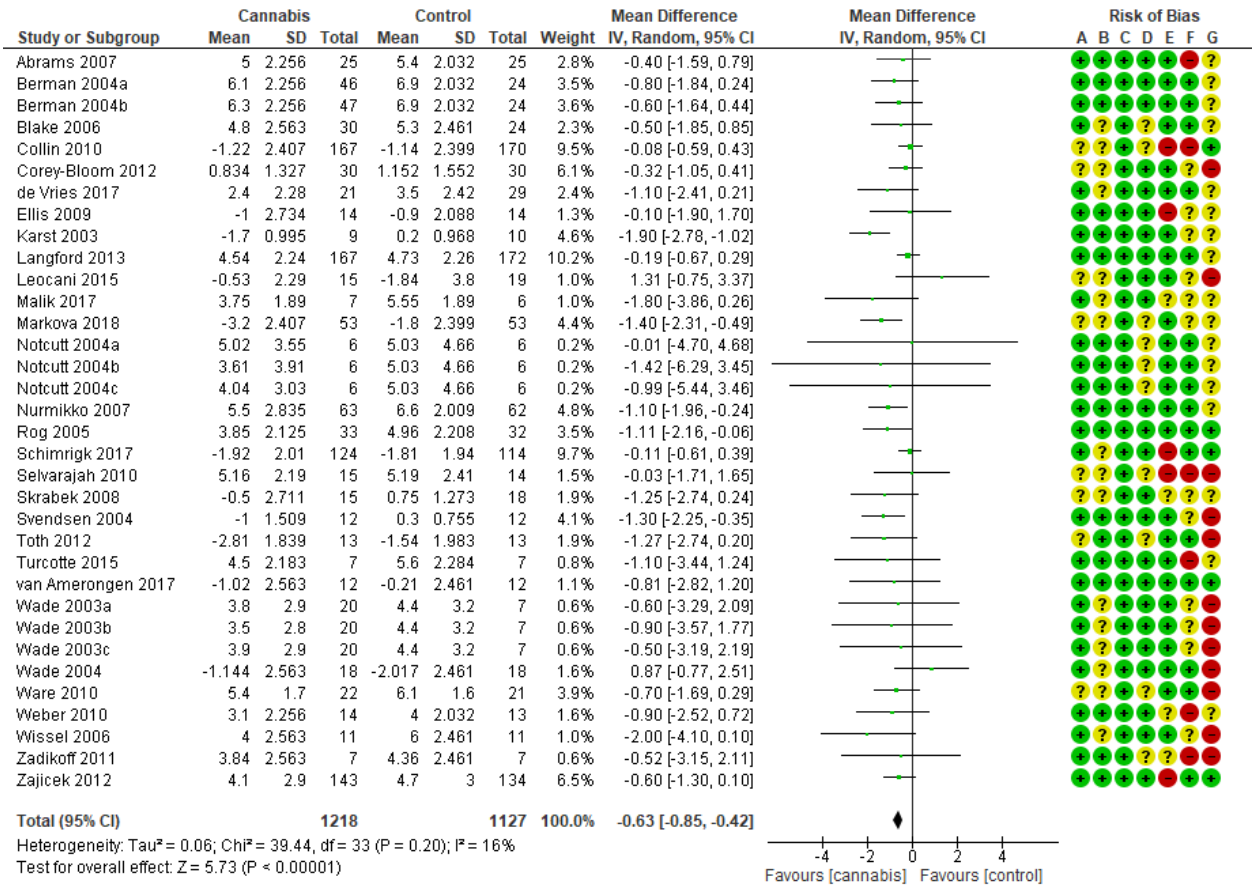


e-Figures 1- 22



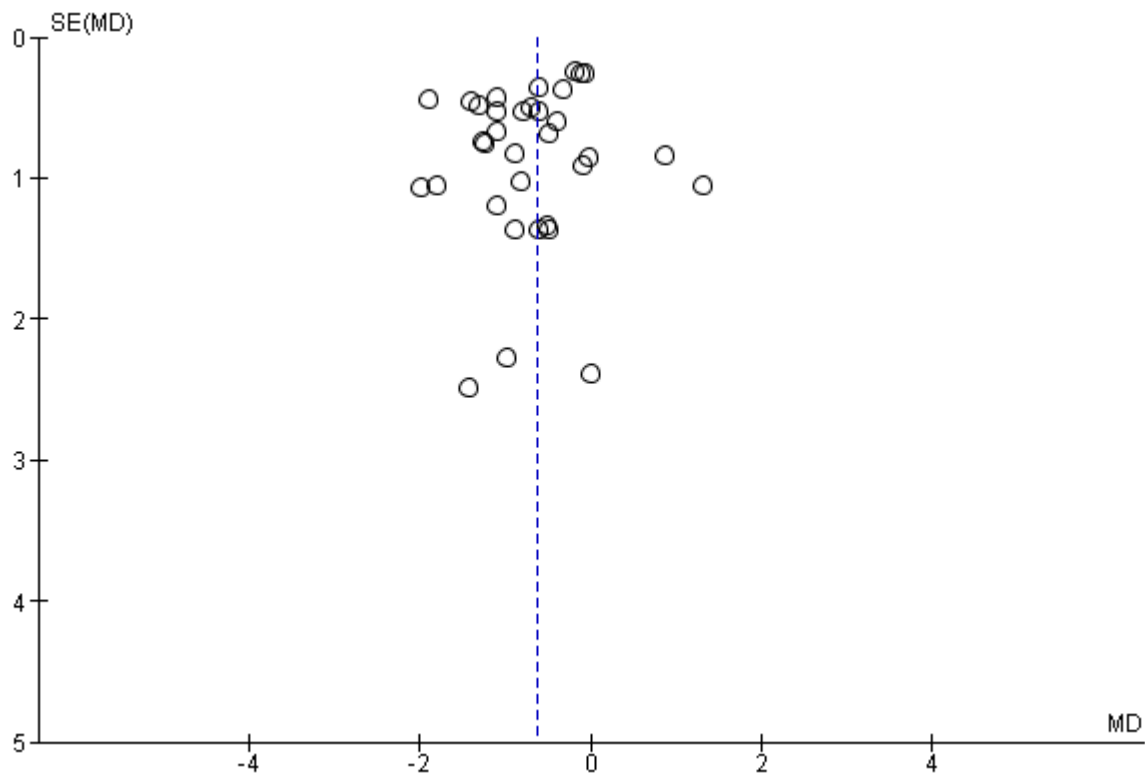
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

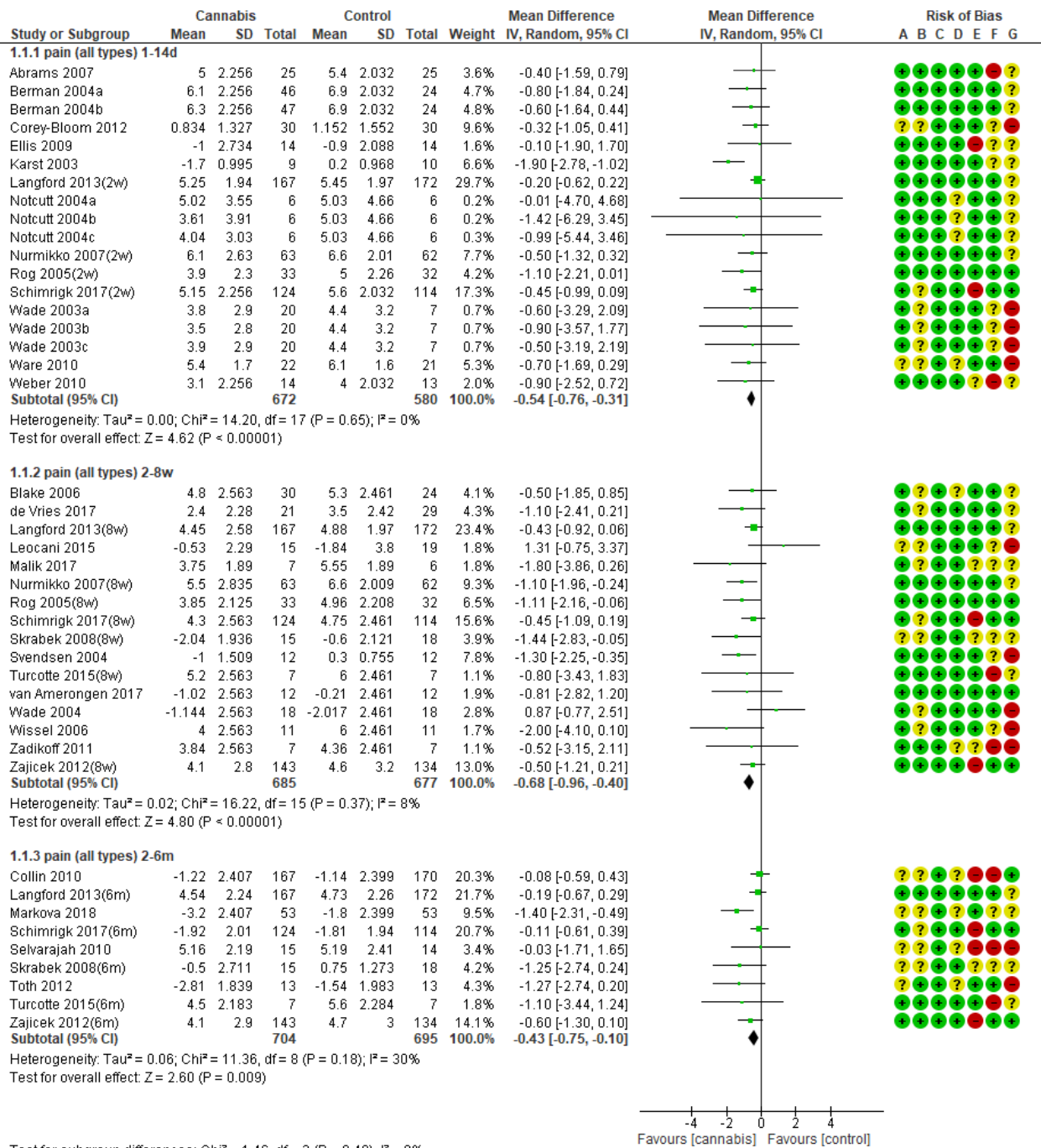
Legend

- Low risk of bias
- High risk of bias
- Unclear risk of bias

e-Figure 1. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain); all included studies at the longest duration of follow-up.



e-Figure 2. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain to assess for publication bias); all included studies at the longest duration of follow-up. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.

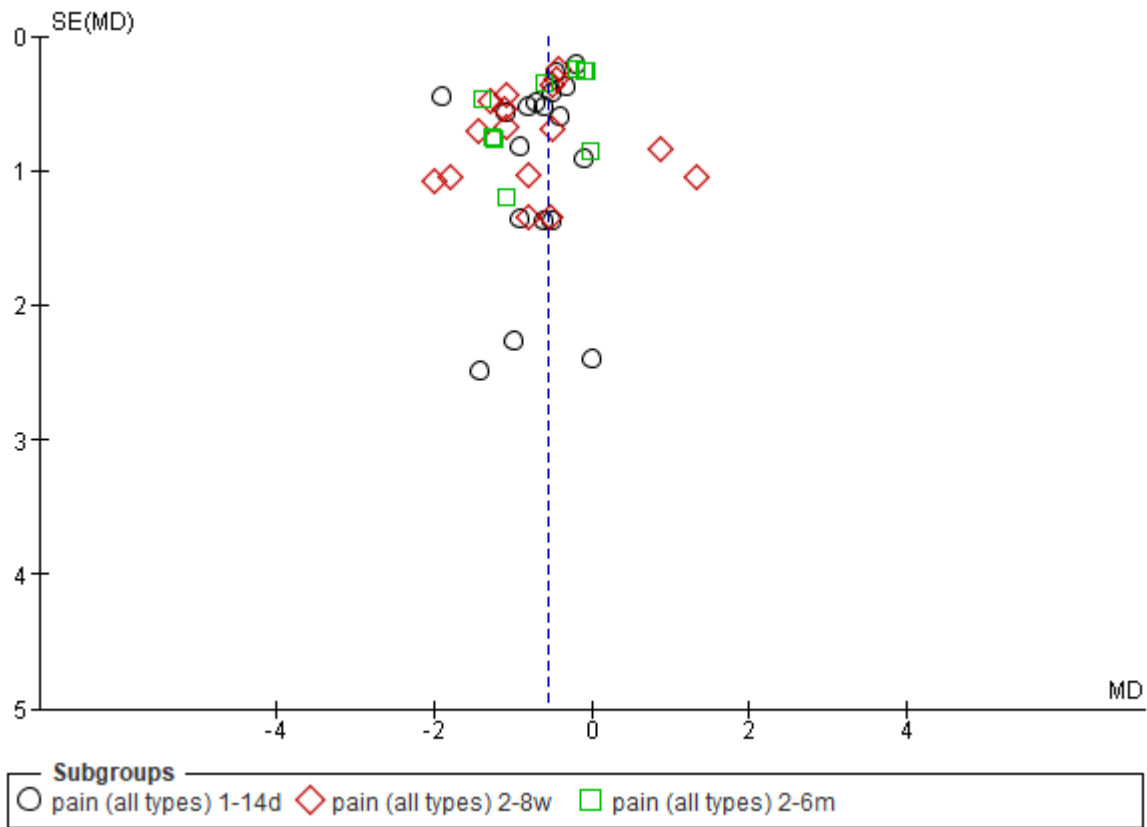


Test for subgroup differences: Chi² = 1.46, df = 2 (P = 0.48), I² = 0%

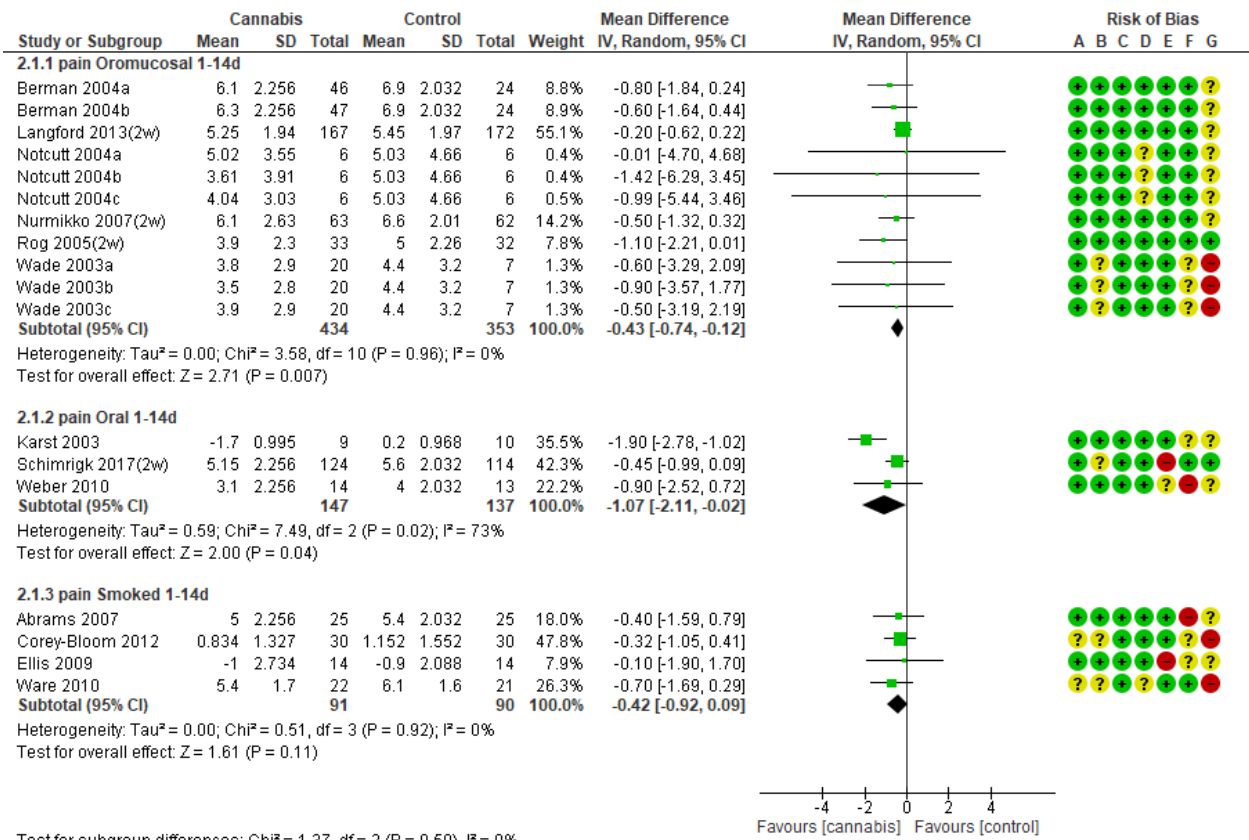
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
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- (F) Selective reporting (reporting bias)
- (G) Other bias

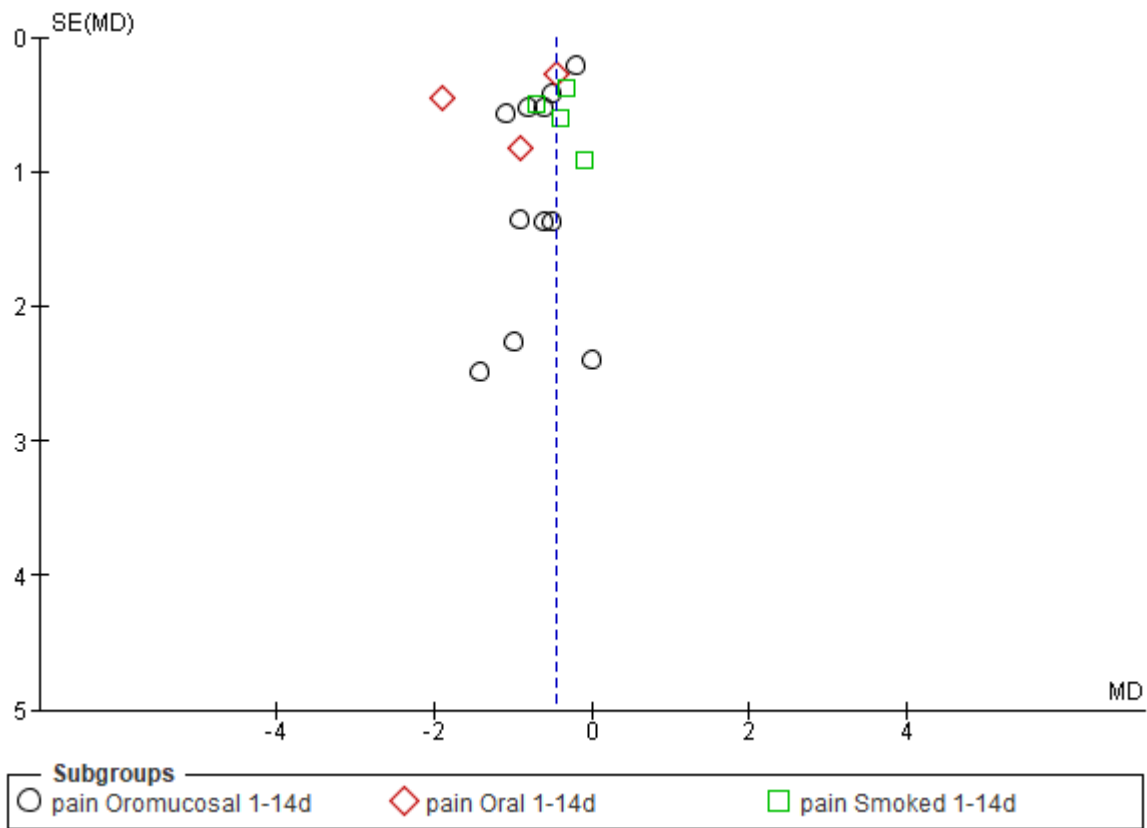
e-Figure 3. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) by duration of follow-up.



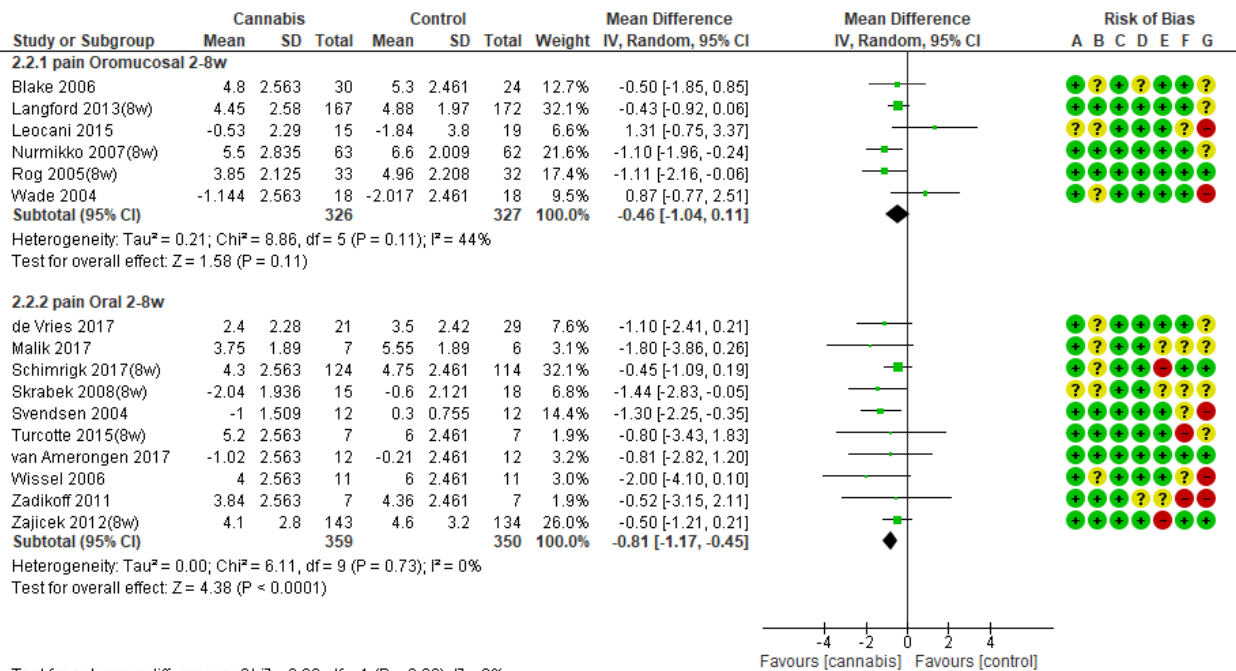
e-Figure 4. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain by duration of treatment, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



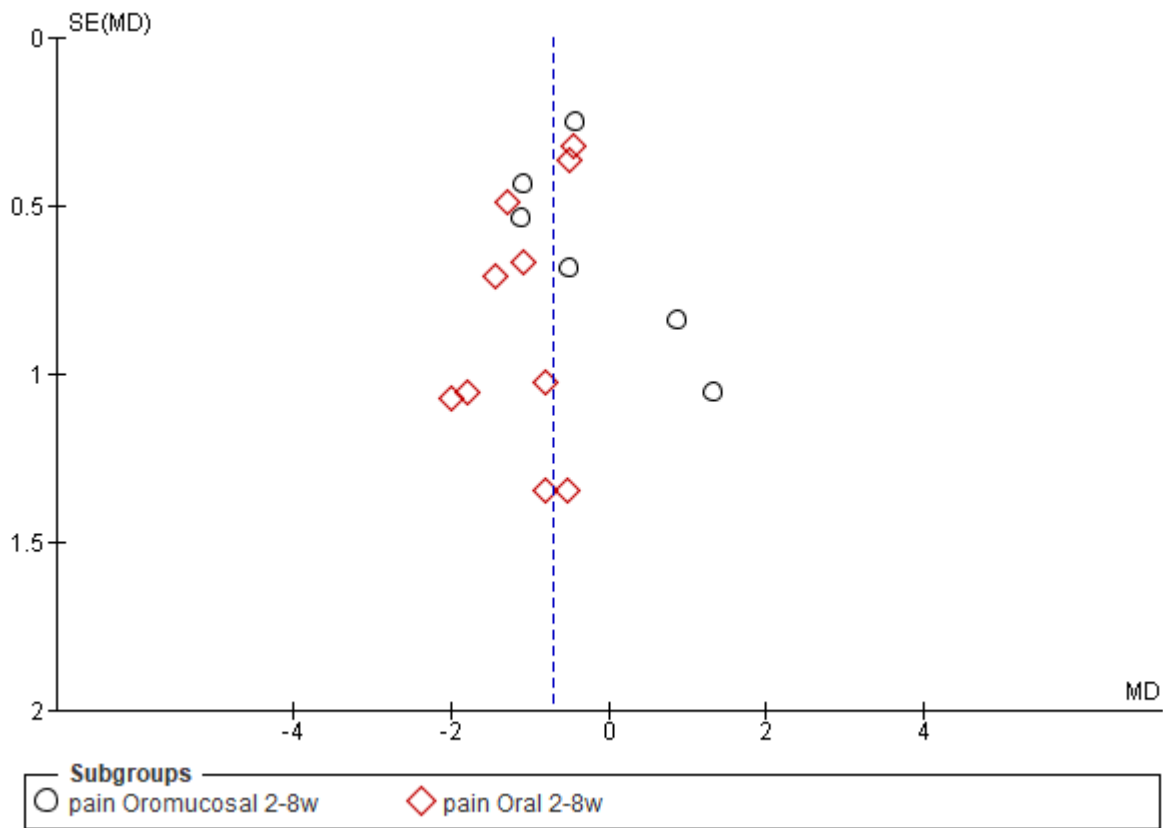
e-Figure 5. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 1-14 days follow-up, stratified by route of administration.



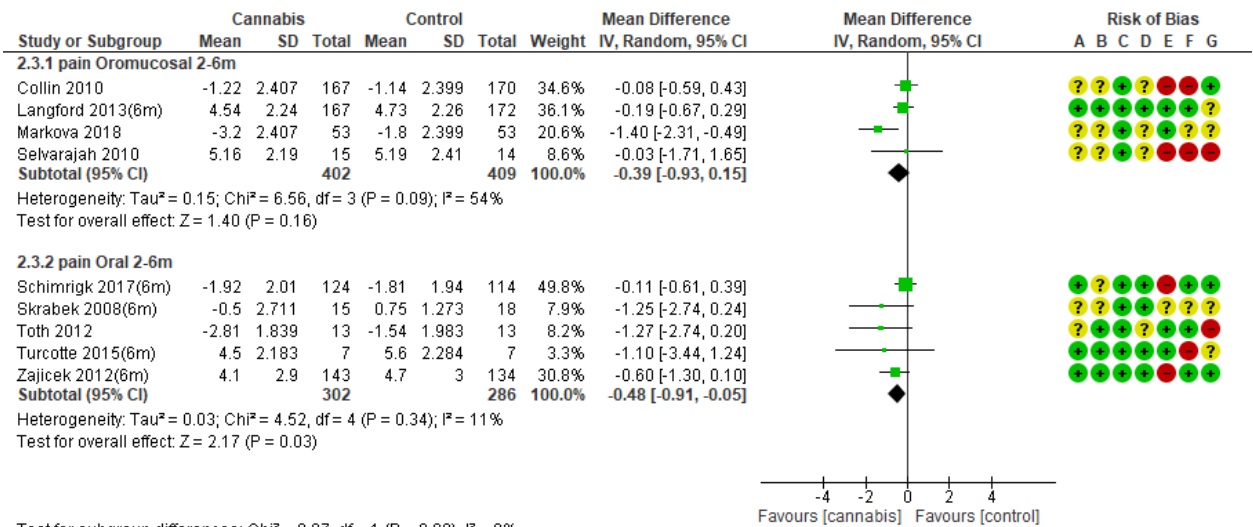
e-Figure 6. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 1-14 days follow-up by route of administration, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



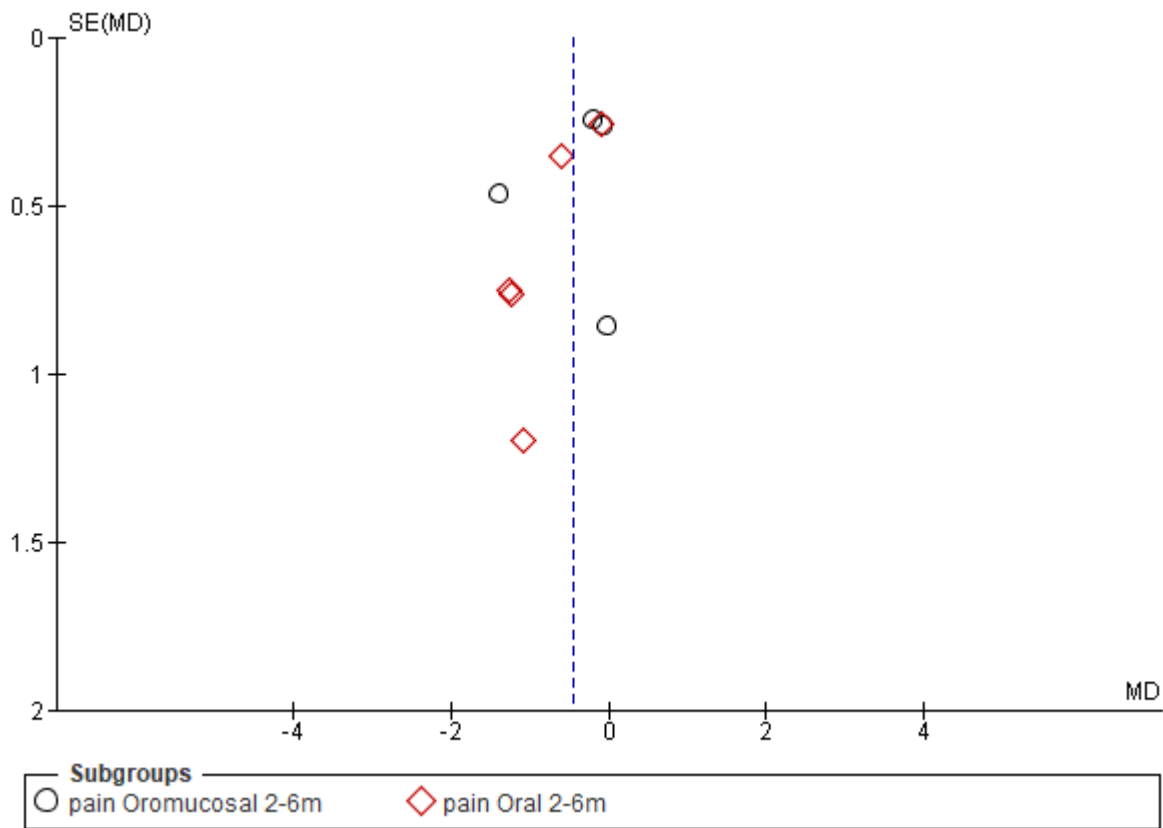
e-Figure 7. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 2-8 weeks follow-up, stratified by route of administration.



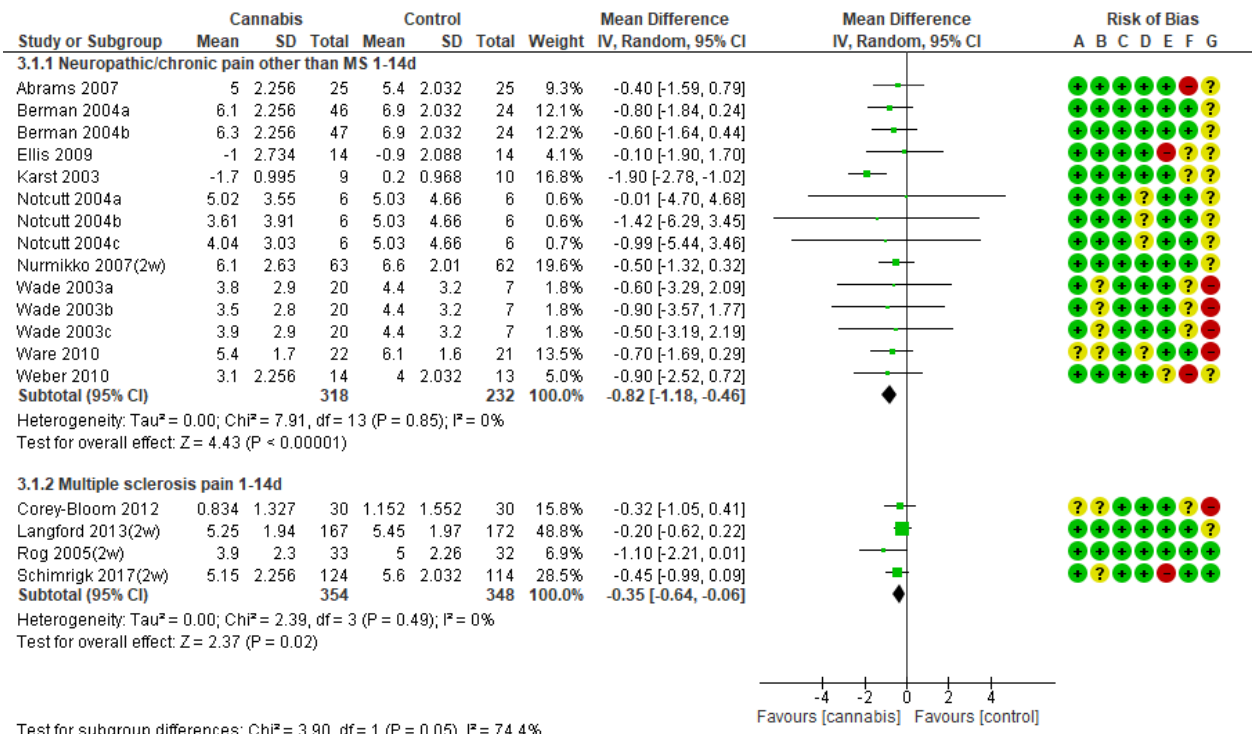
e-Figure 8. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 2-8 weeks follow-up by route of administration, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



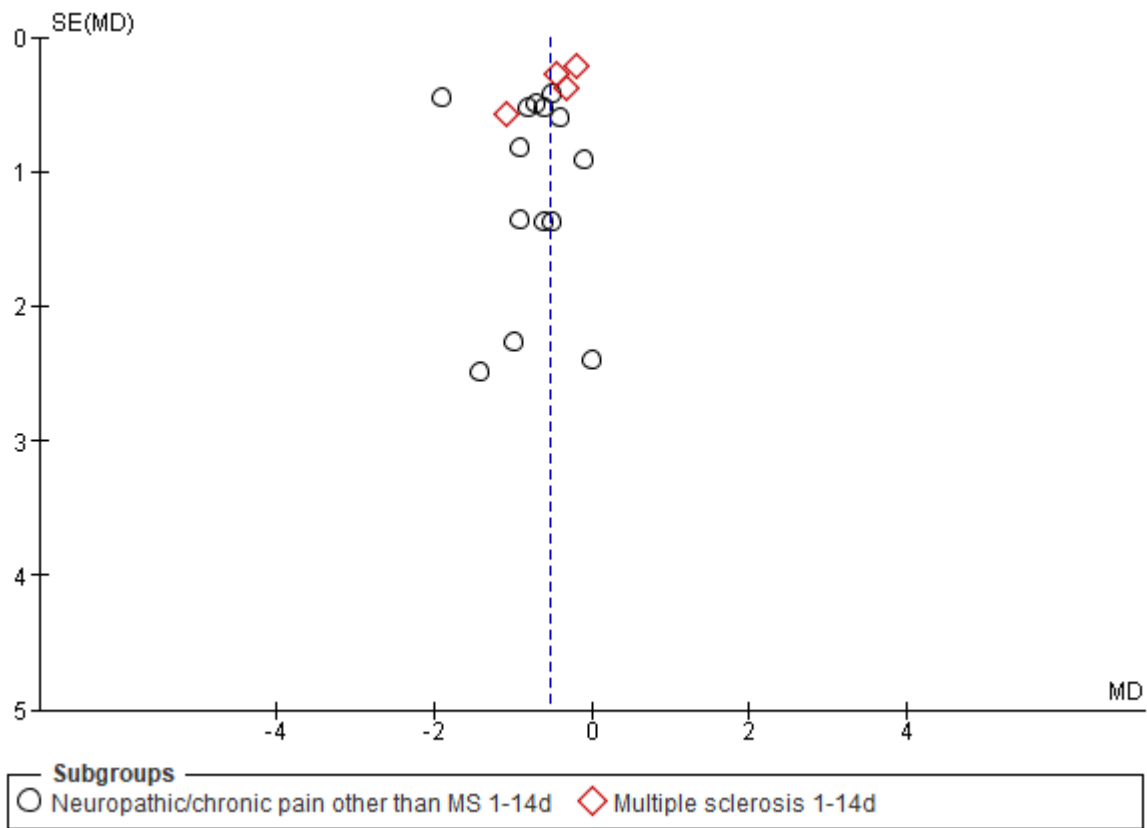
e-Figure 9. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 2-6 months follow-up, stratified by route of administration.



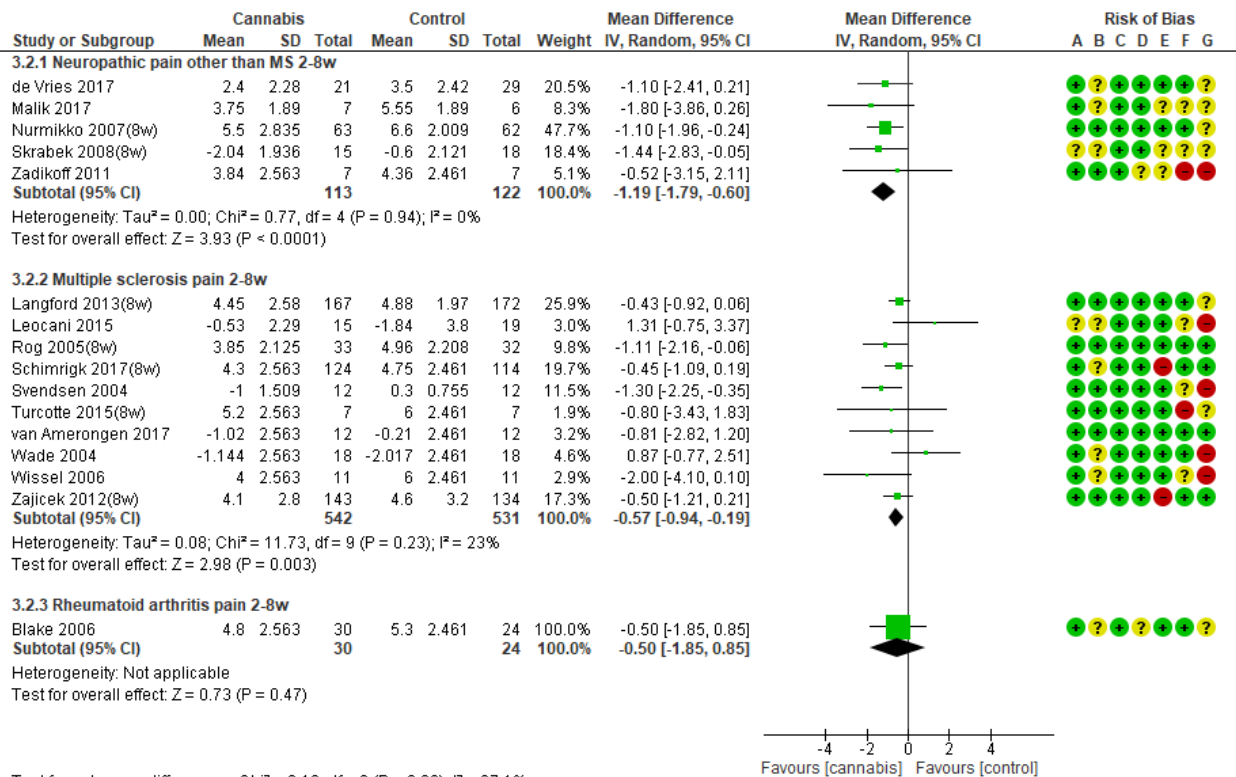
e-Figure 10. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 2-6 months follow-up by route of administration, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



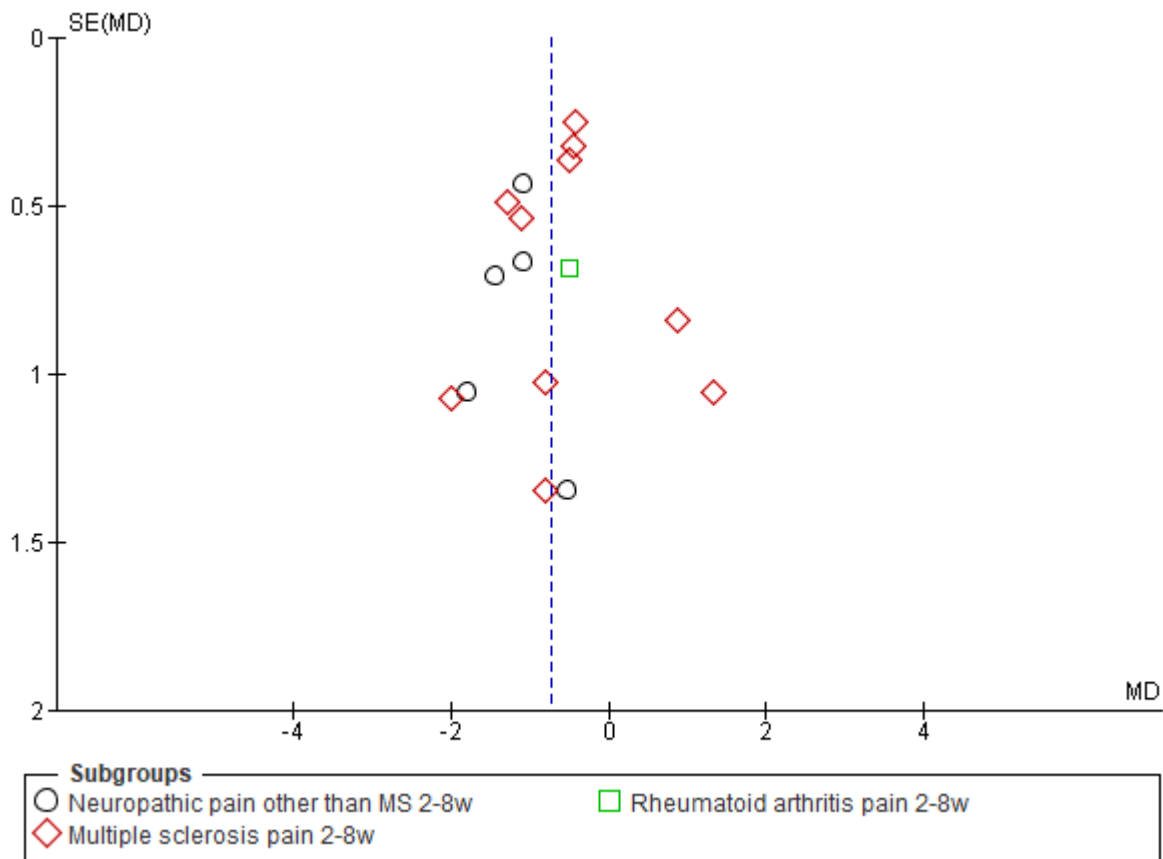
e-Figure 11. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 1-14 days follow-up, stratified by pain condition.



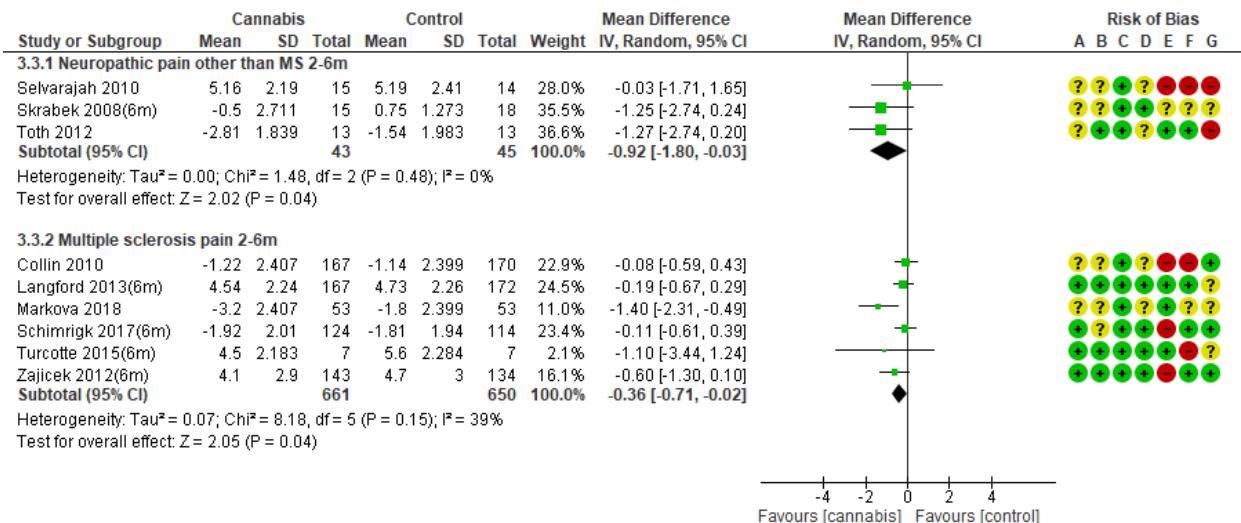
e-Figure 12. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 1-14 days follow-up by pain condition, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



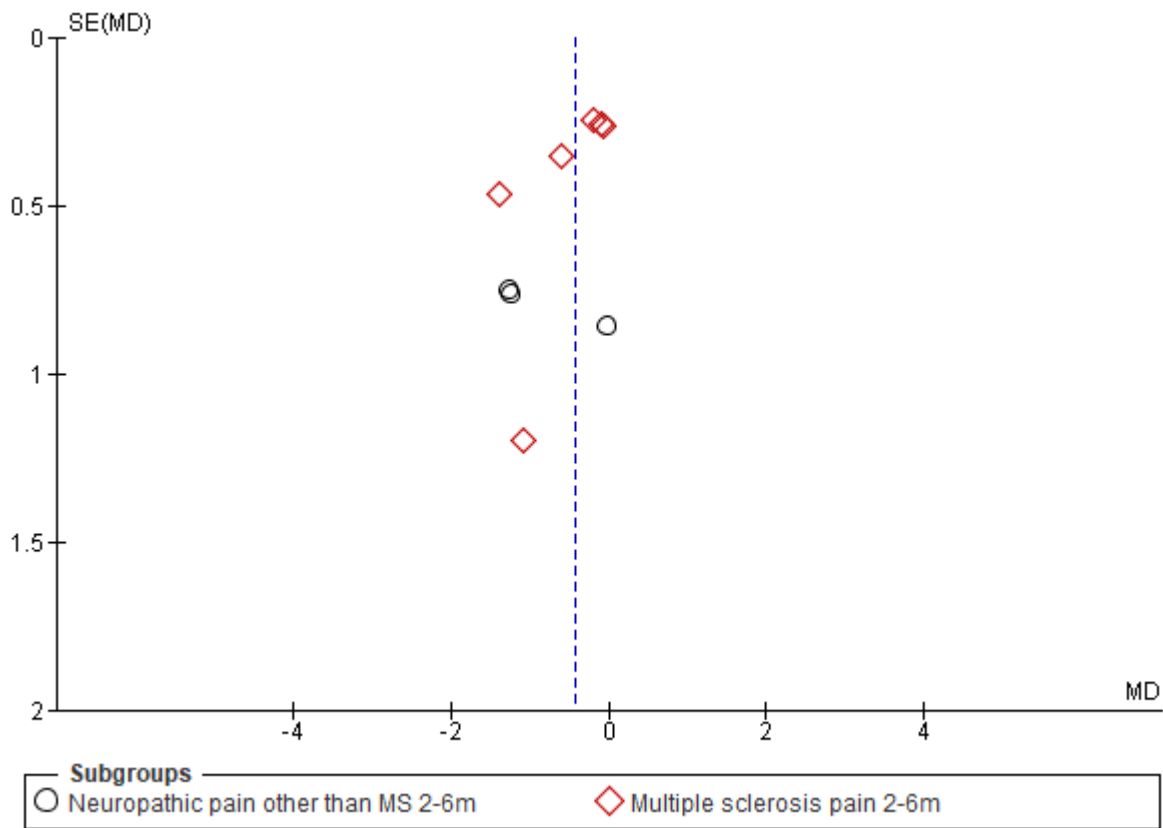
e-Figure 13. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 2-8 weeks follow-up, stratified by pain condition.



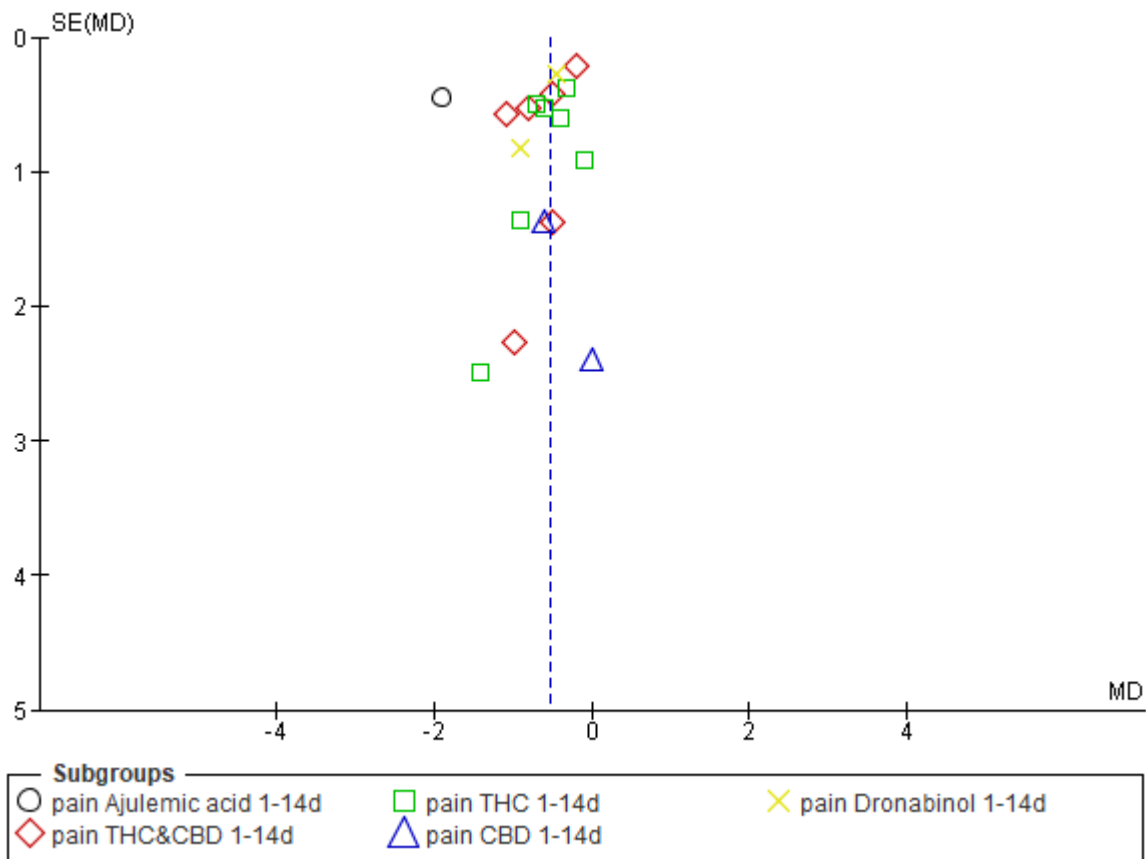
e-Figure 14. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 2-8 weeks follow-up by pain condition, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



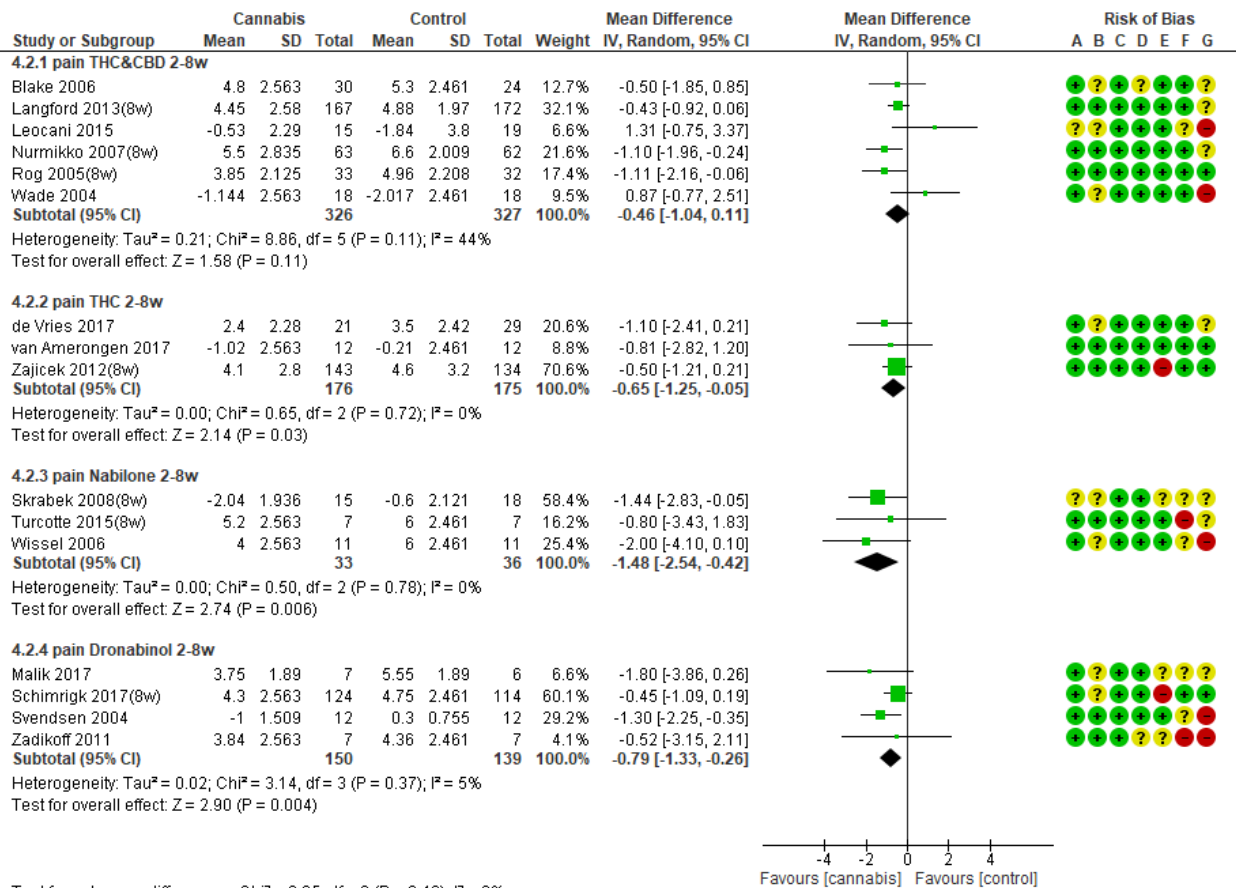
e-Figure 15. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 2-6 months follow-up, stratified by pain condition.



e-Figure 16. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 2-6 months follow-up by pain condition, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



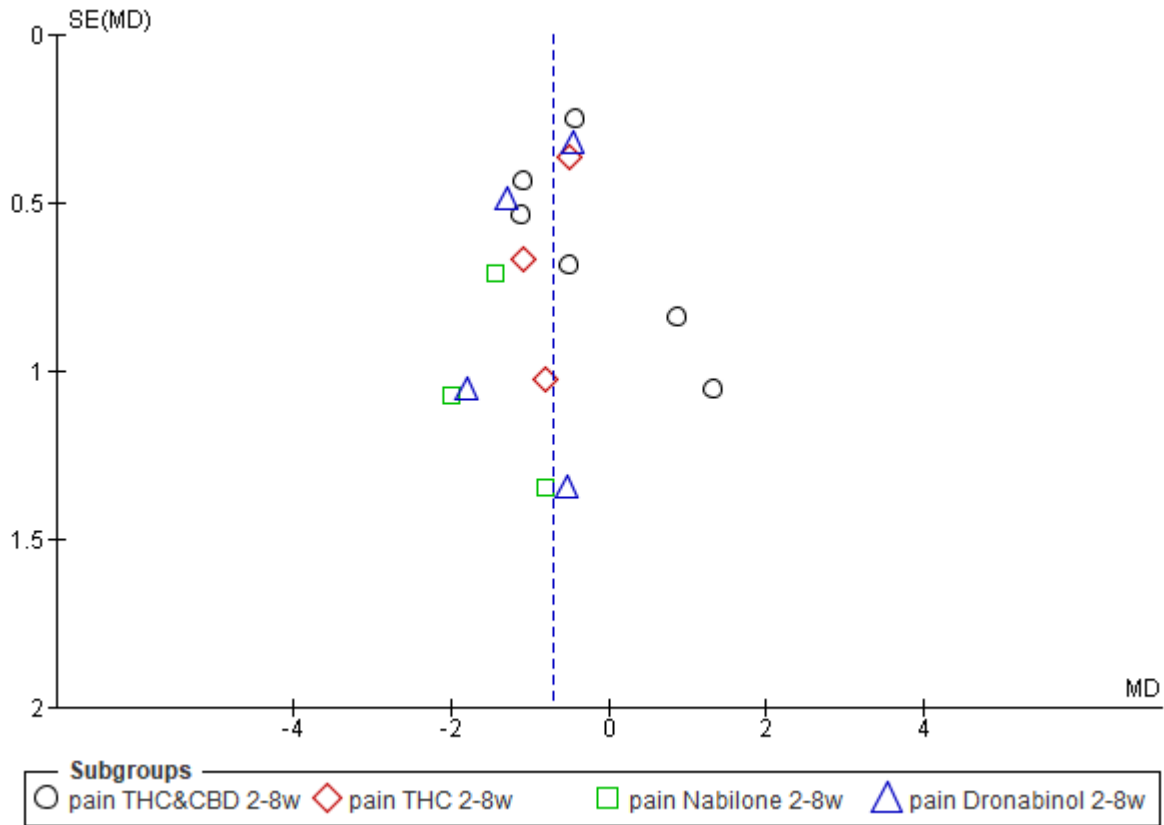
e-Figure 18. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 1-14 days follow-up by type of drug, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



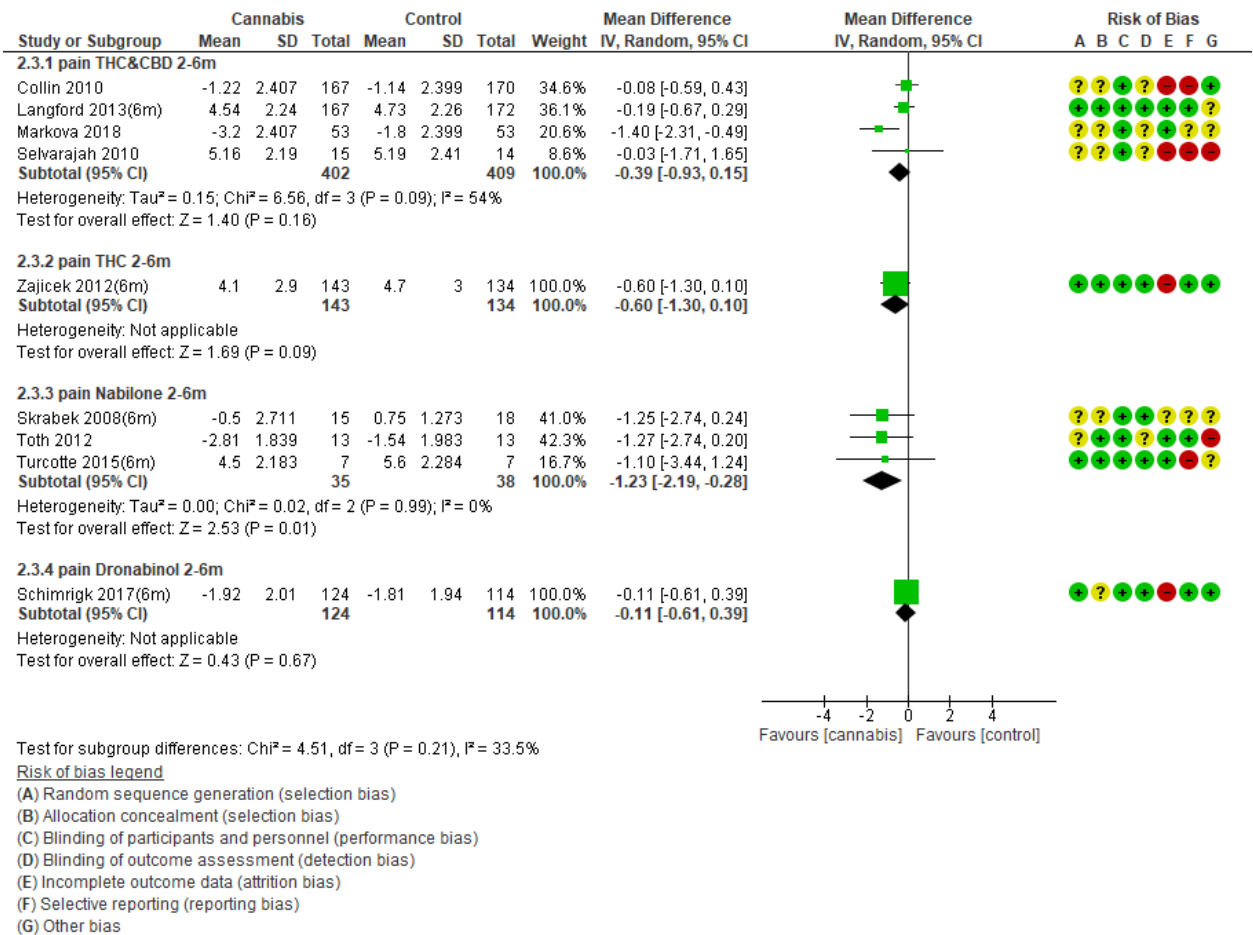
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

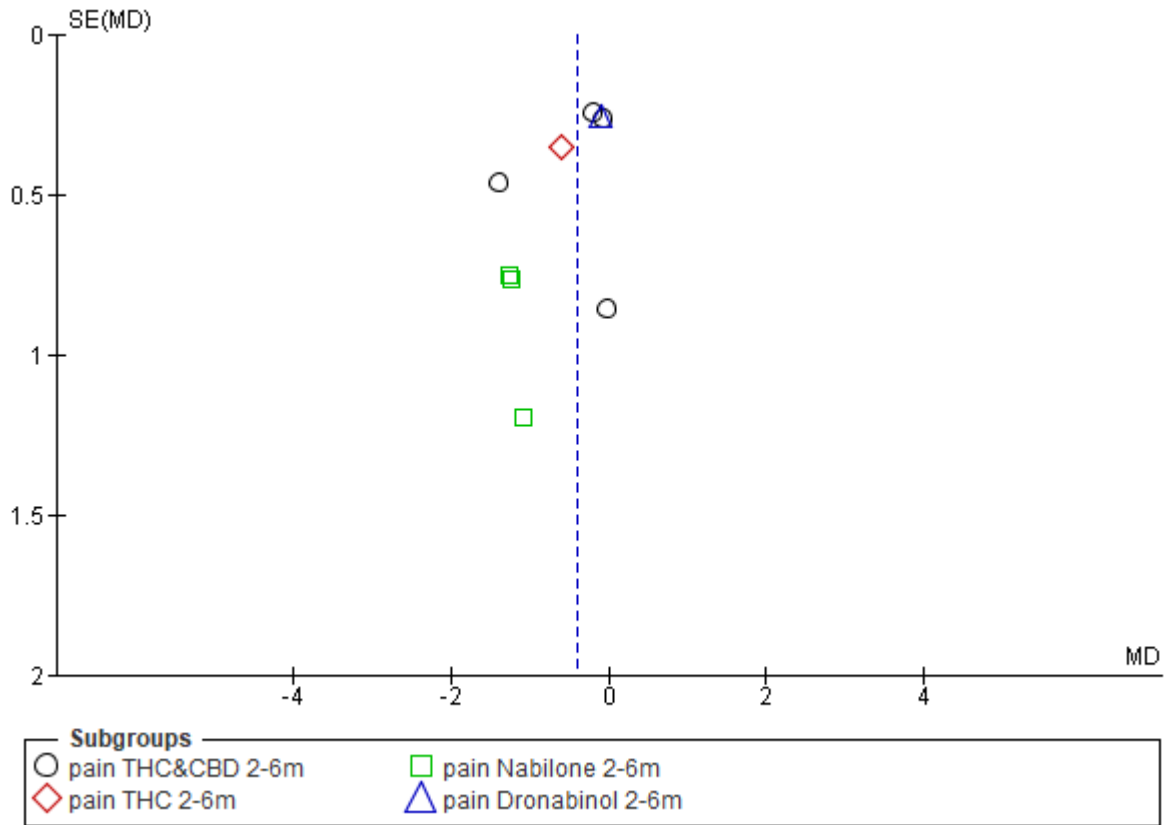
e-Figure 19. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 2-8 weeks follow-up, stratified by type of drug.



e-Figure 20. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 2-8 weeks follow-up by type of drug, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.



e-Figure 21. Forest plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain (0-10 visual analogue scale, higher score more pain) at 2-6 months follow-up, stratified by type of drug.



e-Figure 22. Funnel plot of medical cannabis (intervention) versus placebo (control) for chronic non-cancer pain at 2-6 months follow-up by type of drug, to assess for publication bias. Effect estimates (mean difference MD) is on the x-axis, study precision (standard error, SE) is on the y-axis.

e-Tables 1 and 2

e-Table 1 - MEDLINE Database specific search strategy

1. exp pain/
2. exp chronic pain/
3. pain\$.mp.
4. (chronic or intractable or refractory or persistent).mp.
5. 1 or 3
6. 4 and 5
7. 2 or 6
8. fibromyalgia.mp.
9. fibrositis.mp.
10. arthriti\$.mp.
11. back pain.mp.
12. neck pain.mp.
13. exp musculoskeletal diseases/
14. exp joint diseases/
15. exp back pain/
16. exp multiple sclerosis/
17. multiple sclerosis.mp.
18. allodynia.mp.
19. sciatic\$.mp.
20. neuralgia.mp.
21. neuropath\$.mp.
22. or/7-21
23. cannabis.mp.
24. exp cannabis/
25. cannabinoid\$.mp.
26. exp cannabinoids/
27. tetrahydrocannabinol.mp.
28. exp dronabinol/
29. cannabidiol.mp.

30. exp cannabidiol/
31. sativex.mp.
32. exp medical marijuana/
33. nabiximols.mp.
34. thc.mp.
35. nabilone.mp.
36. cesamet.mp.
37. marinol.mp.
38. marihuana.mp.
39. marijuana.mp.
40. hashish.mp.
41. or/23-40
42. 22 and 41
43. randomized controlled trial.pt.
44. controlled clinical trial.pt.
45. randomized.ab.
46. placebo.ab.
47. drug therapy.fs.
48. randomly.ab.
49. trial.ab.
50. groups.ab.
51. or/43-50
52. 42 and 51
53. exp animals/ not humans/
54. 52 not 53

e-Table 2 – Demographic and treatment arm details for included studies

Author (Year)	Route of admin	Country	RCT Type	No. of Participants randomized	Group	No./ arm
Abrams (2007) ¹	Inhaled (smoked)	United States	Parallel RCT	55	(1) Cannabis (3.56% THC)	27
					(2) Placebo	28
Ball (2015) ²	Oral	United Kingdom	Parallel RCT	498	(1) Dronabinol (Synthetic delta-9 THC, 3.5-28mg/day)	332
					(2) Placebo	166
Berman (2004) ³	Oromucosal spray	United Kingdom	Crossover RCT	48	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	46
					(2) THC only (THC 27mg/ml)	47
					(3) Placebo	48
Blake (2006) ⁴	Oromucosal spray	United Kingdom	Parallel RCT	58	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	31
					(2) Placebo	27
Carroll (2004) ⁵	Oral	United Kingdom	Crossover RCT	19	(1) Cannabis Extract capsule (THC 2.5mg/CBD 1.25mg/5 to 25mg/day)	19
					(2) Placebo	19
Collin (2010) ⁶	Oromucosal spray	Czech Republic United Kingdom	Parallel RCT	337	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	167
					(2) Placebo	170
		United States	Crossover RCT	37	(1) Cannabis (4.0% THC)	30

Corey-Bloom (2012) ⁷	Inhaled (smoked)				(2) Placebo	30
de Vries (2017) ⁸	Oral	Netherlands	Parallel RCT	65	(1) Namisol (Synthetic delta-9 THC, 3mg TID x 5d, 5ma TID x 5d. then 8ma TID)	30
					(2) Placebo	32
Ellis (2009) ⁹	Inhaled (smoked)	United States	Crossover RCT	34	(1) Cannabis (1-8% THC)	34
					(2) Placebo	34
Hagenbach (2007) ¹⁰	Oral	Switzerland	Parallel RCT	13	(1) Dronabinol (Synthetic delta-9 THC, 2.5-10mg/tab)	6
					(2) Placebo	7
Karst (2003) ¹¹	Oral	Germany	Crossover RCT	21	(1) Ajulemic acid, CT3 (Synthetic THC-11, 20mg BID x 4 days, then 40mg BID x 3 days)	21
					(2) Placebo	21
Killenstein (2002) ¹²	Oral	Netherlands	Crossover RCT	16	(1) Dronabinol (Synthetic delta-9 THC, 2.5-10mg/tab)	16
					(2) Cannabis Extract capsule (THC 2.5mg/CBD 20 to 30%) up to 10ma/dav	16
					(3) Placebo	16
Langford (2013) ¹³	Oromucosal spray	Canada Czech Republic France Spain United Kingdom	Parallel RCT	339	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	167
					(2) Placebo	172
Leocani (2015) ¹⁴	Oromucosal spray	Italy	Crossover RCT	44	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	44
					(2) Placebo	44
Malik	Oral	United States	Parallel RCT	13	(1) Dronabinol (Synthetic delta-9 THC, 5mg BID x 4 weeks)	7

(2017) ¹⁵					(2) Placebo	6
Markova (2018) ¹⁶	Oromucosal spray	Czech Republic Austria	Parallel RCT	106	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml) (2) Placebo	53 53
Notcutt (2004) ¹⁷	Oromucosal spray	United Kingdom	Crossover RCT	34	(1) Nabiximol (THC 2.5mg:CBD 2.5/spray) (2) THC only (THC 2.5mg/spray) (3) CBD only (CBD 2.5mg/spray) (4) Placebo	24 24 24 24
Novotna (2011) ¹⁸	Oromucosal spray	Czech Republic Italy Poland Spain United Kingdom	Parallel RCT	241	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml) (2) Placebo	124 117
Nurmikko (2007) ¹⁹	Oromucosal spray	Belgium United Kingdom	Parallel RCT	125	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml) (2) Placebo	63 62
Rog (2005) ²⁰	Oromucosal spray	United Kingdom	Parallel RCT	66	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml) (2) Placebo	34 32
Schimrigk (2017) ²¹	Oral	Germany	Parallel RCT	240	(1) Dronabinol (Synthetic delta-9 THC, 7.5mg to 15mg/day x 4 weeks) (2) Placebo	124 116
		United Kingdom	Parallel RCT	30	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	15

Selvarajah (2010) ²²	Oromucosal spray				(2) Placebo	15
Serpell (2014) ²³	Oromucosal spray	Canada Belgium Czech Republic Romania United Kingdom	Parallel RCT	246	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml)	128
					(2) Placebo	118
Skrabek (2008) ²⁴	Oral	Canada	Parallel RCT	40	(1) Nabilone (Synthetic Cannabinoid, 0.5 - 1.0mg BID x 4 weeks)	20
					(2) Placebo	20
Svendsen (2004) ²⁵	Oral	Denmark	Crossover RCT	24	(1) Dronabinol (Synthetic delta-9 THC, 5mg BID x 20 days)	24
					(2) Placebo	24
Toth (2012) ²⁶	Oral	Canada	Parallel RCT	26	(1) Nabilone (Synthetic Cannabinoid, 1.0 - 4.0mg/day x 9 weeks)	13
					(2) Placebo	13
Turcotte (2015) ²⁷	Oral	Canada	Parallel RCT	15	(1) Nabilone (Synthetic Cannabinoid, 0.5 - 1.0mg BID x 61 days)	8
					(2) Placebo	7
van Amerongen (2017) ²⁸	Oral	Netherlands	Parallel RCT	24	(1) Namisol (Synthetic delta-9 THC, 16mg/day x 4 weeks)	12
					(2) Placebo	12
Wade (2003) ²⁹	Oromucosal spray	United Kingdom	Crossover RCT	24	(1) CBD only (CBD 2.5mg per spray)	24
					(2) THC only (THC 2.5mg per spray)	24
					(3) Nabiximol (THC 2.5mg:CBD 2.5mg per spray)	24

					(4) Placebo	24
Wade (2004) ³⁰	Oromucosal spray	United Kingdom	Parallel RCT	160	(1) Nabiximol (THC 27mg/ml:CBD 25mg/ml) (2) Placebo	80 80
Ware (2010) ³¹	Inhaled (smoked)	Canada	Crossover RCT	23	(1) Smoked cannabis (9.4% THC) (2) Placebo	23 23
Weber (2010) ³²	Oral	Switzerland	Crossover RCT	27	(1) Dronabinol (Synthetic delta-9 THC, 5mg BID x 2 weeks) (2) Placebo	27 27
Wissel (2006) ³³	Oral	Austria	Crossover RCT	13	(1) Nabilone (Synthetic Cannabinoid, 1.0mg/day x 4 weeks) (2) Placebo	13 13
Zadikoff (2011) ³⁴	Oral	Canada	Crossover RCT	9	(1) Dronabinol (Synthetic delta-9 THC, 2.5-15mg/day x 3 weeks) (2) Placebo	9 9
Zajick (2005) ³⁵	Oral	United Kingdom	Parallel RCT	657	(1) Cannabis Extract capsule (THC 2.5mg/CBD 1.25mg. 5 to 25mg/day) (2) Marinol (Synthetic delta-9 THC, 3.5-28mg/day) (3) Placebo	219 216 222
Zajicek (2012) ³⁶	Oral	United Kingdom	Parallel RCT	279	(1) Cannabis Extract capsule (delta-9 THC 5 to 25mg/day x 12 weeks) (2) Placebo	144 135

Notes: THC = tetrahydrocannabinol; CBD = cannabidiol.

