immunotherapeutics, Cochrane database of systematic reviews, PLOS ONE, etc.)
- I have collaborated and actually collaborate with the Cochrane Association

Systematic reviews and meta-analyses: primary and secondary literature (meta-literature)

PRIMARY LITERATURE

- Original research and/or new scientific discoveries
- Immediate results of research activities
- Often includes analysis of data collected in the field or laboratory

EXAMPLES:

- Original research published as articles in peer-reviewed journals.
- Dissertations
- Technical reports
- Conference proceedings

SECONDARY LITERATURE

- Summarizes and synthesizes primary literature
- Usually broader and less current than primary literature

EXAMPLES:

- Literature review articles
- Books

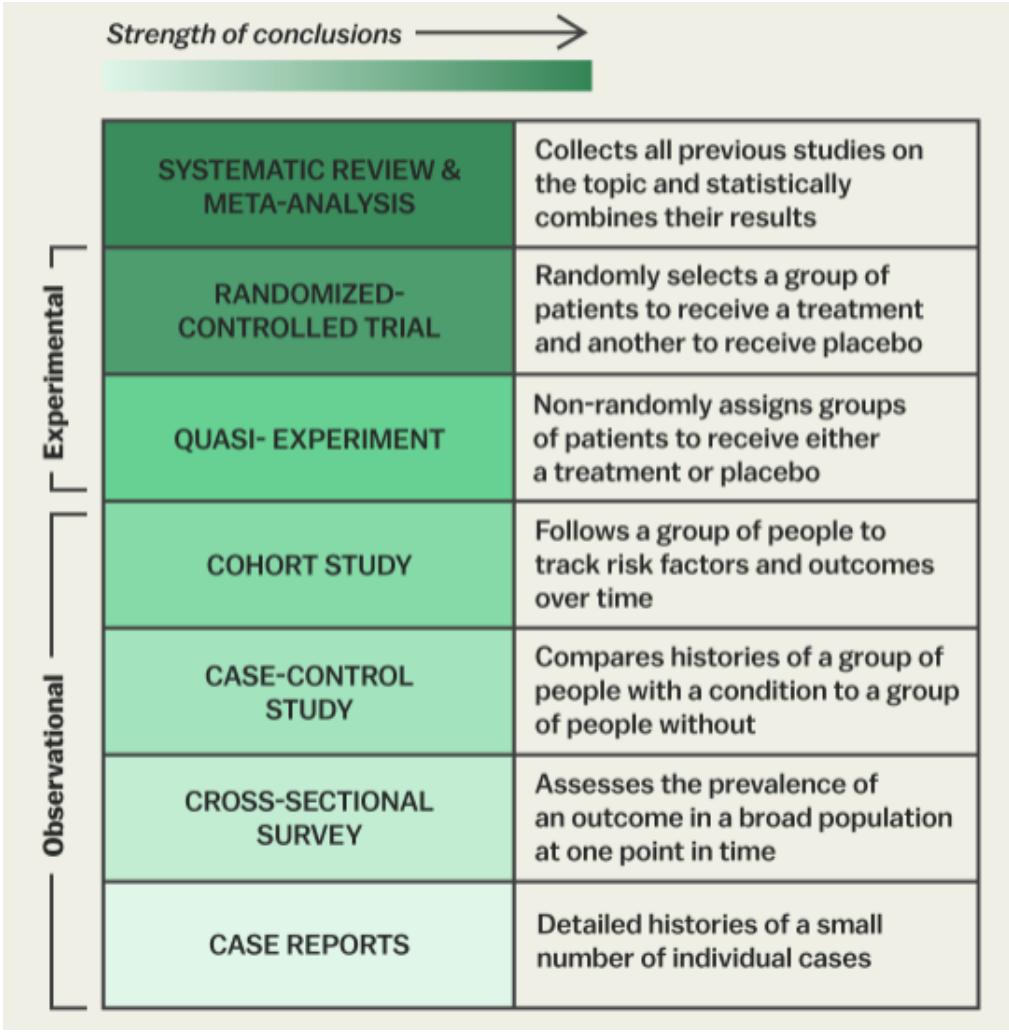
Since most information sources in the secondary literature contain extensive bibliographies, they can be useful for finding more information on a topic

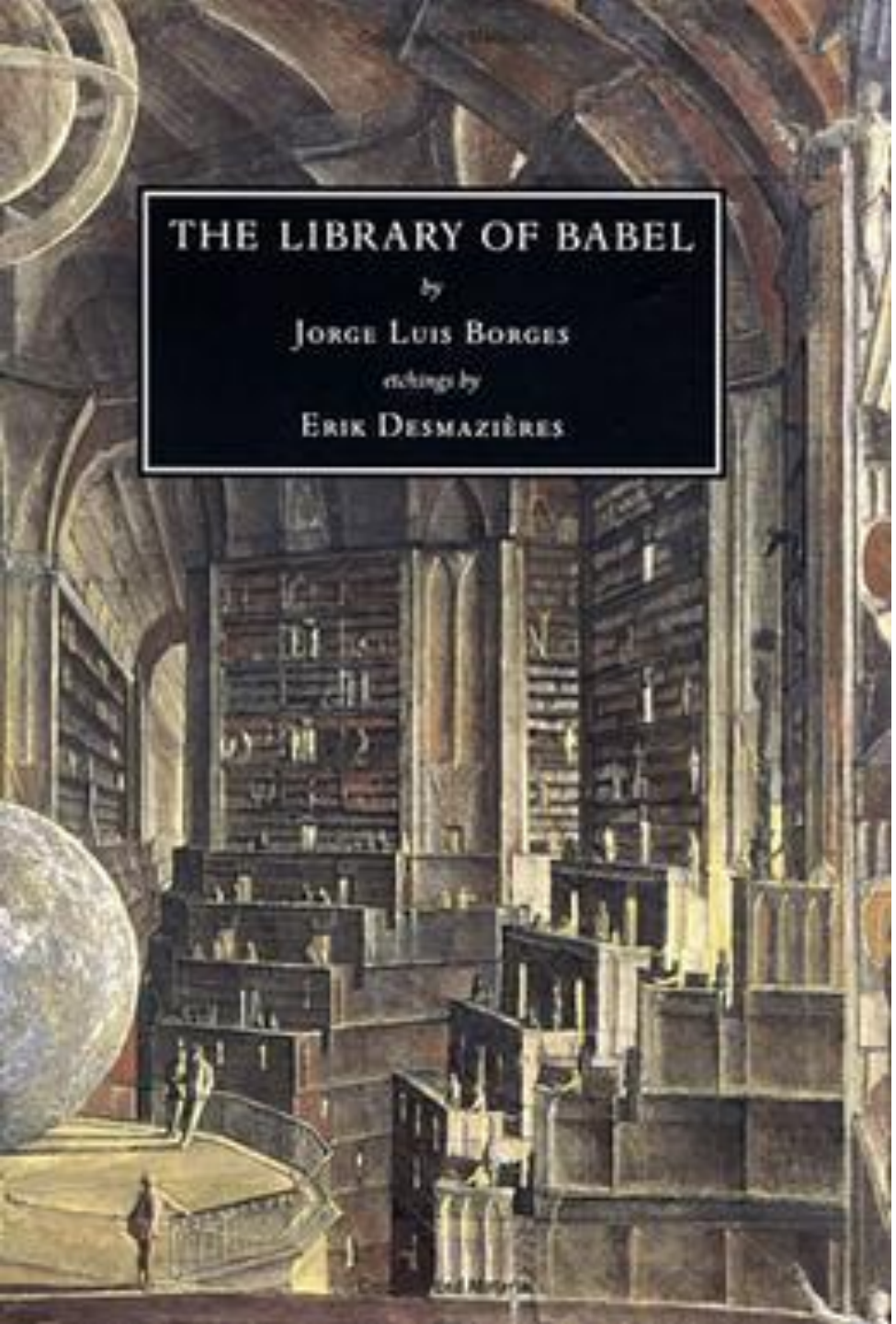
TERTIARY LITERATURE

- Summaries or condensed versions of materials
- Usually with references to primary or secondary sources
- Good place to look up facts or get a general overview of a subject

EXAMPLES:

- Textbooks
- Dictionaries
- Encyclopedias
- Handbooks





A Borgesian scientific library

PubMed

SCOPUS™ Database

ISI Web of KNOWLEDGE
Transforming Research

Label	Description	Methods used (SALSA)			
		Search	Appraisal	Synthesis	Analysis
Critical review	Aims to demonstrate writer has extensively researched literature and critically evaluated its quality. Goes beyond mere description to include degree of analysis and conceptual innovation. Typically results in hypothesis or model	Seeks to identify most significant items in the field	No formal quality assessment. Attempts to evaluate according to contribution	Typically narrative, perhaps conceptual or chronological	Significant component: seeks to identify conceptual contribution to embody existing or derive new theory
Literature review	Generic term: published materials that provide examination of recent or current literature. Can cover wide range of subjects at various levels of completeness and comprehensiveness. May include research findings	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative	Analysis may be chronological, conceptual, thematic, etc.
Mapping review/ systematic map	Map out and categorize existing literature from which to commission further reviews and/or primary research by identifying gaps in research literature	Completeness of searching determined by time/scope constraints	No formal quality assessment	May be graphical and tabular	Characterizes quantity and quality of literature, perhaps by study design and other key features. May identify need for primary or secondary research
Meta-analysis	Technique that statistically combines the results of quantitative studies to provide a more precise effect of the results	Aims for exhaustive, comprehensive searching. May use funnel plot to assess completeness	Quality assessment may determine inclusion/ exclusion and/or sensitivity analyses	Graphical and tabular with narrative commentary	Numerical analysis of measures of effect assuming absence of heterogeneity
Mixed studies review/mixed methods review	Refers to any combination of methods where one significant component is a literature review (usually systematic). Within a review context it refers to a combination of review approaches for example combining quantitative with qualitative research or outcome with process studies	Requires either very sensitive search to retrieve all studies or separately conceived quantitative and qualitative strategies	Requires either a generic appraisal instrument or separate appraisal processes with corresponding checklists	Typically both components will be presented as narrative and in tables. May also employ graphical means of integrating quantitative and qualitative studies	Analysis may characterise both literatures and look for correlations between characteristics or use gap analysis to identify aspects absent in one literature but missing in the other
Overview	Generic term: summary of the [medical] literature that attempts to survey the literature and describe its characteristics	May or may not include comprehensive searching (depends whether systematic overview or not)	May or may not include quality assessment (depends whether systematic overview or not)	Synthesis depends on whether systematic or not. Typically narrative but may include tabular features	Analysis may be chronological, conceptual, thematic, etc.
Qualitative systematic review/qualitative evidence synthesis	Method for integrating or comparing the findings from qualitative studies. It looks for 'themes' or 'constructs' that lie in or across individual qualitative studies	May employ selective or purposive sampling	Quality assessment typically used to mediate messages not for inclusion/exclusion	Qualitative, narrative synthesis	Thematic analysis, may include conceptual models

Label	Description	Methods used (SALSA)			
		Search	Appraisal	Synthesis	Analysis
Rapid review	Assessment of what is already known about a policy or practice issue, by using systematic review methods to search and critically appraise existing research	Completeness of searching determined by time constraints	Time-limited formal quality assessment	Typically narrative and tabular	Quantities of literature and overall quality/direction of effect of literature
Scoping review	Preliminary assessment of potential size and scope of available research literature. Aims to identify nature and extent of research evidence (usually including ongoing research)	Completeness of searching determined by time/scope constraints. May include research in progress	No formal quality assessment	Typically tabular with some narrative commentary	Characterizes quantity and quality of literature, perhaps by study design and other key features. Attempts to specify a viable review
State-of-the-art review	Tend to address more current matters in contrast to other combined retrospective and current approaches. May offer new perspectives on issue or point out area for further research	Aims for comprehensive searching of current literature	No formal quality assessment	Typically narrative, may have tabular accompaniment	Current state of knowledge and priorities for future investigation and research
Systematic review	Seeks to systematically search for, appraise and synthesis research evidence, often adhering to guidelines on the conduct of a review	Aims for exhaustive, comprehensive searching	Quality assessment may determine inclusion/exclusion	Typically narrative with tabular accompaniment	What is known; recommendations for practice. What remains unknown; uncertainty around findings, recommendations for future research
Systematic search and review	Combines strengths of critical review with a comprehensive search process. Typically addresses broad questions to produce 'best evidence synthesis'	Aims for exhaustive, comprehensive searching	May or may not include quality assessment	Minimal narrative, tabular summary of studies	What is known; recommendations for practice. Limitations
Systematized review	Attempt to include elements of systematic review process while stopping short of systematic review. Typically conducted as postgraduate student assignment	May or may not include comprehensive searching	May or may not include quality assessment	Typically narrative with tabular accompaniment	What is known; uncertainty around findings; limitations of methodology
Umbrella review	Specifically refers to review compiling evidence from multiple reviews into one accessible and usable document. Focuses on broad condition or problem for which there are competing interventions and highlights reviews that address these interventions and their results	Identification of component reviews, but no search for primary studies	Quality assessment of studies within component reviews and/or of reviews themselves	Graphical and tabular with narrative commentary	What is known; recommendations for practice. What remains unknown; recommendations for future research

Authors (year)	Description	No. of included studies	Methods described (SALSA)			
			Search	Appraisal	Synthesis	Analysis
Ankem (2006)[19]	Systematic review of the research literature	110 studies	3 databases	None	Narrative and tabular	Meta-analysis and descriptive statistics
Booth *et al.* (2009)[21]	Systematic review	29	14 databases	Standard checklists of quality assessment criteria for different study designs	Qualitative	Thematic using[32]
Boulos *et al.* (2007)[18]	Overview	Not specified	Not specified	None	Narrative	Descriptive
Brettle (2003)[22]	Systematic review of the literature	24	3 databases	Instrument developed by Health Care Practice R&D Unit (University of Salford)	Narrative and tabular	Descriptive
Brettle (2007)[23]	Systematic review	54	7 databases	None	Narrative and tabular	Thematic and descriptive statistics
Brown (2008)[24]	Systematic review	20 peer reviewed, 19 magazine, 146 newspaper and 141 university newspaper articles	23 databases	Articles from popular press, magazine and newspaper articles reviewed for types of information published	Narrative and tabular	Chronological and thematic
Childs *et al.* (2005)[25]	Systematic review of the literature	57	8 databases	None	Narrative	Descriptive
Davies (2007)[14]	Review of the evidence	Not specified (34 from table)	3 databases	None	Narrative and tabular	Descriptive
Fanner & Urquhart (2008)[26]	Systematic review	Not specified	9 databases	None	Narrative	Descriptive
Grant (2007)[27]	Systematic review	13	LISA	None	Narrative	Thematic
Hall & Walton (2004)[17]	Literature review	23	7 databases	None	Narrative	Descriptive
Koufogiannakis & Wiebe (2006)[28]	Systematic review and meta-analysis	55	15 databases	Glasgow checklist	Narrative	Meta-analysis and framework analysis
Rossall *et al.* (2008)[15]	Review of the evidence	Not specified	Not specified	None	Narrative	Descriptive
Wagner & Byrd (2004)[29]	Systematic review	35	5 databases	Criteria for medical informatics evaluative studies plus additional criteria	Narrative and tabular	Descriptive
Ward *et al.* (2008)[16]	Comprehensive review of the research literature	79	12 databases	None	Narrative	Thematic
Weightman & Williamson (2005)[30]	Systematic review	28	7 databases	Internationally accepted criteria from previously published literature	Narrative and tabular	Descriptive
Beverley & Winning (2003)[20]	Systematic review of the literature	Seventeen (16 unique) evaluative and 33 descriptive studies	16 databases	CriSTAL: Critical Skills Training in Appraisal for Librarians Checklist	Narrative and tabular	Descriptive

Fourteen types of reviews according to the SALSA committee

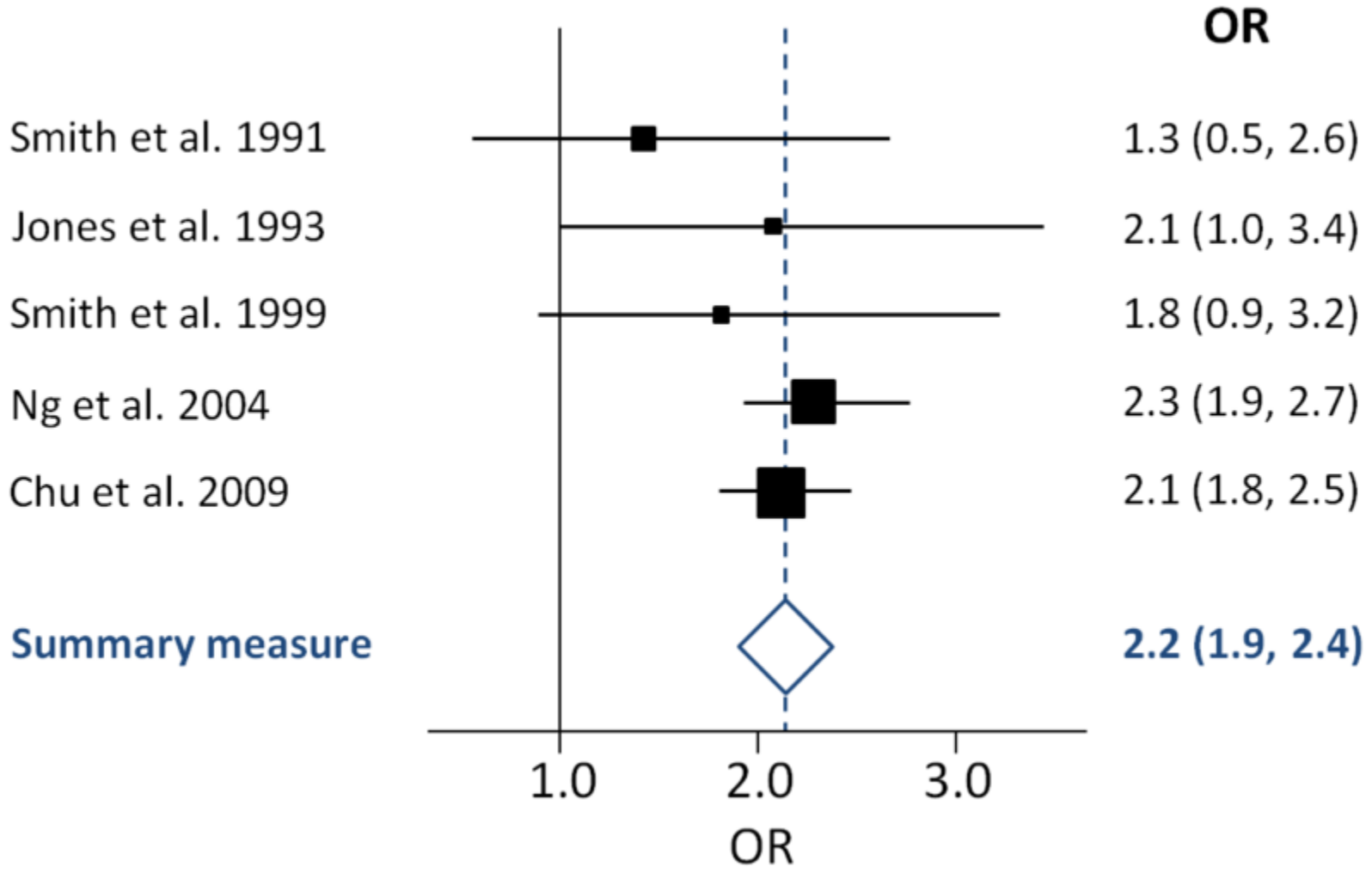
Why a meta-analysis?

- Meta-analysis is a quantitative approach in which individual, primary study findings are statistically pooled and analyzed together.
- This approach is the best way to overcome the very common issue of **small sample sizes** and **low statistical power**.
- Meta-analysis can be defined as the statistical analysis of a large collection of analysis results from individual studies – including, for example, Randomized Controlled Trials (RCTs) - for the purpose of integrating the findings and providing an updated synthesis of the current state of art in that research field (Glass 1976).

What is a meta-analysis?

- Gene Glass was a scientist under psychotherapy. His rival, Eysenck, claimed that psychotherapy was uneffective and did not work. Glass invented meta-analysis to prove Eysenck was wrong
- When Glass published in the American Psychologist an article on the effectiveness of psychotherapy together with Mary Lee Smith in 1977, Eysenck responded to the article by calling it “mega-sillines”

What is a meta-analysis?



An umbrella review of the published systematic reviews/meta-analyses

Search strategy item	**Details**
Databases	PubMed/MEDLINE, Scopus, ISI/Web of Science
Key-words	(ayahuasca OR mescaline OR psilocin OR psilocybin OR psychotropics OR narcotic OR cannabis OR cannabinoid OR cannabidiol OR marijuana OR nabilone OR nabiximols) AND (multiple sclerosis OR cancer pain OR neuropathic pain OR chronic pain OR acute pain OR post-operative pain OR Tourette OR rheumatoid arthritis OR rheumatic OR fibromyalgia) AND (systematic review OR meta-analysis)
Time filter	None applied
Language filter	None applied
Studied outcomes	Efficacy/effectiveness Health-related quality of life Harms/adverse events

An umbrella review of the published systematic reviews/meta-analyses

- The current umbrella review has been performed according to the «Preferred Reporting Items for Systematic Reviews and Meta-analyses» (PRISMA) guidelines
- 4,923 articles have been screened
- The full text of 192 articles has been analyzed in-depth
- 173 articles have been excluded with reasons
- **19** systematic reviews/meta-analyses have been included in the current umbrella review

Psychotropics and efficacy/effectiveness

- Psychotropics and chronic pain
  - Psychotropics and neuropathic pain
  - Psychotropics and chronic cancer-pain
  - Psychotropics and chronic non-cancer pain
- Psychotropics and acute post-operative pain
- Psychotropics and pain (overall)
- Pyshcotropics and neuro-psychiatric disorders
  - Psychotropics and multiple sclerosis
  - Psychotropics and Tourette’s syndrome
- Psychotropics and rheumatic disorders

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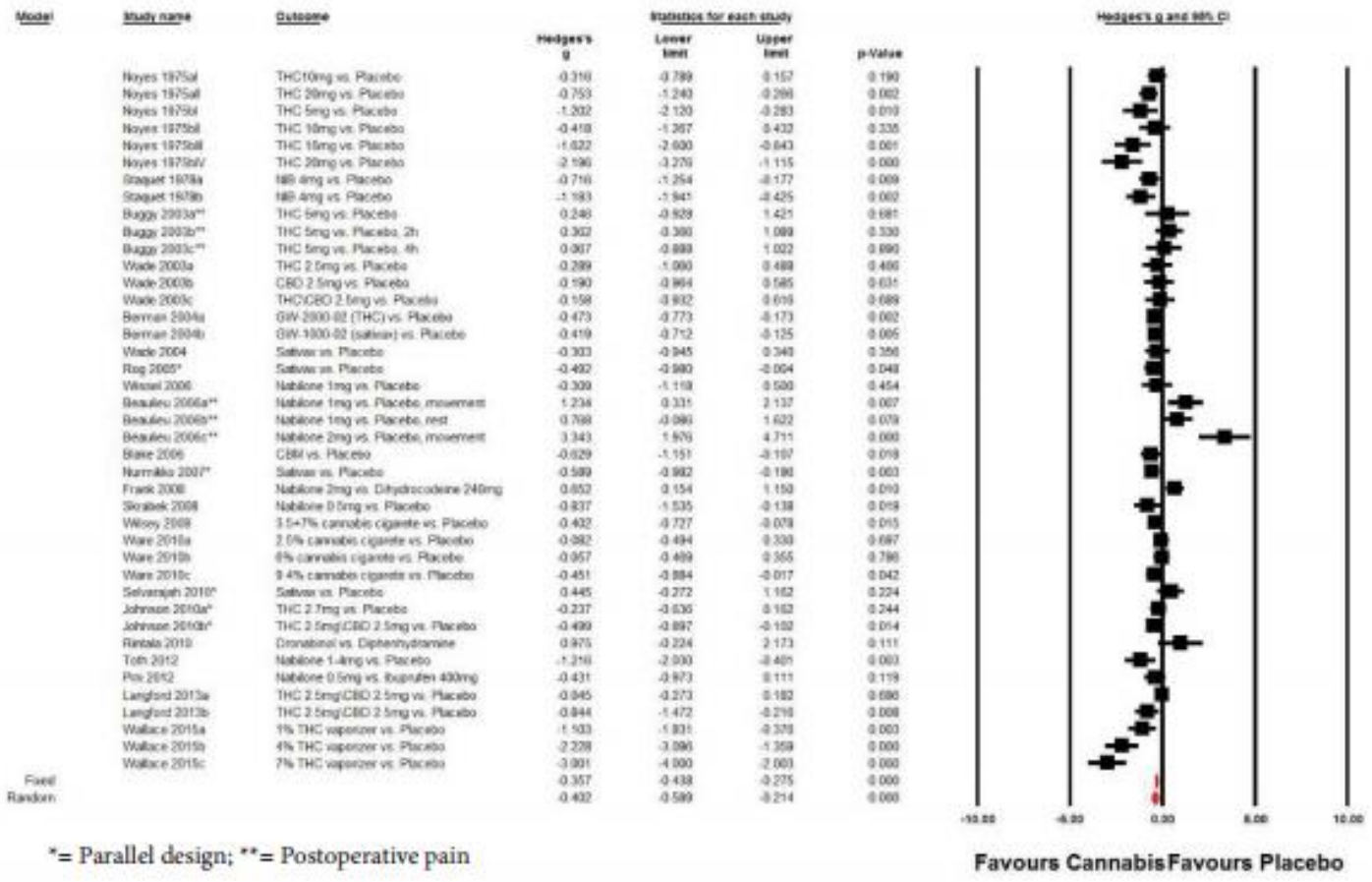
Systematic Review

Psychotropics and chronic pain 1

Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

J. Aviram, RN, PhC[1] and G. Samuelly-Leichtag, PT, PhC[2]



*= Parallel design; **= Postoperative pain

24 crossover and parallel design RCTs were included. Pooled effect sizes were found **favorable** towards CBMs *over* placebo. Not all of the studies yielded results in the same direction, and a statistical heterogeneity was in evidence (I2=77.83%, P <0.0001).

Psychotropics and chronic pain 2

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Systematic Review

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Model	Study name	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
	Noyes 1975a	THC vs. Placebo	-0.497	-0.980	-0.015	0.043
	Noyes 1975b	THC vs. Placebo	-1.215	-2.169	-0.261	0.013
	Staquet 1978a	NB 4mg vs. Placebo	-0.726	-1.272	-0.180	0.009
	Staquet 1978b	NB 4mg vs. Placebo	-1.216	-1.995	-0.437	0.002
	Wade 2003	Sativex vs. Placebo	-0.158	-0.959	0.644	0.700
	Berman 2004a	GW-1000-02 (THC) vs. Placebo	-0.481	-0.786	-0.176	0.002
	Berman 2004b	GW-1000-02 (sativex) vs. Placebo	-0.426	-0.724	-0.127	0.005
	Wade 2004	Sativex vs. Placebo	-0.309	-0.967	0.348	0.356
	Rog 2005*	Sativex vs. Placebo	-0.498	-0.992	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.321	-1.162	0.520	0.454
	Blake 2006	CBM vs. Placebo	-0.638	-1.167	-0.109	0.018
	Numnikko 2007*	Sativex vs. Placebo	-0.593	-0.989	-0.197	0.003
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.858	-1.573	-0.142	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.411	-0.742	-0.080	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.085	-0.514	0.343	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.059	-0.487	0.369	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.468	-0.919	-0.018	0.042
	Sekeanjah 2010*	Sativex vs. Placebo	0.458	-0.280	1.196	0.224
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.239	-0.642	0.163	0.244
	Johnson 2010b*	THC 2.5mg/CBD 2.5mg vs. Placebo	-0.503	-0.904	-0.103	0.014
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.256	-2.097	-0.414	0.003
	Langford 2013a	THC 2.5mg/CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg/CBD 2.5mg vs. Placebo	-0.861	-1.501	-0.221	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.132	-1.878	-0.385	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.286	-3.176	-1.395	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.079	-4.103	-2.055	0.000
Fixed			-0.436	-0.527	-0.344	0.000
Random			-0.579	-0.762	-0.397	0.000

Statistics for each study

Std diff in means and 95% CI

-10.00 -5.00 0.00 5.00 10.00

Favours Cannabis Favours Placebo

x* = Parallel design.

Effect sizes remained **significant** after excluding active-controlled studies.

Psychotropics and neuropathic pain 1

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Systematic Review

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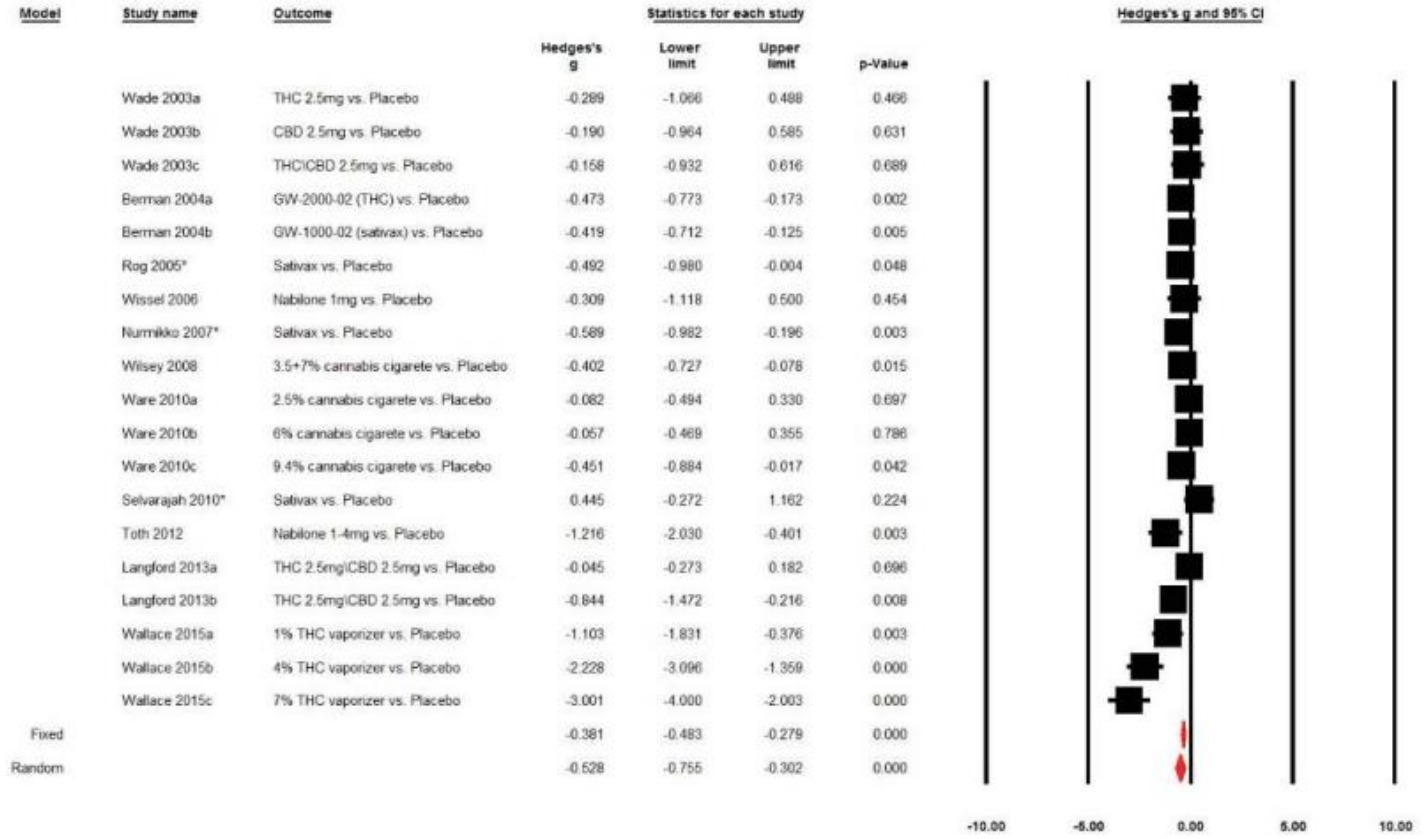
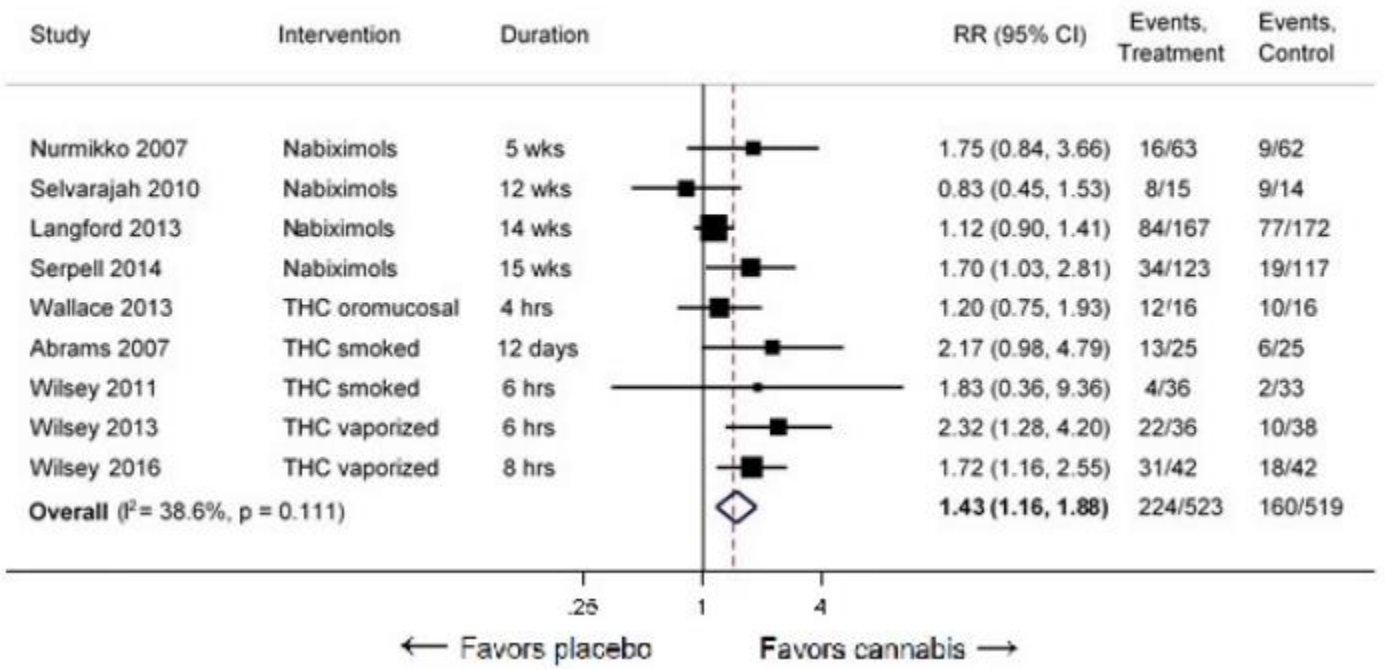


Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Wade 2003a	THC 2.5mg vs. Placebo	-0.289	-1.066	0.488	0.466
	Wade 2003b	CBD 2.5mg vs. Placebo	-0.190	-0.964	0.585	0.631
	Wade 2003c	THC\CBD 2.5mg vs. Placebo	-0.158	-0.932	0.616	0.689
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.473	-0.773	-0.173	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.419	-0.712	-0.125	0.005
	Rog 2005*	Sativax vs. Placebo	-0.492	-0.980	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.309	-1.118	0.500	0.454
	Nurmikko 2007*	Sativax vs. Placebo	-0.589	-0.982	-0.196	0.003
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.402	-0.727	-0.078	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.082	-0.494	0.330	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.057	-0.469	0.355	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.451	-0.884	-0.017	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.445	-0.272	1.162	0.224
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.216	-2.030	-0.401	0.003
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.381	-0.483	-0.279	0.000
Random			-0.528	-0.755	-0.302	0.000

11 RCTs were included. Pooled effect sizes were found **favorable** towards CBMs *over* placebo. However, in this analysis, all of the studies yielded results in the same direction, but there was a statistical heterogeneity in evidence (I2=75.70%, P <0.0001).

Psychotropics and neuropathic pain 2

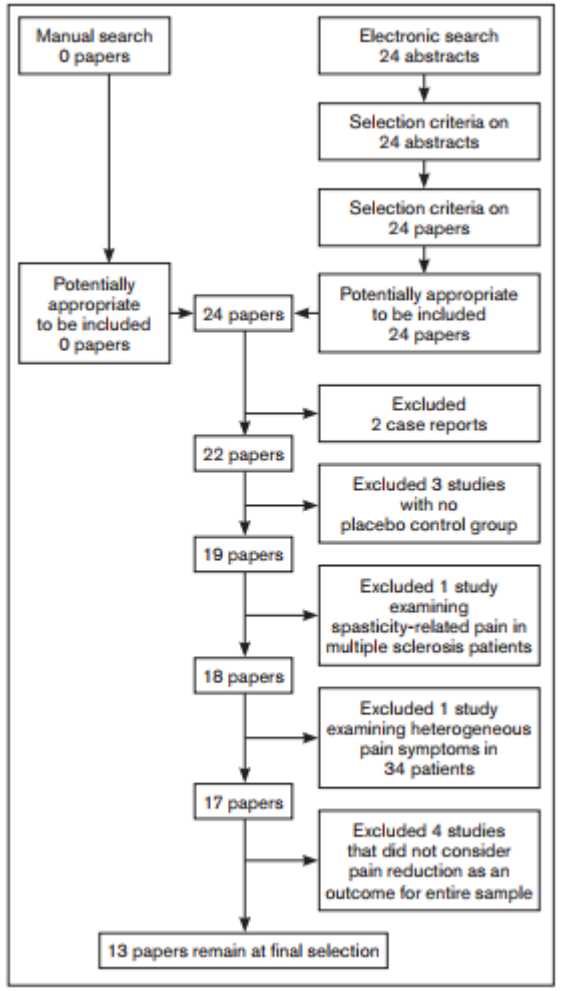
Figure 2. Odds of achieving ≥ 30% pain reduction with cannabis compared to placebo in trials of patients with neuropathic pain



Low-strength evidence was found that cannabis preparations have the potential to improve neuropathic pain but insufficient evidence in other patient populations. Most studies are small, many have methodologic flaws, and the long-term effects are unclear given the brief follow-up duration of most studies. The applicability of these findings to current practice may be low in part because the formulations studied may not be reflective of what most patients are using, and because the consistency and accuracy of labeled content in dispensaries are uncertain.

Psychotropics and neuropathic pain 3

The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review



Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.

Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments

Psychotropics and cancer-pain

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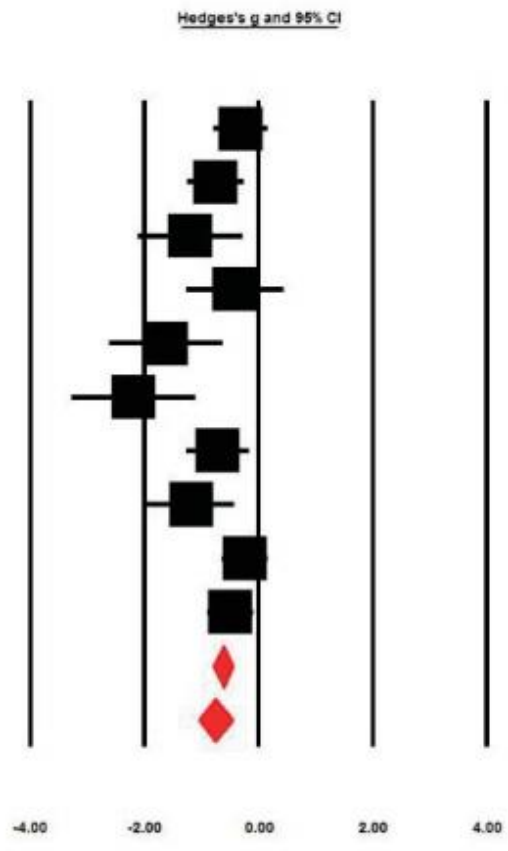
Systematic Review

Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

J. Aviram, RN, PhC[1] and G. Samuelly-Leichtag, PT, PhC[2]

Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Noyes 1975aI	THC10mg vs. Placebo	-0.316	-0.789	0.157	0.190
	Noyes 1975aII	THC 20mg vs. Placebo	-0.753	-1.240	-0.266	0.002
	Noyes 1975bI	THC 5mg vs. Placebo	-1.202	-2.120	-0.283	0.010
	Noyes 1975bII	THC 10mg vs. Placebo	-0.418	-1.267	0.432	0.335
	Noyes 1975bIII	THC 15mg vs. Placebo	-1.622	-2.600	-0.643	0.001
	Noyes 1975bIV	THC 20mg vs. Placebo	-2.196	-3.276	-1.115	0.000
	Staquet 1978a	NIB 4mg vs. Placebo	-0.716	-1.254	-0.177	0.009
	Staquet 1978b	NIB 4mg vs. Placebo	-1.183	-1.941	-0.425	0.002
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.237	-0.636	0.162	0.244
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.499	-0.897	-0.102	0.014
Fixed			-0.625	-0.805	-0.445	0.000
Random			-0.761	-1.063	-0.459	0.000



*= Parallel design

3 RCTs were included. Pooled effect sizes were found **favorable** towards CBMs *over* placebo. In this analysis, all of the studies yielded results in the same direction, but a statistical heterogeneity was in evidence (I2=59.0%, P <0.01).

Psychotropics and chronic non cancer-pain 1

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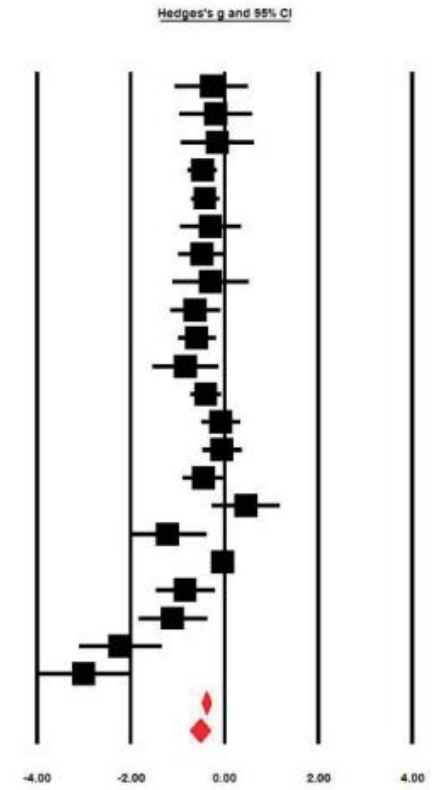
	Langford 2013b	THC 2.5mg/CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.397	-0.495	-0.299	0.000
Random			-0.531	-0.735	-0.327	0.000



*= Parallel design

14 RCTs were included. Pooled effect sizes were found **favorable** towards CBMs *over* placebo. However, in this analysis, all of the studies yielded results in the same direction, but there was a statistical heterogeneity in evidence (I2=72.56%, P <0.0001).

Psychotropics and chronic non cancer-pain 2

Journal of Neuroimmune Pharmacology
June 2015, Volume 10, Issue 2, pp 293–301 | Cite as

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

Authors | Authors and affiliations

M. E. Lynch, Mark A. Ware

An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes.
Eleven trials published since our last review met inclusion criteria.
The quality of the trials was **excellent**.
Seven of the trials demonstrated a significant analgesic effect.
Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity).
Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated.
This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

Psychotropics and chronic pain


Pain Physician 2017; 20:E755-E796 • ISSN 2150-1149

Systematic Review

Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

J. Aviram, RN, PhC[1] and G. Samuelly-Leichtag, PT, PhC[2]

- The results of 43 RCTs (a total of 2,437 patients) were included in this review, of which **24 RCTs (a total of 1,334 patients)** were eligible for meta-analysis.
- This analysis showed **limited** evidence showing more pain reduction in chronic pain -0.61 (-0.78 to -0.43, P <0.0001), especially by inhalation -0.93 (-1.51 to -0.35, P=0.001) compared to placebo.
- Moreover, even though this review consisted of some RCTs that showed a clinically significant improvement with a decrease of pain scores of 2 points or more, 30% or 50% or more, **the majority of the studies did not show an effect**.
- Consequently, although the primary analysis showed that the results were favorable to CBMs over placebo, **the clinical significance of these findings is uncertain**.
- The most prominent AEs were related to the central nervous and the gastrointestinal systems.

Psychotropics and acute post-operative pain

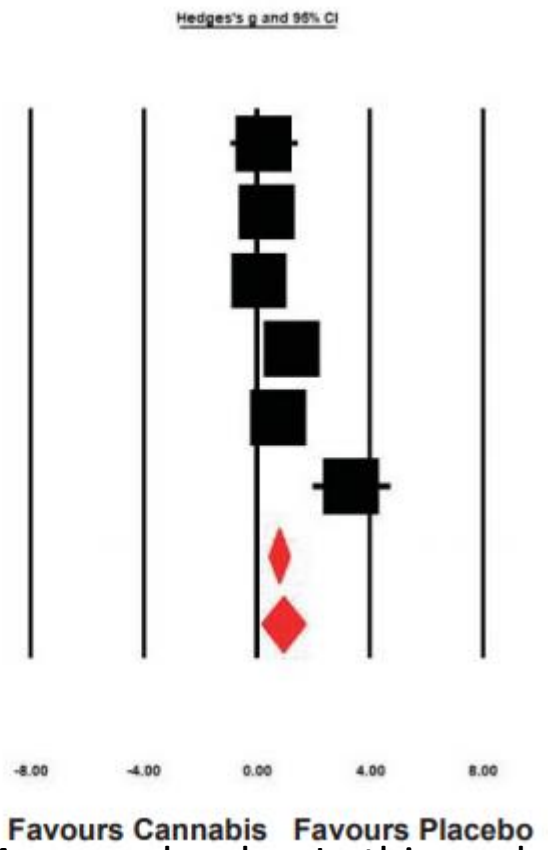
Pain Physician 2017; 20:E755-E796 • ISSN 2150-1149

Systematic Review

Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

J. Aviram, RN, PhC[1] and G. Samuelly-Leichtag, PT, PhC[2]

Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Buggy 2003a	THC 5mg vs. Placebo	0.246	-0.928	1.421	0.681
	Buggy 2003b	THC 5mg vs. Placebo, 2h	0.362	-0.366	1.089	0.330
	Buggy 2003c	THC 5mg vs. Placebo, 4h	0.067	-0.888	1.022	0.890
	Beaulieu 2006a	Nabilone 1mg vs. Placebo, movement	1.234	0.331	2.137	0.007
	Beaulieu 2006b	Nabilone 1mg vs. Placebo, rest	0.768	-0.086	1.622	0.078
	Beaulieu 2006c	Nabilone 2mg vs. Placebo, movement	3.343	1.976	4.711	0.000
Fixed			0.773	0.391	1.155	0.000
Random			0.916	0.157	1.675	0.018



3 RCTs were included. Pooled effect sizes were found **favorable** towards CBMs *over* placebo. In this analysis, all of the studies yielded results in the same direction, but there was a statistical homogeneity in evidence ($I^2=72.99\%$, $P<0.05$).

Psychotropics and pain (overall)

Papers

Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review

BMJ 2001 ; 323 doi: https://doi.org/10.1136/bmj.323.7303.13 (Published 07 July 2001)
Cite this as: *BMJ* 2001;323:13

- Of the 9 included trials (222 patients), 5 trials related to cancer pain, 2 to chronic non-malignant pain, and 2 to acute postoperative pain. No randomised controlled trials evaluated cannabis; all tested active substances were cannabinoids. Oral delta-9-tetrahydrocannabinol (THC) 5-20 mg, an oral synthetic nitrogen analogue of THC 1 mg, and intramuscular levonantradol 1.5-3 mg were about as effective as codeine 50-120 mg, and oral benzopyranoperidine 2-4 mg was less effective than codeine 60-120 mg and no better than placebo. Adverse effects, most often psychotropic, were common.
- Cannabinoids are **no more effective** than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.

Psychotropics and neuro-psychiatric disorders

A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications

Samuel T. Wilkinson, MD; Rajiv Radhakrishnan, MD; and Deepak Cyril D'Souza, MD

J Clin Psychiatry 2016;77(8):1050–1064
10.4088/JCP.15r10036

- **No** RCTs have thus far examined the efficacy of marijuana for Tourette's disorder, post-traumatic stress disorder (PTSD), or Alzheimer's disease.
- **Lower-quality** studies examined the efficacy of marijuana, Δ^9-tetrahydrocannabinol, and nabilone.
- The strength of evidence for the use of cannabinoids for these conditions is **very low** at the present time.

Psychotropics and multiple sclerosis 1

Multiple Sclerosis
http://msj.sagepub.com/

Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis

Derick T Wade, Christine Collin, Colin Stott and Paul Duncombe

Mult Scler 2010 16: 707
DOI: 10.1177/1352458510367462

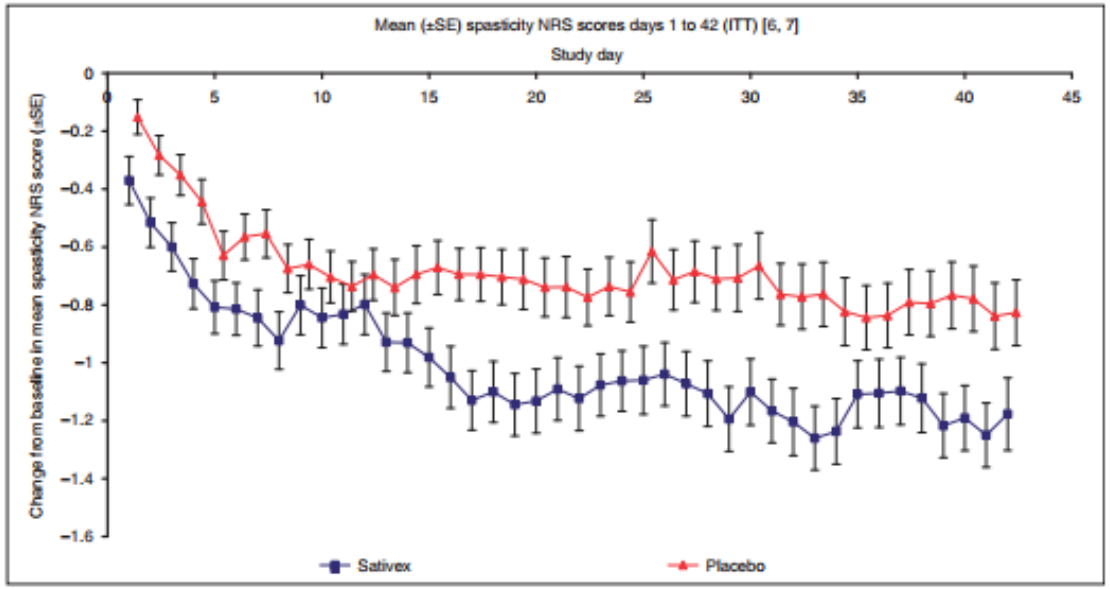


Figure 1. Change from baseline in spasticity over time.

Study	N (%) with ≥30% reduction in spasticity: Nabiximols	Placebo	Odds ratio	95% confidence interval	p-value
Analysis at study endpoint[a]					
Study 1[4]	31/70 (44%)	21/63 (33%)	1.59	0.79, 3.22	
Study 2[6]	48/120 (40%)	14/64 (22%)	2.38	1.19, 4.78	
Study 3[7]	51/166 (31%)	42/169 (25%)	1.34	0.83, 2.17	
Pooled analysis	**130/356 (37%)**	**77/296 (26%)**	**1.62[c]**	**1.15, 2.28***	**0.0073**
Analysis at week 6[b]					
Study 1[4]	31/70 (44%)	21/63 (33%)	1.59	0.79, 3.22	
Study 2[6]	48/120 (40%)	14/64 (22%)	2.38	1.19, 4.78	
Study 3[7]	44/166 (27%)	38/169 (22%)	1.24	0.76, 2.05	
Pooled analysis	**123/356 (35%)**	**73/296 (25%)**	**1.57#**	**1.11, 2.23***	**0.014**

[a]Intention-to-treat population; Timepoints: week 6 for Study 1 and Study 2 and weeks 13–14 for Study 3.
[b]Intention-to-treat population; Timepoints: week 6 for all three studies.
[c]Adjusted for study.

Sativex appears effective in counteracting spasticity in multiple sclerosis patients.

Psychotropics and multiple sclerosis 2

BMC Neurology

BioMed Central

Research article

Open Access

Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review

Shaheen E Lakhan* and Marie Rowland

Address: Global Neuroscience Initiative Foundation, Los Angeles, CA, USA

Email: Shaheen E Lakhan* - slakhan@gnif.org; Marie Rowland - mrowland@gnif.org

* Corresponding author

Six studies were systematically reviewed for treatment dosage and duration, objective and subjective measures of spasticity, and reports of adverse events.

Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted.

Adverse events were reported in each study, however combined TCH and CBD extracts were generally considered to be well-tolerated.

We found evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms. Although some objective measures of spasticity noted improvement trends, there were **no** changes found to be significant in post-treatment assessments.

However, subjective assessment of symptom relief did often show significant improvement posttreatment.

Differences in assessment measures, reports of adverse events, and dosage levels were found.

Psychotropics and multiple sclerosis 3

Complementary Therapies in Medicine 34 (2017) 176–185

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Cannabinoids for spasticity due to multiple sclerosis or paraplegia: A systematic review and meta-analysis of randomized clinical trials

Victoria P. da Rovare[a], Gabriel P.A. Magalhães[a], Guilherme D.A. Jardini[a], Matheus L. Beraldo[a], Mariel O. Gameiro[a], Arnav Agarwal[b,c], Gustavo José Luvizutto[d], Lucas Paula-Ramos[e,*], Samira Esteves Afonso Camargo[e], Luciane Dias de Oliveira[e], Rodrigo Bazan[d], Regina El Dib[e,f,g]

[a] São Paulo State University (Unesp), Botucatu Medical School, São Paulo, Brazil
[b] Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada
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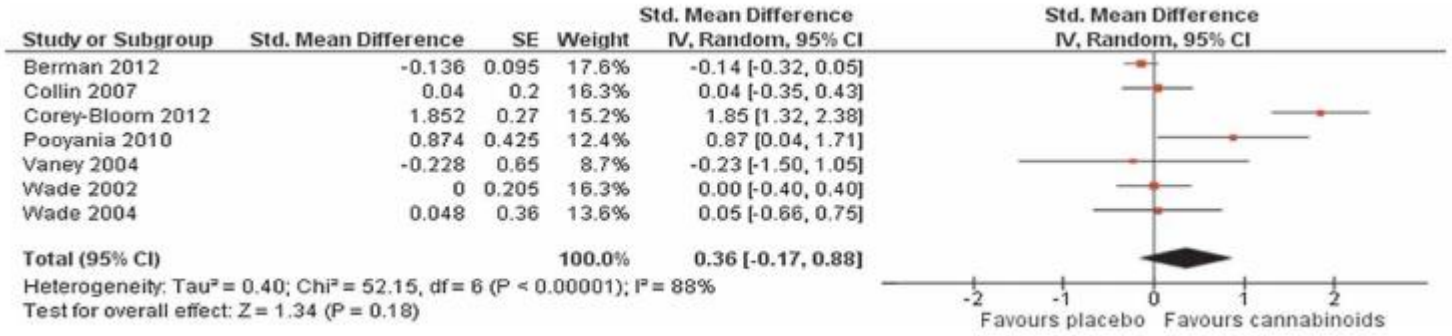
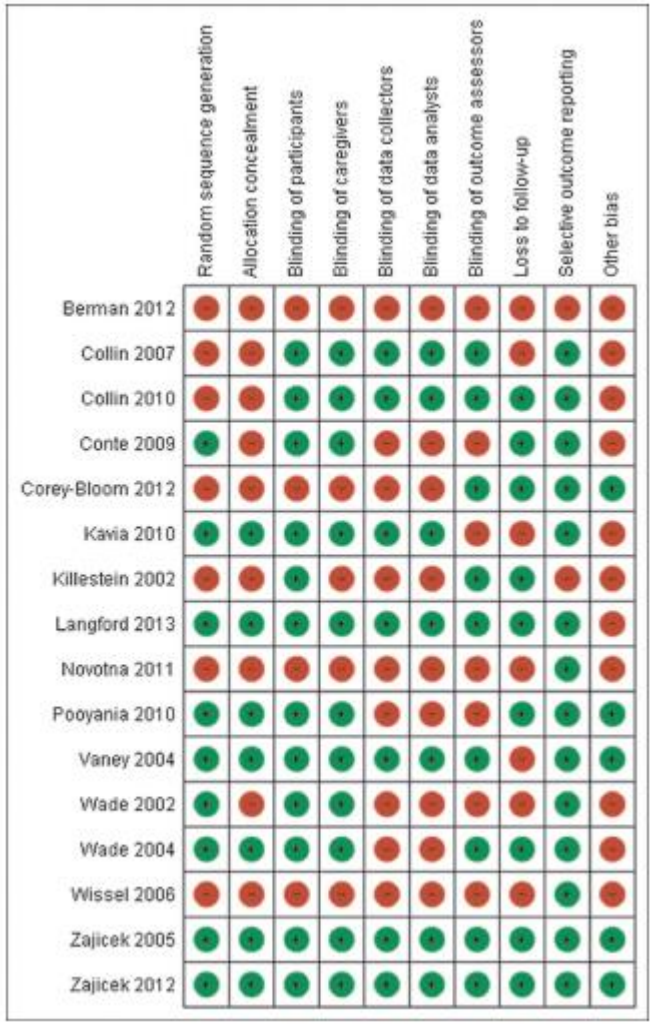
[d] São Paulo State University (Unesp), Department of Neurology, Botucatu Medical School, Brazil
[e] São Paulo State University (Unesp), Department of Biosciences and Oral Diagnosis, Institute of Science and Technology, São Paulo, Brazil
[f] São Paulo State University (Unesp), Department of Anesthesiology, São Paulo, Brazil
[g] McMaster Institute of Urology, McMaster University, St. Joseph's Healthcare, Hamilton, Canada





16 trials including 2597 patients were eligible. Moderate-certainty evidence suggested a non-statistically significant decrease in spasticity (standardized mean difference (SMD) 0.36 [confidential interval (CI) 95% -0.17 to 0.88; p=0.18; I2=88%]), and spasm frequency (SMD 0.04 [CI 95% -0.15 to 0.22]). There was an increase in adverse events such as dizziness (risk ratio (RR) 3.45 [CI 95% 2.71-4.4; p=0.20; I2=23%]), somnolence (RR 2.9 [CI 95% 1.98-4.23; p=0.77; I2=0%]), and nausea (RR 2.25 [CI 95% 1.62-3.13; p=0.83; I2=0%]).

Psychotropics and multiple sclerosis 4

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0300-7995
doi:10.1185/030079906X158066

REVIEW

Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain

Michael Iskedjian[a,b], Basil Bereza[a], Allan Gordon[c], Charles Piwko[a] and Thomas R. Einarson[a,d]

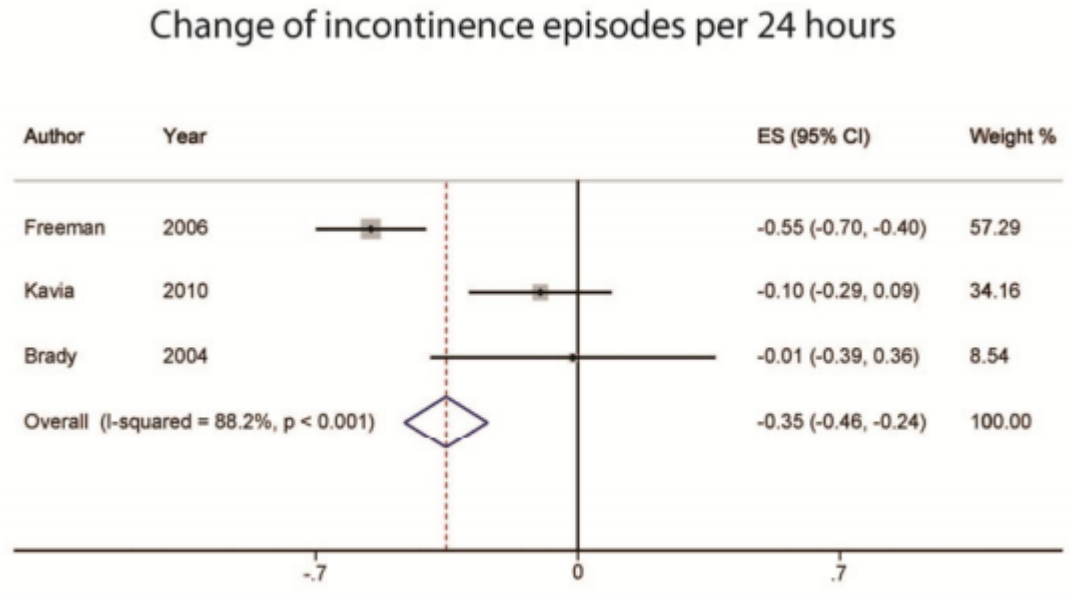
[a] *PharmIdeas Research & Consulting Inc., Oakville, ON, Canada*
[b] *PharmIdeas USA Inc., Charlotte, NC, USA*
[c] *The Wasser Pain Management Centre, Mount Sinai Hospital, Toronto, ON, Canada*
[d] *Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada*

Drug	Trials	Patients	Difference from baseline*	SE	*p*
Cannabidiol/THC buccal spray	6	196	1.7	0.7	0.018
Cannabidiol	5	41	1.5	0.7	0.044
Dronabinol	3	91	1.5	0.6	0.013
All cannabinoids	14	328	1.6	0.4	< 0.001
Placebo	10	250	0.8	0.4	0.023

*Scores recorded on an 11-point scale, with 0 being no pain and 10 being the worst imaginable

6 studies and one RCT-report involved 298 patients (222 treated, 76 placebo); four examined Sativex (a cannabidiol/delta-9-tetrahydrocannabinol (THC) buccal spray) (observations = 196), five cannabidiol (n = 41), and three dronabinol (n = 91). Homogeneity chi(2) values were non-significant, allowing data combination. Analyses focused on baseline-endpoint score differences.
Dizziness was the most commonly observed adverse event in the cannabidiol/THC buccal spray arms (39 +/- 16%), across all cannabinoid treatments (32.5 +/- 16%) as well as in the placebo arms (10 +/- 4%).

Psychotropics and multiple sclerosis 5



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Review

Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: a systematic review and meta-analysis

Nadim Abo Youssef, Marc P. Schneider, Livio Mordasini, Benjamin V. Ineichen, Lucas M. Bachmann, Emmanuel Chartier-Kastler, Jalesh N. Panicker, Thomas M. Kessler

First published: 23 February 2017 Full publication history

DOI: 10.1111/bju.13759 View/save citation

Cannabinoids relevantly decreased the number of incontinence episodes in all three studies. Pooling data showed the mean difference in incontinence episodes per 24 h to be -0.35 (95% confidence interval -0.46 to -0.24). Mild adverse events were frequent (38-100%), but only two patients (0.7%) reported a serious adverse event.

Preliminary data imply that cannabinoids might be an effective and safe treatment option for NLUTD in patients with MS; however, the evidence base is **poor** and more high-quality, well-designed and adequately powered and sampled studies are urgently needed to reach definitive conclusions.

Psychotropics and Tourette's syndrome

Cochrane Database of Systematic Reviews

Cannabinoids for Tourette's Syndrome

Review | Intervention

Adrienne Curtis, Carl E Clarke, Hugh E Rickards

First published: 7 October 2009

Editorial Group: Cochrane Movement Disorders Group

DOI: 10.1002/14651858.CD006565.pub2 View/save citation

Muller-Vahl 2002

Methods	Single centre, double blind, placebo controlled, single dose, crossover trial , Duration 2 single treatment days separated by a 4 week washout phase	
Participants	12 adult patients, 11 male 1 female.Mean age 34 years (Range 18-66 years)Exclusion criteriaUnder 18, history of psychosis and schizophrenia, significant concomitant illness, or pregnant	
Interventions	THC 5.0 or 7.5 or 10.0 mg vs. placebo	
Outcomes	1.Tic severity patient rated using Tourette's Syndrome Symptom list TSSL.2. Tic examiner rated using Shapiro Tourette's Syndrome Severity Scale STSS, Yale Global Tic Severity Scale YGTSS, and Tourette Syndrome Global Scale TSGS, 3. Patients also rated severity of impulse control; Obsessive Compulsive Behaviours OCB, subdivided into obsessions and compulsions such as checking ordering doing things "just right", counting, rituals, washing and doing things an exact number of times;anxiety;depression;Attention Deficit Hyperctivity Disorder ADHD; and Premonitory experiences PE, prior to tics before and after treatment;Patient rated global change and Adverse reactions	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Muller-Vahl 2003/1

Methods	Single centre, double blind, placebo controlled, parallel group 6 week study	
Participants	24 adult patients 19 male 5 female. Mean age 33	
Interventions	THC titrated to target dose10mg/day	
Outcomes	Tic severity using Tourette syndrome Clinical Global Impressions scale; the Shapiro Tourette-syndrome Severity Scale; the Yale Global Tic Severity Scale; a video protocol for assessment of tic intensity and frequency; and a patient self rating scale the Tourette Syndrome Symptom List	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Only **two** trials were found that met the inclusion criteria. Both compared a cannabinoid, delta-9-Tetrahydrocannabinol (Delta(9)THC), either as monotherapy or as adjuvant therapy, with placebo. **Not enough** evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.

Pyschotropics and rheumatic disorders 1

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.03970.x

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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Keywords
cannabinoids, chronic non-cancer pain, neuropathic pain, systematic review

Received
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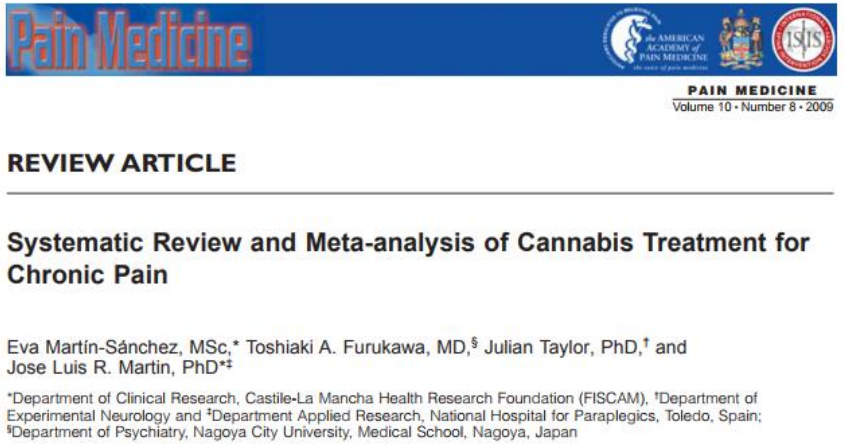
7 March 2011
Accepted Article
23 March 2011

- There is **preliminary** evidence of efficacy in fibromyalgia and rheumatoid arthritis



Pain Medicine

PAIN MEDICINE
Volume 10 • Number 8 • 2009

REVIEW ARTICLE

Systematic Review and Meta-analysis of Cannabis Treatment for Chronic Pain

Eva Martín-Sánchez, MSc,* Toshiaki A. Furukawa, MD,§ Julian Taylor, PhD,† and Jose Luis R. Martin, PhD*‡

*Department of Clinical Research, Castile-La Mancha Health Research Foundation (FISCAM), †Department of Experimental Neurology and ‡Department Applied Research, National Hospital for Paraplegics, Toledo, Spain; §Department of Psychiatry, Nagoya City University, Medical School, Nagoya, Japan

- Efficacy/effectiveness seems to be **moderate**, in part counteracted by potential adverse effects

Pyschotropics and rheumatic disorders 2

Cochrane Database of Systematic Reviews

Cannabinoids for fibromyalgia

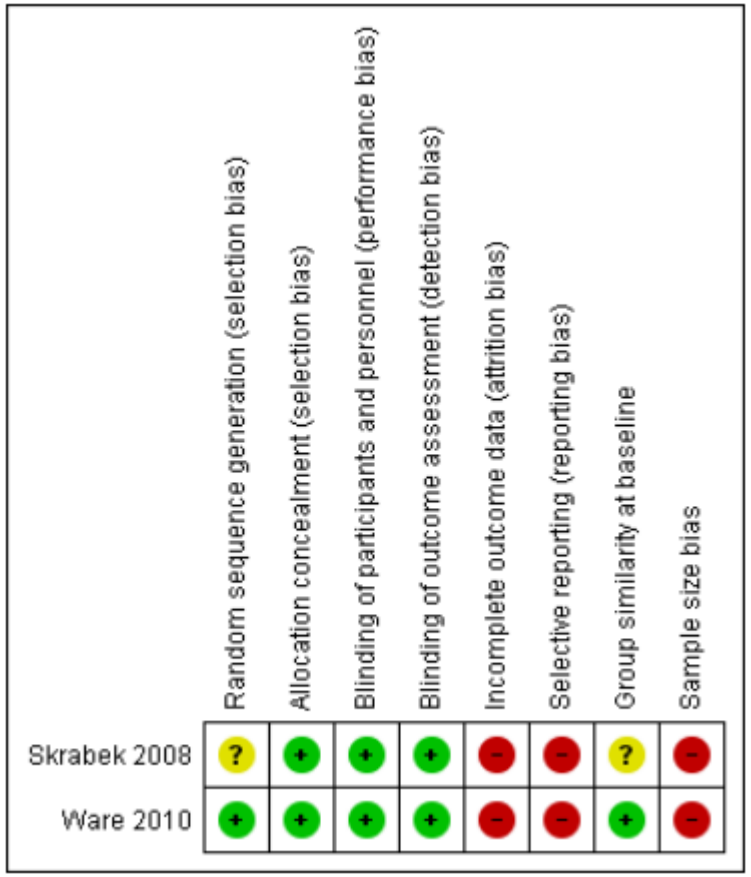
Review | Intervention

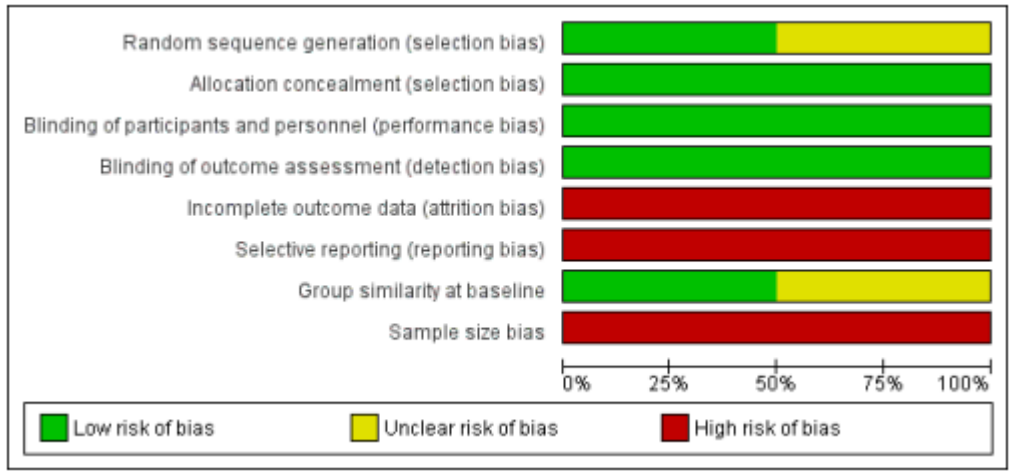
Brian Walitt, Petra Klose, Mary-Ann Fitzcharles, Tudor Phillips, Winfried Häuser

First published: 18 July 2016

Editorial Group: Cochrane Pain, Palliative and Supportive Care Group

DOI: 10.1002/14651858.CD011694.pub2 View/save citation





2 studies were included. We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia.

Pyschotropics and rheumatic disorders 3

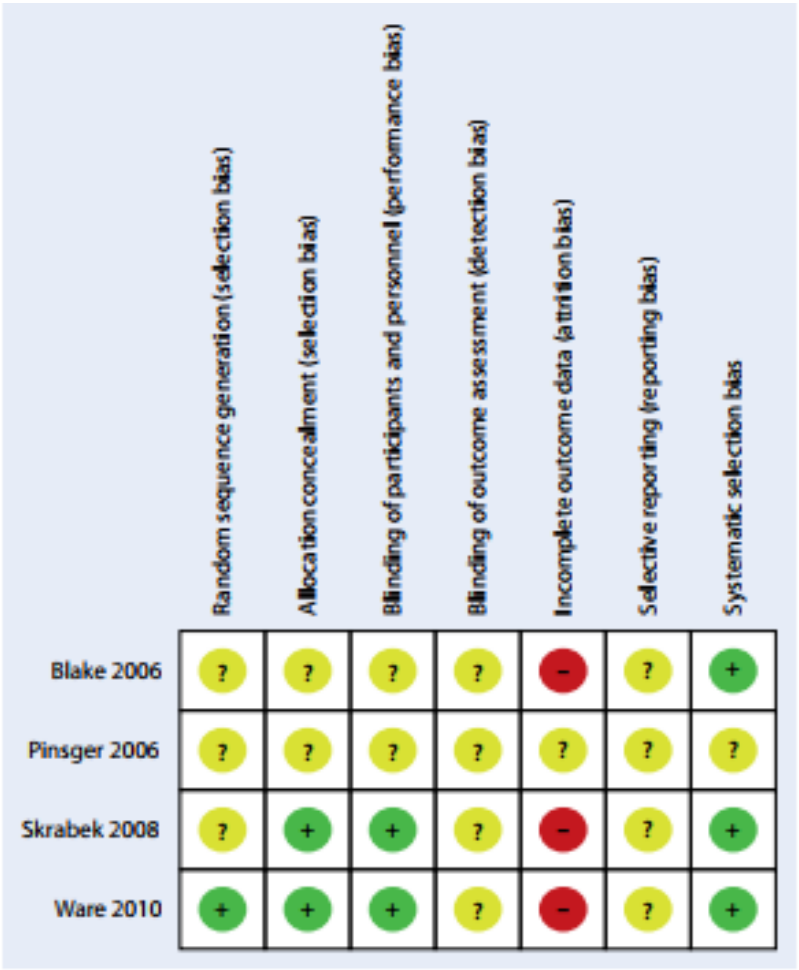
Der Schmerz
February 2016, Volume 30, Issue 1, pp 47–61 | Cite as

Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis)

A systematic review of randomized controlled trials

Authors | Authors and affiliations

M.-A. Fitzcharles, C. Baerwald, J. Ablin, W. Häuser



Two RCTs of 2 and 4 weeks duration respectively with nabilone, including 71 FMS patients, one 4-week trial with nabilone, including 30 spinal pain patients, and one 5-week study with tetrahydrocannbinol/cannabidiol, including 58 RA patients were included.

No RCT with OA patients was found. The risk of bias was high for three studies.

The findings of a superiority of cannabinoids over controls (placebo, amitriptyline) were not consistent. Cannabinoids were generally well tolerated despite some troublesome side effects and safe during the study duration.

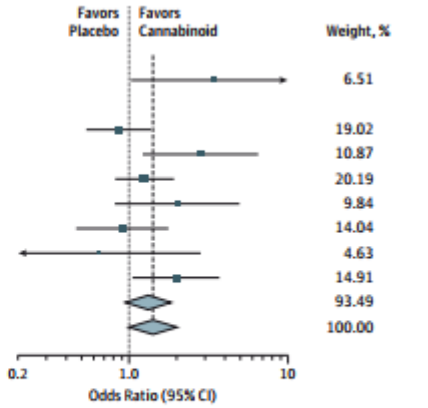
Currently, there is insufficient evidence for recommendation for any cannabinoid preparations for symptom management in patients with chronic pain associated with rheumatic diseases.

Summarizing …

Summarizing … 1

Figure 2. Improvement in Pain

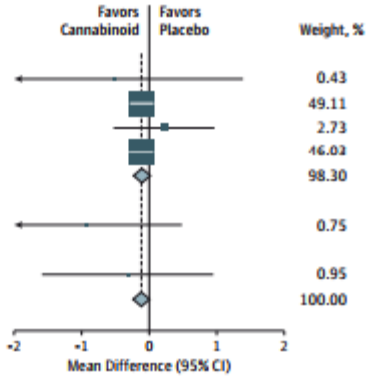
Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)	Weight, %
Tetrahydrocannabinol (smoked)						
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)	6.51
Nabiximols						
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)	19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)	10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)	20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)	9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)	14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)	4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)	14.91
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)	93.49
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)	100.00



Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Figure 3. Change in Ashworth Score for Cannabinoid Compared With Placebo, Stratified According to Cannabinoid

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid No. of Patients	Cannabinoid Mean (SD) Score Change	Placebo No. of Patients	Placebo Mean (SD) Score Change	Mean Difference (95% CI)	Weight, %
Nabiximols						
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)	0.43
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)	49.11
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)	2.73
Berman,[87] 2007	40	-.12 (.42)	44	-.01 (.42)	-0.13 (-0.30 to 0.06)	46.02
Subtotal I^2 = 0.0%, (P = .0.82)	383		337		-0.11 (-0.23 to 0.02)	98.30
Dronabinol						
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)	0.75
Tetrahydrocannabinol/cannabidiol						
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)	0.95
Overall I^2 = 0.0%, (P = .80)	590		544		-0.12 (-0.24 to 0.01)	100.00



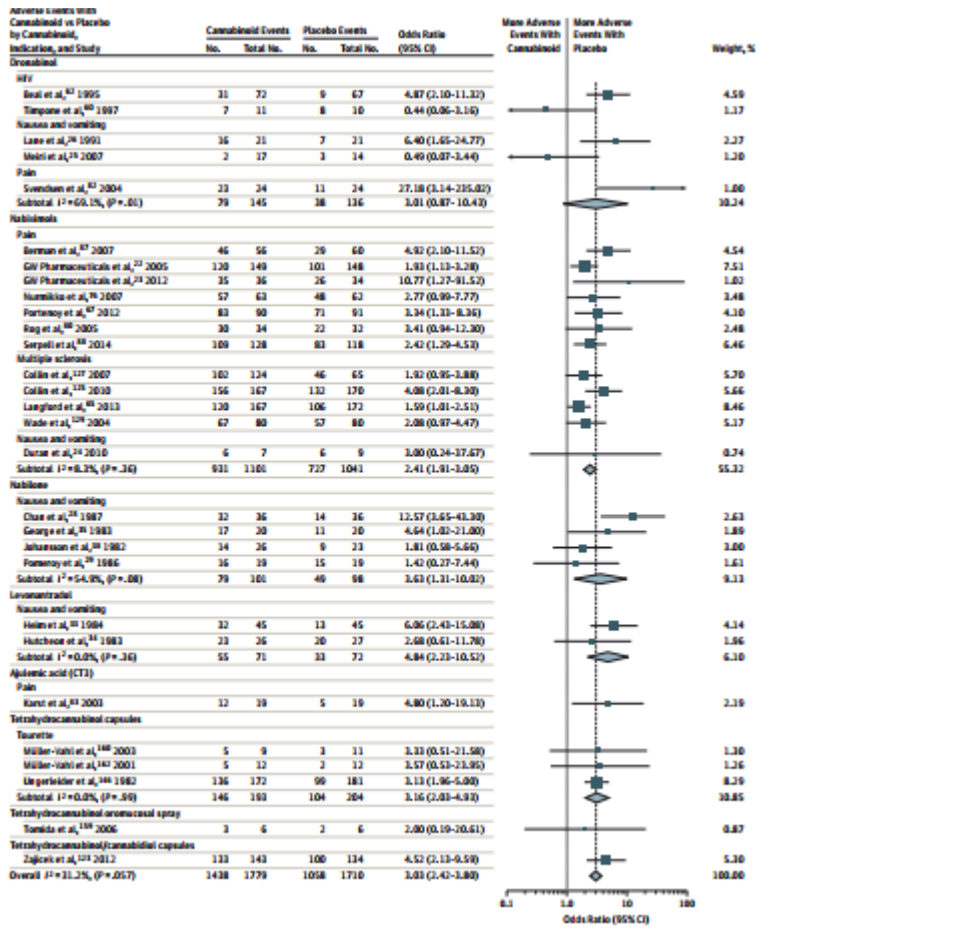
The square data markers indicate mean differences from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal line indicate, 95% CIs. The blue diamond data markers represent the subtotal and overall weighted mean difference and 95% CI. The vertical dashed line shows the summary effect estimate, the solid vertical line shows the line of no effect (mean difference = 0).

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

Figure 4. Odds of Having Any Adverse Event With Cannabinoids Compared With Placebo, Stratified According to Cannabinoid



The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted line shows the line of no effect (OR = 1).

Summarizing … 2

Original Investigation

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

- A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], -0.46 [95% CI, -0.80 to -0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, -0.36 [95% CI, -0.69 to -0.05]; 7 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.
- There was **moderate-quality** evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was **low-quality** evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an **increased** risk of short-term AEs.

Psychotropics and health-related quality of life

Psychotropics and health-related quality of life

Drug and Alcohol Dependence 174 (2017) 80–90

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Review

The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis

Matthew Goldenberg[a], Mark William Reid[a], Waguih William IsHak[a,b,*], Itai Danovitch[a]

[a] Cedars-Sinai Medical Center, Los Angeles, CA, United States
[b] David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

- Results: Twenty studies met our pre-defined selection criteria. Eleven studies were randomized controlled trials (RCTs; 2322 participants); the remaining studies were of cohort and cross-sectional design. Studies of cannabinoids weremostlyRCTs of higher design quality than studies of cannabis, which utilized smaller self-selected samples in observational studies. Although we did not uncover a significant association between cannabis and cannabinoids for medical conditions and HRQoL, some patients who used them to treat pain, multiple sclerosis, and inflammatory bower disorders have reported small improvements in HRQoL, whereas some HIV patients have reported reduced HRQoL.
- Conclusion: The relationship between HRQoL and the use of cannabis or cannabinoids for medical conditions is **inconclusive**. Some patient populations report improvements whereas others report reductions in HRQoL. In order to inform users, practitioners, and policymakers more clearly, future studies should adhere to stricter research quality guidelines and more clearly report patient outcomes.

Psychotropics and harms/adverse effects

Psychotropics and harms/adverse effects 1

Annals of Internal Medicine REVIEW

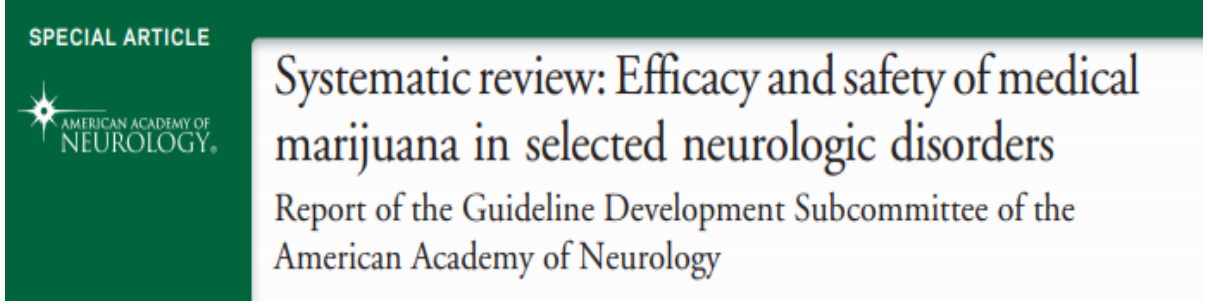
The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms

A Systematic Review

Shannon M. Nugent, PhD; Benjamin J. Morasco, PhD; Maya E. O'Neil, PhD; Michele Freeman, MPH; Allison Low, BA; Karli Kondo, PhD; Camille Elven, MD; Bernadette Zakher, MBBS; Makalapua Motu'apuaka, BA; Robin Paynter, MLIS; and Devan Kansagara, MD, MCR

- According to 11 systematic reviews and 32 primary studies, harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. Although adverse pulmonary effects were not seen in younger populations, evidence on most other long-term physical harms, in heavy or long-term cannabis users, or in older populations is **insufficient**.
- Among general populations, **limited** evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.

Psychotropics and harms/adverse effects 2



- The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of **unknown efficacy** in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy.
- Risk of serious adverse psychopathologic effects was nearly 1%.

Psychotropics and harms/adverse effects 3

CMAJ June 17, 2008 vol. 178 no. 13 doi: 10.1503/cmaj.071178

Research

Adverse effects of medical cannabinoids: a systematic review

Tongtong Wang MSc, Jean-Paul Collet PhD MD, Stan Shapiro PhD, Mark A. Ware MBBS MSc

In the **23** randomized controlled trials, the median duration of cannabinoid exposure was 2 weeks (range 8 hours to 12 months).

A total of 4779 adverse events were reported among participants assigned to the intervention. Most (4615 [96.6%]) were not serious.

Of the 164 serious adverse events, the most common was relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]) and urinary tract infection (15 events [9.1%]). The rate of nonserious adverse events was higher among participants assigned to medical cannabinoids than among controls (rate ratio [RR] 1.86, 95% confidence interval [CI] 1.57-2.21); the rates of serious adverse events did not differ significantly between these 2 groups (RR 1.04, 95% CI 0.78-1.39). Dizziness was the most commonly reported nonserious adverse event (714 events [15.5%]) among people exposed to cannabinoids.

Short-term use of existing medical cannabinoids appeared to increase the risk of nonserious adverse events. The risks associated with long-term use were poorly characterized in published clinical trials and observational studies. High-quality trials of long-term exposure are required to further characterize safety issues related to the use of medical cannabinoids.

Conclusions and take-home-message

- Concerning the studied outcomes (efficacy/effectiveness, impact on health-related quality of life and harms/adverse events), extant evidence is **scarce/insufficient** and of **low** quality
- Further high-quality studies (investigating in particular long-term effects) in the field are warranted