APPENDIX A. SEARCH STRATEGIES

Databases/Websites

- Ovid Medline
- PubMed (non-Medline materials)
- Elsevier EMBASE
- Ovid PsycINFO
- PILOTS Database (PTSD search only)
- EBM Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*)
- Conference Papers Index

- Clinicaltrials.gov
- International Clinical Trials Registry Platform (WHO ICTRP)
- ISRCTN

- NIH Reporter
- AHRQ Gold

- American Cancer Society Database of Studies

Search Strategies

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to December Week 5 2015,

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 11, 2016

Date Searched: Tuesday January 12, 2016

#	Searches	Results
1	medical marijuana/ or cannabis/ or marijuana smoking/ or exp Cannabinoids/ or Cannabaceae/	18682
2	(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw.	38570
3	1 or 2	41269
4	pain/ or acute pain/ or breakthrough pain/ or mastodynia/ or exp musculoskeletal pain/ or exp back pain/ or chronic pain/ or facial pain/ or headache/ or metatarsalgia/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or pain, referred/	205083
5	(pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*).tw.	770253
6	4 or 5	823437
7	3 and 6	2868
8	7 and (humans/ not animals/)	1331
9	7 not (humans/ or animals/)	312
10	8 or 9	1643
11	limit 10 to (case reports or comment or editorial or letter or news)	293

12	cross-section*.tw.	243912
13	10 not (11 or 12)	1313
14	limit 13 to english language	1211
15	stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/	26019
16	(PTSD or post-traumatic stress or posttraumatic stress).ti,ab.	23732
17	15 or 16	32767
18	3 and 17	210
19	18 and (humans/ not animals/)	131
20	18 not (humans/ or animals/)	31
21	19 or 20	162
22	limit 21 to (case reports or comment or editorial or letter or news)	9
23	cross-section*.tw.	243912
24	21 not (22 or 23)	140
25	limit 24 to english language	132
26	medical marijuana/ or cannabis/ or marijuana smoking/ or marijuana abuse/ or exp Cannabinoids/ or Cannabaceae/	22185
27	(cannabis* or canabis* or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana* or marihuana* or hashish* or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw.	38598
28	26 or 27	41948
29	(ae or co or de).fs.	5311331
30	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	3065069
31	29 or 30	7263273
32	28 and 31	25510
33	limit 32 to (meta analysis or systematic reviews)	422
34	32 not 33	25088
35	34 and (humans/ not animals/)	13847
36	34 not (humans/ or animals/)	1758
37	35 or 36	15605
38	limit 37 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	8086
39	limit 38 to (case reports or comment or editorial or letter or news)	1030
40	cross-section*.tw.	243912
41	38 not (39 or 40)	6701
42	limit 41 to english language	6238

PubMed

Date searched: Friday May 6, 2016

#	Searches	Results
#10	Search (#7 OR #8 OR #9)	444
#9	Search ((((((cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]))))) AND (((harm[tiab] OR harms[tiab] OR harmful[tiab] OR safe[tiab] OR safety[tiab] OR side effect*[tiab] OR undesirable effect*[tiab] OR treatment emergent[tiab] OR tolerability[tiab] OR toxic*[tiab] OR adrs[tiab] OR damag*[tiab] OR impair*[tiab] OR disorder*[tiab] OR abuse*[tiab] OR addict*[tiab] OR withdrawal*[tiab] OR adverse effect[tiab] OR adverse effects[tiab] OR adverse reaction[tiab] OR adverse reactions[tiab] OR adverse event[tiab] OR adverse events[tiab] OR adverse outcome[tiab] OR adverse outcomes[tiab]))))) AND (((pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb])))))) AND (((((meta-review*[tiab] OR meta-epidemiolog*[tiab] OR metaepidemiolog*[tiab] OR horizon scan*[tiab] OR systematic* review*[tiab] OR systematic effectiveness review*[tiab] OR comparative effectiveness review*[tiab] OR evidence review*[tiab] OR landscape review*[tiab] OR quantitative review*[tiab] OR qualitative review*or integrative review*or mixed-method* review*or mixed method* review*[tiab] OR research review*or scoping review*[tiab] OR umbrella review*or review of review*[tiab] OR updat* review*[tiab] OR cochrane review*or campbell review*[tiab])) OR (research* aggregat*[tiab] OR evidence aggregat*[tiab] OR evidence map*[tiab] OR evidence brief*[tiab] OR evidence summar*[tiab] OR rapid review*or mini* review*or pragmatic review*or targeted review*or focused review*or brief review*or short review*[tiab])) OR (meta-analy*[tiab] OR metaanaly*[tiab] OR meta-meta-analy*[tiab] OR evidence synthes*[tiab] OR knowledge synthes*[tiab] OR quantitative synthes*[tiab] OR research synthes*[tiab] OR pooled analy*[tiab] OR indirect* comparison*[tiab] OR mixed* comparison*[tiab])) OR (HTA[tiab] OR health technology assessment*[tiab] OR mini-HTA*[tiab] OR relative effectiveness assessment*[tiab]))	16
#8	Search (((((cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]))))) AND (((PTSD[tiab] OR post-traumatic stress[tiab] OR posttraumatic stress[tiab])))) AND (((pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb]))))	39
#7	Search (((((cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab]))))) AND (((pain[tiab] OR pains[tiab] OR painful*[tiab] OR migraine*[tiab] OR headache*[tiab] OR neuropath*[tiab] OR neuralgia*[tiab] OR arthriti*[tiab] OR fibromyalg*[tiab])))) AND (((pubmednotmedline[sb] OR inprocess[sb] OR [publisher[sb]))))	392
#6	Search ((meta-review*[tiab] OR meta-epidemiolog*[tiab] OR metaepidemiolog*[tiab] OR horizon scan*[tiab] OR systematic* review*[tiab] OR systematic effectiveness review*[tiab] OR comparative effectiveness review*[tiab] OR evidence review*[tiab] OR	78086

	landscape review*[tiab] OR quantitative review*[tiab] OR qualitative review*or integrative review*or mixed-method* review*or mixed method* review*[tiab] OR research review*or scoping review*[tiab] OR umbrella review*or review of review*[tiab] OR updat* review*[tiab] OR cochrane review*or campbell review*[tiab])) OR (research* aggregat*[tiab] OR evidence aggregat*[tiab] OR evidence map*[tiab] OR evidence brief*[tiab] OR evidence summar*[tiab] OR rapid review*or mini* review*or pragmatic review*or targeted review*or focused review*or brief review*or short review*[tiab]) OR (meta-analy*[tiab] OR metaanaly*[tiab] OR meta-meta-analy*[tiab] OR evidence synthes*[tiab] OR knowledge synthes*[tiab] OR quantitative synthes*[tiab] OR research synthes*[tiab] OR pooled analy*[tiab] OR indirect* comparison*[tiab] OR mixed* comparison*[tiab]) OR (HTA[tiab] OR health technology assessment*[tiab] OR mini-HTA*[tiab] OR relative effectiveness assessment*[tiab]))	
#5	Search (pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb])	2833028
#4	Search (harm[tiab] OR harms[tiab] OR harmful[tiab] OR safe[tiab] OR safety[tiab] OR side effect*[tiab] OR undesirable effect*[tiab] OR treatment emergent[tiab] OR tolerability[tiab] OR toxic*[tiab] OR adrs[tiab] OR damag*[tiab] OR impair*[tiab] OR disorder*[tiab] OR abuse*[tiab] OR addict*[tiab] OR withdrawal*[tiab] OR adverse effect[tiab] OR adverse effects[tiab] OR adverse reaction[tiab] OR adverse reactions[tiab] OR adverse event[tiab] OR adverse events[tiab] OR adverse outcome[tiab] OR adverse outcomes[tiab])	3137250
#3	Search (PTSD[tiab] OR post-traumatic stress[tiab] OR posttraumatic stress[tiab])	24584
#2	Search (pain[tiab] OR pains[tiab] OR painful*[tiab] OR migraine*[tiab] OR headache*[tiab] OR neuropath*[tiab] OR neuralgia*[tiab] OR arthriti*[tiab] OR fibromyalg*[tiab])	788713
#1	Search (cannabis*[tiab] OR canabis*[tiab] OR cannabinoid*[tiab] OR cannabidiol*[tiab] OR CBD[tiab] OR cannabacae[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish*[tiab] OR hash[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR bhang[tiab] OR charas[tiab] OR THC[tiab] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR 9?tetrahydrocannabinol*[tiab] OR DELTA?9?-tetrahydrocannabinol*[tiab])	39258

EMBASE.COM

Date Searched: Tuesday May 10, 2016

#	Searches	Results
#1	'medical cannabis'/mj OR 'cannabis'/mj OR 'cannabis smoking'/mj OR 'cannabinoid'/exp/mj OR 'cannabaceae'/mj	28,447
#2	cannabis:ab,ti OR canabis:ab,ti OR cannabinoid*:ab,ti OR cannabidiol*:ab,ti OR cbd:ab,ti OR cannabacae:ab,ti OR marijuana:ab,ti OR marihuana:ab,ti OR hashish:ab,ti OR hash:ab,ti OR ganja:ab,ti OR ganjah:ab,ti OR hemp:ab,ti OR bhang:ab,ti OR charas:ab,ti OR thc:ab,ti OR tetrahydrocannabinol*:ab,ti OR 'tetra hydrocannabinol*':ab,ti OR '9 tetrahydrocannabinol*':ab,ti OR 9tetrahydrocannabinol*:ab,ti OR 'delta*9*tetrahydrocannabinol 11carboxylic acid':ab,ti	52,180
#3	#1 OR #2	57,164
#4	'pain'/mj OR 'breakthrough pain'/mj OR 'mastalgia'/mj OR 'musculoskeletal pain'/mj OR 'low back pain'/mj OR 'backache'/exp/mj OR 'chronic pain'/mj OR 'face pain'/mj OR 'headache and facial pain'/exp/mj OR 'metatarsalgia'/mj OR 'neck pain'/mj OR 'neuralgia'/exp/mj OR 'nociceptive pain'/mj OR 'intractable pain'/mj OR 'referred pain'/mj	243,955
#5	pain:ab,ti OR pains:ab,ti OR painful*:ab,ti OR migraine*:ab,ti OR headache*:ab,ti OR neuropath*:ab,ti OR neuralgia*:ab,ti OR arthriti*:ab,ti OR fibromyalg*:ab,ti	1,079,039
#6	#4 OR #5	1,130,556
#7	#3 AND #6	4,553

#8	#7 AND 'human'/de NOT 'nonhuman'/de	2,655
#9	#8 AND ('editorial'/it OR 'letter'/it OR 'note'/it)	80
#10	'cross-section*':ab,ti	297,421
#11	#8 NOT (#9 OR #10)	2,516
#12	#8 NOT (#9 OR #10) AND [english]/lim	2,308
#13	#8 NOT (#9 OR #10) AND [english]/lim AND [embase]/lim	2,088
#14	'posttraumatic stress disorder'/mj	23,335
#15	ptsd:ab,ti OR 'post-traumatic stress':ab,ti OR 'posttraumatic stress':ab,ti	29,813
#16	#14 OR #15	34,693
#17	#3 AND #16	314
#18	#17 AND 'human'/de NOT 'nonhuman'/de	227
#19	#18 AND 'editorial'/it	1
#20	'cross-section*':ab,ti	297,421
#21	#17 NOT (#19 OR #20)	295
#22	#17 NOT (#19 OR #20) AND [english]/lim	286
#23	#17 NOT (#19 OR #20) AND [english]/lim AND [embase]/lim	267
#24	'medical cannabis'/mj OR 'cannabis'/mj OR 'cannabis smoking'/mj OR 'cannabinoid'/exp/mj OR 'cannabaceae'/mj OR 'cannabis addiction'/mj	30,213
#25	#2 OR #24	57,324
#26	#25 AND ('adverse drug reaction'/lnk OR 'complication'/lnk OR 'drug interaction'/lnk OR 'drug toxicity'/lnk OR 'side effect'/lnk)	7,995
#27	harm:ab,ti OR harms:ab,ti OR harmful:ab,ti OR safe:ab,ti OR safety:ab,ti OR 'side effect*':ab,ti OR 'undesirable effect*':ab,ti OR 'treatment emergent':ab,ti OR tolerability:ab,ti OR toxic*:ab,ti OR adrs:ab,ti OR damag*:ab,ti OR impair*:ab,ti OR disorder*:ab,ti OR abuse*:ab,ti OR addict*:ab,ti OR withdrawal*:ab,ti OR 'adverse effect':ab,ti OR 'adverse effects':ab,ti OR 'adverse reaction':ab,ti OR 'adverse reactions':ab,ti OR 'adverse event':ab,ti OR 'adverse events':ab,ti OR 'adverse outcome':ab,ti OR 'adverse outcomes':ab,ti	4,055,060
#28	#26 OR #27	4,059,085
#29	#25 AND #28	25,939
#30	#25 AND #28 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	373
#31	#25 AND #28 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim	335
#32	#25 AND #28 ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [embase]/lim AND [english]/lim	319
#33	#14 OR #24 OR #33	2,616
#34	#33 NOT [medline]/lim	1,592

PSYCINFO 1806 to May Week 1 2016

Date Searched: Tuesday May 10, 2016

#	Searches	Results
1	cannabis/ or hashish/ or marijuana/ or exp cannabinoids/ or tetrahydrocannabinol/ or cannabinoids/ or tetrahydrocannabinol/ or marijuana usage/ or marijuana/	11208
2	(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw.	19269
3	1 or 2	19585
4	pain/ or aphagia/ or back pain/ or chronic pain/ or headache/ or myofascial pain/ or neuralgia/ or neuropathic pain/ or somatoform pain disorder/ or headache/ or migraine headache/ or muscle contraction headache/ or neuralgia/ or trigeminal neuralgia/ or pain management/	50895

5	(pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*).tw.	116341
6	4 or 5	117164
7	3 and 6	915
8	limit 7 to human	599
9	limit 7 to animal	346
10	7 not (8 or 9)	35
11	8 or 10	634
12	limit 11 to english language	582
13	limit 12 to ("column/opinion" or "comment/reply" or editorial or "erratum/correction" or letter)	54
14	12 not 13	528
15	cross-section*.tw.	54490
16	14 not 15	505
17	posttraumatic stress disorder/ or complex ptsd/ or desnos/	25127
18	(PTSD or post-traumatic stress or posttraumatic stress).tw.	33843
19	17 or 18	35163
20	3 and 19	209
21	limit 20 to human	178
22	limit 20 to animal	33
23	20 not (21 or 22)	12
24	21 or 23	190
25	limit 24 to english language	173
26	limit 25 to ("column/opinion" or "comment/reply" or editorial or letter)	9
27	25 not 26	164
28	cross-section*.tw.	54490
29	27 not 28	155
30	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	816214
31	3 and 30	10099
32	limit 31 to ("0830 systematic review" or 1200 meta analysis)	111
33	16 or 29 or 32	750

EBM Reviews Databases

- Cochrane Central Register of Controlled Trials April 2016,
- Cochrane Database of Systematic Reviews 2005 to May 05, 2016,
- Database of Abstracts of Reviews of Effects 1st Quarter 2016,
- Health Technology Assessment 2nd Quarter 2016,
- NHS Economic Evaluation Database 1st Quarter 2016

Date Searched: Tuesday May 10, 2016

#	Searches	Results
1	(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*).tw.	2318
2	(pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*).tw.	100259
3	1 and 2	262
4	(PTSD or post-traumatic stress or posttraumatic stress).tw.	2401
5	1 and 4	20
6	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	274193
7	1 and 6	1227
8	(meta-review* or meta-epidemiolog* or metaepidemiolog* or "horizon scan*" or ((systematic* or "systematic effectiveness" or "comparative effectiveness" or evidence or landscape or methodologic or methodological or quantitative or qualitative or integrative or mixed-method* or "mixed method*" or research or scoping or umbrella or "review* of" or updat* or cochrane or campbell) adj review*) or ((research* or evidence) adj2 aggregat*) or "evidence map*" or "evidence brief*" or "evidence summar*" or ((rapid or mini* or pragmatic or targeted or focused or brief or short*) adj2 (systematic or evidence or knowledge or review* or synthes*)) or meta-analy* or metaanaly* or "meta-meta-analy*" or "evidence synthes*" or "knowledge synthes*" or "quantitative synthes*" or "qualitative synthes*" or "research synthes*" or "integrat* data analys*" or (integrative adj1 analys?s) or "pooled analy*" or (indirect* adj2 comparison*) or (mixed* adj2 comparison*) or ((reliability or validity) adj generali?ation*) or meta-aggregat* or metaaggregat* or meta-ethnograph* or metaethnograph* or meta-interpret* or metainterpret* or meta-narrative* or metanarrative* or meta-review* or metareview* or meta-stud* or metastud* or meta-summar* or metasummar* or meta-synth* or metasynth* or "narrative synth*" or "narrative review*" or "qualitative comparative analy*" or "qualitative cross-case" or realist-synth* or "realist synth*" or "realist review*" or "thematic synth*" or "summary receiver operating characteristic*" or "comparative case study" or "comparative case studies").ti,ab.	41555
9	7 and 8	116
10	3 or 5 or 9	343
11	remove duplicates from 10	334
12	limit 11 to english language	308

PILOTS: Published International Literature On Traumatic Stress Database
(http://www.ptsd.va.gov/professional/pilots-database/)

Date Searched: Tuesday May 10, 2016

ab(cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9?tetrahydrocannabinol* OR DELTA?9?-tetrahydrocannabinol*)
AND
(PTSD OR posttraumatic stress OR post-traumatic stress)

= 177 results

COS Conference Papers Index

Date Searched: Tuesday May 17, 2016

Set	Search	Results
S4	S1 or S2 or S3	**711°**
S3	(cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9?tetrahydrocannabinol* OR DELTA?9?-tetrahydrocannabinol*) AND (harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or (adverse NEAR/2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)))Limits applied	**532°**
S2	(cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9?tetrahydrocannabinol* OR DELTA?9?-tetrahydrocannabinol*) AND (PTSD or post-traumatic stress or posttraumatic stress)Limits applied	**4°**
S1	(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9?tetrahydrocannabinol* or DELTA?9?-tetrahydrocannabinol*) AND (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*)Limits applied	**176°**

ClinicalTrials.gov

Date Searched: Monday May 16, 2015

Chronic Pain Search
(pain OR pains OR painful* OR migraine* OR headache* OR neuropath* OR neuralgia* OR arthriti* OR fibromyalg*) [DISEASE] AND (cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol* OR Δ9-THC) [TREATMENT] = 74 results

Post-traumatic Stress Disorder (PTSD) Search
(PTSD OR post-traumatic stress OR posttraumatic stress) [DISEASE] AND (cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol*) [TREATMENT] = 6 results

Harms Search
(harm* OR safety OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR tolerability OR toxic* OR adrs OR damag* OR impair* OR abuse* OR addict* OR withdrawal* OR "adverse effect*" OR "adverse event*" OR "adverse outcome*") AND ((cannabis OR canabis OR cannabinoid* OR cannabidiol* OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR 9tetrahydrocannabinol*) AND NOT (sativex OR namisol OR POT-4 OR Levodopa OR Carbidopa)) [TREATMENT] = 65 results

WHO ICTRP Database

Date Searched: Wednesday May 18, 2016

*Due to the 256 character limit for searches, the following searches were edited to fit within the proscribed limits. All terms removed were searched separately and found to not change or add additional results compared to the searches below.

Chronic Pain Search
CONDITION = (pain or pains or painful* or migraine* or headache* or neuropath* or neuralgia* or arthriti* or fibromyalg*) AND INTERVENTION=(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or hashish or hash or ganja or ganjah or hemp or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9-tetrahydrocannabinol* or DELTA-9-tetrahydrocannabinol*) = 45 results [24 results were from ClinicalTrials.gov, therefore only 21 results were downloaded]

Post-traumatic Stress Disorder (PTSD) Search
CONDITION = (PTSD or post-traumatic stress or posttraumatic stress) AND INTERVENTION=(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or hashish or hash or ganja or ganjah or hemp or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9-tetrahydrocannabinol* or DELTA-9-tetrahydrocannabinol*) = 4 results [all results were from ClinicalTrials.gov so no results were downloaded]

Harms Search
CONDITION = (harm* or safe or safety or side effect* or undesirable effect* or tolerability or toxic* or adrs or damag* or impair* or disorder* or abuse* or addict* or withdrawal* or adverse effect* or adverse reaction* or adverse event* or adverse outcome*) AND INTERVENTION=(cannabis or canabis or cannabinoid* or cannabidiol* or CBD or cannabacae or marijuana or hashish or hash or ganja or ganjah or hemp or THC or tetrahydrocannabinol* or tetra-hydrocannabinol* or 9-tetrahydrocannabinol* or DELTA-9-tetrahydrocannabinol*) = 203 results [108 results were from ClinicalTrials.gov, therefore only 95 results were downloaded]

ISRCTN Registry

Date Searched: Tuesday May 24, 2016

Text search: cannabis or canabis or cannabinoid or cannabidiol or CBD or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas or THC or tetrahydrocannabinol or tetra-hydrocannabinol or 9-tetrahydrocannabinol or DELTA-9-tetrahydrocannabinol (each keyword searched individually and results reviewed) = 8 results

NIH RePORTER

Date Searched: Monday May 16, 2016

Chronic Pain Search
((cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol) AND (pain OR pains OR painful OR migraine OR migraines OR headache OR headaches OR neuropathy OR neuropathies OR neuralgia OR arthritis OR fibromyalgia)) | Search in: Projects | Limit Project Search To: Project

Title,Project Abstracts | Limit Publication Search To: 2015-2016 = 50 results

Post-traumatic Stress Disorder (PTSD) Search
((cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol) AND (PTSD OR post-traumatic stress OR posttraumatic stress)) Search in: Projects | Limit Project Search To: Project Title,Project Abstracts | Limit Publication Search To: 2015-2016 = 5 results

Harms Search
((cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol) AND (harm OR harms OR harmful OR safe OR safety OR "side effects" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR adrs OR damage OR impaired OR impairing OR abuse OR addicted OR addiction OR addictions OR withdrawal OR "adverse effects" OR "adverse events" OR "adverse outcomes")) (Advanced), Search in: Projects | Limit Project Search To: Project Title,Project Abstracts | Limit Publication Search To: 2015-2016 = 220 results

AHRQ Gold (Grants On-Line Database)

Date Searched: Monday May 16, 2016

cannabis OR canabis OR cannabinoid OR cannabidiol OR CBD OR cannabacae OR marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas OR THC OR tetrahydrocannabinol OR tetra-hydrocannabinol OR 9tetrahydrocannabinol = 0 results

APPENDIX B. STUDY SELECTION

Inclusion Codes, Code Definitions, and Criteria

***Please note:** Important background/discussion papers may be coded "B" followed by an exclusion code, with notes or key words. For example: **B–X2, pearl for references**

1. Does the intervention or exposure consist of cannabis preparations including marijuana, hashish, tincture, hashish oil, infusion, and plant extract (*eg*, Sativex)?

   No " STOP. **Code X1** *(Not relevant to topic)*

   Yes " Proceed to 2.

2. Is the article any of the following study designs or publication types:

   - Non-systematic or narrative review
   - Opinion/editorial
   - Cross-sectional study
   - Individual case report

   No " Proceed to 3.

   Yes " STOP. **Code X2** *(Excluded study design or publication type)*

3. Does the population include adults with chronic pain or PTSD?

   No " Go to 10.

   Yes: Chronic pain " Go to 20.

   Yes: PTSD " Go to 30.

X4 = lab/blood/imaging findings

X5 = superseded by previous high-quality systematic review

Questions 10-13 deal with KQ3 (harms) in the general population

10. Are the majority of the study subjects either of the following:
    - Younger than age 18
    - Adults diagnosed with a psychotic disorder (*eg*, schizophrenia)

    No " Proceed to 11.

    Yes " STOP. **Code X10** (*Excluded pop for KQ3*)

11. Does the study report any of the following harms:

    - Fungal infections
    - Cannabinoid hyperemesis syndrome
    - Other emerging harms (potential example: sudden onset of violent behaviors)

    No " Proceed to 12.

    Yes " **Code I-11** *(Gen pop, rare harms, KQ3)*
    Proceed with items 12 and 13. **Add Code I-13 if applicable.**

12. Does the study report any of the following harms:

    - Psychotic symptoms
    - Cardiovascular events
    - Pulmonary/FEV1 outcomes
    - Infectious disease complications
    - Traffic collisions
    - Mortality

    No " STOP. **Code X12** *(Gen pop, no harms of interest reported)*

    Yes " Proceed to 13.

13. Does the study design include a control group? The control group should differ from the primary group in dose or duration of cannabis use (including no use). However, a study comparing onset of cannabis use during adolescence vs adulthood would be excluded.

    No " STOP. **Code X13** (G*en pop, no control group for specified harms*)

    Yes " STOP. **Code I-13** *(Gen pop, has control group for specified harms)*

Questions 20-22 deal with chronic pain

20. Do the study outcomes include either of the following:

    · Cannabis use disorder
    · Withdrawal symptoms

    No " Proceed to 21.

    Yes " **Code I-20** *(Pain pop, no controls needed for specified harms)*
    Proceed with items 21 and 22. **Add Code I-22 if applicable.**

21. Does the study report any of the following outcomes? The list below includes effectiveness outcomes and specific adverse effects of interest:

    · Validated measures of pain intensity and pain-related function (including spasticity)
    · Validated measures of pain-related outcomes (mood, depression, anxiety)
    · Validated measures of sleep quality
    · Validated measures of quality of life
    · Utilization of health services
    · Reduction in opioid use or dosage
    · Social functioning/disability
    · Other substance use/substance use disorder
    · Mental health symptoms including depression, anxiety, *etc* (not psychotic symptoms)
    · Cognitive effects (*eg*, IQ, SLUMS, or measures of memory, processing speed, attention, learning, executive function, *etc*)
    · Employment
    · Weight gain
    · Diversion
    · Insomnia

    No " STOP. **Code X21** *(Pain pop, no outcomes of interest)*

    Yes " Proceed to 22.

22. Is the study design a controlled clinical trial, case-control, or cohort study with a comparison group?

    No " STOP. **Code X22** *(Pain pop, excluded study design)*

    Yes " STOP. **Code I-22** *(Pain pop, addresses KQ1 and/or KQ3)*

Questions 30-32 deal with PTSD

30. Do the study outcomes include either of the following:

    · Cannabis use disorder
    · Withdrawal symptoms

    No " Proceed to 31.

    Yes " **Code I-30** *(PTSD, no controls needed for specified harms)*
    Proceed with items 31 and 32. **Add Code I-32 if applicable.**

31. Does the study report any of the following outcomes? The list below includes effectiveness outcomes and specific adverse effects of interest:
    · Validated PTSD clinical interviews and symptom inventories, such as:
        v Clinician Administered PTSD Scale (CAPS)
        v PSTD Checklist (PCL)
        v PTSD Symptom Scale (PSS)
        v Posttraumatic Diagnostic Scale (PDS).
    · Validated measures of mental health symptoms commonly associated with PTSD (mood, depression, anxiety)
    · Validated measures of sleep quality
    · Validated measures of quality of life
    · Utilization of health services
    · Reduction in benzodiazepine use or dosage
    · Social functioning/disability
    · Other substance use/substance use disorder
    · Mental health symptoms including depression, anxiety, *etc* (not psychotic symptoms)
    · Cognitive effects (*eg*, IQ, SLUMS or measures of memory, processing speed, attention, learning, executive function)
    · Employment
    · Weight gain
    · Diversion
    · Insomnia

    No " STOP. **Code X31** *(PTSD, no outcomes of interest)*

    Yes " Proceed to 32.

32. Is the study design a controlled clinical trial, case-control, or cohort study with a comparison group?
    No " STOP. **Code X32** *(PTSD, excluded study design)*

    Yes " STOP. **Code I-32** *(PTSD, addresses KQ2 and/or KQ3)*

APPENDIX C. QUALITY ASSESSMENT

Cochrane Risk of Bias (ROB) Assessment Criteria for Trials[20]

Domain	**Criteria**
Sequence generation	Was the allocation sequence adequately generated?
Allocation concealment	Was allocation adequately concealed?
Blinding	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data	Were incomplete outcome data adequately addressed? Consider attrition, intention-to-treat analysis
Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	Was the study apparently free of other problems that could put it at a high risk of bias (ROB)?
Overall assessment of potential for bias	Low/Unclear/High

Trials in Patients with Chronic Pain – Risk of Bias (ROB) Assessment

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Abrams, 2007 [35] HIV-associated sensory neuropathy	Yes: Randomization (1:1) to cannabis or placebo cigarettes was computer-generated by the study statistician	Yes: allocation managed by an independent research pharmacist	Yes: Treatment was double-blind, NOS. The National Institute on Drug Abuse provided identically appearing pre-rolled cannabis and placebo cigarettes	Yes: Low loss to follow-up.	Probably yes. Does not state protocol was reported prior to study.	Yes	Low
Berman, 2004 [36] Neuropathic Pain from Brachial Plexus Avulsion	Yes - computer generated list	Unclear	Uncertain; notes that treatment sequence was blinded via sealed code break envelopes but no further details given	Yes: ITT analysis, attrition described	Unclear: No protocol mentioned, but outcomes reported in the methods are included in results	Unclear: No washout period between treatment regimens	Low
Blake, 2006 [59] Rheumatoid arthritis	Unclear (permuted blocks of four)	Unclear (not reported)	Unclear (not reported)	Yes: low attrition, comparable across groups	Yes	Unclear (COI statement notes the study was funded by a drug company)	Unclear
Collin, 2010 [47] MS	Unclear, method not described	Unclear, method not described	Probably yes, but not described in detail	Yes: ITT	Yes	The data on pain is limited only to spasticity responders.	Unclear
Corey-Bloom, 2012 [48] MS	Unclear, method not described	Unclear, method not described	Yes: identical placebo cigarettes	Yes: < 80% attrition; also did worst case scenario analysis	Yes	Excluded high doses of narcotic medications for pain, but did not control for or examine concomitant use of analgesics because spasticity was primary criteria and outcome of interest. No mention of analgesic use for pain.	Unclear

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
De Vries, 2016 [58] Abdom-inal pain	Yes: computer-generated randomization list stratified for opioid and non-opioid users by using separate lists	Yes: central allocation ("Independent pharmacists dispensed either active or placebo tablets according to a computer-generated randomization list")	Yes: "Treatment allocation was strictly concealed from participants, investigators, and all other study personnel involved in the study until end of study and database lock."	No: ITT analysis not performed	Unclear: for several secondary outcomes (depression, quality of life, EEG, *etc*), researchers simply stated "did not change after THC treatment compared with placebo" but did not give any values.	No power calculation, likely inadequate power to detect differences. Also, what was originally supposed to be 2 trials were combined into one study "because of a disappointing recruitment."	High
Ellis, 2009 [37] HIV-associated sensory neuropathy	Yes: Randomization was performed by a research pharmacist using a random number generator, and the key to study assignment was withheld from investigators until completion statistical analyses.	Yes: key was withheld from study investigators until completion of analysis.	Yes: double blind, cigarettes "were constructed of the same base material." Assessed effectiveness of blinding among participants	Moderate: 6/34 lost. ITT. Similar baseline characteristics.	Yes: all outcomes in methods were reported.	This is a specific population of HIV pain; Patients allowed to use own analgesia; Used validated scales for pain measures	Low
Johnson, 2010 [55] Cancer	Not described; Table 1 shows general similarities between groups but baseline opioid use was lower in one group vs others	Not described	Not described for investigators; Yes for patients; bottles were similar between active and placebo, though patients on active were able to guess their group	Yes; ITT done and overall attrition >80%, though one group lost >80%	Yes	This is a specific population of cancer pain; Patients allowed to use own analgesia; Used validated scale and self-reported scale as co-outcomes for pain	Unclear

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Langford, 2013 [49] MS	Yes: "Randomization occurred using a pre-determined computer-generated randomization code in which treatment allocation was stratified by center, and used randomly permuted blocks of variable sizes."	Yes	Yes: double-blind	Yes - ITT, but in group A, 26/167 (cannabis) and 16/172 (placebo) withdrew.	Yes: outcome measures reported	No: Strong placebo effect; Placebo group patients who titrated to the maximum dose had disproportionate improvements in pain scores, and a number of these patients reached the maximum permitted dose as the study period was drawing to a close. Self-titration combined with a subjective endpoint seems therefore to have significantly impacted the placebo response.	Unclear
Lynch, 2014 [38] Chemotherapy-Induced Neuropathic Pain	Yes	Yes	Yes	Yes (16/18 completers)	Yes	Yes	Low
Notcutt, 2004 [33] Mostly neuro-pathic; 47% MS	Yes	Yes: randomization done externally	Yes: trial stated as being double-blind and delivery of intervention and placebo were matched	Unclear: for the trial portion, 71% (24/34) patients were included in analysis due to withdrawal/use of rescue meds	Yes	Excluded those who had to use rescue medications; also, only randomized pts who reported a positive response to medical cannabis.	Low

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Notcutt 2012[29]	Yes: independent statistician produced an allocation schedule using balanced permuted blocks of 4 with computer-based algorithm	Yes: independent statistician	Unclear: no methods described	Yes: had high attrition (~50%) and only some subjects met treatment failure but based on disposition tree, all included subjects were analyzed	Yes: appeared to report on relevant outcomes	No: underpowered (though CI adjusted to help with this), some participants restarted on their own nabiximols prior to final assessment (likely to reduce the effect of the drug)	Unclear: multiple areas of uncertainty; study was under-powered and patients could have restarted nabiximols prior to assessment
Novotna 2011[27]	Unclear, methods not described	Unclear, methods not described	Unclear: states that trial was double-blind but no details on methods; comment that inclusion into trial based on investigator assessment that patient remained blinded during initial phase of study	Yes: ITT though patients without post-randomization efficacy data were excluded, all patients who had received one dose of medication included in safety analyses; attrition reported (12% for nabiximols group and 2% for placebo).	Yes: had clearly stated pre-specified primary outcome and included multiple secondary outcomes	Yes: no major issues identified aside from lack of clarity around the methods used for allocation, randomization	Low: though limited data on methodology around allocation and blinding, authors state that study was double-blind and had low attrition with ITT analyses and pre-specified outcomes
Noyes, 1975[56] Cancer	No	No	Yes (patients), No (providers)	Unclear, though 34/36 patients were reported to be completers.	No (only reported results for significant tests, refer to "other differences" that did not reach significance)	Pain measure not validated	High

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Nurmikko, 2007 [39] Neuropathic Pain Characterised by Allodynia	Yes: "randomly permuted blocks stratified by center and was generated using a computer based pseudo-random number algorithm"	No: a copy of randomization schedule in patient-specific sealed envelopes sent to the pharmacy in each center	Yes	Yes: ITT analysis, attrition described	Unclear: no protocol mentioned, but outcomes reported in the methods seem to be included in results	Unclear: "GW Pharma acted as the sponsor of the study, provided the medication, participated in the study design, coordinated the study between centers and carried out the first set of analyses. The analyses were verified by an independent statistician."	High
Portenoy, 2012 [57] Cancer	Unclear	Unclear	Yes (patients), Unclear (research staff)	No (attrition 27%)	Yes	Yes	Unclear
Rog, 2005 [50] MS	Yes: "Patients were randomized using a predetermined randomization code drawn up by a statistician who remained unknown to study personnel throughout the duration of the trial."	Yes: "statistician remained unknown to study personnel throughout the duration of the trial….Treatment allocation was made using randomized permuted blocks of four (two active drug, two placebo), with treatments sequentially assigned."	Yes: double-blind, and "Placebo was designed to match the appearance, smell, and taste of the active formulation but contained no active components, in ethanol: propylene glycol (50:50) excipient. To facilitate blinding, patients completed pain and sleep	Yes: only 2/64 did not complete. Both received cannabis - one adverse event, one withdrew consent. ITT.	Yes: all outcomes reported in methods were reported.	Unclear: Required no change of concomitant meds, but no mention of controlling for meds/sensitivity analysis, or analyzing by med class.	Low

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Selvarajah, 2010 [40] Diabetic Neuropathy	Unclear: no information other than saying it was randomized	Unclear: no information	Unclear: no information about blinding except stating that it was a double-blind trial	Unclear: completed ITT analysis included but 1 patient with protocol violation was excluded.	Unclear: states "Tolerability and side effects were evaluated using standardized forms" but does not report these results (except saying 6 patients overall withdrew due to AEs). Unlikely to have introduced significant bias.	No power calculation reported, very likely the study had inadequate power to detect differences	Unclear
Serpell, 2014 [41] Peripheral neuropathic pain (PNP) associated with allodynia	Yes: a predetermined computer-generated randomization code	Unclear	Yes	Yes: ITT analysis, attrition described	Yes: protocol available (https://clinicaltrials.gov/ct2/show/NCT00710554), study reports all outcomes mentioned	Recorded medications used; also did allodynia testing	Low
Van Amerongen, 2017 [51] MS	Unclear: randomization schedule prepared by independent statistician; allocated "on the basis of the date of eligibility of the individual because the identification numbers are assigned at that moment."	Unclear: "The schedule was sent to the hospital pharmacy, and sealed envelopes for code breaking were available for the investigator"; opaque envelopes not specified	Yes: matching placebo tablets, "All staff involved in the clinical execution of the study were blinded until all data were collected and the database was locked."	Yes: attrition with reasons reported by group, and ITT analysis performed.	Unclear: the McGill Pain Questionnaire was mentioned as a secondary endpoint in the online protocol and Methods section, but was not reported in the Results.	Yes	Unclear
Wade 2003 [30] MS (67%)	Yes: sequence generated with Williams squares	Yes: stated that participants and staff were blinded.	Yes: identical sprays used with masking flavor; investigators were not aware of coding	Yes: attempted to analyze those who took rescue medications vs entire sample	Yes: looked at range of symptoms	Small sample size	Low

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Wade, 2004 [52] MS	Unclear: permuted blocks of 4, stratified by primary symptom and center	Unclear: the pharmacist at each center was provided with a randomization scheme and assigned the treatments in sequential patient number order	Unclear: investigators did not assess the degree of blinding of patients and outcome assessors, though a stronger effect was found for pain outcome in placebo compared with active treatment.	Yes	Unclear	Unclear: study was underpowered for pain outcome	Unclear
Wallace, 2015 [42] Diabetic Neuropathy	Yes: "Randomization was performed by a research pharmacist using a random number permutations..."	Yes: "Randomization was performed by a research pharmacist using a random number permutations and the key to study assignment was withheld from investigators until completion of statistical analyses"	Unclear: blinding may have been compromised due to crossover design and euphoria from the drug, but analyses didn't find this to be significant	Yes: did not appear to be any missing data; one patient only participating in some of the sessions were only analyzed for those sessions	Yes: reports the outcomes mentioned in the CT.gov protocol (https://clinicaltrials.gov/ct2/show/NCT00781001) – although some of results are mostly in charts which may make it hard to abstract all data accurately	Study only enrolled 16 patients, rather than 20 in power calculation. Also, only very short-term	Low
Ware, 2010 [43] Post-surgical or post-traumatic neuro-pathic pain	Unclear (just notes a Latin Square design)	Unclear (not reported)	Yes (notes factors to maintain blinding such as placebo comparability confirmed by objective assessment)	Yes (very low attrition)	Yes	Yes	Low
Wilsey, 2008 [44] Neuro-pathic pain	Yes	Yes	Uncertain: no details given on blinding, beyond statement to the effect	Yes: Attrition <80% for all arms; all available data used in analysis	Yes	Pain scales were self-report; also used neurocognitive testing and evoked pain threshold	Low
Wilsey, 2013 [45] Neuro-pathic pain	Yes	Yes	Uncertain: no details given on blinding, beyond statement to the effect	Yes: Attrition <80% for all arms; all available data used in analysis	Yes	Yes: pain scales were self-report; also used neurocognitive testing	Low

Study; Pain type	*Sequence generation*	*Allocation concealment*	*Blinding*	*Incomplete outcome data*	*Selective outcome reporting*	*Other sources of bias*	*Overall: Low/Unclear/ High ROB*
Wilsey, 2016 [46] Spinal cord injury	Yes: used a Web-based random number-generating program…to determine the sequence of administration.	Yes: The allocation schedule was maintained by a research pharmacist and concealed from other study personnel.	Yes: Placebo cannabis was derived from whole plant material with extraction of delta 9-THC.	Unclear: Attrition with reasons reported by group, method for handling missing data was not described.	Yes: Protocol available and all outcomes mentioned appear to be reported	No power calculation reported, but since a significant difference was found between interventions, this is unlikely to have introduced significant bias	Low
Zajicek, 2003 [53] MS	Yes: The coordinating center allocated the patient a trial number and then forwarded relevant details to the central trial pharmacy, where randomization took place, using a dedicated stand-alone computer.	Yes: Throughout the study, the list of treatment allocation codes was kept at the central trial pharmacy, located separately from the coordinating office.	No: most in the active treatment group guessed correctly that they were on active treatment; potential bias despite that placebo group was effectively blinded.	Yes	Yes	Patients selected for spasticity, not pain. Power calculation based on projected effects on spasticity. Baseline pain scores not reported, only whether improved, unchanged, or deteriorated. Unclear whether pain levels were high or low to begin with.	High
Zajicek, 2012 [54] MS	Yes: Computer generated permuted block randomization	Yes	Yes: Matched placebo capsules.	Yes	Yes	Yes	Low

Trials Assessing the Risk of Psychotic Symptoms with Cannabis Use – Risk of Bias (ROB) Assessment

Criteria	**Englund 2013[91]**	**Kaufmann 2010[89]**
Sequence generation	Unclear - methods not described	Unclear - methods not described
Allocation concealment	Unclear - methods not described	Unclear - methods not described
Blinding	Yes - double blind, randomly allocated	Unclear - double blind. No details provided.
Incomplete outcome data	NA - all participants completed study	No - One participant developed acute psychotic symptoms and was not included in the statistical analysis, but was qualitatively described.
Selective outcome reporting	Yes - All relevant outcomes appear to be reported	Yes - appear to report all outcomes.
Other sources of bias	Yes - no major issues identified aside from lack of clarity around the methods used for sequence generation and allocation.	No - small sample/under powered.
Overall assessment of potential for bias	Low - despite lack of clarity about sequence generation and allocation concealment.	Moderate - due to lack of clarity about sequence generation and allocation concealment and small sample size.

Quality Assessment Criteria for Observational Studies, Based on the Newcastle-Ottawa Scale[21]

Representativeness of the exposed cohort *Enter 0 or 1:* 1 = truly representative of the average patient in the community 1 = somewhat representative of the average patient in the community 0 = selected group of users (*eg*, nurses, volunteers) 0 = no description of the derivation of the cohort
Selection of the non-exposed cohort *Enter 0 or 1:* 1 = drawn from the same community as the exposed cohort 0 = drawn from a different source 0 = no description of the derivation of the non-exposed cohort
Ascertainment of exposure *Enter 0 or 1:* 1 = biological test (*eg*, blood/urine) 1 = structured interview 1 = written self-report that characterizes dose (current or cumulative) 0 = written self-report without quantification of exposure 0 = no description
Precision of Exposure Dose Ascertainment *Enter 0 or 1:* 1 = amount and time 0 = no information about amount and time
Ascertainment of exposure done prospectively or retrospectively *Enter 0 or 1:* 1 = Prospectively 0 = Retrospectively
Demonstration that outcome of interest was not present at start of study, OR baseline assessment *Enter 0 or 1:* 1= yes 0 = no
Adjustment for confounding (rendering comparability of cohorts on the basis of the design or analysis) *Add points: Minimum 0, Maximum 2* 1 = study accounts/controls for other substance use 1 = study controls for any additional factor (mental health comorbidity; medication use; severity of PTSD; mental health comorbidity and treatment; socioeconomic status) 0 = no adjustment for potential confounders
Assessment of outcome *Enter 0 or 1:* 1 = objective measure 1 = validated self-report measures 0 = no information or non-validated measures
Was follow-up long enough for outcomes to occur? *Enter 0 or 1:* 1 = yes (need to define adequate follow-up period for outcome of interest) 0 = no
Adequacy of follow-up of cohorts *Enter 0 or 1:* 1 = complete follow-up; all subjects accounted for. 1 = subjects lost to follow-up unlikely to introduce bias; small number (less than 20 %) lost, or description was provided of those lost. 0 = follow-up rate < 80% and no description of those lost. 0 = no statement

Observational Studies in Patients with Chronic Pain – Risk of Bias (ROB) Assessment

Criteria	Ware 2015[31]	Storr 2014[32]	Fiz 2011[34]
Representativeness of the exposed cohort	1 - included patients with non-cancer pain but had to be moderate/severe and refractory	1 - exposed cohort was equal for males and females although IBS impacts females at a slightly higher base rate	1 - somewhat; these are treatment resistant patients in particular
Selection of the non-exposed cohort	1 - all drawn from same clinical centers	1 - drawn from same source	0 - 2 of the recruitment sites were the same (FM associations and outpatient rheumatology) but cannabis group also recruited from cannabis association.
Ascertainment of exposure	1 - pharmacy dispensed and recorded use	0 - self-report; only method of administration (*ie*, smoking) recorded	0 - information reported about duration of cannabis use (*ie*, 1 year) and administration modality, but no info provided about dose or cannabinoid concentration.
Precision of Exposure Dose Ascertainment	1 - dosing described	0 - no dosing information provided	0 - method of administration varied among users (smoking 54%; oral 46%; combined 43%), duration and frequency of use varied among users. Dosage varied among users ("1-2 cigarettes each time when smoked or 1 spoonful each time when eating"). No info on THC/CBD content given. 39% used daily, 18% used 2-5 days per week.
Ascertainment of exposure done prospectively or retrospectively	1 - prospectively	0 - cross-sectional so ascertainment based on one timepoint	0 - exposure groups established by use status
Demonstration that outcome of interest was not present at start of study, OR baseline assessment	1 - all results compared to baseline	0 - no baseline	1 - baseline data gathered 2 hours prior to exposure
Adjustment for confounding	2 - cohort significantly different on age, gender, disability status, tobacco status, past cannabis use, drug abuse screening, average pain intensity (cannabis users higher) and medications – however, these group differences were controlled for in the inferential statistics.	2 - study adjusts for demographic variables, tobacco smoking status, time since diagnosis, and biological use	0 - no adjustments made

Criteria	**Ware 2015[31]**	**Storr 2014[32]**	**Fiz 2011[34]**
Assessment of outcome	1 - objective/validated measures used	0 - surgical history gleaned from medical chart (only measure of utilization provided) no other validated measures reported for our PICOTS. Side effects and perceived utility of cannabis for treatment of IBD symptoms all subjective and only descriptive data is provided for users.	1 - validated self-report measures for outcomes (*eg*, VAS, SF-36)
Was follow-up long enough for outcomes to occur?	1 - (12 months follow-up)	0 - no follow-up	0 - difficult to ascertain sustainability of outcomes, only 2 hours of follow-up
Adequacy of follow-up of cohorts	1 - > 20% loss to follow-up in the cannabis group but all subjects are accounted for and all subjects included in the primary safety analysis	0	1 - appears to be complete follow-up
Comments on study quality	Low ROB - there are some concerns as noted below but what is measurable by scale appears to be properly done - Study's primary outcomes were adverse events, other outcomes were secondary; Study notes that protocol changes were made but no details provided; Study did not recruit pre-specified sample size for power; Multiple adjustments and subgroup analyses were undertaken; Also, strange that inclusion into cannabis group relied on use of cannabis but there are persons included there who are cannabis naïve and who were ex-users; baseline demographics/ population details differed by group, though adjustments made in analyses...the majority (66%) of the cannabis users were experienced, making the generalizability to cannabis-naïve users difficult, and differences in the follow-up times between the control and exposure group may have artificially inflated the number of AEs reported by cannabis users.	High ROB - dosing information was not provided or consistent for users, data collection only at one time point so no f/u data provided. Minimal outcomes of interest.	High ROB - dosing information was not provided or consistent for users, participants gathered from different sources introducing selection bias; groups were established by exposure status and those using cannabis are likely to differ from others not using cannabis (although baseline characteristics are not different per study authors and this is the only way to conduct a cohort study), also concern that there were no adjustments made for other medications used, small sample size, use of self-reported measures, very limited follow-up with a pre-, post-design rather than between group comparison for primary outcome
Notes on Applicability	Patients had treatment moderate/severe, refractory chronic pain but otherwise applicable, especially since drawn from clinical centers		Patients had treatment resistant FM

Observational Studies in Patients with PTSD – Risk of Bias (ROB) Assessment

Criteria	**Wilkinson 2015[60]**	**Johnson 2016[61]**
Representativeness of the exposed cohort	1	1
Selection of the non-exposed cohort	1	1
Ascertainment of exposure	0 (self-report)	0 (self-report)
Precision of Exposure Dose Ascertainment	0 (not specific)	0 (not specific)
Ascertainment of exposure done prospectively or retrospectively	1	0
Demonstration that outcome of interest was not present at start of study, OR baseline assessment	1	n/a
Adjustment for confounding	1 (included all assessed confounders related to cannabis use)	0
Assessment of outcome	1 (validated self-report measures)	1 (validated self-report measures)
Was follow-up long enough for outcomes to occur?	1 (4 months)	n/a
Adequacy of follow-up of cohorts	1	n/a
Comments on study quality	Medium ROB	High ROB
Notes on Applicability	VA population with PTSD	VA population with PTSD

Observational Studies of Medical Harms Associated with Cannabis Use – Risk of Bias (ROB) Assessment

Criteria	Pletcher 2012[70]	Hancox 2010[69]	Mittleman 2001[73]	Frost 2013[72]	Carvalho 2015[74]
Representative-ness of the exposed cohort	1 - truly representative Community based study in 4 cities representing different parts of country, ethnically diverse group.	1 - somewhat representative (birth cohort, but for that reason does not represent older patients in the community)	1 - somewhat representative of MI patients - not community, but most MI patients would get cared for in hospital and this was multisite hospital study	1 - somewhat representative of MI patients - not community, but most MI patients would get cared for in hospital and this was multisite hospital study	1 - in half the studies, these were hospital patients, half the studies used cancer registry data
Selection of the non-exposed cohort	1 - drawn from same community	1 - same community	1 - self-control	1 - same community	1 - most studies found general population controls (*eg*, electoral rolls, random digit dialing)
Ascertainment of exposure	1 - structured interview	1 - interview	0 - risk of recall bias, not clear how accurate recalled pattern of use over prior year was - since this formed basis for control (expected frequency of hourly use) there is some potential for bias.	1 - interview	1 - most studies used structured interview
Precision of Exposure Dose Ascertainment	1 - amount and time	1 - amount and time	0 - not enough information about amount and time	0 - time only, and only at baseline	1 - most gathered information about amount and time
Ascertainment of exposure done prospectively or retrospectively	1 - prospectively	1 - prospectively	0 - retrospectively	0 - retrospectively	0 - retrospectively
Demonstration that outcome of interest was not present at start of study, OR baseline assessment	1 - yes - PFTs were longitudinally collected - baseline PFT data were available and outcomes were reported as change from baseline	1 - yes, serial PFT measures, and they adjusted for spirometry at age 15	n/a	1 - yes (inception cohort)	0 - no

Criteria	**Pletcher 2012[70]**	**Hancox 2010[69]**	**Mittleman 2001[73]**	**Frost 2013[72]**	**Carvalho 2015[74]**
Adjustment for confounding	1 - for PFT outcomes, most important covariate is tobacco exposure along with gender, age, race all of which were well accounted for.	1 - accounts for tobacco exposure, age, gender which are probably most relevant for the PFT outcomes - did not account for race, SES, second hand smoke exposure, *etc*	0 - not clear that they account for tobacco use in hour prior to MI	1 - propensity score matching - adjusted for tobacco, other substance use, SES other factors	1 - most studies adjusted for tobacco use and alcohol use
Assessment of outcome	1 - PFTs, objective measure	1 - PFTs	1- objective assessment of MI outcome	1 - national death index	1 - only included studies of patients with definitive HNC
Was follow-up long enough for outcomes to occur?	1 - yes	1 - yes	n/a	1 - yes, partly - the exposed group was younger and the number of mortality events therefore relatively small, but 18 year f/u	n/a
Adequacy of follow-up of cohorts	1 - data from 98% of participants, 95% of all visits had complete data	1 - data from 96% of original cohort at 32 years	n/a	1 - national death index	n/a
Comments on study quality	Low ROB. Well-conducted, prospective cohort study. Should be one of the better sources of data for this outcome.	Low ROB. Well-conducted, prospective cohort study. Similar to Pletcher study, but did not have data on linear trends.	High ROB. Case-crossover study with several potential sources of bias including recall bias, small # patients with exposure of interest, and lack of clarity re: accounting for tobacco use.	High ROB. Information on exposure (both cannabis and tobacco) only available at baseline interview. Assess long-term mortality, but no information on total use over the period of follow-up, making it difficult to assess relationship between exposure and outcome. Moreover, cannabis users were different than non-users - confounders were adjusted for, but strong possibility of residual confounding.	Medium ROB. Ascertainment of exposure is necessarily limited by retrospective nature and issues of recall bias.

Criteria	**Pletcher 2012[70]**	**Hancox 2010[69]**	**Mittleman 2001[73]**	**Frost 2013[72]**	**Carvalho 2015[74]**
Notes on Applicability	Applicable to younger populations (< 30)	Applicable to younger populations	Most cannabis users were male	Most cannabis users were male, younger than nonusers	Very wide range of ever cannabis use - some of the studies with very low rates of use may not be applicable, but the consistency of results across different study populations is reassuring.

Medical Harms Observational Studies – Risk of Bias (ROB), Continued

Criteria	Zhang 2015[75]	Callaghan 2013[76]	Gurney 2015[77]	Chacko 2006[78]
Representative-ness of the exposed cohort	1 - international, mix of hospital-based and community studies	1 - nearly all (98%) 18-20 year old males	1 - cancer registry cases with community-based controls	1 - representative of transitional cell ca population, at least in VA
Selection of the non-exposed cohort	1 - all drew controls either from same hospital/clinic, or the community	1 - drawn from same population	1 - drawn from same population (random general population in 2 studies and friends of cases in one study which is a potential source of selection bias)	0 - drawn from urology clinic, presenting for different reason - not representative of community
Ascertainment of exposure	1 - written self-report with information on duration and frequency	0 - self-report without adequate quantification	0 - interview in 2 studies and written self-report with quantification in other, but not clear that interviewers were blinded to case/control status of participant	1 - written self-report with information on duration and frequency
Precision of Exposure Dose Ascertainment	1 - amount and time	0 - minimal information about exposure over time	1 - amount and time	1 - amount and time
Ascertainment of exposure done prospectively or retrospectively	0 - retrospectively	0 - retrospectively, and only at time of conscription	0 - retrospectively	0 - retrospectively
Demonstration that outcome of interest was not present at start of study, OR baseline assessment	1 - performed additional analyses excluding patients who had used within 2 years of cancer diagnosis (to evaluate possibility of reverse causality)	0 - no, but very unlikely that outcome was present in young age group	1 - (case-control)	n/a
Adjustment for confounding	1 - adjusted for tobacco use and some other sociodemographic factors	0 - adjusted for multiple factors, but did not have a way of quantifying tobacco exposure after conscription which is likely to have been heaviest amongst those with heavier cannabis use	1 - adjusted for major confounders relevant to disease (including cryptorchidism), but one study did not adjust for alcohol or tobacco use (but was also the smallest of the studies)	0 - important confounders considered, but they did not report adequately the adjusted analyses
Assessment of outcome	1 - only histologically confirmed lung cancer	1 - based on national medical records, claims - fair validation	1 - histologically confirmed cancers	1 - confirmed cancers
Was follow-up long enough for outcomes to occur?	n/a	1 - yes	n/a	n/a
Adequacy of follow-up of cohorts	n/a	1 - 1.9% lost to f/u due to emigration	n/a	n/a

Criteria	**Zhang 2015[75]**	**Callaghan 2013[76]**	**Gurney 2015[77]**	**Chacko 2006[78]**
Comments on study quality	Medium ROB - ascertainment of exposure is necessarily limited by retrospective nature and issues of recall bias.	High ROB - biggest issue was that the main exposure and main confounder (tobacco use) were only determined at time of conscription. High risk of residual confounding due to ongoing tobacco exposure for finding of heavy cannabis use association with lung cancer.	High ROB - the meta-analysis itself was well done, but there were methodologic deficiencies in all 3 included studies. The smallest study did not control for important confounders such as tobacco. Low response rates among controls or cases in the 2 bigger studies. There was a potential for ascertainment bias, and recall bias is also an issue. Use of friends as controls in one study is a potential source of bias. The largest and methodologically strongest study showed results consistent with overall findings, direction of effect was consistent across studies, there was a dose-response relationship, and the authors do highlight some biologic plausibility to findings.	High ROB - small study, 2 VA sites, very little information on adjusted analyses, control group were symptomatic patients in urology clinic so not representative of community, reverse causality a real concern (*ie*, cancer patients may have been using cannabis to palliate symptoms - no information on timing of use and diagnosis), recall bias
Notes on Applicability	Variety of settings, included squamous cell and adenocarcinoma patients but few patients with other types of lung cancer.	--	--	VA only - 2 sites. One of the sites located in a town with prominent textile industry (and, thus, dye exposure). Small number of patients.

Observational Studies of Adverse Mental Health Effects Associated with Cannabis Use – Risk of Bias (ROB) Assessment

Criteria	Di Forti 2009[92]	Dominguez 2010[87]	Kuepper 2011[86]	Mason 2008[90]	Rossler 2011[88]	van Nierop 2013[137]
Representative-ness of the exposed cohort	1 - first episode psychosis (presenting to the hospital)	1 - representative population study.	1 - representative population study.	0 - No information about the population from which the sample was recruited. Recreational cannabis smokers who used cannabis at least once a month. No personal history of diagnosed mental illness. Lifetime drug usage of other illicit drugs in the cannabis group commonly included amphetamines, benzodiazepines, cocaine, ketamine, LSD, and heroin.	1 - representative population based sample. Males identified from a military screening test, and females from an electoral roster.	1 - somewhat representative (siblings of individuals with psychotic disorders and healthy controls in the same geographical areas)
Selection of the non-exposed cohort	0 - No description of source. Control group was individuals with no psychotic episodes.	1 - same population	1 - same population	0 - No description of source	1 - same population	1 - same community
Ascertainment of exposure	1 - Cannabis Experience Questionnaire	1 - Munich composite international diagnostic interview (DIA-X/M-CIDI)	1 - Munich composite international diagnostic interview (DIA-X/M-CIDI)	1 - self-report and urinalysis	1 - Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology (SPIKE)	1 - urinalysis and CIDI

Criteria	**Di Forti 2009[92]**	**Dominguez 2010[87]**	**Kuepper 2011[86]**	**Mason 2008[90]**	**Rossler 2011[88]**	**van Nierop 2013[137]**
Precision of Exposure Dose Ascertainment	1 - Assessed type and frequency, as well as potency	0 - > or < 5 times since last exposure	0 - > or < 5 times since last exposure	0.5 - Participants contacted researchers when they were using cannabis recreationally. The study team went to meet them for testing. Dose not ascertained.	1 - frequency of use	0.5 - used interviews to determine lifetime use and urinalysis to determine current use. No information re: dose, frequency, *etc*
Ascertainment of exposure done prospectively or retrospectively	0 - retrospectively	0 - retrospectively	0 - retrospectively	1 - prospectively	0 - retrospectively	0 - retrospectively
Demonstration that outcome of interest was not present at start of study, OR baseline assessment	1 - first psychotic episode	0 - not excluded	0 - not excluded	0 - not excluded, and no baseline assessment.	1 - although clinical diagnoses of psychotic disorders were not assessed with the SPIKE at baseline through 1999, two-thirds of the sample were at "high risk" for subclinical psychosis symptoms based on Symptom Checklist 90—Revised (SCL-90-R) scores.	1 - healthy siblings of individuals with a psychotic disorder (high risk) and healthy controls.
Adjustment for confounding	2 - adjusted for age, gender, ethnicity, other stimulant use, education, and employment status.	1 - controls for depression but not other substance use	2 - Adjusted for age at baseline, sex, baseline SES, use of other drugs at baseline and T2, trauma before the age of 14 as assessed at baseline, and urban/rural environment.	1 - performed sensitivity analysis for other drug/alcohol use	2 - adjusted for sex, familial background, socio- economic status, family history of mental disorders, other family problems, and school problems, and used step wise multivariate analysis with each substance entered individually.	0 - adjusts only for age, sex, high-risk sibling status

Criteria	**Di Forti 2009[92]**	**Dominguez 2010[87]**	**Kuepper 2011[86]**	**Mason 2008[90]**	**Rossler 2011[88]**	**van Nierop 2013[137]**
Assessment of outcome	1 - hospital admission	1 - Munich composite international diagnostic interview (DIA-X/M-CIDI)	1 - Munich composite international diagnostic interview (DIA-X/M-CIDI)	0 - Psychotomimetic States Inventory (PSI) - the study is a validation study.	1 - SPIKE and SCL-90-R	1 - Community Assessment of Psychic Experience (CAPE)
Was follow-up long enough for outcomes to occur?	NA	1 - Mean T1 1.6, T2 3.5, and T3 8.4 years (range=7.3-10.5)	1 - Mean T1 1.6, T2 3.5, and T3 8.4 years (range=7.3-10.5)	1 - interested in acute symptoms. Assessed at time of exposure, then 3 to 4 days later.	1 - 30 years	0 - Mean 3.3 years
Adequacy of follow-up of cohorts	NA	0 - 84% at T2 and 73% at T3. No description provided.	0 - 84% at T2 and 73% at T3. No description provided.	NA - no follow-up other than 3-4 days post use.	1 - 57% assessed at 30 year follow-up. Description of lost provided.	1 - 78% assessed at follow-up. Description of participants lost provided.
Comments on study quality	Low ROB study despite lack of detail on ascertainment of control group. Nicely conducted retrospective study.	Moderate ROB study. Included participants with negative/disorganized symptoms at baseline.	Moderate ROB study. Included participants with negative/disorganized symptoms at baseline.	High ROB study. No information about the source of the exposed or non-exposed sample. Exposed sample used drugs in addition to cannabis, and there was no baseline assessment. No information about dose ascertained.	Low ROB study. Well-conducted, good description of follow-up and loss to follow-up, description of methods, *etc*	High ROB due to lack of controlling for important confounders, short follow-up

APPENDIX D. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES

Rev #	Comment	Response
Are the objectives, scope, and methods for this review clearly described?		
1-7	Yes	Noted.
9	No - page 4, line 35: please add risk of cannabis use disorder to the list of adverse events in this phrase- "assess the impact of short- and long-term marijuana use on the risk of adverse effects such as pulmonary diseases, cardiovascular diseases, cancer, and psychosis in the general adult population"	This change has been made.
Are there any published or unpublished studies that we may have overlooked?		
1, 2, 4, 7	No	Noted.
3	Yes - There is a recently published systematic review of medical marijuana in psychiatric indications (Wilkinson et al., 2016) that wasn't included. This may have been a timing issue. But now that it is published, it should be included - especially since it informs the PTSD literature.	We have added information from this recent systematic review to our report.
5	Yes - A couple of studies regarding harms have come out since your February 2016 deadline. Considering that the review is not likely to be formally published much before 2017. I uploaded the pdfs of these papers. · One is a new analysis of the Dunedin study showing that cannabis users are more likely to develop periodontal disease. · The second one is an epidemiologic study from Sweden that shows an association between early, heavy cannabis use and mortality.	We added the new Dunedin analysis to the emerging harms section. We had assessed another analysis from the Swedish military conscript study – there was no data on ongoing tobacco or cannabis use after conscription and, since the outcomes were many decades later, the lack of exposure information made the study results very difficult to interpret.
6	Yes - See Review.	We have reviewed the studies you suggested and included them in our report if they met our inclusion criteria or if they were relevant for background and discussion sections.
9	Yes - In assessing risk of harm, it would be more appropriate to include studies assessing harm among daily marijuana users (whether or not they have pain or PTSD) than to assess risk of harm amongst pain or PTSD patients who do not use or who occasionally use marijuana.	We broadly included studies with varying levels of use (including heavy use) and in broad patient populations. We have clarified throughout the summary table and manuscript whether the results apply to light or heavy use and we have clearly noted when there is a lack of data on heavy (daily) use.
Is there any indication of bias in our synthesis of the evidence?		
1-5, 7	No	Noted.
6	Yes - The choice of only including plant-based and not synthetic cannabinoid studies seems biased, given that they have the same molecular structure.	We have rewritten the methods and the KQ1 results section to better clarify the rationale for this decision and we note how the exclusion of synthetic cannabinoid studies would likely not have affected our overall findings (since there were no large, good quality studies of synthetics in the populations of interest for this report).
9	Yes - There appears to be a bias in favor of state-	We agree. We have added language to the results

	approved retail marijuana products for treatment of pain and PTSD. The executive summary introduction states that the purpose of the paper is to examine health effects of marijuana use because of increased state legalization of marijuana plant products for the indications of pain and PTSD, but the review of the literature conflates studies of plant-based pharmaceutical grade products (i.e. Sativex) with those of retail smoked marijuana and other marijuana products. As written, the two types of cannabis products are conflated in the summaries of the evidence and in the recommendations. The differences between the two types of products need to be clearly explained and then considered separately in all of the analyses. While Sativex is not currently FDA-approved, it is approved as a pharmaceutical in other countries, is manufactured to known standards of purity and potency and is therefore distinct from retail marijuana products. I recommend a clear explanation in the introduction of the differences between pharmaceutical products manufactured to specific potency and purity versus retail marijuana products. THC and cannabidiol concentrations vary widely in retail marijuana. The trend toward higher THC and lower cannabidiol in retail marijuana renders studies of lower THC/higher cannabidiol pharmaceuticals and plant products irrelevant or only indirectly relevant to many currently marketed marijuana products. Given these differences, the level of evidence should be appropriately downgraded for "indirectness" when citing studies of cannabinoid pharmaceuticals, as these do not directly address the benefits and harms of smoked marijuana or other retail marijuana products.	clarifying that most studies examined preparations with precisely defined THC/CBD content. We also added to the applicability section in the Executive Summary and main report that preparations studied may not reflect what is widely available in dispensaries, and we added a reference to a study that suggested measured content differed from labeled content in dispensaries. Finally, we added the issue of applicability to the rationale for strength of evidence in the summary of evidence table.
9	In assessing potential risks, studies of "low to moderate use" are not appropriate for inclusion. When used for medical purposes, the usual pattern is daily consumption. Therefore, in order to evaluate potential risk, only studies that systematically assess for risk among daily users would be relevant to the question of potential harm from medical use. At least one cited study includes cannabis non-users in the denominator when reporting rates of cannabis use disorder among patients with pain, and is therefore implies a much lower risk of cannabis use disorder than would be expected among daily "medical marijuana" users.	With regard to the cannabis use disorder studies, we agree that we did not clearly describe the cited study and the limitations in the overall evidence base. We revised this section to clearly state that there were no studies in cannabis users. We also de-emphasized the cross-sectional data in chronic pain users in the summary of evidence section since these were not studies in a cannabis-using population. With regard to the other harms, we were broadly inclusive in part because clinicians may encounter a broad range of use among patients. We were careful to describe the evidence as being applicable to low levels of use (as with effects on pulmonary function) when appropriate, and added clarification on the lack of data (or even potential for harm in case of pulmonary function) with heavy use.
Additional suggestions or comments.		
1	Excellent review. Clarify on page 4 and in methods the reasons for choice in key exposure (e.g., what is typically found at dispensaries, and not synthetic forms that have been	See above.

	systematically reviewed already)	
2	My comments are all fairly minor. 1. A brand name, “Sativex,” is used many times in tables and intermittently throughout the text. I believe the generic name (nabiximols) should be used instead in all text and tables.	We agree and have made this change.
2	2. Page 6, line 18 (also page 18, line 39): “and an estimated 6.2%-39% of chronic pain patients are utilizing cannabis in addition to opioid medication for pain management.” The denominator is unclear in this sentence. Should it be “among patients on opioid medication for chronic pain, 6-39% also use cannabis”?	This language was clarified.
2	3. Page 6: The introduction alternates between “marijuana” and “cannabis.” Is there any distinction? If not, I suggest selecting a preferred term and using it consistently for clarity.	We agree and have changed it to “cannabis” throughout.
2	4. Page 6, Methods: A brief rationale for the decision to exclude synthetic cannabinoids would be helpful.	This has been added.
2	5. Page 66, last paragraph of discussion: When considering implications for pain management, it seems appropriate to mention that multiple pharmacological and nonpharmacological therapies have stronger evidence for chronic pain than either cannabis or opioids. Given the state of the science on cannabis and the existence of many efficacious medical and complementary therapies for pain, I am aware of no scientific rationale for singling out cannabis as an important "opioid sparing" therapeutic option. (This is a common line of argument for increasing cannabis availability, so I don't fault the authors for mentioning it.) The first recommendation from CDC guidelines on opioid prescribing, as well as treatment guidelines for common conditions such as back pain and arthritis, could be cited here.	We added language from the 1st recommendation in the CDC guidelines. We also added references and language about other evidence based pharmacologic and non-pharmacologic therapies.
3	Overall this is a very thorough review. The risks of psychosis are underestimated and understated. There is a body of evidence that exposure to cannabis is associated with a risk for a psychotic disorder. There is an entire special issue of Biological Psychiatry (April, 2016) dedicated to cannabinoids and psychosis. The authors are strongly urged to review this special issue. There is robust evidence (unlike what the review states) of direct experimental evidence that cannabinoids at certain doses can induce psychosis-like effects in healthy individuals and that cannabinoids can exacerbate psychosis in individuals at risk for or with an established, psychotic disorder. Restating the risk of psychosis is important because of the numbers of veterans with SMI who seek out certification for medical marijuana. I see a number of veterans diagnosed with chronic psychotic disorders	We generally agree, though we have to stick to the strength of evidence grading approach we have used throughout the report – we did include mention of experimental studies, though they were small and had some methodologic flaws. However, we had not incorporated these into the summary statement – we have changed this and clarified the extent of evidence. The SOE rating is low because much of the evidence is observational (though not entirely), it is difficult to know the magnitude of effect, and there is little data specific to chronic pain and PTSD populations – we have clarified this rationale throughout.

	who have asked for medical marijuana certification from VA doctors. They go to non-VA providers get a card, start using marijuana and end up in the hospital. While this is anecdotal, stating that the link to psychosis is "low" or "entirely observational" is not without risk.	
5	Obviously, compiling all the papers need to generate this review took a lot of effort. Overall, the review seems comprehensive and generally accurate. When fully refined, it will make an important contribution to our knowledge base. There is some sloppiness in the preparation as though the draft did not undergo careful and extensive proofreading before being sent out for review. In certain presentations of various studies there is a lack of needed detail and occasionally lack of rigor in interpretation. Most of the examples of these concerns that I could find are detailed below, but I cannot confirm that this list is exhaustive of all miscues.	Thank you for the suggestions – we have detailed our responses below and additionally went through the entire report and did an additional round of copyediting.
5	Page 5, lines 12-13: The assumption that rates of pulmonary effects or cancer would not be influenced by presence of PTSD or pain seems flawed at least on the basis that individuals with these disorders use tobacco at higher rates than the general population, and tobacco and cannabis might have additive or synergistic effects. In addition, it seems likely that both PTSD and pain might have subtle hormonal or immune system effects that could interact negatively with cannabis use.	We agree that there is some risk in considering studies in broader populations. We did so after considering likely important confounding factors as related to chronic pain or PTSD. We agree tobacco use is an important confounder and levels might be higher in chronic pain or PTSD populations, but the studies that contributed findings all accounted for tobacco use (and usually conducted analyses among never smokers *etc*) – studies that did not adequately control for tobacco use were downgraded in quality and did not contribute to findings. There are certainly other factors that might theoretically confound findings – we have added to the limitations section this issue (and, in general, this is one of the reasons why bodies of evidence based only on observational data typically start with a lower strength of evidence rating).
5	Page 5, line 45: Change “size” to “sizes.”	We have made this change.
5	Page 6, lines 4-13: Given the nature of the uncontrolled studies reviewed, it would probably be better to say that “cannabis is potentially associated with either harmful or neutral effects” rather than is potentially harmful.	We have made this change.
5	Page 8, line 36: Change “is” to “are.”	Done
5	Table (Page 9): Calls medication Sativex when text calls it nabiximols. Should use generic name throughout document to be consistent. Acronym ROB should be footnoted to explain it to anyone perusing the table.	Done
5	PTSD: It seems incorrect to say that marijuana is potentially harmful since these studies were observational. Is it likely the marijuana is causing more violence and use of other substances? Possibly, but it seems more intuitively probable that patients who are more violent and certainly who use other	We changed the executive summary paragraph accordingly. There is more detail in the main body of the report, but the strength of evidence related to bias and small number of studies is clearly indicated.

	substances are more likely to use marijuana. It is more credible to say that there is no evidence that it is helpful.	
5	Page 21, lines 54-57: This sentence does not make sense. If they inhaled a 25 mg dose, the per cent THC is irrelevant because the dose would be the same. What is the preparation here? It does not sound like herbal marijuana.	Language regarding the preparation was clarified; it was indeed an herbal preparation obtained from Prairie Plant Systems Inc. (Saskatoon, Sask.). Regarding dose and potency, this is the language that the authors use to describe the potency and dose. The 0% THC was prepared using "ethanolic extraction of cannabinoids" (see Ware 2010 pg. E695). Concentrations/potencies (percent THC) were varied, but were delivered in the same dose (25 mg).
5	Page 22, lines 42-59: This study is very poorly described. The reader needs to know more about the cannabis product used. If the study was observational, how was assignment to condition determined? The word "native" should be "naïve."	Cannabis product described in more detail. Assignment to conditions described in more detail. Native changed to naïve.
5	Page 23, lines 7-21: These studies are also exceedingly poorly described. What were the basic study methodologies?	Designs for both studies were described in more detail.
5	Table 3: How can the Wilkinson study be medium risk of bias? Shouldn't it be high risk of bias? Obviously, the participants self-selected into their groups. We know that people who use marijuana are more likely to use alcohol and vice-versa. Most likely individuals with PTSD and a propensity to violence are more likely impulsive and more likely to use marijuana. The marijuana may not be causing the violence. The p-value given for primary outcome of Johnson study is inconsistent with what the text says.	We used a standard risk of bias tool to evaluate the observational studies (Newcastle-Ottawa Scale), and using this tool classified the study as medium risk of bias (individual item scores are included in the Appendix C PTSD risk of bias table). This particular study adjusted for confounders which contributed to the medium rating. We agree that causation is very difficult to assume here and this is part of what contributes to rating the body of evidence as insufficient. Regarding the Johnson et al. paper, we have checked the values and confirmed that those reported in our table correspond to those reported in the paper.
5	Page 26, lines 21-23: Serious adverse events mentioned twice with different ORs.	Thanks – this was a typo and was corrected (last should have been withdrawal due to AE).
5	Page 26, lines 25-26: Information on specific serious adverse events should be provided in more detail. It is hard to see how paranoia or agitation by themselves would meet the FDA definition of serious adverse event unless they resulted in hospital admission.	We believe the section provides the detail we have available, while remaining circumspect about the seriousness of most of the short-term adverse events reported. The definition of serious adverse event is not provided in the Whiting review or its review protocol. We do clarify that many of the side effects were minor and common effects of cannabis. We have rewritten the sentence and taken out the modifier "serious". The definition of serious adverse events includes medical events for which an intervention might be necessary to prevent something like hospitalization – this is obviously somewhat at the discretion of the monitoring board and investigators and we simply report what the review authors reported.
5	Page 26, line 34: add "and" between "pain" and "found."	This change has been made.
5	Page 34, line 13: Change "was" to "were."	This change has been made.

5	Page 36, line 8: Describe dose and route of administration of cannabis in this study.	This change has been made.
5	Page 37, line 42: Delete "…who were diagnosed with CUD."	We have left this statement in the text for clarification.
5	Page 38, lines 4-15: An apparent issue with the Bonn-Miller study described here which may warrant mention is that the Veterans who had CUD and checked into an inpatient unit presumably had to undergo cannabis withdrawal absent any treatment for it. Was it their CUD per se or the withdrawal symptoms (or both) that interfered with their treatment improvement? It would be good to know also if their PTSD severity at treatment entry was equivalent to that of the non-CUD group.	Our summary describes the results and adjustments for confounders, but we have not included a discussion about whether or not withdrawal symptoms vs CUD was responsible for the findings because it is not possible to determine based on the methods.
5	Page 40, line 7: Change "abuse" to "misuse."	This change has been made.
5	Page 41, line 4: Remove "is."	This change has been made.
5	Page 42, line 47: Need route of administration of cannabis oil.	This was not specified in the ClinicalTrials.gov entry; we have clarified this in table.
5	Page 43, line 42: 0 mg does not make sense.	This is what was reported in the ClinicalTrials.gov entry, but we have clarified (it was a titration up to 250 mg).
5	Page 52, Table 8: Additional suggestions: All clinical trials of cannabis should obtain blood levels of THC and CBD so that there is some objective measure of how much drug exposure has occurred. Almost all studies done thus far have been quite low dose. Thus, higher doses must be tested. CBD should be much better studied acutely and longitudinally to determine whether it is reinforcing and whether tolerance and withdrawal occur with chronic use.	Thanks, this has been added.
6	Excellent work! Remaining points to consider are highlighted below... Major Issues: 1. One of the larger issues with the report, as written, is the choice to exclude "synthesized, pharmaceutically prepared cannabinoids (e.g., dronabinol, nabilone)." The authors chose to include studies of whole-plant or plant-derived cannabinoid preparations, but synthetic preparations with the same exact molecular structure and delivery method were excluded. There are very few organizations that produce plant-derived cannabinoids (e.g., NIDA, GW Pharmaceuticals), whereas synthetic cannabinoids (e.g., dronabinol, nabilone) are not only more widely available to researchers, but have been produced and used in research for quite some time. Without a clear rationale, which I think would be difficult to make, the choice of excluding synthetics appears to introduce bias particularly as a number of studies on pain and PTSD have utilized synthetic preparations. For example, Jetly et al., 2015 conducted a pilot RCT of nabilone for PTSD and nightmares, Fraser (2009) conducted a chart review	We added rationale in methods section. We also added information to both the chronic pain and PTSD section regarding the findings from recent systematic reviews on synthetics as they relate to our populations of interest. There was an SR published that included PTSD data very recently – while it was published after our search dates ended, we did include a description of the review and the studies relevant to PTSD. We added discussion of the applicability of the synthetic studies to our questions of interest – there was only one trial of nabilone with very few patients – the other studies would not have met inclusion criteria. Regardless, even after considering all the additional studies, the authors of the recent SR came to the same conclusion re: insufficient evidence.

	of 47 patients diagnosed with PTSD who received nabilone, and Roitman et al., 2014 conducted an open-label trial of oral THC for PTSD symptoms. While there is currently debate regarding the necessity of using plant-derived versus synthetic cannabinoids in research and treatment, the heart of this debate lies in the importance of secondary cannabinoids and terpenes, which are present in plant-derived products and not in synthetic ones. As it is unlikely that the role of these secondary compounds informed the selection criteria, given that secondary cannabinoids and terpenes are not even reported in the studies discussed in this review, it seems as though it would be difficult to provide a compelling case for this choice.	
6	2. An additional consideration for the section entitled "Emerging Harms" could be the recent proliferation of new methods of cannabinoid delivery and the resulting risks of adverse events. For example, the use of "dabs" appears to be associated with particularly heightened risk of tolerance and withdrawal (e.g., Loflin & Earleywine, 2014), and the use of edibles with a number of more acute consequences (e.g., Hudak et al., 2015; Lamy et al., 2016).	We added this information to the emerging harms section.
6	3. While the authors are correct in stating that the majority of the literature describes the effects of "cannabis" or "marijuana" without a clear definition of the cannabinoid profile of the product tested or used, the authors similarly make broad comments about consequences of "cannabis," where a more nuanced understanding is emerging. For example, the authors discuss a negative consequence of cannabis use as being psychosis. While this is indeed a finding that has been described in-depth within the literature, and even tied to a genetic vulnerability (i.e., catechol-O-methyltransferase), emerging evidence suggests that the association between cannabis and psychosis is specific to THC and that CBD can actually provide anti-psychotic effects (e.g., Leweke et al., 2012). This level of nuance is not currently provided in the review.	We agree. We have added clarification that it is the THC component that is most likely to be associated with psychotic symptoms and we added a statement to the discussion that CBD has actually been studied as an antipsychotic agent.
6	4. Somewhat related to the inclusion and selection of studies for the review, it is puzzling that the Bonn-Miller, Boden, Vujanovic, & Drescher, 2013 study was not included in the list of studies of the effects of cannabis on PTSD symptoms. That study appears to meet inclusion criteria as it was prospective, involved validated measures of PTSD (i.e., PCL), and included a comparison group (CUD diagnosis was compared to those without CUD diagnosis). The sample was adults and there is no indication that they used synthetics. While the study did use data from medical records, so did the administrative study by Wilkinson et al., 2015. This is just confusing.	Although this study included a control group, the controls didn't have CUD, but might have used cannabis; therefore, it did not meet our criteria because we were comparing studies with a non-cannabis using control group.
6	5. On page 7, the authors note that they "…did not find any literature comparing rates of CUD among individuals with chronic pain or PTSD to rates in other	Although these studies don't meet inclusion criteria, we have added the 2012 data on prevalence to the background paragraph of our CUD section.

	populations…" While this may be true, a study by Bonn-Miller, Harris, & Trafton (2012) documented the prevalence of PTSD among Veterans with CUD (29.05% in FY12), and a VA fact-sheet by Bonn-Miller & Rousseau utilized VA PERC data to document the percentage of Veterans with PTSD-SUD who had a CUD diagnosis (22.7% in FY14). These data seem to provide information close to what the authors note as being missing from the literature.	
6	Minor Issues: 1. The authors switch between using the terms "cannabis" and "marijuana." The manuscript may flow more nicely if consistent terminology was used throughout. Indeed, the term "cannabis" is generally preferable over "marijuana."	We agree and have made this change.
6	2. p. 7: "…found that about 2% if Veterans with non-cancer…" should be "…found that about 2% of Veterans with non-cancer…"	This change has been made.
6	3. p. 46: The description of the study by Eades et al. within the text is not consistent with the table. The table is correct and the text is inaccurate. The text should note that the three groups are "High/Low, High/High, and Low/Low".	This change has been made.
6	4. p. 46: "…marijuana use versus no marijuana use in the past 6 months is associated with PTSD symptoms and sleep" should be "…marijuana use versus no marijuana use in the past 6 months is associated with differential trajectories of PTSD symptoms over the course of a year."	This change has been made.
6	5. p. 48: Replace "In addition, we obtain lab analysis results of the cannabis donated through the Santa Cruz Veterans Alliance to the Veterans. This includes lab analysis results of percent cannabinoids within each product." with "In addition, all product provided to Veterans by the Santa Cruz Veterans Alliance is tested for cannabinoid content by an independent laboratory."	This change has been made.
6	6. The authors cite one of the two epidemiological studies of cannabis and PTSD (i.e., Kevorkian et al., 2015), but not the earlier study conducted among the NCS-R (i.e., Cougle et al., 2011).	The Cougle et al. study only reports data on cannabis use, not CUD, and therefore is not included in this section.
7	I was primarily interested/knowledgeable of the evidence for its use in PTSD and think that you did an excellent job reviewing that sparse literature and mentioning the fact that there are two current RCTs in progress that will add to the literature. Overall, very nice job and I have no further suggestions.	Noted.
9	Page 6-line 20. "There is low strength evidence that low levels of marijuana smoking do not adversely impact lung function over about 20 years in young adults." Low levels of marijuana smoking are irrelevant to the question of possible harm associated with "medical" that is, frequent/daily use.	We included any data regarding harms from studies that met inclusion criteria. We clearly state that these data apply to low level users and not daily users. We feel that the breadth of evidence will be useful to clinicians who can assess patients' frequency of use and decide whether or not the available data apply to an individual patient. While it is likely that many patients using medical marijuana do so daily, we do not know this to be universally true and there may be

		substantial proportion of patients who use less frequently. In any case, the lack of information in older or multimorbid populations (which we clearly state) is perhaps an even bigger issue in applying the data in VA clinical settings – again, we attempted to present our broadest look at harms with clarification on generalizability issues.
9	Page 7-line 38. Recommend deleting this sentence: "One large cross-sectional study of Veterans found that about 2% if (sic) Veterans with non-cancer pain had a diagnosis of CUD, and that this increased to 4%..." This is irrelevant to the question of the risk of cannabis use disorder among patients using marijuana for chronic pain treatment who would more likely use it multiple times daily. If it is possible to discern from the paper the prevalence of CUD among those with pain who used marijuana to treat pain, that would be worth mentioning. THC concentration would also be important to note, as more potent varieties (10 - 20+%) currently marketed would pose a greater risk for CUD than the more common low potency (3%) of a decade ago.	We have corrected this sentence and provided this information (as well as some additional, new information) on prevalence as part of our background.
9	Page 8-line 30. Ibid. "Light to moderate use" is irrelevant to the question of harm among daily users.	We have clarified that the data does not apply to heavy (daily) users.
9	Page 8 line 34- also needs to include cannabis use disorder among the serious mental health adverse events. Including indirect evidence about the risk of cannabis use disorder among daily users would better inform decision-making than the indirect study of pain patients who have not used marijuana.	We rewrote the sections on CUD to clarify that there was no evidence with which to assess rates of CUD, and we mention cross-sectional data.