

**Supplementary Table 1. Search Strategy**

PubMed: November 14, 2019

1. “cannabis use disorder”/4158
2. “pharmacotherapy”/3135179
3. 1 and 2/1028
4. Limit 3 to (Clinical Trial, Human population, and English Language)/100

MEDLINE: November 14, 2019

1. Exp cannabis dependence.mp. or exp Marijuana Abuse/6268
2. Exp pharmacotherapy.mp. or exp Drug Therapy/1346508
3. 1 and 2/298
4. Limit 3 to (English Language and Humans)/253

EMBASE: November 14, 2019

1. Exp cannabis addiction/9646
2. Exp pharmacotherapy.mp. or exp drug therapy/2796749
3. 1 and 2/1009
4. Limit 3 to (English Language and Humans)/929

PsycINFO: November 14, 2019

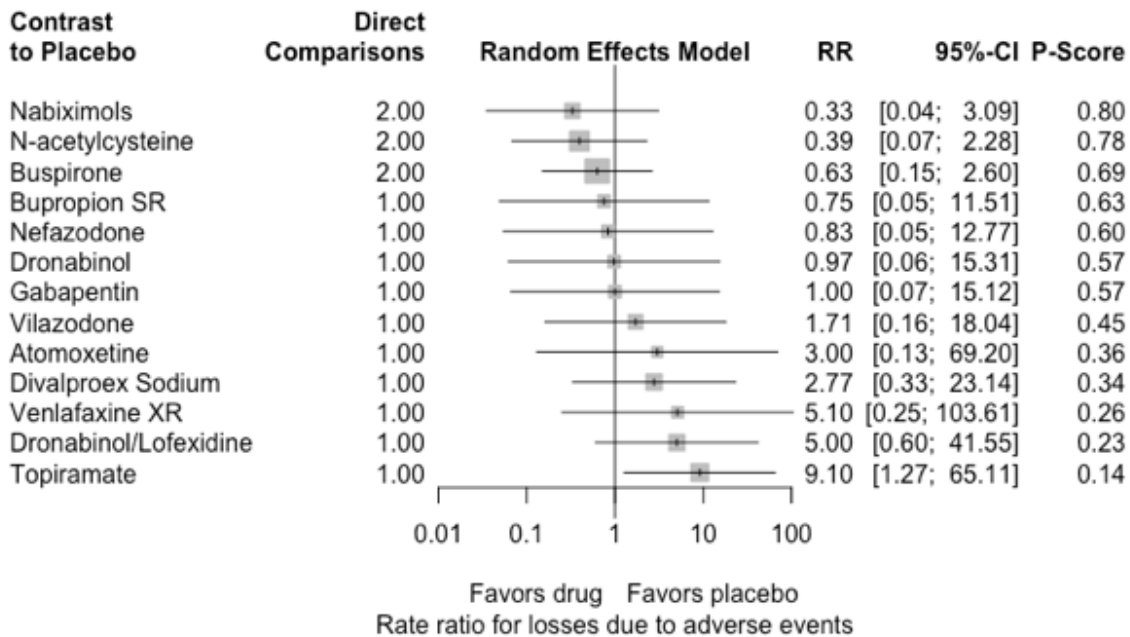
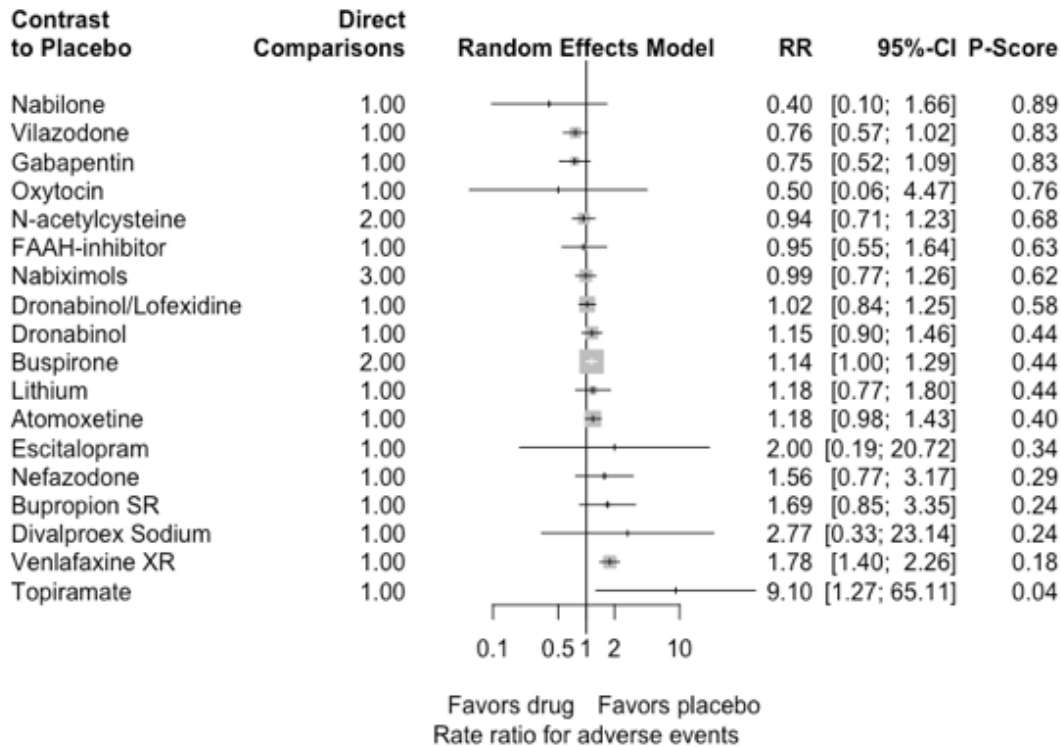
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2. Exp pharmacotherapy.mp. or exp drug therapy/146907
3. 1 and 2/466
4. Limit 3 to (English Language and Humans)/432

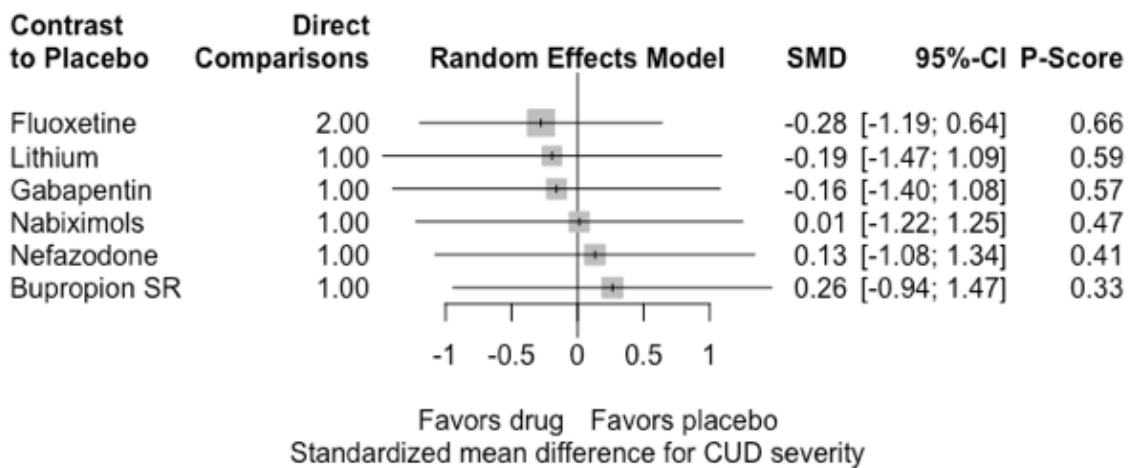
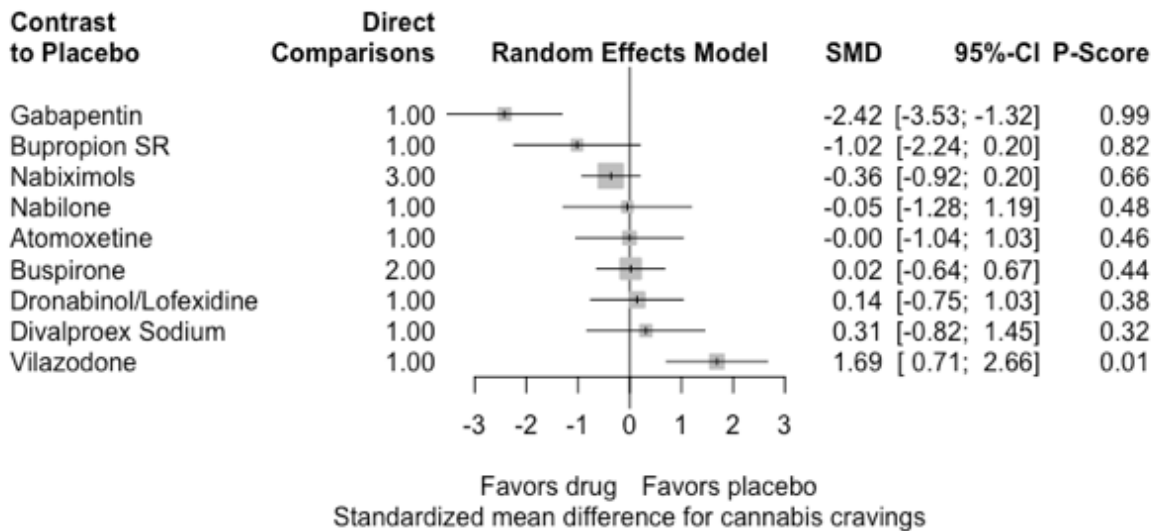
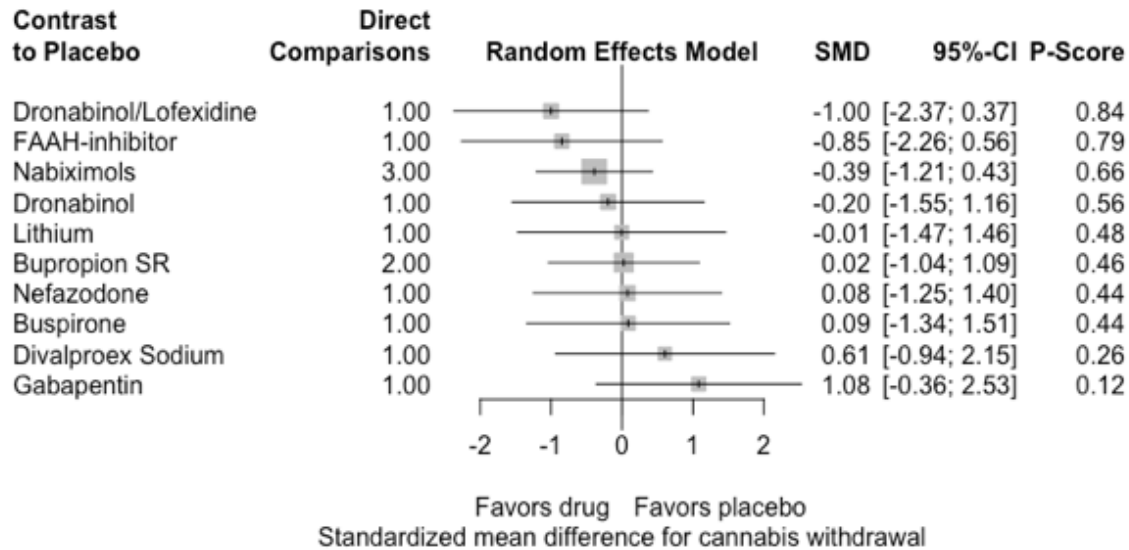
Cochrane Central Register of Controlled Trials: November 14, 2019

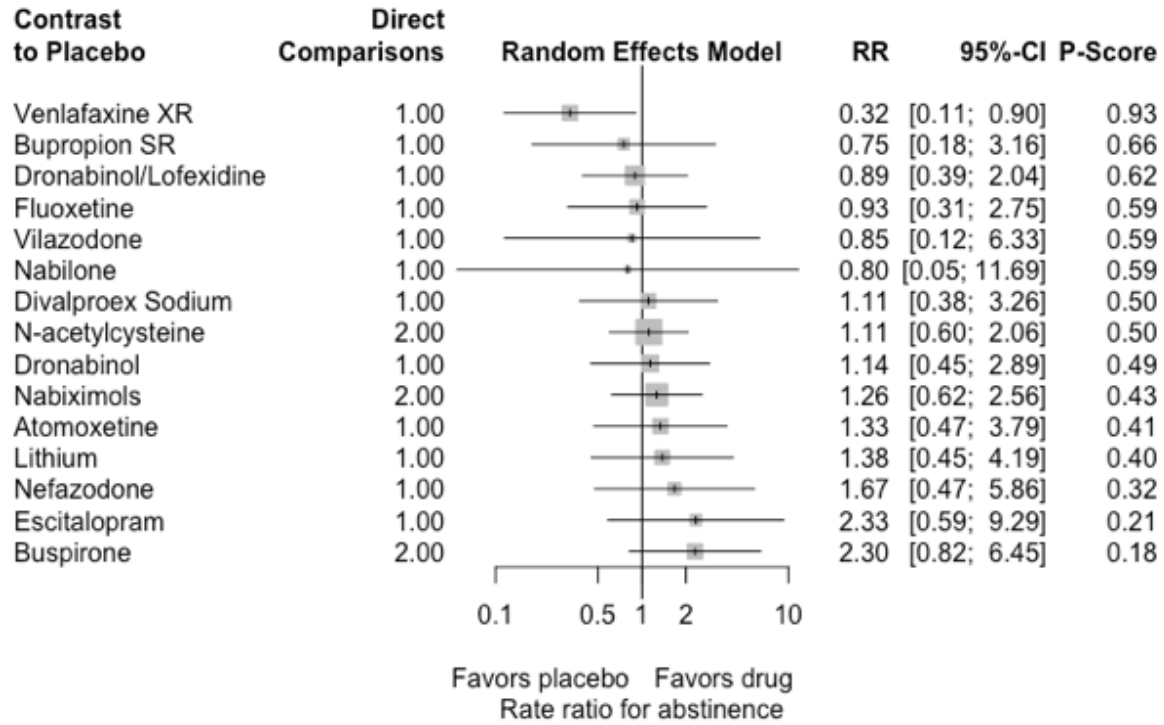
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2. Exp pharmacotherapy.mp. or exp drug therapy/7331
3. 1 and 2/30

**Supplementary Table 2. Secondary outcomes**

<b>Study</b>	<b>Abstinence</b>	<b>Adverse events</b>	<b>Withdrawal Severity</b>	<b>Cravings Severity</b>	<b>CUD Severity</b>
<i>Allsop 2014</i>	Not reported	13/27 vs. 12/24	1.88 (1.64) vs. 2.22 (1.62)	1.87 (2.28) vs. 1.81 (2.26)	4.11 (5.29) vs. 4.04 (5.21)
<i>Carpenter 2009</i>	8/36 vs. 4/30	15/36 vs. 8/30	3.1 (1.9) vs. 1.9 (1.9)	Not reported	2.5 (1.4) vs. 2.3 (1.6)
<i>Carpenter 2009b</i>	4/40 vs. 4/30	18/40 vs. 8/30	4.0 (2.1) vs. 1.9 (1.9)	Not reported	2.7 (1.5) vs. 2.3 (1.6)
<i>Cornelius 1999</i>	Not reported	0/11 vs. 0/11	Not reported	Not reported	40.2 (8.5) vs. 47.5 (8.5)
<i>Cornelius 2010</i>	7/34 vs. 8/36	0/34 vs. 0/36	Not reported	Not reported	3.88 (2.51) vs. 3.61 (1.92)
<i>D'Souza 2019</i>	Not reported	20/46 vs. 11/24	7.65 (1.32) vs. 9.04 (2.08)	Not reported	Not reported
<i>Gray 2012</i>	11/58 vs. 6/58	24/58 vs. 27/58	Not reported	Not reported	Not reported
<i>Gray 2017</i>	33/153 vs. 36/149	41/153 vs. 41/149	Not reported	Not reported	Not reported
<i>Hill 2017</i>	1/10 vs. 1/8	2/10 vs. 4/8	Not reported	51.7 (14) vs. 52.3 (10.4)	Not reported
<i>Johnston 2014</i>	6/16 vs. 6/22	12/16 vs. 14/22	1.24 (1.66) vs. 1.25 (1.97)	Not reported	3.07 (4.04) vs. 3.85 (3.91)
<i>Levin 2004</i>	6/13 vs. 5/12	3/13 vs. 1/12	19.22 (10.15) vs. 12.83 (10.22)	27.56 (36.71) vs. 16.83 (28.94)	Not reported
<i>Levin 2011</i>	14/79 vs. 12/77	53/79 vs. 45/77	4 (4.7) vs. 5 (5.4)	Not reported	Not reported
<i>Levin 2013</i>	6/51 vs. 19/52	51/51 vs. 29/52	Not reported	Not reported	Not reported
<i>Levin 2016</i>	17/61 vs. 19/61	47/61 vs. 46/61	4.8 (0.61) vs. 5.5 (0.77)	42.4 (16.9) vs. 40.1 (15.4)	Not reported
<i>Lintzeris 2019</i>	18/61 vs. 11/67	15/61 vs. 17/67	30.7 (28.9) vs. 43.6 (37.3)	27.2 (18.9) 31.2 (15.2)	Not reported
<i>Mason 2012</i>	Not reported	15/25 vs. 20/25	1.5 (1.0) vs. 0.4 (1.0)	0.2 (0.1) vs. 0.75 (0.3)	1.4 (1.6) vs. 1.6 (0.7)
<i>McRae-Clark 2009</i>	5/23 vs. 2/27	22/23 vs. 21/27	7.73 (8.99) vs. 7.00 (7.73)	19.95 (16.29) vs. 26.9 (15.75)	Not reported
<i>McRae-Clark 2010</i>	8/19 vs. 6/19	19/19 vs. 16/19	Not reported	25.51 (13.28) vs. 25.55 (15.97)	Not reported
<i>McRae-Clark 2015</i>	8/88 vs. 4/87	73/88 vs. 66/87	Not reported	46.4 (1.79) vs. 45.8 (1.48)	Not reported
<i>McRae-Clark 2016</i>	2/41 vs. 2/35	25/41 vs. 28/35	Not reported	49.9 (2.55) vs. 46.7 (0.11)	Not reported
<i>Miranda 2017</i>	Not reported	14/40 vs. 1/26	Not reported	Not reported	Not reported
<i>Penetar 2012</i>	Not reported	0/10 vs. 0/12	3.0 (0.51) vs. 4.1 (0.97)	1.2 (0.31) vs. 1.5 (0.26)	Not reported
<i>Sherman 2017</i>	0/8 vs. 0/8	1/8 vs. 2/8	Not reported	Not reported	Not reported
<i>Trigo 2018</i>	5/20 vs. 7/20	16/20 vs. 16/20	4.5 (0.6) vs. 4 (1)	7.0 (2.0) vs. 9.0 (2.0)	Not reported
<i>Weinstein 2014</i>	7/26 vs. 3/26	2/26 vs. 1/26	Not reported	Not reported	Not reported







**Supplementary Table 3.** *Cochrane risk of bias tool results for individual studies. Colours indicate the risk of bias per study domain: green = low risk of bias; yellow = unclear risk of bias; and red = high risk of bias.*

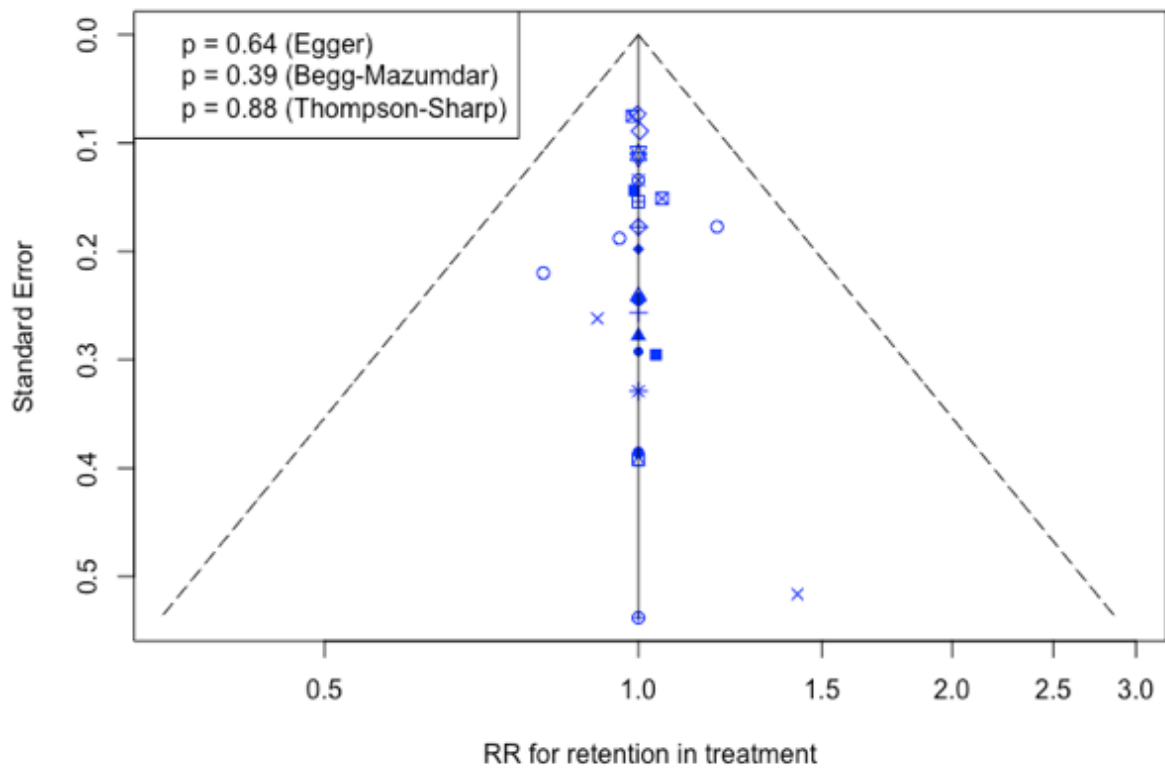
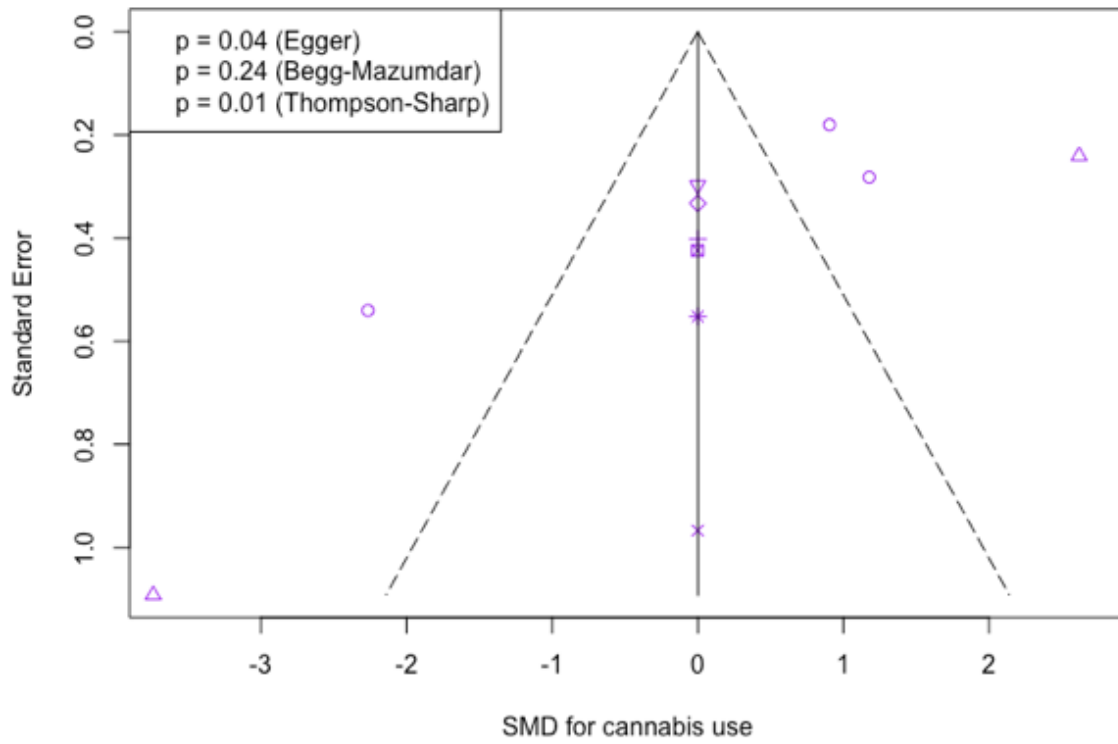
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall Risk of Bias
Alsop 2014	+	+	+	+	+	+	+	+
Carpenter 2009	?	+	+	+	+	+	+	+
Cornellus 1999	+	+	+	+	+	+	+	+
Cornellus 2010	+	+	+	+	+	+	+	+
D'Souza 2019	+	+	+	+	+	+	+	+
Gray 2012	+	+	+	+	+	+	+	+
Gray 2017	+	+	+	+	+	+	+	+
Hill 2017	+	+	+	+	+	+	+	+
Johnston 2014	?	?	+	+	+	+	+	?
Levin 2004	?	?	+	+	+	+	+	?
Levin 2011	+	+	+	+	+	+	+	+
Levin 2013	+	+	+	+	+	+	+	+
Levin 2016	+	+	+	+	+	+	+	+
Lintzeris 2019	+	+	+	+	+	+	+	+
Mason 2012	+	+	+	+	+	+	+	+
McRae-Clark 2009	+	+	+	+	+	+	+	+
McRae-Clark 2010	+	+	+	+	+	+	+	+
McRae-Clark 2015	?	?	+	+	+	+	+	?
McRae-Clark 2016	+	?	?	?	+	+	+	?
Miranda 2017	+	+	+	+	+	+	+	+
Penetar 2012	?	?	+	+	+	+	+	?
Sherman 2017	?	?	+	+	+	+	+	?
Trigo 2018	+	+	+	+	+	+	+	+
Weinstein 2014	?	?	+	+	+	+	+	?

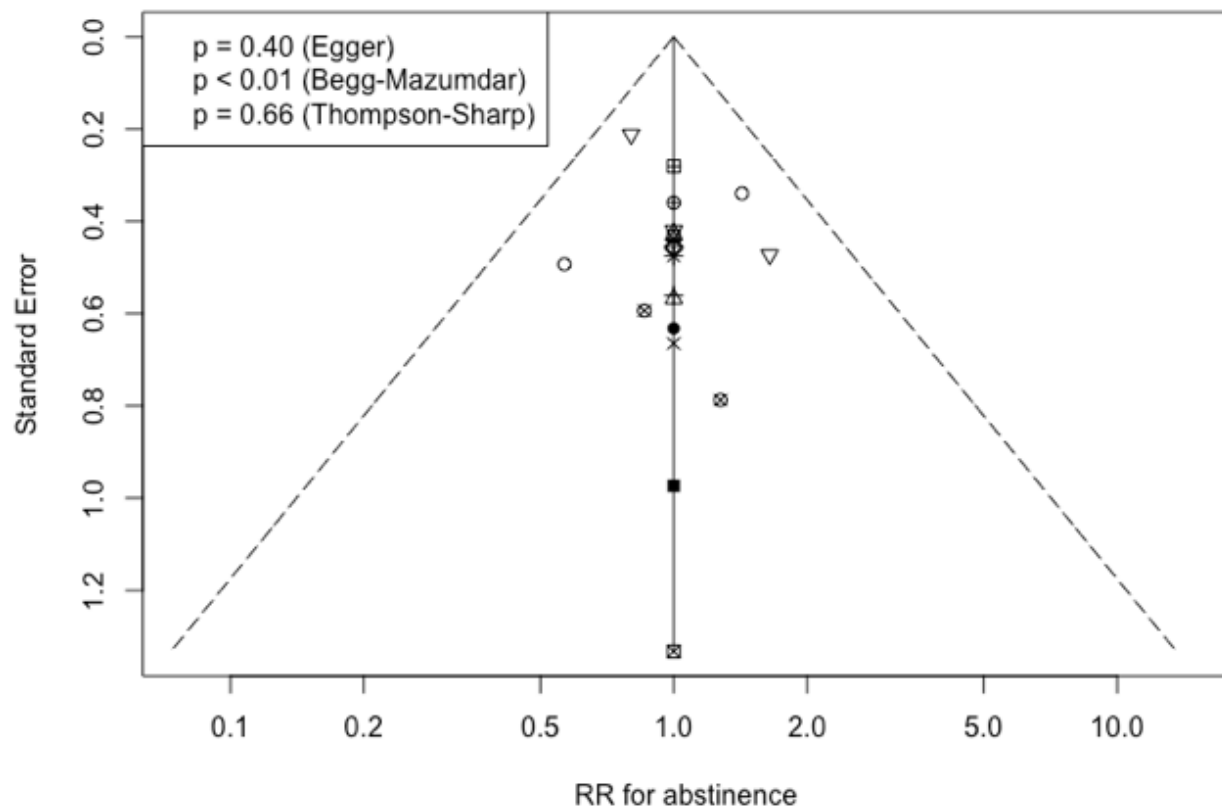
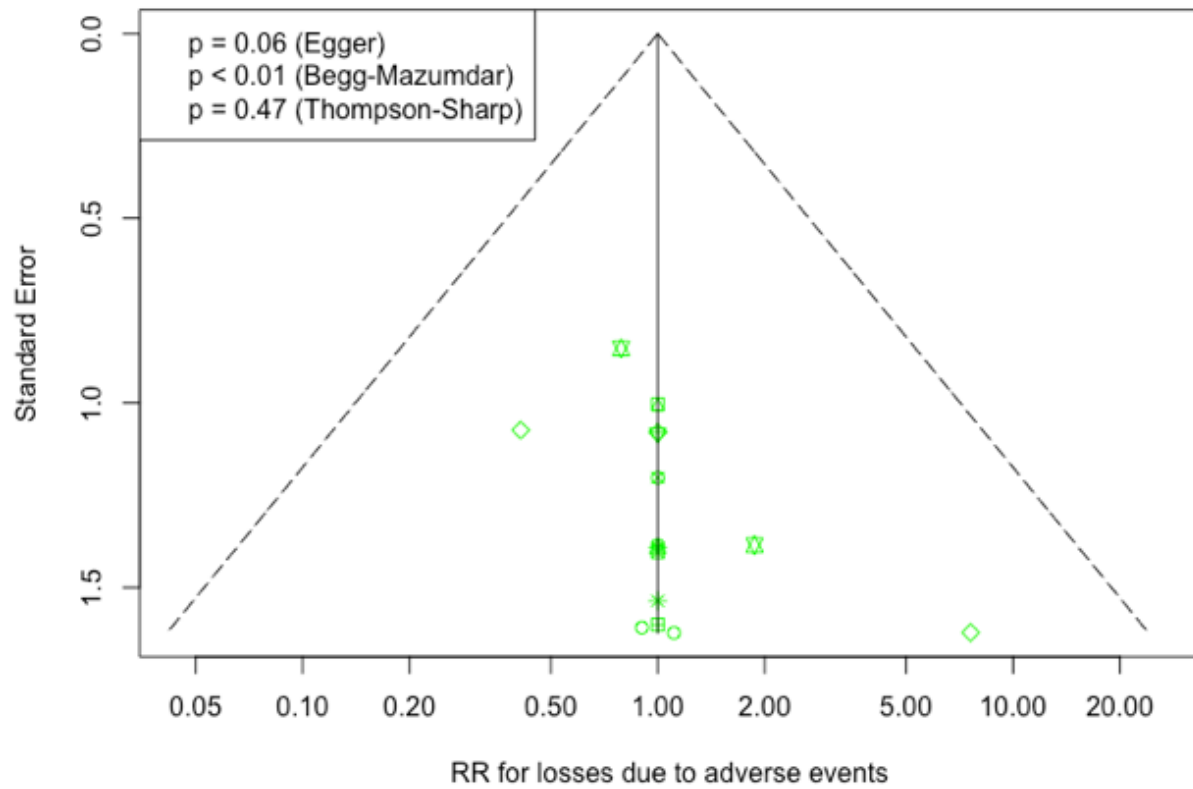
<i>Study</i>	<b>Randomization</b>	<b>Allocation</b>	<b>Participant blinding</b>	<b>Assessment blinding</b>	<b>Attrition bias</b>	<b>Selective reporting</b>	<b>Other bias</b>	<b>The overall risk of bias</b>
<i>Allsop 2014</i>	Low risk	High risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk
<i>Carpenter 2009</i>	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>Cornelius 1999</i>	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
<i>Cornelius 2010</i>	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>D'Souza 2019</i>	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
<i>Gray 2012</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>Gray 2017</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>Hill 2017</i>	Low risk	High risk	High risk	High risk	High risk	Low risk	Low risk	High risk
<i>Johnston 2014</i>	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
<i>Levin 2004</i>	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	Low risk	Unclear risk
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<i>Levin 2013</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>Levin 2016</i>	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
<i>Lintzeris 2019</i>	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
<i>Mason 2012</i>	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
<i>McRae-Clark 2009</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>McRae-Clark 2010</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>McRae-Clark 2015</i>	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
<i>McRae-Clark 2016</i>	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk
<i>Miranda 2017</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>Penetar 2012</i>	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk	Low risk	Unclear risk
<i>Sherman 2017</i>	Unclear risk	Unclear risk	High risk	High risk	Low risk	High risk	Low risk	High risk
<i>Trigo 2018</i>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
<i>Weinstein 2014</i>	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	Low risk	Unclear risk

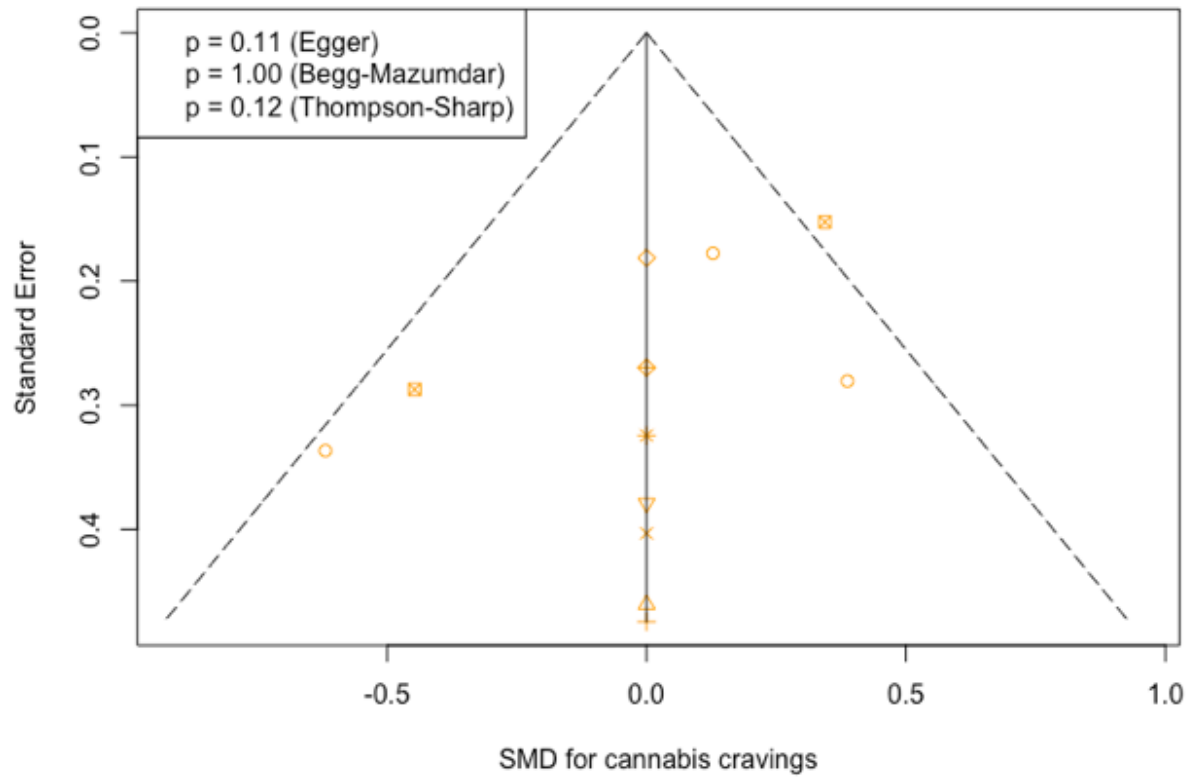
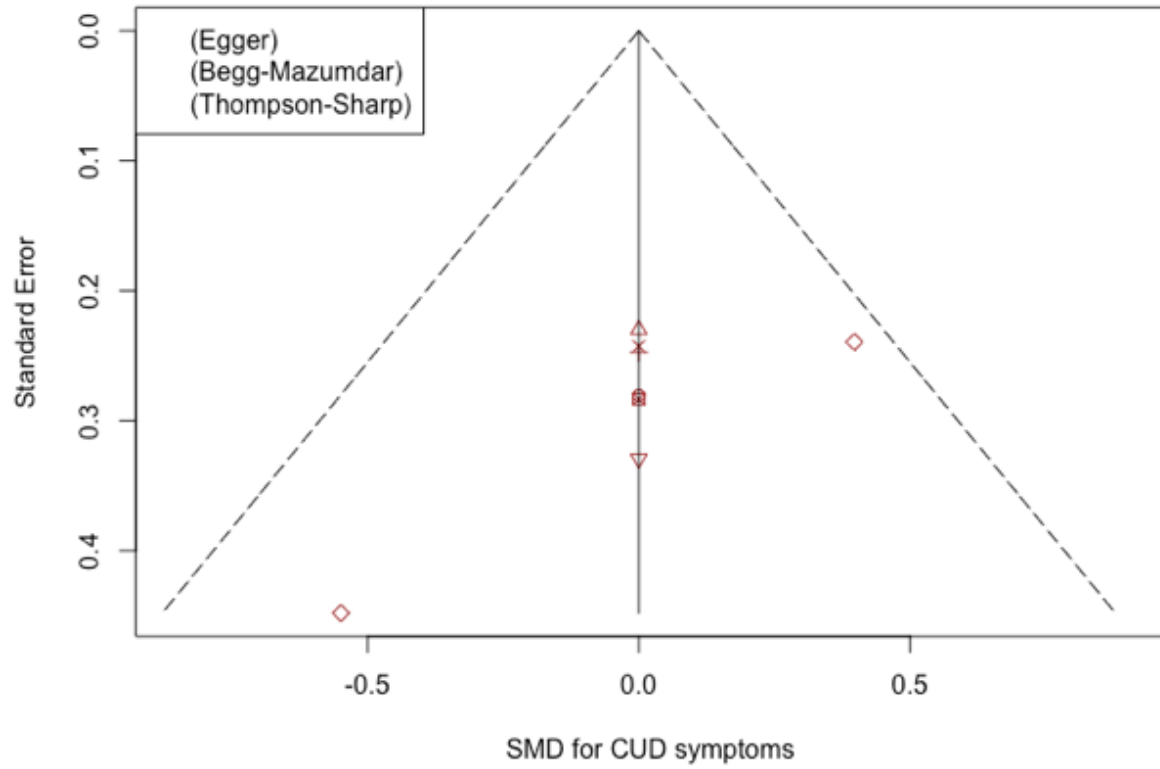


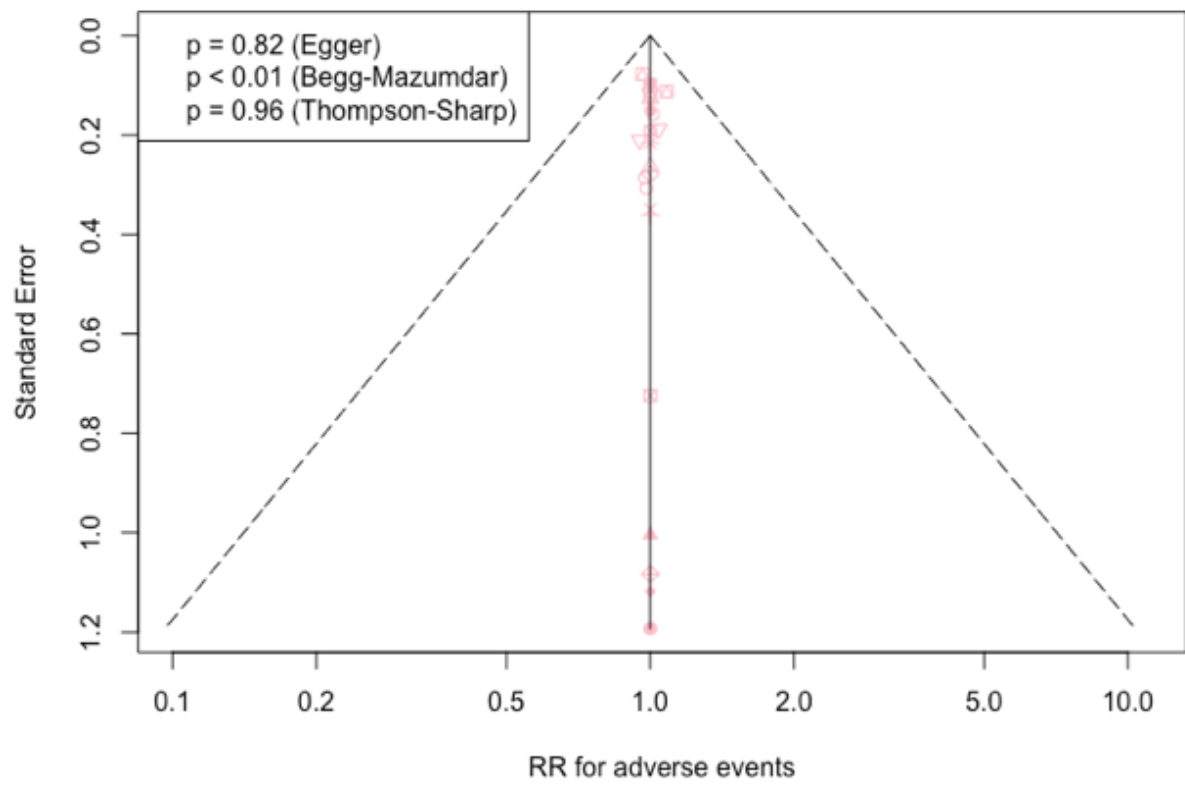
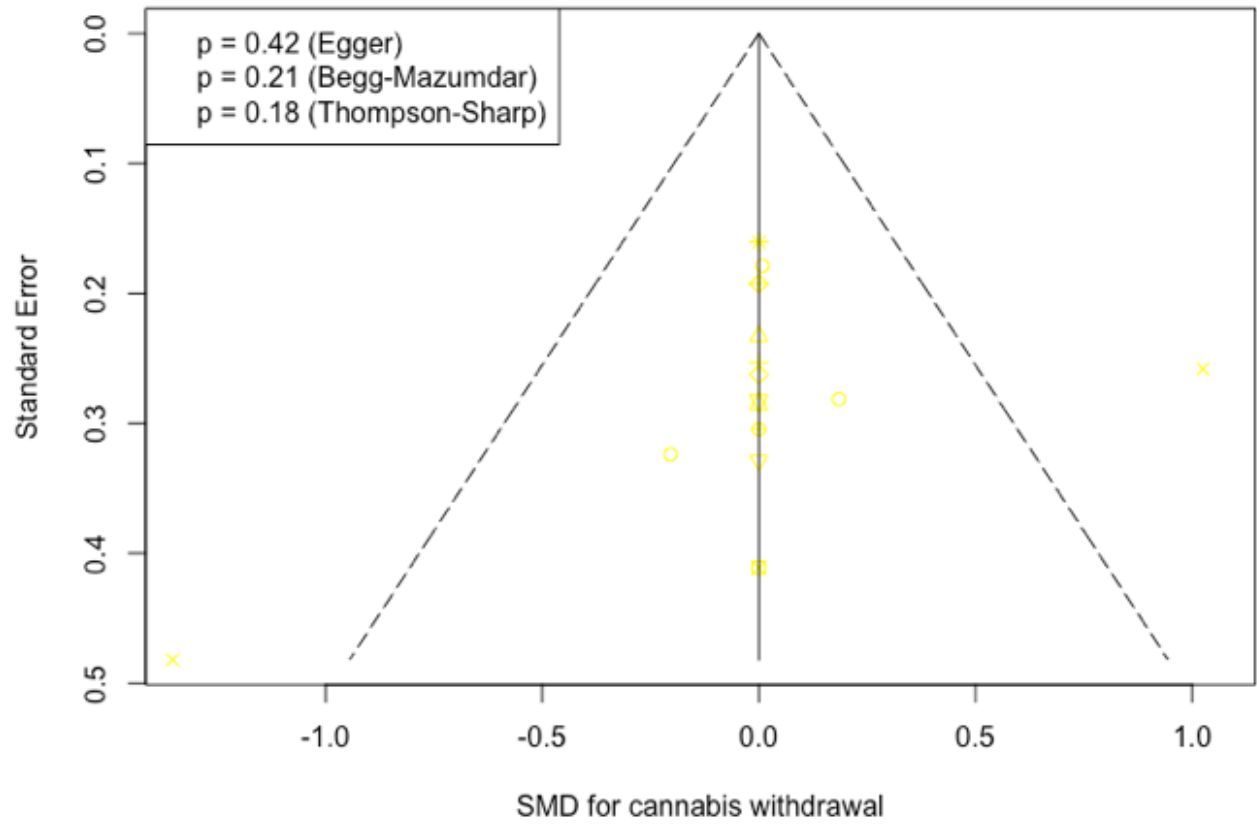


Supplementary Table 4. *Funnel plots*









**Supplementary Table 5.** Sensitivity analysis after removing the high risk of bias studies.

Cannabis use ( <i>d</i> ) vs. placebo	Nabiximols -1.45 [-3.32; 0.41] Fluoxetine -2.30 [-4.75; 0.15] <b>FAAH-inhibitor</b> -3.60 [-6.86; -0.35] <b>Nabilone</b> -4.47 [-8.15; -0.79] Lithium -0.43 [-3.65; 2.80] Gabapentin -0.88 [-4.09; 2.33] <b>Topiramate</b> -3.80 [-7.06; -0.54] Oxytocin 1.15 [-2.19; 4.48]
Retention in treatment (RR) vs. placebo	Nabiximols 1.15 [0.92; 1.42] Nefazodone 1.13 [0.69; 1.83] Bupropion SR 1.06 [0.67; 1.67] Fluoxetine 1.00 [0.89; 1.11] FAAH-inhibitor 0.99 [0.79; 1.24] N-acetylcysteine 1.06 [0.93; 1.21] Nabilone 0.80 [0.42; 1.52] Lithium 1.12 [0.79; 1.58] Divalproex Sodium 1.15 [0.40; 3.31] Dronabinol 1.27 [1.02; 1.57] Venlafaxine XR 0.96 [0.71; 1.30] Dronabinol/Lofexidine 0.88 [0.68; 1.15] Gabapentin 0.64 [0.30; 1.37] Buspirone 0.96 [0.74; 1.23] Atomoxetine 1.29 [0.60; 2.74] Vilazodone 0.70 [0.41; 1.21] <b>Topiramate</b> 0.62 [0.42; 0.91] Oxytocin 0.86 [0.53; 1.38] Escitalopram 0.62 [0.35; 1.11]
Treatment discontinuation (RR) vs. placebo	Nabiximols 0.88 [0.66; 1.19] Nefazodone 0.89 [0.57; 1.40] Bupropion SR 0.95 [0.65; 1.38] Fluoxetine 1.06 [0.23; 4.89] FAAH-inhibitor 1.04 [0.35; 3.12] N-acetylcysteine 0.87 [0.66; 1.15] Nabilone 1.60 [0.39; 6.62] Lithium 0.69 [0.20; 2.35] Divalproex Sodium 0.92 [0.51; 1.66] Dronabinol 0.58 [0.36; 0.96] Venlafaxine XR 1.07 [0.65; 1.76] Dronabinol/Lofexidine 1.26 [0.78; 2.05] Gabapentin 1.29 [0.84; 1.97] Buspirone 1.05 [0.80; 1.37] Atomoxetine 0.83 [0.48; 1.44] Vilazodone 1.28 [0.87; 1.89]

	<b>Topiramate</b> 2.28 [1.06; 4.87] Oxytocin 2.00 [0.22; 17.89] Escitalopram 1.60 [0.90; 2.84]
Discontinuation due to adverse events (RR) vs. placebo	Nabiximols 0.33 [0.04; 3.09] Nefazodone 0.83 [0.05; 12.77] Bupropion SR 0.75 [0.05; 11.51] N-acetylcysteine 0.39 [0.07; 2.28] Divalproex Sodium 2.77 [0.33; 23.14] Dronabinol 0.97 [0.06; 15.31] Venlafaxine XR 5.10 [0.25; 103.61] Dronabinol/Lofexidine 5.00 [0.60; 41.55] Gabapentin 1.00 [0.07; 15.12] Buspirone 0.63 [0.15; 2.60] Atomoxetine 3.00 [0.13; 69.20] Vilazodone 1.71 [0.16; 18.04] <b>Topiramate</b> 9.10 [1.27; 65.11]
Cannabis withdrawal ( <i>d</i> ) vs. placebo	Nabiximols -0.39 [-1.21; 0.43] Nefazodone 0.08 [-1.25; 1.40] Bupropion SR 0.02 [-1.04; 1.09] FAAH-inhibitor -0.85 [-2.26; 0.56] Lithium -0.01 [-1.47; 1.46] Divalproex Sodium 0.61 [-0.94; 2.15] Dronabinol -0.20 [-1.55; 1.16] Dronabinol/Lofexidine -1.00 [-2.37; 0.37] Gabapentin 1.08 [-0.36; 2.53] Buspirone 0.09 [-1.34; 1.51]
Cannabis cravings ( <i>d</i> ) vs. placebo	Nabiximols -0.36 [-0.92; 0.20] Bupropion SR -1.02 [-2.24; 0.20] Nabilone -0.05 [-1.28; 1.19] Divalproex Sodium 0.31 [-0.82; 1.45] Dronabinol/Lofexidine 0.14 [-0.75; 1.03] <b>Gabapentin</b> -2.42 [-3.53; -1.32] Buspirone 0.02 [-0.64; 0.67] Atomoxetine -0.00 [-1.04; 1.03] Vilazodone 1.69 [0.71; 2.66]
Cannabis use disorder symptoms ( <i>d</i> ) vs. placebo	Nabiximols 0.01 [-1.22; 1.25] Nefazodone 0.13 [-1.08; 1.34] Bupropion SR 0.26 [-0.94; 1.47] Fluoxetine -0.28 [-1.19; 0.64] Lithium -0.19 [-1.47; 1.09] Gabapentin -0.16 [-1.40; 1.08]
Adverse events (RR) vs. placebo	Nabiximols 0.99 [0.77; 1.26] Nefazodone 1.56 [0.77; 3.17] Bupropion SR 1.69 [0.85; 3.35] FAAH-inhibitor 0.95 [0.55; 1.64] N-acetylcysteine 0.94 [0.71; 1.23]

	Nabilone 0.40 [0.10; 1.66] Lithium 1.18 [0.77; 1.80] Divalproex Sodium 2.77 [0.33; 23.14] Dronabinol 1.15 [0.90; 1.46] Venlafaxine XR 1.78 [1.40; 2.26] Dronabinol/Lofexidine 1.02 [0.84; 1.25] Gabapentin 0.75 [0.52; 1.09] Buspirone 1.14 [1.00; 1.29] Atomoxetine 1.18 [0.98; 1.43] Vilazodone 0.76 [0.57; 1.02] Topiramate 9.10 [1.27; 65.11] Oxytocin 0.50 [0.06; 4.47] Escitalopram 2.00 [0.19; 20.72]
Abstinence (RR) vs. placebo	Nabiximols 1.26 [0.62; 2.56] Nefazodone 1.67 [0.47; 5.86] Bupropion SR 0.75 [0.18; 3.16] Fluoxetine 0.93 [0.31; 2.75] N-acetylcysteine 1.11 [0.60; 2.06] Nabilone 0.80 [0.05; 11.69] Lithium 1.37 [0.45; 4.19] Divalproex Sodium 1.11 [0.38; 3.26] Dronabinol 1.14 [0.45; 2.89] Venlafaxine XR 0.32 [0.11; 0.90] Dronabinol/Lofexidine 0.89 [0.39; 2.04] Buspirone 2.30 [0.82; 6.45] Atomoxetine 1.33 [0.47; 3.79] Vilazodone 0.85 [0.12; 6.33] Escitalopram 2.33 [0.59; 9.29]

**Supplementary Table 6.** Medications included in this analysis and their current medical use

Agent	Mechanism of action	Clinical use
Nabiximols	A mixture of tetrahydrocannabinol (THC) and cannabidiol (CBD)	Spasticity in multiple sclerosis
Nefazodone	Serotonin antagonist and reuptake inhibitor (SARI)	Antidepressant
Bupropion sustained-release	Noradrenergic and dopaminergic reuptake inhibitor (NDRI)	Antidepressant, smoking cessation, attention-deficit hyperactivity disorder (ADHD)
Fluoxetine	Selective serotonin reuptake inhibitor (SSRI)	Antidepressant, anxiolytic
N-acetylcysteine	Glutathione precursor, role in glutamatergic neurotransmission	Acetaminophen overdose, treatment of several psychiatric disorders
Nabilone	Synthetic cannabinoid	Antiemetic, analgesic, nightmares in post-traumatic stress disorder
Lithium	Unclear, but appears to modulate secondary messenger systems	Mood stabilizer in bipolar disorder, augmentation agent in depression
Divalproex	An antagonist of the voltage-gated sodium channel that enhances gamma-aminobutyric acid (GABA) neurotransmission	Anticonvulsant, mood-stabilizing agent, anti-migraine agent
Dronabinol	Synthetic cannabinoid	Antiemetic, analgesic, appetite stimulant
Venlafaxine extended-release	Serotonin-norepinephrine reuptake inhibitor (SNRI)	Antidepressant, anxiolytic, analgesic for neuropathic pain
Lofexidine	$\alpha_{2A}$ adrenergic receptor agonist	Opioid withdrawal, hypertension
Buspirone	Non-benzodiazepine anxiolytic	Anxiety disorders
Atomoxetine	Noradrenergic reuptake inhibitor (NRI)	ADHD
Vilazodone	Serotonin reuptake inhibitor and 5-HT <sub>1A</sub> receptor partial agonist	Antidepressant
Escitalopram	Selective serotonin reuptake inhibitor (SSRI)	Antidepressant, anxiolytic