Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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1. Supplementary eReferences

eReferences 1: Full-text Records Excluded From Eligibility

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2. Supplementary eTables

eTable 1: Characteristics of the included studies

Data are mean (SD), N/n (%). Percentages may not add to 100% due to rounding. *Estimated by the authors of this systematic review from study data. †Interpreted by the authors of this systematic review based on study data. ‡ Computed only for the serious adverse events analysis, so not included in the total adverse events or in any other kind of adverse event analyses since only appeared in one of the included studies. DD = duration of disease. CBD = cannabidiol. CE = *Cannabis sativa* plant extract. IQR = interquartile range. ITT = intention-to-treat. MS = multiple sclerosis. N/n = no. of participants. PP = per-protocol. PPMS = primary progressive MS. PRMS = progressive relapsing MS. RCT = randomized clinical trial. RRMS = relapsing-remitting MS. SD = standard deviation. SPMS = secondary progressive MS. THC = δ-9-tetrahydrocannabinol. **Assessment:** 9-HPT = 9-Hole Peg Test. ADL = Activities of Daily Living. AMIPB = Adult Memory and Information Processing Battery. AS = Ashworth Scale. BDI = Beck Depression Inventory. BI = Barthel Index. BPI-SF = Brief Pain Inventory-Short Form. CRS = Category Rating Scale. C-SSRS = Columbia-Suicide Severity Rating Scale. DS of the WAIS-R= Digit Span of the Wechsler Adult Intelligence Scale-Revised. EDSS = Expanded Disability Status Scale. EQ-5D = European Quality of Life-5 Dimensions. FIM = Functional Independence Measure. fMRI = Functional Magnetic Resonance Imaging. FSS = Fatigue Severity Scale. GHQ-28 = General Health Questionnaire-28. GHQ-30 = General Health Questionnaire-30. GIC = Global Impression of Change. GNDS = Guy's Neurological Disability Scale. GSI = General Symptomatic Index. HADS = Hospital Anxiety and Depression Scale. HR-QoL = Health-Related Quality of Life. MAS = Modified Ashworth Scale. MI = Motricity Index. MRI = Magnetic Resonance Imaging. MSFC = Multiple Sclerosis Functional Composite Scale. MSIS-29 = Multiple Sclerosis Impact Scale-29. MSQoL-54 = Multiple Sclerosis Quality of Life-54. MSSS-88 = Multiple Sclerosis Spasticity Scale-88. MSWS-12 = Multiple Sclerosis Walking Scale-12. NNH = Number Needed to Harm. NNT = Number Needed to Treat. NOS = Not Otherwise Specified. NPS = Neuropathic Pain Scale. NRS = Numerical Rating Scale. PASAT = Paced Auditory Serial Addition Test. PDI = Pain Disability Index. PSQI = Pittsburgh Sleep Quality Index. PSS = Primary Symptom Score. QoL = Quality of Life. RMI = Rivermead Mobility Index. SAS = Self-rating Anxiety Scale. SCL-90-R = Symptom Checklist-90 Revised. SDMT = Symbol Digit Modalities Test. SF-36 = Short Form-36 Health Survey/Short Form questionnaire-36 items. SF-36 (PH) = Short Form questionnaire-36 items version 2 (physical health subscale). SF-MPQ = Short-Form McGill Pain Questionnaire. SPART = 10/36 Spatial Recall Test. SRT = Selective Reminding Test. TMS = Transcranial Magnetic Stimulation. T10-MW = Timed 10-m walk. T25-FW = Timed 25-foot walk. UIE = Urge incontinence episode. UKNDS = United Kingdom Neurological Disability Scale. VAS = Visual Analog Scale. WLG = Word List Generation.

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Killestein 2002[25]					
Design	Progressive MS patients with spasticity Setting not specified RCT, placebo-controlled Double-blind Crossover 20 weeks (4-week/intervention, 4-week washout between treatment periods) ITT analysis	Oral CE caps.: (2.5 mg THC + 20 to 30% CBD of standardized THC content)/cap.	Oral dronabinol caps.: 2.5 mg THC/cap.	Placebo caps.	No reduction of spasticity.
		Dose = 2-4 caps./day (5-10 mg THC + approx. 1.25-2.5 mg CBD)	Dose = 2-4 caps./day (5-10 mg THC)	Dose = 2-4 caps./day	
$N/n_{initial}$	16	16	16	16	
Sex	..	..	..	..	
Subtype of MS					
SPMS	10 (63%)	..	..	..	
PPMS	6 (38%)	..	..	..	
Mean age (SD) years	46.0 (7.90)	..	..	..	
Mean DD (SD) years	15.0 (10.70)	..	..	..	
Mean EDSS (SD)	6.2 (1.20)	..	..	..	
N/n_{final}	16	16	16	16	
Assessment					
Efficacy: *Included in our analysis*: AS. *Excluded from our analysis*: 9-HPT; Concentration VAS; EDSS, and EDSS-Brainstem functional systems domain; Fatigue VAS; HR-QoL Questionnaire, and HR-QoL-Psychological status domain; Micturition VAS; Mood VAS; MSFC; MS-specific FSS; Pain VAS; PASAT; SF-36, and SF-36-Mental health subscale; Spasticity VAS; Subject´s Global Impression VAS; T25-FW; Tremor VAS; Vision VAS; and Walking VAS. *Tolerability:* *Included in our analysis*: Ataxia; dizziness; dry mouth; headache; increased spasticity; somnolence; and withdrawals due to adverse events. *Excluded from our analysis*: Acute psychosis; emotional lability; and others.					

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eTable 1: Characteristics of the included studies *(continued)*					
		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Zajicek 2003[26]/Freeman 2006[27] (2 publications with same cohort of study) *(continue)*					
Zajicek 2003[26]					
Design	MS patients with spasticity Multicentric (UK) RCT, placebo-controlled Double-blind Parallel 15 weeks (13-week treatment, 1-week dose withdrawal, 1-week off trial medication) ITT analysis	Oral CE caps.: (2.5 mg THC + 1.25 mg CBD)/cap.	Oral dronabinol caps.: 2.5 mg THC/cap.	Placebo caps.	No beneficial effect on spasticity.
		Dose = 4-10 caps./day (10-25 mg THC + 5-12.5 mg CBD) Body weight based	Dose = 4-10 caps./day (10-25 mg THC) Body weight based	Dose = 4-10 caps./day Body weight based	
		Mean dose (SD) = 5.42 (2.11) caps./day (13.56 mg THC + 6.78 mg CBD)*	Mean dose (SD) = 5.47 (2.08) caps./day (13.67 mg THC)*	Mean dose (SD) = 6.24 (1.71) caps./day*	
$N/n_{initial}$	630	211	206	213	
Sex					
M	217 (34%)	76 (36%)	63 (31%)	78 (37%)	
F	413 (66%)	135 (64%)	143 (69%)	135 (63%)	
Subtype of MS					
RRMS	33 (5%)	6 (3%)	14 (7%)	13 (6%)	
SPMS	452 (72%)	152 (72%)	149 (72%)	151 (71%)	
PPMS	145 (23%)	53 (25%)	43 (21%)	49 (23%)	
Mean age (SD) years	..	50.5 (7.60)	50.2 (8.20)	50.9 (7.60)	
Mean AS (SD)	..	21.8 (8.70)	22.6 (10.10)	21.4 (8.50)	
EDSS, number of patients (range)	..	209 (6.4-7.7)*	203 (6.4-7.7)*	212 (6.3-7.6)*	
N/n_{final}	611 (97%)	207 (98%)	197 (96%)	207 (97%)	
Assessment					
Efficacy: *Included in our analysis*: AS; Bladder symptoms Questionnaire; Pain CRS; Pain Questionnaire; and Spasticity Questionnaire. *Excluded from our analysis*: BI; Depression CRS; EDSS; Energy (amount of energy) CRS; GHQ-30; Irritability CRS; Muscle spasms CRS; RMI; Shake/tremor (tremor) CRS; Sleep quality CRS; Spasticity (Muscle stiffness) CRS; T10-MW; Tiredness CRS; Tremor Questionnaire; and UKNDS. *Tolerability:* *Included in our analysis*: Abdominal pain of unknown cause; active duodenal ulcer and helicobacter pylori; back pain; chest infection/urinary tract infection; collapse of unknown cause; collapse/bradycardia; constipation; death; deep-vein thrombosis; diarrhoea; dizzy or lightheadedness; dry mouth; fall at home; grand mal seizures; infection; minor cerebrovascular event; MS relapse or possible relapse; numbness or paraesthesia; pain; pneumonia; possible transient ischaemic attack/syncope; sleep; tremor or lack coordination; urinary tract infection; urinary tract infection/relapse; viral gastroenteritis; vision; and withdrawals due to adverse events. *Excluded from our analysis*: Bladder; blocked/insertion of suprapubic catheter‡; cellulitis of leg/diarrhoea and vomiting‡; chronic pleural effusion‡; depression or anxiety; disease progression (not relapse) ‡; dizziness (inappropriate SAE report); emergency hip replacement‡; gastrointestinal tract; improvements in symptoms; increased appetite; miscellaneous; pneumonia and renal stones‡; spasms or stiffness; urinary tract infection/diarrhoea and vomiting‡; and weakness or reduced mobility.					
					(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Zajicek 2003[26]/Freeman 2006[27] (2 publications with same cohort of study) *(continued)*					
Freeman 2006[27] (same as Zajicek 2003,[26] unless specified)					
Design	Patients recruited to Zajicek 2003[26] (CAMS study), excepting of those with a permanent catheter.	..	..	..	Clinical effect on incontinence episodes.
$N/n_{initial}$ (% with respect to Zajicek 2003[26] initial data)	522 (83%)	181 (86%)	174 (84%)	167 (78%)	
N/n_{final} (% with respect to Zajicek 2003[26] initial data)	255 (40%)	88 (42%)	86 (42%)	81 (38%)	
Assessment					
Efficacy: *Included in our analysis*: UIEs Diary. *Excluded from our analysis*: King's Health Questionnaire; Pad test (weight); Post-void residual; and Voiding cystometry. *Tolerability:* *Included in our analysis*: Urinary tract infections (included in Zajicek 2003[26], but not specified as urinary tract infections), and worsening of detrusor-sphincter-dyssynergia (D-S-D) and urinary retention. *Excluded from our analysis*: None.					

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eTable 1: Characteristics of the included studies *(continued)*					
		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Svendsen 2004[28]					
Design	MS patients with central neuropathic pain Unicentric (Denmark) RCT, placebo-controlled Double-blind Crossover 9 weeks (3-week/intervention, 3-week washout between treatment periods) ITT analysis	..	Oral dronabinol caps.: 2.5 mg THC/cap.	Placebo caps.	Clinical effect on central pain.
			Dose = 2.5 mg-10 mg THC/day (1-4 caps.)	Dose = 2.5 mg-10 mg/day	
			Mean dose (range) = 3.1 [2.7-3.6] caps./day (7.75 [6.75-9.00] mg THC)	Mean dose (range) = 3.3 [2.8-3.6] caps./day (8.25 [7.00-22.50] mg)	
$N/n_{initial}$	24	..	24	24	
Sex					
M	10 (42%)	..	..	..	
F	14 (58%)	..	..	..	
Subtype of MS					
RRMS	9 (38%)	..	..	..	
SPMS	9 (38%)	..	..	..	
PPMS	6 (25%)	..	..	..	
Median age (range)	50 (23-55)	..	..	..	
Median DD (range)	7.0 (0.3-25.0)	..	..	..	
Median EDSS (range)	6.0 (2.5-6.5)	..	..	..	
Median Pain intensity NRS (range)	5.5 (3.0-8.0)	..	..	..	
N/n_{final}	24	..	24	24	
Assessment					
Efficacy: *Included in our analysis*: Pain-relief NRS Diary; Radiating pain NRS Diary; SF-36-Bodily pain subscale; and Spontaneous pain intensity NRS Diary. *Excluded from our analysis*: 50% Pain relief; EDSS; NNT (50% reduction in central pain), Use of scape medication Diary; Quantitative sensory testing; SF-36-General health, SF-36-Mental health, SF-36-Physical functioning, SF-36-Role emotional, SF-36-Role physical, SF-36-Social functioning, and SF-36-Vitality subscales; and Treatment preference. *Tolerability:* *Included in our analysis*: Abdominal pain; anorexia; balance difficulty; diplopia; distortion of wrist; dizziness or lightheadedness; euphoria; fatigue; feeling of drunkenness; fever; headache; migraine; mouth dryness; muscle weakness; myalgia; nausea; palpitations; speech disorders; upper airway infection; weight decrease; and withdrawals due to adverse events. *Excluded from our analysis*: Chills; hot flushes; hyperactivity; limb heaviness; multiple sclerosis aggravated (one patient admitted to the hospital); nervousness; sleep difficulty; tenderness in nose; and tiredness or drowsiness.					
					(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Vaney 2004[29]					
Design	MS patients with spasticity Unicentric (Switzerland) RCT, placebo-controlled Double-blind Crossover 4 weeks (2-week cannabinoids treatment, 1-week placebo, 3-day washout between/after interventions) ITT/PP analyses	Oral CE caps.: (2.5 mg THC + 0.9 mg CBD)/cap.	..	Placebo caps.	Reduction of spasm frequency and increase of mobility.
		Dose = 6-12 caps./day (15-30 mg THC + 5.4-10.8 mg CBD)		Dose = 6-12 caps./day	
		Mean dose (SD) = (17.99 [7.63] mg THC + 6.48 [2.75] mg CBD)/day (7.20 caps.)*		Mean dose not specified	
$N/n_{initial}$	57	57	..	57	
Sex					
M	28 (49%)	..	..	..	
F	29 (51%)	..	..	..	
Subtype of MS					
RRMS	2 (4%)	..	..	..	
SPMS	26 (46%)	..	..	..	
PPMS	29 (51%)	..	..	..	
Mean age (SD) years	54.9 (10.00)	..	..	..	
Mean DD (SD) years	17.0 (8.40)	..	..	..	
Median EDSS (range)	7.0 (6.00)	..	..	..	
Mean AS (SD)	12.5 (6.20)	..	..	..	
N/n_{final}	50 (88%)	50 (88%)	..	50 (88%)	
Assessment					
Efficacy: *Included in our analysis*: AS; and Micturition problems Questionnaire Diary. *Excluded from our analysis*: 9-HPT; DS of the WAIS-R; EDSS; Falling asleep fast Diary; FIM; PASAT; RMI; Spasm-frequency Diary; T10-MW; Tremor Questionnaire Diary; and Waking up again Diary. *Tolerability:* *Included in our analysis*: Blurred vision; constipation; dizziness; dry mouth; euphoria, "high"; headache; nausea, feeling sick; pain in extremities; palpitations; sleepiness; sleeplessness; tremor or shakes; and withdrawals due to adverse events. *Excluded from our analysis*: Cannabinoid toxicity Questionnaire Diary-Likert Scale, difficulty concentrating; fall; feeling aggressive; flu-like symptoms; and inadequate laughing.					

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eTable 1: Characteristics of the included studies *(continued)*

Study	All participants	Interventions THC/CBD (CE or nabiximols)	THC (dronabinol or nabilone)	Placebo	Conclusions
Wade 2004[30]					
Design Registered in *ClinicalTrials.gov* (NCT01610700, study results posted)	MS patients with spasticity, spasms, bladder problems, tremor, or pain (not musculoskeletal) Multicentric (UK) RCT, placebo-controlled Double-blind Parallel 6 weeks (6-week treatment) PP analysis	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo spray	Reduction of spasticity.
		Dose = 1-48 sprays/day (2.7-129.6 mg THC + 2.5-120 mg CBD Self-titrated dose		Dose =1-48 sprays/day Self-titrated dose	
		Mean dose (SD) = 12.37 (6.05) sprays/day (33.40 mg THC + 30.93 mg CBD)*		Mean dose (SD) = 18.87 (6.17) sprays/day*	
$N/n_{initial}$	160	80	..	80	
Sex					
M	61 (38%)	33 (41%)	..	28 (35%)	
F	99 (62%)	47 (59%)	..	52 (65%)	
Subtype of MS	..	..	..	..	
Mean age (SD) years	50.7 (9.32)	51.0 (9.36)	..	50.4 (9.33)	
Mean MAS (SD)	..	5.0 (3.70)	..	4.6 (4.40)	
N/n_{final}	154 (96%)	77 (96%)	..	77 (96%)	
Assessment					
Efficacy: *Included in our analysis*: Bladder (Bladder Problems) VAS; Bladder Questionnaire (Bladder Control Test); Bladder VAS Diary; MAS; Pain VAS Diary; Pain VAS; Spasticity VAS Diary; and Spasticity VAS. *Excluded from our analysis*: 9-HPT; AMIPB; BDI-II; BI; Care-giver Strain Index Score; Feeling upon waking VAS; FSS; GHQ-28; GNDS (UKNDS); How much sleep (Sleep Amount) VAS; PSS (Composite Primary Impairment VAS); Quality of sleep (Sleep Quality) VAS; Reading Visual Acuity Test; RMI; Short Orientation-Memory-Concentration Test; Spasm Frequency VAS Diary; Spasm severity VAS Diary; Spasms (Muscle Spasm) VAS; Subject Global Opinion of Effect on Multiple Sclerosis; Summed Symptom Score; T10-MW (Ten-metre Mobility Score); Tremor ADL Scale; Tremor VAS Diary; and Tremor VAS. *Tolerability:* *Included in our analysis*: Appendicitis; application site discomfort; application site pain; application site reaction NOS; diarrhoea; disorientation; disturbance in attention; dizziness; dry mouth; euphoric mood; fatigue; feeling drunk; headache; hypoaesthesia; lower respiratory tract infection NOS; mouth ulceration; muscle spasms; muscle weakness NOS; nausea; oral discomfort; oral pain; pain in limb; respiratory distress; sepsis NOS; somnolence; upper respiratory tract infection NOS; urinary tract infection NOS; vertigo; and withdrawals due to adverse events. *Excluded from our analysis*: Arthritis NOS‡; cough; and Feeling of intoxication VAS Diary.					

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Rog 2005[31]					
Design Registered in *ClinicalTrials.gov* (NCT01604265, study results posted)	MS patients with central neuropathic pain Unicentric(UK) RCT, placebo-controlled Double-blind Parallel 5 weeks (1-week run in, 4-week treatment) ITT analysis	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	Reduction of central neuropathic pain and sleep disturbance.
		Dose = 1-48 sprays/day (2.7-129.6 mg THC + 2.5-120 mg CBD) Self-titrated dose		Dose =1-48 sprays/day Self-titrated dose	
		Mean dose (SD) = 9.6 (6.1) sprays/day (week 4) (25.92 mg THC + 24.00 mg CBD)		Mean dose (SD) = 19.1 (12.9) sprays/day (week 4)	
$N/n_{initial}$	66	34	..	32	
Sex					
M	14 (21%)	6 (18%)	..	8 (25%)	
F	52 (79%)	28 (82%)	..	24 (75%)	
Subtype of MS					
RRMS	23 (35%)	..	..	..	
SPMS	33 (50%)	..	..	..	
PPMS	9 (14%)	..	..	..	
Benign MS	1 (2%)	..	..	..	
Mean age (SD) years	49.2 (8.32)	50.3 (6.70)	..	48.1 (9.73)	
Mean DD (SD) years	11.6 (7.70)	10.4 (7.30)	..	12.8 (8.10)	
Mean EDSS (SD)	5.9 (1.30)	6.0 (1.10)	..	5.8 (1.50)	
Mean Pain NRS (SD)	6.5 (1.60)	6.5 (1.60)	..	6.4 (1.70)	
N/n_{final}	64 (97%)	32 (94%)	..	32 (100%)	
Assessment					
Efficacy: *Included in our analysis*: NPS; Pain (central neuropathic pain) NRS; and Sleep disturbance (due to neuropathic pain) NRS. *Excluded from our analysis*: GNDS (UKNDS); HADS-Anxiety, and HADS-Depression items; MSFC; NNT (50% reduction in central pain); PASAT; Patient´s (Subject) GIC; SDMT; SPART; SRT; and WLG. *Tolerability:* *Included in our* analysis: Application site burning; back pain; breast pain; confusion; diarrhoea; diplopia; disorientation; dissociation; disturbance in attention; dizziness; dry mouth; dyspepsia; dyspnea; euphoria; falls; fatigue; feeling abnormal; feeling drunk; gamma-glutamyltransferase increased; glossodynia; hallucination; headache; hypoaesthesia; intoxication (agitation, tachycardia and hypertension)†; ligament sprain; logorrhea; migraine NOS; mouth ulceration; nasopharyngitis; nausea; oral pain; otitis media NOS; paraesthesia; paranoia; paranoid ideation; pharyngitis; rash NOS; sinusitis NOS; skin irritation; somnolence; urinary tract infection NOS; vomiting; weakness; white blood cell count increased; and withdrawals due to adverse events. *Excluded from our analysis*: Chest discomfort; crying; hoarseness; Intoxication Levels VAS; low mood; NNH; thirst; and throat irritation.					

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Collin 2007[32]					
Design Registered in *ClinicalTrials.gov* (NCT00711646, study results posted)	MS patients with spasticity, failed to gain adequate relief using current therapy Multicentric (UK and Romania) RCT, placebo-controlled Double-blind Parallel 6 weeks (6-week treatment) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	Reduction of spasticity.
		Dose = 1-48 sprays/day (2.7-129.6 mg THC + 2.5-120 mg CBD) Self-titrated dose		Dose =1-48 sprays/day Self-titrated dose	
		Mean dose (SD) = 9.4 (6.4) sprays/day (25.38 mg THC + 23.50 mg CBD)		Mean dose (SD) = 14.7 (8.4) sprays/day	
$N/n_{initial}$	189	124	..	65	
Sex					
M	75 (40%)	44 (35%)	..	31 (48%)	
F	114 (60%)	80 (65%),	..	34 (52%)	
Mean age (SD) years	49.1 (9.90)	49.7 (10.20)	..	47.8 (9.50)	
Mean DD (SD) years	12.6 (SD not specified)	13.6 (8.60)	..	12.2 (7.70)	
N/n_{final}	174 (92%)	112 (90%)	..	62 (95%)	
Assessment					
Efficacy: *Included in our analysis*: AS; and Spasticity NRS Diary. *Excluded from our analysis*: MI (arms), and MI (legs) items; Patient´s GIC; Spasm-frequency NRS Diary; Spasticity NRS 30% responder analysis; and Spasticity NRS 50% responder analysis. *Tolerability:* *Included in our analysis*: Appendicitis; balance impaired; Bartholin's abscess; confusion; constipation; depressed mood; diarrhoea; disorientation; disturbance in attention; dizziness; dry mouth; dysgeusia; euphoric mood; fatigue; headache; lower respiratory tract infection NOS; nausea; oral pain; pain in limb; pancreatic carcinoma NOS; pulmonary embolism; somnolence; urinary tract infection; urinary tract infection NOS; vision blurred; vomiting; weakness; and withdrawals due to adverse events. *Excluded from our analysis*: Mobility decreased‡; Intoxication NRS Diary; and urinary incontinence aggravated‡.					

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eTable 1: Characteristics of the included studies *(continued)*

Study	All participants	Interventions THC/CBD (CE or nabiximols)	THC (dronabinol or nabilone)	Placebo	Conclusions
Aragona 2009[33]/Tomassini 2014[34] (2 publications with same cohort of study) *(continue)*					
Aragona 2009[33]					
Design	SPMS patients with spasticity Unicentric (Italy) RCT, placebo-controlled Double-blind Crossover 10 weeks (3-week/intervention, 2-week washout between/after treatment periods) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	No psychopathology induction and no cognition impairment.
		Dose (specified in Tomassini 2014[34])		Dose (specified in Tomassini 2014[34])	
		Mean dose (SD) = 8.20 (3.15) sprays/day (22.14 mg THC + 20.50 mg CBD)		Mean dose (SD) = 15.16 (4.51) sprays/day	
$N/n_{initial}$ (% with respect to Tomassini 2014[34] initial data)	17 (94%)	17	..	17	
Sex					
M	6 (35%)	..	..	..	
F	11 (65%)	..	..	..	
Subtype of MS					
SPMS	17	..	..	..	
Mean age (SD) years	49.8 (6.64)	..	..	..	
Mean DD (SD) years	20.76 (8.42)	..	..	..	
Mean EDSS (SD)	6.1 (0.30)	..	..	..	
N/n_{final} (% with respect to Tomassini 2014[34] initial data)	17 (94%)	17	..	17	
Assessment					
Efficacy: *Included in our analysis*: None. *Excluded from our analysis*: 9-HPT; FSS; HR-QoL VAS (EQ-5D Health status VAS); MSIS-29 Physical, and MSIS-29 Psychological items; PASAT; SAS; SCL-90-R-Aggressive behaviour, SCL-90-R-Anxiety, SCL-90-R-Depression, SCL-90-R-Obsessive-compulsive features, SCL-90-R-Paranoiac tendencies, SCL-90-R-Phobic anxiety, SCL-90-R-Psychotic symptoms, SCL-90-R-Sensitivity, and SCL-90-R-Somatized anxiety dimensions; SCL-90-R-GSI item; and T25-FW. Plasma measurements. *Tolerability:* *Included in our analysis*: Craving†; depression; dizziness and vertigo; drowsiness and/or slower thinking; euphoria; fatigue; headache; intoxication (transient mental confusion with temporal and spatial disorientation, tachycardia, increased blood pressure, and mydriasis)†;lower limb weakness; mouth dryness or burning; nausea and vomiting; secondary depression; tremor; and withdrawals due to adverse events. *Excluded from our analysis*: None.					

(continue)

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eTable 1: Characteristics of the included studies *(continued)*					
		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Aragona 2009[33]/Tomassini 2014[34] (2 publications with same cohort of study) *(continued)*					
Tomassini 2014[34] (same as Aragona 2009,[33] unless specified)					
Design Registered in *ClinicalTrials.gov* (NCT00202423, no study results posted)	..	Dose = 1-48 sprays/day (2.7-129.6 mg THC + 2.5-120 mg CBD) Self-titrated dose Median dose (range) = 7.4 (2.7-12.5) sprays/day (19.98 mg THC + 18.50 mg CBD)	..	Dose = 1-48 sprays/day Self-titrated dose Median dose (range) = 16.1 (6.7-26) sprays/day	No significant benefits on spasticity. No change in fMRI motor-evoked brain activation. No difference in intracortical and spinal motor excitability.
$N/n_{initial}$	18	18	..	18	
Sex					
M	6 (33%)	..	..	..	
F	12 (67%)	..	..	..	
Subtype of MS					
SPMS	18	..	..	..	
Median age (range) years	51 (37-59)	..	..	..	
Median DD (range) years	21.5 (5-35)	..	..	..	
Median EDSS (range)	6.0 (6.0-6.5)	..	..	..	
Median AS (range)	12 (4-22)	..	..	..	
Median Spasticity NRS (range)	7 (3-9)	..	..	..	
N/n_{final}	18	18	..	18	
Assessment					
Efficacy: *Included in our analysis*: AS; and Spasticity NRS. *Excluded from our analysis*: AS (upper/lower extremities) 30% responders; and Spasticity NRS 30% responders. Neurophysiological assessment (fMRI, H-reflex, and TMS); and plasma measurements. *Tolerability:* None.					
					(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Collin 2010[35]					
Design Registered in *ClinicalTrials.gov* (NCT01599234, study results posted)	MS patients with spasticity, not wholly relieved with current therapy Multicentric (UK and Czech Republic) RCT, placebo-controlled Double-blind Parallel 15 weeks (1-week baseline, 14-week treatment) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	No significant improvement in spasticity NRS.
		Dose = 1-24 sprays/day (2.7-64.8 mg THC + 2.5-60 mg CBD) Self-titrated dose		Dose = 1-24 sprays/day Self-titrated dose	
		Mean dose (range) = 8.5 (1-22) sprays/day (22.95 mg THC + 21.25 mg CBD)		Mean dose (range) = 15.4 (2-23) sprays/day	
$N/n_{initial}$	337	167	..	170	
Sex					
M	130 (39 %)	61 (37%)	..	69 (41%)	
F	207 (61%)	106 (63%)	..	101 (59%)	
Mean age (SD) years	47.5 (9.61)	48.0 (10.06)	..	47.1 (9.15)	
Mean DD (SD) years	15.2 (8.41)	14.4 (8.29)	..	16.0 (8.48)	
Mean EDSS (SD)	6.0 (1.53)	6.0 (1.56)	..	6.0 (1.50)	
N/n_{final}	305 (91%)	150 (90%)	..	155 (91%)	
Assessment					
Efficacy: *Included in our analysis*: Bladder symptoms NRS; MAS; Pain NRS; Sleep quality (due to spasticity) NRS; and Spasticity NRS Diary. *Excluded from our analysis*: BI; Caregiver´s GIC; EQ-5D Health state index, and EQ-5D Health status VAS items; Fatigue NRS; MSQoL-54-Mental health, and MSQoL-54-Physical health composites; Number of subjects with a 50% or greater improvement in mean Spasticity NRS; Spasm severity NRS; Spasticity NRS 30% responder analysis; Spasticity NRS Time to 30% response; T10-MW; and Tremor NRS. *Tolerability:* *Included in our analysis*: Anxiety; asthenia; back pain; burns third degree; confusional state; constipation; death; dehydration; depressed mood; depression; diarrhoea; disorientation; dissociation; disturbance in attention; dizziness; drug dependence; dry mouth; dysarthria; dysgeusia; dyspepsia; epilepsy; erysipelas; euphoric mood; fall; fatigue; feeling abnormal; foot fracture; gastrointestinal carcinoma with liver metastases; hallucination; headache; infections and infestations; insomnia; metastatic oesophageal carcinoma; MS relapse; muscle spasms; muscle spasticity; nausea; orchitis; paranoia; peripheral ischaemia; phlebothrombosis; sepsis; sleep attacks; somnolence; suicidal ideation; tetany; urinary tract infection; urinary retention; urinary tract infection NOS; vertigo; vomiting; withdrawal syndrome (aggression, agitation, delusions, irritability, insomnia and muscle spasms)†; and withdrawals due to adverse events. *Excluded from our analysis*: Apathy; decubitus ulcer‡; haemoptysis‡; malaise; road traffic accident‡; and worsened depression‡.					

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Kavia 2010[36]					
Design Registered in *ClinicalTrials.gov* (NCT00678795, study results posted)	MS patients with overactive bladder (OAB), failed to respond adequately to first-line therapies Multicentric (UK, Belgium and Romania) RCT, placebo-controlled Double-blind Parallel 10 weeks (2-week baseline, 8-week treatment) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	Non-statistical significance reduction in Number of episodes of incontinence. Some significant positive effects on other bladder symptoms.
		Dose = 1-48 sprays/day (2.7-129.6 mg THC + 2.5-120 mg CBD) Self-titrated dose		Dose = 1-48 sprays/day Self-titrated dose	
		Mean dose (median) = 8.91 (7.19) sprays/day (24.06 mg THC + 22.28 mg CBD)		Mean dose (median) = 17.05 (14.22) sprays/day	
$N/n_{initial}$	135	67	..	68	
Sex					
M	37 (27%)	15 (22%)	..	22 (32%)	
F	98 (73%)	52 (78%)	..	46 (68%)	
Mean age (SD) years	47.7 (10.31)	48.6 (9.31)	..	46.8 (11.20)	
Episodes of Incontinence/day (number of patients)	..	1.8 (n = 63)	..	2.1 (n = 66)	
Episodes of Nocturia/day (number of patients)	..	1.6 (n = 63)	..	1.5 (n = 66)	
N/n_{final}	118 (87%)	56 (84%)	..	62 (91%)	
Assessment					
Efficacy: *Included in our analysis*: Bladder symptom severity (Overall Bladder Condition, OBC) NRS; Daily number of incontinence episodes Diary; Incontinence pad weight; Incontinence QoL Questionnaire; Nocturia episodes Diary (per day); Number Daytime voids Diary (per day); Number of incontinence pads used Diary (per day); and Void urgency episodes Diary (per day). *Excluded from our analysis*: Cystometric capacity (Voiding cystometry); Patient´s GIC; Post-void residual volume; Responder analysis of the frequency of urgency; Total number of voids Diary (per 24 h); and Volume voided (per 24h). *Tolerability:* *Included in our analysis*: Abdominal pain upper; anorexia; application site pain; balance impaired; chest pain; confusion; constipation; cystitis; dehydration; diarrhoea; disorientation; dissociation; disturbance in attention; dizziness; fatigue; feeling abnormal; feeling drunk; haemorrhagic cystitis; headache; influenza; intoxication (shaking, coordination problems and severe absence)†; memory impairment; MS relapse; nasopharyngitis; nausea; neck pain; paraesthesia; pharyngitis; pharyngitis viral NOS; pyrexia; somnolence; toothache; urinary tract infection; vertigo; vomiting; weakness; and withdrawals due to adverse events. *Excluded from our analysis*: Intoxication NRS; and sweating increased.					

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Novotna 2011[37]					
Design (enriched study design) Registered in *ClinicalTrials.gov* (NCT00681538, study results posted)	MS patients with spasticity, not wholly relieved with current antispasticity medication, and at least a 20% reduction in mean Spasticity NRS score after 4 weeks of the previous single-blind phase A treatment (responders) Multicentric (UK, Spain, Poland, Czech Republic and Italy) RCT, placebo-controlled Double-blind (phase B) Parallel 12 weeks (12-week treatment) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	Significant reduction in spasticity.
		Dose = 1-12 sprays/day (2.7-32.4 mg THC + 2.5-30 mg CBD) Self-titrated dose		Dose = 1-12 sprays/day Self-titrated dose	
		Mean dose (SD) = 8.3 (2.43) sprays/day (22.41 mg THC + 20.75 mg CBD)		Mean dose (SD) = 8.9 (2.31) sprays/day	
$N/n_{initial}$	241	124	..	117	
Sex					
M	96 (40%)	52 (42%)	..	44 (38%)	
F	145 (60%)	72 (58%)	..	73 (62%)	
Mean age (SD) years	48.6 (9.33)	49.1 (9.09)	..	48.1 (9.59)	
Mean DD (SD) years	12.6 (7.88)	13.3 (8.29)	..	11.8 (7.38)	
Mean EDSS (SD)	6.0 (1.45)	6.5 (1.46)	..	6.0 (1.44)	
Mean spasticity NRS (SD)	3.9 (1.51)	3.9 (1.49)	..	3.9 (1.55)	
N/n_{final}	224 (93%)	109 (88%)	..	115 (98%)	
Assessment					
Efficacy: *Included in our analysis*: MAS; SF-36-Bodily pain subscale; Sleep Disruption (due to spasticity) NRS; and Spasticity NRS. *Excluded from our analysis*: BDI-II; BI; Carer GIC; Clinician GIC; EQ-5D Health state index; EQ-5D Health status VAS items; MI (arms), and MI (legs) items; Physician GIC; SF-36-General health, SF-36-Mental health, SF-36-Physical functioning, SF-36-Role emotional, SF-36-Role physical, SF-36-Social functioning, and SF-36-Vitality subscales; Spasm frequency NRS; Spasticity NRS 30% responders; Spasticity NRS 50% responders; Subject´s GIC; and T10-MW. *Tolerability:* *Included in our analysis*: Abdominal pain (upper); back pain; balance disorder; bronchopneumonia; diarrhoea; dizziness; dry mouth; euphoric mood; fatigue; headache; infections and infestations; MS relapse; muscle spasms; muscle spasticity; nasopharyngitis; nausea; pain in extremity; septic shock; somnolence; suicidal ideation; urinary tract infection; urosepsis; vertigo; and withdrawals due to adverse events. *Excluded from our analysis*: Pregnancy‡.					

(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Zajicek 2012[38]					
Design Registered in *ClinicalTrials.gov* (NCT00552604, no study results posted)	MS patients with muscle stiffness Multicentric (UK) RCT, placebo-controlled Double-blind Parallel 14 weeks (2-week screening, 12-week treatment) ITT analysis	Oral CE caps.: (2.5 mg THC + 1.25 mg CBD)/caps.	..	Placebo caps.	Effect in the treatment of muscle stiffness.
		Dose = 2-10 caps./day (5 mg-25 mg THC + 2.5 mg-12.5 mg CBD) Self-titrated dose		Dose = 2-10 caps./day (5 mg-25 mg/day) Self-titrated dose	
		Mean dose (SD) = 7.81 (2.75) caps./day (end of titration period) (19.52 mg THC + 9.76 mg CBD)* Mean dose (SD) = 6.81 (2.99) caps./day (end of study period) (17.02 mg THC + 8.51 mg CBD)*		Mean dose (SD) = 9.60 (1.27) caps./day (end of titration period) (24.00 mg)* Mean dose (SD) = 9.36 (1.51) caps./day (end of study period) (23.40 mg)*	
$N/n_{initial}$	277	143	..	134	
Sex					
M	102 (37%)	55 (38%)	..	47 (35%)	
F	175 (63%)	88 (62%)	..	87 (65 %)	
Subtype of MS					
RRMS	21 (8%)	13 (9%)	..	8 (6%)	
SPMS	190 (69%)	96 (67%)	..	94 (70%)	
PPMS	66 (24%)	34 (24%)	..	32 (24%)	
Mean age (SD) years	..	51.9 (7.70)	..	52.0 (7.90)	
Mean DD (SD) years	..	14.5 (9.50)	..	15.1 (8.40)	
N/n_{final}	224 (81%)	109 (76%)	..	115 (86%)	
Assessment					
Efficacy: *Included in our analysis:* Body pain CRS; and MSSS-88-Ability to walk, MSSS-88-ADL/Daily activities, MSSS-88-Body movement, MSSS-88-Feelings, MSSS-88-Muscle spasms, MSSS-88-Muscle stiffness, MSSS-88-Pain and discomfort, and MSSS-88-Social functioning subscales. *Excluded from our analysis*: EDSS; MSIS-29 Physical impact, and MSIS-29 Psychological impact items; MSWS-12; Muscle spasms CRS; Muscle stiffness CRS; and Sleep quality (Quality of sleep) CRS. *Tolerability:* *Included in our analysis*: Asthenia; dizziness; dry mouth; fatigue; headache; urinary tract infection; and withdrawals due to adverse events. *Excluded from our analysis*: Balance disorder; confusional state; diarrhoea; disorientation; disturbance in attention; fall; feeling abnormal; head injury; interstitial lung; nausea; pain in extremities; and somnolence.					

(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Langford 2013[39]					
Design Registered in *ClinicalTrials.gov* (NCT00391079, study results posted)	MS patients with central neuropathic pain Multicentric (UK, Czech Republic, Canada, Spain and France) RCT, placebo-controlled Double-blind (phase A) Parallel 15 weeks (1-week baseline, 14-week treatment) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	No statistical significant reduction of pain.
		Dose = 8-12 sprays/day (21.6-32.4 mg THC + 20-30 mg CBD) Self-titrated dose		Dose = 8-12 sprays/day Self-titrated dose	
		Mean dose (SD) = 8.8 (3.87) sprays/day (23.76 mg THC + 22.00 mg CBD)		Mean dose (SD) = 11.1 (4.6) sprays/day	
$N/n_{initial}$	339	167	..	172	
Sex					
M	109 (32%)	54 (32 %)	..	55 (32 %)	
F	230 (68%)	113 (68 %)	..	117 (68 %)	
Subtype of MS					
RRMS	157 (46%)	80 (48%)	..	77 (45%)	
SPMS	136 (40%)	65 (39%)	..	71 (41%)	
PPMS	40 (12%)	18 (11%)	..	22 (13%)	
PRMS	6 (2%)	4 (2%)	..	2 (1%)	
Mean age (SD) years	48.97 (10.47)	48.42 (10.43)	..	49.51 (10.50)	
Mean DD (SD) years	11.99 (8.26)	11.42 (8.00)	..	12.53 (8.50)	
Mean Pain NRS (SD)	6.58 (1.32)	6.55 (1.35)	..	6.61 (1.29)	
N/n_{final}	297 (88%)	141 (84%)	..	156 (91%)	
Assessment					
Efficacy: *Included in our analysis*: Bladder symptoms NRS; BPI-SF; NPS; Pain (due to MS) NRS; PDI; SF-36-Bodily pain subscale; Sleep quality (Sleep Disruption, due to pain) NRS; Spasticity NRS; and Subjec´s GIC for pain. *Excluded from our analysis*: Breakthrough analgesia; EQ-5D Health state index, and EQ-5D Health status VAS items; Fatigue NRS; Pain NRS 30% responder analysis; Pain NRS 50% responder analysis; SF-36-General health, SF-36-Mental health, SF-36-Physical functioning, SF-36-Role emotional, SF-36-Role physical, SF-36-Social functioning, and SF-36-Vitality subscales; Spasms severity NRS; and Tremor NRS. *Tolerability:* *Included in our analysis*: Balance disorder; constipation; depression; diarrhoea; disturbance in attention; dizziness; dry mouth; dysgeusia; fatigue; feeling abnormal; headache; hepatic enzyme increased; infections and infestations; memory impairment; muscular weakness; nausea; neuralgia; orthostatic hypotension; pain; pain in extremity; pharyngolaryngeal pain; somnolence; suicidal ideation; syncope; vertigo; vision blurred; vomiting; and withdrawals due to adverse events. *Excluded from our analysis*: Motor dysfunction‡; and psychomotor skills impaired.					

(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Vachová 2014[40]					
Design Registered in *ClinicalTrials.gov* (NCT01964547, study results posted)	MS patients with spasticity, not wholly relieved with current anti-spasticity therapy Multicentric (Czech Republic) RCT, placebo-controlled Double-blind Parallel 50 weeks (48-week treatment, 2-week end of treatment follow-up period) ITT/PP analyses	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	No association with cognitive decline or significant changes in mood (long-term treatment). No statistical significant difference in spasticity.
		Dose = 1-12 sprays/day (2.7-32.4 mg THC + 2.5-30 mg CBD) Self-titrated dose		Dose = 1-12 sprays/day Self-titrated dose	
		Mean dose (SD) = 7.6 (3.1) sprays/day (first month) (20.52 mg THC + 19.00 mg CBD) 6.4 (3.1) sprays/day (last three months) (17.28 mg THC + 16.00 mg CBD)		Mean dose (SD) = 9.5 (2.4/2.6).sprays/day (from first to last three months)	
$N/n_{initial}$	121	62	..	59	
Sex					
M	45 (37%)	23 (37%)	..	22 (37%)	
F	76 (63%)	39 (63%)	..	37 (63%)	
Subtype of MS					
RRMS	59 (49%)	26 (42%)	..	33 (56%)	
SPMS	43 (36%)	24 (39%)	..	19 (32%)	
PPMS	16 (13%)	11 (18%)	..	5 (8%)	
PRMS	3 (2%)	1 (2%)	..	2 (3%)	
Mean age (SD) years	48.6 (9.64)	49.0 (8.95)	..	48.2 (10.38)	
Mean DD (SD) years	13.9 (8.55)	13.9 (8.09)	..	13.9 (9.08)	
Mean Spasticity NRS (SD)	6.7 (1.86)	6.7 (2.04)	..	6.7 (1.67)	
N/n_{final}	98 (81%)	50 (81%)	..	48 (81%)	
Assessment					
Efficacy: *Included in our analysis*: MAS; and Subject´s GIC for spasticity. *Excluded from our analysis*: BDI-II; Caregiver´s GIC; C-SSRS; Number of visits to a healthcare professional; PASAT; Physician´s GIC; and T10-MW. *Tolerability:* *Included in our analysis*: Acute myocardial infarction; anxiety disorder due to a general medical condition; application site discomfort; asthenia; back pain; bacterial infection; blood alkaline phosphatase increased; bronchitis; cerebellar ataxia; death; decreased appetite; dermatitis allergic; diarrhoea; disorientation; dizziness; drug withdrawal syndrome; dry mouth; dysarthria; euphoric mood; fatigue; foot fracture; forearm fracture; gingivitis; headache; herpes zoster; joint dislocation; ligament sprain; lower limb fracture; memory impairment; MS relapse; muscle spasms; muscle spasticity; nausea; neuralgia; oral mucosal erythema; oropharyngeal blistering; overdose; pain in extremity; paraesthesia; paraparesis; pneumonia; pyrexia; somnolence; subcutaneous abscess; suicidal ideation; tetany; thermal burn; tonsillitis; tremor; trigeminal neuralgia; upper limb fracture; upper respiratory tract infection; upper respiratory tract infection bacterial; urinary tract infection; vertigo; viral infection; visual impairment; vitamin D decreased; vomiting; weight decreased; and withdrawals due to adverse events. *Excluded from our analysis*: Cognitive disorder; contusion; drug hypersensitivity; erectile dysfunction; face injury; inguinal hernia‡; lipoma excision; MS; procedural vomiting; radiculopathy; stupor; and tooth extraction.					

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eTable 1: Characteristics of the included studies *(continued)*					
		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Turcotte 2015[41]					
Design Registered in *ClinicalTrials.gov* (NCT00480181, no study results posted)	RRMS patients with neuropathic pain, on a non-effective treatment with gabapentin at a stabilized dose of ≥1800 mg/day for at least 1 month Unicentric (Canada) RCT, placebo-controlled Double-blind Parallel 9 weeks (9-week treatment) ITT/PP analyses	..	Oral nabilone caps.: Available 0.5 or 1 mg THC/cap.	Placebo caps.	Nabilone as an adjunctive to gabapentin is an effective, well-tolerated combination for MS-induced neuropathic pain.
			Dose = 1 (0.5 mg THC/caps.)-2 (1 mg THC/caps.) caps./day (0.5-2 mg THC)	Dose = 1 (0.5 mg/caps.)-2 (1 mg /caps.) caps./day (0.5-2 mg)	
			Mean dose not specified	Mean dose not specified	
$N/n_{initial}$	15	..	8	7	
Sex					
M	2 (13%)	..	1 (13%)	1 (14%)	
F	13 (87%)	..	7 (88%)	6 (86%)	
Subtype of MS					
RRMS	15	..	..	..	
Mean age (SD) years	45.5 (10.84)	..	42.12 (11.20)	50.0 (8.48)	
Median DD (IQR) years	6.5 (5-8.75)	..	5.5 (4.5-7.25)	8 (6.25-9)	
Mean EDSS (SD)	2.82 (0.77)	..	2.56 (0.77)	3.17 (1.07)	
Mean Pain intensity (SD)	77.00 (14.04)	..	79.00 (13.76)	74.33 (13.99)	
Mean Pain impact (SD)	59.85 (23.47)	..	63.00 (19.23)	54.8 (30.86)	
N/n_{final}	14 (93%)	..	7 (88%)	7 (100%)	
Assessment					
Efficacy: *Included in our analysis*: Impact of pain on daily activities VAS Diary (VAS_{impact}); Pain intensity VAS Diary (VAS_{pain}); Patient-rated GIC for neuropathic pain. *Excluded from our analysis*: EDSS; SF-36; and SF-MPQ. *Tolerability:* *Included in our analysis*: Withdrawals due to adverse events. *Excluded from our analysis*: Dizziness; drowsiness; dry mouth; and headache.					
					(continue)

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eTable 1: Characteristics of the included studies *(continued)*

		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Ball 2015[42]					
Design	Progressive MS patients Multicentric (UK) RCT, placebo-controlled Double-blind Parallel 3 years (3-year treatment) ITT/PP analyses	..	Oral THC caps. (dronabinol): 3.5 mg THC	Placebo caps.	No effect in slowing progression of MS.
			Dose = 2-8 caps./day (7-28 mg THC) Titrated against body weight and adverse effects	Dose = 2-8 caps./day Titrated against body weight and adverse effects	
			Median dose = 4 (25th–75th percentiles 2–6) caps./day (final year of follow-up) (14.00 mg THC)	Median dose = 6 (25th–75th percentiles 4–8) caps./day (final year of follow-up)	
$N/n_{initial}$	493	..	329	164	
Sex					
M	201 (41%)	..	133 (40%)	68 (41%)	
F	292 (59%)	..	196 (60%)	96 (59%)	
Subtype of MS					
SPMS	302 (61%)	..	203 (62%)	99 (60%)	
PPMS	191 (39%)	..	126 (38%)	65 (40%)	
Mean age (SD) years	52.19 (7.80)	..	52.29 (7.60)	51.97 (8.20)	
Mean EDSS (SD)	5.9 (0.69)	..	5.8 (0.69)	5.9 (0.67)	
N/n_{final}	415 (84%)	..	267 (81%)	148 (90%)	
Assessment					
Efficacy: (3 years, unless specified) *Included in our analysis*: Bladder problems CRS; and MSSS-88-Ability to walk/Walking, MSSS-88-ADL/Daily activities, MSSS-88-Body movements, MSSS-88-Feelings, MSSS-88-Muscle spasms, MSSS-88-Muscle stiffness, MSSS-88-Pain and discomfort, and MSSS-88-Social functioning subscales. *Excluded from our analysis*: 9-HPT (annual change); BDI-II; Co-ordination CRS; Depression CRS; EDSS (number of first progression events per patient-year); EQ-5D five dimensions questionnaire; Fatigue CRS; Forgetfulness CRS; Irritability CRS; MSFC; MSIS-29 Physical and MSIS-29 Psychological items; MSWS-12; PASAT (annual change); RMI (annual change); Sensory loss or numbness CRS; SF-36, SF-36 (PH) (annual change); T25-FW (annual change); and Tremor CRS. Neurophysiological measures (MRI). *Tolerability:* *Included in our analysis*: Death; dissociative and thinking or perception disorders; dizziness and lightheadedness; falls and injuries; fatigue and tiredness; infections (excluding urinary tract); joint disorders; mobility, balance, and coordination problems; mood disorders (depression); muscle disorders (weakness); musculoskeletal pain and aches; urinary tract infections; and withdrawals due to adverse events. *Excluded from our analysis*: Admission to hospital‡; constipation, diarrhoea, or faecal incontinence; life-threatening or important medical event‡; and muscle disorders (spasticity, stiffness, spasms, or tremor).					

(continue)

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eTable 1: Characteristics of the included studies *(continued)*					
		Interventions			
Study	**All participants**	**THC/CBD (CE or nabiximols)**	**THC (dronabinol or nabilone)**	**Placebo**	**Conclusions**
Leocani 2015[43]					
Design Registered in *ClinicalTrials.gov* (NCT01538225, no study results posted)	Progressive MS patients with lower limb spasticity, stable drug treatment not able to relieve symptoms as a whole Unicentric (Italy) RCT, placebo-controlled Double-blind Crossover 10 weeks (4-week/intervention, 2-week washout between treatment periods) PP analysis	Oromucosal CE (nabiximols): (2.7 mg THC + 2.5 mg CBD)/spray	..	Placebo	Clinical benefit in objective lower limb spasticity. Lack of corresponding changes in corticospinal excitability and on the monosynaptic component of the stretch reflex.
		Dose = 1-12 sprays/day (2.7-32.4 mg THC + 2.5-30 mg CBD) Self-titrated dose		Dose = 1-12 sprays/day Self-titrated dose	
		Mean dose (SD) = 7 (3) sprays/day (18.90 mg THC + 17.50 mg CBD)		Mean dose (SD) = 10 (3) sprays/day	
$N/n_{initial}$	43	43	..	43	
Sex					
M	23 (53%)	..	..	..	
F	20 (47%)	..	..	..	
Subtype of MS					
Progressive MS	43	..	..	..	..
Mean age (SD) years	48 (8.00)	..	..	..	
Mean DD (SD) years	17.1 (8.40)	..	..	..	
Mean EDSS (SD)	5.5 (1.00)	..	..	..	
Mean MAS (SD), lower limbs	8.1 (3.90)				
Mean MAS (SD), total	9.3 (5.20)	..	..	..	
Mean Spasticity NRS (SD)	7.0 (1.50)	..	..	..	
N/n_{final}	34 (79%)	34 (79%)	..	34 (79%)	
Assessment					
Efficacy: *Included in our analysis*: MAS (lower limbs, extreme outliner value retained); Pain NRS; and Spasticity NRS. *Excluded from our analysis*: 9-HPT (dominant hand), and 9-HPT (non-dominant hand); FSS; MAS (lower limbs, extreme outliner value removed); MAS (upper limbs); MAS 20% responders; Sleep quality NRS (PSQI); Spasm frequency; Spasticity NRS 20% responders; and T10-MW. Neurophysiological assessment (H-reflex, and TMS). *Tolerability:* *Included in our analysis*: Dizziness; faringodynia; fever; hypotension; lower limb weakness; somnolence; subjective weakness; vertigo; and withdrawals due to adverse events. *Excluded from our analysis*: Acute pancreatitis‡; and hypertension.					

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eTable 2: Summary of the selected clinical assessment tools

†Items, or some of them, composing the tool were included individually in the statistical analysis.
CRS = Category Rating Scale. GIC = Global Impression of Change. MS = multiple sclerosis. NRS = Numerical Rating Scale. QoL = quality of life. VAS = Visual Analog Scale.

Clinical assessment tool **Publication where analyzed**	**Description**	**Evaluated outcomes**
Ashworth scale[25,26,29,32,34]	Scored by an observer. Measures passive resistance to movement during muscle stretching.	Spasticity (Ashworth)
Bladder (Bladder Problems) VAS[30]	Bladder problems.	Bladder dysfunction
Bladder problems CRS[42]	Bladder problems.	Bladder dysfunction
Bladder questionnaire (Bladder Control Test)[30]	Bladder symptoms and control, and effects on the patient's life.	Bladder dysfunction
Bladder symptom severity (Overall Bladder Condition, OBC) NRS[36]	Severity of urinary incontinence and general bladder symptoms.	Bladder dysfunction
Bladder symptoms questionnaire[26]	Overall effect of medication in bladder function.	Bladder dysfunction
Bladder symptoms NRS[35,39]	Bladder symptoms.	Bladder dysfunction
Bladder VAS Diary[30]	Severity of bladder symptoms.	Bladder dysfunction
Body pain CRS[38]	Pain.	Pain
Brief Pain Inventory-Short Form (BPI-SF)[39]	Rate pain and the degree to which pain interferes with activities.	Pain
Daily number of incontinence episodes Diary[36]	Incontinence episode frequency.	Bladder dysfunction
Impact of pain on daily activities VAS Diary (VAS_{impact})[41]	Impact of pain on daily activities.	Pain
Incontinence pad weight[36]	Weight of the incontinence pads used.	Bladder dysfunction
Incontinence QoL Questionnaire[36]	Impact of lower urinary tract symptoms on patient´s quality of life.	Bladder dysfunction
Micturition problems questionnaire Diary[29]	Micturition.	Bladder dysfunction
Modified Ashworth scale[30,35,37,40,43]	Modified version of the Ashworth scale adding a 1+ grade for resistance throughout the reminder (less than half) of the range of movement.	Spasticity (Ashworth)
Multiple Sclerosis Spasticity Scale-88 (MSSS-88)†	Self-reported assessment of impact of spasticity in MS patients in 8 areas (ability to walk, activities of daily living, body movement, feelings, muscle spasms, muscle stiffness, pain and discomfort, and social functioning).	..
MSSS-88-Ability to walk/Walking subscale[38,42]	Effect of spasticity on walking mobility.	Spasticity (subjective)
MSSS-88-Activities of daily living/Daily activities subscale[38,42]	Effect of spasticity on daily activities.	Spasticity (subjective)
MSSS-88-Body movement subscale[38,42]	Effect of spasticity on body movements.	Spasticity (subjective)

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eTable 2: Summary of the selected clinical assessment tools *(continued)*		
Clinical assessment tool[Publication where analyzed]	**Description**	**Evaluated outcomes**
MSSS-88-Feelings subscale[38,42]	Effect of spasticity on feelings.	Spasticity (subjective)
MSSS-88-Muscle spasms subscale[38,42]	Muscle spasms due to spasticity.	Spasticity (subjective)
MSSS-88-Muscle stiffness subscale[38,42]	Muscle stiffness due to spasticity.	Spasticity (subjective)
MSSS-88-Pain and discomfort subscale[38,42]	Pain and discomfort due to spasticity.	Pain Spasticity (subjective)
MSSS-88-Social functioning subscale[38,42]	Effect of spasticity on social functioning.	Spasticity (subjective)
Neuropathic Pain Scale (NPS)[31,39]	Level of neuropathic pain.	Pain
Nocturia episodes Diary (per day)[36]	Instances of nocturia, and the time that each took place.	Bladder dysfunction
Number Daytime voids Diary (per day)[36]	Number of voids.	Bladder dysfunction
Number of incontinence pads used Diary (per day)[36]	Number of incontinence pads used.	Bladder dysfunction
Pain (central neuropathic pain) NRS[31]	Central neuropathic pain.	Pain
Pain (pain due to MS) NRS[39]	Level of pain due to MS.	Pain
Pain disability index (PDI)[39]	Degree to which aspects of patient´s life are disrupted by chronic pain.	Pain
Pain intensity VAS Diary (VAS_{pain})[41]	Pain intensity.	Pain
Pain questionnaire[26]	Overall effect of medication in pain.	Pain
Pain CRS[26]	Pain.	Pain
Pain NRS[35,43]	Pain.	Pain
Pain-relief NRS Diary[28]	Measurement of the level of relief in pain.	Pain
Pain VAS[30]	Pain.	Pain
		(continue)

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eTable 2: Summary of the selected clinical assessment tools *(continued)*		
Clinical assessment tool[Publication where analyzed]	**Description**	**Evaluated outcomes**
Pain VAS Diary[30]	Severity of pain.	Pain
Patient-rated GIC for neuropathic pain[41]	Overall patient-perceived effect of treatment on their pain levels.	Pain
Radiating pain NRS Diary [28]	Pain.	Pain
Short Form-36 Health Survey/Short Form questionnaire-36 items (SF-36)†	Self-rated health status questionnaire. Two summary scales (physical component summary and the mental component summary) are generated from 8 subscales (physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role-limitations due to emotional problems, and mental health).	..
SF-36-Bodily pain subscale[28,37,39]	Pain level and interference with normal work.	Pain
Sleep Disruption (due to spasticity) NRS [37]	Sleep disruption due to spasticity.	Spasticity (subjective)
Sleep disturbance (due to neuropathic pain) NRS[31]	Sleep disruption due to neuropathic pain.	Pain
Sleep quality (Sleep Disruption, due to pain) NRS[39]	Sleep disruption due to pain.	Pain
Sleep quality (due to spasticity) NRS[35]	Sleep disruption due to spasticity.	Spasticity (subjective)
Spasticity questionnaire[26]	Overall effect of medication in spasticity.	Spasticity (subjective)
Spasticity NRS[34,37,39,43]	Spasticity.	Spasticity (subjective)
Spasticity NRS Diary[32,35]	Spasticity.	Spasticity (subjective)
Spasticity VAS[30]	Spasticity.	Spasticity (subjective)
Spasticity VAS Diary[30]	Spasticity.	Spasticity (subjective)
Spontaneous pain intensity NRS Diary[28]	Pain.	Pain
Subject´s GIC (SGIC) for pain[39]	Status of pain due to multiple sclerosis since entry into the study.	Pain
Subject´s GIC (SGIC) for spasticity[40]	Change in spasticity since immediately before receiving the first dose of study treatment.	Spasticity (subjective)
Urge Incontinence Episodes Diary[27]	Number of incontinence episodes.	Bladder dysfunction
Void urgency episodes Diary (per day)[36]	Instances of urgency, and the time that each took place.	Bladder dysfunction

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eTable 3: Sensitivity analysis results for efficacy outcomes

Results obtained performing meta-analysis using the inverse of variance method and the random effects model (except SA1, where fixed effects model was used) on an ITT basis. Sensitivity analysis was conducted using the same statistical methods than the main analysis, but modifying the parameter specified in each of the five performed analyses (SA1 to SA5): Main analysis (all studies included[25–43]). SA1: Use of the fixed-effects model instead of random effects (all studies included[25–43]). SA2: Exclusion of studies with crossover design (5 studies, 6 publications, excluded[25,28,29,33,34,43]). SA3: Exclusion of studies with a sample size of 50 patients or fewer (5 studies, 6 publications, excluded[25,28,33,34,41,43]). SA4: Exclusion of studies with a length of treatment of 4 weeks or less (6 studies, 7 publications, excluded[25,28,29,31,33,34,43]). SA5: Exclusion of studies with a high risk of bias (7 studies, 9 publications, excluded[25–27,33,34,37,41–43]). Not estimable: Not available studies in the intervention group. Results with statistical significance shown in bold type.
SA = Sensitivity analysis. SMD = *Hedges´g* standardized mean difference.

		SMD (95% CI)					
Outcome	**Intervention**	**Main analysis**	**SA1**	**SA2**	**SA3**	**SA4**	**SA5**
Spasticity (Ashworth)	Cannabis extract	0.01 (-0.18 to 0.20)	0.01 (-0.18 to 0.20)	-0.05 (-0.29 to 0.18)	0.05 (-0.22 to 0.31)	-0.05 (-0.29 to 0.18)	0.23 (-0.14 to 0.60)
	Nabiximols	-0.11 (-0.22 to 0.01)	-0.11 (-0.22 to 0.01)	-0.10 (-0.22 to 0.02)	-0.10 (-0.22 to 0.02)	-0.10 (-0.22 to 0.02)	-0.06 (-0.20 to 0.08)
	Dronabinol	-0.16 (-0.38 to 0.07)	-0.16 (-0.38 to 0.07)	-0.16 (-0.39 to 0.07)	-0.16 (-0.39 to 0.07)	-0.16 (-0.39 to 0.07)	Not estimable
	Cannabinoids	-0.09 (-0.18 to 0.0027)	-0.09 (-0.18 to 0.0027)	**-0.10 (-0.20 to -0.0035**)	-0.08 (-0.17 to 0.02)	**-0.10 (-0.20 to -0.0035**)	-0.03 (-0.17 to 0.12)
Spasticity (subjective)	Cannabis extract	**-0.27 (-0.44 to -0.09**)	**-0.27 (-0.44 to -0.09**)	**-0.27 (-0.44 to -0.09**)	**-0.27 (-0.44 to -0.09**)	**-0.27 (-0.44 to -0.09**)	-0.20 (-0.44 to 0.04)
	Nabiximols	**-0.29 (-0.47 to -0.12**)	**-0.26 (-0.36 to -0.15**)	**-0.32 (-0.53 to -0.11**)	**-0.32 (-0.53 to -0.11**)	**-0.32 (-0.53 to -0.11**)	**-0.27 (-0.49 to -0.06**)
	Dronabinol	-0.13 (-0.46 to 0.20)	-0.09 (-0.24 to 0.06)	-0.13 (-0.46 to 0.20)	-0.13 (-0.46 to 0.20)	-0.13 (-0.46 to 0.20)	Not estimable
	Cannabinoids	**-0.25 (-0.38 to -0.13**)	**-0.22 (-0.29 to -0.14**)	**-0.26 (-0.40 to -0.13**)	**-0.26 (-0.40 to -0.13**)	**-0.26 (-0.40 to -0.13**)	**-0.25 (-0.43 to -0.08**)
Pain	Cannabis extract	**-0.33 (-0.50 to -0.16**)	**-0.33 (-0.50 to -0.16**)	**-0.33 (-0.50 to -0.16**)	**-0.33 (-0.50 to -0.16**)	**-0.33 (-0.50 to -0.16**)	**-0.29 (-0.53 to -0.05**)
	Nabiximols	-0.07 (-0.26 to 0.12)	-0.07 (-0.18 to 0.05)	-0.12 (-0.29 to 0.05)	-0.12 (-0.29 to 0.05)	-0.07 (-0.19 to 0.05)	-0.09 (-0.29 to 0.11)
	Dronabinol	-0.23 (-0.55 to 0.09)	**-0.15 (-0.29 to -0.0041**)	-0.17 (-0.53 to 0.20)	-0.17 (-0.53 to 0.20)	-0.17 (-0.53 to 0.20)	-0.50 (-1.08 to 0.08)
	Nabilone	**-1.40 (-2.78 to -0.03**)	**-1.40 (-2.78 to -0.03**)	**-1.40 (-2.78 to -0.03**)	Not estimable	**-1.40 (-2.78 to -0.03**)	Not estimable
	Cannabinoids	**-0.17 (-0.31 to -0.03**)	**-0.15 (-0.23 to -0.07**)	**-0.19 (-0.33 to -0.06**)	**-0.18 (-0.31 to -0.05**)	**-0.17 (-0.29 to -0.04**)	-0.17 (-0.34 to 0.01)

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eTable 3: Sensitivity analysis results for efficacy outcomes *(continued)*							
		SMD (95% CI)					
Outcome	**Intervention**	**Main analysis**	**SA1**	**SA2**	**SA3**	**SA4**	**SA5**
Bladder dysfunction	Cannabis extract	**-0.29 (-0.50 to -0.09**)	**-0.29 (-0.50 to -0.09**)	**-0.27 (-0.52 to -0.02**)	**-0.29 (-0.50 to -0.09**)	**-0.27 (-0.52 to -0.02**)	-0.34 (-0.71 to 0.03)
	Nabiximols	-0.07 (-0.22 to 0.08)	-0.06 (-0.18 to 0.07)	-0.07 (-0.22 to 0.08)	-0.07 (-0.22 to 0.08)	-0.07 (-0.22 to 0.08)	-0.07 (-0.22 to 0.08)
	Dronabinol	-0.06 (-0.27 to 0.16)	-0.04 (-0.19 to 0.11)	-0.06 (-0.27 to 0.16)	-0.06 (-0.27 to 0.16)	-0.06 (-0.27 to 0.16)	Not estimable
	Cannabinoids	**-0.11 (-0.22 to -0.0008**)	**-0.09 (-0.18 to -0.01**)	-0.09 (-0.20 to 0.02)	**-0.11 (-0.22 to -0.0008**)	-0.09 (-0.20 to 0.02)	-0.11 (-0.26 to 0.04)

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eTable 4: Sensitivity analysis results for tolerability outcomes

Results obtained performing meta-analysis using the inverse of variance method and the random effects model (except SA1, where fixed effects model was used) on an ITT basis. Sensitivity analysis was conducted using the same statistical methods than the main analysis, but modifying the parameter specified in each of the five performed analyses (SA1 to SA5): Main analysis (all studies included[25–43]). SA1: Use of fixed-effects model instead of random effects (all studies included[25–43]). SA2: Exclusion of studies with crossover design (5 studies, 6 publications, excluded[25,28,29,33,34,43]). SA3: Exclusion of studies with a sample size of 50 patients or fewer (5 studies, 6 publications, excluded[25,28,33,34,41,43]). SA4: Exclusion of studies with a length of treatment of 4 weeks or less (6 studies, 7 publications, excluded[25,28,29,31,33,34,43]). SA5: Exclusion of studies with a high risk of bias (7 studies, 9 publications, excluded[25–27,33,34,37,41–43]). Not estimable: Not available studies in the intervention group. Results with statistical significance shown in bold type.
SA = Sensitivity analysis. RR = rate ratio.

		RR (95% CI)					
Outcome	**Intervention**	**Main analysis**	**SA1**	**SA2**	**SA3**	**SA4**	**SA5**
Total adverse events	Cannabis extract	1.51 (0.87 to 2.63)	**1.74 (1.53 to 1.99)**	**2.09 (1.28 to 3.42)**	1.41 (0.74 to 2.66)	**2.09 (1.28 to 3.42)**	1.24 (0.26 to 5.93)
	Nabiximols	**1.80 (1.53 to 2.12)**	**1.85 (1.68 to 2.03)**	**1.72 (1.48 to 2.01)**	**1.72 (1.48 to 2.01)**	**1.74 (1.47 to 2.06)**	**1.82 (1.60 to 2.09)**
	Dronabinol	**1.62 (1.12 to 2.34)**	**1.42 (1.29 to 1.56)**	**1.42 (1.07 to 1.88)**	**1.42 (1.07 to 1.88)**	**1.42 (1.07 to 1.88)**	**3.43 (2.16 to 5.46)**
	Cannabinoids	**1.72 (1.46 to 2.02)**	**1.65 (1.55 to 1.75)**	**1.70 (1.47 to 1.98)**	**1.61 (1.37 to 1.89)**	**1.72 (1.47 to 2.00)**	**1.80 (1.45 to 2.24)**
Serious adverse events	Cannabis extract	0.99 (0.26 to 3.74)	0.82 (0.40 to 1.70)	0.99 (0.26 to 3.74)	0.99 (0.26 to 3.74)	0.99 (0.26 to 3.74)	2.19 (0.57 to 8.46)
	Nabiximols	1.43 (0.66 to 3.09)	**1.60 (1.002 to 2.56)**	1.38 (0.60 to 3.15)	1.38 (0.60 to 3.15)	1.38 (0.60 to 3.15)	1.18 (0.49 to 2.85)
	Dronabinol	1.21 (0.89 to 1.63)	1.21 (0.89 to 1.63)	1.20 (0.88 to 1.62)	1.20 (0.88 to 1.62)	1.20 (0.88 to 1.62)	3.00 (0.12 to 73.64)
	Cannabinoids	1.23 (0.82 to 1.85)	1.25 (0.98 to 1.58)	1.20 (0.78 to 1.84)	1.20 (0.78 to 1.84)	1.20 (0.78 to 1.84)	1.35 (0.67 to 2.71)
Withdrawals due to adverse events	Cannabis extract	**3.11 (1.54 to 6.28)**	**3.11 (1.54 to 6.28)**	**3.09 (1.50 to 6.36)**	**3.11 (1.54 to 6.28)**	**3.09 (1.50 to 6.36)**	**3.14 (1.53 to 6.48)**
	Nabiximols	**2.20 (1.34 to 3.59)**	**2.20 (1.34 to 3.59)**	**2.13 (1.29 to 3.50)**	**2.13 (1.29 to 3.50)**	**2.11 (1.27 to 3.49)**	**1.99 (1.20 to 3.31)**
	Dronabinol	**4.12 (2.39 to 7.11)**	**4.12 (2.39 to 7.11)**	**4.12 (2.39 to 7.11)**	**4.12 (2.39 to 7.11)**	**4.12 (2.39 to 7.11)**	Not estimable
	Nabilone	2.63 (0.11 to 64.44)	2.63 (0.11 to 64.44)	2.63 (0.11 to 64.44)	Not estimable	2.63 (0.11 to 64.44)	Not estimable
	Cannabinoids	**2.95 (2.14 to 4.07)**	**2.95 (2.14 to 4.07)**	**2.91 (2.10 to 4.03)**	**2.92 (2.11 to 4.05)**	**2.91 (2.10 to 4.04)**	**2.32 (1.53 to 3.51)**
Dizziness or vertigo	Cannabis extract	2.51 (0.84 to 7.47)	**3.28 (2.39 to 4.49)**	**5.20 (2.23 to 12.12)**	2.62 (0.74 to 9.21)	**5.20 (2.23 to 12.12)**	2.17 (0.15 to 31.20)
	Nabiximols	**3.33 (2.55 to 4.34)**	**3.33 (2.55 to 4.34)**	**3.29 (2.50 to 4.33)**	**3.29 (2.50 to 4.33)**	**3.29 (2.47 to 4.37)**	**3.22 (2.45 to 4.25)**
	Dronabinol	**4.00 (2.43 to 6.58)**	**4.10 (3.00 to 5.62)**	**4.15 (2.97 to 5.80)**	**4.15 (2.97 to 5.80)**	**4.15 (2.97 to 5.80)**	**5.20 (2.00 to 13.54)**
	Cannabinoids	**3.40 (2.55 to 4.53)**	**3.52 (2.97 to 4.18)**	**3.83 (3.20 to 4.59)**	**3.42 (2.52 to 4.65)**	**3.86 (3.17 to 4.69)**	**3.22 (2.06 to 5.04)**

(continue)

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eTable 4: Sensitivity analysis results for tolerability outcomes *(continued)*

		RR (95% CI)					
Outcome	**Intervention**	**Main analysis**	**SA1**	**SA2**	**SA3**	**SA4**	**SA5**
Dry mouth	Cannabis extract	**3.17** (**1.91 to 5.25**)	**3.17** (**1.91 to 5.25**)	**3.18** (**1.89 to 5.35**)	**3.16** (**1.89 to 5.28**)	**3.18** (**1.89 to 5.35**)	**3.15** (**1.58 to 6.25**)
	Nabiximols	**2.30** (**1.42 to 3.73**)	**2.30** (**1.42 to 3.73**)	**2.20** (**1.34 to 3.59**)	**2.20** (**1.34 to 3.59**)	**2.11** (**1.28 to 3.48**)	**2.14** (**1.28 to 3.60**)
	Dronabinol	**4.32** (**2.12 to 8.81**)	**4.32** (**2.12 to 8.81**)	**4.12** (**1.93 to 8.79**)	**4.12** (**1.93 to 8.79**)	**4.12** (**1.93 to 8.79**)	7.00 (0.36 to 135.53)
	Cannabinoids	**2.94** (**2.15 to 4.03**)	**2.94** (**2.15 to 4.03**)	**2.84** (**2.06 to 3.92**)	**2.84** (**2.06 to 3.91**)	**2.80** (**2.02 to 3.88**)	**2.49** (**1.67 to 3.73**)
Fatigue	Cannabis extract	**2.60** (**1.22 to 5.58**)	**2.60** (**1.22 to 5.58**)	**2.60** (**1.22 to 5.58**)	**2.60** (**1.22 to 5.58**)	**2.60** (**1.22 to 5.58**)	**2.60** (**1.22 to 5.58**)
	Nabiximols	**1.64** (**1.17 to 2.28**)	**1.64** (**1.17 to 2.28**)	**1.70** (**1.12 to 2.56**)	**1.70** (**1.12 to 2.56**)	**1.80** (**1.13 to 2.86**)	**1.60** (**1.08 to 2.37**)
	Dronabinol	1.09 (0.74 to 1.60)	1.09 (0.74 to 1.60)	1.06 (0.72 to 1.56)	1.06 (0.72 to 1.56)	1.06 (0.72 to 1.56)	5.00 (0.24 to 104.14)
	Cannabinoids	**1.61** (**1.18 to 2.21**)	**1.46** (**1.15 to 1.85**)	**1.61** (**1.14 to 2.30**)	**1.61** (**1.14 to 2.30**)	**1.67** (**1.14 to 2.43**)	**1.76** (**1.25 to 2.47**)
Feeling drunk	Nabiximols	3.70 (0.70 to 19.55)	3.70 (0.70 to 19.55)	3.70 (0.70 to 19.55)	3.70 (0.70 to 19.55)	**8.01** (**1.0001 to 64.14**)	3.70 (0.70 to 19.55)
	Dronabinol	11.00 (0.61 to 198.93)	11.00 (0.61 to 198.93)	Not estimable	Not estimable	Not estimable	11.00 (0.61 to 198.93)
	Cannabinoids	**4.85** (**1.15 to 20.53**)	**4.85** (**1.15 to 20.53**)	3.70 (0.70 to 19.55)	3.70 (0.70 to 19.55)	**8.01** (**1.0001 to 64.14**)	**4.85** (**1.15 to 20.53**)
Impaired balance or ataxia	Cannabis extract	3.50 (0.18 to 67.77)	3.50 (0.18 to 67.77)	Not estimable	Not estimable	Not estimable	Not estimable
	Nabiximols	**2.93** (**1.04 to 8.27**)	**2.93** (**1.04 to 8.27**)	**2.93** (**1.04 to 8.27**)	**2.93** (**1.04 to 8.27**)	**2.93** (**1.04 to 8.27**)	**3.81** (**1.27 to 11.42**)
	Dronabinol	1.28 (0.90 to 1.81)	1.28 (0.90 to 1.81)	1.25 (0.88 to 1.78)	1.25 (0.88 to 1.78)	1.25 (0.88 to 1.78)	5.00 (0.24 to 104.14)
	Cannabinoids	**1.40** (**1.01 to 1.95**)	**1.40** (**1.01 to 1.95**)	1.37 (0.98 to 1.91)	1.37 (0.98 to 1.91)	1.37 (0.98 to 1.91)	3.93 (1.40 to 11.04)
Memory impairment	Nabiximols	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)
	Cannabinoids	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)	**4.93** (**1.07 to 22.70**)

(continue)

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eTable 4: Sensitivity analysis results for tolerability outcomes *(continued)*							
		RR (95% CI)					
Outcome	**Intervention**	**Main analysis**	**SA1**	**SA2**	**SA3**	**SA4**	**SA5**
Somnolence	Cannabis extract	1.32 (0.95 to 1.83)	1.32 (0.95 to 1.83)	1.32 (0.94 to 1.85)	1.32 (0.94 to 1.85)	1.32 (0.94 to 1.85)	1.50 (0.06 to 36.82)
	Nabiximols	**3.47** (**2.10 to 5.73**)	**3.47** (**2.10 to 5.73**)	**3.50** (**2.04 to 6.00**)	**3.50** (**2.04 to 6.00**)	**3.42** (**1.98 to 5.93**)	**3.48** (**1.99 to 6.07**)
	Dronabinol	0.55 (0.06 to 4.74)	1.08 (0.77 to 1.53)	1.12 (0.79 to 1.58)	1.12 (0.79 to 1.58)	1.12 (0.79 to 1.58)	Not estimable
	Cannabinoids	**1.87** (**1.24 to 2.81**)	**1.46** (**1.18 to 1.81**)	**1.92** (**1.25 to 2.96**)	**1.88** (**1.25 to 2.82**)	**1.88** (**1.22 to 2.90**)	**3.39** (**1.96 to 5.88**)

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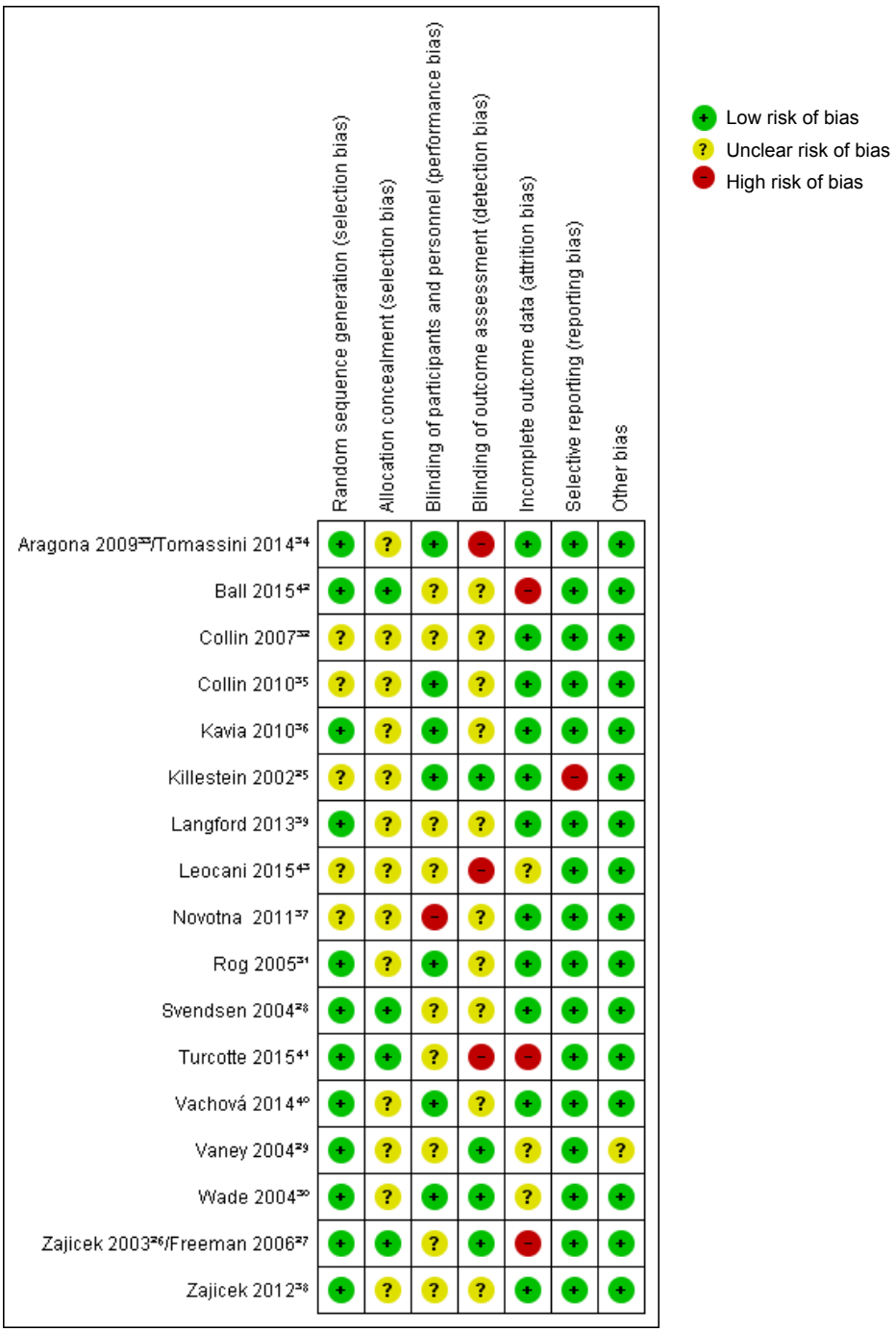
3. Supplementary eFigures

eFigure 1: Risk of bias summary of the included studies

Review authors' judgements about each risk of bias item for each included study.



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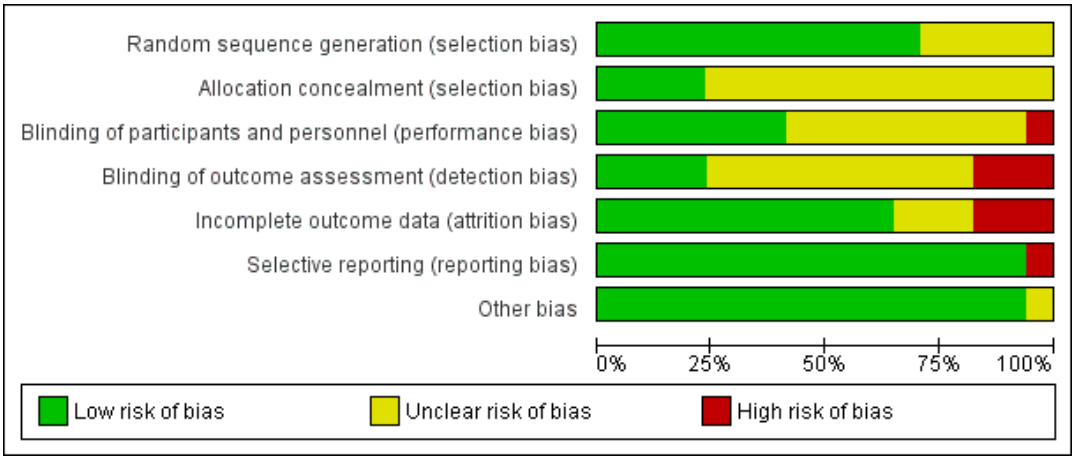
eFigure 2: Risk of bias graph of the included studies

Review authors' judgements about each risk of bias item presented as percentages across all included studies.[25-43]



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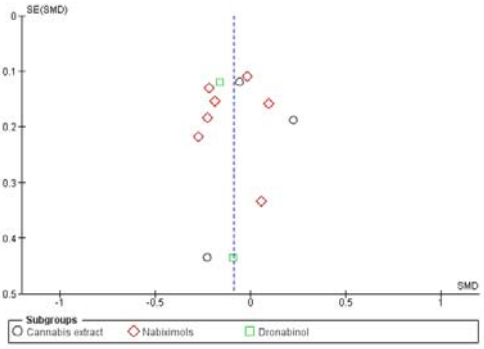
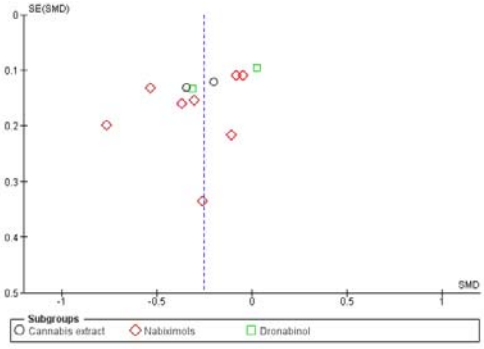
eFigure 3: Funnel plots for efficacy outcomes

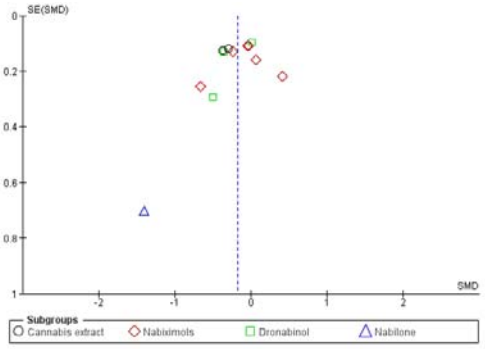
Panels 3a) Spasticity (Ashworth), 3b) Spasticity (subjective), 3c) Pain, and 3d) Bladder dysfunction



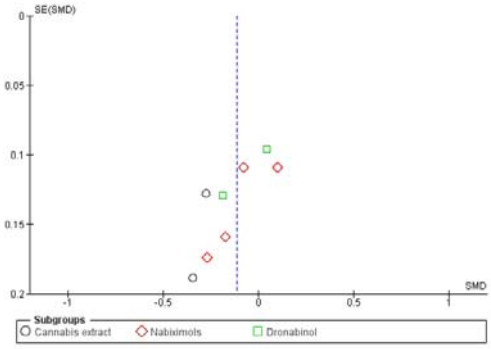
Panel 3a) Spasticity (Ashworth)



Panel 3b) Spasticity (subjective)



Panel 3c) Pain



Panel 3d) Bladder dysfunction

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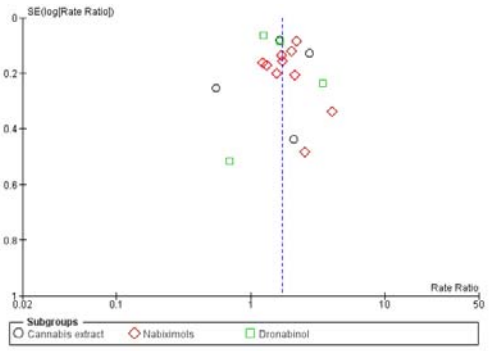
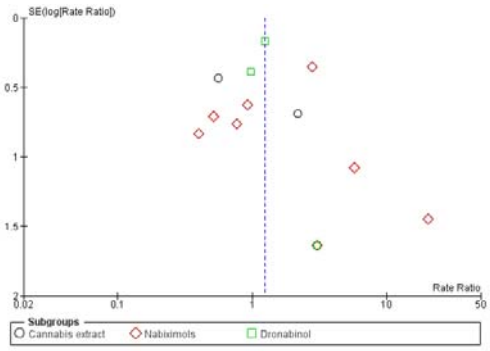
eFigure 4: Funnel plots for tolerability outcomes

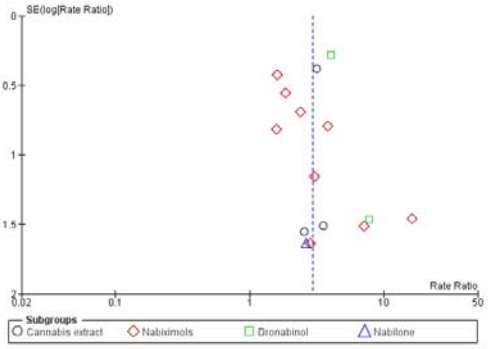
Panels 4a) Total adverse events, 4b) Serious adverse events, 4c) Withdrawals due to adverse events, 4d) Dizziness/vertigo, 4e) Dry mouth, 4f) Fatigue, 4g) Feeling drunk, 4h) Impaired balance/ataxia, 4i) Memory impairment, and 4j) Somnolence



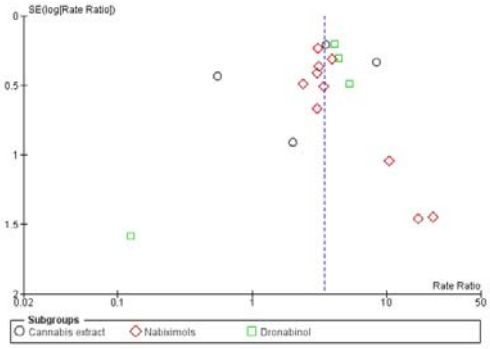
Panel 4a) Total adverse events



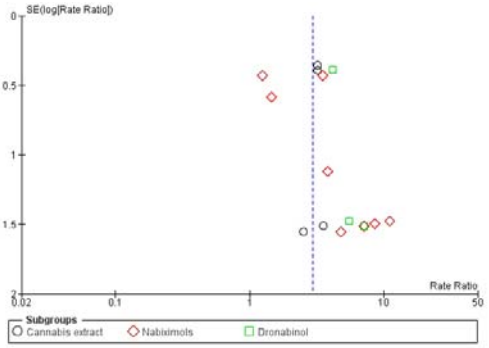
Panel 4b) Serious adverse events



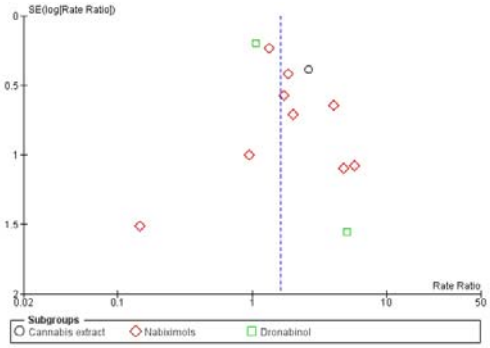
Panel 4c) Withdrawals due to adverse events



Panel 4d) Dizziness or vertigo



Panel 4e) Dry mouth



Panel 4f) Fatigue

(continue)

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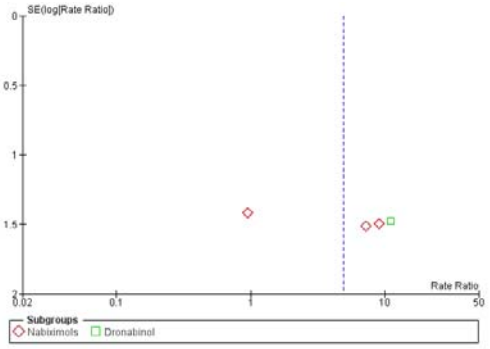
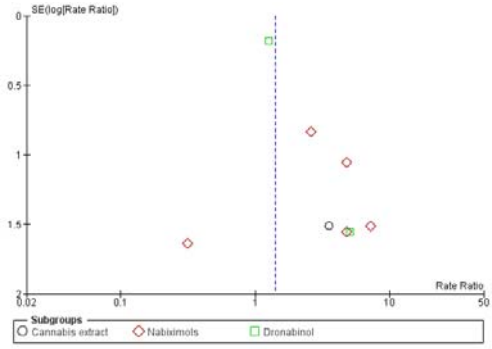
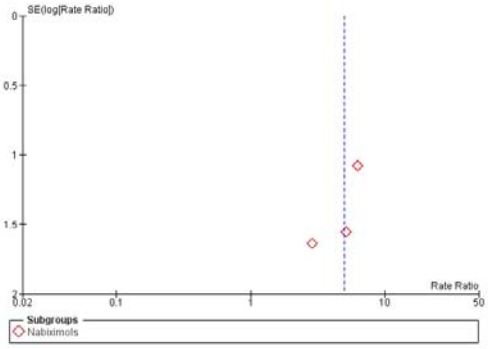
eFigure 4: Funnel plots for tolerability outcomes *(continued)*
Panels 4a) Total adverse events, 4b) Serious adverse events, 4c) Withdrawals due to adverse events, 4d) Dizziness/vertigo, 4e) Dry mouth, 4f) Fatigue, 4g) Feeling drunk, 4h) Impaired balance/ataxia, 4i) Memory impairment, and 4j) Somnolence



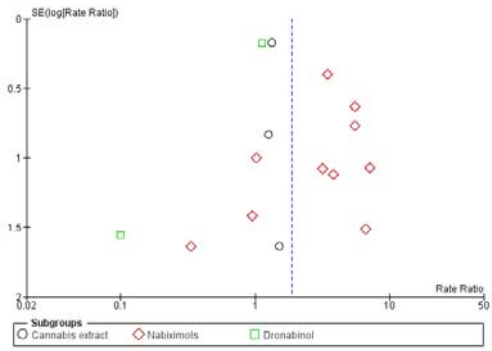
Panel 4g) Feeling drunk



Panel 4h) Impaired balance or ataxia



Panel 4i) Memory impairment



Panel 4j) Somnolence

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