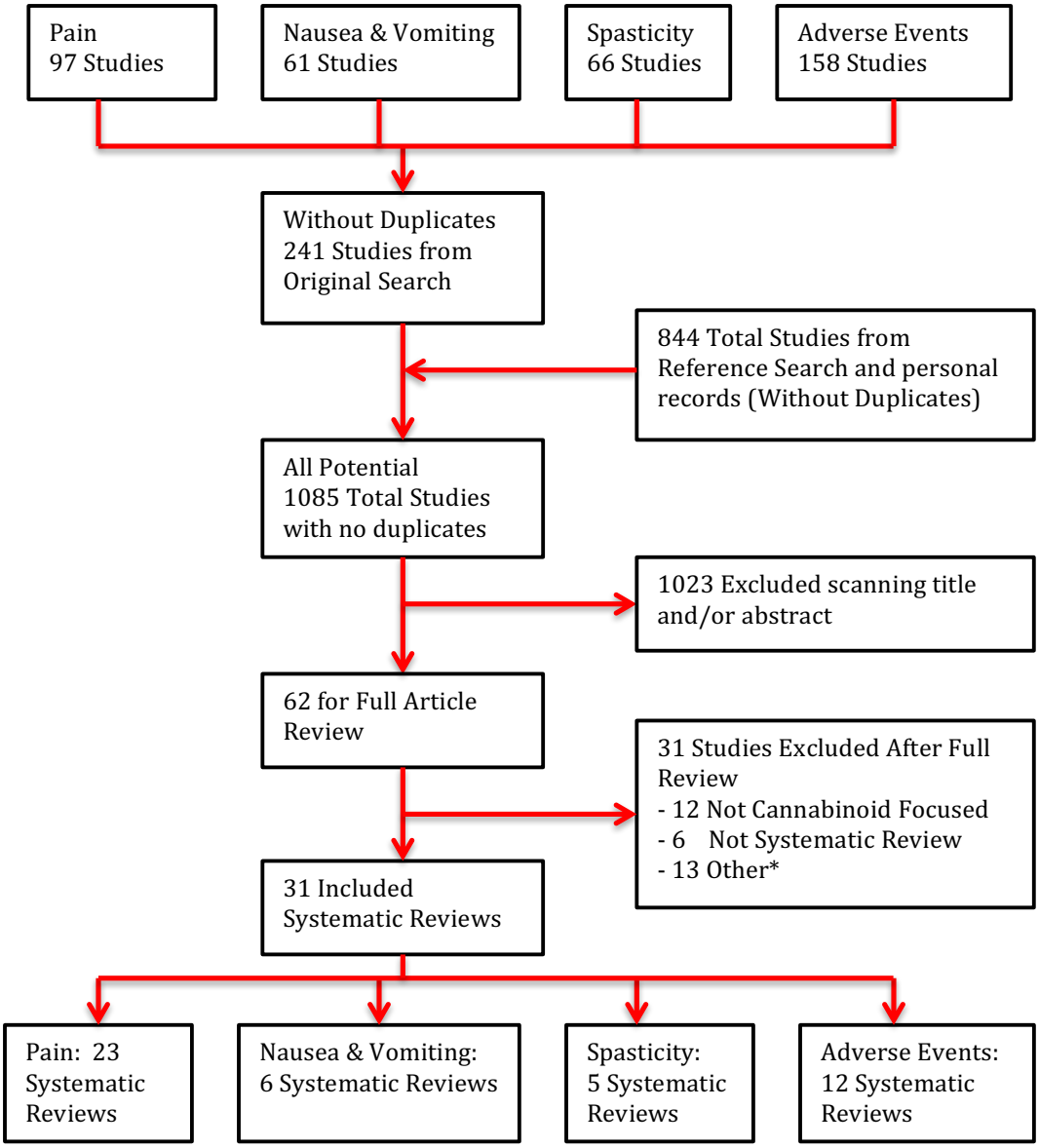
Systematic Review of Systematic Reviews on Medical Cannabinoids for Pain, Nausea/Vomiting, Spasticity, and Harms: Appendix

Figure A1. Study Flow



* Other includes 3 systematic reviews of observational studies, 3 available by abstract only, 2 systematic reviews of pediatrics, 2 not on core topics, 2 systematic reviews of systematic reviews and 1 systematic review with only one randomized controlled trial.

Table A2. Studies excluded after full review and reason for exclusion

Excluded Study	Reason for Exclusion
Anonymous. Delta-9-tetrahydrocannabinol + cannabidiol. A reasonable option for some patients with multiple sclerosis. Prescrire Int 2014;23(150):145-8.	Not a systematic review
Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2010;5(12):e14433.	Not cannabinoid focused
Mehta S, McIntyre A, Janzen S, Loh E, Teasell R, Spinal Cord Injury Rehabilitation Evidence Team. Systematic review of pharmacologic treatments of pain after spinal cord injury: an update. Arch Phys Med Rehab 2016;97(8):1381-1391.e1.	Not cannabinoid focused
Baldinger R, Katzberg HD, Weber M. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2012;(4)CD004157.	Not cannabinoid focused
Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technol Asses 2003;7(40):iii, ix-x, 1-111.	Not cannabinoid focused
Benze G, Geyer A, Alt-Epping B, Nauck F. Treatment of nausea and vomiting with 5HT3 receptor antagonists, steroids, antihistamines, anticholinergics, somatostatinantagonists, benzodiazepines and cannabinoids in palliative care patients : A systematic review. Der Schmerz 2012;26(5):481-99.	Not cannabinoid focused
Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. Cannabis in palliative medicine: Improving care and reducing opioid-related morbidity. Am J Hosp Palliat Care 2011;28(5):297-303.	Not a systematic review
Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. Expert Opin Inv Drug 2008;17(1):85-95.	Not a systematic review
Fife TD, Moawad H, Moschonas C, Shepard K, Hammond N. Clinical perspectives on medical marijuana (cannabis) for neurologic disorders. Neurol Clin Pract 2015;5(4):344-351.	Not a systematic review
Goldenberg M, Reid MW, IsHak WW, Danovitch I. The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. Drug Alcohol Depen 2017;174:80-90.	Systematic review included observational studies
Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. Drugs 2013;73(15):1711-22.	Not cannabinoid focused
Keeley PW. Nausea and vomiting in people with cancer and other chronic diseases. BMJ Clin Evid 2009. 2009:pii2406.	Not cannabinoid focused
Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev 2013;(4)CD005175.	One randomized controlled trial in systematic review
McPartland JM, Pruitt PL. Side effects of pharmaceuticals not elicited by comparable herbal medicines: the case of tetrahydrocannabinol and marijuana. Altern Ther Health Med 1999;5(4):57-62.	Systematic review included observational studies
Ng L, Khan F, Young CA, Galea M. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2017;2.1:CD011776.	Not cannabinoid focused
Phillips RS, Gopaul S, Gibson F, Houghton E, Craig JV, Light K, Pizer B. Antiemetic medication for prevention and treatment of chemotherapy	Pediatric focused

induced nausea and vomiting in childhood. Cochrane Database Syst Rev 2010;(9)CD007786.	
Pringsheim T, Doja A, Gorman D, McKinlay D, Day L, Billinghurst L, et al. Canadian guidelines for the evidence-based treatment of tic disorders: Pharmacotherapy. Can J Psychiatry 2012;57(3):133-43.	Not a core topic
Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;1:CD008921.	Not cannabinoid focused
Sanadgol N, Zahedani SS, Sharifzadeh M, Khalseh R, Barbari GR, Abdollahi M. Recent updates in imperative natural compounds for healthy brain and nerve function: A systematic review of implications for multiple sclerosis. Curr Drug Targets 2016; Nov 8 (epub ahead of print).	Not Cannabinoid Focused
Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Desai P, Jalundhwala YJ, et al. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. J Pain Res 2013;6:539-47.	Not cannabinoid focused
Tafelski S, Hauser W, Schafer M. Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting--a systematic review of systematic reviews. Der Schmerz 2016;30(1):14-24.	Systematic review of systematic reviews
Taylor HG. Analysis of the medical use of marijuana and its societal implications. J Am Pharm Assoc 1998;38(2):220-7.	Not a systematic review
van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, Dijkstra D, Mostovaya I, Vissers KC. National Guideline Working Group "Diagnosis treatment of cancer pain". Pharmacological treatment of pain in cancer patients: The role of adjuvant analgesics, a systematic review. Pain Pract 2017;17(3):409-419.	Not cannabinoid focused
van den Elsen GA, Ahmed AI, Lammers M, Kramers C, Verkes RJ, van der Marck MA, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing Res Rev 2014;14:56-64.	Not a core topic
National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017. Available from:https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state.	Systematic review of systematic reviews
Grant I, Gonzalez R, Carey CL, et al. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc 2003;9:679-89.	Systematic review included observational studies
Kung T, Hochman J, Sun Y, et al. Efficacy and safety of cannabinoids for pain in musculoskeletal diseases: A systematic review and meta-analysis. J Rheumatol 2011;38(6):1171.	Abstract only
Landry T, Fitzcharles MA, Ste-Marie PA, Shir Y. Efficacy and safety of cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. Arthritis Rheum 2014; 66(11):S110-S111.	Abstract only
Musty RE, Rossi, R. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. J Cannabis Ther 2001;1(1), 26-56.	Not a systematic review
Parsai S, Herman R, Johnson S. Systematic literature review of randomized controlled trials to evaluate the efficacy of medical marijuana for analgesia. Pharmacotherapy 2014;34(10):e287.	Abstract only
Phillips RS, Gopaul S, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. Cochrane Database Syst Rev 2010;(9):CD007786.	Pediatric focused

Table A3. Risk of bias assessment using a modified AMSTAR criteria.

Study	Dual Selection and Extraction	Comprehensive Literature Search	Characteristics of Included Studies	Quality Assessment of Studies	Pooled Estimates	Conflicts of Interest Stated	Total Score
Andreae 2015[15]	1	1	1	1	1	1	6
Boychuk 2015[32]	1	1	0	1	0	1	4
CADTH 2010a[33]	0	0	1	0	0	0	1
CADTH 2010b[34]	0	0	0	0	0	0	0
CADTH 2011[35]	0	0	1	1	0	0	2
Campbell 2001[36]	1	1	1	1	0	1	5
Cotter 2009[37]	0	1	1	0	0	1	3
Deshpande 2015[38]	1	1	1	1	0	1	5
Fitzcharles 2016a[20]	1	1	1	1	0	1	5
Fitzcharles 2016b[21]	1	1	1	1	0	0	4
Iskedjian 2007[18]	1	1	1	1	1	1	6
Jensen 2015[39]	0	0	0	0	0	1	1
Koppel 2014[31]	0	1	1	1	0	1	4
Lakhan 2009[40]	1	1	1	1	0	1	5
Lobos Urbina 2016[17]	0	0	0	0	0	1	1
Lynch 2015[42]	0	1	1	1	0	1	4
Lynch 2011[41]	0	1	1	1	0	1	4
Machado Rocha 2008[26]	0	1	1	1	1	1	5
Martin-Sanchez 2009[14]	0	1	1	1	1	1	5
Meza 2017[29]	0	0	0	0	0	1	1
Mucke 2016[19]	1	1	1	1	1	1	6
Petzke 2016[16]	1	1	1	1	1	0	5
Smith 2015[25]	1	1	1	1	1	1	6
Stevens 2017[23]	1	1	1	1	0	1	5
Tateo 2017[24]	0	1	1	1	0	0	3
Tramer 2001[27]	1	0	0	0	0	1	2
Tsang 2016[43]	0	1	1	0	0	0	2
Wade DT 2010[28]	0	0	1	0	1	0	2
Walitt 2016[22]	1	1	1	1	0	1	5
Wang T 2008[30]	1	1	1	0	1	1	5
Whiting 2015[2]	1	1	1	1	1	1	6

Table A4. Breakdown of the included meta-analyses and their randomized controlled trials [RCT] incorporated to meta-analyses original to this study.

Area	Outcome	Total RCTs (Total Patients)	Population (Comparator)	Systematic Reviews & Meta-Analyses Contributing	RCTs from the Included Meta-Analyses and Incorporated into this Study's Novel Meta-analyses
Pain	≥30% improvement in pain scores	15 RCTs (1985)	13 RCTs Neuropathic Pain, 2 RCTs Cancer Pain (Versus Placebo)	Andreae 2015[15]	Abrams 2007,* Ellis 2009,* Ware 2010,* Wilsey 2008,* Wilsey 2013*
				Whiting 2015[2]	GW Pharmaceuticals 2005,** Johnson 2010,** Portenoy 2012**
				Petzke 2016[16]	Berman 2004,** Langford 2013,** Lynch 2014,** Nurmikko 2007,** Rog 2005,** Selvarajah 2010,** Serpell 2014**
Nausea/ Vomiting	Complete Response (No Nausea/ Vomiting)	7 RCTs (500)	(Versus Placebo)	Machado Rocha 2008[26]	Frytak 1979,† Orr 1980†
				Smith 2015[25]	Sallan 1975a,† Wada 1982.†
				Whiting 2015[2]	Meiri 2007,† Duran 2010,** Melham-Bertrandt 2014.†
	Complete Response (No Nausea/ Vomiting)	14 RCTs (1022)	(Versus Neuroleptics)	Smith 2015[25]	Frytak 1979,† Herman 1979,† Lane 1991,† McCabe 1988.†
				Machado Rocha 2008[26]	Ahmedzai 1983,† Chan 1987,† Dalzell 1986,† Hutcheon 1983,†† Johansson 1982,† Niederle 1986,† Niiranen 1985,† Orr 1980,† Sallan 1980,† Sheidler 1984.††
Spasticity	Global Impression of Change in Spasticity	4 RCTs (746)	3 RCTs Multiple Sclerosis, 1 RCT paraplegia (Versus Placebo)	Wade 2010[28]	Collin 2010**
				Whiting 2015[2]	Berman 2007,** Collin 2007,** Wade 2004**

* Smoked or inhaled cannabinoid

** Buccal spray (nabiximol) cannabinoid
† Oral (Dronabinol or Nabilone)
†† Intramuscular (Levonantradol)

Figure A5. Funnel plot of randomized controlled trials in responder meta-analysis of pain.

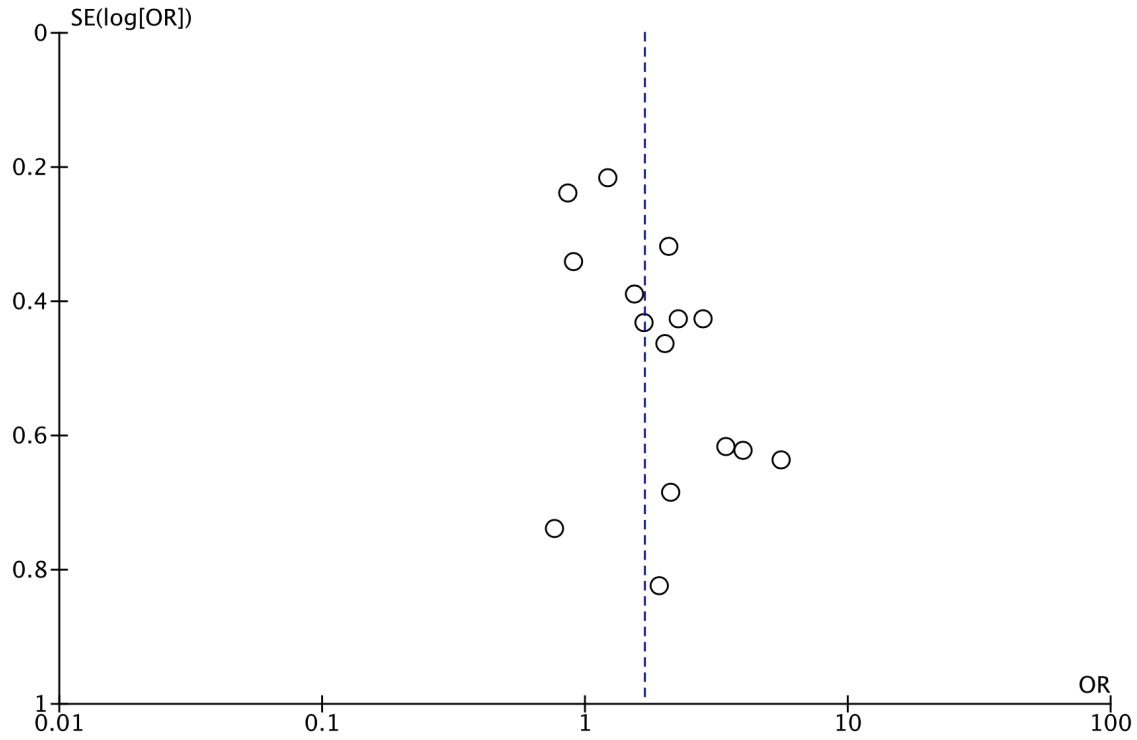
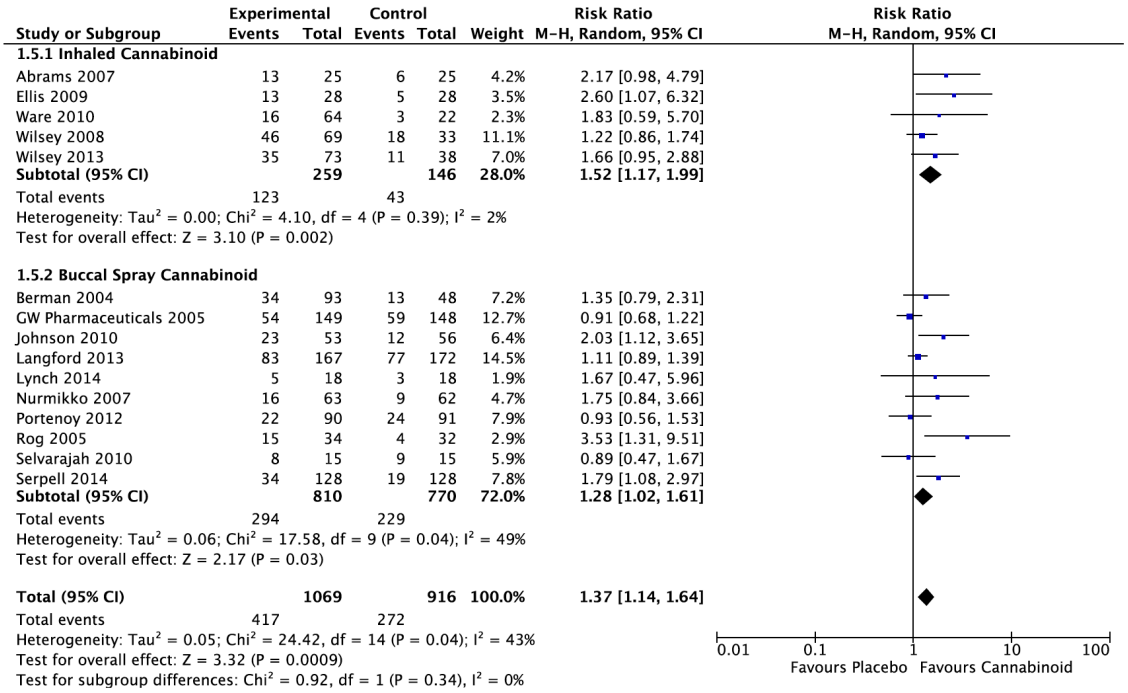
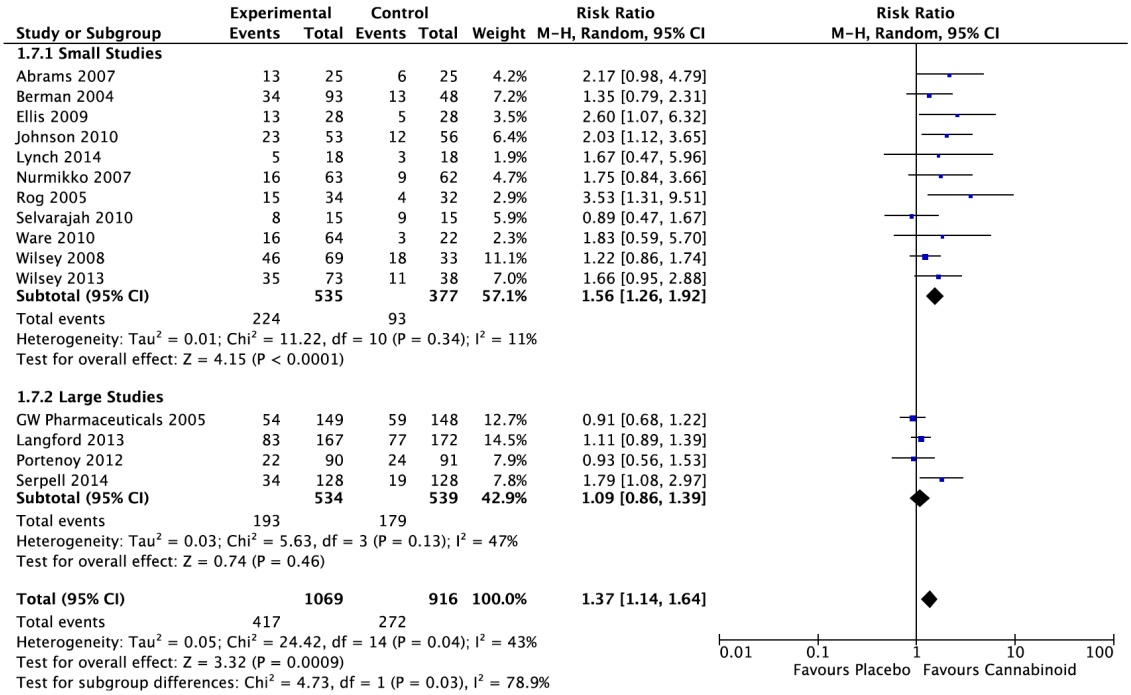


Figure A6. Sensitivity analyses of the responder meta-analyses for ≥30% reduction in pain with medical cannabinoids compared to placebo.
[A6a] Analysis by type of cannabinoid studied (inhaled versus buccal spray)



[A6b] Analysis by size of randomized controlled trials (small trials ≤150 patients, large trials >150 patients)



[A6c] Analysis by duration of randomized controlled trials (<1 week, 2-5 weeks, 9-15 weeks)

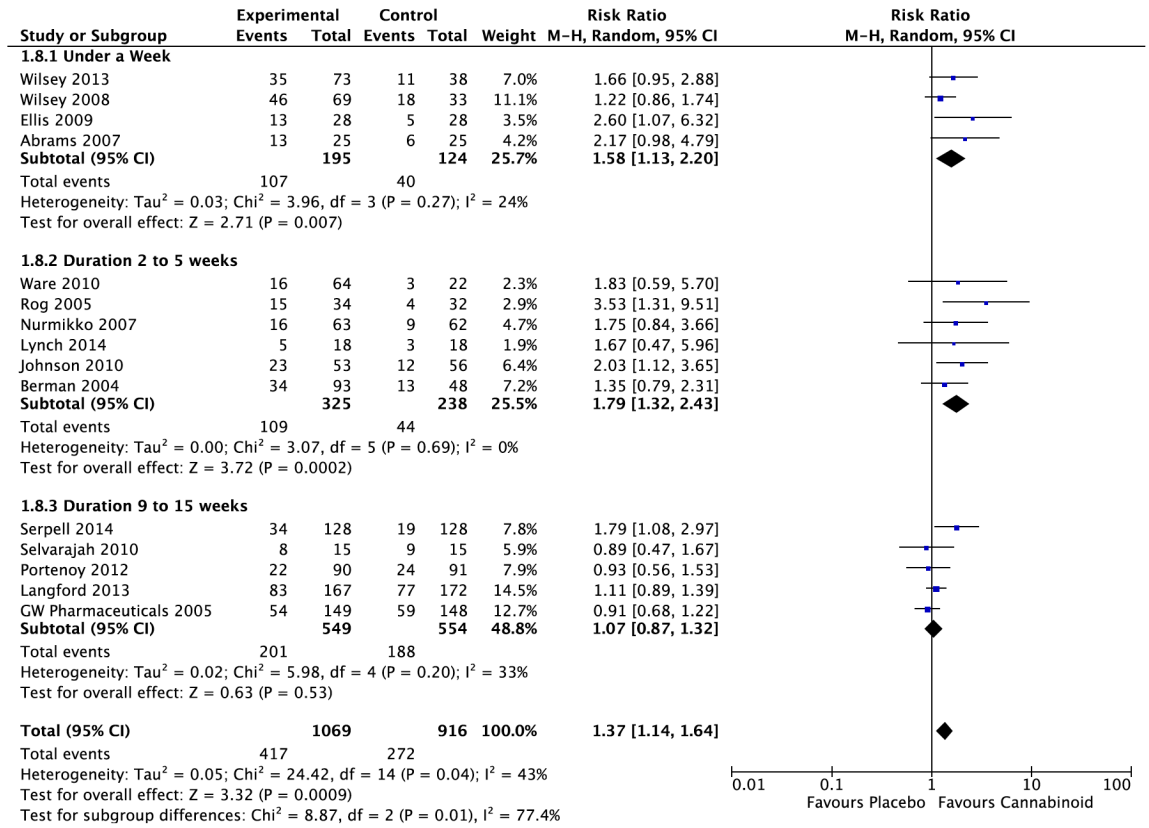


Figure A7. Funnel plot of randomized controlled trials in responder meta-analysis of nausea and vomiting (medical cannabinoids versus neuroleptics).

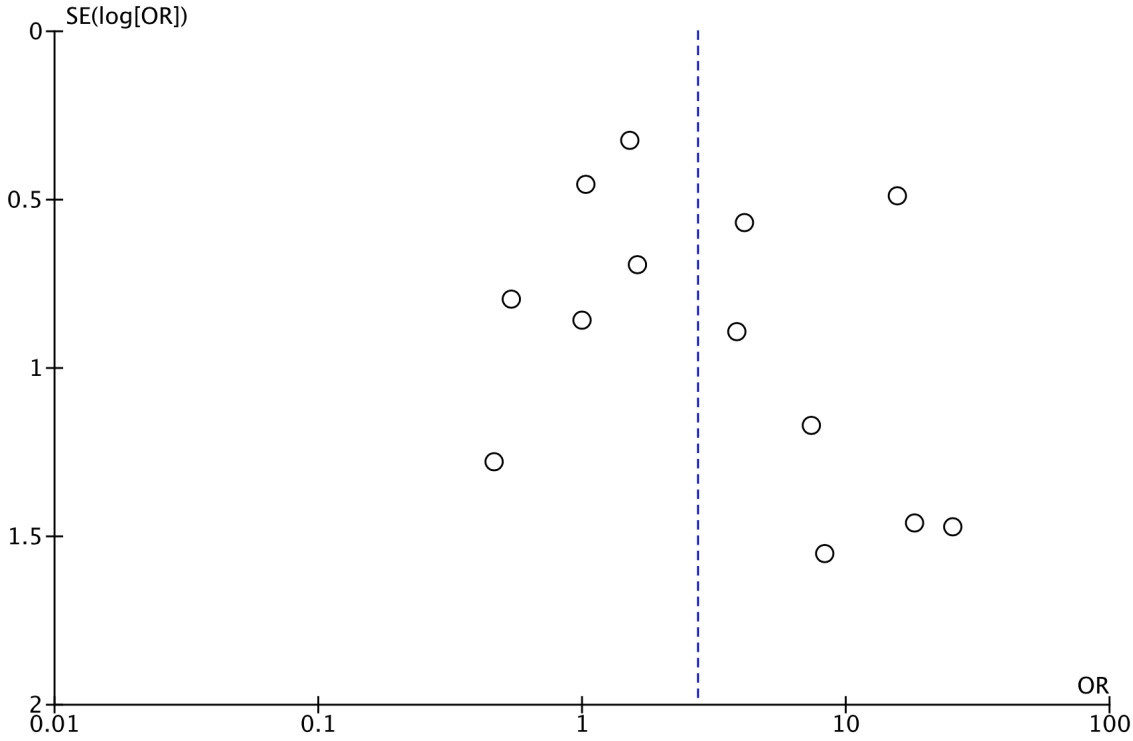
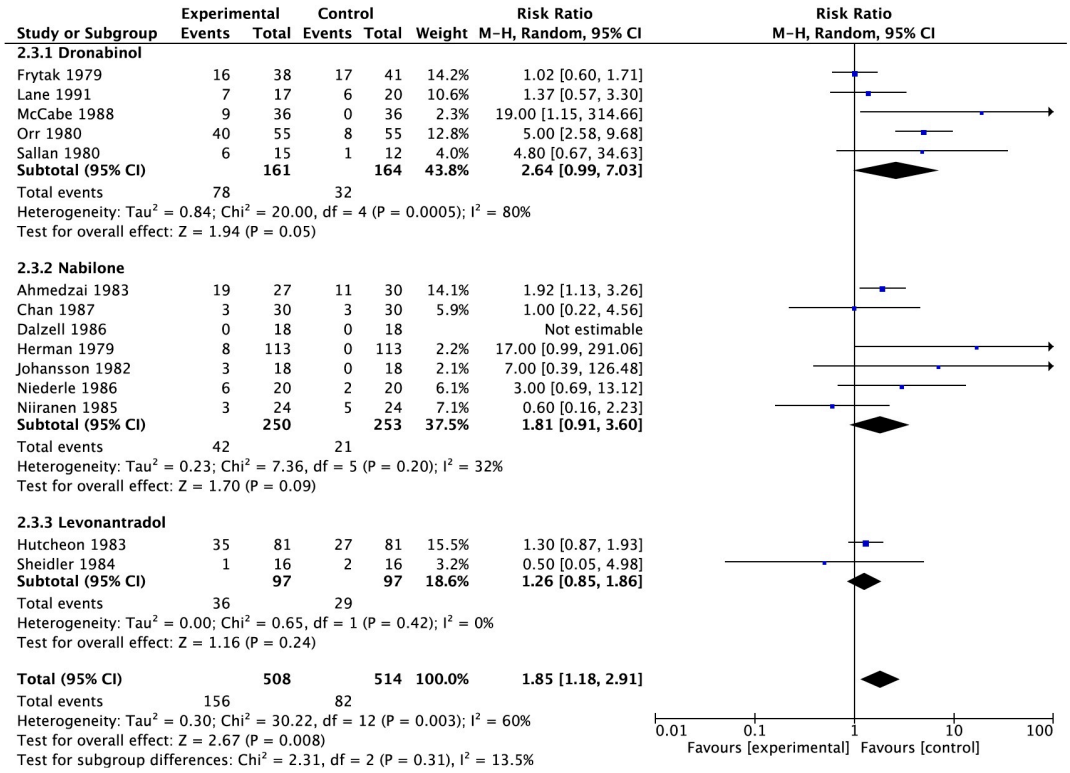


Figure A8. Sensitivity analyses of the responder meta-analyses for control of chemotherapy induced nausea and vomiting for medical cannabinoids compared to other anti-emetic.

[A8a] Analysis by type of cannabinoid studied (dronabinol, nabilone, levonantradol)



[A8b] Analysis by size of randomized controlled trials (small trials ≤50 patients, large trials >50 patients).

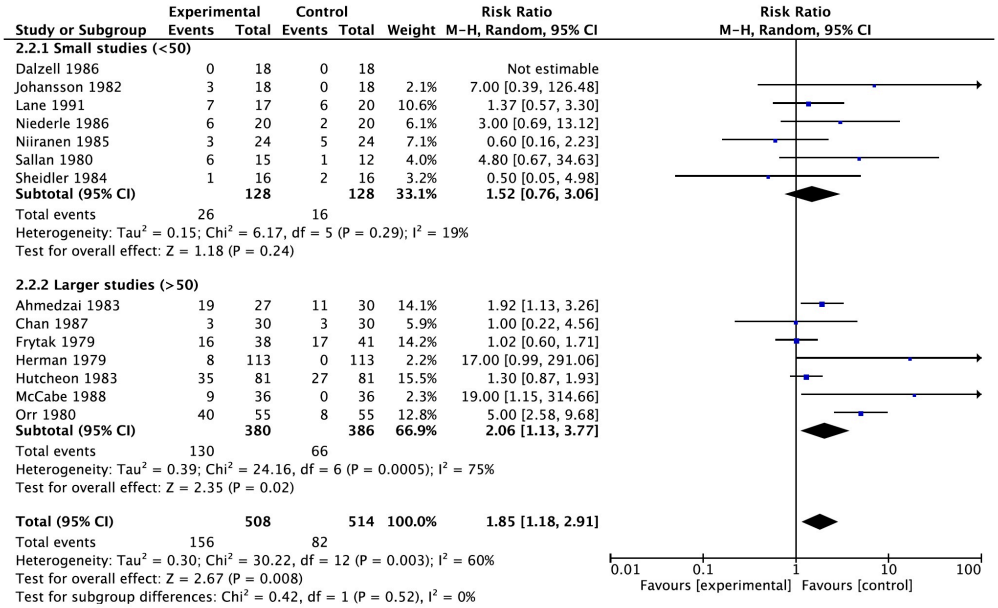


Table A9. Issues in Included Cannabinoid Research Influencing Validity and GRADE Evaluation.

Issue	Area of Concern	GRADE Relevance	Description
Small Studies	RCTs	Risk of Bias	Small studies were common. For example, of the 28 RCTs included in the Whiting[2] chronic pain systematic review, 21 (75%) had less than 100 patients. Smaller studies are underpowered, at risk of spurious results and may be selectively published.
Duration	RCTs	Risk of Bias	Many included studies were short in duration. For example, of the 28 RCTs included in the Whiting[2] chronic pain systematic review, 18 (64%) were four weeks or less and five RCTs (18%) were one day or less. Short studies are inappropriate for chronic conditions as they do not reflect actual practice and will not capture the risk of adverse events. Furthermore, benefits may decrease over time and this would be missed.
Quality of RCTs	RCTs	Risk of Bias	The underlying quality of RCTs was frequently poor. Quality or risk of bias scores for RCTs were provided in 15 of the 23 pain systematic reviews and the median score was 60%. Whiting[2] classified only two of 28 RCTs as low risk of bias.
Inconsistent Reporting	RCTs	Risk of Bias	Within pain studies particularly, outcome reporting varied. Only seven of the 23 systematic reviews felt that included RCTs had enough similarity to permit pooling and a primary contributor was the lack of similarity in outcome reporting. Measurement also varied within RCTs, meaning that some may be assessing present symptoms (example pain) while others may be asking patients to reflect on symptoms over a certain time period (example pain in the last week).
Enrolment	RCTs	Indirectness (often trialed	Previous cannabinoid use was common in some groups. For example, Andreae[15] and Deshpande[38] examined inhaled cannabis

		on previous users)	for pain in five RCTs. Previous cannabis use was required in three, not limited in two and not reported in one. Previous users were more likely to benefit and have reduced risk of adverse events because they had established it seemed to work and had likely avoided most adverse events. For example, Smith[25] found that previous cannabinoid users had significantly better control of nausea and vomiting than cannabinoid naïve patients. Martin-Sanchez[14] reported that naïve users were the ones to report psychosis as an adverse event. Previous users are also at risk for unblinding (see next).
Blinding	RCTs	Risk of Bias	Blinding was rarely examined but when it was, it appears blinding was often unsuccessful. In a cross-over RCT of inhaled cannabis, 57% of could identify what product they were getting over all six phases of the study.[38] In another inhaled cannabis cross-over RCT, over 90% of patients knew when given the active cannabis compared to cannabis cigarettes without THC/CBD.[34] In a study of dronabinol, 95% of patients could identify active treatment over placebo. Surprisingly, even 85% of the nurse observers could determine whether patients were on the active treatment or not. Another study found nabilone users could often tell as well.[27] Cannabinoid studies should be considered unblinded unless authors test for blinding and verify it was maintained.
Co-Analgesia	RCTs	Indirectness (for first or perhaps second line)	In RCTs of pain, cannabinoids are often added to existing analgesia. For example, in both the Whiting[2] and Andreae[15] meta-analyses, all included RCTs allowed patients to continue their existing analgesia. This would imply that cannabinoids are generally studied as second or third line options.
Inconsistent Inclusion	Systematic Reviews	Risk of Bias	Inclusion criteria and study selection varied considerably between the systematic reviews. A systematic review of systematic reviews for cannabinoids for nausea/vomiting

			identified 43 RCTs. However, none of the 43 RCTs was included in every systematic review.[44]
Inconsistent Reporting	Systematic Reviews	Risk of Bias	In regards to pain, most systematic reviews (16 of 23) did not perform meta-analysis but instead present the results descriptively. There was no consistent pattern to how these results were presented. As these types of RCTs may be already at risk for selective reporting, inconsistent reporting within the systematic reviews may only exacerbate this concern.
Inconsistent Results	Systematic Reviews	Inconsistency	Even when authors opted to perform meta-analyses on the same populations for the same outcome (example ≥30% pain reduction), there were frequent differences in which studies were pooled. Additionally, heterogeneity in meta-analyses was common. In two of the four meta-analyses we performed, the I^{2}-statistic was 60%.