Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A systematic review and meta-analysis of non-randomized studies

Appendix

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Contents

Appendix 1: Search strategy

MEDLINE	10649
EMBASE	6382
Central	2426
PsycInfo	3801
Subtotal	23260
-dupes	-6085
Total	17175

April 1, 2020

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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1 Epidemiologic Studies/ (8256)

2 exp Case-Control Studies/ (1067341)

3 exp Cohort Studies/ (1974212)

4 Case control.tw. (123081)

5 (cohort adj (study or studies)).tw. (199133)

6 Cohort analy$.tw. (7799)

7 (Follow up adj (study or studies)).tw. (48708)

8 (observational adj (study or studies)).tw. (103255)

9 Longitudinal.tw. (239715)

10 Retrospective.tw. (515751)

11 Cross sectional.tw. (342224)

12 Cross-sectional studies/ (322752)

13 or/1-12 (2953281)

14 exp animals/ not humans.sh. (4685189)

15 13 not 14 (2889789)

Annotation: SIGN observational studies filter

16 randomized controlled trial.pt. (503041)

17 controlled clinical trial.pt. (93591)

18 randomized.ab. (474985)

19 placebo.ab. (206552)

20 drug therapy.fs. (2191450)

21 randomly.ab. (330409)

22 trial.ab. (500400)

23 groups.ab. (2028909)

24 or/16-23 (4670111)

25 exp animals/ not humans.sh. (4685189)

26 24 not 25 (4048339)

Annotation: Cochrane HSSS RCT filter

27 15 or 26 (6033576)

Annotation: study design filter broad

28 Cannabis/ (8968)

29 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (13810)

30 Endocannabinoids/ (5630)

31 exp Receptors, Cannabinoid/ (9240)

32 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. (54925)

33 or/28-32 (54925)

Annotation: strategy from 2020 cannabis review

34 27 and 33 (16307)

Annotation: cannabis AND study design filter

35 exp "Drug-Related Side Effects and Adverse Reactions"/ (114376)

36 (ae or to or po or co).fs. (3890270)

37 (safe or safety).ti,ab. (758301)

38 side effect$.ti,ab. (243706)

39 ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (501888)

40 exp Product Surveillance, Postmarketing/ (15237)

41 adverse drug reaction reporting systems/ (7463)

42 clinical trials, phase iv/ (295)

43 exp Poisoning/ (156177)

44 exp Substance-Related Disorders/ (274845)

45 Abnormalities, Drug-Induced/ (14514)

46 Drug Monitoring/ (20599)

47 exp Drug Hypersensitivity/ (45642)

48 (toxicity or complication$ or noxious or tolerability).ti,ab. (1298802)

49 or/35-48 (5596308)

Annotation: OVID AE filter

50 34 and 49 (10649)

Annotation: Study design filter AND Cannabis AND AE Filter (broad)

Database: Embase <1974 to 2020 March 31>

Search Strategy:

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1 cannabis/ (33859)

2 exp cannabinoid/ (65694)

3 medical cannabis/ (2104)

4 exp cannabinoid receptor/ (14557)

5 exp endocannabinoid/ (8589)

6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (86550)

7 or/1-6 (87843)

Annotation: cannabis

8 clinical study/ (154879)

9 case control study/ (153658)

10 family study/ (26012)

11 longitudinal study/ (137463)

12 retrospective study/ (897628)

13 prospective study/ (590879)

14 randomized controlled trials/ (176633)

15 13 not 14 (584662)

16 cohort analysis/ (564001)

17 (Cohort adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (296961)

18 (Case control adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (211490)

19 (follow up adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (65948)

20 (observational adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (242526)

21 (epidemiologic$ adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (109669)

22 (cross sectional adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (385983)

23 or/8-12,15-22 (2808984)

Annotation: SIGN observational studies filter

24 7 and 23 (9720)

Annotation: cannabis AND observational studies

25 randomized controlled trial/ (597702)

26 Controlled clinical study/ (463832)

27 random$.ti,ab. (1518977)

28 randomization/ (86491)

29 intermethod comparison/ (258334)

30 placebo.ti,ab. (303428)

31 (compare or compared or comparison).ti. (504683)

32 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2082229)

33 (open adj label).ti,ab. (78190)

34 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (229917)

35 double blind procedure/ (171048)

36 parallel group$1.ti,ab. (25201)

37 (crossover or cross over).ti,ab. (104010)

38 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (325625)

39 (assigned or allocated).ti,ab. (383429)

40 (controlled adj7 (study or design or trial)).ti,ab. (343515)

41 (volunteer or volunteers).ti,ab. (244577)

42 human experiment/ (490389)

43 trial.ti. (295850)

44 or/25-43 (4952112)

Annotation: Cochrane RCT filter

45 7 and 44 (14036)

Annotation: cannabis AND RCTs

46 24 or 45 (21357)

Annotation: cannabis AND (Obs studies OR RCTs)

47 7 and (23 or 44) (21357)

Annotation: logic check

48 (ae or si or to or co).fs. (3204803)

49 (safe or safety).ti,ab. (1154971)

50 side effect$.ti,ab. (358075)

51 ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (787739)

52 exp adverse drug reaction/ (522775)

53 exp drug toxicity/ (125051)

54 exp intoxication/ (366563)

55 exp drug safety/ (393912)

56 exp drug monitoring/ (53058)

57 exp drug hypersensitivity/ (56248)

58 exp postmarketing surveillance/ (35831)

59 exp drug surveillance program/ (26017)

60 exp phase iv clinical trial/ (3822)

61 (toxicity or complication$ or noxious or tolerability).ti,ab. (1868476)

62 or/48-61 (6002309)

Annotation: OVID AE filter 1-14

63 47 and 62 (6382)

Cannabis AEs

Search Name: cannabis AEs

Date Run: 01/04/2020 18:42:40

Comment:

ID	Search	Hits
#1	MeSH descriptor: [Cannabis] explode all trees	298
#2	MeSH descriptor: [Cannabinoids] explode all trees	790
#3	MeSH descriptor: [Endocannabinoids] explode all trees	48

#4 MeSH descriptor: [Endocannabinoids] explode all trees 48

#5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 4370

#6 #1 or #2 or #3 or #4 or #5 4370

#7 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 3463

#8 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE, toxicity - TO, poisoning - PO, complications - CO] 169278

#9 (safe or safety):ti,ab,kw (Word variations have been searched) 258304

#10 (side effect*):ti,ab,kw (Word variations have been searched) 149400

#11 ((adverse or undesirable or harms* or serious or toxic) near/3 (effect* or reaction* or event* or outcome*)):ti,ab,kw (Word variations have been searched) 279577

#12 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 191

#13 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 82

#14 MeSH descriptor: [Clinical Trial, Phase IV] explode all trees 0

#15 MeSH descriptor: [Poisoning] explode all trees 2101

#16 MeSH descriptor: [Substance-Related Disorders] explode all trees 14586

#17 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees 47

#18 MeSH descriptor: [Drug Monitoring] explode all trees 1725

#19 MeSH descriptor: [Drug Hypersensitivity] explode all trees 965

#20 (toxicity or complication* or noxious or tolerability):ti,ab,kw (Word variations have been searched) 332240

#21 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 626064

#22 #6 and #21 in Trials 2426

PsycInfo

Database: APA PsycInfo <1806 to March Week 4 2020>

Search Strategy:

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1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (12819)

2 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or

marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (26466)

3 1 or 2 (26466)

4 exp "side effects (drug)"/ (57604)

5 (safe or safety).ti,ab. (84148)

6 side effect$.ti,ab. (31950)

7 ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (44183)

8 toxic disorders/ (1433)

9 exp "substance use disorder"/ (127742)

10 (toxicity or complication$ or noxious or tolerability).ti,ab. (42844)

11 or/4-10 (310848)

12 3 and 11 (10984)

13 epidemiology/ (49562)

14 ((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id. not "Literature Review".md. (95810)

15 ((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md. (286455)

16 (cross section* or "prevalence study").ti,ab,id. (80384)

17 clinical trials/ or "treatment outcome clinical trial".md. or ((randomi?ed adj7 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*)) or (controlled adj3 trial*) or (clinical adj2 trial*)).ti,ab,id. (101001)

18 Case control.mp. (10736)

19 (cohort adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (21026)

20 Cohort analy$.mp. (2099)

21 (Follow up adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (12876)

22 (Longitudinal or Retrospective or Cross sectional).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (218589)

23 or/13-22 (561443)

24 12 and 23 (3801)

Appendix 2: Detailed methods for the assessment of risk of bias

We rated studies at serious risk of confounding bias when they when they did not adjust for important predictors of adverse events and cannabis use, including, at minimum, pain intensity, concomitant pain medication, disability status, alcohol use, past cannabis use and at critical risk if they did not include a control group. We rated studies at serious risk of selection bias when studies included prevalent medical cannabis users (i.e., patients who experience serious or debilitating adverse events are more likely to discontinue cannabis and hence less likely to be included in studies of prevalent users). We rated studies at serious risk of misclassification of the intervention if there was evidence that medical cannabis users were not appropriately classified. We rated studies at serious risk of bias due to departure from the intended intervention if the intervention was not delivered as intended or more than 20% of patients discontinued the intervention for reasons unrelated to adverse effects (e.g., costs). We rated studies at serious risk of missing data when 20% or more of the original patients did not have adverse event data. Finally, we rated studies at moderate risk of selective reporting when the study did not differentiate between minor and serious adverse events or when there were indications that adverse events were selectively, and not comprehensively, reported.

Appendix 3: List of included studies

1. Anderson SP, Zylla DM, McGriff DM, Arneson TJ. Impact of medical cannabis on patient-reported symptoms for patients with cancer enrolled in Minnesota's medical cannabis program. Journal of Oncology Practice. 2019;15(6):E338-E45.

2. Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. The Mental Health Clinician. 2018;8(3):110-5.

3. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Practice. 2011;11(4):353-68.

4. Bonar EE, Cranford JA, Arterberry BJ, Walton MA, Bohnert KM, Ilgen MA. Driving under the influence of cannabis among medical cannabis patients with chronic pain. Drug & Alcohol Dependence. 2019;195:193-7.

5. Cervigni M, Nasta L, Schievano C, Lampropoulou N, Ostardo E. Micronized Palmitoylethanolamide-Polydatin Reduces the Painful Symptomatology in Patients with Interstitial Cystitis/Bladder Pain Syndrome. BioMed Research International. 2019;2019 (no pagination)(9828397).

6. Chirchiglia D, Chirchiglia P, Signorelli F. Nonsurgical lumbar radiculopathies treated with ultramicronized palmitoylethanolamide (umPEA): A series of 100 cases. Neurologia i Neurochirurgia Polska. 2018;52(1):44-7.

7. Cranford JA, Arnedt JT, Conroy DA, Bohnert KM, Bourque C, Blow FC, et al. Prevalence and correlates of sleep-related problems in adults receiving medical cannabis for chronic pain. Drug & Alcohol Dependence. 2017;180:227-33.

8. Cremer-Schaeffer P, Schmidt-Wolf G, Broich K. [Cannabis medicines in pain management : Interim analysis of the survey accompanying the prescription of cannabis-based medicines in Germany with regard to pain as primarily treated symptom]. Der Schmerz. 2019;33(5):415-23.

9. Crowley K, de Vries ST, Moreno-Sanz G. Self-Reported Effectiveness and Safety of Trokie R Lozenges: A Standardized Formulation for the Buccal Delivery of Cannabis Extracts. Frontiers in Neuroscience. 2018;12:564.

10. Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies. Pain and Therapy. 2015;4(2):169-78.

11. Domínguez CM, Martín AD, Ferrer FG, Puertas MI, Muro AL, González JM, et al. N-palmitoylethanolamide in the treatment of neuropathic pain associated with lumbosciatica. Pain Manag. 2012;2(2):119-24.

12. Fanelli G, De Carolis G, Leonardi C, Longobardi A, Sarli E, Allegri M, et al. Cannabis and intractable chronic pain: an explorative retrospective analysis of Italian cohort of 614 patients. Journal of pain research. 2017;10:1217-24.

13. Feingold D, Goor-Aryeh I, Bril S, Delayahu Y, Lev-Ran S. Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain. Pain Medicine. 2017;18(2):294-306.

14. Fiz J, Duran M, Capella D, Carbonell J, Farre M. Cannabis use in patients with Fibromyalgia: Effect on symptoms relief and health-related quality of life. PLoS ONE. 2011;6 (4) (no pagination)(e18440).

15. Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Medicine. 2012;13(9):1121-30.

16. Giorgi V, Bongiovanni S, Atzeni F, Marotto D, Salaffi F, Sarzi-Puttini P. Adding medical cannabis to standard analgesic treatment for fibromyalgia: a prospective observational study. Clinical & Experimental Rheumatology. 2020;38 Suppl 123(1):53-9.

17. Habib G, Artul S. Medical Cannabis for the Treatment of Fibromyalgia. JCR: Journal of Clinical Rheumatology. 2018;24(5):255-8.

18. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. Clinical Journal of Pain. 2016;32(12):1036-43.

19. Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejcko J, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. Journal of Neurology. 2015;262(1):27-40.

20. Lejczak S, Rousselot H, Di Patrizio P, Debouverie M. Dronabinol use in France between 2004 and 2017. Revue Neurologique. 2019;175(5):298-304.

21. Loi ES, Pontis A, Cofelice V, Pirarba S, Fais MF, Daniilidis A, et al. Effect of ultramicronized-palmitoylethanolamide and co-micronizedpalmitoylethanolamide/polydatin on chronic pelvic pain and quality of life in endometriosis patients: An open-label pilot study. International Journal of Women's Health. 2019;11:443-9.

22. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. Journal of Pain & Symptom Management. 2006;32(5):497-501.

23. Naftali T, Bar-Lev Schleider L, Sklerovsky Benjaminov F, Lish I, Konikoff FM, Ringel Y. Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects. European Journal of Gastroenterology & Hepatology. 2019;31(11):1376-81.

24. Paladini A, Varrassi G, Bentivegna G, Carletti S, Piroli A, Coaccioli S. Palmitoylethanolamide in the Treatment of Failed Back Surgery Syndrome. Pain Res Treat. 2017;2017:1486010.

25. Passavanti MB, Fiore M, Sansone P, Aurilio C, Pota V, Barbarisi M, et al. The beneficial use of ultramicronized palmitoylethanolamide as add-on therapy to Tapentadol in the treatment of low back pain: a pilot study comparing prospective and retrospective observational arms. BMC Anesthesiology. 2017;17(1):171.

26. Perron BE, Holt KR, Yeagley E, Ilgen M. Mental health functioning and severity of cannabis withdrawal among medical cannabis users with chronic pain. Drug & Alcohol Dependence. 2019;194:401-9.

27. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clinical Therapeutics. 2007;29(9):2068-79.

28. Sagy I, Bar-Lev Schleider L, Abu-Shakra M, Novack V. Safety and Efficacy of Medical Cannabis in Fibromyalgia. Journal of Clinical Medicine. 2019;8(6):05.

29. Schifilliti C, Cucinotta L, Fedele V, Ingegnosi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. Pain Res Treat. 2014;2014:849623.

30. Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. European Neurology. 2017;78(5-6):320-9.

31. Sinclair J, Smith CA, Abbott J, Chalmers KJ, Pate DW, Armour M. Cannabis Use, a Self-Management Strategy Among Australian Women With Endometriosis: Results From a National Online Survey. Journal of Obstetrics & Gynaecology Canada: JOGC. 2020;42(3):256-61.

32. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflammatory Bowel Diseases. 2014;20(3):472-80.

33. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012;153(10):2073-82.

34. Ueberall MA, Essner U, Mueller-Schwefe GHH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: Analysis of 12-week open-label real-world data provided by the German pain e-registry. Journal of Pain Research. 2019;12:1577-604.

35. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS ONE [Electronic Resource]. 2017;12(11):e0187795.

36. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain. 2003;102(1-2):211-6.

37. Ware MA, Wang T, Shapiro S, Collet JP, team Cs. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). Journal of Pain. 2015;16(12):1233-42.

38. Weber J, Schley M, Casutt M, Gerber H, Schuepfer G, Rukwied R, et al. Tetrahydrocannabinol (Delta 9-THC) treatment in chronic central neuropathic pain and fibromyalgia patients: Results of a multicenter survey. Anesthesiology Research and Practice. 2009;2009 (no pagination)(827290).

39. Yassin M, Oron A, Robinson D. Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. Clinical & Experimental Rheumatology. 2019;37 Suppl 116(1):13-20.

Appendix 4: Studies excluded at the full-text screening stage

Not a full-text report of a non-randomized study

1. Aapro MS. Prevention of chemotherapy-induced nausea and vomiting in patients with cancer. Arizona Medicine. 1981;38(11):843-5.

2. Abrams DI, Guzman M. Cannabis in cancer care. Clinical Pharmacology & Therapeutics. 2015;97(6):575-86.

3. Actrn. Cannabis-Based Medicine (Sativex) in the Treatment of Pain in Kidney Failure. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12610000783022. 2010.

4. Actrn. The CANBACK trial, to determine the efficacy of oral cannabidiol, when compared to placebo, as an adjunct for the treatment of acute non-traumatic low back pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12618000487213. 2018.

5. Adhiyaman V, Arshad S. Cannabis for intractable nausea after bilateral cerebellar stroke. Journal of the American Geriatrics Society. 2014;62(6):1199.

6. Ahmed A, van der Marck MA, van den Elsen G, Olde Rikkert M. Cannabinoids in late-onset Alzheimer's disease. Clinical Pharmacology & Therapeutics. 2015;97(6):597-606.

7. Ahmed AI, van den Elsen GA, van der Marck MA, Olde Rikkert MG. Cannabinoids for pain in dementia: the good, the bad, and the ugly. Journal of the American Geriatrics Society. 2014;62(5):1001-2.

8. Anonymous. Latest trial suggests cannabis does not relieve spasticity of multiple sclerosis. Pharmaceutical Journal. 2002;268(7198):675.

9. Anonymous. Cannabis derivatives and pain. A small role for delta9-tetrahydrocannabinol (THC) in some forms of multiple sclerosis. Prescrire International. 2009;18(103):226.

10. Anonymous. Association between cannabis use and complications related to ulcerative colitis in hospitalized patients: A propensity matched retrospective cohort study: Erratum. Medicine. 2019;98(35):e17046.

11. Arboleda MF, Dam V, Prosk E, Dworkind M, Vigano A. Cannabis-Based Medications: The Future Co-analgesics of Choice for Cancer Patients? Journal of Pain and Symptom Management. 2018;56 (6):e68.

12. Arboleda MF, Dam V, Prosk E, Dworkind M, Vigano A. Tranforming symptom management in cancer patients: Is medical cannabis a new paradigm? Supportive Care in Cancer. 2018;26 (2 Supplement 1):S53.

13. Ashton CH. Adverse effects of cannabis and cannabinoids. British Journal of Anaesthesia. 1999;83(4):637-49.

14. Ballas SK. Use of marijuana in patients with sickle cell disease increased the frequency of hospitalization for acute painful vaso-occlusive crises. Blood Conference: 58th Annual Meeting of the American Society of Hematology, ASH. 2016;128(22).

15. Bergamaschi V, Konrad G, Battaglia MA, Brichetto G. Efficacy and discontinuation of nabiximols in patients with multiple sclerosis: A real-life study. Multiple Sclerosis Journal. 2018;24 (2 Supplement):959.

16. Bertsche T, Schulz M. Cannabis can relieve spasticity associated with multiple sclerosis. [German]. Pharmazeutische Zeitung. 2003;148(8):32-3.

17. Bialas P, Drescher B, Gottschling S, Juckenhofel S, Konietzke D, Kuntz W, et al. [Cannabis-based medicines for chronic pain: indications, selection of drugs, effectiveness and safety : Experiences of pain physicians in Saarland]. Der Schmerz. 2019;33(5):399-406.

18. Blondin N. The evolving role of complementary cannabis therapy in glioblastoma treatment. Neuro-Oncology. 2018;20 (Supplement 6):vi214-vi5.

19. Bronstein K, Dhaliwal J, Leider H. Rates of inappropriate drug use in the chronic pain population: An update. Journal of Pain. 2011;1):P5.

20. Brusberg M, Kang D, Larsson H, Lindstrom E, Martinez V. Inhibition of fatty acid amide hydrolase (FAAH) activity enhances the analgesic action of the endocannabinoid anandamide on visceral pain. Gastroenterology. 2009;1):A141.

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Appendix 5: Risk of bias ratings

Study	Confounding	Selection of participants into the study	Classification of the intervention	Departures from the intended intervention	Missing data	Measurement of outocmes	Selection of the reported Results
Ware, 2003	Critical	Serious	Low	Low	Low	Moderate	Low
Lynch, 2006	Critical	Low	Low	Low	Low	Moderate	Low
Rog, 2007	Critical	Low	Low	Serious	Low	Moderate	Low
Weber, 2009	Critical	Low	Low	Serious	Low	Moderate	Moderate
Bestard, 2011*	Critical	Low	Low	Moderate	Low	Moderate	Low
Fiz, 2011	Critical	Serious	Low	Low	Low	Moderate	Low
Dominguez, 2012	Critical	Low	Low	Moderate	Low	Moderate	Low
Gatti, 2012	Critical	Low	Low	Low	Low	Moderate	Low
Toth, 2012	Critical	Low	Low	Low	Low	Moderate	Low
Schifilliti, 2014	Critical	Low	Low	Low	Low	Moderate	Moderate
Storr, 2014	Critical	Serious	Low	Low	Low	Moderate	Moderate
Del Giorno, 2015	Critical	Low	Low	Low	Low	Moderate	Low
Hoggart, 2015	Critical	Serious	Low	Moderate	Low	Moderate	Low
Ware, 2015†	Critical	Serious	Low	Moderate	Low	Moderate	Low
Haroutounian, 2016	Critical	Low	Low	Low	Low	Moderate	Low
Bellnier, 2017	Critical	Low	Low	Low	Low	Moderate	Moderate
Cranford, 2017	Critical	Serious	Low	Low	Low	Moderate	Low
Fanelli, 2017	Critical	Low	Low	Serious	Critical	Moderate	Low
Feingold, 2017	Critical	Serious	Low	Low	Low	Moderate	Moderate
Paladini, 2017	Critical	Low	Low	Low	Low	Moderate	Low
Passavanti, 2017	Critical	Low	Low	Low	Low	Moderate	Low
Schimrigk, 2017	Critical	Serious	Low	Low	Low	Moderate	Low
Chirchiglia, 2018	Critical	Low	Low	Low	Low	Serious	Low
Crowley, 2018	Critical	Serious	Low	Low	Low	Moderate	Low
Habib, 2018	Critical	Low	Low	Low	Low	Moderate	Low
Anderson, 2019	Critical	Low	Low	Low	Serious	Moderate	Low
Bonar, 2019	Critical	Serious	Low	Low	Low	Serious	Moderate
Cervigni, 2019	Critical	Low	Low	Low	Serious	Moderate	Low
Cremer-Schaeffer, 2019 ‡	Critical	Low	Low	Serious	Low	Moderate	Moderate
Lejczak, 2019	Critical	Low	Low	Critical	Serious	Moderate	Moderate
Loi, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Naftali, 2019	Critical	Serious	Low	Low	Moderate	Moderate	Low
Perron, 2019	Critical	Serious	Low	Low	Low	Moderate	Low
Sagy, 2019	Critical	Low	Low	Moderate	Serious	Moderate	Moderate
Sinclair, 2019	Critical	Serious	Low	Low	Low	Moderate	Moderate
Ueberall, 2019	Critical	Low	Low	Moderate	Low	Moderate	Low
Vigil, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Yassin, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Giorgi, 2020	Critical	Low	Low	Serious	Low	Moderate	Low

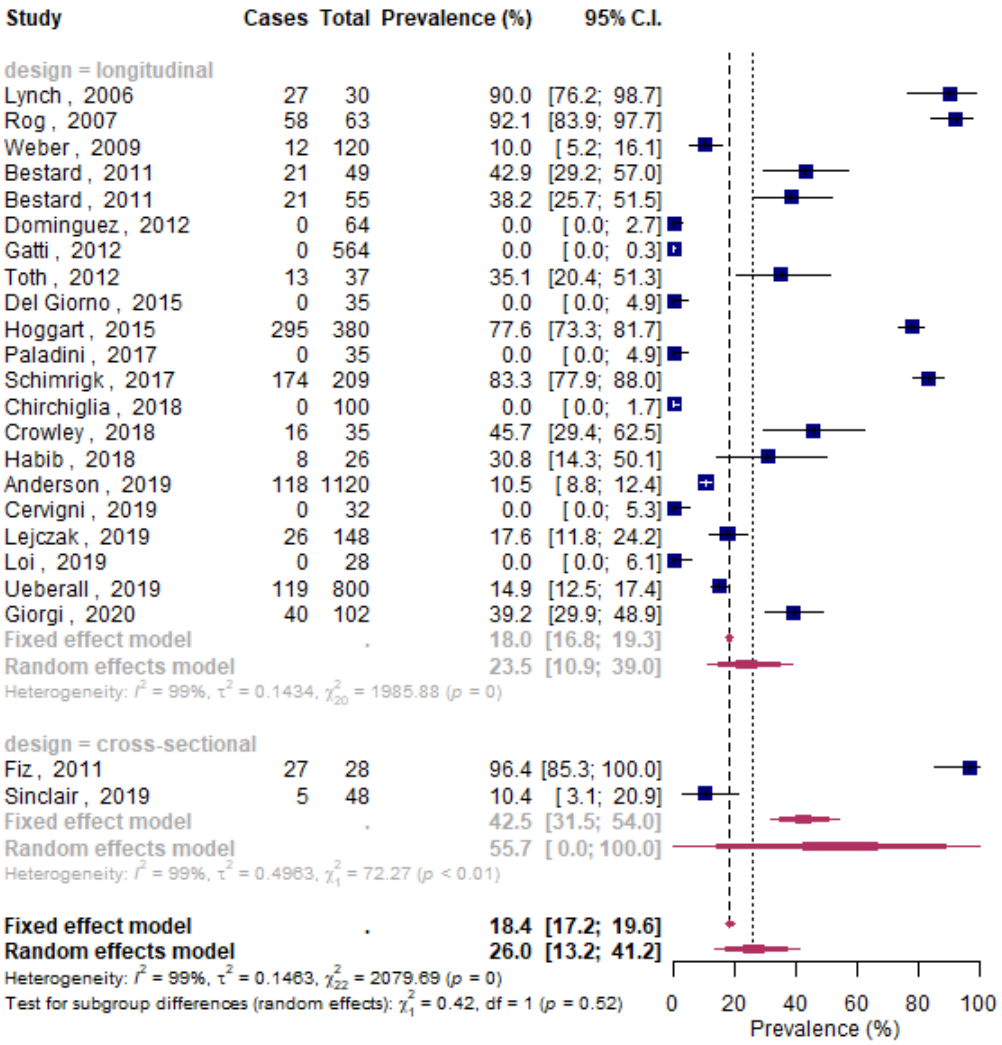
Low risk of bias
Moderate risk of bias
Serious risk of bias
Critical risk of bias

* Risk of bias for confounding for comparative results were rated as serious.

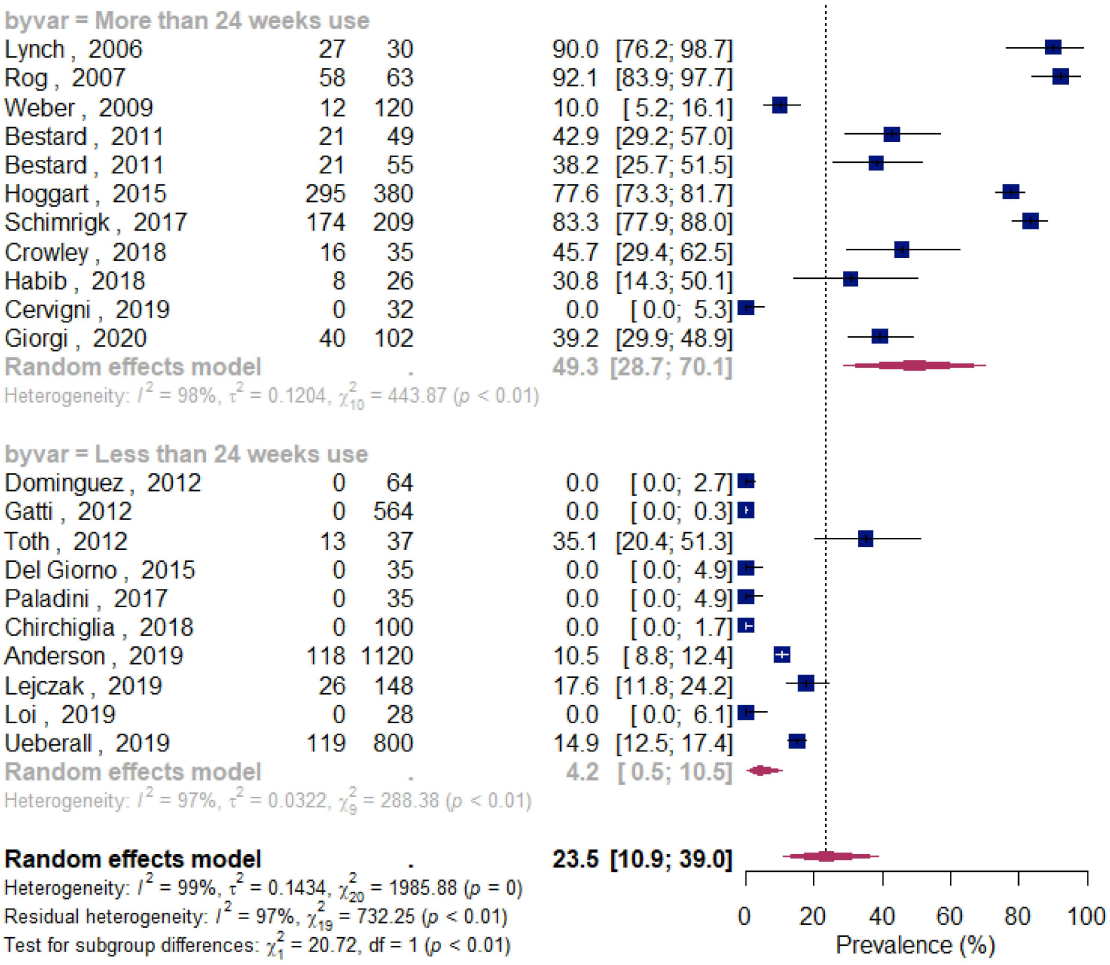
† Risk of bias for confounding for unadjusted comparative comparative results were rated as serious. Adjusted comparative results were rated as moderate.

‡ The study reported on dronabinol, nabiximols, and herbal cannabis separately. The results for herbal cannabis were at serious risk of selection bias due to prior herbal cannabis use among particpants.

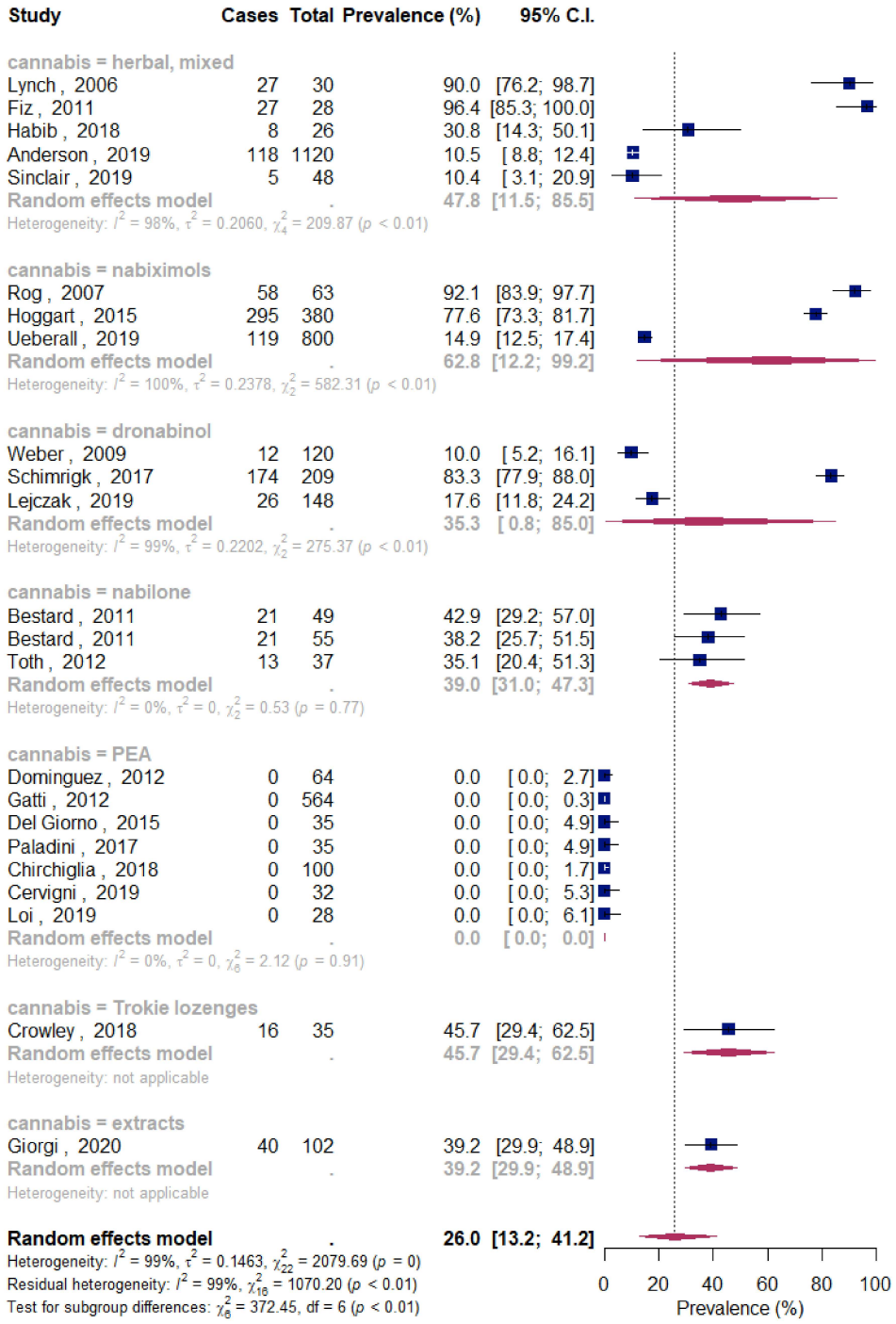
Appendix 6: Results for all adverse events (subgroup by design)



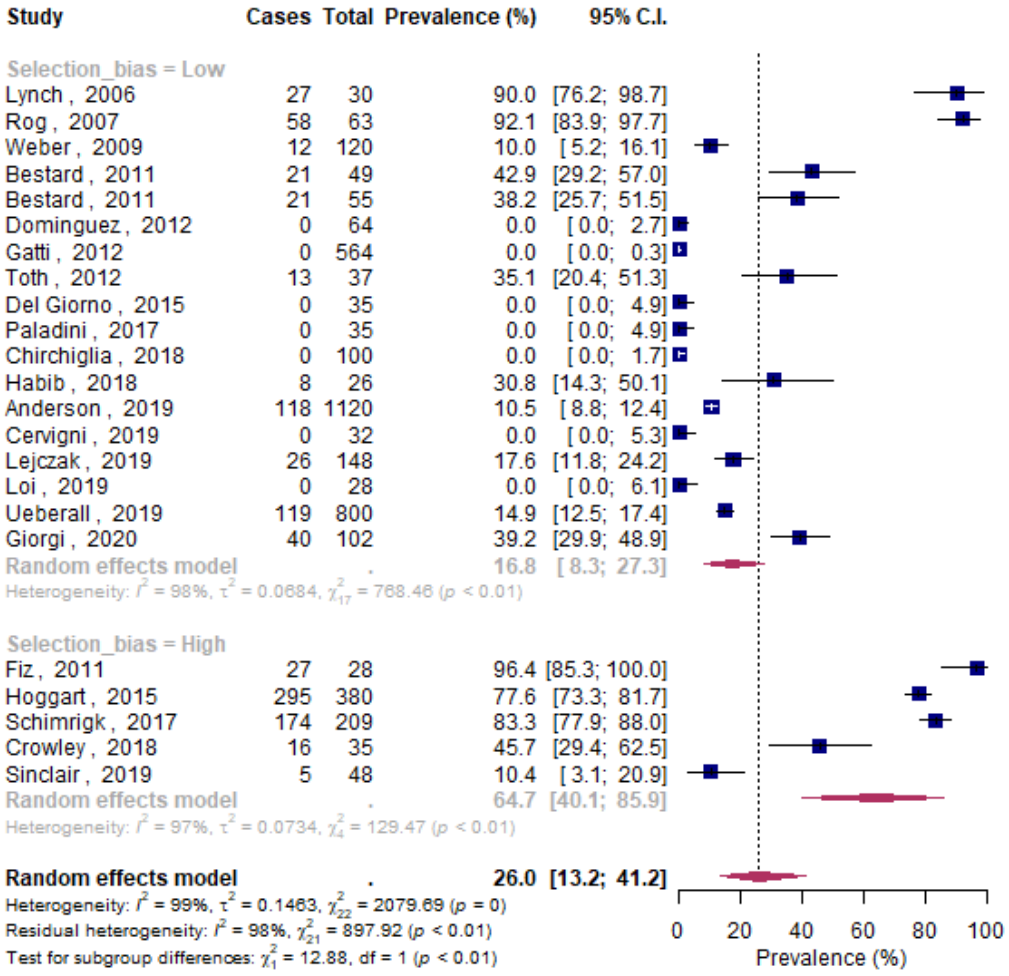
Appendix 7: Results for all adverse events (subgroup by duration)



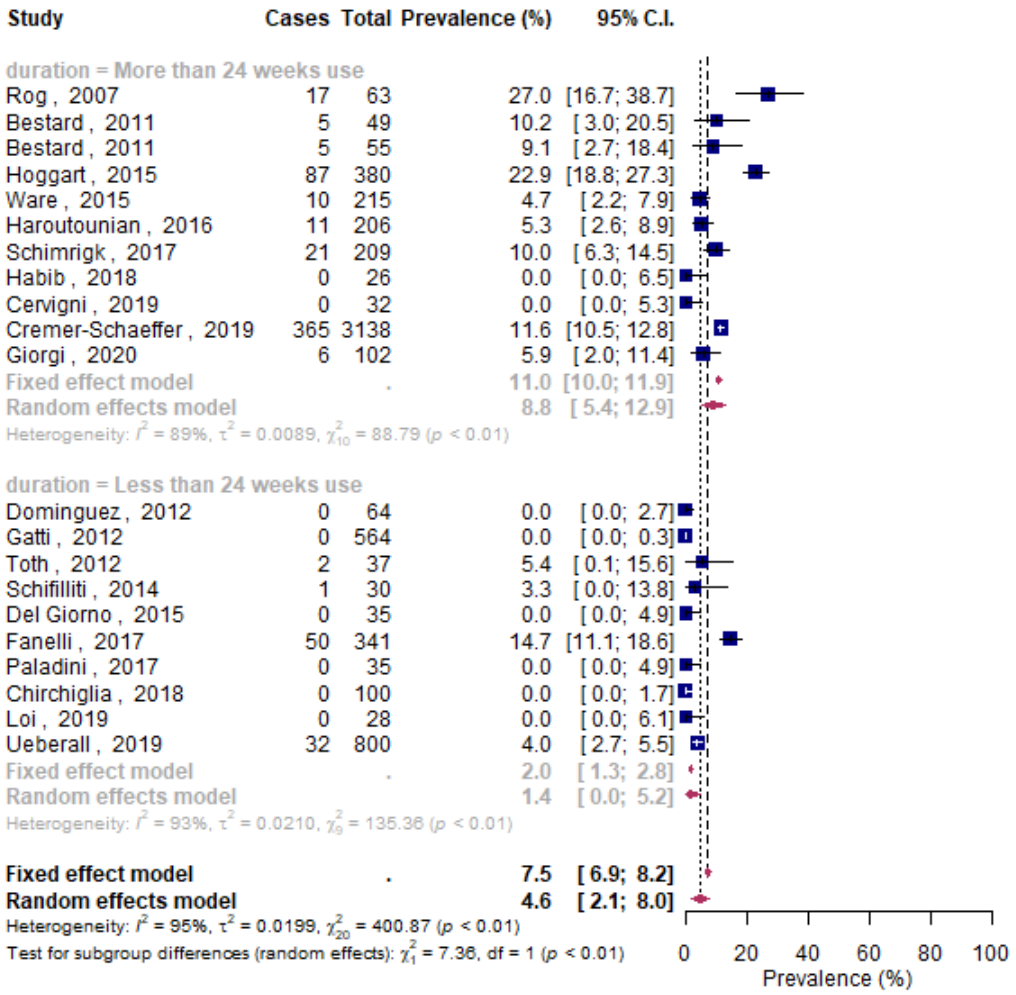
Appendix 8: Results for all adverse events (subgroup by cannabis)



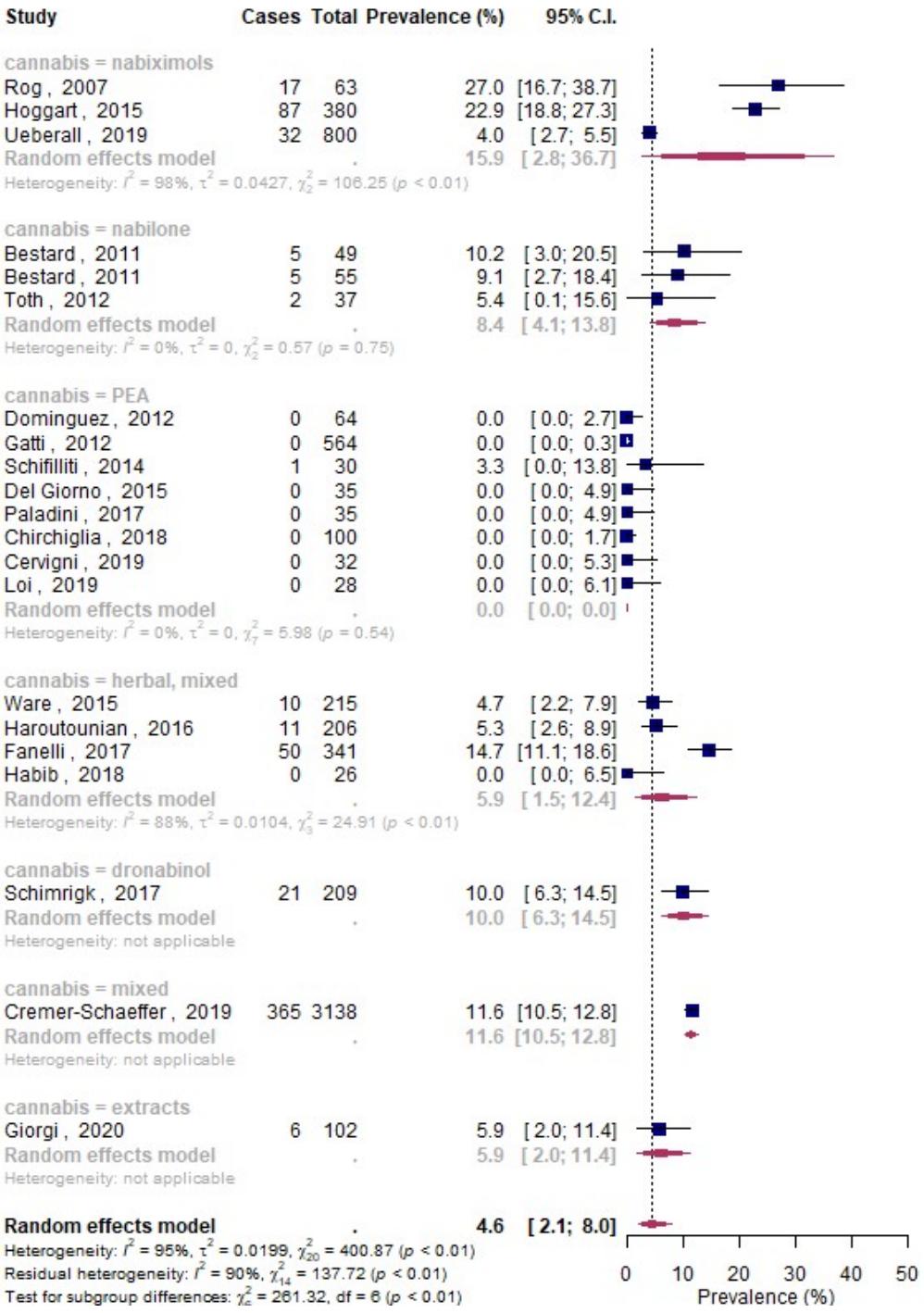
Appendix 9: Results for all adverse events (subgroup by selection bias)



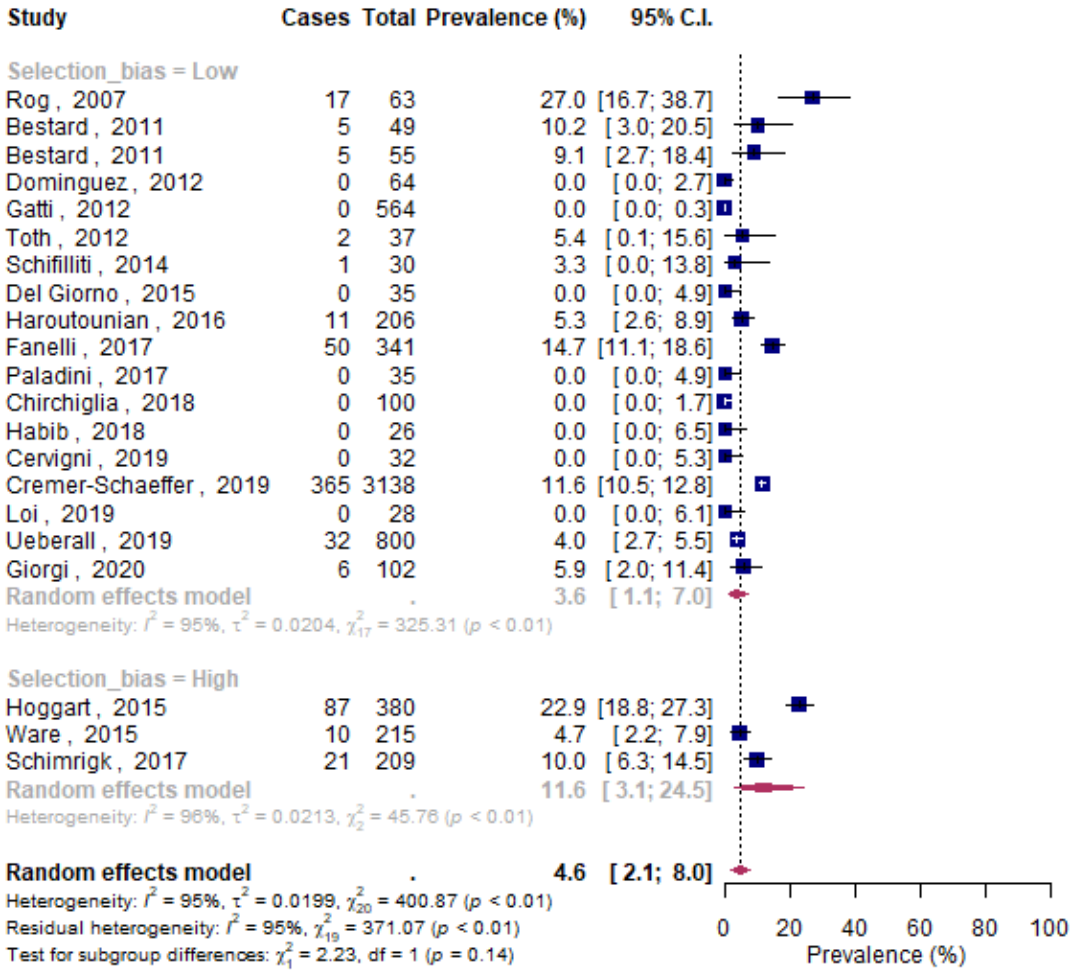
Appendix 10: Results for adverse events leading to discontinuation (subgroup by duration)



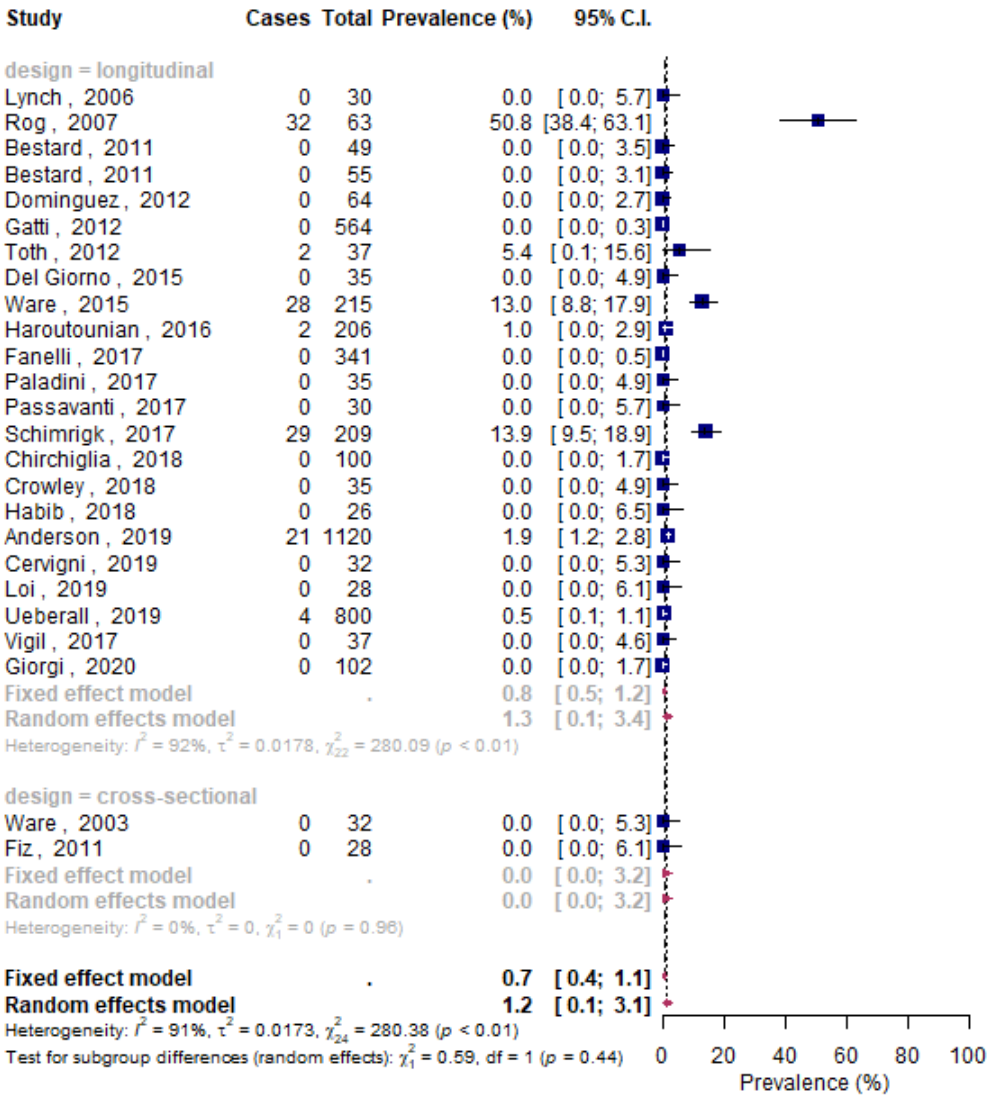
Appendix 11: Results for adverse events leading to discontinuation (subgroup by cannabis)



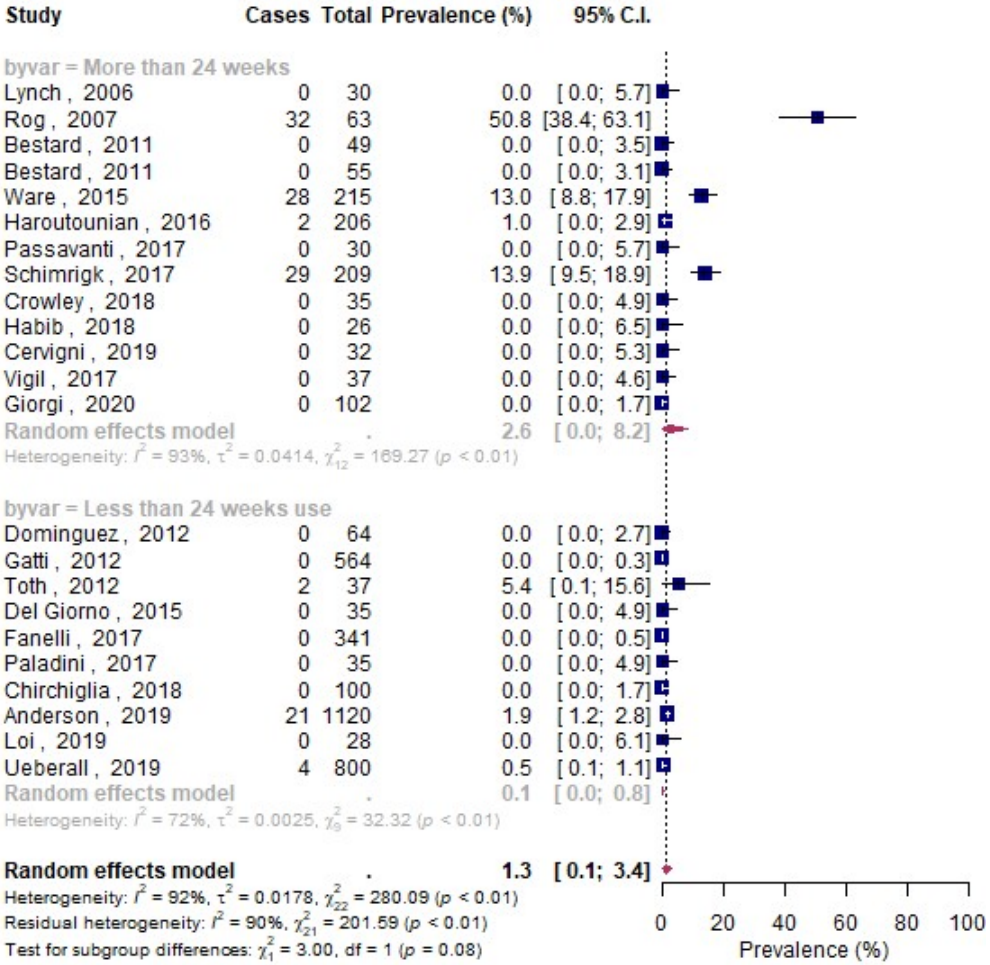
Appendix 12: Results for adverse events leading to discontinuation (subgroup by selection bias)



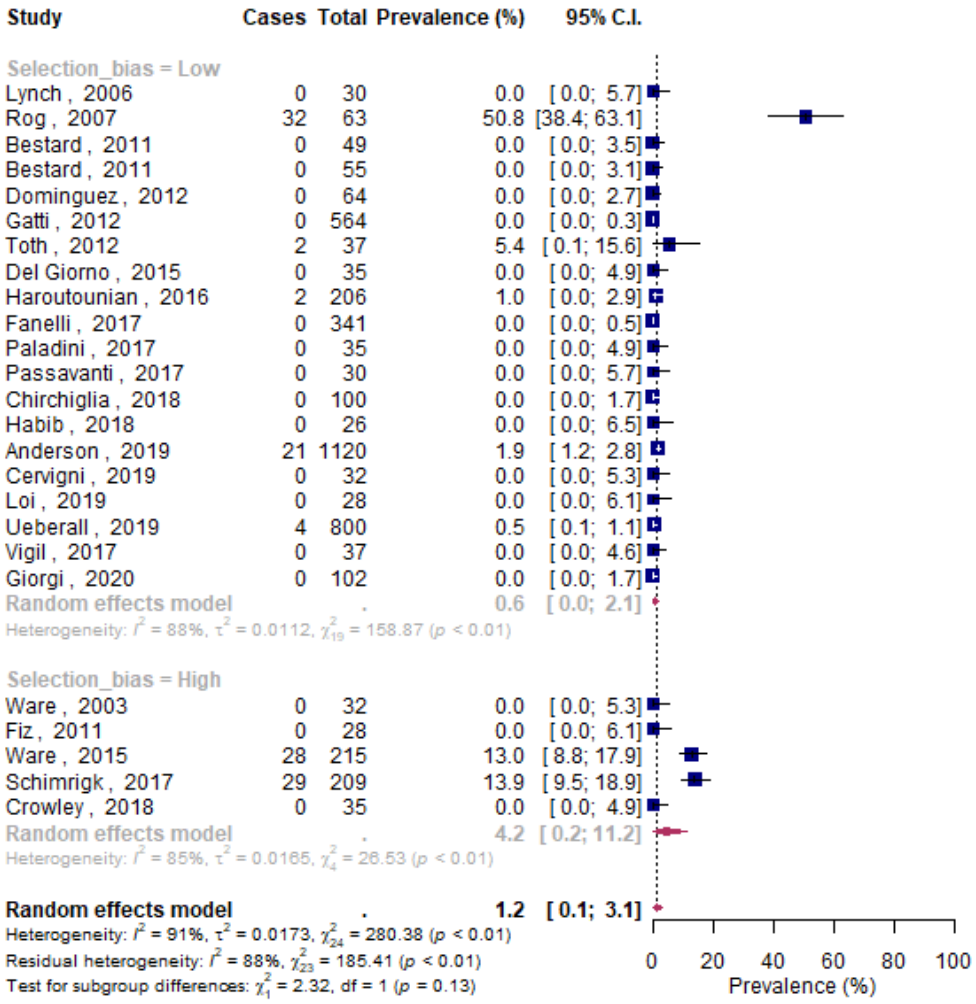
Appendix 13: Results for serious adverse events (subgroup by design)



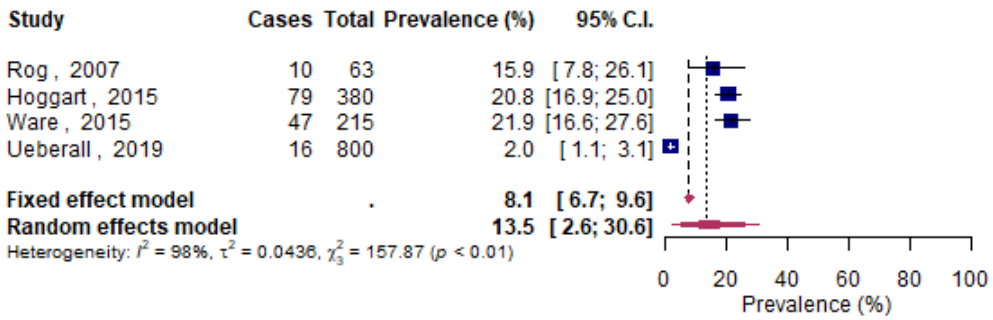
Appendix 14: Results for serious adverse events (subgroup by duration)



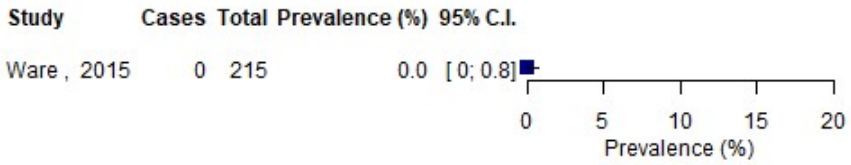
Appendix 15: Results for serious adverse events (subgroup by selection bias)



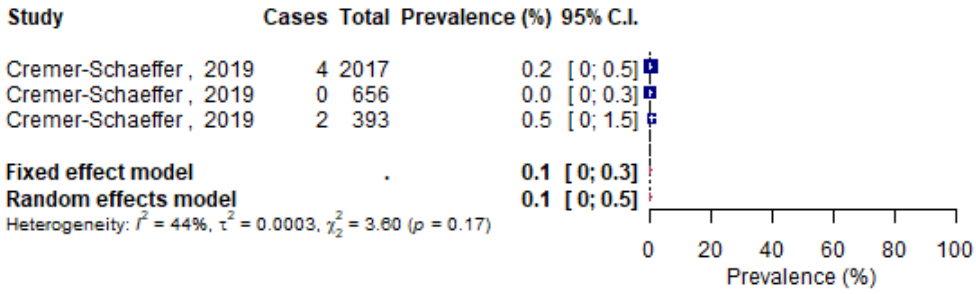
Appendix 16: Results for psychiatric adverse events



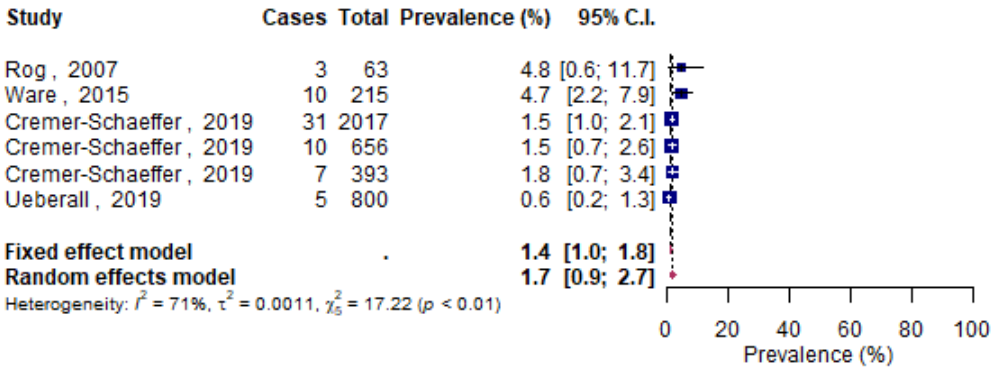
Appendix 17: Results for suicide



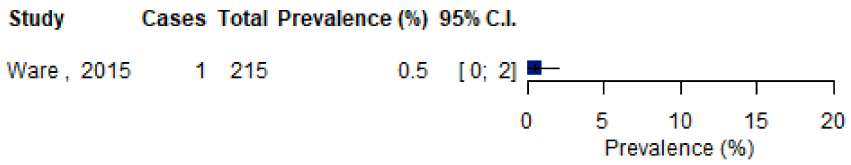
Appendix 18: Results for suicidal thoughts



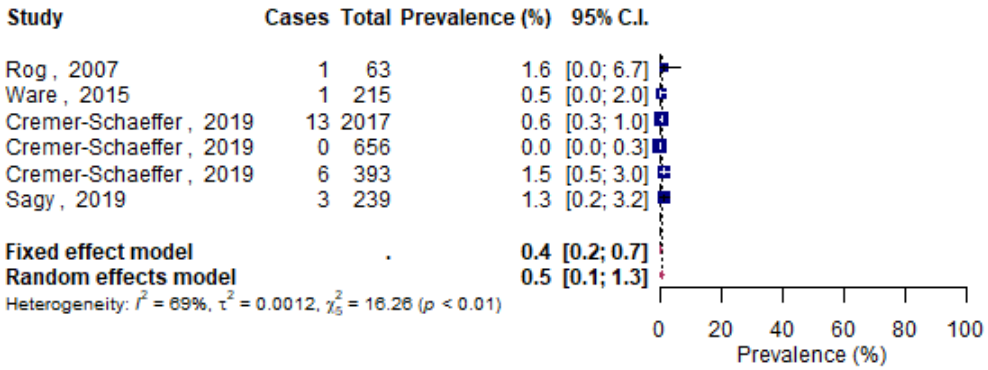
Appendix 19: Results for depression



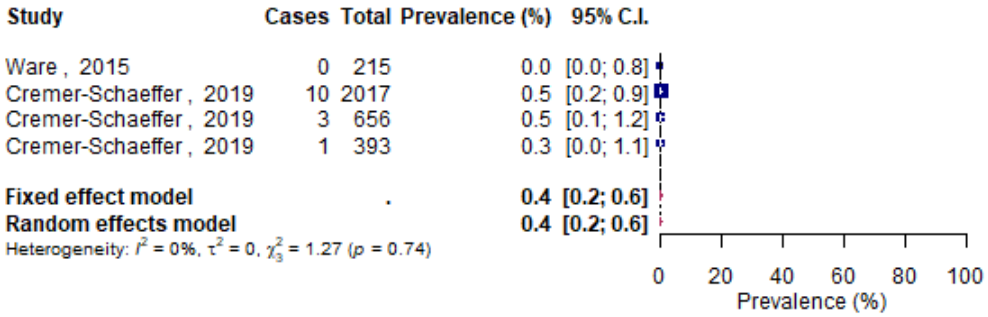
Appendix 20: Results for mania



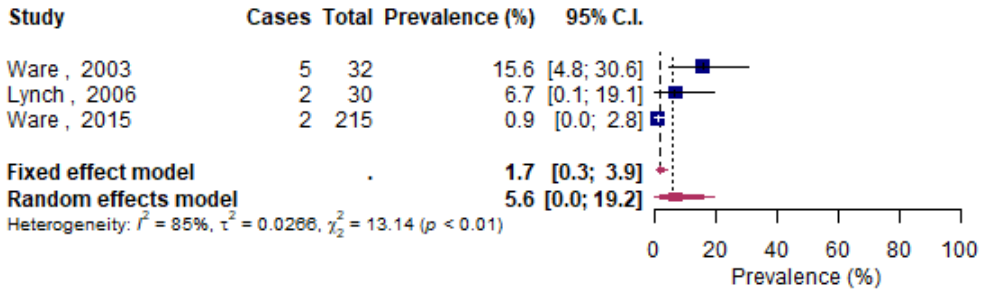
Appendix 21: Results for hallucinations



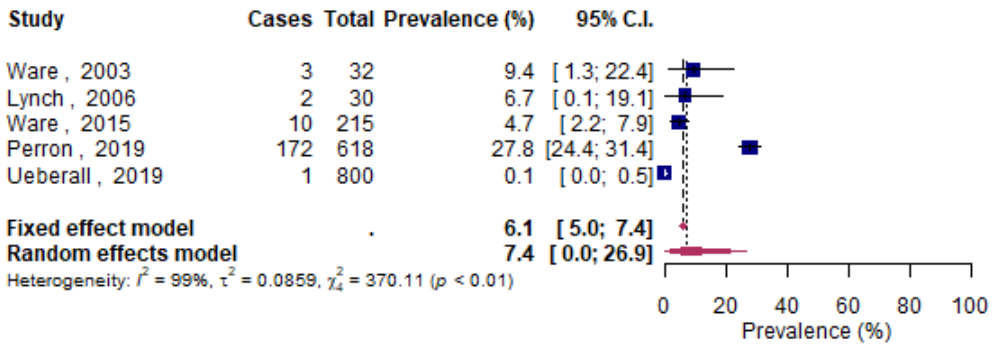
Appendix 22: Results for delusions



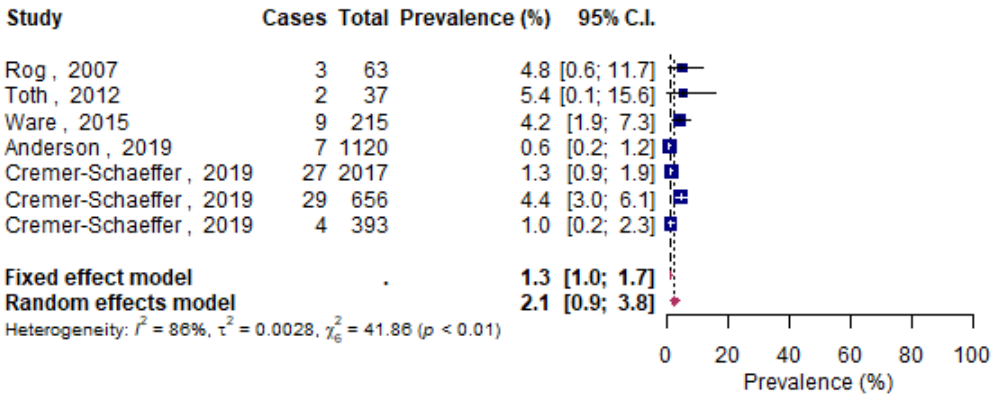
Appendix 23: Results for paranoia



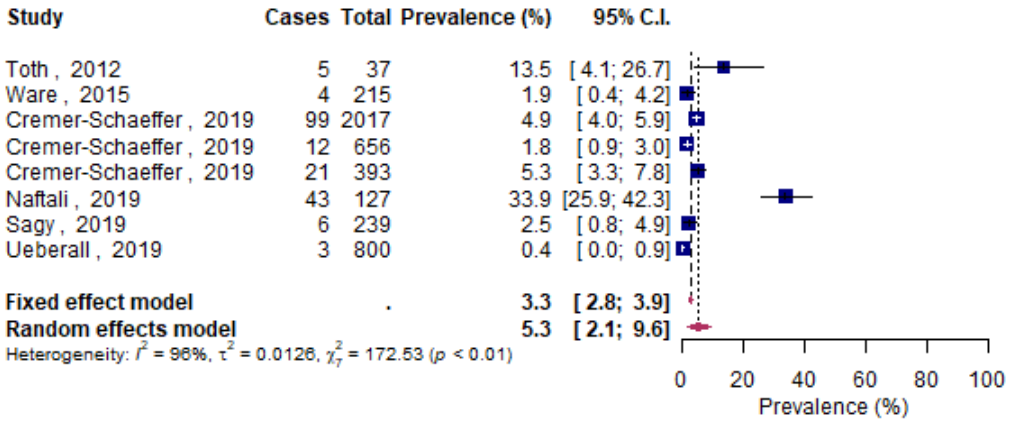
Appendix 24: Results for anxiety



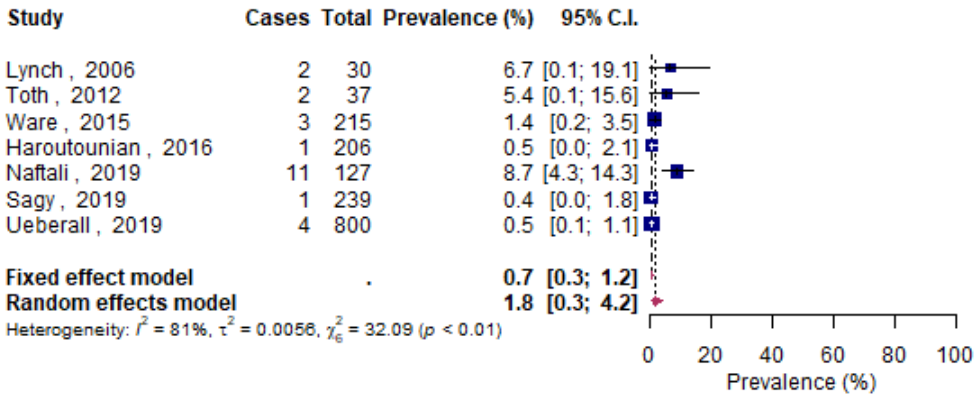
Appendix 25: Results for euphoria



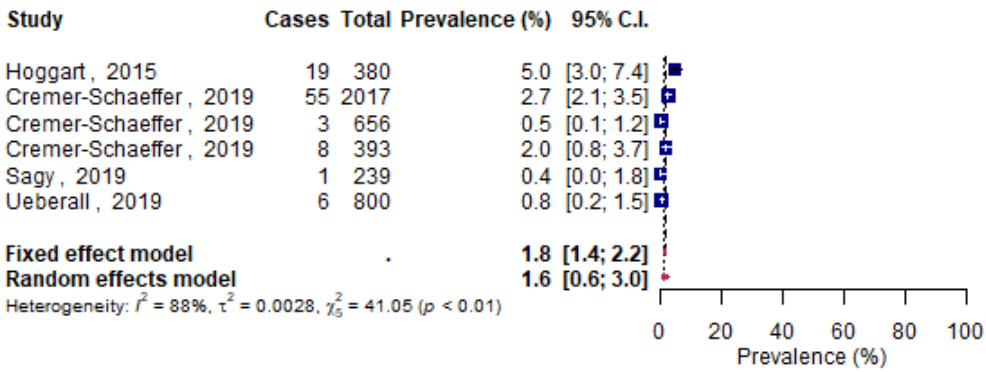
Appendix 26: Results for memory impairment



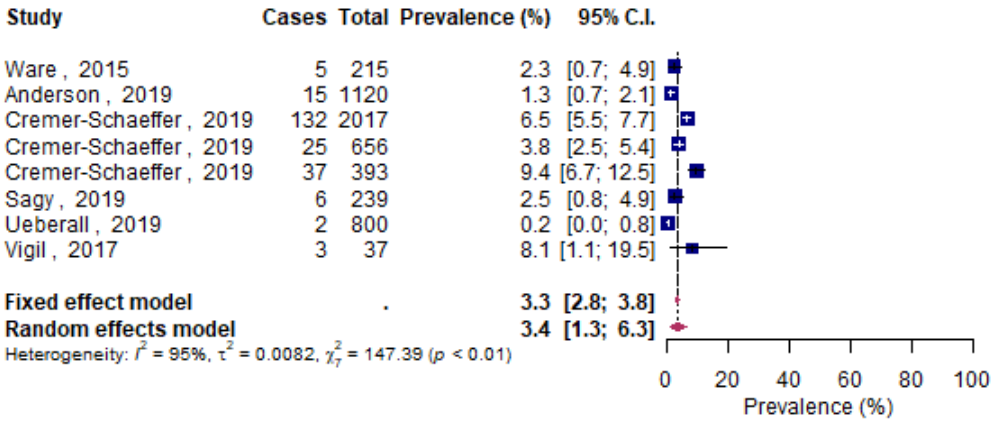
Appendix 27: Results for confusion



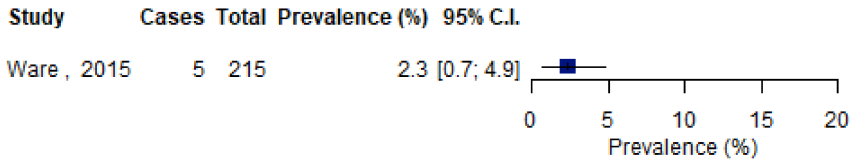
Appendix 28: Results for disorientation



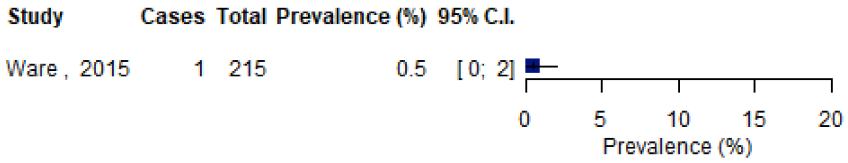
Appendix 29: Results for impaired attention



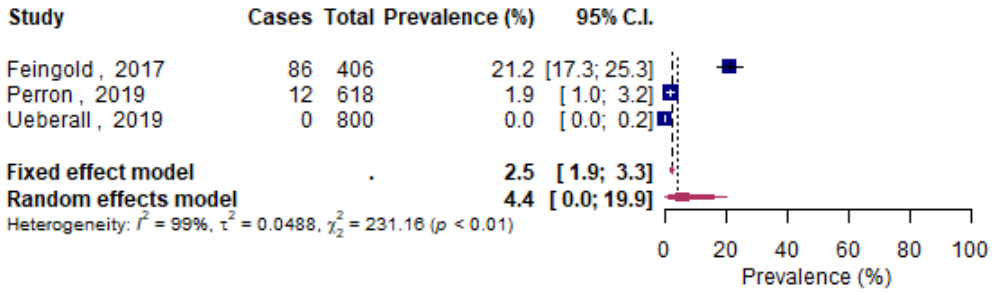
Appendix 30: Results for falls



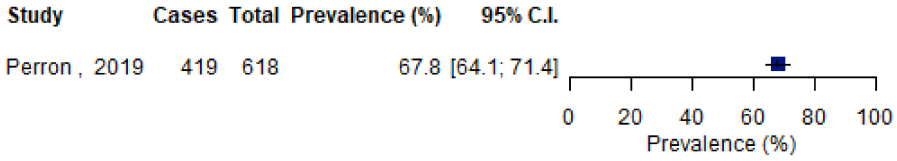
Appendix 31: Results for motor vehicle accidents



Appendix 32: Results for dependence



Appendix 33: Results for withdrawal symptoms



Appendix 34: Results for withdrawal syndrome