APPENDIX A. SEARCH STRATEGIES

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily 1946 to July 17, 2018
Date Searched: July 18, 2018
Searched by: Robin Paynter, MLIS

#	Searches	Results
1	Marijuana Abuse/dt, th or ((Cannabis/ or Marijuana Smoking/) and (Drug Dependency/dt, th or Substance Related Disorders/dt, th))	630
2	((cannabis or canabis or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas) adj3 (abuse* or abusing or addict* or chronic* or daily or disorder* or depend* or habitual* or heavy or misuse* or overuse or quit*)).tw,kf.	4367
3	or/1-2	4699
4	Substance Withdrawal Syndrome/dt, th or exp Inactivation, Metabolic/ or Drug Therapy/ or ae,ai,co,ct,dt,po,th,to.fs.	40116
5	(abstain* or abstinen* or craving or detox* or desintox* or medication* or pharmacotherap* or pharmaco-therap* or reduce* or reducing or reduction or relaps* or retain* or retention or sobriety or therap* or treat* or withdraw*).tw,kf.	8279582
6	or/4-5	8289740
7	and/3,6	2502
8	randomized controlled trial.pt.	464336
9	controlled clinical trial.pt.	92503
10	randomized.ti,ab.	448654
11	placebo.ti,ab.	195474
12	"drug therapy".ti,ab.	33021
13	randomly.ti,ab.	294694
14	trial.ti,ab.	508714
15	groups.ti,ab.	1838965
16	or/8-15	2713265
17	and/7,16	720
18	(animals not (humans and animals)).sh.	4441716
19	17 not 18	701
20	limit 19 to yr="2014-Current"	286

Ovid PsycINFO 1806 to July Week 2 2018
Date Searched: July 18, 2018

#	Searches	Results
1	(Cannabis/ or Hashish/ or Marijuana/ or Marijuana Usage/) and (Addiction/ or Drug Abuse/ or Drug Addiction/ or Drug Dependency/ or "Substance Use Disorder"/)	3014
2	((cannabis or canabis or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas) adj3 (abuse* or abusing or addict* or chronic* or daily or disorder* or depend* or habitual* or heavy or misuse* or overuse or quit*)).tw.	3996
3	or/1-2	5413
4	exp Drug Therapy/ or drug withdrawal/ or detoxification/ or drug rehabilitation/ or craving/ or drug abstinence/	161862

5	(abstain* or abstinen* or craving or detox* or desintox* or "drug therap*" or medication* or pharmacotherap* or pharmaco-therap* or reduce* or reducing or reduction or relaps* or retain* or retention or sobriety or "substance withdrawal syndrome" or therap* or treat* or withdraw*).tw.	1228340
6	or/4-5	1241264
7	and/3,6	2835
8	Treatment Effectiveness Evaluation/ or exp Treatment Outcomes/ or Placebo/ or Followup Studies/	71506
9	(((placebo* or random* or comparative or clinical) adj3 trial*) or (research adj3 design) or ((evaluat* or prospect*) adj3 stud*) or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.	182379
10	or/8-9	237297
11	and/7,10	534
12	limit 11 to yr="2014 -Current"	199

Ovid EBM Reviews Cochrane Central Register of Controlled Trials June 2018, Cochrane Database of Systematic Reviews 2005 to July 11, 2018 Database of Abstracts of Reviews of Effects 1st Quarter 2016 Health Technology Assessment 4th Quarter 2016

Date Searched: July 18, 2018

#	Searches	Results
1	((cannabis or canabis or cannabacae or marijuana or marihuana or hashish or hash or ganja or ganjah or hemp or bhang or charas) adj3 (abuse* or abusing or addict* or chronic* or daily or disorder* or depend* or habitual* or heavy or misuse* or overuse or quit*)).tw.	774
2	(abstain* or abstinen* or craving or detox* or desintox* or "drug therap*" or medication* or pharmacotherap* or pharmaco-therap* or reduce* or reducing or reduction or relaps* or retain* or retention or sobriety or therap* or treat* or withdraw*).tw.	824767
3	1 and 2	639
4	limit 3 to yr="2014 -Current" [Limit not valid in DARE; records were retained]	297

ClinicalTrials.gov

Date Searched: July 18, 2018

(cannabis OR canabis or marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas) AND (abuse* OR abusing OR addict* OR chronic* OR daily OR disorder* OR depend* OR habitual* OR heavy OR misuse* OR overuse OR quit*) | (cannabis OR canabis or marijuana OR marihuana OR hashish OR hash OR ganja OR ganjah OR hemp OR bhang OR charas) | First posted from 01/01/2014 to 07/18/2018
= 92 studies

WHO ICTRP

Date Searched: July 18, 2018

CONDITION: (cannabis OR canabis or marijuana OR marihuana OR hashish OR hash) AND (abuse* OR abusing OR addict* OR chronic* OR daily OR disorder* OR depend* OR habitual* OR heavy OR misuse* OR overuse OR quit*)
INTERVENTION: ("drug therap*" OR medication* OR pharmacotherap* OR pharmaco-therap* OR therap* OR treat*)
RECRUITMENT STATUS: ALL
DATE OF REGISTRATION: 01/01/2018 and 18/07/2018
= 53 results

Open Trials

Date Searched: July 18, 2018

CONDITION: (cannabis OR canabis OR marijuana OR marihuana OR hashish OR hash)
REGISTRATION PERIOD START DATE: 01/01/2014

APPENDIX B. STUDY SELECTION

Inclusion codes, code definitions, and criteria

1. Is the population made up of non-pregnant/non-postpartum adolescents and/or adults with known or suspected cannabis use disorder?

   Yes " Proceed to 2.
   No " STOP. **Code X1** *(Excluded population)*

2. Does the intervention include pharmacotherapy to treat cannabis use disorder?
   Exclude: Pharmacotherapies intended to treat comorbid substance dependence (eg, stimulants, alcohol or heroin) rather than cannabis use.

   Yes " Proceed to 3.
   No " STOP. **Code X2** *(Not relevant to topic)*

3. Is the study design a randomized controlled trial with follow-up of 4 weeks or longer (unless the outcome being examined is withdrawal, in which case shorter studies are acceptable)?

   Yes " Proceed to 4.
   No " STOP. **Code X3** (*Excluded study design or publication type)*

   Exclude: Narrative or non-systematic review; opinion/editorial; cross-sectional study; case report/case series; case-control; cohort study; conference proceeding
   Also exclude RCTs that compare dosage levels of the same drug, without a placebo group or other active comparator. Duration of less than 4 weeks for studies of abstinence/reduction in use.

   Note: Systematic reviews, meta-analyses, and other important background/discussion papers should be coded **B-X3**, followed by notes/keywords**.**

   Examples:
   B-X3 – SR, pearl references
   B-X3 – narrative review with good background
   B-X3 – useful for discussion
   B-X3 – conference proceeding potentially useful

4. Does the study measure cannabis abstinence and/or use by urinalysis and/or validated self-report scale (*ie*, TimeLine Follow Back, ASI, ASSIST, DAST, SCID, DIS, MINI, results of diagnostic interviews)? AND/OR Does it measure withdrawal with validated measures (*eg*, Cannabis Withdrawal Scale, Drug Effects Questionnaire (DEQ), Marijuana Withdrawal Checklist (MWC); Marijuana Craving Questionnaire± Short Form (MCQ-SF)).

   Yes " Proceed to 5.

No " STOP. **Code X4** *(No outcomes of interest)*

Note: We will not analyze the following outcomes:
- Outcomes with lack of clinical implication (*eg*, brainwave Stroop)

5. Do all study arms receive identical treatment with the exception of the medication being tested? For example, if the active arm receives psychotherapy, the comparator arm should receive an identical form of psychotherapy with the same frequency and level of intensity as the primary arm.
   Yes " Proceed to 6.
   No " STOP. **Code X5** (*Unbalanced study design*)

6. Does the comparator arm consist of another active medication for treating cannabis use disorder?
   Yes " **Code H2H.** Proceed to 7.
   No " **Code RCT.** Proceed to 7.

7. Enter the medication(s) being tested.

APPENDIX C. QUALITY ASSESSMENT CRITERIA

Domain	***Criteria***[15]
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 and missing outcome data adequately addressed?
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?
Overall assessment of potential for bias	Low/Unclear/High

Risk of Bias	***Interpretation***	***Within a Trial***
Low	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains
Unclear	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains
High	Bias may alter the results seriously	High risk of bias for one or more key domains

APPENDIX D. QUALITY ASSESSMENT OF INCLUDED STUDIES

Author, year	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Risk of Bias
Allsop, 2014[34]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Carpenter, 2009[21]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Cornelius, 2010[20]	Yes	Unclear	Yes	Yes	Yes	Yes	Low
Gray, 2012[38]	Unclear	Yes	Yes	Yes	Yes	Yes	Low
Gray, 2017[37]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hill, 2017[32]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Johnston, 2014[27]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Levin, 2004[28]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	High
Levin, 2011[30]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Levin, 2013[19]	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Levin, 2016[31]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Mason, 2012[36]	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
McRae-Clark, 2009[26]	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
McRae-Clark, 2010[29]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear
McRae-Clark, 2015[25]	Yes	Yes	Yes	Yes	Yes	Yes	Low
McRae-Clark, 2016[18]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Miranda, 2017[35]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
The Scripps Research Institute[39]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Penetar, 2012[23]	Unclear	Unclear	Yes	Unclear	Unclear	No	High
Schnell, 2014[24]	Yes	Yes	No	No	Yes	No	High
Sherman, 2017[40]	Unclear	Unclear	Unclear	No	Unclear	Unclear	High
Trigo, 2018[33]	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear
Weinstein, 2014[22]	Unclear	Unclear	Yes	Unclear	Yes	No	High

Yes = adequately addressed; Unclear = unclear or not reported; No = not adequately addressed

APPENDIX E. PEER REVIEW

Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?		
1	Yes	Thank you.
2	Yes	Thank you.
3	Yes	Thank you.
4	Yes	Thank you.
5	Yes	Thank you.
6	Yes	Thank you.
7	Yes	Thank you.
8	Yes	Thank you.
Is there any indication of bias in our synthesis of the evidence?		
1	No	Thank you.
2	No	Thank you.
3	No. There does not appear to be bias based on the study design, and information.	Thank you.
4	No	Thank you.
5	No	Thank you.
6	No	Thank you.
7	No	Thank you.
8	No	Thank you.
Are there any published or unpublished studies that we may have overlooked?		
1	No	Thank you.
2	No	Thank you.
3	No. I am not aware of any study that has been overlooked, and the authors describe inclusion/exclusion criteria well.	Thank you.
4	No	Thank you.
5	No	Thank you.
6	No	Thank you.
7	No	Thank you.
8	No	Thank you.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.		
1	Overall comment: Would use terminology “treatment dropout” rather than “treatment withdrawal” so as not to risk confusion with measurement of withdrawal symptoms.	Thank you. We have made this change.
1	Page 7, line 14: Change “control” to “controlled.”	Thank you, corrected.
1	Page 10, line 26: Physiologic dependence is NOT required to make a diagnosis of cannabis use disorder. See DSM-5 page 509.	Changed to “consequences in daily living.”

Reviewer Number	Comment	Response
1	Page 11, line 11: Check Drexler's title. What is there does not seem to be correct.	Thank you, corrected.
1	Table 1 under "Outcomes," should "severe" be changed to "serious?"	Yes – I think this may be discipline specific; however, we have changed all instances of "severe adverse events" to "serious adverse events."
1	Page 16, line 35: Presumably, the THC levels referred to here are urinary THC. This point should be explicitly stated.	Thank you, we added "urinary" for clarity.
1	Page 20, line 27: Add "evidence" after "strength."	Thank you, added.
1	Page 20, line 30: Change "a" to "across."	Thank you, this has been changed.
1	Page 21, line 38: Should "severe" be changed to "serious?" Same question for Table 3 and Table 5, possibly elsewhere.	Yes – I think this may be discipline specific; however, we have changed all instances of "severe adverse events" to "serious adverse events."
1	Page 46, line 25: Awkward wording. Rewrite.	changed
1	Page 47, line 42: Specify urinary cannabinoid levels	Added "urinary"
1	Page 52, line 43: Specify urinary cannabinoid levels.	Added "urinary"
1	Page 54, lines 26-28: This summary seems far too critical of the methods and outcomes reporting of the gabapentin study. It may be that lumping gabapentin with topiramate as anticonvulsants obscures the findings with gabapentin.	Thank you. We've revised the summary to read," However, there were only 2 small unclear ROB trials…" the gabapentin study was an unclear ROB study with N=50, so alone would result in insufficient SOE.
1	Page 54, lines 30-36: Gabapentin was found to reduce withdrawal symptoms. Why is that finding not mentioned here? It may be that lumping gabapentin with topiramate as anticonvulsants obscures the findings with gabapentin.	Thank you. This is because the study examining gabapentin had a sample size of 50 and was determined by dual review to be unclear ROB. Alone, this small study provides insufficient evidence on the use of gabapentin to mitigate withdrawal symptoms.
1	Page 55, Limitations: It may be worth mentioning the limitations in interpreting quantitative urine THC metabolite levels. If not mentioned, readers may assume that urinary levels are somehow superior to self-report or perhaps a reliable, objective outcome measure.	Thank you. We have revised this statement to include additional concerns related to the interpretation of THC metabolite levels.
1	Page 58, line 28: Is this p-value correct? It does not indicate significance.	Thank you – great catch! It should be 0.024. We have corrected it.
1	Page 58, line 38: Is this p-value correct? It does not indicate significance.	Another great catch. We have corrected it to 0.022. Thank you!
2	The present systematic review provides a needed comprehensive summary of a generally limited literature. Below are some minor comments for authors to consider: 1. Consider asking the expert panelists to review their affiliations (e.g., see at least two individuals	Thank you. We have confirmed affiliations with those authors.

Reviewer Number	Comment	Response
	affiliated with CESATE who are not listed as such).	
2	2. Buspirone and N-acetylcysteine are mentioned by name in the conclusions but not in the results section of the Executive Summary. Consider consistency across sections for the uneducated reader and/or listing the drug classes examined somewhere in the Executive Summary (if the goal is to have the executive summary be a stand-alone document). It was surprising to see Busprione and N-acetylcystine listed in the conclusion when there had been no prior mention of these drugs earlier in the summary.	Thank you. We have added both Buspirone and N-acetylcysteine to the results.
2	3. On page 15, the text above the figure notes "The 7 RCTs included in KQ2 were also included in KQ1", however, the footnote states "*All 6 KQ 2 studies were also included in KQ 1."	Thank you. Corrected so all read “7.”
2	4. On page 15, authors note "Trials examined antidepressants (ie, escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, vilazodone), antipsychotics (ie, clozapine, ziprasidone), buspirone, mood stabilizers (ie, divalproex, lithium), and atomoxetine" but later in this section additional categories/types of drugs are given their own section/group (e.g., glutamatergic modulator, antinauseant, etc). Is there a reason these latter categories/groups weren't included in the above-referenced list?	Thank you. The listed trials are those that fall under the subheading of psychopharmacological interventions; whereas, the others you mentioned do not fit this category. We have added an introductory paragraph for the KQ1 section to make this clearer.
2	5. There are two periods at the end of the first sentence at the top of page 46.	Thank you, corrected.
3	Overall, this systematic review is of very high quality. The most important issue that I have is the unclear definition of cannabis use disorder. If possible, early on it would be helpful if the authors gave a definition of what cannabis use disorder is, and whether they use the DSM or another convention. Relatedly, it would be helpful for each study in the table (Table 2) to have a description of what classification system was used (DSM-IV abuse and/or dependence; DSM-5 cannabis use disorder, etc), and potentially examine differences by studies that included, e.g., those with DSM-IV abuse versus those that did not.	Thank you, we have added an abbreviated description of DSM V criteria and cited it. We have added the inclusion criteria to tables. We did not perform additional analyses because no studies used DSM V criteria (all were DSM IV or DSM IV-TR, or self reported use). The one study that used self-reported use was in a drug/outcome that was SOE insufficient. Furthermore, there were two studies that included Two studies included participants meeting DSM IV/IV-TR criteria for Cannabis abuse and dependence. Once drug/outcome was insufficient, and the other was a high ROB study that was the only trial that found a positive impact of bupropion on retention – the exclusion of this study would not have made a difference in the conclusion of no difference from placebo.

Reviewer Number	Comment	Response
3	Also, I may have missed where the authors define “risk of bias” levels. If this is not included, it may be helpful to include for readers (e.g., what does “low” risk of bias entail?).	Thank you. We have added an in-text citation, as well as an additional table to Appendix C that better describes the interpretation of risk of bias.
3	Minor- There is a typo on pg. 56 line 39 “addition”	Thank you, corrected.
4	1) Page 7, Line 33: spell out ‘risk of bias’ before the acronym is presented in parentheses.	Thank you, corrected.
4	2) Page 10, last paragraph: Include contingency management as an available psychosocial treatment for cannabis use disorder.	Thank you, that was an oversight – added.
4	3) Page 12, line 50: Present the rationale for including studies that were at least 4 weeks in duration, i.e. because of the detection window for THC via toxicology testing. This rationale is referenced later in the report on page 55. Also note that the 4 or more week inclusion criterion was not used for the selection of studies on withdrawal symptoms.	Thank you. We have revised this for clarity.
4	4) Page 16, lines 52-54: The data appear to suggest that cannabis use might blunt the antidepressant effects of antidepressant medication among patients with severe depression. This would be an important, possible adverse effect to explore further in the report.	Thank you. We have added a statement in the conclusion addressing the lack of reduction in depressive symptoms in the comorbid CUD/MDD population, and have also added a statement in the section on future research.
4	5) Page 20, line 30: Change “a” to “across”	Thank you, corrected.
5	Page 7, Line 41: It's odd that these two medications are mentioned in the conclusion, but not in the Results?	Thank you. We have added both Buspirone and N-acetylcysteine to the results.
5	Page 10, Line 12: Clarify whether this is a national estimate of the prevalence.	Thank you, revised
5	Page 10, Line 27: Use of prevalence here is confusing (implies overall prevalence), as the next sentence reports prevalence of CUD among patients with prior year cannabis use.	Thank you. We have added a statement and reference for population based prevalence, followed by the statement related to those with prior year use.
5	Page 16, Line10: Should this [12] be 23?	Thank you. We apologize for the confusion, and for clarity, we have added a paragraph at the beginning of the results section clarifying different drug classes. This particular reference/section is specific to Psychopharmacology.
5	Page 16, Line 20-21: I believe this sentence suggests that there was insufficient evidence for all other findings. Regardless, consider clarifying to make it clear.	Thank you. We have revised this sentence for clarity.
5	Page 16, Line 44: It's not clear what "these authors" is referring to here.	Thank you, this refers to the authors of the Fluoxetine trial. We have edited the sentence for clarity.
5	Page 20, Lines 29-31: Sentence is unclear.	Thank you, corrected.

Reviewer Number	Comment	Response
5	Page 46, Line 19: Less effective in terms of which outcomes?	Thank you, we have revised this sentence for clarity.
5	Page 46, Line 20: Clarify on what outcome might women receive greater benefit.	Thank you, we have revised this sentence for clarity.
5	Page 54, Line 26-28: Consider highlighting gabapentin in this paragraph as only treatment retention was the only promising finding among topiramate users.	Thank you. The study examining gabapentin was a small (N=50) unclear ROB study; thus, alone provides insufficient evidence to form conclusions. We have added the sample size to the text to better clarify.
6	This evidence-based synthesis was comprehensive and well-written. The key questions are clear and directly addressed by the review. I have no substantive concerns about the EBS. Minor comments: The conclusions section begins “The effectiveness of pharmacotherapies for cannabis use disorder remains, for the most part, poorly studied.” I’m not sure that I would describe this topic as “poorly studied”. The findings are not particularly encouraging but… several of the studies were reasonably well-designed. I would suggest leading this section with a statement that involves less conjecture (e.g., there are few studies, the findings do not provide strong support for pharmacotherapy for CUD, *etc*).	Thank you. We have revised this sentence to read, “There is limited research examining the effectiveness of pharmacotherapies for cannabis use disorder, and many of the existing studies are hampered by poor methodological quality or reporting.”
6	I was intrigued by the finding that antidepressants may be associated with lower rates of abstinence. This seems to have important implications for a large system like VHA that treats many patients with antidepressants. It would be helpful to comment on the implications of this finding within the sections on research gaps and/or implications for VHA.	Thank you. We have added a statement in the conclusion addressing the lack of reduction in depressive symptoms in the comorbid CUD/MDD population, and have also added a statement in the section on future research.
6	It is worth noting that the subgroup analyses likely lacked power to detect meaningful differences between groups. Thus, there is the potential that important differences exist between subgroups but these have yet to be identified in the literature.	We have added a statement to the limitations section addressing the lack of power in subgroup analyses.
7	This is a well-written report and thorough examination of outcomes of pharmacotherapy for CUD. Comments below are meant to improve the clarity and consistency of writing. 1. In the Executive Summary (p. 7, line 14), the search strategy is stated to have included articles up to November 2018. In Appendix A, the search appears to have ended in July 2018.	Thank you for noting the discrepancy. The search ended in July 2018, and the ES has been revised.
7	2. In figure 2 on p. 15, it is unclear how many articles were extracted from the 2014 review and, thus, how many of the 23 studies analyzed for this	Thank you. We have edited the figure and text for clarity.

Reviewer Number	Comment	Response
	review were new literature not previously synthesized. Also, line 60 on this page indicates 6 studies were included for KQ2. This should be 7.	
7	3. In the narrative description of results, the authors make statements about studies' risk of bias (e.g., p. 16, line 26), yet all studies appear to provide equal weighting in determining strength of evidence and are low ROB studies are not differentiated from high/unclear ROB studies in the narrative description. I suggest greater explanation of how risk of bias factors in to determining strength of evidence in order to make this determination more transparent to readers.	Thank you. The determination of strength of evidence (SOE) is based on a number of factors, of which the ROB of studies is an important and often driving factor. The conclusions table provides rationale for SOE determinations. In addition, for clarity, we have added more detail about the factors considered in SOE determinations to the methods section.
7	4. It would be helpful to see combined sample size (N), RR, and 95% CIs for all outcomes. For example, this is not presented for the outcome reduction in cannabis use for antidepressants on p. 17, lines 7-9.	There was heterogeneity in the definition of and reporting of reduction of use outcomes, and we only combined outcomes that provided data that could be combined. This was true for these antidepressant studies. Given the consistent findings we were able to conclude moderate strength evidence of no benefit, but were not able to combine them in a meta-analysis
7	5. It is unclear why in Figure 4, some of the percentage weightings do not add to 100% (e.g., venlafaxine, p. 18, line 12; other antidepressants, p. 18, lines 20-21).	The weights were incorrect because the figure combined results from multiple subgroup analyses. The weights have been removed from the figure to avoid confusion
7	6. In Table 2, retention in treatment data sometimes include percentages and other times do not. Please be consistent with reporting format.	Thank you, the formatting has been corrected to include percentages for all retention data.
7	7. A strength of evidence determination is not made for studies synthesized in KQ2 on p. 46, lines 16 and 34.	Thank you. We state in the first paragraph that all findings were insufficient to form conclusions – this is due heterogeneity in pharmacotherapy/sub-population studies. We have added an additional statement in the conclusion to better clarify.
7	8. The report would benefit from additional detail of how risk of bias (as summarized in Appendix D) is quantified. Appendix C provides categories over with ROB is assessed but provides no detail of how ratings across categories are used to determine and overall ROB.	Thank you. We have added an additional table to Appendix C that better describes the interpretation risk of bias.
8	Excellent, thorough review of a very small research literature. Conclusions are appropriate given the results. No additional comments.	Thank you.