Table e-1: Efficacy of cannabinoids in neurologic conditions: Bladder dysfunction

Reference	Class	Design	Group size	Completion rate	Treatment (technique, dose)	Study duration	Outcomes	Dropouts	Adverse events/ comments
Kavia 2010[26]	I	R-DB-PC	135	118 (87%) 86 per protocol due to lack of information in diary	Spray CBE 2.7 mg THC+2.5 CBD /pump max 25 mg each/d	8 weeks, treated, 10 total	No significant reduction in incontinence episodes (1.8/d CBE, 2.1 placebo), nocturia (1.6 vs 1.5), and urgency. Sig dec number of voids in daytime, (*p*=0.048), nighttime (*p*=0.007), or 24 h (*p*=0.007), improved Incontinence QOL	17 total, 11 CBE, (7 due to AE) 6 placebo (3 due to AE)	2 serious in each group, considered due to CBE: hemorrhagic cystitis, possible "TIA", MS relapse, UTI in placebo
Zajicek 2003[7]	I	R-DB-PC	630 total 522 bladder, same group as Freeman 2006	Not given for these groups but was 93% overall	Oral THC, combined CBE (CE:THC 2:1), placebo maximum THC 25 mg/d	13 weeks	Improvement in CRS (-7.98) for bladder symptoms not significant for either THC or CBE	19 total, 4 CE (2 due to AE), 9THC (7 due to AE), 6 placebo (0 AE, 3 lack efficacy)	Dizziness 50%–59%, Sleep 40,35,33% Diarrhea 37,30,20% Increased appetite in treated only/ 12, 18, 20 serious but unrelated to treatment
Wade 2004[6]	I	R-DB-PC	160 total, 32 bladder	154 (96%)	Spray CBE 2.7 mg THC+2.5 CBD /pump max 25 mg each/d	6 weeks 4 weeks optional continuation	100-point VAS for patient's chosen primary target and 5 other symptoms No difference in decrease in mean VAS for bladder dysfunction (-34.32 CBE vs -26.347 placebo; *p*=0.408). No difference in bladder questionnaire (-.12; *p*=0.83) Sig difference (13.3, -24.39 CBE vs -11.10 placebo, *p*=0.006) for patient's diary card.	6 total, 3 AE in CE, 1 each illicit cannabis use, withdrawal consent, headache in placebo	Dizziness 32%, site discomfort 26%, fatigue 15%, somnolence, dec attention, nausea, headache 9%
Vaney 2004[5]	I	R-DB-PC	57 total, 36 bladder	37 (79%)	Oral THC 2.5mg:CBE 0.9 mg Max dose 30 mg THC/d	4 week total, 10 days treatment then switch	No significant difference in micturition problems in pt diary (*p*=0.24 after Bonferroni)	6 CBD (3 due to AE), 1 placebo (not AE)	Dizziness, "high, difficulty concentrating
Freeman 2006[28]	II	R-DB-PC	522	255 had bladder information in diary (49%)	Capsules 2.5 mg THC, 1.25 mg CBE, placebo	3-day diary measured at beginning and at end of 13-week study	Change from baseline in incontinence episodes 0.616 CBE, 0.666 THC, 0.822 placebo, z values significant. Also dec weight of incontinence pads and no differences on QOL questionnaire, urodynamics	Not specified for bladder patients, 19 dropouts in main study (Zajicek 2003)	UTIs in all groups, Urinary retention or worsening of detrusor-sphincter dysnergy, 2 treated, 3 placebo patients

R = randomized, DB = double-blind, PC = placebo-controlled, CBE = cannabinoid extract, CBD = cannabidiol, QOL = quality of life, THC = tetrahydrocannabinol, AE = adverse event, TIA = transient ischemic attack, UTI = urinary tract infection, CE = cannabis extract, CRS = category rating scale, VAS = visual analog scale.

Table e-2: Efficacy of cannabinoids in neurologic conditions: Abnormal movements (HD, PD, cervical dystonia), Tourette tics

Reference	Class	Design	Group Size	Completion rate	Treatment (technique, dose)	Study duration	Outcomes	Dropouts	Adverse events/ comments
Consroe 1991[35]	III	R-DB-PC	18	15 (83%)	CBE oral 10 mg/kg/d, mean 700 mg/d	12 weeks	Chorea score of M&Q no difference (11.5 CBD, 13.7 placebo; *p*=0.71), No difference in 11 other therapeutic response variables	3, not related to trial	None reported, suspect too low dose of CBE
Curtis 2009[31]	II	R-DB-PC	44	37 (84%)	Nabilone 1 mg or 2 mg/d	5 weeks	No improvement in total motor score of UHDRS (*p*=0.5) Improvement in two NPI outcome measures (*p*=0.06) and chorea score (*p*=0.0009)	7 total, 3 for AEs, 1 treated, 2 placebo (excess sleepiness, unable to understand trial)	2 AEs in placebo, asthma attack and seizure, sleepiness in treated pt. Most reported drowsiness; forgetfulness in both treated and placebo
Carroll 2004[36]	I	R-DB-PC-crossover	19	17(89%)	CBD 1.25 2.5 mg THC/capsules (mean 0.146 mg/kg/d	4 weeks active, 10 total	Dopa-induced dyskinesia in Parkinson disease: non-sig (*p*=0.09) worsening (+0.52) of dyskinesia score (Q 32–34) of UPDRS, no sig effect on CRS, motor function	1 CBE, not due to AE (worsening of off period), 1 placebo (panic attack)	Mild, but most pts did not reach target dose
Müller-Vahl 2002[39]	II	R-DB-PC	12	12	THC capsule (5.0, 7.5 or 10.0 mg) single dose	Single dose	Tics of Tourette showed significant improvement on self-rated TSSL score (*p*=0.015) and OCB (*p* = 0.041) in treated patients. Complex motor tics improved by examiner measure (*p*=0.015)	None—single dose	Mild, transient
Müller-Vahl 2003[40]	III	R-DB-PC	24	17 (70%)	10 mg/d THC capsule	6 weeks	Tics of Tourettes decreased by self-rated Tourette score (*p*=0.05) and by observer-rated scores (TS-CGI, STSSS, TGTSS, and video rating)	7 total, 1 for AE	Not stated

R = randomized, DB = double-blind, PC = placebo-controlled, CBE = cannabinoid extract, M&Q = Mardsen and Quinn Chorea Scale,[e18] CBD = cannabidiol, THC = tetrahydrocannabinol, UPDRS=United Parkinson's Disease Rating Scale,[37] AE = adverse event, CRS = category rating scale, UHDRS = Unified Huntington's Disease Rating Scale,[32] NPI = Neuropsychiatric Inventory,[e19] TSSL = Tourette Syndrome Symptom List,[e20] OCB = obsessive-compulsive behavior, TS-CGI = Tourette Syndrome Clinical Global Impressions scale,[e20] STSSS = Shapiro Tourette Syndrome Severity Scale,[e21] TGTSS = Tourette Global Tic Severity Scale.[e22]

Table e-3: Efficacy of cannabinoids in neurologic conditions: central pain and spasms

Reference	Class	Design	Group size	Completion rate	Treatment (technique, dose)	Study duration	Outcomes	Dropouts	Adverse events/ comments
Zajicek 2012[8]	I	R-DB-PC	279	224 (80.8%)	Titrated doses of oral CBD/THC 2.5–5 mg/capsule bid	12 weeks	Patient-rated NRS scales 0–11 Muscle stiffness (primary), spasms, pain, insomnia (secondary) Significant relief of muscle stiffness 29.4% CE vs 15.7% placebo, $p<0.025$) with most marked response in group reporting highest pain levels at baseline ($p=0.001$)	53 total, 34 CE (30 AE), 19 placebo (9 AE) 47% CE, 87% placebo reached max dose	71% nervous system disorders in AEs, 41.3% GI
Zajicek 2003[7]	I	R-DB-PC	630 total, 419 pain, 520 spasm	Not given for these groups but was 93% overall	Oral THC, CBE (CBD:THC 2:1), placebo Dose related bid, maximum 25 mg/d, mean 25.9 THC, 24 CBE)	13 weeks	Improvement in CRS for pain, (46% CE, 50% THC, 30% placebo) and spasms (53%,49%,39%); Improved walk time (12%, ns) attributed to less pain	19 total, 4 CE (2 due to AE), 9 THC (7 due to AE), 6 placebo (0 AE, 3 lack efficacy)	Dizziness 50%–59%, Sleep 40,35,33% Diarrhea 37,30,20% Increased appetite in treated only/ 12,18,20 serious but unrelated to treatment
Wade 2004[6]	I	R-DB-PC	160 total, 36 pain, 38 spasms	154 (96%)	Spray CBE 2.7 mg THC+2.5 CBD /pump max 25 mg each/d	6 weeks 4 weeks optional continuation	100-point VAS for patient's chosen primary target and 5 other symptoms No difference in decrease in mean VAS for pain (-11.44 CBE vs -20.17 placebo, $p=0.360$). No difference in mean spasms -26.5 CBE, -21.2 spasms. No difference in patient's diary card, (spasm frequency -1.27, $p=0.869$, spasm severity -0.008, $p=0.992$, pain 10.04, $p=0.203$)	3 each group, for AEs in CE, for using cannabis, withdrawing consent and headache in placebo	Dizziness 32%, site discomfort 26%,fatigue 15%, somnolence, dec attention, nausea, headache 9%
Vaney 2004[5]	I	R-DB-PC	57, 49 reported spasms	37 (79%)	Oral CE 2.5 mg THC+0.9 mg CBD	14 days	1.76 mean difference (improvement) in self-reported spasm frequency and mobility, sleep, $p=0.058$ in ITT group, 0.013 in PP group with significant change over trial period	7 total, 6 in treatment group, 3 for AEs, 3 withdrew consent, 1 for placebo, withdrew consent	Max tolerated dose 27.5 mg THC, reached in 14 pts
Rog 2005[24]	I	R-DB-PC	66	64 (97%)	Nabiximols spray 2.7 mg CE/2.5 THC Maximum 48 sprays/d, mean 9.6 mg THC/d	4 weeks treated, 5 total	Patient-rated 0–11 NRS scale, decrease in mean intensity of pain, 2.7 treated, 1.49 placebo Secondary outcome of response on neuropathic pain score of significant effect on intense, dull, and sensitive pain	2 total, 1 treated AE hyperten-sion and tachycardia, 1 placebo no consent	Dizziness, dry mouth, decrease long-term memory
Collin 2010[10]	II	R-DB-PC	337	265 (79%)	Nabiximols spray assessed 2,6,10,14 weeks	14 weeks	Secondary outcomes of NRS score, no significant difference seen in change in spasm frequency (-0.86 treated vs -0.85 placebo, $p=0.955$) or pain NRS (-1.22 treated vs -1.14 placebo, $p=0.763$).	Total 55, 35 treated, 9 for AE, 20 placebo, 5 for AE	15 serious, 4 psychosis, 2 insomnia after withdrawal from treatment. Overall AEs 87% active, 56%

									placebo
Zajicek 2005[11]	II	R-DB-PC	502 in follow-up to 2003 study, 356 pain, 438 spasm	80% from initial study	Oral THC, CBD (CBD:THC 2:1), placebo	12 months	Improvement in CRS for pain (31% CE, 28% THC, 14% placebo, *p*=0.002) and for spasms (36% CE, 29% THC, 23% placebo, *p*=0.002)	20% dropout	Continuation of CAMS with similar loss for multiple reasons, including lack of efficacy, difficulty with travel, no reason given
Centzone 2009[13]	III	Open-label study (placebo requested but rejected by IRB)	20	Not specified	Nabiximols spray	6 weeks	There was no significant difference in weekly patient-reported NRS of pain (no statistics given)	Unknown	Not discussed
Corey-Bloom 2012[14]	III	R-DB-PC	37	30 (91%)	Smoked MJ cig 4% THC by weight, tid	2 weeks	Secondary outcome of decrease points on VAS for pain by 5.28 points more in MJ than placebo (*p*=0.008)	7 total, 5 due to AEs (felt "high":2, dizzy: 2, fatigue:1)	5-point increase in feeling of "highness" and most patients guessed their treatment at most visits. 8.67-point dec cognitive function on PASAT when using MJ
Svendsen 2004[25]	III	R-DB-PC	24	24 (100%)	Dronabinol 2.5 mg, maximum 10 mg/d	3 weeks total, 10 days treatment	Sig decrease in median spontaneous pain intensity, (4 vs 5 placebo, scale 0–10, *p*=0.02) and -0.6 difference in median pain relief score (3 treated, 0 placebo, *p*=0.035) No effect on secondary median radiating-pain intensity, pain relief, use of escape medication, QOL, and EDSS	46% placebo, 96% treatment reported AEs but only 17% had dose reduction due to AEs	Most AEs were dizziness, somnolence and occurred in first week of treatment.
Wade 2006[18]	III	R-DB-C followed by open-label phase. This article reports on open-label phase.	137	79 (57%)	Nabiximols spray	Mean duraton >400 days	VAS for symptoms decreased from baseline of 65–70 (depending on symptom) to 23–32. For pain, went from 68.1 (10.6 standard deviation) to 26.4 (18.7).	lack of efficacy 24, patients withdrew consent 6, lost to follow-up 3, AE 17, other 8	n=1 to 2 for a variety of complaints. The most concerning was a possibly related death in 1.

R = randomized, DB = double-blind, PC = placebo-controlled, CBD = cannabidiol, THC = tetrahydrocannabinol, CE = cannabis extract, AE = adverse event, GI = gastrointestinal, NRS = numeric rating scale, CBE = cannabinoid extract, CAMS = cannabinoids for treatment of spasticity and other symptoms related to multiple sclersosis, IRB = institutional review board, MJ = marijuana, VAS = visual analog scale, PASAT = Paced Auditory Serial Addition Test,[e23] QOL = quality of life, EDSS = Expanded Disability Status Scale.[e24]

Table e-4: Efficacy of cannabinoids in neurologic conditions: Spasticity

Reference	Class	Design	Group size	Completion rate	Treatment (technique, dose)	Study duration	Outcomes	Dropouts	Adverse events/ comments
Zajicek 2012[8]	I	R-DB-PC	279	224 (80.8%)	Titrated doses of CBD/THC, placebo 2.5 mg/capsule bid	12 weeks	NRS scales 0–11 Muscle stiffness, (primary), spasms, pain, insomnia (secondary) measured at 2,4,8,12 weeks Significant relief of muscle stiffness 29.4% CE vs 15.7% placebo, *p*=0.04)	53 total, 34 CE (30 AE), 19 placebo (9 AE)	47% CE, 87% placebo reached max dose 71% nervous system disorders in AEs, 41.3% GI
Wade 2004[6]	I	R-DB-PC	160 39 spasticity	154 (96%)	Spray CBE 2.7 mgTHC+2.5CBD /pump max 25 mg each/d 100-point VAS for patient's chosen primary target and 5 other symptoms	6 weeks, 4 weeks, optional continuation	No overall difference, but in those with spasticity as most troublesome symptom significant reduction in VAS.-31.2 CBE, -8.4 placebo (-22.79 difference, *p*=0.001 after Bonferroni correction), Trend for decrease 2.35-second difference 10-m walking time Secondary outcome no difference in Ashworth (0.22, *p*=0.305), diary card difference -8.4, *p*=0.009)	3 each group, for AEs in CE, for using cannabis, withdrawing consent and headache in placebo	Dizziness 32%, site discomfort 26%, fatigue 15%, somnolence, dec attention, nausea, headache 9%
Zajicek 2003[7]	I	R-DB-PC	657 randomized; 630 ITT	611 (93%)	Oral THC, CE+THC, placebo Dose related, bid, maximum 25mg/d	13 weeks	No effect in mean decrease in Ashworth spasticity scale (*p*=0.40), Rivermead mobility index, Barthel index, QOL scales, no effect. Patient-reported benefit in CRS for spasticity (*p*=0.003)	19 total, 4 CE (2 due to AE), 9 THC (7 due to AE), 6 placebo (0 AE, 3 lack efficacy)	Dizziness 50%–59%, Sleep 40,35,33% Diarrhea 37,30,20% Increased appetite in treated group only
Vaney 2004[5]	I	R-DB-PC	57	50 (88%)	Oral CE 2.5 mg THC+0.9 mg CBD	4 weeks total, 14 days on treatment	Ashworth scale no difference (-0.8, *p*=0.2379) in ITT group. In pts tolerating 90% of dose, -2.2, *p*=0.0018) improvement in self-reported spasm frequency and Rivermead mobility index=0.003 if corrected for patient who fell	6 in treatment group, 3 for AEs, 3 withdrew consent, 1 for placebo, withdrew consent	Max tolerated dose 27.5 mg THC, reached in 14 pts
Zajicek 2005[11]	II	R-DB-PC	630	502 (80%) in follow-up to 2003 study	Oral THC, CE+THC, placebo	12 months	Ashworth spasticity score dec for THC and CE vs placebo (small effect). Patient-rated CRS 33% THC, 29% CE, 17% placebo showed improvement *p*=0.004. Overall improvement noted in 7 of 9 self-rated measures	6 deaths, group not specified. 4 THC drop due to AE, 5 THC, 7 placebo. Minor AEs in 109 THC, 125 CBE, 127 placebo	Continuation of CAMS study of 2003 Similar loss to follow-up reasons for all groups (e.g., no reason, travel, lack of efficacy) Some concern for increase MS relapse 8 THC and 8 CBE, 1 placebo pt

Collin 2010[10]	II	R-DB-PC	337	265 (79%)	Nabiximols spray Assessed 2, 6, 10, 14 week	14 weeks	NRS of spasticity -1.3-point improvement treatment, -0.84 placebo, *p*=0.035. No significant improvement in ITT, but 30% in per-protocol treated group from baseline in secondary outcomes of timed walk, ADL index, impression of change no improvement	Total 55, 35 treated, 9 for AE, 20 placebo, 5 for AE	15 serious, 4 psychosis, 2 insomnia after withdrawal from treatment. Overall AEs 87% active, 56% placebo
Collin 2007[9]	II	R-DB-PC	189	174 (92%)	CE spray 2:1 placebo Self-titrated dose	6 weeks	Patient-rated NRS, 0–11 points, diff reduced 0.52 points, reduced 1.18 from mean 5.49 in CE vs 0.63 from 5.39 in placebo (*p*=0.048) Secondary outcomes mean difference Ashworth 0.11, *p*=0.218), Motricity index 0.054, daily spasm 0.766, global impression change no difference	8 total, 6 active, 2 placebo, not AE	7 serious, 4 treated, 3 placebo (vomiting), overall 82% AE treated, 71% placebo, most CNS effects
Centzone 2009[13]	III	open-label study (placebo requested but rejected by IRB)	20	Not specified	Nabiximols spray	6 weeks	There was no significant difference in Ashworth scale and weekly patient-reported NRS of spasticity (no statistics given)	Unknown	Not discussed
Corey-Bloom 2012[14]	III	R-DB-PC	37	30 (91%)	Smoked MJ cig with 4% THC by weight, tid	2 weeks	2.74-point dec mean Ashworth MJ vs 0.21 placebo from 9.0 (*p*<0.001). No sig change in mean timed walk (1.23 s vs 0.03, *p*=0.2)	7 total, 5 due to AEs (felt "high":2, dizzy: 2, fatigue:1)	5-point increase in feeling of "highness" and most patients guessed their treatment at most visits
Greenberg 1994[15]	III	R-DB-PC	20	None	2 days of smoked MJ cigarette and 1 day of placebo alcohol-extracted cigarette	3 days	Significant increases in phase lag (eyes closed) and noise variance (eyes open or closed) in patients with spastic MS, but only noise variance (eyes open or closed) with the matched normals	None	Not discussed
Killestein 2002[16]	III	R-DB-PC	16	16 (100%)	Dronabinol capsules THC 2.5–5mg/d, CBE containing THC + 20%–30% CBD, placebo	20 weeks total, 4 active, with double crossover	No change Ashworth score from placebo (1.2 to 0.9 placebo, 1.2 to 0.8 CBE, 1.0 to 0.8 THC), no change in EDSS score. Secondary outcomes VAS spasticity score, no change; worsening in patients' global impression of change in both THC (F=9.2) and CBE (F=7.1) as compared with placebo F=0.130, worsening brainstem functional symptom score (F=4.3 CBE), peg hold test F=7.6 (*p*=0.02)	None	5 patients reported increased spasticity during CBE treatment, 1 severe AE: psychosis for 5 h Most patients had mild AEs, dizziness, somnolence

Ungerleider 1987[17]	III	R-DB-C	13	13 (100%)	THC capsule 2.5–5 mg/d	2 weeks total, 5 days on treatment (crossover)	Pt-rated scores improved -0.48 THC, placebo. Ashworth no change	Not stated	Not stated
Wade 2006[18]	III	R-DB-C followed by open-label phase. This article reports on open-label phase	137	79 (57%)	Nabiximols spray	Mean duraton >400 days	VAS for symptoms decreased from baseline of 65–70 (depending on symptom) to 23–32. For spasm, went from 65.1 (14.7 standard deviation) to 26.7 (18.1)	Lack of efficacy 24 patients, withdrew consent 6, lost to follow-up 3, AE 17, other 8	n=1 to 2 for a variety of complaints. The most concerning was a possibly related death in 1

R = randomized, DB = double-blind, PC = placebo-controlled, CBD = cannabidiol, THC = tetrahydrocannabinol, NRS = numeric rating scale, CBE = cannabidiol extract, VAS = visual analog scale, AE = adverse event, QOL = quality of life, CE = cannabis extract, ITT = intent to treat, CRS = category rating scale.

Table e-5: Efficacy of cannabinoids in neurologic conditions: Tremor (MS)

Reference	Class	Design	Group size	Completion rate	Treatment (technique, dose)	Study duration	Outcomes	Dropouts	Adverse events/ comments
Wade 2004[6]	I	R-DB-PC	160 total 13 tremor	154 (96%)	Spray CBE 2.7 mg THC+2.5 CBD /pump max 25 mg each/d 100-point VAS for patient's chosen primary target and 5 other symptoms	6 weeks 4 weeks optional continuation	No difference in decrease of VAS when tremor is primary symptom (mean -21.42 CBE, -25.17 placebo, *p*= 0.810); same from patient's diary card	3 each group, for adverse events in CE, for using cannabis, withdrawing consent and headache in placebo	Dizziness 32%, site discomfort 26%, fatigue 15%, somnolence, dec attention, nausea, headache 9%
Zajicek 2003[7]	I	R-DB-PC	630 total, 391 tremor	Not given for these groups but was 93% overall	Oral THC, CE (CE:THC 2:1), placebo maximum 25 mg THC/d	13 weeks	No Improvement in CRS for tremor, (38% CE, 41% THC, 33% placebo; *p*=0.308)	19:4 CE (2 due to AE), 9 THC (7 due to AE), 6 placebo (0 AE, 3 lack efficacy)	Dizziness 50%–59%, Sleep 40,35,33% Diarrhea 37,30,20% Increased appetite in treated only/ 12,18,20 serious but unrelated to treatment
Vaney 2004[5]	I	R-DB-PC	57, 26 tremor	50(88%)	Oral CE capsules 2.5 mgTHC+0.9 mg CBD	14 days	No effect in pt diary for tremor after Bonferroni correction (*p*=0.25)	7 total, 6 in treatment group, 3 for AE, 1 placebo, withdrew consent	Max tolerated dose 27.5 mg THC, reached in 14 pts
Collin 2010[10]	II	R-DB-PC	337	265 (79%)	CE spray 2:1 placebo Self-titrated dose	14 weeks	No response in patient-rated NRS for tremor (-0.56 vs -0.31, *p*=0.255)	14 total, 9 treated, 5 placebo for AEs	15 serious, 4 psychosis, 2 insomnia on withdrawal from treatment. Overall 87% reported in treated, 56% in placebo group
Fox 2004[30]	III	R-DB-PC	14	13 (93%)	Titrated doses of CBD/THC 2.5 mg/capsule target dose 125 mg/kg bid, mean dose 0.107 mg/kg/bid	2 weeks	No effect on mean tremor index mean score (14.2, *p*=0.55). Secondary outcome no improvement in spiral construction, accelerometry, functional tests of pegboard and tapping or ataxia scale. Worse score on finger-tapping rate in treated group	1 (not due to AE)	Mild side effects of drowsiness, lightheadedness 2 in placebo, 2 in CE
Fox 2002[29]	III	R-DB-PC	15	15 (100%)	Single dose nabilone 1–2 mg	Single dose	No improvement in BFM dystonia movement score	None	Not serious

R = randomized, DB = double-blind, PC = placebo-controlled, CBE = cannabidiol extract, CBD = cannabidiol, VAS = visual analog scale, THC = tetrahydrocannabinol, CE = cannabis extract, NRS = numeric rating scale, AE = adverse event, BFM = Burke-Fahn-Marsden scale.[e25]