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

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3 1 **Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A**
4
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6
7
8 3
9

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4
5 51 **Running head:** Harms of medical cannabis

6 52 **Abbreviations:** Cochrane Central Register of Controlled Trials (CENTRAL), Palmitoylethanolamide (PEA),
7
8 53 tetrahydrocannabinol (THC)

9
10 54 **Keywords:** Medical cannabis, chronic pain, adverse events, harms, non-randomized studies,
11
12 55 observational, systematic review, meta-analysis

13 56 **Disclaimers:** None.

14
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17
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19
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21
22 61 on the selection of the adverse events of interest. We thank James MacKillop, PhD, for his help with the
23
24 62 interpretation of problematic cannabis use, abuse, dependence and withdrawal syndrome within studies.

25 63 **Authors' Contributions:** JWB and TA conceived the idea. RC designed and conducted the search. DZ, MAC,
26
27 64 AA, GL, KL, JD, BYH, CH, and PJH screened search records, extracted data, and assessed the risk of bias of
28
29 65 the eligible studies. DZ conducted analyses. DZ, JWB, and TA interpreted the data. DZ wrote the first draft
30
31 66 of the manuscript. JWB and TA critically revised the manuscript. All authors reviewed and approved the
32
33 67 final version. DZ and JWB are the guarantors.

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60 76 Word count: 5,170

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2
3 77 **Abstract**
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5
6 78 **Objective:** To establish the risk and prevalence of long-term and serious harms of medical cannabis and
7
8 79 cannabinoids for chronic pain.
9

10 80 **Design:** Systematic review and meta-analysis.
11

12
13 81 **Data sources:** MEDLINE, EMBASE, PsycInfo, and the Cochrane Central Register of Controlled Trials
14
15 82 (CENTRAL) from inception to April 1, 2020.
16

17 83 **Study selection:** Non-randomized studies reporting on harms of medical cannabis or cannabinoids in
18
19 84 adults or children living with chronic pain with ≥ 4 weeks of follow-up.
20

21
22 85 **Data extraction and synthesis:** A parallel guideline panel provided input on the design and interpretation
23
24 86 of the systematic review, including selection of adverse events for consideration. Two reviewers, working
25
26 87 independently and in duplicate, screened the search results, extracted data, and assessed risk of bias. We
27
28 88 used random-effects models for all meta-analyses and the GRADE approach to evaluate the certainty of
29
30 89 evidence.
31

32 90 **Results:** We identified 39 eligible studies that enrolled 12,143 adult patients with chronic pain. Very low
33
34 91 certainty evidence suggests that adverse events are common (prevalence: 26.0%; 95% CI 13.2 to 41.2)
35
36 92 among users of medical cannabis or cannabinoids for chronic pain, particularly any psychiatric adverse
37
38 93 events (prevalence: 13.5%; 95% CI 2.6 to 30.6). Very low certainty evidence, however, indicates serious
39
40 94 adverse events, adverse events leading to discontinuation, cognitive adverse events, accidents and
41
42 95 injuries, and dependence and withdrawal syndrome are uncommon and each typically occur in fewer than
43
44 96 one in 20 patients. We compared studies with < 24 weeks and ≥ 24 weeks of cannabis use and found more
45
46 97 adverse events reported among studies with longer follow-up (test for interaction $p < 0.01$).
47
48 98 Palmitoylethanolamide was usually associated with few to no adverse events. We found insufficient
49
50 99 evidence addressing the harms of medical cannabis compared to other pain management options, such
51
52 100 as opioids.
53

54 101 **Conclusions:** There is very low certainty evidence that adverse events are common among people living
55
56 102 with chronic pain who use medical cannabis or cannabinoids, but that few patients experience serious
57
58 103 adverse events. Future research should compare long-term and serious harms of medical cannabis with
59
60 104 other management options for chronic pain, including opioids.

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105 **Systematic review registration** <https://osf.io/25bxf>

For peer review only

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2
3 106 **What is already known on this topic**
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5

- 6 107 • Medical cannabis and cannabinoids are increasingly used for the management of chronic pain.
7
8 108 • Clinicians and patients considering medical cannabis or cannabinoids as a treatment option for
9
10 109 chronic pain require evidence on benefits and harms, including long-term and serious adverse
11 110 events to make informed decisions.
12

13
14 111 **What this study adds**
15

- 16 112 • Very low certainty evidence suggests that adverse events are common among people living with
17 113 chronic pain who use medical cannabis or cannabinoids, including psychiatric adverse events,
18 114 though serious adverse events, adverse events leading to discontinuation, cognitive adverse
19 115 events, accidents and injuries, and dependence and withdrawal syndrome are uncommon.
20
21 116 • There is insufficient evidence comparing the harms of medical cannabis or cannabinoids to other
22 117 pain management options, such as opioids.
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120 **Background**

121 Chronic pain is the primary cause of health care resource use and disability among working adults in North
122 America and Western Europe.^{1 2} The use of cannabis for the management of chronic pain is becoming
123 increasingly common due to pressure to reduce opioid use, increased availability and changing legislation,
124 shift in public attitudes and decreased stigma, and aggressive marketing.^{3 4} The two most-studied
125 cannabinoids in medical cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).⁵ THC
126 binds to cannabinoid receptors type 1 and 2, is an analog to the endogenous cannabinoid, anandamide,
127 and has shown psychoactive, analgesic, anti-inflammatory, antioxidant, antipruritic, anti-spasmodic, and
128 muscle-relaxant activities. CBD directly interacts with various ion channels to produce analgesic, anti-
129 inflammatory, anti-convulsant and anxiolytic activities, without the psychoactive effect of THC.⁵ Use of
130 cannabis for therapeutic purposes, however, remains contentious due to the social and legal context and
131 its known and suspected harms.⁶⁻⁹

132 Though common adverse events caused by medical cannabis, including nausea, vomiting, headache,
133 drowsiness, and dizziness, have been well documented in randomized controlled trials and reviews of
134 randomized controlled trials,^{10 11} less is known about potentially uncommon but serious adverse events,
135 particularly events that may occur with longer durations of medical cannabis use, such as dependence,
136 withdrawal symptoms, and psychosis.^{4 12-17} Such adverse events are usually observed in large non-
137 randomized studies that recruit larger numbers of patients and typically follow them for longer durations
138 of time. Further, evidence from non-randomized studies may be more generalizable, since randomized
139 controlled trials typically use strict eligibility criteria. There have been no reviews of systematic reviews
140 and existing systematic reviews have not consistently meta-analyzed the risks or prevalence of adverse
141 events from non-randomized studies nor have they addressed adverse events that may be particularly
142 important to patients such as serious and potentially fatal adverse events.

143 The objective of this systematic review and meta-analysis is to summarize the evidence on the risks and,
144 when evidence on risk is not available, the prevalence of adverse events related to medical cannabis and
145 cannabinoids from non-randomized studies for a new *BMJ Rapid Recommendation* guideline addressing
146 medical cannabis for chronic pain.¹⁸ This evidence synthesis is part of the *BMJ Rapid Recommendations*
147 project, a collaborative effort from the *MAGIC Evidence Ecosystem Foundation* (www.magicevidence.org)
148 and the *BMJ*.¹⁹ A guideline panel helped define the study question and selected adverse events for review.
149 The adverse events of interest include psychiatric and cognitive adverse events, injuries and accidents,

1
2
3 150 and dependence and withdrawal. It is one of four systematic reviews that together informed a parallel
4
5 151 guideline.^{11 18 20 21} A parallel systematic review addressed evidence from randomized trials.¹¹

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7 152

10 153 **Methods**

11
12 154 We report our systematic review in accordance with the PRISMA Harms Checklist.²² We registered the
13
14 155 protocol for our review at OSF (<https://osf.io/25bxf>) and followed this protocol unless otherwise reported
15
16 156 in this manuscript.²²

18 157 ***Guideline panel involvement***

19
20
21 158 A guideline panel helped define the study question and selected the adverse events for review. The panel
22
23 159 included nine content experts (two general internists, two family physicians, a pediatrician, a physiatrist,
24
25 160 a pediatric anesthesiologist, a clinical pharmacologist, and a rheumatologist), nine methodologists (five of
26
27 161 whom are also front-line clinicians), and three people living with chronic pain (one of whom used
28
29 162 cannabinoids for medical purposes).

30 163 ***Patient and public involvement***

31
32 164 Three patient partners were included as part of the guideline panel and contributed to the selection and
33
34 165 prioritization of outcomes, protocol, and interpretation of review findings, and provided insight on values
35
36 166 and preferences.

38 167 ***Search***

39
40 168 A medical librarian searched MEDLINE, EMBASE, PsychInfo, and Cochrane Central Register of Controlled
41
42 169 Trials (CENTRAL) from inception to April 1, 2020, with no restrictions on language, for non-randomized
43
44 170 studies reporting on harms or adverse events of medical cannabis or cannabinoids for chronic pain
45
46 171 (Appendix 1). We scanned reference lists of relevant reviews to identify any eligible studies not retrieved
47
48 172 by our electronic search and solicited content experts from our panel for unpublished studies. Search
49
50 173 records, and later full-texts of studies, not reported in English were translated by a native speaker of the
51
52 174 language.

175 **Study selection**

176 Reviewers (DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CJH, PJH), working independently and in
177 duplicate, reviewed titles and abstracts of search records and subsequently full texts of records found
178 potentially eligible at the title and abstract screening stage. Reviewers resolved disagreements by
179 discussion or by adjudication by a third reviewer (DZ).

180 We included all non-randomized studies that reported on any patient-important harm or adverse event
181 associated with the use of any formulation of medical cannabis or cannabinoids in adults or children, living
182 with chronic pain (pain lasting for ≥ 3 months) or a medical condition associated with chronic pain (i.e.,
183 fibromyalgia, arthritis, multiple sclerosis, neuropathy, inflammatory bowel disease, stroke, or advanced
184 cancer) or that compared adverse events associated with medical cannabis or cannabinoids with another
185 pharmacologic or non-pharmacologic intervention. We considered herbal cannabis consumed for medical
186 reasons as medical cannabis. Based on input from the guideline panel, we excluded studies in which
187 patients used cannabis for less than 4 weeks because we anticipated that four weeks would be the
188 minimum amount of time after which we would reasonably expect to observe potential serious or long
189 term harms associated with medical cannabis.²³ We looked for explicit statements or evidence that
190 patients were experiencing chronic pain. We excluded studies in which: (1) fewer than 25 patients used
191 medical cannabis or cannabinoids (to exclude studies that would not appreciably contribute to pooled
192 estimates and studies that may be too small to reliably estimate the prevalence of adverse events), (2)
193 patients did not suffer from chronic pain or a condition that commonly causes chronic pain or more than
194 20% of patients reported using medical cannabis or cannabinoids for a condition other than chronic pain
195 (to exclude studies in which patients did not predominantly suffer from chronic pain), (3) patients were
196 using medical cannabis for recreational reasons, (4) only surrogate measures of patient-important harms
197 and adverse effects (e.g., performance on cognitive tests, lab values) were reported, and (5) systematic
198 reviews and other types of studies that did not describe primary data. We also excluded studies that
199 reported on the same data for the same participants.

200 **Data extraction and risk of bias**

201 Reviewers (DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CJH, PJH), working independently and in
202 duplicate and using a standardized and pilot-tested data collection form, extracted the following
203 information from each eligible study: (1) study design, (2) patient characteristics (age, sex,
204 condition/diagnosis), (3) characteristics of medical cannabis or cannabinoids (name of product, dose, and

1
2
3 205 duration), and (4) number of patients that experienced adverse events, including all adverse events,
4
5 206 serious adverse events, and withdrawal due to adverse events. Reviewers resolved disagreements by
6
7 207 discussion or by adjudication with a third party (DZ). We classified adverse events as serious based on the
8
9 208 classification used in primary studies. For comparative studies, we collected results from models adjusted
10
11 209 for confounders, when reported, and unadjusted models when results for adjusted models were not
12
13 210 reported.

14 211 When studies reported the number of events rather than the number of patients experiencing adverse
15
16 212 events, we only extracted the number of events if they were infrequent (the number of events accounted
17
18 213 for less than 10% of the total number of study participants). For studies that reported on adverse events
19
20 214 at multiple timepoints, we extracted data for the longest point of follow-up that included, at minimum,
21
22 215 80% of the patients recruited into the study. Reviewers resolved disagreements by discussion or by
23
24 216 adjudication with a third reviewer (DZ).

25 217 Reviewers (DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CJH, PJH), working independently and in
26
27 218 duplicate, used the Cochrane-endorsed ROBINS-I tool to rate the risk of bias of studies as low, moderate,
28
29 219 serious, or critical across seven domains: (1) bias due to confounding, (2) selection of patients into the
30
31 220 study, (3) classification of the intervention, (4) bias due to deviations from the intended intervention, (5)
32
33 221 missing data, (6) measurement of outcomes, and (7) selection of reported results.²⁴ Reviewers resolved
34
35 222 discrepancies by discussion or by adjudication by a third party (DZ). Appendix 2 presents additional details
36
37 223 on the assessment of risk of bias. Studies were considered to adequately adjust for confounders if they
38
39 224 adjusted, at minimum, for pain intensity, concomitant pain medication, disability status, alcohol use, past
40
41 225 cannabis use. Studies were rated at low risk of bias overall when all domains were at low risk of bias;
42
43 226 moderate risk of bias if all domains were rated at low or moderate risk of bias; at serious risk of bias when
44
45 227 all domains were rated either at low, moderate, or serious risk of bias; and at critical risk of bias when one
46
47 228 or more domains were rated as critical.

48 229 ***Data synthesis***

49 230 In this review, we synthesized data on serious adverse events and adverse events that may emerge with
50
51 231 longer duration of medical cannabis use for which data is typically not reported in randomized trials.
52
53 232 Identified by a parallel BMJ Rapid Recommendations guideline panel as important, these patient-
54
55 233 important outcomes included psychiatric and cognitive adverse events, injuries and accidents, and
56
57 234 dependence and withdrawal. Data on all other adverse events reported in primary studies are available

235 in an open-access database (<https://osf.io/ut36z/>). We classified adverse events as serious based on the
236 classification used in primary studies.

237 Adverse events are reported as binary outcomes. For comparative studies, when possible, we present risk
238 differences and associated 95% confidence intervals (95% CIs). Since there were only two eligible
239 comparative studies, each with different comparators, we did not perform meta-analysis. For single-arm
240 studies, we pooled the proportion of patients experiencing adverse events of interest by first applying a
241 Freeman-Tukey type arcsine square root transformation to stabilize the variance. Without this
242 transformation, very high or very low prevalence estimates can produce confidence intervals that contain
243 values lower than 0% or higher than 100%. All meta-analyses used DerSimonian-Laird random-effects
244 models, which are conservative as they consider both within- and between-study variability.²⁵⁻²⁷ We
245 evaluated heterogeneity for all pooled estimates through visual inspection of forest plots and calculation
246 of tau-squared (τ^2), because some statistical tests of heterogeneity (I^2 and Cochrane's Q) can be misleading
247 when sample sizes are large and CIs are therefore narrow.²⁸ Higher values of τ^2 , I^2 , and Cochrane's Q
248 indicate higher statistical heterogeneity. For studies that reported estimates for all-cause adverse events
249 and those deemed to be potentially related to cannabis use, we preferentially synthesized results for all
250 adverse events.

251 For analyses for which we observed high clinical heterogeneity (i.e., substantial differences in the
252 estimates of individual studies and minimal overlap in the confidence intervals), we presented results
253 narratively.

254 In consultation with the parallel BMJ Rapid Recommendations guideline panel, we also prespecified six
255 subgroup hypotheses to explain heterogeneity between studies: (1) study design (longitudinal vs. cross-
256 sectional), (2) type of medical cannabis, (3) cancer vs. non-cancer pain, (4) children vs. adults, (5) duration
257 of medical cannabis use (shorter or longer than the median duration of follow-up across studies), and (6)
258 risk of bias (low/moderate vs. serious/critical). We also performed two post-hoc subgroup analyses: (1)
259 duration of follow-up (shorter or longer than the median duration of follow-up across studies) and (2)
260 selection bias (studies at moderate, serious, or critical risk of selection bias vs. studies at low risk of
261 selection bias). We anticipated that studies reporting on shorter use of medical cannabis, as well as cross-
262 sectional studies, studies on cancer patients, studies including adults, studies with active comparators,
263 studies at high risk of bias would report fewer adverse events. We anticipated that studies at moderate,
264 serious, or critical risk of selection bias that included prevalent cannabis users (i.e., people who were using

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3 265 medical cannabis before the inception of the study) or were preceded by a run-in period or clinical trial
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5 266 during which patients that experienced adverse events or found medical cannabis intolerable could
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7 267 discontinue would report fewer adverse events because prevalent of medical cannabis are likely to
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9 268 represent populations that have self-selected for tolerance to cannabis. We performed tests for
10
11 269 interaction to establish whether subgroups differed significantly from one another. We assessed the
12
13 270 credibility of significant subgroup effects (test for interaction $p < .05$) using published criteria.^{29 30}

14 271 We performed all analyses using the 'meta' package in R (version 3.5.1, R Foundation for Statistical
15
16 272 Computing).³¹

18 273 ***Certainty of evidence***

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21 274 We used the GRADE approach to rate the certainty of evidence.^{32 33} Based on GRADE guidance for using
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23 275 the ROBINS-I tool, evidence starts at high certainty and is downgraded by one level when the majority of
24
25 276 the evidence comes from studies at moderate risk of bias, two levels when the majority of the evidence
26
27 277 comes from studies at high risk of bias, and three levels when the majority of the evidence comes from
28
29 278 studies rated at critical risk of bias.³² We additionally considered potential limitations due to indirectness
30
31 279 if the population, intervention, or adverse events assessed in studies did not reflect the populations,
32
33 280 interventions, or adverse events of interest, inconsistency if there was important unexplained differences
34
35 281 in the results of studies, and imprecision if the upper and lower bounds of confidence intervals indicated
36
37 282 appreciably different rates of adverse events. For assessing inconsistency and imprecision for the outcome
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39 283 all adverse events, based on feedback from the guideline panel, we deemed a 20% difference in the
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41 284 prevalence of all adverse evidence to be patient-important; a 10% difference for adverse events leading
42
43 285 to discontinuation, serious adverse events, and psychiatric, cognitive, withdrawal and dependence,
44
45 286 injuries; and a 3% difference for potentially fatal adverse events, such as suicides and motor vehicle
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47 287 accidents. We followed GRADE guidance for communicating our findings.³⁴ Guideline panel members
48
49 288 interpreted the magnitude of adverse events and decided whether the observed prevalence of adverse
50
51 289 events was sufficient to affect patients' decisions to use medical cannabis or cannabinoids for chronic pain.

49 290 **Results**

52 291 ***Study selection***

53
54 292 Our search yielded 17,178 unique records of which 434 were reviewed in full. We excluded more than
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56 293 half of references because they did not describe a non-randomized study, a quarter because they did not

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2
3 294 include patients with chronic pain, and a small minority because they did not report on adverse events.
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5 295 Of these records, 39 non-randomized studies were eligible for review (Appendix 3).³⁵⁻⁷³ Figure 1 presents
6
7 296 additional details related to study selection. Appendix 4 presents studies excluded at the full-text
8
9 297 screening stage and accompanying reasons for exclusion.

11 298 **Description of studies**

13 299 One study was published in German and the remainder in English. Studies included 12,143 adults living
14
15 300 with chronic pain and included a median of 100 (IQR 34 to 361) participants (Table 1). Most studies (30/39;
16
17 301 76.9%) were longitudinal in design. Eighteen studies (46.2 %) were conducted in Western Europe,
18
19 302 fourteen (35.9%) in North America, six (15.4%) in Israel, and two (5.1%) in the United Kingdom. Ten studies
20
21 303 (25.6%) were funded by industry alone or industry in combination with government and institutional
22
23 304 funds; the remainder were funded either by governments, institutions, or not-for-profit organizations
24
25 305 (n=9; 23.1%), did not receive funds (n=3; 7.7%), or did not report funding information (n=17; 43.6%).

26 306 Thirty studies (76.9%) reported on people living with chronic non-cancer pain, eight (n=20.5%) with mixed
27
28 307 cancer and non-cancer chronic pain, and one (2.6%) with chronic cancer pain. All studies reported on
29
30 308 adults. Sixteen studies reported on mixed types of herbal cannabis (e.g., buds for smoking, vaporizing, and
31
32 309 ingesting, hashish, oils, extracts, edibles), nine on palmitoylethanolamide (PEA), four each on nabiximols
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34 310 and dronabinol, two on nabilone, one each on Trokie lozenges and extracts, and four did not report the
35
36 311 type of medical cannabis used. One study reported on three types of medical cannabis (dronabinol,
37
38 312 nabiximols, and mixed herbal) separately. The median duration of medical cannabis use was 24 weeks
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40 313 (IQR 12.0 to 33.8 weeks). Two studies were comparative: one study compared nabilone with gabapentin
41
42 314 and another compared herbal cannabis with standard care.^{39 48} Studies reported a total of 525 unique
43
44 315 adverse events.

44 316 **Risk of bias**

46 317 Appendix 5 presents the risk of bias of included studies. We rated all results at critical risk of bias except
47
48 318 for the comparative results from two studies,^{39 48} which were rated at serious and moderate risk of bias.
49
50 319 The primary limitation across studies was inadequate control for potential confounding either due to the
51
52 320 absence of a control group or inadequate adjustment for confounders. A third of studies were rated at
53
54 321 serious risk of bias for selection bias, primarily because they included prevalent users of medical cannabis.
55
56 322 Such studies may underestimate the incidence of adverse events since patients that experience adverse

1
2
3 323 events are more likely to discontinue medical cannabis early. Such studies may also include adverse events
4
5 324 that may have been present at inception and that are unrelated to medical cannabis use.

6
7 325 ***All adverse events***

8
9 326 Twenty longitudinal and two cross-sectional studies, including 4,108 patients, reported the number of
10
11 327 patients experiencing one or more adverse events.^{36-43 46 47 54 56-60 62 64 65 69 70 73} Seven studies reported on
12
13 328 PEA, five on mixed herbal cannabis, three each on nabilone and nabiximols, two on dronabinol, and one
14
15 329 each on extracts and Trokie lozenges. The median duration of medical cannabis use was 24 weeks [IQR 12
16
17 330 to 32]. We observed substantial unexplained heterogeneity and so summarize the results descriptively
18
19 331 (Appendices 6 to 9). The prevalence of any adverse event ranged between 0% to 92.1%. Studies with less
20
21 332 than 24 weeks of cannabis use (the median duration of cannabis) typically reported fewer adverse events
22
23 333 than those with more than 24 weeks. Patients using PEA experienced no adverse events. The evidence
24
25 334 was overall very uncertain due to risk of bias and inconsistency.

26 335 One study suggested that nabilone may reduce the risk of adverse events compared to gabapentin (-
27
28 336 13.1%; 95% CI -26.2 to 0), but the certainty of evidence was very low due to risk of bias and imprecision
29
30 337 (Table 2).

31
32 338 ***Adverse events leading to discontinuation***

33
34 339 Twenty longitudinal studies, including 6,509 patients, reported on the number of patients that
35
36 340 discontinued medical cannabis or cannabinoids due to adverse events.^{37 39 41-44 46-49 52 54 56 57 59 62 63 65 70 73}
37
38 341 Eight studies reported on PEA, four studies on mixed herbal cannabis, three on nabiximols, two on
39
40 342 nabilone, and one each on dronabinol and extracts, and one study did not report the type of medical
41
42 343 cannabis used by patients. The median duration of cannabis use was 24 weeks [IQR 8.6 to 32]. We
43
44 344 observed substantial unexplained heterogeneity and so summarize the results descriptively (Appendices
45
46 345 10 to 12). The prevalence of discontinuations due to adverse events ranged between 0% to 27.0%. Studies
47
48 346 with less than 24 weeks of cannabis use typically reported fewer discontinuations than those with more
49
50 347 than 24 weeks. Patients using PEA experienced no adverse events. The evidence was overall very
51
52 348 uncertain due to risk of bias and inconsistency.

53
54 349 One study suggested herbal cannabis may increase the risk of adverse events leading to discontinuation
55
56 350 compared to standard care without cannabis (4.7%; 95% CI 1.8 to 7.5). Another study suggested that
57
58 351 nabilone may reduce the risk of adverse events leading to discontinuation compared to gabapentin (-

352 9.4%; 95% CI -18.5 to -0.2). The certainty of evidence was low to very low due to risk of bias and
353 imprecision.

354 ***Serious adverse events***

355 Twenty-two longitudinal and two cross-sectional studies, including 4,273 patients, reported on the
356 number of patients experiencing one or more serious adverse events.^{35-37 39-43 46 48 49 52 54-60 62 65 70 71 73} Eight
357 studies reported on mixed herbal cannabis, eight on PEA, two each on nabilone and nabiximols each, and
358 one study each on dronabinol, extracts, and Trokie lozenges, and one study did not report the type of
359 cannabis used. The median duration of medical cannabis or cannabinoid use was 24 weeks (IQR 12 to 32),
360 and few patients experienced serious adverse events (1.2%; 95% CI 0.1 to 3.1; $I^2=91%$) (Figure 2)
361 (Appendices 13 to 15). There was a statistically significant subgroup effect across different types of
362 medical cannabis though serious adverse events appeared consistently uncommon among different types
363 (low credibility). The certainty of evidence was very low overall due to serious risk of bias.

364 One study suggested herbal cannabis increased the risk of serious adverse events compared to standard
365 care without cannabis (1.5%; 95% CI -8.3 to 20.2). Another study found use of nabilone vs. gabapentin
366 showed no difference in the risk of serious adverse events. The certainty of evidence was low to very low
367 for both studies due to risk of bias and imprecision.

368 ***Psychiatric adverse events***

369 Eleven longitudinal and two cross-sectional studies, including 6,600 patients, reported on any psychiatric
370 adverse events, including psychiatric disorders, suicide, suicidal thoughts, depression, mania,
371 hallucinations, delusions, paranoia, anxiety, and euphoria (Appendices 16 to 25).^{35-37 43 47 48 60 63 67 68 70} Five
372 studies reported on mixed herbal cannabis, four on nabiximols, one each on dronabinol, nabilone, and
373 mixed types and one study did not specify the type of medical cannabis. The median duration of cannabis
374 use across studies was 52 weeks (IQR 20 to 52). Approximately one in seven medical cannabis users
375 experienced one or more psychiatric disorders or adverse events (13.5%; 95% CI 2.6 to 30.6; $I^2=98%$). The
376 most frequently occurring psychiatric adverse events were paranoia (5.6%; 9% CI 0 to 19.2; $I^2=85%$) and
377 anxiety (7.4%; 95% CI 0 to 26.9; $I^2=99%$). The certainty of evidence was very low due to risk of bias,
378 inconsistency (for psychiatric disorders and paranoia), and imprecision (for psychiatric disorder, paranoia,
379 and anxiety).

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2
3 380 One study suggested that herbal cannabis may result in a trivial to moderate increase in the risk for
4
5 381 psychiatric disorders, mania, hallucinations, depression, paranoia, anxiety, and euphoria and a reduction
6
7 382 in the risk for suicides and delusions, compared with standard care without cannabis, though the certainty
8
9 383 of evidence was low to very low due to risk of bias and imprecision.

10 384 ***Cognitive and attentional adverse events***

11
12 385 Eleven longitudinal studies, including 6,257 patients, reported on cognitive adverse events, including
13
14 386 memory impairment, confusion, disorientation, and impaired attention (Appendices 26 to 29).^{35-37 43 47 48}
15
16 387 ^{60 63 67 68 70} Five studies reported on herbal cannabis, three on nabiximols, three on mixed types of cannabis,
17
18 388 and one each on dronabinol and nabilone. The median duration of cannabis use was 52 weeks (IQR 24 to
19
20 389 52). The prevalence of cognitive adverse events ranged from 1.6% (95% CI 0.6 to 3.0; I²=88%) to 5.3% (95%
21
22 390 CI 2.1 to 9.6; I²=96%) for disorientation and memory impairment, respectively. The certainty of evidence
23
24 391 was very low due to risk of bias.

25
26 392 One study suggests herbal cannabis may slightly increase the risk for memory impairment and
27
28 393 disturbances in attention compared to standard care without cannabis, but reduce the risk for confusion,
29
30 394 though the certainty of evidence was low to very low due to risk of bias and imprecision.

31 395 ***Accidents and injuries***

32
33
34 396 One longitudinal study, including 431 patients, reported on accidents and injuries in patients using mixed
35
36 397 herbal cannabis for 52 weeks (Appendices 30 & 31).⁴⁸ This study suggests herbal cannabis used for medical
37
38 398 purposes may slightly increase the risk of motor vehicle accidents (0.5%; 95% CI -0.4 to 1.4) but may not
39
40 399 increase the risk of falls (0%; 95% CI -2.8 to 2.9). The certainty of evidence was low due to risk of bias.

41 400 ***Dependence and withdrawal***

42
43 401 Four longitudinal and one cross-sectional study, including 2,248 patients, reported on dependence-
44
45 402 related adverse events, including dependence (one study reported on 'abuse' based on unspecified
46
47 403 criteria, one study reported on 'problematic use' using the Alcohol Use Disorder and Associated
48
49 404 Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition
50
51 405 (AUDADIS-IV)⁷⁴, and one study reported on 'dependence' using the Alcohol, Smoking, and Substance
52
53 406 Involvement Screening Test⁷⁵), withdrawal symptoms (defined as one or moderate or severe withdrawal
54
55 407 symptoms including sleep difficulties, anxiety, irritability, and appetite disturbance), and withdrawal
56
57 408 syndrome (two studies that used unspecified criteria) (Appendices 32 to 34).^{48 53 56 67 70} Two studies

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2
3 409 reported on herbal cannabis, one each on nabiximols and nabilone, and one did not specify type of
4
5 410 medical cannabis used by patients. Follow-up ranged from 12 to 52 weeks. Though dependence and
6
7 411 withdrawal syndrome were uncommon with a prevalence of 4.4% (95% CI 0.0 to 19.9; $I^2=99%$) and 2.1%
8
9 412 (95% CI 0 to 8.2; $I^2=89%$), respectively, withdrawal symptoms were common (67.8%; 95% CI 64.1 to 71.4).
10 413 The certainty of evidence was very low due to risk of bias, inconsistency, imprecision (for dependence),
11 414 and indirectness due to definitions of outcomes in studies were too vague to confidently distinguish
12
13 415 between dependence, addiction, withdrawal symptoms, and withdrawal syndrome.

14
15
16 416 One study suggested that herbal cannabis compared to standard care may slightly increase the risk of
17
18 417 withdrawal syndrome (0.5%; 95% CI -0.4 to 1.4) but the certainty of evidence was low due to risk of bias.

418 **Discussion**

419 ***Main findings***

420 Our systematic review and meta-analysis provides evidence that adverse events are common among
421 people living with chronic pain who use medical cannabis or cannabinoids, with approximately one in four
422 experiencing at least one adverse event—though the certainty of evidence is very low and the true
423 prevalence of adverse events may be substantially different. In contrast, serious adverse events, adverse
424 events leading to discontinuation, cognitive adverse events, accidents and injuries, and dependence and
425 withdrawal syndrome are uncommon. We compared studies with <24 weeks and ≥ 24 weeks cannabis
426 use and found more adverse events reported among studies with longer follow-up. This may be explained
427 by increased tolerance (tachyphylaxis) with prolonged exposure, necessitating increases in dosage with
428 consequent increased risk of harms. PEA, compared to other formulations of medical cannabis, may result
429 in the fewest adverse events. Though adverse events appear to be common, few patients discontinued
430 medical cannabis due to adverse events suggesting that most adverse events are transient and/or
431 outweighed by perceived benefits.

432 Our review represents the most comprehensive review of evidence from non-randomized studies
433 addressing adverse events of medical cannabis or cannabinoid use in people living with chronic pain.
434 While several previous reviews have summarized the evidence on short-term and common adverse events
435 of medical cannabis reported in randomized trials, such as oral discomfort, dizziness, and headaches, our
436 review focuses on serious and rare adverse events—the choice of which was informed by a panel including
437 patients, clinicians, and methodologists—and non-randomized studies, which can follow larger numbers
438 of patients for longer periods of time and thus may detect adverse events that are infrequent or that are

1
2
3 439 associated with longer durations of cannabis use.^{10 76-80} A parallel systematic review of evidence from
4
5 440 randomized controlled trials found no evidence to inform long-term harms of medical cannabis as no
6
7 441 eligible trial followed patients for more than 5.5 months.¹¹ One previously published review that included
8
9 442 non-randomized studies searched the literature until 2007, included studies exploring medical cannabis
10
11 443 for any indication (excluding synthetic cannabinoids) of which only two enrolled people living with chronic
12
13 444 pain.¹² The review also did not synthesize adverse event data from non-randomized studies.¹² Unlike
14
15 445 previous reviews, we focused exclusively on medical cannabis for chronic pain and excluded recreational
16
17 446 cannabis, because cannabis used for recreational purposes often contains higher concentrations of
18
19 447 tetrahydrocannabinol (THC) than medical cannabis. We also focused on chronic pain because this patient
20
21 448 population may be susceptible to different adverse events. Depression and anxiety, for example, are
22
23 449 commonly occurring comorbidities of chronic pain, which may be exacerbated by cannabis.¹⁵⁻¹⁷

24 25 450 ***Strengths and limitations***

26
27 451 Strengths of this systematic review and meta-analysis include a comprehensive search for non-
28
29 452 randomized studies, explicit eligibility criteria, screening of studies and collection of data in duplicate to
30
31 453 increase reliability, and use of the GRADE approach to evaluate the certainty of evidence.

32
33 454 Our review is limited by the non-comparative design of most studies, which precludes confident
34
35 455 inferences regarding the proportion of adverse events that can be attributed to medical cannabis or
36
37 456 cannabinoids and the magnitude by which medical cannabis may increase or decrease the risk of adverse
38
39 457 events compared to other pain management options. Though adverse events appear common among
40
41 458 medical cannabis users, it is possible that other management options for chronic pain, particularly opioids,
42
43 459 may be associated with more (and more severe) adverse events.⁸¹ Partly due to the non-comparative
44
45 460 design of most studies, nearly all results included in our review were at serious or critical risk of bias for
46
47 461 confounding and Simpson's paradox,⁸² either due to the absence of a control group or due to insufficient
48
49 462 adjustment for important confounders. Further, a third of studies were at high risk of selection bias,
50
51 463 primarily because they included prevalent cannabis users. In such studies, the prevalence of adverse
52
53 464 events may be underestimated. Our review provides limited evidence on the harms of medical cannabis
54
55 465 beyond one year of use since most studies reported adverse events for less than one year of follow-up.

56
57 466 We observed some inconsistency for many adverse events of interest and substantial inconsistency for all
58
59 467 adverse events and adverse events leading to discontinuation. We downgraded the certainty of evidence
60
468 when we observed important inconsistency and we did not present estimates from meta-analyses for all

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2
3 469 adverse events and adverse events leading to discontinuation due to substantial inconsistency. Further,
4
5 470 some analyses included too few studies or participants, due to which estimates were imprecise.
6

7
8 471 Sixteen of 39 studies reported on herbal medical cannabis, some of which were consumed by smoking or
9
10 472 vaporizing, and may be associated with different adverse events (e.g. respiratory) than other formulations
11
12 473 of medical cannabis. We attempted to perform subgroup analyses based on the type of medical cannabis.
13
14 474 Results for subgroups, however, lacked credibility due to inconsistency and/or imprecision.

15
16 475 Clinicians and patients may be more inclined to use medical cannabis or cannabinoids for pain relief if
17
18 476 adverse events are mild; however, the evidence on whether adverse events are transient, life threatening,
19
20 477 or the extent to which they impact quality of life is limited. While more than half of studies reported on
21
22 478 the proportion of adverse events that were serious, criteria for ascertaining severity were rarely reported.
23
24 479 None of the included studies reported the duration for which patients experienced adverse events.
25
26 480 Further, most primary studies did not report adequate details on methods for the ascertainment of
27
28 481 adverse events, including definitions or diagnostic criteria. The two studies that reported on withdrawal
29
30 482 syndrome, for example, did not provide diagnostic criteria.^{48 56} However, the DSM-5 requires ≥ 3 of 7
31
32 483 withdrawal symptoms to be present within a week of stopping cannabis use to meet a diagnosis of
33
34 484 cannabis withdrawal syndrome.⁸³ It is therefore reasonable that people living with chronic pain that use
35
36 485 medical cannabis would be more likely to experience withdrawal symptoms vs. withdrawal syndrome.

37
38 486 While children and youth account for approximately 15% of all chronic pain patients, we did not identify
39
40 487 any evidence addressing the harms of medical cannabis in this population.⁸⁴ As such, the extent to which
41
42 488 our findings are generalizable to pediatric populations is uncertain. Although there is evidence that
43
44 489 cannabis use during youth is associated with increased risk of acute psychotic disorders, particularly acute
45
46 490 psychosis,⁸⁵ such studies have explored use of recreational cannabis that contains greater amounts of THC
47
48 491 than is typically seen in medical preparations. Further, the population of patients with chronic pain on
49
50 492 which the studies report may not be representative of all patients with chronic pain—particularly rare
51
52 493 conditions that cause chronic pain.

53
54 494 We used the DerSimonian and Laird method for meta-analysis.²⁶ A growing body of evidence, however,
55
56 495 suggests that this model has important limitations that may be addressed by alternative models⁸⁶—
57
58 496 though there is limited evidence on the performance of these models for meta-analyses of proportions
59
60 497 and prevalence.

1
2
3 498 Finally, we excluded studies from meta-analyses when they did not explicitly report the adverse events of
4
5 499 interest to our panel members. This may have overestimated the prevalence of adverse events if the
6
7 500 adverse events of interest were not observed in the studies in which they were not reported. This was,
8
9 501 however, not possible to confirm because methods for the collection and reporting of adverse event data
10
11 502 across studies were variable (e.g., active monitoring vs. passive surveillance; collecting data on specific
12
13 503 adverse events vs. all adverse events) and poorly described in study reports.

14 504 **Implications**

15
16 505 Our systematic review and meta-analysis shows that evidence regarding long-term and serious harms of
17
18 506 medical cannabis or cannabinoids is insufficient—an issue with important implications for patients and
19
20 507 clinicians considering this management option for chronic pain. While the evidence suggests that adverse
21
22 508 events are common in patients using medical cannabis for chronic pain, serious adverse events appear
23
24 509 uncommon, which suggests that the potential benefits of medical cannabis or cannabinoids (although
25
26 510 very modest) may outweigh potential harms for some patients.^{11 18}

27
28 511 Clinicians and patients considering medical cannabis should be aware that more adverse events were
29
30 512 reported among studies with longer follow-up, necessitating long term follow-up of patients and re-
31
32 513 evaluation of pain treatment options. Our findings also have implications for the choice of medical
33
34 514 cannabis. We found PEA, for example, to consistently be associated with few or no adverse events across
35
36 515 studies, though the evidence on the efficacy of PEA is limited.¹¹

37
38 516 We found very limited evidence comparing medical cannabis or cannabinoids with other pain
39
40 517 management options. Other pharmacological treatments for chronic pain, such as gabapentinoids,
41
42 518 antidepressants, and opioids, may be associated with more (and more serious) adverse events.⁸⁷⁻⁸⁹ To
43
44 519 guide patients' and clinicians' decisions on medical cannabis for chronic pain, future research should
45
46 520 compare the harms of medical cannabis and cannabinoids with other pain management options, including
47
48 521 opioids, ideally beyond one year of use, and adjust results for confounders. Comparative studies may be
49
50 522 synthesized by way of network meta-analysis, which would allow indirect comparisons across
51
52 523 formulations of medical cannabis. Future research could also explore whether the harms of medical
53
54 524 cannabis vary depending on the type of chronic pain.

55
56 525 Our review highlights the need for standardization of reporting of adverse events in non-randomized
57
58 526 studies since such studies represent a critical source of data on long-term and infrequently occurring

1
2
3 527 harms. To enhance the interpretability of adverse event data, future studies should also report the
4
5 528 duration and severity of adverse events, since these factors are important to patients' decisions.
6

7
8 529 A valuable output of our systematic review is an open-source database of over 500 unique adverse events
9
10 530 reported to date in non-randomized studies of medical cannabis or cannabinoids for chronic pain with
11
12 531 corresponding assessments of risk of bias. This database was compiled in duplicate by trained and
13
14 532 calibrated data extractors and is freely available to those interested in further analyzing the prevalence of
15
16 533 different types of adverse events or to those interested in expanding the database to include adverse
17
18 534 events in patients using medical cannabis or cannabinoids for other indications.

19 535 **Conclusion**

20
21 536 Our systematic review and meta-analysis found very low certainty evidence that suggests ~~that~~ adverse
22
23 537 events are common among people living with chronic pain using medical cannabis or cannabinoids, but
24
25 538 that serious adverse events, adverse events causing discontinuation, cognitive adverse events, motor
26
27 539 vehicle accidents, falls, and dependence and withdrawal syndrome are uncommon. We also found very
28
29 540 low certainty evidence that longer duration of use was associated more adverse events and that PEA,
30
31 541 compared with other types of medical cannabis, may result in few or no adverse events. Future research
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33 542 should compare the risks of adverse events of medical cannabis and cannabinoids with alternative pain
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35 543 management options, including opioids, and adjust for potential confounders.
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545 Tables

Table 1: Study characteristics

Study	Design	Country	Condition	Cannabis/ comparator	Dose	# of participants	Duration of cannabis use (weeks)
Ware, 2003 ³⁵	cross-sectional*	Canada	mixed non-cancer pain	mixed herbal	frequency: rarely (n=9), weekly (n=8), daily (n=5), >once daily (n=7) dose: 1-2 puffs (n=4), 3-4 puffs (n=13), whole joint (n=8), more than one joint (n=4)	32	NR
Lynch, 2006 ³⁶	longitudinal*	Canada	mixed non-cancer pain	mixed herbal	mean: 2.5 g/day	30	mean: 94.4
Rog, 2007 ³⁷	longitudinal*	UK	multiple sclerosis	nabiximols	mean: 7.5 sprays/day	63	66.1
Weber, 2009 ³⁸	longitudinal*†	Germany	mixed non-cancer pain	dronabinol	median: 7.5 mg/day	172	mean: 31
Bestard, 2011 ³⁹	longitudinal*	Canada	peripheral neuropathic pain	nabilone	mean: 3.0 mg/day	104	24
				gabapentin	mean: 2.3 g/day	107	
Fiz, 2011 ⁴⁰	cross-sectional*	Spain	fibromyalgia	mixed herbal	~1 to 2 cigarettes or spoonful daily (n=12) once every 2 to 4 days (n=5), less than twice a week (n=3), or occasionally (n=8)	28	<52 (n=11), 52 to 156 (n=9), >156 weeks (n=8)
Dominguez, 2012 ⁴¹	longitudinal*	Spain	lumbosciatica	PEA	300 mg bid	64	4
Gatti, 2012 ⁴²	longitudinal††	Italy	mixed cancer and non-cancer pain	PEA	600 mg bid three weeks; 600 mg/day for four weeks	564	7
Toth, 2012 ⁴³	longitudinal*†	Canada	diabetic peripheral neuropathy	nabilone	mean: 2.85 mg/day	37	4
Schifilliti, 2014 ⁴⁴	longitudinal††	Italy	diabetic neuropathy	PEA	300 mg bid	30	8.6
Storr, 2014 ⁴⁵	cross-sectional*	Canada	Crohn's disease (n=42), ulcerative colitis (n=10), indeterminate colitis (n=4)	mixed herbal	NR	56	<4 (n=3), 4 to 24 (n=9), 24 to 52 (n=5), >52 (n=32)
Del Giorno, 2015 ⁴⁶	longitudinal††	Italy	fibromyalgia	PEA	600 mg bid first month; 300 mg bid in the next 2 months	35	12
Hoggart, 2015 ⁴⁷	longitudinal††	UK, Czech Republic, Romania, Belgium, Canada	diabetic neuropathy	nabiximols	median: 6 to 8 sprays/day	380	median: 35.6
Ware, 2015 ⁴⁸	longitudinal*†	Canada	mixed non-cancer pain	mixed herbal	median: 2.5 g/day	215	52

1					standard care		216	
2								
3								
4								
5	Haroutounian, 2016 ⁴⁹	longitudinal*	Israel	mixed cancer and non-cancer pain	mixed herbal	mean: 43.2 g/month	206	30
6		longitudinal*				Capsule: 10 mg /8 to 10 hours		
7								
8	Bellnier, 2017 ⁵⁰		US	mixed cancer and non-cancer pain	mixed herbal	Vapor pen inhaler for breakthrough pain: 2 mg THC, 0.1 mg CBD; 1 to 5 puffs every 15 minutes until pain relief; could be used every 4 to 6 hours	29	12
9								
10								
11		cross-sectional*						
12	Cranford, 2017 ⁵¹		US	mixed non-cancer pain	NR	0 (n=69), <1/8 oz/week (n=130), 1/8 to 1/4 oz/week (n=156), 1/4 to 1/2 oz/week (n=179), 1/2 to 1 oz/week (n=122), 1 or more oz/week (n=115)	775	NR
13								
14								
15	Fanelli, 2017 ⁵²	longitudinal††	Italy	mixed cancer and non-cancer pain	mixed herbal	mean: 69.5 mg/day bediol; 67.0 mg/day bedrocan	341	mean: 14.01
16	Feingold, 2017 ⁵³	cross-sectional*	Israel	mixed cancer and non-cancer pain	mixed herbal	NR	406	NR
17								
18	Paladini, 2017 ⁵⁴	longitudinal††	Italy	failed back surgery syndrome	PEA	600 mg bid for one month; 600 mg/day for one month	35	8
19	Passavanti, 2017 ⁵⁵	longitudinal††	Italy	lower back pain	PEA	600 mg bid	30	24
20	Schimrigk, 2017 ⁵⁶	longitudinal*†	Germany, Austria	multiple sclerosis	dronabinol	range: 7.5 to 15 mg/day	209	32
21	Chirchiglia, 2018 ⁵⁷	longitudinal††	Italy	lower back pain	PEA	1.2 g/day	100	4
22	Crowley, 2018 ⁵⁸	longitudinal*	US	mixed non-cancer pain	Trokie lozenges	NR	35	4 to 60
23	Habib, 2018 ⁵⁹	longitudinal*	Israel	fibromyalgia	mixed herbal	mean: 26 g/month	26	mean: 41.6
24	Anderson, 2019 ⁶⁰	longitudinal*	US	cancer pain	mixed herbal	NR	1120	16
25								
26								
27		cross-sectional††						
28	Bonar, 2019 ⁶¹		US	mixed non-cancer pain	NR	0 (n=95), <1/8 oz/week (n=126), 1/8 to 1/4 oz/week (n=158), 1/4 to 1/2 oz/week (n=174), 1/2 to 1 oz/week (n=119), 1 or more oz/week (n=119)	790	NR
29								
30								
31	Cervigni, 2019 ⁶²	longitudinal†	Italy	interstitial cystitis/bladder pain syndrome	PEA	400 mg m-PEA plus 40 mg polydatin bid for 3 months, od for 3 months	32	24
32	Cremer-Schaeffer, 2019 ⁶³	longitudinal††	Germany	mixed cancer and non-cancer pain	dronabinol	NR	2017	52
33								
34					mixed herbal	NR	656	
35					nabiximols	NR	393	
36								
37	Lejczak, 2019 ⁶⁴	longitudinal†	France	mixed cancer and non-cancer pain	dronabinol	range: 2.5 to 30 mg/day	148	range: 4 to 24 weeks
38	Loi, 2019 ⁶⁵	longitudinal*	Italy	endometriosis	PEA	600 mg/bid for 10 days; 400 mg m-PEA plus 40 mg polydatin bid	28	12.9
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3							
4	Naftali, 2019 ⁶⁶	longitudinal*	Israel	inflammatory bowel disease	mixed herbal	mean: 31 g/month	
5							127
6	Perron, 2019 ⁶⁷	cross-sectional*	US	mixed non-cancer pain	NR	mean: 21 g/day THC; 170 g/day CBD	618
7							≥12
8	Sagy, 2019 ⁶⁸	longitudinal††	Israel	mixed cancer and non-cancer pain	mixed herbal	median: 1000 mg/day cannabis	239
9							24
10	Sinclair, 2019 ⁶⁹	cross-sectional*	Australia	endometriosis	mixed herbal	median: 140 mg/day THC; 39 mg/day CBD	48
11						less than once per week (n=12), once per week (n=6), two to six times per week (n=9), daily or multiple times per day (n=21)	NR
12		longitudinal*					
13				low back pain (n=234), failed back surgery syndrome (n=148), shoulder/neck pain (n=91), post-herpetic neuralgia (n=72), peripheral diabetic neuropathy (n=56), brachial plexus injury (n=48), lumbar spinal stenosis (n=38), cancer (n=31), fibromyalgia (n=26), peripheral/focal nerve lesions (n=22), phantom pain (n=19), osteoarthritis (n=15)			
14	Ueberall, 2019 ⁷⁰		Germany		nabiximols	mean: 7.1 sprays/day	800
15							12
16							
17							
18							
19							
20							
21							
22							
23	Vigil, 2017 ⁷¹	longitudinal*	US	mixed non-cancer pain	NR	NR	37
24							mean: 82.4
25	Yassin, 2019 ⁷²	longitudinal††	Israel	fibromyalgia	mixed herbal	20 to 30 g/month	31
26							24
27	Giorgi, 2020 ⁷³	longitudinal††	Italy	fibromyalgia	extracts	10 to 30 drops/day; no more than 120 drops/day	102
28							24

NR=not reported
 *Patient-report
 †Clinician-report
 ††NR

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Table 2: Prevalence of adverse events from non-comparative studies

Outcome	Number of studies	Number of participants	Duration of follow-up (weeks)	Prevalence % (95% CI)	I ² (τ ²)	Certainty	Reasons for downgrading
All adverse events	22	4,108	4 to 94	The prevalence of adverse events ranged between 0% to 92.1%. Studies with less than 24 weeks of cannabis use typically reported fewer adverse events than those with more than 24 weeks. Patients using PEA experienced no adverse events. The evidence was overall very uncertain due to risk of bias and inconsistency.		very low	risk of bias (3 levels), inconsistency
Adverse events causing discontinuation	20	6,509	4 to 66	The prevalence of discontinuations due to adverse events ranged between 0% to 27.0%. Studies with less than 24 weeks of cannabis use typically reported fewer discontinuations than those with more than 24 weeks. Patients using PEA experienced no adverse events. The evidence was overall very uncertain due to risk of bias and inconsistency.		very low	risk of bias (3 levels), inconsistency
Serious adverse events	24	4,273	4 to 94	1.2 (0.1 to 3.1)	91 (0.01273)	very low	risk of bias (3 levels)
Psychiatric adverse events							
Psychiatric disorder	4	1,458	12 to 66	13.5 (2.6 to 30.6)	98 (0.0436)	very low	risk of bias (3 levels), inconsistency, imprecision
Suicide	1	215	52	0 (0 to 0.8)	NA	very low	risk of bias (3 levels)
Suicidal thoughts	1	3,066	52	0.1 (0 to 0.5)	44 (0.0003)	very low	risk of bias (3 levels)
Depression	6	4,144	12 to 66	1.7 (0.9 to 2.7)	71 (0.0011)	very low	risk of bias (3 levels)
Mania	1	215	52	0.5 (0 to 2)	NA	very low	risk of bias (3 levels)
Hallucinations	6	3,583	24 to 66	0.5 (0.1 to 1.3)	69 (0.0012)	very low	risk of bias (3 levels)
Delusions	4	3,281	52	0.4 (0.2 to 0.6)	0 (0)	very low	risk of bias (3 levels)
Paranoia	3	277	52 to 94; one cross-sectional study	5.6 (0 to 19.2)	85 (0.0266)	very low	risk of bias (3 levels), inconsistency, imprecision
Anxiety	5	1,695	12 to 94; two cross-sectional studies	7.4 (0 to 26.9)	99 (0.0859)	very low	risk of bias (3 levels), imprecision
Euphoria	7	4,501	4 to 66	2.1 (0.9 to 3.8)	96 (0.0028)	very low	risk of bias (3 levels)
Cognitive adverse events							

Memory impairment	6	4,484	4 to 176	5.3 (2.1 to 9.6)	96 (0.0126)	very low	risk of bias (3 levels)
Confusion	7	1,654	4 to 176	1.8 (0.3 to 4.2)	81 (0.0056)	very low	risk of bias (3 levels)
Disorientation	6	4,485	12 to 52	1.6 (0.6 to 3.0)	88 (0.0028)	very low	risk of bias (3 levels)
Attention disorder or deficit	8	5,477	12 to 82	3.4 (1.3 to 6.3)	95 (0.0082)	very low	risk of bias (3 levels)
Accidents and injuries							
Falls	1	215	52	2.3 (0.7 to 4.9)	NA	very low	risk of bias (3 levels)
Motor vehicle accidents	1	215	52	0.5 (0 to 2.0)	NA	very low	risk of bias (3 levels)
Dependence and withdrawal							
Dependence	3	1,824	12; one cross-sectional study	4.4 (0.0 to 19.9)	99 (0.0488)	very low	risk of bias (3 levels), inconsistency, imprecision, indirectness
Withdrawal syndrome	2	424	32 to 52	2.1 (0 to 8.2)	89 (0.0091)	very low	risk of bias (3 levels), indirectness
Withdrawal symptoms	1	618	NA; cross-sectional	67.8 (64.1 to 71.4)	NA	very low	risk of bias (3 levels), indirectness

Table 3: Risk differences for adverse events from comparative studies

Outcome	Exposure	Number of studies	Number of participants	Follow-up (weeks)	Risk with cannabis (/1000)	Risk with comparator (/1000)	Risk difference (95% CI)	Certainty	Reasons for downgrading
All adverse events	Nabilone vs. gabapentin	1	220	24	404	534	-13.1% (-26.2 to 0)	Very low	Risk of bias (2 levels), imprecision
Adverse events causing discontinuation	Herbal cannabis vs. standard care	1	431	52	47	0	4.7% (1.8 to 7.5)	Low	Risk of bias (2 levels),
	Nabilone vs. gabapentin	1	220	24	96	190	-9.4% (-18.5 to -0.2)	Very low	Risk of bias (2 levels), imprecision
Serious	Herbal cannabis vs. standard care	1	431	52	130	194	1.5% (-8.3 to 20.2) *	Low	Risk of bias, imprecision
	Nabilone vs. gabapentin	1	220	24	0	0	0% (0 to 0)	Very low	Risk of bias (2 levels), imprecision
Psychiatric disorder	Herbal cannabis vs. standard care	1	431	52	219	97	16.9% (5.8 to 40.5) †	Very low	Risk of bias (2 levels), imprecision
Suicide	Herbal cannabis vs. standard care	1	431	52	0	5	-0.5% (-1.4 to 0.4)	Low	Risk of bias (2 levels)
Mania	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Low	Risk of bias (2 levels)
Hallucinations	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Low	Risk of bias (2 levels)
Delusions	Herbal cannabis vs. standard care	1	431	52	0	5	-0.5% (-1.4 to 0.4)	Low	Risk of bias (2 levels)
Depression	Herbal cannabis vs. standard care	1	431	52	47	46	0.1% (-4 to 4)	Low	Risk of bias (2 levels)
Paranoia	Herbal cannabis vs. standard care	1	431	52	9	0	0.9% (-0.4 to 2.2)	Low	Risk of bias (2 levels)
Anxiety	Herbal cannabis vs. standard care	1	431	52	47	9	3.8% (0.6 to 6.8)	Low	Risk of bias (2 levels)
Euphoria	Herbal cannabis vs. standard care	1	431	52	42	0	4.2% (1.5 to 6.9)	Low	Risk of bias (2 levels)

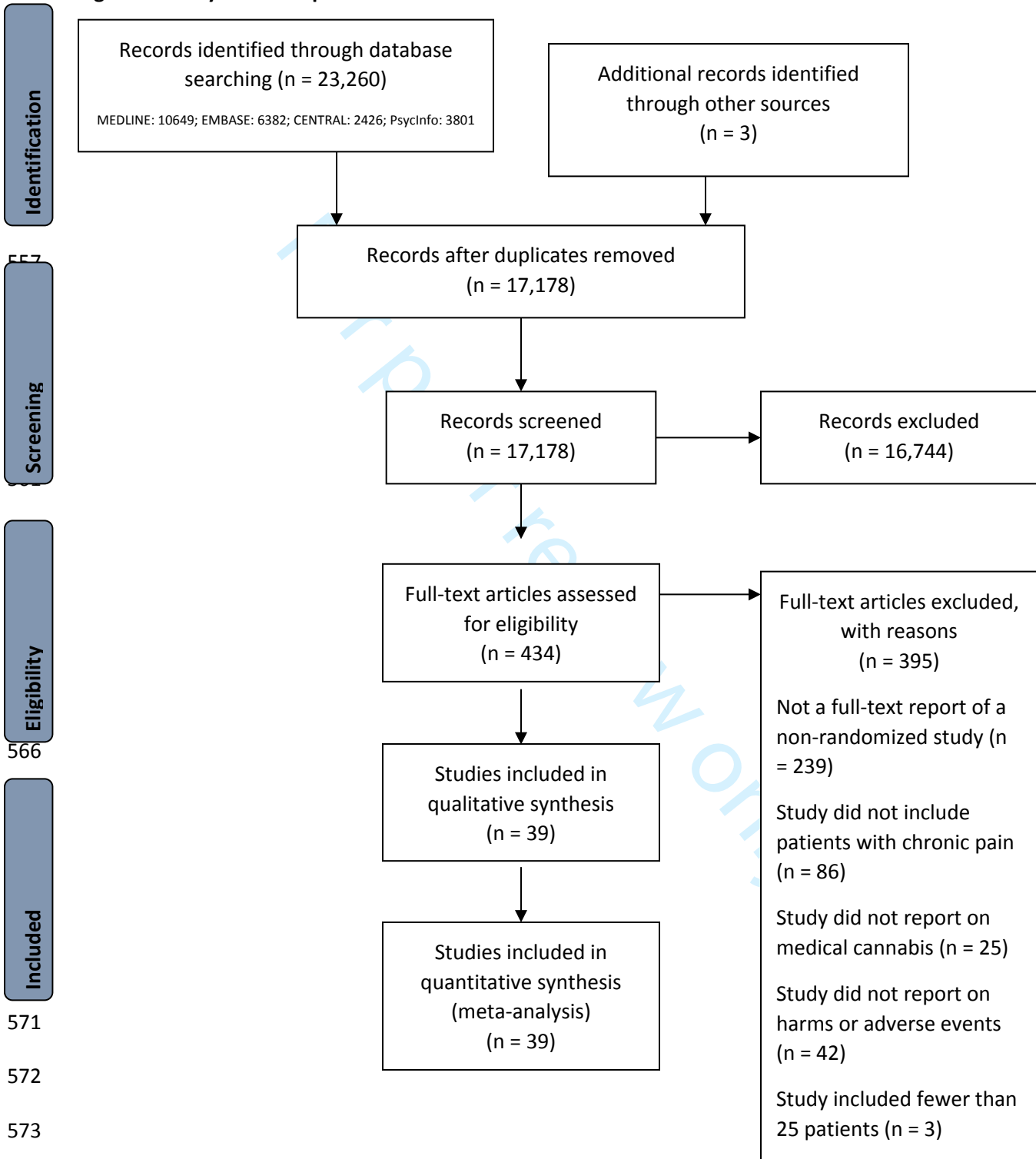
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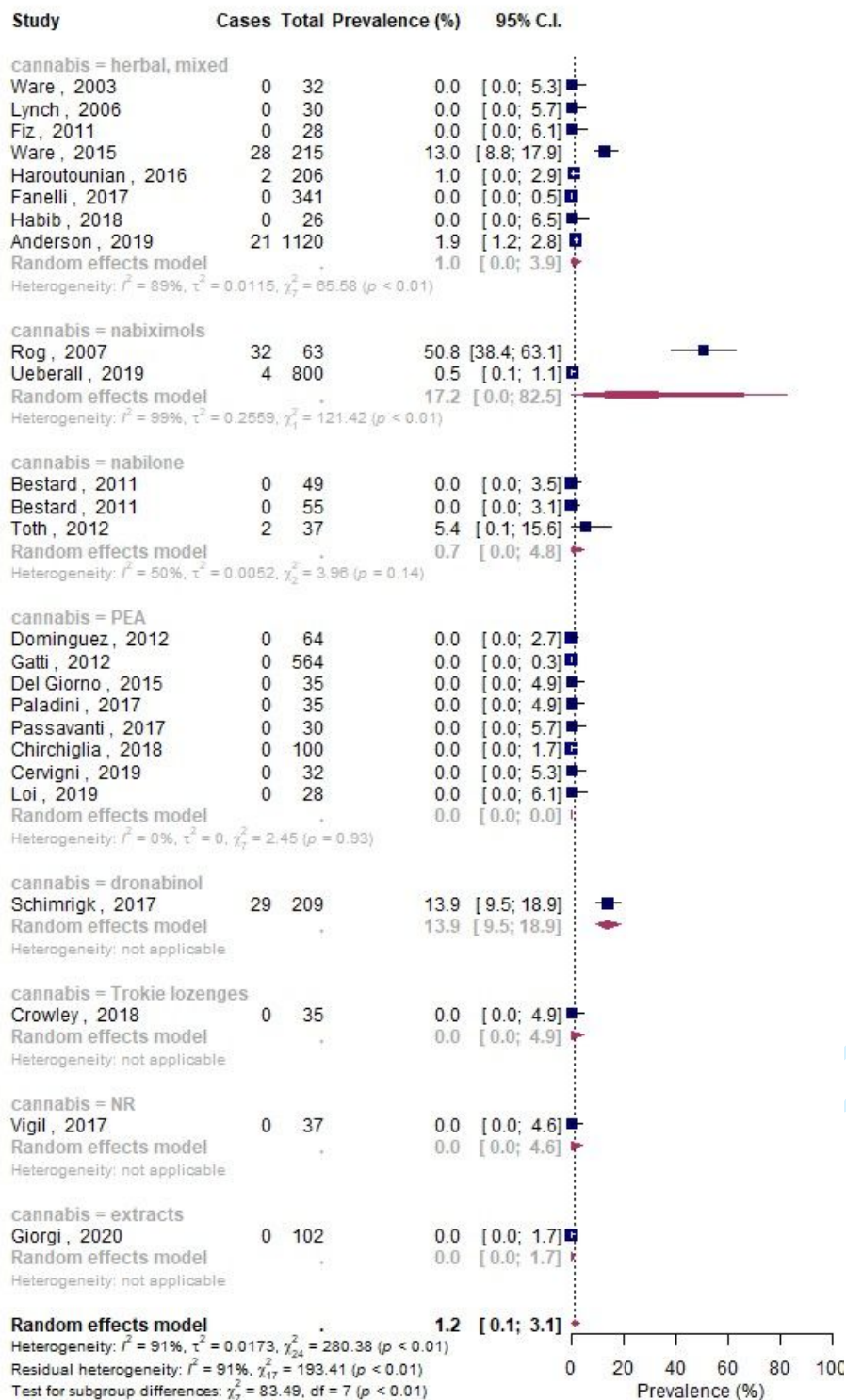
Memory impairment	Herbal cannabis vs. standard care	1	431	52	19	0	1.9% (0.1 to 3.7)	Low	Risk of bias (2 levels)
Confusion	Herbal cannabis vs. standard care	1	431	52	14	19	-0.5% (-2.8 to 1.9)	Low	Risk of bias (2 levels)
Disturbance in attention	Herbal cannabis vs. standard care	1	431	52	23	9	1.4% (-1 to 3.8)	Low	Risk of bias (2 levels)
Falls	Herbal cannabis vs. standard care	1	431	52	23	23	0% (-2.8 to 2.9)	Low	Risk of bias (2 levels)
Motor vehicle accidents	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Low	Risk of bias (2 levels)
Withdrawal syndrome	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Very low	Risk of bias (2 levels),

* Risk difference calculated from adjusted incident rate ratio reported in study.

† Risk difference calculated from unadjusted incident rate ratio reported in study.

551 **Figures**552 **Figure 1: Study selection process**

575 **Figure 2: Forest plot of the meta-analysis for all adverse events stratified by type of medical cannabis**



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2
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2
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6
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Figure 1: Study selection process

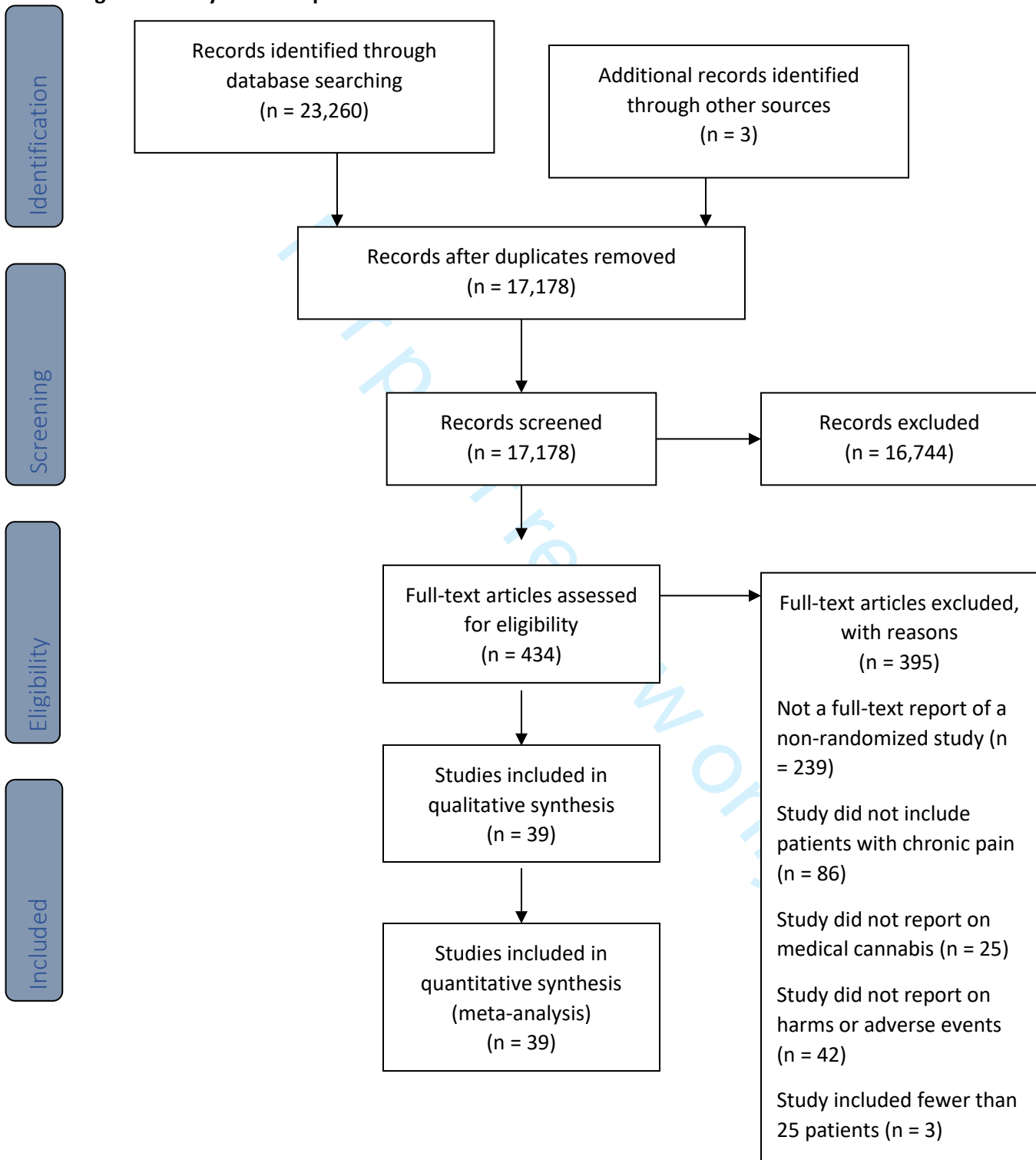
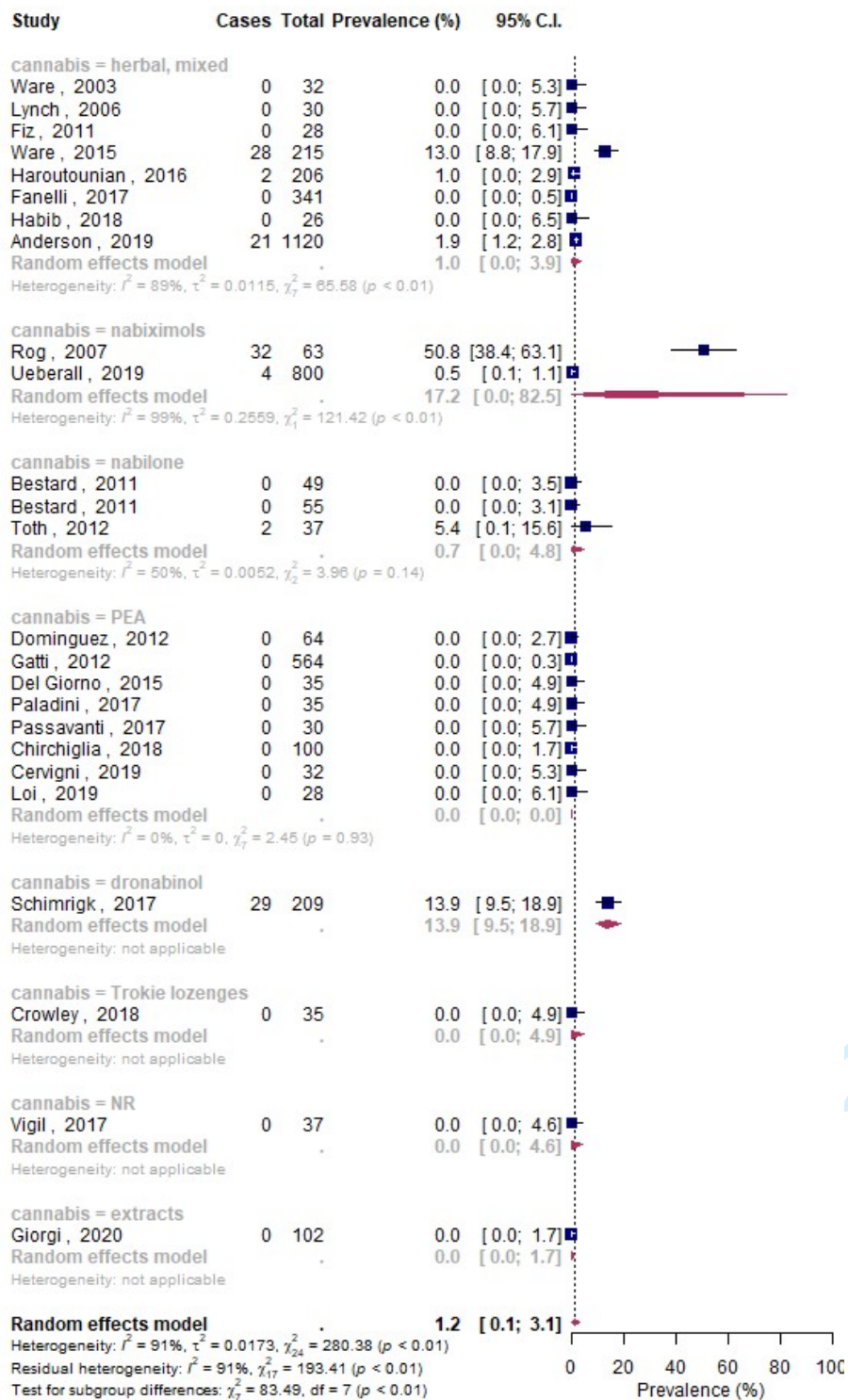


Figure 2: Forest plot of the meta-analysis for all adverse events stratified by type of medical cannabis



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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Appendix 1: Search strategy

MEDLINE	10649
EMBASE	6382
Central	2426
PsycInfo	3801
Subtotal	23260
-duplicates	-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:

-
- 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)

- 1
- 2
- 3 6 Cohort analy\$.tw. (7799)
- 4
- 5
- 6
- 7 7 (Follow up adj (study or studies)).tw. (48708)
- 8
- 9
- 10
- 11 8 (observational adj (study or studies)).tw. (103255)
- 12
- 13
- 14
- 15 9 Longitudinal.tw. (239715)
- 16
- 17
- 18 10 Retrospective.tw. (515751)
- 19
- 20
- 21
- 22 11 Cross sectional.tw. (342224)
- 23
- 24
- 25
- 26 12 Cross-sectional studies/ (322752)
- 27
- 28
- 29 13 or/1-12 (2953281)
- 30
- 31
- 32
- 33 14 exp animals/ not humans.sh. (4685189)
- 34
- 35
- 36
- 37 15 13 not 14 (2889789)
- 38
- 39

40 Annotation: SIGN observational studies filter

- 41
- 42
- 43
- 44 16 randomized controlled trial.pt. (503041)
- 45
- 46
- 47
- 48 17 controlled clinical trial.pt. (93591)
- 49
- 50
- 51
- 52 18 randomized.ab. (474985)
- 53
- 54
- 55
- 56 19 placebo.ab. (206552)
- 57
- 58
- 59
- 60

1
2
3
4
5 20 drug therapy.fs. (2191450)
6
7

8
9 21 randomly.ab. (330409)
10

11
12 22 trial.ab. (500400)
13
14

15
16 23 groups.ab. (2028909)
17
18

19
20 24 or/16-23 (4670111)
21
22

23
24 25 exp animals/ not humans.sh. (4685189)
25
26

27
28 26 24 not 25 (4048339)
29
30

31 Annotation: Cochrane HSSS RCT filter
32
33

34
35 27 15 or 26 (6033576)
36
37

38
39 Annotation: study design filter broad
40
41

42 28 Cannabis/ (8968)
43
44

45
46 29 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (13810)
47
48

49
50 30 Endocannabinoids/ (5630)
51
52

53
54 31 exp Receptors, Cannabinoid/ (9240)
55
56
57
58
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1
2
3 32 (Cannabis or cannabiniol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or
4 ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
5 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
6 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabiniol or
7 marinol or tetranabinex or sativex or endocannabinoid*).mp. (54925)
8
9

10
11
12 33 or/28-32 (54925)
13
14

15 Annotation: strategy from 2020 cannabis review
16
17

18
19 34 27 and 33 (16307)
20
21

22
23 Annotation: cannabis AND study design filter
24
25

26
27 35 exp "Drug-Related Side Effects and Adverse Reactions"/ (114376)
28
29

30
31 36 (ae or to or po or co).fs. (3890270)
32
33

34
35 37 (safe or safety).ti,ab. (758301)
36
37

38
39 38 side effect\$.ti,ab. (243706)
40
41

42 39 ((adverse or undesirable or harms\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or
43 outcome\$)).ti,ab. (501888)
44
45

46
47 40 exp Product Surveillance, Postmarketing/ (15237)
48
49

50
51 41 adverse drug reaction reporting systems/ (7463)
52
53

54
55 42 clinical trials, phase iv/ (295)
56
57

1
2
3
4
5 43 exp Poisoning/ (156177)
6
7

8
9 44 exp Substance-Related Disorders/ (274845)
10

11
12 45 Abnormalities, Drug-Induced/ (14514)
13
14

15
16 46 Drug Monitoring/ (20599)
17
18

19
20 47 exp Drug Hypersensitivity/ (45642)
21
22

23
24 48 (toxicity or complication\$ or noxious or tolerability).ti,ab. (1298802)
25
26

27
28 49 or/35-48 (5596308)
29
30

31 Annotation: OVID AE filter
32
33

34
35 50 34 and 49 (10649)
36
37

38
39 Annotation: Study design filter AND Cannabis AND AE Filter (broad)
40
41

42 Database: Embase <1974 to 2020 March 31>
43
44

45
46 Search Strategy:
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49
50 -----
51
52
53 1 cannabis/ (33859)
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1
2
3 2 exp cannabinoid/ (65694)
4
5

6
7 3 medical cannabis/ (2104)
8
9

10 4 exp cannabinoid receptor/ (14557)
11
12

13
14 5 exp endocannabinoid/ (8589)
15
16

17
18 6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or
19 ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
20 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
21 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or
22 marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug
23 trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating
24 subheading word, candidate term word] (86550)
25
26

27
28
29 7 or/1-6 (87843)
30
31

32
33 Annotation: cannabis
34
35

36 8 clinical study/ (154879)
37
38

39 9 case control study/ (153658)
40
41

42
43 10 family study/ (26012)
44
45

46
47 11 longitudinal study/ (137463)
48
49

50
51 12 retrospective study/ (897628)
52
53

54
55 13 prospective study/ (590879)
56
57

1
2
3
4
5 14 randomized controlled trials/ (176633)
6
7

8
9 15 13 not 14 (584662)
10
11

12 16 cohort analysis/ (564001)
13
14
15

16 17 (Cohort adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title,
17 device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word,
18 candidate term word] (296961)
19
20

21
22 18 (Case control adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original
23 title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word,
24 candidate term word] (211490)
25
26

27
28 19 (follow up adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original
29 title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word,
30 candidate term word] (65948)
31
32

33
34 20 (observational adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
35 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
36 word, candidate term word] (242526)
37
38

39
40 21 (epidemiologic\$ adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
41 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
42 word, candidate term word] (109669)
43
44

45
46 22 (cross sectional adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
47 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
48 word, candidate term word] (385983)
49
50

51
52 23 or/8-12,15-22 (2808984)
53
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1
2
3 Annotation: SIGN observational studies filter
4
5

6
7 24 7 and 23 (9720)
8
9

10 Annotation: cannabis AND observational studies
11
12

13
14 25 randomized controlled trial/ (597702)
15
16

17
18 26 Controlled clinical study/ (463832)
19
20

21
22 27 random\$.ti,ab. (1518977)
23
24

25
26 28 randomization/ (86491)
27
28

29
30 29 intermethod comparison/ (258334)
31
32

33
34 30 placebo.ti,ab. (303428)
35
36

37
38 31 (compare or compared or comparison).ti. (504683)
39
40

41 32 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing
42 or comparison)).ab. (2082229)
43
44

45
46 33 (open adj label).ti,ab. (78190)
47
48

49
50 34 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (229917)
51
52

53
54 35 double blind procedure/ (171048)
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1
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3 36 parallel group\$1.ti,ab. (25201)
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7 37 (crossover or cross over).ti,ab. (104010)
8
9

10
11 38 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or
12 patient\$1 or subject\$1 or participant\$1)).ti,ab. (325625)
13
14

15
16 39 (assigned or allocated).ti,ab. (383429)
17
18

19
20 40 (controlled adj7 (study or design or trial)).ti,ab. (343515)
21
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23
24 41 (volunteer or volunteers).ti,ab. (244577)
25
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27
28 42 human experiment/ (490389)
29
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31
32 43 trial.ti. (295850)
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36 44 or/25-43 (4952112)
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38
39 Annotation: Cochrane RCT filter
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42
43 45 7 and 44 (14036)
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46
47 Annotation: cannabis AND RCTs
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49

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51 46 24 or 45 (21357)
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54 Annotation: cannabis AND (Obs studies OR RCTs)
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3 47 7 and (23 or 44) (21357)
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7 Annotation: logic check
8
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10 48 (ae or si or to or co).fs. (3204803)
11
12

13
14 49 (safe or safety).ti,ab. (1154971)
15
16

17
18 50 side effect\$.ti,ab. (358075)
19
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21
22 51 ((adverse or undesirable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or
23 outcome\$)).ti,ab. (787739)
24
25

26
27 52 exp adverse drug reaction/ (522775)
28
29

30
31 53 exp drug toxicity/ (125051)
32
33

34
35 54 exp intoxication/ (366563)
36
37

38
39 55 exp drug safety/ (393912)
40
41

42
43 56 exp drug monitoring/ (53058)
44
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46
47 57 exp drug hypersensitivity/ (56248)
48
49

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51 58 exp postmarketing surveillance/ (35831)
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55 59 exp drug surveillance program/ (26017)
56
57
58
59
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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

- 1
2
3 #4 MeSH descriptor: [Endocannabinoids] explode all trees 48
4
5
6
7 #5 (Cannabis or cannabinal or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja
8 or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
9 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
10 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinal or
11 marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched)
12 4370
13
14
15
16 #6 #1 or #2 or #3 or #4 or #5 4370
17
18
19
20 #7 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 3463
21
22
23
24 #8 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE, toxicity - TO,
25 poisoning - PO, complications - CO] 169278
26
27
28
29 #9 (safe or safety):ti,ab,kw (Word variations have been searched) 258304
30
31
32
33 #10 (side effect*):ti,ab,kw (Word variations have been searched) 149400
34
35
36
37 #11 ((adverse or undesirable or harms* or serious or toxic) near/3 (effect* or reaction* or event* or
38 outcome*)):ti,ab,kw (Word variations have been searched) 279577
39
40
41
42 #12 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 191
43
44
45 #13 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 82
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49 #14 MeSH descriptor: [Clinical Trial, Phase IV] explode all trees 0
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53 #15 MeSH descriptor: [Poisoning] explode all trees 2101
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3 #16 MeSH descriptor: [Substance-Related Disorders] explode all trees 14586
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7 #17 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees 47
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11 #18 MeSH descriptor: [Drug Monitoring] explode all trees 1725
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14 #19 MeSH descriptor: [Drug Hypersensitivity] explode all trees 965
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18 #20 (toxicity or complication* or noxious or tolerability):ti,ab,kw (Word variations have been
19 searched) 332240
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23 #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
24 626064
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28 #22 #6 and #21 in Trials 2426
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31 PsycInfo

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35 Database: APA PsycInfo <1806 to March Week 4 2020>
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39 Search Strategy:
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47 1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (12819)
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51 2 (Cannabis or cannabinal or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or
52 ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
53 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
54 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinal or
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3 marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of
4 contents, key concepts, original title, tests & measures, mesh] (26466)
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6
7

8 3 1 or 2 (26466)
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10
11
12 4 exp "side effects (drug)"/ (57604)
13

14
15 5 (safe or safety).ti,ab. (84148)
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18
19 6 side effect\$.ti,ab. (31950)
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22
23 7 ((adverse or undesirable or harms\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or
24 outcome\$)).ti,ab. (44183)
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28 8 toxic disorders/ (1433)
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32 9 exp "substance use disorder"/ (127742)
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35
36 10 (toxicity or complication\$ or noxious or tolerability).ti,ab. (42844)
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40 11 or/4-10 (310848)
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44 12 3 and 11 (10984)
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48 13 epidemiology/ (49562)
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51 14 ((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id. not
52 "Literature Review".md. (95810)
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3 15 ((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or
4 prospective study.md. or retrospective study.md.) not "Literature Review".md. (286455)
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8 16 (cross section* or "prevalence study").ti,ab,id. (80384)
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12 17 clinical trials/ or "treatment outcome clinical trial".md. or ((randomi?ed adj7 trial*) or ((single or
13 doubl* or tripl* or treb*) and (blind* or mask*)) or (controlled adj3 trial*) or (clinical adj2 trial*)).ti,ab,id.
14 (101001)
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17
18 18 Case control.mp. (10736)
19
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21
22 19 (cohort adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key concepts,
23 original title, tests & measures, mesh] (21026)
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27 20 Cohort analy\$.mp. (2099)
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31 21 (Follow up adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key
32 concepts, original title, tests & measures, mesh] (12876)
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36 22 (Longitudinal or Retrospective or Cross sectional).mp. [mp=title, abstract, heading word, table of
37 contents, key concepts, original title, tests & measures, mesh] (218589)
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41 23 or/13-22 (561443)
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44 24 12 and 23 (3801)
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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.
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4 with low back pain related to fibromyalgia: an observational cross-over single centre study. *Clinical &*
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For peer review only

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

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

1. Apro 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.
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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://www.who.int/trialssearch/Trial2.aspx?TrialID=ACTRN12618000487213>. 2018.
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23 36. Erbe B. [Cannabis - medicinal use]. *Deutsche Medizinische Wochenschrift*. 2014;139(3):74-5.
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26 <http://www.who.int/trialssearch/Trial2.aspx?TrialID=EUCTR2015-004451-40-AT>. 2016.
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35 <http://www.who.int/trialssearch/Trial2.aspx?TrialID=EUCTR2012-005328-14-DK>. 2013.
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37 41. Euctr DK. The effect of cannabis products on nerve pain and muscle stiffness in patients with
38 multiple sclerosis and in patients with spinal cord injury.
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50 45. Euctr NL. Perioperative ?9-THC for postsurgical pain.
51 <http://www.who.int/trialssearch/Trial2.aspx?TrialID=EUCTR2012-005808-17-NL>. 2013.
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7 *European Neurology*. 2014;72:9-11.
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14 of nabiximols for the treatment of multiple sclerosis related spasticity: An Italian monocentric study.
15 *Multiple Sclerosis*. 2015;1):728-9.
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17 50. Ferre L, Pavan G, Nuara A, Radaelli M, Liberatore G, Guaschino C, et al. Efficacy, safety and
18 response rate to Nabiximol for the treatment of MS-related spasticity in an Italian monocentric cohort.
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21 51. Ferre L, Sorosina M, Santoro S, Moiola L, Rodegher M, Colombo B, et al. Efficacy, safety and
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43 **Study did not include patients with chronic pain**

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12 problematic oral cannabinoid use. *Psychopharmacology*. 2018;235(2):409-17.
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15 **Study included <25 patients**

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Appendix 5: Risk of bias ratings

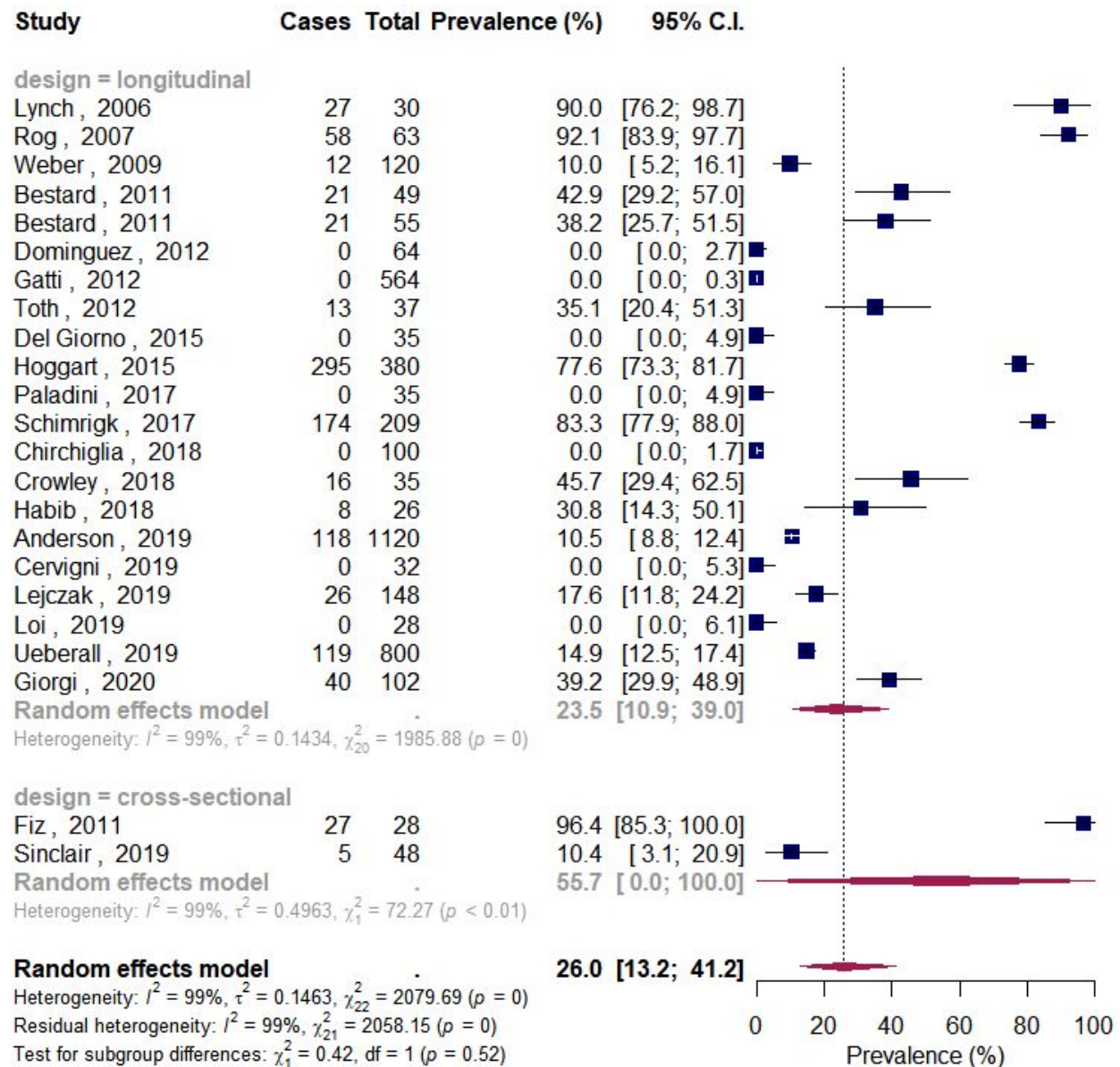
Study	Confounding	Selection of participants into the study	Classification of the intervention	Departures from the intended intervention	Missing data	Measurement of outcomes	Selection of the reported Results
Ware, 2003	●	●	●	●	●	●	●
Lynch, 2006	●	●	●	●	●	●	●
Rog, 2007	●	●	●	●	●	●	●
Weber, 2009	●	●	●	●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

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

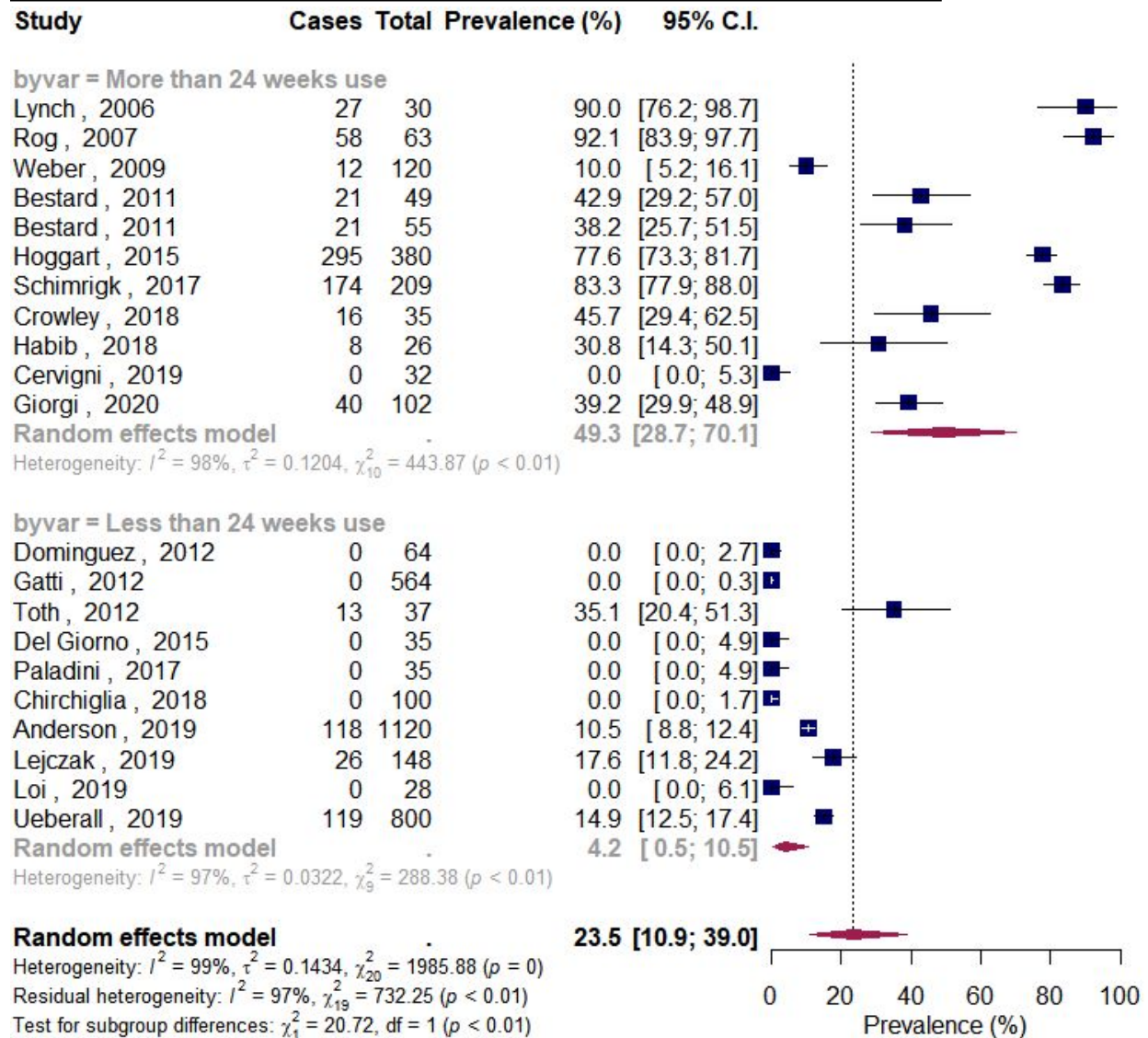
* Risk of bias for confounding for comparative results were rated as serious.

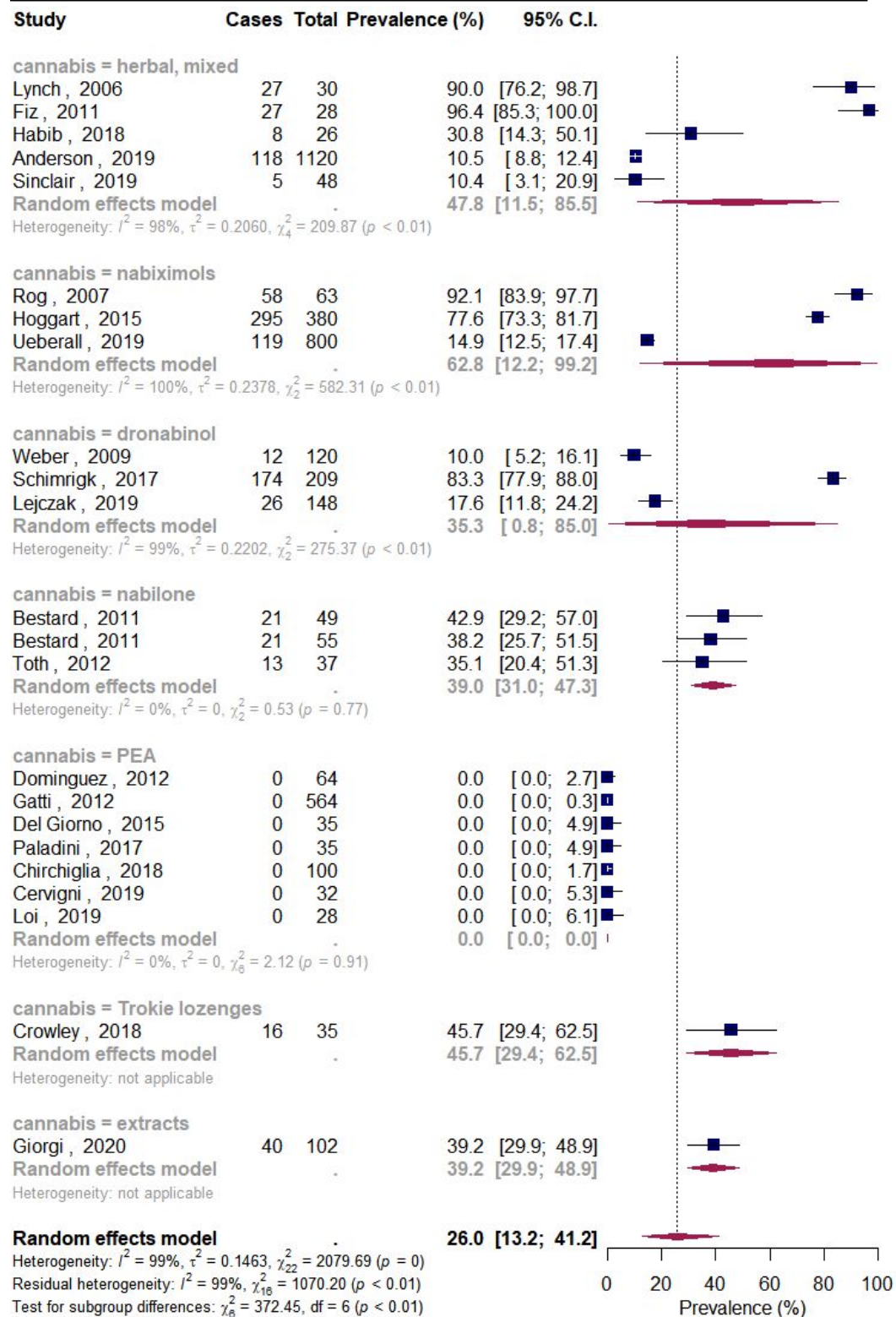
† Risk of bias for confounding for unadjusted comparative comparative results were rated as serious. Adjusted comparative results were rated as moderate.

‡ 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 participants.

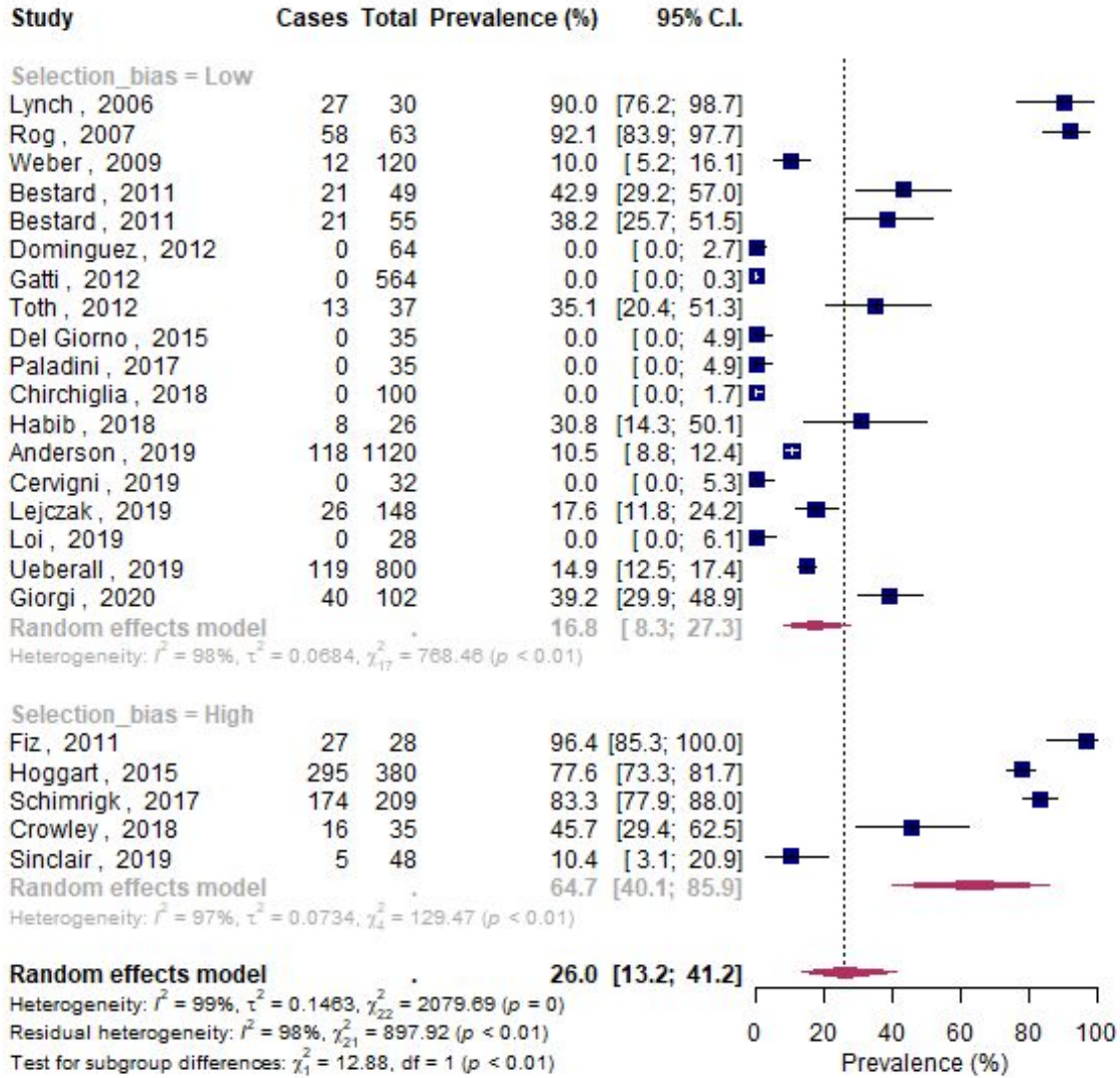
Appendix 6: Results for all adverse events (subgroup by design)

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

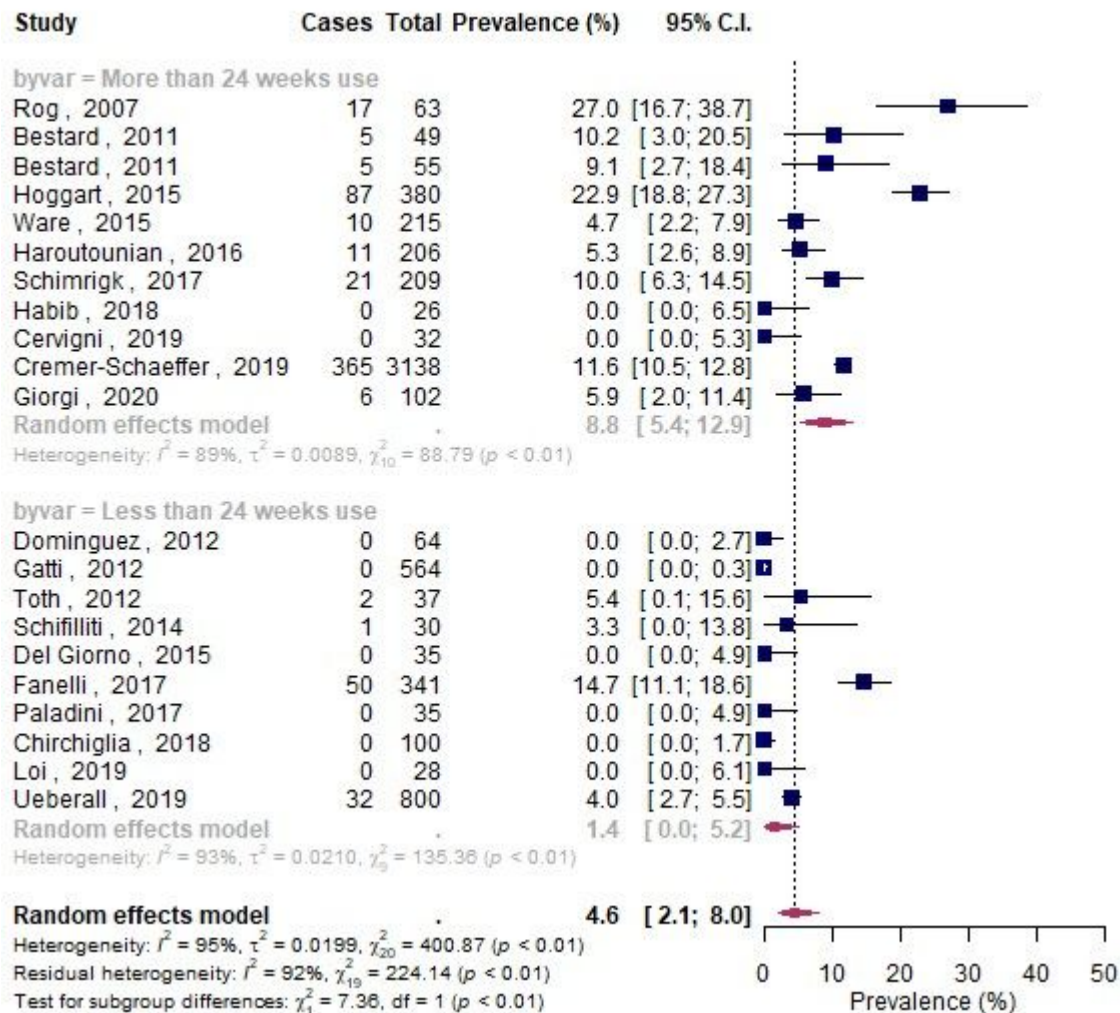


Appendix 8: Results for all adverse events (subgroup by cannabis)

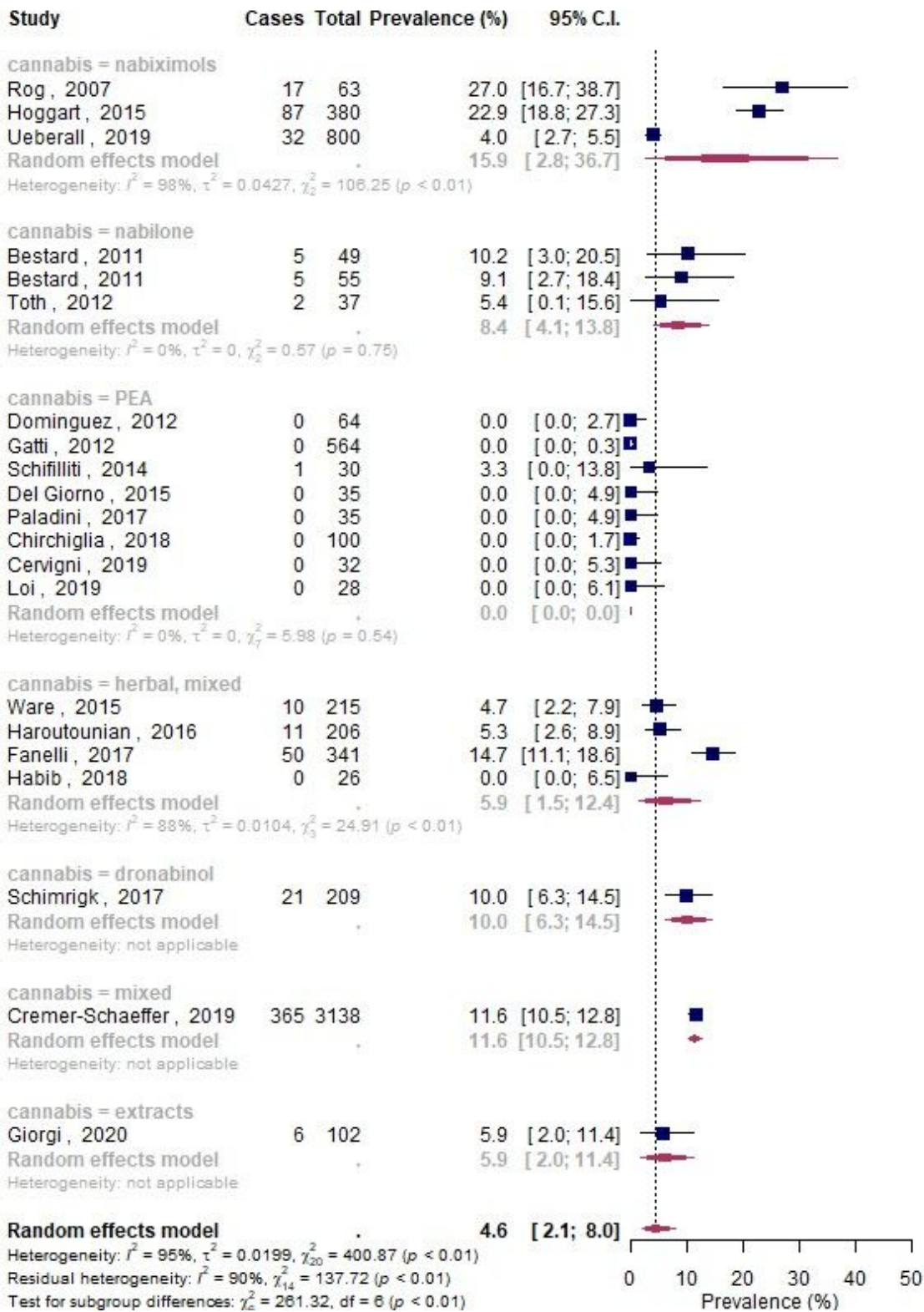
Appendix 9: Results for all adverse events (subgroup by selection bias)



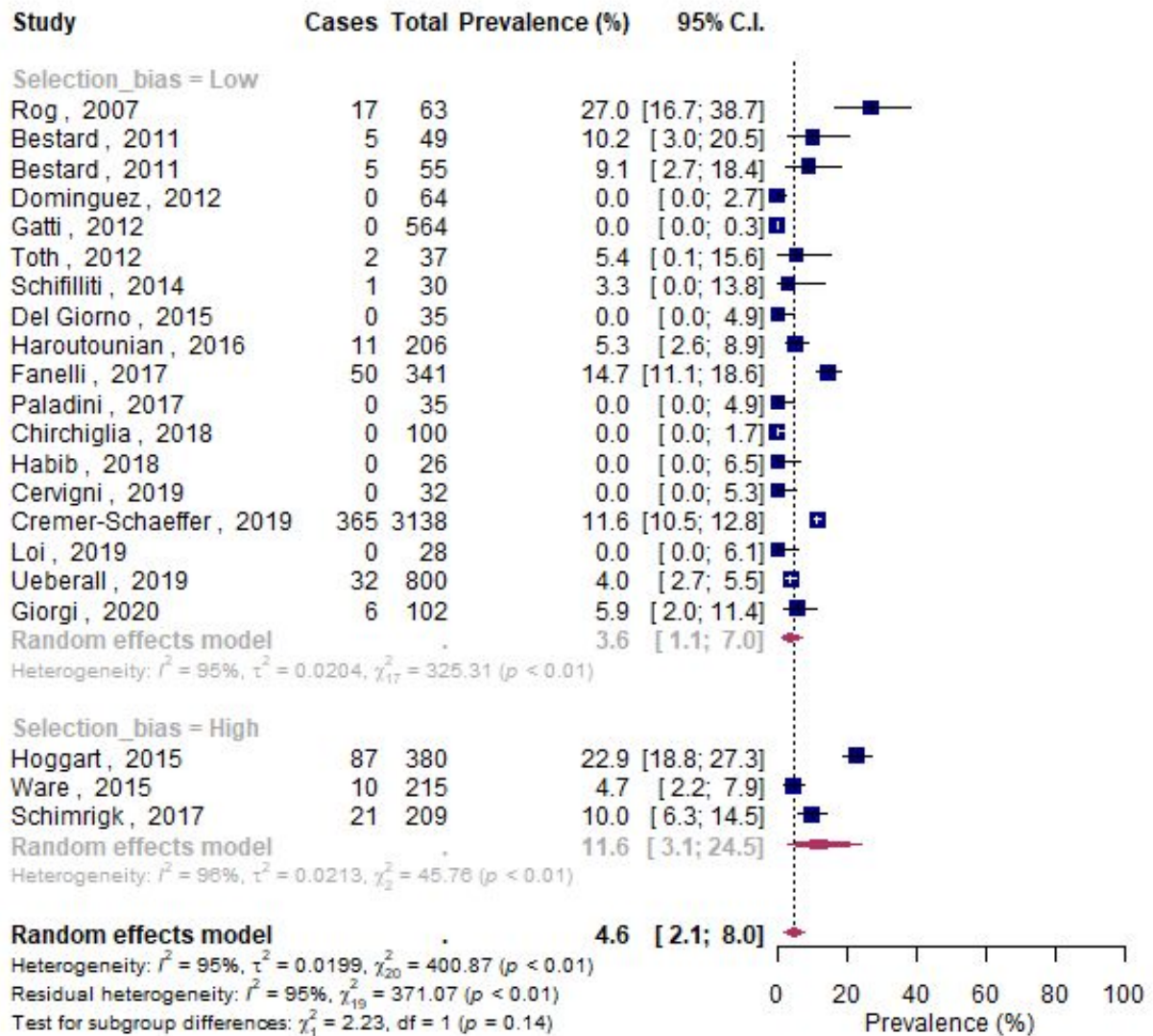
Appendix 10: Results for adverse events leading to discontinuation (subgroup by duration)



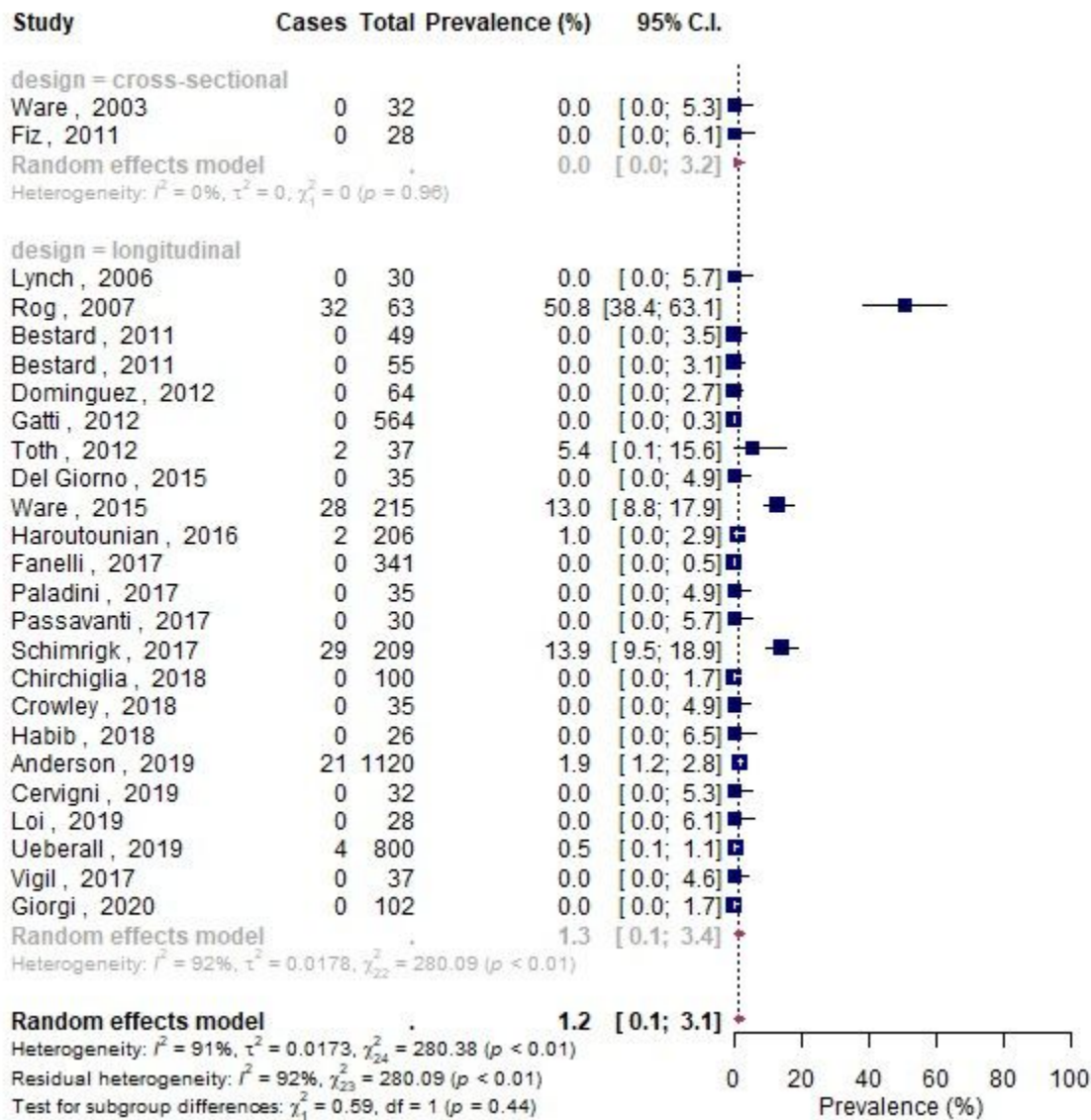
Appendix 11: Results for adverse events leading to discontinuation (subgroup by cannabis)



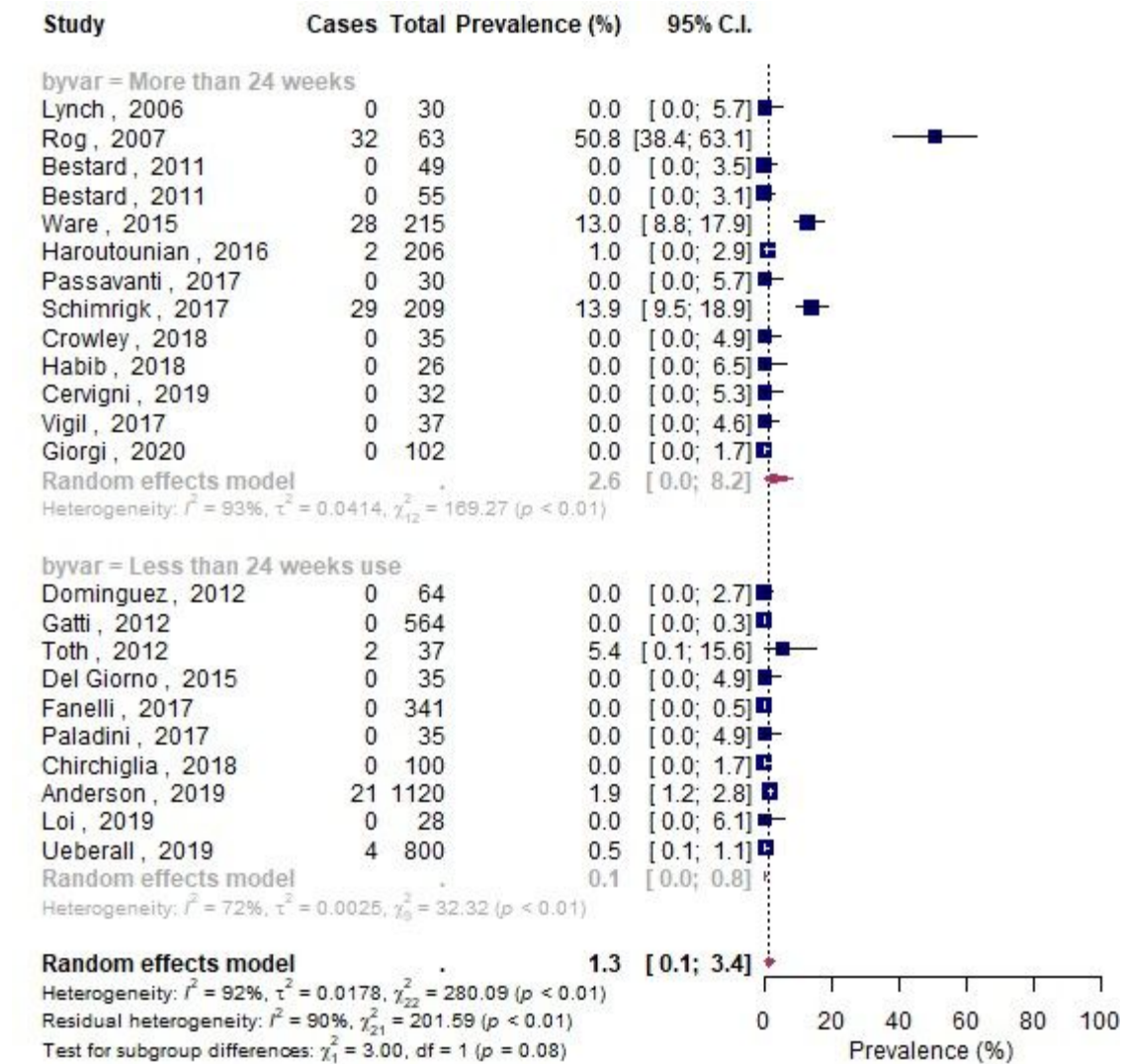
Appendix 12: Results for adverse events leading to discontinuation (subgroup by selection bias)



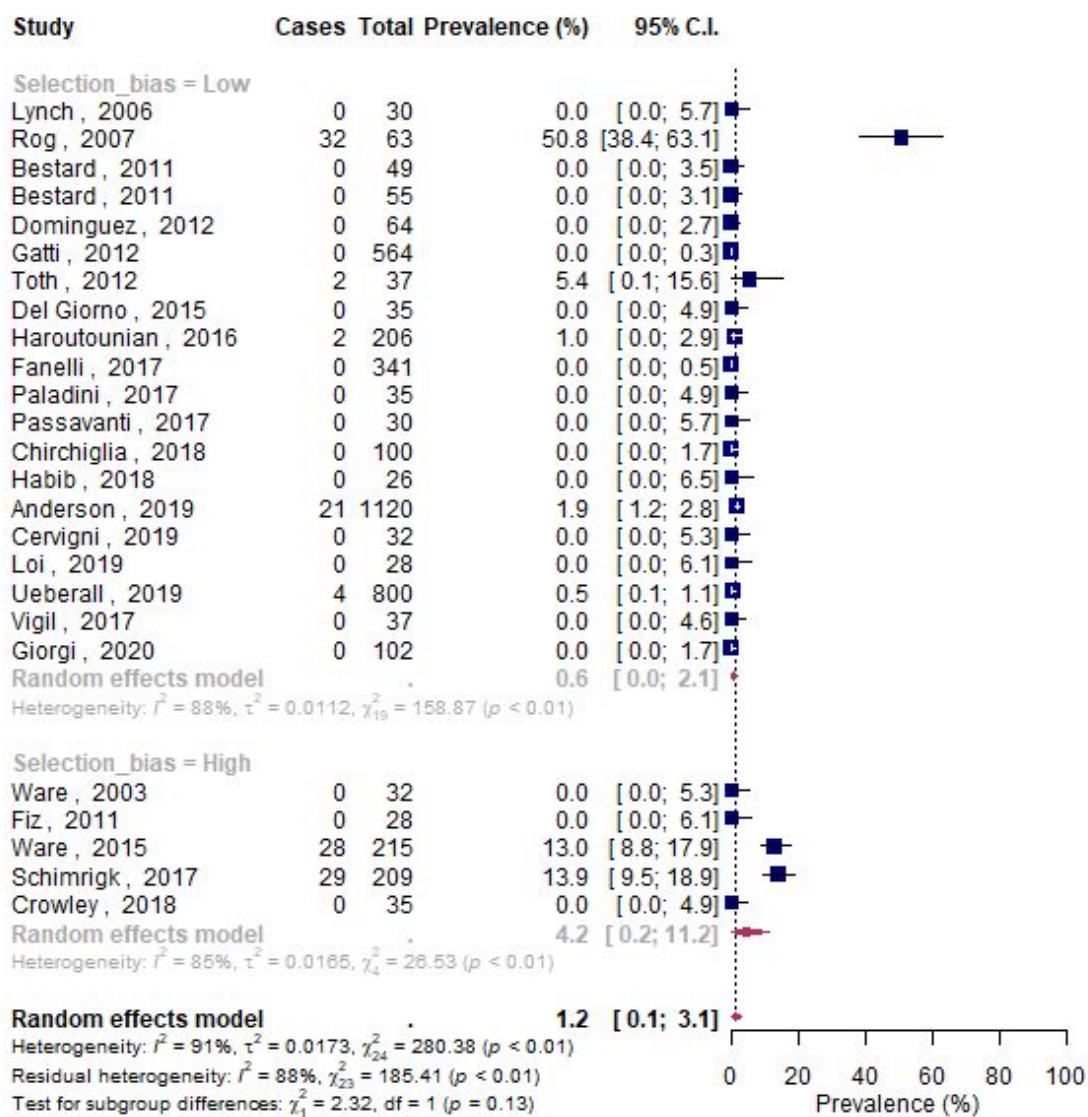
Appendix 13: Results for serious adverse events (subgroup by design)



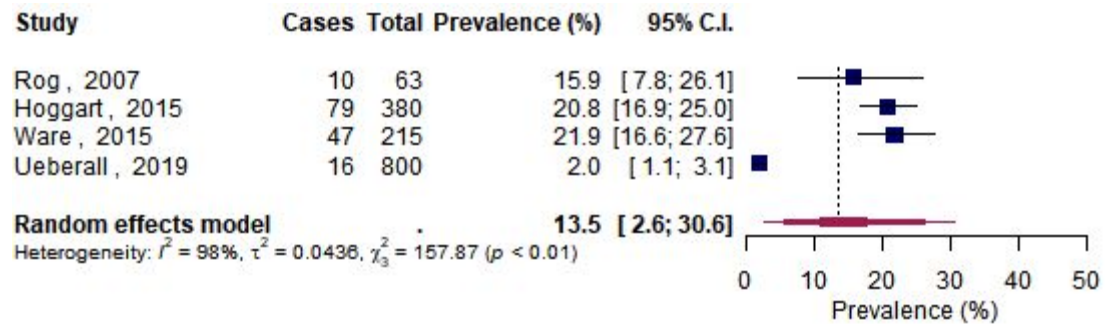
Appendix 14: Results for serious adverse events (subgroup by duration)



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

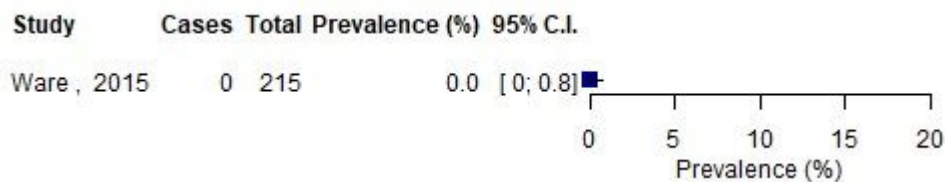


Appendix 16: Results for psychiatric adverse events



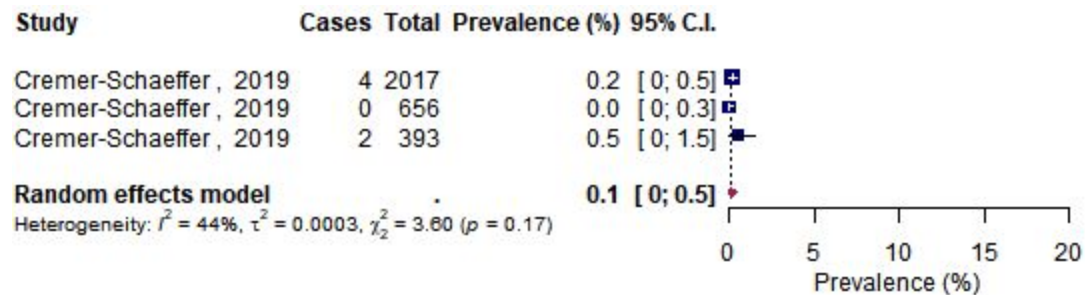
Or peer review only

Appendix 17: Results for suicide



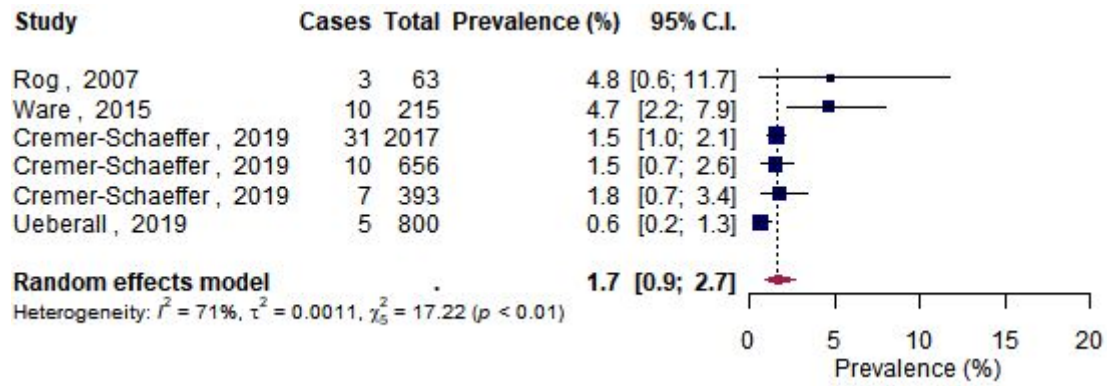
For peer review only

Appendix 18: Results for suicidal thoughts



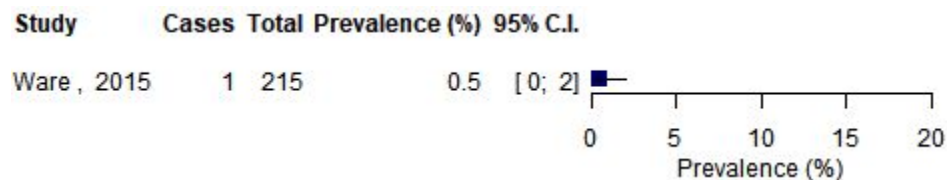
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Appendix 19: Results for depression



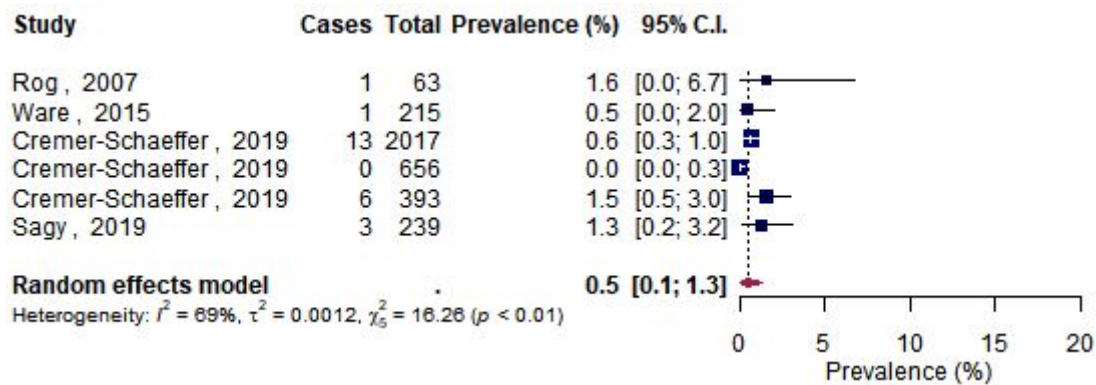
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Appendix 20: Results for mania



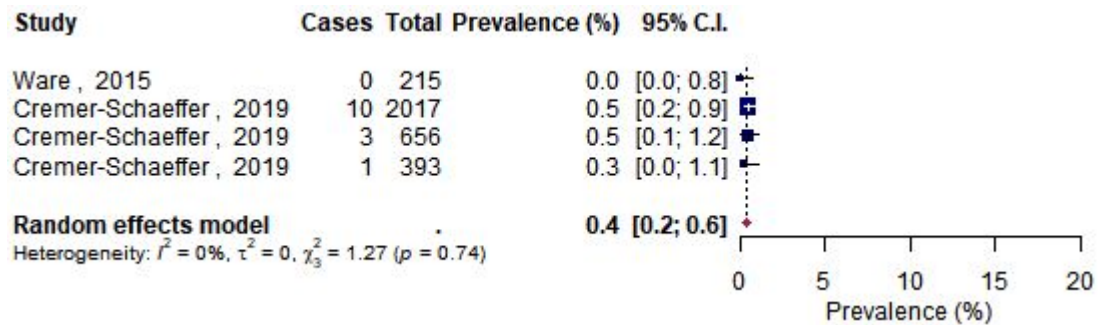
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Appendix 21: Results for hallucinations



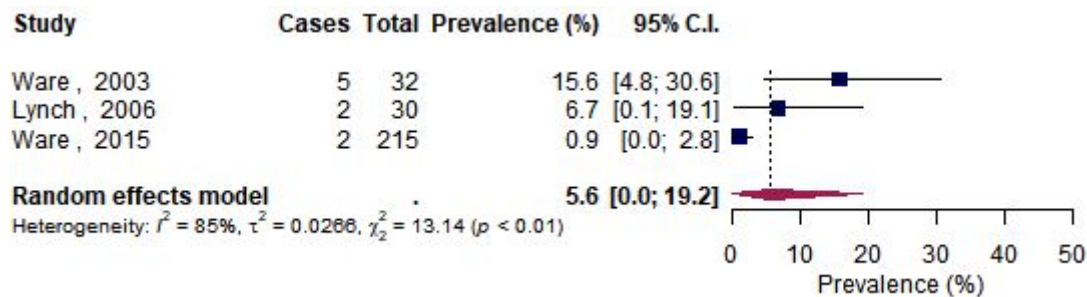
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Appendix 22: Results for delusions



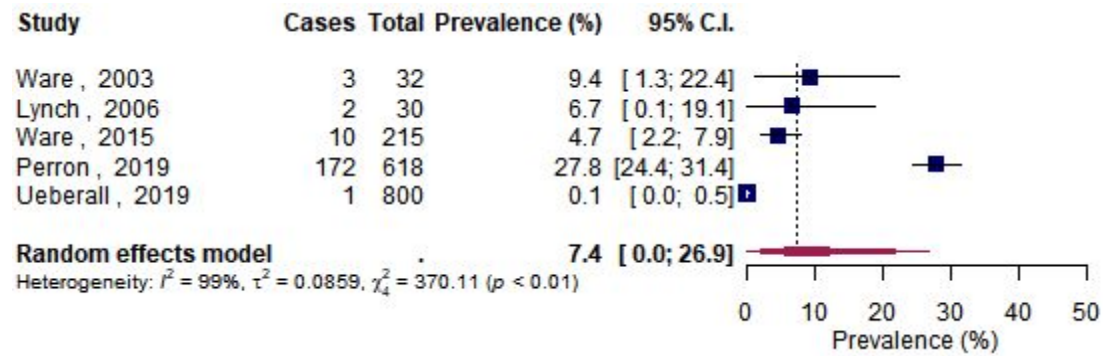
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Appendix 23: Results for paranoia



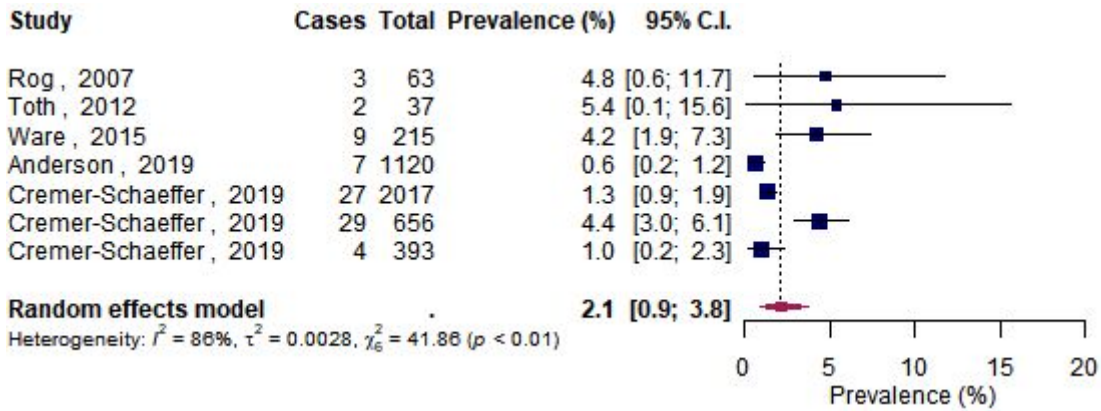
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Appendix 24: Results for anxiety



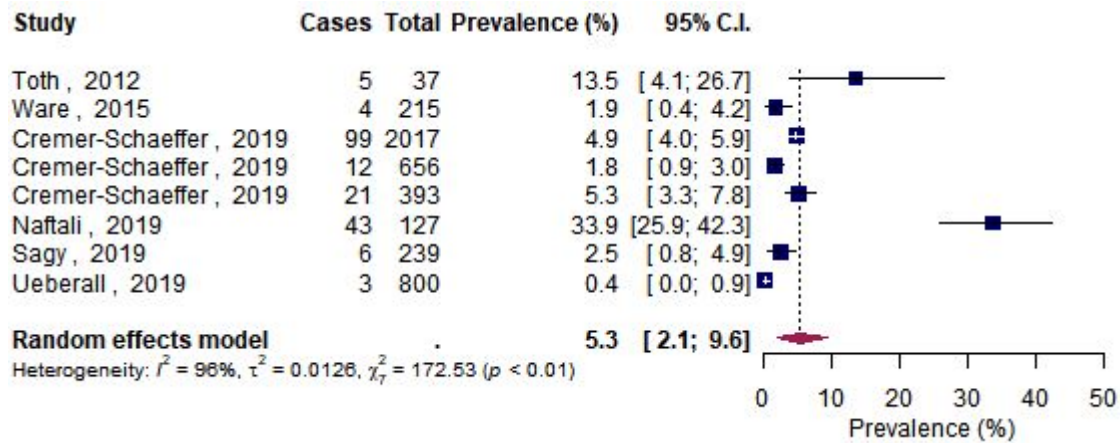
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Appendix 25: Results for euphoria



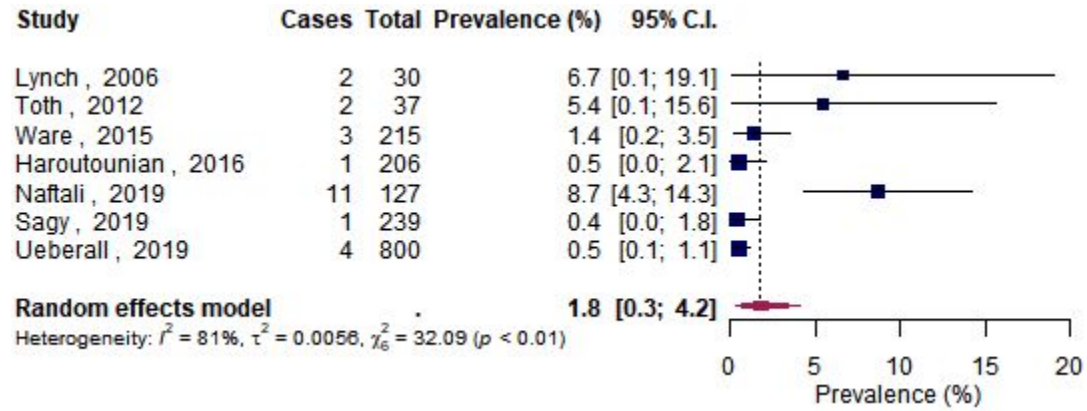
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Appendix 26: Results for memory impairment



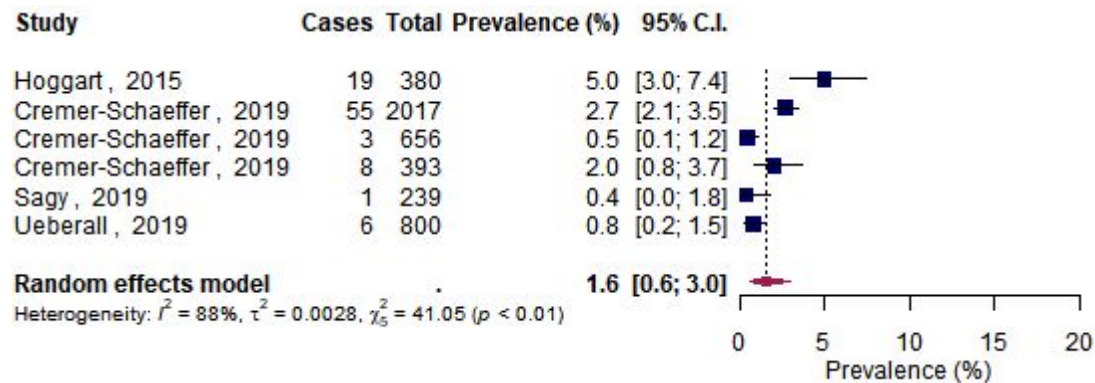
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Appendix 27: Results for confusion

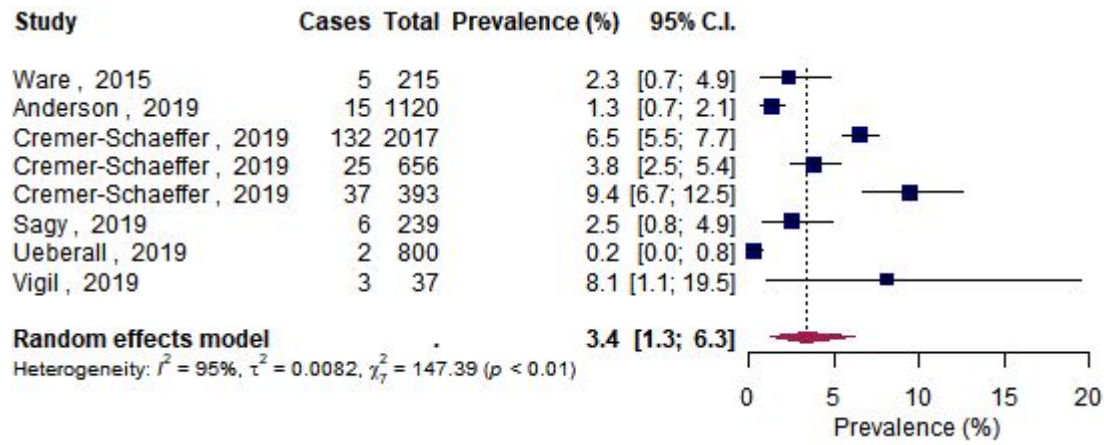


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Appendix 28: Results for disorientation

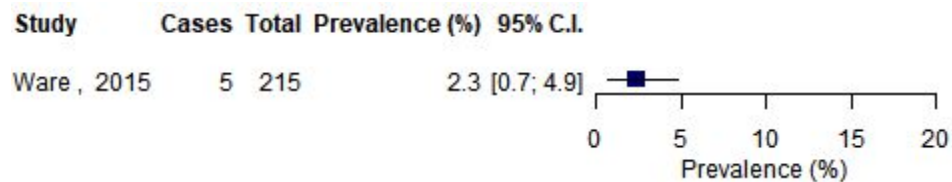


Appendix 29: Results for impaired attention



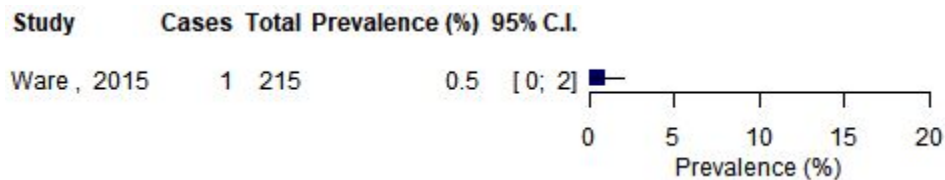
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Appendix 30: Results for falls



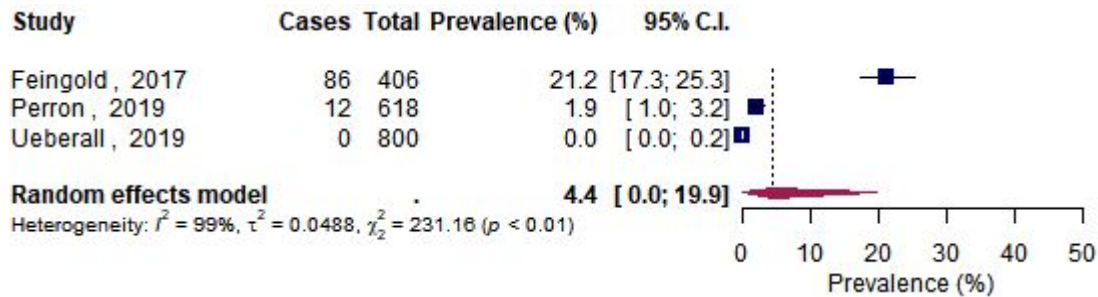
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Appendix 31: Results for motor vehicle accidents



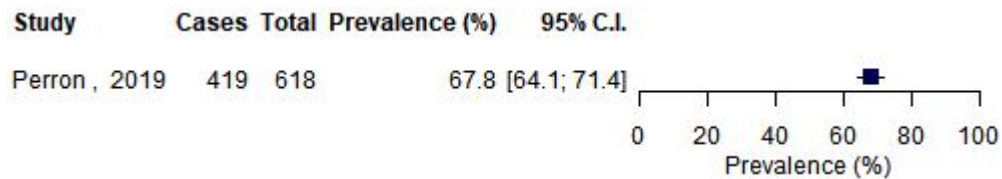
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Appendix 32: Results for dependence



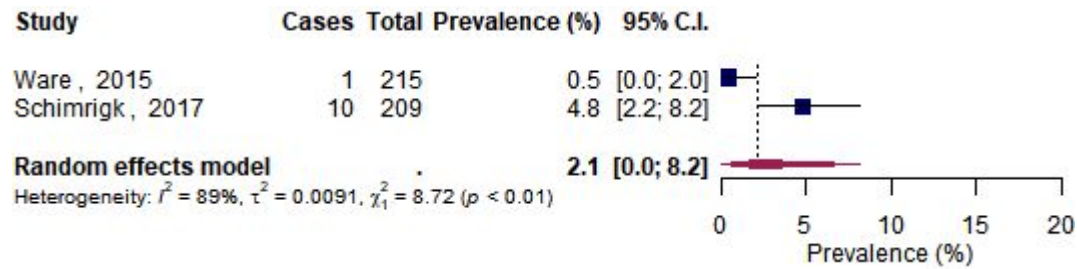
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Appendix 33: Results for withdrawal symptoms



For peer review only

Appendix 34: Results for withdrawal syndrome



For peer review only

Section/top ic (page no)	Item	PRISMA checklist item	PRISMA harms (minimum)	Recommendations for reporting harms in systematic reviews (desirable)	Check if done
Title Title (3)	1	Identify the report as a systematic review, meta-analysis, or both.	Specifically mention “harms” or other related terms, or the harm of interest in the review.	—	X
Abstract Structured summary (4)	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	—	Abstracts should report any analysis of harms undertaken in the review, if harms are a primary or secondary outcome.	X
Introduction Rationale (5)	3	Describe the rationale for the review in the context of what is already known.	—	It should clearly describe in introduction or in methods section which events are considered harms and provide a clear rationale for the specific harm(s), condition(s), and patient group(s) included in the review.	X
Objectives (5)	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	—	PICOS format should be specified, although in systematic reviews of harms the selection criteria for P, C, and O may be very broad (same intervention may have been used for heterogeneous indications in a diverse range of patients)	X
Methods Protocol and registration (6)	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	—	No specific additional information is required for systematic reviews of harms.	X
Eligibility Criteria (6)	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	—	Report how handled relevant studies (based on population and intervention) when the outcomes of interest were not reported. Report choices for specific study designs and length of follow-up.	X
Information Sources (7)	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	—	Report if only searched for published data, or also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If includes unpublished data, provide the source and the process of obtaining it.	X
Search (7)	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	—	If additional searches were used specifically to identify adverse events, authors should present the full search process so it can be replicated.	X

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3	Study	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	—	If only included studies reporting on adverse events of interest, defined if screening was based on adverse event reporting in title/abstract or full text. If no harms reported in the text, report if any attempt was made to retrieve relevant data from authors.	X
4	Selection (8)					
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10	Data	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	—	No specific additional information is required for systematic reviews of harms.	X
11	collection					
12	process (9)					
13						
14	Data	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	—	Report the definition of the harm and seriousness used by each included study (if applicable). Report if multiple events occurred in the same individuals, if this information is available. Consider if the harm may be related to factors associated with participants (eg, age, sex, use of medications) or provider (eg, years of practice, level of training). Specify if information was extracted and how it was used in subsequent results. Specify if extracted details regarding the specific methods used to capture harms (active/passive and timing of adverse event).	X
15	items (9)					
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29	Risk of bias in	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	—	The risk of bias assessment should be considered separately for outcomes of benefit and harms.	X
30	individual					
31	studies (10)					
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35	Summary	13	State the principal summary measures (eg, risk ratio, difference in means).	—	No specific additional information is required for systematic reviews of harms.	X
36	measures (11)					
37						
38	Synthesis of	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	Specify how zero events were handled, if relevant.		
39	results (11)					
40						
41	Risk of bias	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	—	Present the extent of missing information (studies without harms outcomes), any factors that may account for their absence, and whether these reasons may be related to the results.	X
42	across studies					
43	(11)					
44						
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46	Additional	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	—	Sensitivity analyses may be affected by different definitions, grading, and attribution of adverse events, as adverse events are typically infrequent or reported using heterogeneous classifications. Report the number of participants and studies included in each subgroup.	X
47	analyses (12)					
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52	Results					
53	Study	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each	—	If a review addresses both efficacy and harms, display a flow diagram specific for each (efficacy and harm).	X
54	selection (13)					
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3		stage, ideally with a flow diagram.			
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6	Study characteristics (14)	18 For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Define each harm addressed, how it was ascertained (eg, patient report, active search), and over what time period.	Add additional characteristics to: “P” (population) patient risk factors that were considered as possibly affecting the risk of the harm outcome. “I” (intervention) professional expertise/skills if relevant (for example if the intervention is a procedure). “T” (time) timing of all harms assessments and the length of follow-up.	X
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13	Risk of bias within studies (15)	19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	—	Consider the possible sources of biases that could affect the specific harm under consideration within the review. Sample selection, dropouts and measurement of adverse events should be evaluated separately from the outcomes of benefit as described in item 12, above.	X
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20	Results of individual studies (16)	20 For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	—	Report the actual numbers of adverse events in each study, separately for each intervention.	X
21	Synthesis of results (17)	21 Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Describe any assessment of possible causality.	If included data from unpublished sources, report clearly the data source and the impact of these studies to the final systematic review.	X
22	Risk of bias across studies (18)	22 Present results of any assessment of risk of bias across studies (see item 15).	—	No specific additional information is required for systematic reviews of harms. See item 15 above.	X
23	Additional analysis (18)	23 Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression (see item 16)).	—	No specific additional information is required for systematic reviews of harms.	X
24	Discussion				
25	Summary of evidence (18)	24 Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	—	No specific additional information is required for systematic reviews of harms.	X
26	Limitations (18)	25 Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	—	Recognise possible limitations of meta-analysis for rare adverse events (ie, quality and quantity of data), issues noted previously related to collection and reporting.	X
27	Conclusions (18)	26 Provide a general interpretation of the results in the context of other evidence, and implications for future research.	—	State conclusions in coherence with the review findings. When adverse events were not identified we caution against the conclusion that the intervention is “safe,” when, in reality, its safety remains unknown.	X
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51	Funding (19)	27 Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	—	No specific additional information is required for systematic reviews of harms.	X
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054282.R1
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3 **1 Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A**
4
5 **2 systematic review of non-randomized studies**
6
7

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3 51 **Running head:** Harms of medical cannabis
4

5 52
6 53 **Abbreviations:** Cochrane Central Register of Controlled Trials (CENTRAL), Palmitoylethanolamide (PEA),
7 tetrahydrocannabinol (THC)
8
9

10 55
11 56 **Keywords:** Medical cannabis, chronic pain, adverse events, harms, non-randomized studies,
12 observational, systematic review, meta-analysis
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15 58
16 59 **Competing Interests:** There are no competing interests for any author
17
18

19 60
20 61 **Funding:** DZ is supported by a Banting Postdoctoral Fellowship.
21
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23 63 **Ethics approval:** The systematic review is exempt from ethics approval.
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25

26 65 **Data:** Data are available in a public, open access repository: <https://osf.io/ut36z/>
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29 66
30 67 **Acknowledgements:** We thank the members of the Rapid Recommendations panel for critical feedback
31 on the selection of the adverse events of interest. We thank James MacKillop, PhD, for his guidance
32 regarding the interpretation of problematic cannabis use, abuse, dependence and withdrawal syndrome
33 within studies included in our review.
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36 71
37 72 **Data Sharing:** Data on all other adverse events not included in our review, but reported in primary studies,
38 are available in an open-access database (<https://osf.io/ut36z/>).
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41 74
42 75 **Authors' Contributions:** JWB and TA conceived the idea. RC designed and conducted the search. DZ, MAC,
43 AA, RWMV, GL, KL, JED, MMA, BYH, CH, and PJH screened search records, extracted data, and assessed
44 the risk of bias of the eligible studies. DZ conducted all analyses. DZ, JWB, and TA interpreted the data. DZ
45 wrote the first draft of the manuscript. JWB and TA critically revised the manuscript. All authors reviewed
46 and approved the final version. DZ and JWB are the guarantors.
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1
2
3 **88 Abstract**
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5
6 **89 Objective:** To establish the prevalence of long-term and serious harms of medical cannabis for chronic
7
8 **90 pain.**

9
10 **91 Design:** Systematic review and meta-analysis.
11

12
13 **92 Data sources:** MEDLINE, EMBASE, PsycInfo, and CENTRAL from inception to April 1, 2020.
14

15
16 **93 Study selection:** Non-randomized studies reporting on harms of medical cannabis or cannabinoids in
17
18 **94 adults or children living with chronic pain with ≥ 4 weeks of follow-up.**

19
20 **95 Data extraction and synthesis:** A parallel guideline panel provided input on the design and interpretation
21
22 **96 of the systematic review, including selection of adverse events for consideration. Two reviewers, working**
23
24 **97 independently and in duplicate, screened the search results, extracted data, and assessed risk of bias. We**
25
26 **98 used random-effects models for all meta-analyses and the GRADE approach to evaluate the certainty of**
27
28 **99 evidence.**

29
30 **100 Results:** We identified 39 eligible studies that enrolled 12,143 adult patients with chronic pain. Very low
31
32 **101 certainty evidence suggests that adverse events are common (prevalence: 26.0%; 95% CI 13.2 to 41.2)**
33
34 **102 among users of medical cannabis for chronic pain, particularly any psychiatric adverse events (prevalence:**
35
36 **103 13.5%; 95% CI 2.6 to 30.6). Very low certainty evidence, however, indicates serious adverse events,**
37
38 **104 adverse events leading to discontinuation, cognitive adverse events, accidents and injuries, and**
39
40 **105 dependence and withdrawal syndrome are less common and each typically occur in fewer than one in 20**
41
42 **106 patients. We compared studies with < 24 weeks and ≥ 24 weeks of cannabis use and found more adverse**
43
44 **107 events reported among studies with longer follow-up (test for interaction $p < 0.01$).**
45
46 **108 Palmitoylethanolamide was usually associated with few to no adverse events. We found insufficient**
47
48 **109 evidence addressing the harms of medical cannabis compared to other pain management options, such**
49
50 **110 as opioids.**

51
52 **111 Conclusions:** There is very low certainty evidence that adverse events are common among people living
53
54 **112 with chronic pain who use medical cannabis or cannabinoids, but that few patients experience serious**
55
56 **113 adverse events.**

57
58 **114 Systematic review registration** <https://osf.io/25bxf>
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3 115 ***Strengths and limitations of this study***
4

- 5 116 • Strengths of this systematic review include a comprehensive search for non-randomized studies,
6 117 explicit eligibility criteria, screening of studies and collection of data in duplicate to increase
7 118 reliability, and use of the GRADE approach to evaluate the certainty of evidence.
8
9 119 • Our review is limited by the non-comparative design of most studies, which precludes confident
10 120 inferences regarding the proportion of adverse events that can be attributed to medical cannabis or
11 121 cannabinoids.
12
13 122 • A third of studies were at high risk of selection bias, primarily because they included prevalent
14 123 cannabis users. In such studies, the prevalence of adverse events may be underestimated.
15
16 124 • Our review provides limited evidence on the harms of prolonged medical cannabis use since most
17 125 studies reported adverse events for less than one year of follow-up.
18
19 126 • Some studies reported on smoked or vaporized medical cannabis, which may be associated with
20 127 different adverse events (e.g. respiratory) than oral or topical formulations. We performed
21 128 subgroup analyses based on the type of medical cannabis, but our findings were of low credibility
22 129 due to inconsistency and/or imprecision.
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131 Background

132 Chronic pain is the primary cause of health care resource use and disability among working adults in North
133 America and Western Europe.^{1 2} The use of cannabis for the management of chronic pain is becoming
134 increasingly common due to pressure to reduce opioid use, increased availability and changing legislation,
135 shift in public attitudes and decreased stigma, and aggressive marketing.^{3 4} The two most-studied
136 cannabinoids in medical cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).⁵ THC
137 binds to cannabinoid receptors type 1 and 2, is an analog to the endogenous cannabinoid, anandamide,
138 and has shown psychoactive, analgesic, anti-inflammatory, antioxidant, antipruritic, anti-spasmodic, and
139 muscle-relaxant activities. CBD directly interacts with various ion channels to produce analgesic, anti-
140 inflammatory, anti-convulsant and anxiolytic activities, without the psychoactive effects of THC.⁵ Use of
141 cannabis for therapeutic purposes, however, remains contentious due to the social and legal context and
142 its known and suspected harms.⁶⁻⁹

143 Though common adverse events caused by medical cannabis, including nausea, vomiting, headache,
144 drowsiness, and dizziness, have been well documented in randomized controlled trials and reviews of
145 randomized controlled trials,^{10 11} less is known about potentially uncommon but serious adverse events,
146 particularly events that may occur with longer durations of medical cannabis use, such as dependence,
147 withdrawal symptoms, and psychosis.^{4 12-17} Such adverse events are usually observed in large non-
148 randomized studies that recruit larger numbers of patients and typically follow them for longer durations
149 of time. Further, evidence from non-randomized studies may be more generalizable, since randomized
150 controlled trials often use strict eligibility criteria.

151 The objective of this systematic review and meta-analysis is to summarize the evidence on the risks and,
152 when evidence on risk is not available, the prevalence of adverse events related to medical cannabis and
153 cannabinoids from non-randomized studies for a *BMJ Rapid Recommendation* addressing medical
154 cannabis for chronic pain.¹⁸ This evidence synthesis is part of the *BMJ Rapid Recommendations* project, a
155 collaborative effort from the *MAGIC Evidence Ecosystem Foundation* (www.magicevidence.org) and the
156 *BMJ*.¹⁹ A guideline panel helped define the study question and selected adverse events for review. The
157 adverse events of interest include psychiatric and cognitive adverse events, injuries and accidents, and
158 dependence and withdrawal. It is one of four systematic reviews that together informed a parallel
159 guideline.^{11 18 20 21} A parallel systematic review addressed evidence from randomized trials.¹¹

160

161 **Methods**

162 We report our systematic review in accordance with the PRISMA Harms Checklist.²² We registered the
163 protocol for our review at OSF (<https://osf.io/25bxf>) and followed this protocol unless otherwise reported
164 in this manuscript.²²

165 ***Guideline panel involvement***

166 A guideline panel helped define the study question and selected the adverse events for review. The panel
167 included nine content experts (two general internists, two family physicians, a pediatrician, a physiatrist,
168 a pediatric anesthesiologist, a clinical pharmacologist, and a rheumatologist), nine methodologists (five of
169 whom are also front-line clinicians), and three people living with chronic pain (one of whom used
170 cannabinoids for medical purposes).

171 ***Patient and public involvement***

172 Three patient partners (two women and one man) were included as part of the guideline panel and
173 contributed to the selection and prioritization of outcomes, protocol, and interpretation of review
174 findings, and provided insight on values and preferences. Each of our patient partners was living with
175 chronic pain and were selected to represent a range of experiences regarding medical cannabis. One had
176 tried and discontinued medical cannabis due to lack of efficacy. One had found success with use of medical
177 cannabis (primarily oral CBD). The third had no personal experience with medical cannabis.

178 ***Search***

179 A medical librarian searched MEDLINE, EMBASE, PsychInfo, and Cochrane Central Register of Controlled
180 Trials (CENTRAL) from inception to April 1, 2020, with no restrictions on language, for non-randomized
181 studies reporting on harms or adverse events of medical cannabis or cannabinoids for chronic pain
182 (Supplement Appendix 1). We scanned reference lists of relevant reviews to identify any eligible studies
183 not retrieved by our electronic search and solicited content experts from our panel for unpublished
184 studies. Search records, and later full-texts of studies, not reported in English were translated by a native
185 speaker of the language.

186 ***Study selection***

187 Reviewers (DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CJH, PJH), working independently and in
188 duplicate, reviewed titles and abstracts of search records and subsequently full texts of records found

189 potentially eligible at the title and abstract screening stage. Reviewers resolved disagreements by
190 discussion or by adjudication by a third reviewer (DZ).

191 We included all non-randomized studies that reported on any patient-important harm or adverse event
192 associated with the use of any formulation of medical cannabis or cannabinoids in adults or children, living
193 with chronic pain (pain lasting for ≥ 3 months) or a medical condition associated with chronic pain (i.e.,
194 fibromyalgia, arthritis, multiple sclerosis, neuropathy, inflammatory bowel disease, stroke, or advanced
195 cancer) or that compared adverse events associated with medical cannabis or cannabinoids with another
196 pharmacologic or non-pharmacologic intervention. We considered herbal cannabis consumed for medical
197 reasons as medical cannabis. Based on input from the guideline panel, we excluded studies in which
198 patients used cannabis for less than 4 weeks because we anticipated that four weeks would be the
199 minimum amount of time after which we would reasonably expect to observe potential serious or long
200 term harms associated with medical cannabis.²³ We looked for explicit statements or evidence that
201 patients were experiencing chronic pain. We excluded studies in which: (1) fewer than 25 patients used
202 medical cannabis or cannabinoids (to exclude studies that would not appreciably contribute to pooled
203 estimates and studies that may be too small to reliably estimate the prevalence of adverse events), (2)
204 patients did not suffer from chronic pain or a condition commonly associated with chronic pain or more
205 than 20% of patients reported using medical cannabis or cannabinoids for a condition other than chronic
206 pain (to exclude studies in which patients did not predominantly suffer from chronic pain), (3) patients
207 were using cannabis for recreational reasons, (4) only surrogate measures of patient-important harms
208 and adverse effects (e.g., performance on cognitive tests, lab values) were reported, and (5) systematic
209 reviews and other types of studies that did not provide primary data.

210 ***Data extraction and risk of bias***

211 Reviewers (DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CJH, PJH), working independently and in
212 duplicate and using a standardized and pilot-tested data collection form, extracted the following
213 information from each eligible study: (1) study design, (2) patient characteristics (age, sex,
214 condition/diagnosis), (3) characteristics of medical cannabis or cannabinoids (name of product, dose, and
215 duration), and (4) number of patients that experienced adverse events, including all adverse events,
216 serious adverse events, and withdrawal due to adverse events. Reviewers resolved disagreements by
217 discussion or by adjudication with a third party (DZ). We classified adverse events as serious based on the
218 classification used in primary studies. For comparative studies, we collected results from models adjusted

219 for confounders, when reported, and unadjusted models when results for adjusted models were not
220 reported.

221 When studies reported the number of events rather than the number of patients experiencing adverse
222 events, we only extracted the number of events if they were infrequent (the number of events accounted
223 for less than 10% of the total number of study participants). For studies that reported on adverse events
224 at multiple timepoints, we extracted data for the longest point of follow-up that included, at minimum,
225 80% of the patients recruited into the study. Reviewers resolved disagreements by discussion or by
226 adjudication with a third reviewer (DZ).

227 Reviewers (DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CJH, PJH), working independently and in
228 duplicate, used the Cochrane-endorsed ROBINS-I tool to rate the risk of bias of studies as low, moderate,
229 serious, or critical across seven domains: (1) bias due to confounding, (2) selection of patients into the
230 study, (3) classification of the intervention, (4) bias due to deviations from the intended intervention, (5)
231 missing data, (6) measurement of outcomes, and (7) selection of reported results.²⁴ Reviewers resolved
232 discrepancies by discussion or by adjudication by a third party (DZ). Supplement Appendix 2 presents
233 additional details on the assessment of risk of bias. Studies were considered to adequately adjust for
234 confounders if they adjusted, at minimum, for pain intensity, concomitant pain medication, disability
235 status, alcohol use, and past cannabis use. Studies were rated at low risk of bias overall when all domains
236 were at low risk of bias; moderate risk of bias if all domains were rated at low or moderate risk of bias; at
237 serious risk of bias when all domains were rated either at low, moderate, or serious risk of bias; and at
238 critical risk of bias when one or more domains were rated as critical.

239 ***Data synthesis***

240 In this review, we synthesized data on serious adverse events and adverse events that may emerge with
241 longer duration of medical cannabis use. Identified by a parallel BMJ Rapid Recommendations guideline
242 panel as important, these patient-important outcomes included psychiatric and cognitive adverse events,
243 injuries and accidents, and dependence and withdrawal. Data on all other adverse events reported in
244 primary studies are available in an open-access database (<https://osf.io/ut36z/>).²⁵ We classified adverse
245 events as serious based on the classification used in primary studies.

246 Adverse events are reported as binary outcomes. For comparative studies, when possible, we present risk
247 differences and associated 95% confidence intervals (95% CIs). Since there were only two eligible

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3 248 comparative studies, each with different comparators, we did not perform meta-analysis. For single-arm
4
5 249 studies, we pooled the proportion of patients experiencing adverse events of interest by first applying a
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7 250 Freeman-Tukey type arcsine square root transformation to stabilize the variance. Without this
8
9 251 transformation, very high or very low prevalence estimates can produce confidence intervals that contain
10
11 252 values lower than 0% or higher than 100%. All meta-analyses used DerSimonian-Laird random-effects
12
13 253 models, which are conservative as they consider both within- and between-study variability.²⁶⁻²⁸ We also
14
15 254 pooled all effect estimates using fixed-effects models as a sensitivity analysis. We evaluated heterogeneity
16
17 255 for all pooled estimates through visual inspection of forest plots and calculation of tau-squared (τ^2),
18
19 256 because some statistical tests of heterogeneity (I^2 and Cochrane's Q) can be misleading when sample sizes
20
21 257 are large and CIs are therefore narrow.²⁹ Higher values of τ^2 , I^2 , and Cochrane's Q indicate higher statistical
22
23 258 heterogeneity. For studies that reported estimates for all-cause adverse events and those deemed to be
24
25 259 potentially related to cannabis use, we preferentially synthesized results for all adverse events.

26
27 260 For analyses for which we observed high clinical heterogeneity (i.e., substantial differences in the
28
29 261 estimates of individual studies and minimal overlap in the confidence intervals), we presented results
30
31 262 narratively.

32
33 263 In consultation with the parallel BMJ Rapid Recommendations guideline panel, we also prespecified six
34
35 264 subgroup hypotheses to explain heterogeneity between studies: (1) study design (longitudinal vs. cross-
36
37 265 sectional), (2) type of medical cannabis, (3) cancer vs. non-cancer pain, (4) children vs. adults, (5) duration
38
39 266 of medical cannabis use (shorter or longer than the median duration of follow-up across studies), and (6)
40
41 267 risk of bias (low/moderate vs. serious/critical). We also performed two post-hoc subgroup analyses: (1)
42
43 268 duration of follow-up (shorter or longer than the median duration of follow-up across studies) and (2)
44
45 269 selection bias (studies at moderate, serious, or critical risk of selection bias vs. studies at low risk of
46
47 270 selection bias). We anticipated that studies reporting on shorter use of medical cannabis, as well as cross-
48
49 271 sectional studies, studies on cancer patients, studies including adults, studies with active comparators,
50
51 272 studies at high risk of bias would report fewer adverse events. We anticipated that studies at moderate,
52
53 273 serious, or critical risk of selection bias that included prevalent cannabis users (i.e., people who were using
54
55 274 medical cannabis before the inception of the study) or were preceded by a run-in period or clinical trial
56
57 275 during which patients that experienced adverse events or found medical cannabis intolerable could
58
59 276 discontinue would report fewer adverse events because prevalent of medical cannabis are likely to
60
277 represent populations that have self-selected for tolerance to cannabis. We performed tests for

278 interaction to establish whether subgroups differed significantly from one another. We assessed the
279 credibility of significant subgroup effects (test for interaction $p < .05$) using published criteria.^{30 31}

280 We performed all analyses using the 'meta' package in R (version 3.5.1, R Foundation for Statistical
281 Computing).³²

282 ***Certainty of evidence***

283 We used the GRADE approach to rate the certainty of evidence.^{33 34} Based on GRADE guidance for using
284 the ROBINS-I tool, evidence starts at high certainty and is downgraded by one level when the majority of
285 the evidence comes from studies at moderate risk of bias, two levels when the majority of the evidence
286 comes from studies at high risk of bias, and three levels when the majority of the evidence comes from
287 studies rated at critical risk of bias.³³ We additionally considered potential limitations due to indirectness
288 if the population, intervention, or adverse events assessed in studies did not reflect the populations,
289 interventions, or adverse events of interest, inconsistency if there was important unexplained differences
290 in the results of studies, and imprecision if the upper and lower bounds of confidence intervals indicated
291 appreciably different rates of adverse events. For assessing inconsistency and imprecision for the outcome
292 all adverse events, based on feedback from the guideline panel, we deemed a 20% difference in the
293 prevalence of all adverse evidence to be patient-important; a 10% difference for adverse events leading
294 to discontinuation, serious adverse events, and psychiatric, cognitive, withdrawal and dependence,
295 injuries; and a 3% difference for potentially fatal adverse events, such as suicides and motor vehicle
296 accidents. We followed GRADE guidance for communicating our findings.³⁵ Guideline panel members
297 interpreted the magnitude of adverse events and decided whether the observed prevalence of adverse
298 events was sufficient to affect patients' decisions to use medical cannabis or cannabinoids for chronic pain.

299 **Results**

300 ***Study selection***

301 Our search yielded 17,178 unique records of which 434 were reviewed in full. We excluded more than
302 half of references because they did not describe a non-randomized study, a quarter because they did not
303 include patients with chronic pain, and a small minority because they did not report on adverse events.
304 Of these records, 39 non-randomized studies were eligible for review (Supplement Appendix 3).³⁶⁻⁷⁴ Figure
305 1 presents additional details related to study selection. Supplement Appendix 4 presents studies excluded
306 at the full-text screening stage and accompanying reasons for exclusion.

307 **Description of studies**

308 One study was published in German and the remainder in English. Studies included 12,143 adults living
309 with chronic pain and included a median of 100 (IQR 34 to 361) participants (Table 1). Most studies (30/39;
310 76.9%) were longitudinal in design. Eighteen studies (46.2%) were conducted in Western Europe, fourteen
311 (35.9%) in North America, six (15.4%) in Israel, and two (5.1%) in the United Kingdom. Ten studies (25.6%)
312 were funded by industry alone or industry in combination with government and institutional funds; the
313 remainder were funded either by governments, institutions, or not-for-profit organizations (n=9; 23.1%),
314 did not receive funds (n=3; 7.7%), or did not report funding information (n=17; 43.6%).

315 Thirty studies (76.9%) reported on people living with chronic non-cancer pain, eight (n=20.5%) with mixed
316 cancer and non-cancer chronic pain, and one (2.6%) with chronic cancer pain. All studies reported on
317 adults. Sixteen studies reported on mixed types of herbal cannabis (e.g., buds for smoking, vaporizing, and
318 ingesting, hashish, oils, extracts, edibles), nine on palmitoylethanolamide (PEA), four each on nabiximols
319 and dronabinol, two on nabilone, one each on Trokie lozenges and extracts, and four did not report the
320 type of medical cannabis used. Herbal cannabis, lozenges, extracts, and nabiximols are mixed CBD and
321 THC products whereas nabilone and dronabinol only contain THC. One study reported on three types of
322 medical cannabis (dronabinol, nabiximols, and mixed herbal) separately. The median duration of medical
323 cannabis use was 24 weeks (IQR 12.0 to 33.8 weeks). Two studies were comparative: one study compared
324 nabilone with gabapentin and another compared herbal cannabis with standard care.^{40,49} Studies reported
325 a total of 525 unique adverse events.

326 **Risk of bias**

327 Supplement Appendix 5 presents the risk of bias of included studies. We rated all results at critical risk of
328 bias except for the comparative results from two studies,^{40,49} which were rated at serious and moderate
329 risk of bias. The primary limitation across studies was inadequate control for potential confounding either
330 due to the absence of a control group or inadequate adjustment for confounders. A third of studies were
331 rated at serious risk of bias for selection bias, primarily because they included prevalent users of medical
332 cannabis. Such studies may underestimate the incidence of adverse events since patients that experience
333 adverse events are more likely to discontinue medical cannabis early. Such studies may also include
334 adverse events that may have been present at inception and that are unrelated to medical cannabis use.

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3 335 **All adverse events**
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5 336 Twenty longitudinal and two cross-sectional studies, including 4,108 patients, reported the number of
6 337 patients experiencing one or more adverse events.^{37-44 47 48 55 57-61 63 65 66 70 71 74} Seven studies reported on
8 338 PEA, five on mixed herbal cannabis, three each on nabilone and nabiximols, two on dronabinol, and one
9 339 each on extracts and Trokie lozenges. The median duration of medical cannabis use was 24 weeks [IQR 12
10 340 to 32]. We observed substantial unexplained heterogeneity and so summarize the results descriptively
11 341 (Table 2; Supplement Appendices 6 to 9). The prevalence of any adverse event ranged between 0% to
12 342 92.1%. Studies with less than 24 weeks of cannabis use (the median duration of cannabis) typically
13 343 reported fewer adverse events than those with more than 24 weeks. Patients using PEA experienced no
14 344 adverse events. The evidence was overall very uncertain due to risk of bias and inconsistency.

15 345 One study suggested that nabilone may reduce the risk of adverse events compared to gabapentin (-
16 346 13.1%; 95% CI -26.2 to 0), but the certainty of evidence was very low due to risk of bias and imprecision
17 347 (Table 3).

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23 348 **Adverse events leading to discontinuation**
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28 349 Twenty longitudinal studies, including 6,509 patients, reported on the number of patients that
29 350 discontinued medical cannabis or cannabinoids due to adverse events.^{38 40 42-45 47-50 53 55 57 58 60 63 64 66 71 74}
30 351 Eight studies reported on PEA, four studies on mixed herbal cannabis, three on nabiximols, two on
31 352 nabilone, and one each on dronabinol and extracts, and one study did not report the type of medical
32 353 cannabis used by patients. The median duration of cannabis use was 24 weeks [IQR 8.6 to 32]. We
33 354 observed substantial unexplained heterogeneity and so summarize the results descriptively (Supplement
34 355 Appendices 10 to 12). The prevalence of discontinuations due to adverse events ranged between 0% to
35 356 27.0%. Studies with less than 24 weeks of cannabis use typically reported fewer discontinuations than
36 357 those with more than 24 weeks. Patients using PEA experienced no adverse events. The evidence was
37 358 overall very uncertain due to risk of bias and inconsistency.

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41 359 One study suggested herbal cannabis may increase the risk of adverse events leading to discontinuation
42 360 compared to standard care without cannabis (4.7%; 95% CI 1.8 to 7.5). Another study suggested that
43 361 nabilone may reduce the risk of adverse events leading to discontinuation compared to gabapentin (-
44 362 9.4%; 95% CI -18.5 to -0.2). The certainty of evidence was low to very low due to risk of bias and
45 363 imprecision.

364 ***Serious adverse events***

365 Twenty-two longitudinal and two cross-sectional studies, including 4,273 patients, reported on the
366 number of patients experiencing one or more serious adverse events.^{36-38 40-44 47 49 50 53 55-61 63 66 71 72 74} Eight
367 studies reported on mixed herbal cannabis, eight on PEA, two each on nabilone and nabiximols each, and
368 one study each on dronabinol, extracts, and Trokie lozenges, and one study did not report the type of
369 cannabis used. The median duration of medical cannabis or cannabinoid use was 24 weeks (IQR 12 to 32),
370 and few patients experienced serious adverse events (1.2%; 95% CI 0.1 to 3.1; $I^2=91%$) (Figure 2)
371 (Supplement Appendices 13 to 15). There was a statistically significant subgroup effect across different
372 types of medical cannabis though serious adverse events appeared consistently uncommon (low
373 credibility). The certainty of evidence was very low overall due to serious risk of bias.

374 One study suggested use of herbal cannabis may make little to no difference in the risk of serious adverse
375 events compared to standard care without cannabis (1.5%; 95% CI -8.3 to 20.2). Another study found use
376 of nabilone vs. gabapentin may make little to no difference in the risk of serious adverse events. The
377 certainty of evidence was low to very low for both studies due to risk of bias and imprecision.

378 ***Psychiatric adverse events***

379 Eleven longitudinal and two cross-sectional studies, including 6,600 patients, reported on any psychiatric
380 adverse events, including psychiatric disorders, suicide, suicidal thoughts, depression, mania,
381 hallucinations, delusions, paranoia, anxiety, and euphoria (Supplement Appendices 16 to 25).^{36-38 44 48 49 61}
382^{64 68 69 71} Five studies reported on mixed herbal cannabis, four on nabiximols, one each on dronabinol,
383 nabilone, and mixed types and one study did not specify the type of medical cannabis. The median
384 duration of cannabis use across studies was 52 weeks (IQR 20 to 52). Approximately one in seven medical
385 cannabis users experienced one or more psychiatric disorders or adverse events (13.5%; 95% CI 2.6 to
386 30.6; $I^2=98%$). The most frequently occurring psychiatric adverse events were paranoia (5.6%; 9% CI 0 to
387 19.2; $I^2=85%$) and anxiety (7.4%; 95% CI 0 to 26.9; $I^2=99%$). The certainty of evidence was very low due to
388 risk of bias, inconsistency (for psychiatric disorders and paranoia), and imprecision (for psychiatric
389 disorder, paranoia, and anxiety).

390 One study suggested that herbal cannabis may result in a trivial to moderate increase in the risk for
391 psychiatric disorders, mania, hallucinations, depression, paranoia, anxiety, and euphoria and a reduction
392 in the risk for suicides and delusions, compared with standard care without cannabis, though the certainty
393 of evidence was low to very low due to risk of bias and imprecision.

394 ***Cognitive and attentional adverse events***

395 Eleven longitudinal studies, including 6,257 patients, reported on cognitive adverse events, including
396 memory impairment, confusion, disorientation, and impaired attention (Supplement Appendices 26 to
397 29).^{36-38 44 48 49 61 64 68 69 71} Five studies reported on herbal cannabis, three on nabiximols, three on mixed
398 types of cannabis, and one each on dronabinol and nabilone. The median duration of cannabis use was
399 52 weeks (IQR 24 to 52). The prevalence of cognitive adverse events ranged from 1.6% (95% CI 0.6 to 3.0;
400 $I^2=88%$) for disorientation to 5.3% (95% CI 2.1 to 9.6; $I^2=96%$) for memory impairment. The certainty of
401 evidence was very low due to risk of bias.

402 One study suggested herbal cannabis may slightly increase the risk for memory impairment and
403 disturbances in attention compared to standard care without cannabis, but reduce the risk for confusion,
404 though the certainty of evidence was low to very low due to risk of bias and imprecision.

405 ***Accidents and injuries***

406 One longitudinal study, including 431 patients, reported on accidents and injuries in patients using mixed
407 herbal cannabis for 52 weeks (Supplement Appendices 30 & 31).⁴⁹ This study suggested herbal cannabis
408 used for medical purposes may slightly increase the risk of motor vehicle accidents (0.5%; 95% CI -0.4 to
409 1.4) but may not increase the risk of falls (0%; 95% CI -2.8 to 2.9). The certainty of evidence was low due
410 to risk of bias.

411 ***Dependence and withdrawal***

412 Four longitudinal and one cross-sectional study, including 2,248 patients, reported on dependence-
413 related adverse events, including dependence (one study reported on 'abuse' based on unspecified
414 criteria, one study reported on 'problematic use' using the Alcohol Use Disorder and Associated
415 Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition
416 [AUDADIS-IV]⁷⁵, and one study reported on 'dependence' using the Alcohol, Smoking, and Substance
417 Involvement Screening Test⁷⁶), withdrawal symptoms (defined as one or moderate or severe withdrawal
418 symptoms including sleep difficulties, anxiety, irritability, and appetite disturbance), and withdrawal
419 syndrome (two studies that used unspecified criteria) (Supplement Appendices 32 to 34).^{49 54 57 68 71} Two
420 studies reported on herbal cannabis, one each on nabiximols and nabilone, and one did not specify type
421 of medical cannabis used by patients. Follow-up ranged from 12 to 52 weeks. The pooled prevalence of
422 dependence was 4.4% (95% CI 0.0 to 19.9; $I^2=99%$) and 2.1% (95% CI 0 to 8.2; $I^2=89%$) for withdrawal

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3 423 syndrome; however, withdrawal symptoms were much more common (67.8%; 95% CI 64.1 to 71.4). The
4 424 certainty of evidence was very low due to risk of bias, inconsistency, imprecision (for dependence), and
5 425 indirectness due to vagueness of definitions in studies that precluded confident distinction between
6 426 dependence, addiction, withdrawal symptoms, and withdrawal syndrome.

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11 427 One study suggested that herbal cannabis compared to standard care may slightly increase the risk of
12 428 withdrawal syndrome (0.5%; 95% CI -0.4 to 1.4) but the certainty of evidence was low due to risk of bias.

15 429 **Discussion**

17 430 ***Main findings***

19 431 Our systematic review and meta-analysis suggests that adverse events are common among people living
20 432 with chronic pain who use medical cannabis or cannabinoids, with approximately one in four experiencing
21 433 at least one adverse event—though the certainty of evidence is very low and the true prevalence of
22 434 adverse events may be substantially different. In contrast, serious adverse events, adverse events leading
23 435 to discontinuation, cognitive adverse events, accidents and injuries, and dependence and withdrawal
24 436 syndrome are less common. We compared studies with <24 weeks and ≥ 24 weeks cannabis use and found
25 437 more adverse events reported among studies with longer follow-up. This may be explained by increased
26 438 tolerance (tachyphylaxis) with prolonged exposure, necessitating increases in dosage with consequent
27 439 increased risk of harms. PEA, compared to other formulations of medical cannabis, may result in the
28 440 fewest adverse events. Though adverse events associated with medical cannabis appear to be common,
29 441 few patients discontinued use due to adverse events suggesting that most adverse events are transient
30 442 and/or outweighed by perceived benefits.

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41 443 Our review represents the most comprehensive review of evidence from non-randomized studies
42 444 addressing adverse events of medical cannabis or cannabinoid use in people living with chronic pain.
43 445 While several previous reviews have summarized the evidence on short-term and common adverse events
44 446 of medical cannabis reported in randomized trials, such as oral discomfort, dizziness, and headaches, our
45 447 review focuses on serious and rare adverse events—the choice of which was informed by a panel including
46 448 patients, clinicians, and methodologists—and non-randomized studies, which typically follow larger
47 449 numbers of patients for longer periods of time and thus may detect adverse events that are infrequent or
48 450 that are associated with longer durations of cannabis use.^{10 77-81} A parallel systematic review of evidence
49 451 from randomized controlled trials found no evidence to inform long-term harms of medical cannabis as
50 452 no eligible trial followed patients for more than 5.5 months.¹¹ One previously published review that

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3 453 included non-randomized studies searched the literature until 2007, included studies exploring medical
4 454 cannabis for any indication (excluding synthetic cannabinoids) of which only two enrolled people living
5 455 with chronic pain.¹² This review did not synthesize adverse event data from non-randomized studies.¹²
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7 456 Unlike previous reviews, we focused exclusively on medical cannabis for chronic pain and excluded
8 457 recreational cannabis, because cannabis used for recreational purposes often contains higher
9 458 concentrations of THC than medical cannabis. We focused on chronic pain because this patient population
10 459 may be susceptible to different adverse events. Depression and anxiety, for example, are commonly
11 460 occurring comorbidities of chronic pain, which may be exacerbated by cannabis.¹⁵⁻¹⁷

17 461 ***Strengths and limitations***

19 462 Strengths of this systematic review and meta-analysis include a comprehensive search for non-
20 463 randomized studies, explicit eligibility criteria, screening of studies and collection of data in duplicate to
21 464 increase reliability, and use of the GRADE approach to evaluate the certainty of evidence.

23 465 Our review is limited by the non-comparative design of most studies, which precludes confident
24 466 inferences regarding the proportion of adverse events that can be attributed to medical cannabis or
25 467 cannabinoids and the magnitude by which medical cannabis may increase or decrease the risk of adverse
26 468 events compared to other pain management options. Though adverse events appear common among
27 469 medical cannabis users, it is possible that other management options for chronic pain, particularly opioids,
28 470 may be associated with more (and more severe) adverse events.⁸² Partly due to the non-comparative
29 471 design of most studies, nearly all results included in our review were at serious or critical risk of bias for
30 472 confounding and Simpson's paradox,⁸³ either due to the absence of a control group or due to insufficient
31 473 adjustment for important confounders. Further, a third of studies were at high risk of selection bias,
32 474 primarily because they included prevalent cannabis users. In such studies, the prevalence of adverse
33 475 events may be underestimated. Our review provides limited evidence on the harms of medical cannabis
34 476 beyond one year of use since most studies reported adverse events for less than one year of follow-up.

36 477 We observed some inconsistency for many adverse events of interest and substantial inconsistency for all
37 478 adverse events and adverse events leading to discontinuation. We downgraded the certainty of evidence
38 479 when we observed important inconsistency and we did not present estimates from meta-analyses for all
39 480 adverse events and adverse events leading to discontinuation due to substantial inconsistency. Further,
40 481 some analyses included too few studies or participants, due to which estimates were imprecise.

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3 482 Sixteen of 39 studies reported on herbal medical cannabis, some of which were consumed by smoking or
4 483 vaporizing, and may be associated with different adverse events (e.g. respiratory) than other formulations
5 484 of medical cannabis. We attempted to perform subgroup analyses based on the type of medical cannabis.
6 485 Results for subgroups, however, lacked credibility due to inconsistency and/or imprecision.
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11 486 Clinicians and patients may be more inclined to use medical cannabis or cannabinoids for pain relief if
12 487 adverse events are mild; however, the evidence on whether adverse events are transient, life threatening,
13 488 or the extent to which they impact quality of life is limited. While more than half of studies reported on
14 489 the proportion of adverse events that were serious, criteria for ascertaining severity were rarely reported.
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16 490 None of the included studies reported the duration for which patients experienced adverse events.
17 491 Further, most primary studies did not report adequate details on methods for the ascertainment of
18 492 adverse events, including definitions or diagnostic criteria. The two studies that reported on withdrawal
19 493 syndrome, for example, did not provide diagnostic criteria.^{49 57} However, the DSM-5 requires ≥ 3 of 7
20 494 withdrawal symptoms to be present within a week of stopping cannabis use to meet a diagnosis of
21 495 cannabis withdrawal syndrome.⁸⁴ It is therefore reasonable that people living with chronic pain that use
22 496 medical cannabis would be more likely to experience withdrawal symptoms vs. withdrawal syndrome.
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30 497 While children and youth account for approximately 15% of all chronic pain patients, we did not identify
31 498 any evidence addressing the harms of medical cannabis in this population.⁸⁵ As such, the extent to which
32 499 our findings are generalizable to pediatric populations is uncertain. Although there is evidence that
33 500 cannabis use during youth is associated with increased risk of acute psychotic disorders, particularly acute
34 501 psychosis,⁸⁶ such studies have focussed on use of recreational cannabis that contains greater amounts of
35 502 THC than is typically seen in medical preparations. Further, the population of patients with chronic pain
36 503 included in the studies we reviewed may not be representative of all patients with chronic pain—
37 504 particularly rare conditions that cause chronic pain.
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45 505 We used the DerSimonian and Laird method for meta-analysis.²⁷ A growing body of evidence, however,
46 506 suggests that this model has important limitations that may be addressed by alternative models⁸⁷—
47 507 though there is limited evidence on the performance of these models for meta-analyses of proportions
48 508 and prevalence.
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52 509 Finally, we excluded studies from meta-analyses when they did not explicitly report the adverse events of
53 510 interest to our panel members. This may have overestimated the prevalence of adverse events if the
54 511 adverse events of interest were not observed in the studies in which they were not reported. This was,
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3 512 however, not possible to confirm because methods for the collection and reporting of adverse event data
4 513 across studies were variable (e.g., active monitoring vs. passive surveillance; collecting data on specific
5 514 adverse events vs. all adverse events) and poorly described in study reports.
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8 9 515 **Implications**

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11 516 Our systematic review and meta-analysis shows that evidence regarding long-term and serious harms of
12 517 medical cannabis or cannabinoids is insufficient—an issue with important implications for patients and
13 518 clinicians considering this management option for chronic pain. While the evidence suggests that adverse
14 519 events are common in patients using medical cannabis for chronic pain, serious adverse events appear
15 520 less common, which suggests that the potential benefits of medical cannabis or cannabinoids (although
16 521 modest) may outweigh potential harms for some patients.^{11 18}
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22 522 Clinicians and patients considering medical cannabis should be aware that more adverse events were
23 523 reported among studies with longer follow-up, necessitating long term follow-up of patients and re-
24 524 evaluation of pain treatment options. Our findings also have implications for the choice of medical
25 525 cannabis. We found PEA, for example, to consistently be associated with few or no adverse events across
26 526 studies, though the evidence on the efficacy of PEA is limited.¹¹
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32 527 We found very limited evidence comparing medical cannabis or cannabinoids with other pain
33 528 management options. Other pharmacological treatments for chronic pain, such as gabapentinoids,
34 529 antidepressants, and opioids, may be associated with more (and more serious) adverse events.⁸⁸⁻⁹⁰ To
35 530 guide patients' and clinicians' decisions on medical cannabis for chronic pain, future research should
36 531 compare the harms of medical cannabis and cannabinoids with other pain management options, including
37 532 opioids, ideally beyond one year of use, and adjust results for confounders.
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43 533 Our review highlights the need for standardization of reporting of adverse events in non-randomized
44 534 studies since such studies represent a critical source of data on long-term and infrequently occurring
45 535 harms. To enhance the interpretability of adverse event data, future studies should also report the
46 536 duration and severity of adverse events and whether adverse events are life-threatening, since these
47 537 factors are critical to patients' decisions.
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52 538 A valuable output of our systematic review is an open-source database of over 500 unique adverse events
53 539 reported to date in non-randomized studies of medical cannabis or cannabinoids for chronic pain with
54 540 corresponding assessments of risk of bias (<https://osf.io/ut36z/>). This database was compiled in duplicate
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3 541 by trained and calibrated data extractors and is freely available to those interested in further analyzing
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5 542 the prevalence of different types of adverse events or to those interested in expanding the database to
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7 543 include adverse events in patients using medical cannabis or cannabinoids for other indications.
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9 544 **Conclusion**

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11 545 Our systematic review and meta-analysis found very low certainty evidence that suggests adverse events
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13 546 are common among people living with chronic pain using medical cannabis or cannabinoids, but that
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15 547 serious adverse events, adverse events causing discontinuation, cognitive adverse events, motor vehicle
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17 548 accidents, falls, and dependence and withdrawal syndrome are less common. We also found very low
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19 549 certainty evidence that longer duration of use was associated more adverse events and that PEA,
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21 550 compared with other types of medical cannabis, may result in few or no adverse events. Future research
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23 551 should compare the risks of adverse events of medical cannabis and cannabinoids with alternative pain
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553 **Figure Legends**

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555 **Figure 1: Study selection process**

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557 **Figure 2: Forest plot of the meta-analysis for serious adverse events stratified by type of medical**
558 **cannabis**

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Table 1: Study characteristics

Study	Design	Country	Condition	Cannabis/ comparator	Dose	# of participants	Duration of cannabis use (weeks)
Ware, 2003 ³⁵	cross-sectional*	Canada	mixed non-cancer pain	mixed herbal (CBD + THC)	frequency: rarely (n=9), weekly (n=8), daily (n=5), >once daily (n=7) dose: 1-2 puffs (n=4), 3-4 puffs (n=13), whole joint (n=8), more than one joint (n=4)	32	NR
Lynch, 2006 ³⁶	longitudinal*	Canada	mixed non-cancer pain	mixed herbal (CBD + THC)	mean: 2.5 g/day	30	mean: 94.4
Rog, 2007 ³⁷	longitudinal*	UK	multiple sclerosis	nabiximols (CBD + THC)	mean: 7.5 sprays/day	63	66.1
Weber, 2009 ³⁸	longitudinal*†	Germany	mixed non-cancer pain	dronabinol (THC)	median: 7.5 mg/day	172	mean: 31
Bestard, 2011 ³⁹	longitudinal*	Canada	peripheral neuropathic pain	nabilone (THC)	mean: 3.0 mg/day	104	24
				gabapentin	mean: 2.3 g/day	107	
Fiz, 2011 ⁴⁰	cross-sectional*	Spain	fibromyalgia	mixed herbal (CBD + THC)	~1 to 2 cigarettes or spoonful daily (n=12) once every 2 to 4 days (n=5), less than twice a week (n=3), or occasionally (n=8)	28	<52 (n=11), 52 to 156 (n=9), >156 weeks (n=8)
Dominguez, 2012 ⁴¹	longitudinal*	Spain	lumbosciatica	PEA	300 mg bid	64	4
Gatti, 2012 ⁴²	longitudinal††	Italy	mixed cancer and non-cancer pain	PEA	600 mg bid 3 weeks; 600 mg/day for 4 weeks	564	7
Toth, 2012 ⁴³	longitudinal*†	Canada	diabetic peripheral neuropathy	nabilone (THC)	mean: 2.85 mg/day	37	4
Schifilliti, 2014 ⁴⁴	longitudinal††	Italy	diabetic neuropathy	PEA	300 mg bid	30	8.6
Storr, 2014 ⁴⁵	cross-sectional*	Canada	Crohn's disease (n=42), ulcerative colitis (n=10), indeterminate colitis (n=4)	mixed herbal (CBD + THC)	NR	56	<4 (n=3), 4 to 24 (n=9), 24 to 52 (n=5), >52 (n=32)
Del Giorno, 2015 ⁴⁶	longitudinal††	Italy	fibromyalgia	PEA	600 mg bid first month; 300 mg bid in the next 2 months	35	12
Hoggart, 2015 ⁴⁷	longitudinal††	UK, Czech Republic, Romania, Belgium, Canada	diabetic neuropathy	nabiximols (CBD + THC)	median: 6 to 8 sprays/day	380	median: 35.6
Ware, 2015 ⁴⁸	longitudinal*†	Canada	mixed non-cancer pain	mixed herbal (CBD + THC)	median: 2.5 g/day	215	52
				standard care		216	
Haroutounian, 2016 ⁴⁹	longitudinal*	Israel	mixed cancer and non-cancer pain	mixed herbal (CBD + THC)	mean: 43.2 g/month	206	30
	longitudinal*				Capsule: 10 mg /8 to 10 hours		
Bellnier, 2017 ⁵⁰		US	mixed cancer and non-cancer pain	mixed herbal (CBD + THC)	Inhaler for breakthrough pain: 2 mg THC, 0.1 mg CBD; 1 to 5 puffs every 15 minutes until pain relief; could be used every 4 to 6 hours	29	12
Cranford, 2017 ⁵¹	cross-sectional*	US	mixed non-cancer pain	NR	0 (n=69), <1/8 oz/week (n=130), 1/8 to 1/4 oz/week (n=156), 1/4 to 1/2 oz/week (n=179), 1/2 to 1 oz/week (n=122), 1 or more oz/week (n=115)	775	NR

	Author, Year	Study Design	Country	Condition	Intervention	Outcome	n	Effect Size
	Fanelli, 2017 ⁵²	longitudinal††	Italy	mixed cancer and non-cancer pain	mixed herbal (CBD + THC)	mean: 69.5 mg/day bediol; 67.0 mg/day bedrocan	341	mean: 14.01
1	Feingold, 2017 ⁵³	cross-sectional*	Israel	mixed cancer and non-cancer pain	Mixed herbal (CBD + THC)	NR	406	NR
2	Paladini, 2017 ⁵⁴	longitudinal††	Italy	failed back surgery syndrome	PEA	600 mg bid for one month; 600 mg/day for one month	35	8
3	Passavanti, 2017 ⁵⁵	longitudinal††	Italy	lower back pain	PEA	600 mg bid	30	24
4	Schimrigk, 2017 ⁵⁶	longitudinal*†	Germany, Austria	multiple sclerosis	dronabinol (THC)	range: 7.5 to 15 mg/day	209	32
5	Chirchiglia, 2018 ⁵⁷	longitudinal††	Italy	lower back pain	PEA	1.2 g/day	100	4
6	Crowley, 2018 ⁵⁸	longitudinal*	US	mixed non-cancer pain	Trokie lozenges (CBD + THC)	NR	35	4 to 60
7	Habib, 2018 ⁵⁹	longitudinal*	Israel	fibromyalgia	mixed herbal (CBD + THC)	mean: 26 g/month	26	mean: 41.6
8	Anderson, 2019 ⁶⁰	longitudinal*	US	cancer pain	mixed herbal (CBD + THC)	NR	1120	16
9	Bonar, 2019 ⁶¹	cross-sectional††	US	mixed non-cancer pain	NR	0 (n=95), <1/8 oz/week (n=126), 1/8 to 1/4 oz/week (n=158), 1/4 to 1/2 oz/week (n=174), 1/2 to 1 oz/week (n=119), 1 or more oz/week (n=119)	790	NR
10	Cervigni, 2019 ⁶²	longitudinal†	Italy	interstitial cystitis/bladder pain syndrome	PEA	400 mg m-PEA plus 40 mg polydatin bid for 3 months, od for 3 months	32	24
11	Cremer-Schaeffer, 2019 ⁶³	longitudinal††	Germany	mixed cancer and non-cancer pain	dronabinol (THC)	NR	2017	52
12					mixed herbal	NR	656	
13					nabiximols	NR	393	
14	Lejczak, 2019 ⁶⁴	longitudinal†	France	mixed cancer and non-cancer pain	dronabinol (THC)	range: 2.5 to 30 mg/day	148	range: 4 to 24 weeks
15	Loi, 2019 ⁶⁵	longitudinal*	Italy	endometriosis	PEA	600 mg/bid for 10 days; 400 mg m-PEA plus 40 mg polydatin bid	28	12.9
16	Naftali, 2019 ⁶⁶	longitudinal*	Israel	inflammatory bowel disease	mixed herbal (CBD + THC)	mean: 31 g/month	127	median: 176
17	Perron, 2019 ⁶⁷	cross-sectional*	US	mixed non-cancer pain	NR	mean: 21 g/day THC; 170 g/day CBD	618	≥12
18	Sagy, 2019 ⁶⁸	longitudinal††	Israel	mixed cancer and non-cancer pain	mixed herbal (CBD + THC)	daily (n=580), weekly (n=85)	239	24
19	Sinclair, 2019 ⁶⁹	cross-sectional*	Australia	endometriosis	mixed herbal (CBD + THC)	median: 1000 mg/day cannabis	48	NR
20	Ueberall, 2019 ⁷⁰	longitudinal*	Germany	mixed cancer and non-cancer pain	nabiximols (CBD + THC)	median: 140 mg/day THC; 39 mg/day CBD	800	12
21	Vigil, 2017 ⁷¹	longitudinal*	US	mixed non-cancer pain	NR	less than once per week (n=12), once per week (n=6), two to six times per week (n=9), daily or multiple times per day (n=21)	37	mean: 82.4
22	Yassin, 2019 ⁷²	longitudinal††	Israel	fibromyalgia	mixed herbal (CBD + THC)	mean: 7.1 sprays/day	31	24
23	Giorgi, 2020 ⁷³	longitudinal††	Italy	fibromyalgia	extracts (CBD + THC)	20 to 30 g/month	102	24
24						10 to 30 drops/day; no more than 120 drops/day		

† NR=not reported, *Patient-report, †Clinician-report, ††NR

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Table 2: Prevalence of adverse events from non-comparative studies

Outcome	Number of studies	Number of participants	Duration of follow-up (weeks)	Prevalence % (95% CI)	I ² (τ ²)	Certainty	Reasons for downgrading
All adverse events	22	4,108	4 to 94	The prevalence of adverse events ranged between 0% to 92.1%. Studies with less than 24 weeks of cannabis use typically reported fewer adverse events than those with more than 24 weeks. Patients using PEA experienced no adverse events. The evidence was overall very uncertain due to risk of bias and inconsistency.		very low	risk of bias (3 levels), inconsistency
Adverse events causing discontinuation	20	6,509	4 to 66	The prevalence of discontinuations due to adverse events ranged between 0% to 27.0%. Studies with less than 24 weeks of cannabis use typically reported fewer discontinuations than those with more than 24 weeks. Patients using PEA experienced no adverse events. The evidence was overall very uncertain due to risk of bias and inconsistency.		very low	risk of bias (3 levels), inconsistency
Serious adverse events	24	4,273	4 to 94	1.2 (0.1 to 3.1)	91 (0.01273)	very low	risk of bias (3 levels)
Psychiatric adverse events							
Psychiatric disorder	4	1,458	12 to 66	13.5 (2.6 to 30.6)	98 (0.0436)	very low	risk of bias (3 levels), inconsistency, imprecision
Suicide	1	215	52	0 (0 to 0.8)	NA	very low	risk of bias (3 levels)
Suicidal thoughts	1	3,066	52	0.1 (0 to 0.5)	44 (0.0003)	very low	risk of bias (3 levels)
Depression	6	4,144	12 to 66	1.7 (0.9 to 2.7)	71 (0.0011)	very low	risk of bias (3 levels)
Mania	1	215	52	0.5 (0 to 2)	NA	very low	risk of bias (3 levels)
Hallucinations	6	3,583	24 to 66	0.5 (0.1 to 1.3)	69 (0.0012)	very low	risk of bias (3 levels)
Delusions	4	3,281	52	0.4 (0.2 to 0.6)	0 (0)	very low	risk of bias (3 levels)
Paranoia	3	277	52 to 94; one cross-sectional study	5.6 (0 to 19.2)	85 (0.0266)	very low	risk of bias (3 levels), inconsistency, imprecision
Anxiety	5	1,695	12 to 94; two cross-sectional studies	7.4 (0 to 26.9)	99 (0.0859)	very low	risk of bias (3 levels), imprecision
Euphoria	7	4,501	4 to 66	2.1 (0.9 to 3.8)	96 (0.0028)	very low	risk of bias (3 levels)
Cognitive adverse events							

Memory impairment	6	4,484	4 to 176	5.3 (2.1 to 9.6)	96 (0.0126)	very low	risk of bias (3 levels)
Confusion	7	1,654	4 to 176	1.8 (0.3 to 4.2)	81 (0.0056)	very low	risk of bias (3 levels)
Disorientation	6	4,485	12 to 52	1.6 (0.6 to 3.0)	88 (0.0028)	very low	risk of bias (3 levels)
Attention disorder or deficit	8	5,477	12 to 82	3.4 (1.3 to 6.3)	95 (0.0082)	very low	risk of bias (3 levels)
Accidents and injuries							
Falls	1	215	52	2.3 (0.7 to 4.9)	NA	very low	risk of bias (3 levels)
Motor vehicle accidents	1	215	52	0.5 (0 to 2.0)	NA	very low	risk of bias (3 levels)
Dependence and withdrawal							
Dependence	3	1,824	12; one cross-sectional study	4.4 (0.0 to 19.9)	99 (0.0488)	very low	risk of bias (3 levels), inconsistency, imprecision, indirectness
Withdrawal syndrome	2	424	32 to 52	2.1 (0 to 8.2)	89 (0.0091)	very low	risk of bias (3 levels), indirectness
Withdrawal symptoms	1	618	NA; cross-sectional	67.8 (64.1 to 71.4)	NA	very low	risk of bias (3 levels), indirectness

Table 3: Risk differences for adverse events from comparative studies

Outcome	Exposure	Number of studies	Number of participants	Follow-up (weeks)	Risk with cannabis (/1000)	Risk with comparator (/1000)	Risk difference (95% CI)	Certainty	Reasons for downgrading
All adverse events	Nabilone vs. gabapentin	1	220	24	404	534	-13.1% (-26.2 to 0)	Very low	Risk of bias (2 levels), imprecision
Adverse events causing discontinuation	Herbal cannabis vs. standard care	1	431	52	47	0	4.7% (1.8 to 7.5)	Low	Risk of bias (2 levels),
	Nabilone vs. gabapentin	1	220	24	96	190	-9.4% (-18.5 to -0.2)	Very low	Risk of bias (2 levels), imprecision
Serious	Herbal cannabis vs. standard care	1	431	52	130	194	1.5% (-8.3 to 20.2) *	Low	Risk of bias, imprecision
	Nabilone vs. gabapentin	1	220	24	0	0	0% (0 to 0)	Very low	Risk of bias (2 levels), imprecision
Psychiatric disorder	Herbal cannabis vs. standard care	1	431	52	219	97	16.9% (5.8 to 40.5) †	Very low	Risk of bias (2 levels), imprecision
Suicide	Herbal cannabis vs. standard care	1	431	52	0	5	-0.5% (-1.4 to 0.4)	Low	Risk of bias (2 levels)
Mania	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Low	Risk of bias (2 levels)
Hallucinations	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Low	Risk of bias (2 levels)
Delusions	Herbal cannabis vs. standard care	1	431	52	0	5	-0.5% (-1.4 to 0.4)	Low	Risk of bias (2 levels)
Depression	Herbal cannabis vs. standard care	1	431	52	47	46	0.1% (-4 to 4)	Low	Risk of bias (2 levels)
Paranoia	Herbal cannabis vs. standard care	1	431	52	9	0	0.9% (-0.4 to 2.2)	Low	Risk of bias (2 levels)
Anxiety	Herbal cannabis vs. standard care	1	431	52	47	9	3.8% (0.6 to 6.8)	Low	Risk of bias (2 levels)
Euphoria	Herbal cannabis vs. standard care	1	431	52	42	0	4.2% (1.5 to 6.9)	Low	Risk of bias (2 levels)

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Memory impairment	Herbal cannabis vs. standard care	1	431	52	19	0	1.9% (0.1 to 3.7)	Low	Risk of bias (2 levels)
Confusion	Herbal cannabis vs. standard care	1	431	52	14	19	-0.5% (-2.8 to 1.9)	Low	Risk of bias (2 levels)
Disturbance in attention	Herbal cannabis vs. standard care	1	431	52	23	9	1.4% (-1 to 3.8)	Low	Risk of bias (2 levels)
Falls	Herbal cannabis vs. standard care	1	431	52	23	23	0% (-2.8 to 2.9)	Low	Risk of bias (2 levels)
Motor vehicle accidents	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Low	Risk of bias (2 levels)
Withdrawal syndrome	Herbal cannabis vs. standard care	1	431	52	5	0	0.5% (-0.4 to 1.4)	Very low	Risk of bias (2 levels),

* Risk difference calculated from adjusted incident rate ratio reported in study.

† Risk difference calculated from unadjusted incident rate ratio reported in study.

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- 1
2
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6
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832

Figure 1: Study selection process

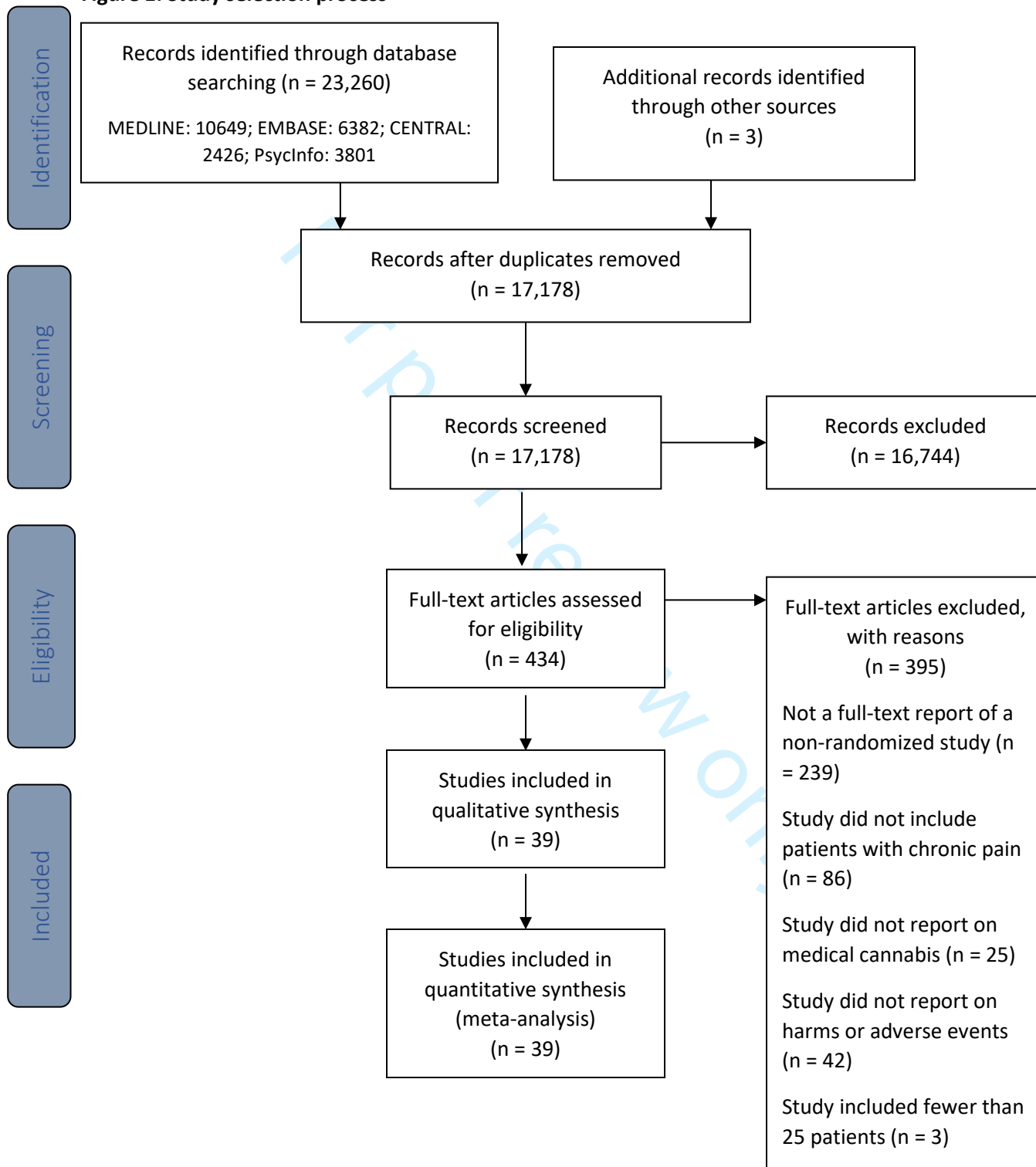
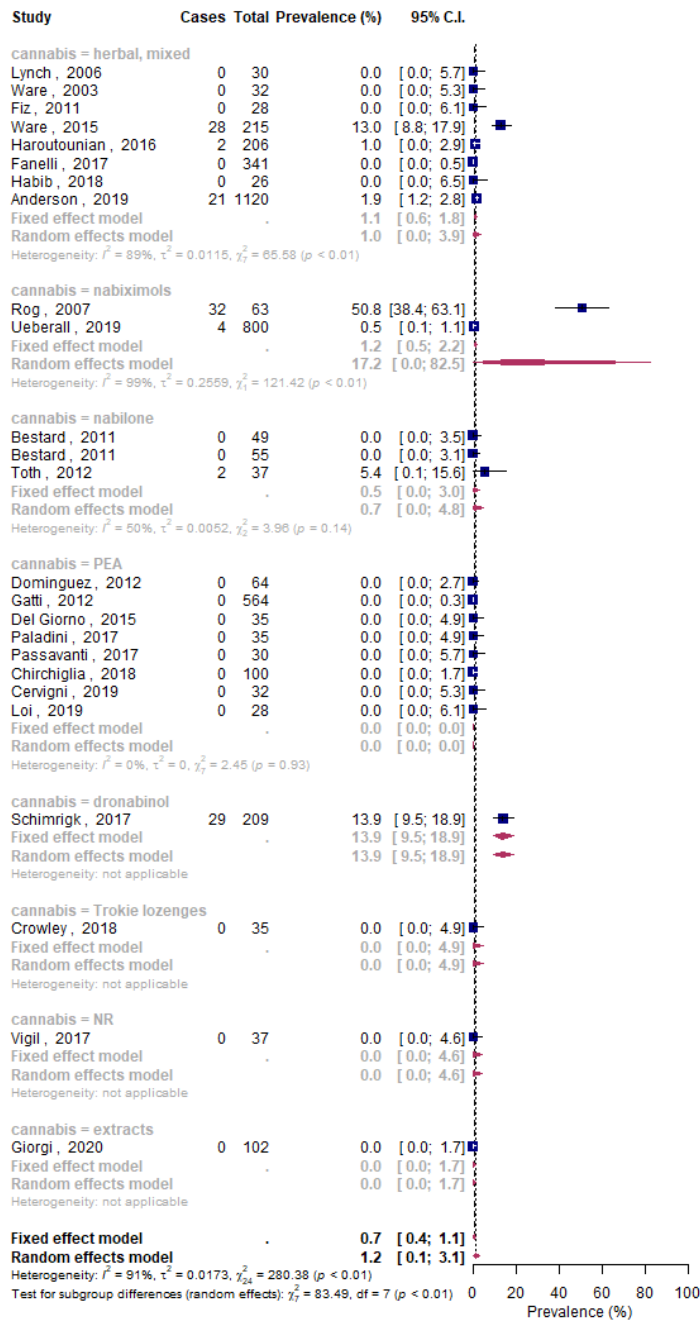


Figure 2: Forest plot of the meta-analysis for serious adverse events stratified by type of medical cannabis



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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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:

- 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)

- 1
- 2
- 3 6 Cohort analy\$.tw. (7799)
- 4
- 5
- 6
- 7 7 (Follow up adj (study or studies)).tw. (48708)
- 8
- 9
- 10
- 11 8 (observational adj (study or studies)).tw. (103255)
- 12
- 13
- 14
- 15 9 Longitudinal.tw. (239715)
- 16
- 17
- 18 10 Retrospective.tw. (515751)
- 19
- 20
- 21
- 22 11 Cross sectional.tw. (342224)
- 23
- 24
- 25
- 26 12 Cross-sectional studies/ (322752)
- 27
- 28
- 29
- 30 13 or/1-12 (2953281)
- 31
- 32
- 33 14 exp animals/ not humans.sh. (4685189)
- 34
- 35
- 36
- 37 15 13 not 14 (2889789)
- 38
- 39

40 Annotation: SIGN observational studies filter

- 41
- 42
- 43
- 44 16 randomized controlled trial.pt. (503041)
- 45
- 46
- 47
- 48 17 controlled clinical trial.pt. (93591)
- 49
- 50
- 51
- 52 18 randomized.ab. (474985)
- 53
- 54
- 55
- 56 19 placebo.ab. (206552)
- 57
- 58
- 59
- 60

1
2
3
4
5 20 drug therapy.fs. (2191450)
6
7

8
9 21 randomly.ab. (330409)
10

11
12 22 trial.ab. (500400)
13
14

15
16 23 groups.ab. (2028909)
17
18

19
20 24 or/16-23 (4670111)
21
22

23
24 25 exp animals/ not humans.sh. (4685189)
25
26

27
28 26 24 not 25 (4048339)
29
30

31 Annotation: Cochrane HSSS RCT filter
32
33

34
35 27 15 or 26 (6033576)
36
37

38
39 Annotation: study design filter broad
40
41

42
43 28 Cannabis/ (8968)
44
45

46
47 29 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (13810)
48
49

50
51 30 Endocannabinoids/ (5630)
52
53

54
55 31 exp Receptors, Cannabinoid/ (9240)
56
57
58
59
60

1
2
3 32 (Cannabis or cannabiniol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or
4 ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
5 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
6 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabiniol or
7 marinol or tetranabinex or sativex or endocannabinoid*).mp. (54925)
8
9

10
11
12 33 or/28-32 (54925)
13

14
15 Annotation: strategy from 2020 cannabis review
16
17

18
19 34 27 and 33 (16307)
20
21

22
23 Annotation: cannabis AND study design filter
24
25

26
27 35 exp "Drug-Related Side Effects and Adverse Reactions"/ (114376)
28
29

30
31 36 (ae or to or po or co).fs. (3890270)
32
33

34
35 37 (safe or safety).ti,ab. (758301)
36
37

38
39 38 side effect\$.ti,ab. (243706)
40
41

42 39 ((adverse or undesirable or harms\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or
43 outcome\$)).ti,ab. (501888)
44
45

46
47 40 exp Product Surveillance, Postmarketing/ (15237)
48
49

50
51 41 adverse drug reaction reporting systems/ (7463)
52
53

54
55 42 clinical trials, phase iv/ (295)
56
57

1
2
3
4
5 43 exp Poisoning/ (156177)
6
7

8
9 44 exp Substance-Related Disorders/ (274845)
10

11
12 45 Abnormalities, Drug-Induced/ (14514)
13
14

15
16 46 Drug Monitoring/ (20599)
17
18

19
20 47 exp Drug Hypersensitivity/ (45642)
21
22

23
24 48 (toxicity or complication\$ or noxious or tolerability).ti,ab. (1298802)
25
26

27
28 49 or/35-48 (5596308)
29
30

31 Annotation: OVID AE filter
32
33

34
35 50 34 and 49 (10649)
36
37

38
39 Annotation: Study design filter AND Cannabis AND AE Filter (broad)
40
41

42 Database: Embase <1974 to 2020 March 31>
43
44

45
46 Search Strategy:
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49
50 -----
51
52
53 1 cannabis/ (33859)
54
55
56
57
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59
60

1
2
3 2 exp cannabinoid/ (65694)
4
5

6
7 3 medical cannabis/ (2104)
8
9

10
11 4 exp cannabinoid receptor/ (14557)
12
13

14
15 5 exp endocannabinoid/ (8589)
16
17

18 6 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or
19 ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
20 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
21 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or
22 marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug
23 trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword,
24 floating subheading word, candidate term word] (86550)
25
26
27

28
29 7 or/1-6 (87843)
30
31

32
33 Annotation: cannabis
34
35

36
37 8 clinical study/ (154879)
38
39

40
41 9 case control study/ (153658)
42
43

44
45 10 family study/ (26012)
46
47

48
49 11 longitudinal study/ (137463)
50
51

52
53 12 retrospective study/ (897628)
54
55

56
57 13 prospective study/ (590879)
58
59

1
2
3
4
5 14 randomized controlled trials/ (176633)
6
7

8
9 15 13 not 14 (584662)
10
11

12 16 cohort analysis/ (564001)
13
14
15

16 17 (Cohort adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original
17 title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word,
18 candidate term word] (296961)
19
20

21
22 23 18 (Case control adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
24 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
25 word, candidate term word] (211490)
26
27

28
29 30 19 (follow up adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original
31 title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word,
32 candidate term word] (65948)
33
34

35 36 20 (observational adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
37 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
38 word, candidate term word] (242526)
39
40

41 42 21 (epidemiologic\$ adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
43 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
44 word, candidate term word] (109669)
45
46

47 48 22 (cross sectional adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name,
49 original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading
50 word, candidate term word] (385983)
51
52

53 23 or/8-12,15-22 (2808984)
54
55
56
57

1
2
3 Annotation: SIGN observational studies filter
4
5

6
7 24 7 and 23 (9720)
8
9

10 Annotation: cannabis AND observational studies
11
12

13
14 25 randomized controlled trial/ (597702)
15
16

17
18 26 Controlled clinical study/ (463832)
19
20

21
22 27 random\$.ti,ab. (1518977)
23
24

25
26 28 randomization/ (86491)
27
28

29
30 29 intermethod comparison/ (258334)
31
32

33
34 30 placebo.ti,ab. (303428)
35
36

37
38 31 (compare or compared or comparison).ti. (504683)
39
40

41 32 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or
42 comparing or comparison)).ab. (2082229)
43
44

45
46 33 (open adj label).ti,ab. (78190)
47
48

49
50 34 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (229917)
51
52

53
54 35 double blind procedure/ (171048)
55
56
57
58
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1
2
3 36 parallel group\$1.ti,ab. (25201)
4
5

6
7 37 (crossover or cross over).ti,ab. (104010)
8
9

10
11 38 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or
12 patient\$1 or subject\$1 or participant\$1)).ti,ab. (325625)
13
14

15
16 39 (assigned or allocated).ti,ab. (383429)
17
18

19
20 40 (controlled adj7 (study or design or trial)).ti,ab. (343515)
21
22

23
24 41 (volunteer or volunteers).ti,ab. (244577)
25
26

27
28 42 human experiment/ (490389)
29
30

31
32 43 trial.ti. (295850)
33
34

35
36 44 or/25-43 (4952112)
37

38
39 Annotation: Cochrane RCT filter
40
41

42
43 45 7 and 44 (14036)
44
45

46
47 Annotation: cannabis AND RCTs
48
49

50
51 46 24 or 45 (21357)
52

53
54 Annotation: cannabis AND (Obs studies OR RCTs)
55
56
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1
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3 47 7 and (23 or 44) (21357)
4
5
6

7 Annotation: logic check
8
9

10 48 (ae or si or to or co).fs. (3204803)
11
12

13
14 49 (safe or safety).ti,ab. (1154971)
15
16

17
18 50 side effect\$.ti,ab. (358075)
19
20

21
22 51 ((adverse or undesirable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or
23 outcome\$)).ti,ab. (787739)
24
25

26
27 52 exp adverse drug reaction/ (522775)
28
29

30
31 53 exp drug toxicity/ (125051)
32
33

34
35 54 exp intoxication/ (366563)
36
37

38
39 55 exp drug safety/ (393912)
40
41

42
43 56 exp drug monitoring/ (53058)
44
45

46
47 57 exp drug hypersensitivity/ (56248)
48
49

50
51 58 exp postmarketing surveillance/ (35831)
52
53

54
55 59 exp drug surveillance program/ (26017)
56
57
58
59
60

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

- 1
2
3 #4 MeSH descriptor: [Endocannabinoids] explode all trees 48
4
5
6
7 #5 (Cannabis or cannabinal or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja
8 or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or
9 ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or
10 dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro
11 cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have
12 been searched) 4370
13
14
15
16
17 #6 #1 or #2 or #3 or #4 or #5 4370
18
19
20 #7 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees 3463
21
22
23
24 #8 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE, toxicity - TO,
25 poisoning - PO, complications - CO] 169278
26
27
28
29 #9 (safe or safety):ti,ab,kw (Word variations have been searched) 258304
30
31
32
33 #10 (side effect*):ti,ab,kw (Word variations have been searched) 149400
34
35
36
37 #11 ((adverse or undesirable or harms* or serious or toxic) near/3 (effect* or reaction* or event* or
38 outcome*)):ti,ab,kw (Word variations have been searched) 279577
39
40
41
42 #12 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 191
43
44
45 #13 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 82
46
47
48
49 #14 MeSH descriptor: [Clinical Trial, Phase IV] explode all trees 0
50
51
52
53 #15 MeSH descriptor: [Poisoning] explode all trees 2101
54
55
56
57
58
59
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- 1
2
3 #16 MeSH descriptor: [Substance-Related Disorders] explode all trees 14586
4
5
6
7 #17 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees 47
8
9
10
11 #18 MeSH descriptor: [Drug Monitoring] explode all trees 1725
12
13
14 #19 MeSH descriptor: [Drug Hypersensitivity] explode all trees 965
15
16
17
18 #20 (toxicity or complication* or noxious or tolerability):ti,ab,kw (Word variations have been
19 searched) 332240
20
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23 #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
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28 #22 #6 and #21 in Trials 2426
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35 Database: APA PsycInfo <1806 to March Week 4 2020>
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39 Search Strategy:
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47 1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (12819)
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51 2 (Cannabis or cannabinal or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or
52 ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic
53 acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or
54 levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinal or
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3 marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, table of
4 contents, key concepts, original title, tests & measures, mesh] (26466)
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8 3 1 or 2 (26466)
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12 4 exp "side effects (drug)"/ (57604)
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15 5 (safe or safety).ti,ab. (84148)
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19 6 side effect\$.ti,ab. (31950)
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23 7 ((adverse or undesirable or harms\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or
24 outcome\$)).ti,ab. (44183)
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28 8 toxic disorders/ (1433)
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31 9 exp "substance use disorder"/ (127742)
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34
35 10 (toxicity or complication\$ or noxious or tolerability).ti,ab. (42844)
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39 11 or/4-10 (310848)
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43 12 3 and 11 (10984)
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47 13 epidemiology/ (49562)
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51 14 ((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id.
52 not "Literature Review".md. (95810)
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3 15 ((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or
4 prospective study.md. or retrospective study.md.) not "Literature Review".md. (286455)
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8 16 (cross section* or "prevalence study").ti,ab,id. (80384)
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12 17 clinical trials/ or "treatment outcome clinical trial".md. or ((randomi?ed adj7 trial*) or ((single or
13 doubl* or tripl* or treb*) and (blind* or mask*)) or (controlled adj3 trial*) or (clinical adj2
14 trial*)).ti,ab,id. (101001)
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18 18 Case control.mp. (10736)
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22 19 (cohort adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key
23 concepts, original title, tests & measures, mesh] (21026)
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27 20 Cohort analy\$.mp. (2099)
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31 21 (Follow up adj (study or studies)).mp. [mp=title, abstract, heading word, table of contents, key
32 concepts, original title, tests & measures, mesh] (12876)
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36 22 (Longitudinal or Retrospective or Cross sectional).mp. [mp=title, abstract, heading word, table of
37 contents, key concepts, original title, tests & measures, mesh] (218589)
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41 23 or/13-22 (561443)
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44 24 12 and 23 (3801)
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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.
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For peer review only

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

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

1. Apro MS. Prevention of chemotherapy-induced nausea and vomiting in patients with cancer. *Arizona Medicine*. 1981;38(11):843-5.
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16 problematic oral cannabinoid use. *Psychopharmacology*. 2018;235(2):409-17.
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19 **Study included <25 patients**

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22 complementary and alternative medicine? *Complementary Therapies in Medicine*. 2005;13(4):258-63.
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29 syndromes and response to pharmacological therapy. *Pain*. 2008;138(3):657-66.
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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 outcomes	Selection of the reported Results
Ware, 2003	●	●	●	●	●	●	●
Lynch, 2006	●	●	●	●	●	●	●
Rog, 2007	●	●	●	●	●	●	●
Weber, 2009	●	●	●	●	●	●	●
Bestard, 2011*	●	●	●	●	●	●	●
Fiz, 2011	●	●	●	●	●	●	●
Dominguez, 2012	●	●	●	●	●	●	●
Gatti, 2012	●	●	●	●	●	●	●
Toth, 2012	●	●	●	●	●	●	●
Schifilliti, 2014	●	●	●	●	●	●	●
Storr, 2014	●	●	●	●	●	●	●
Del Giorno, 2015	●	●	●	●	●	●	●
Hoggart, 2015	●	●	●	●	●	●	●
Ware, 2015†	●	●	●	●	●	●	●
Haroutounian, 2016	●	●	●	●	●	●	●
Bellnier, 2017	●	●	●	●	●	●	●
Cranford, 2017	●	●	●	●	●	●	●
Fanelli, 2017	●	●	●	●	●	●	●
Feingold, 2017	●	●	●	●	●	●	●
Paladini, 2017	●	●	●	●	●	●	●
Passavanti, 2017	●	●	●	●	●	●	●
Schimrigk, 2017	●	●	●	●	●	●	●
Chirchiglia, 2018	●	●	●	●	●	●	●
Crowley, 2018	●	●	●	●	●	●	●
Habib, 2018	●	●	●	●	●	●	●
Anderson, 2019	●	●	●	●	●	●	●
Bonar, 2019	●	●	●	●	●	●	●
Cervigni, 2019	●	●	●	●	●	●	●
Cremer-Schaeffer, 2019‡	●	●	●	●	●	●	●
Lejczak, 2019	●	●	●	●	●	●	●
Loi, 2019	●	●	●	●	●	●	●
Naftali, 2019	●	●	●	●	●	●	●
Perron, 2019	●	●	●	●	●	●	●
Sagy, 2019	●	●	●	●	●	●	●
Sinclair, 2019	●	●	●	●	●	●	●
Ueberall, 2019	●	●	●	●	●	●	●
Vigil, 2019	●	●	●	●	●	●	●
Yassin, 2019	●	●	●	●	●	●	●
Giorgi, 2020	●	●	●	●	●	●	●

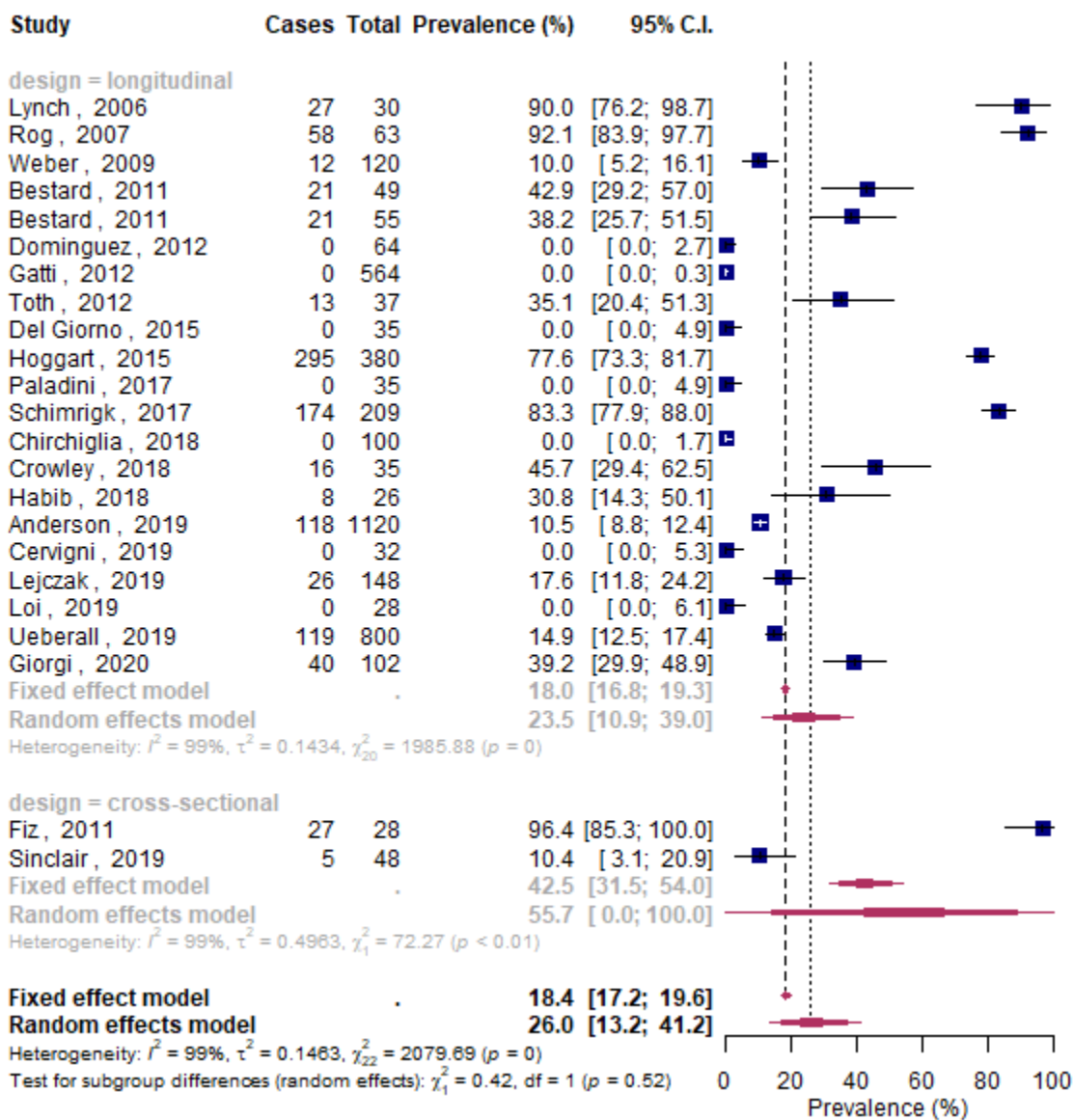
Low risk of bias	●
Moderate risk of bias	●
Serious risk of bias	●
Critical risk of bias	●

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

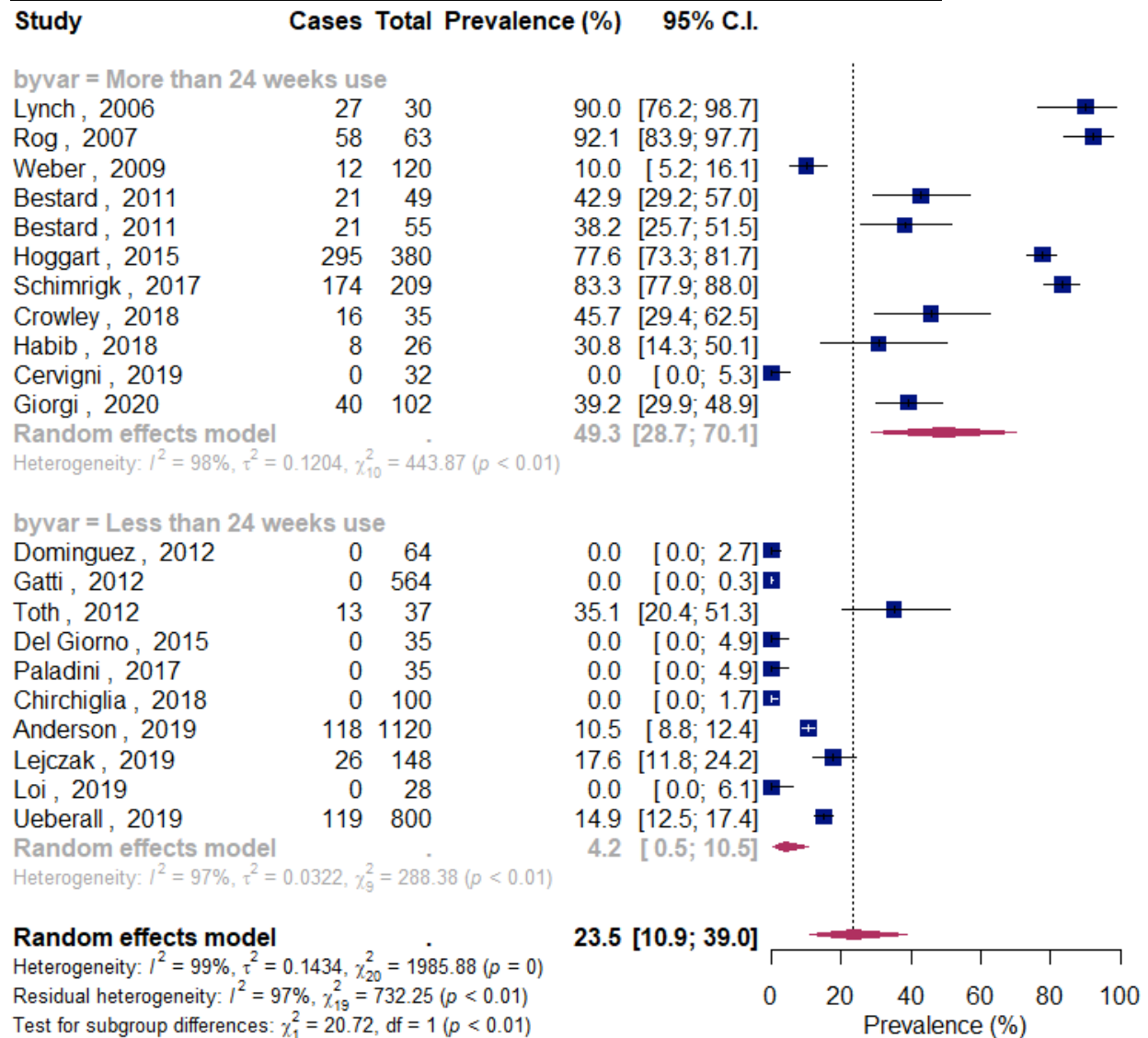
† Risk of bias for confounding for unadjusted comparative comparative results were rated as serious. Adjusted comparative results were rated as moderate.

‡ 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 participants.

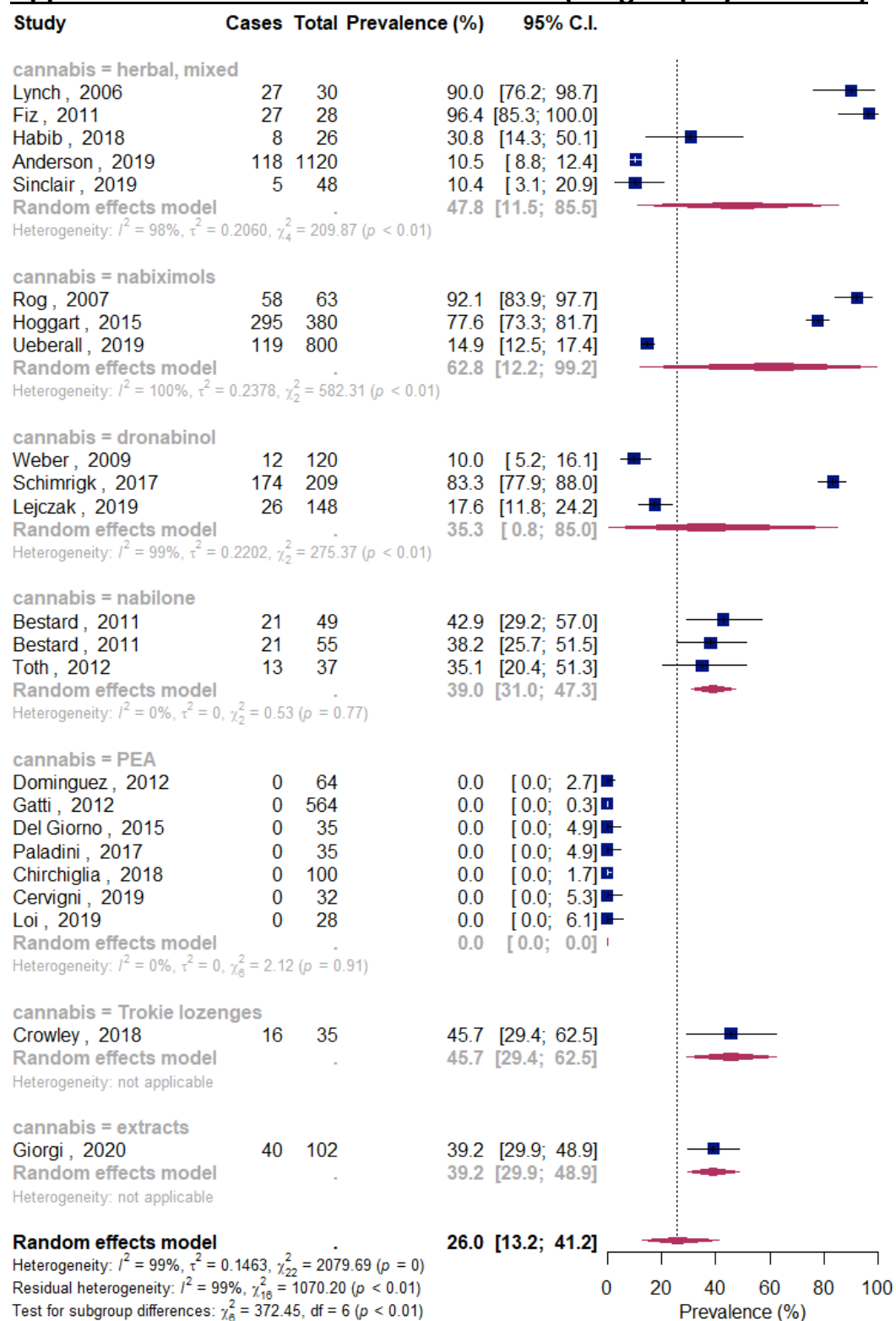
Appendix 6: Results for all adverse events (subgroup by design)



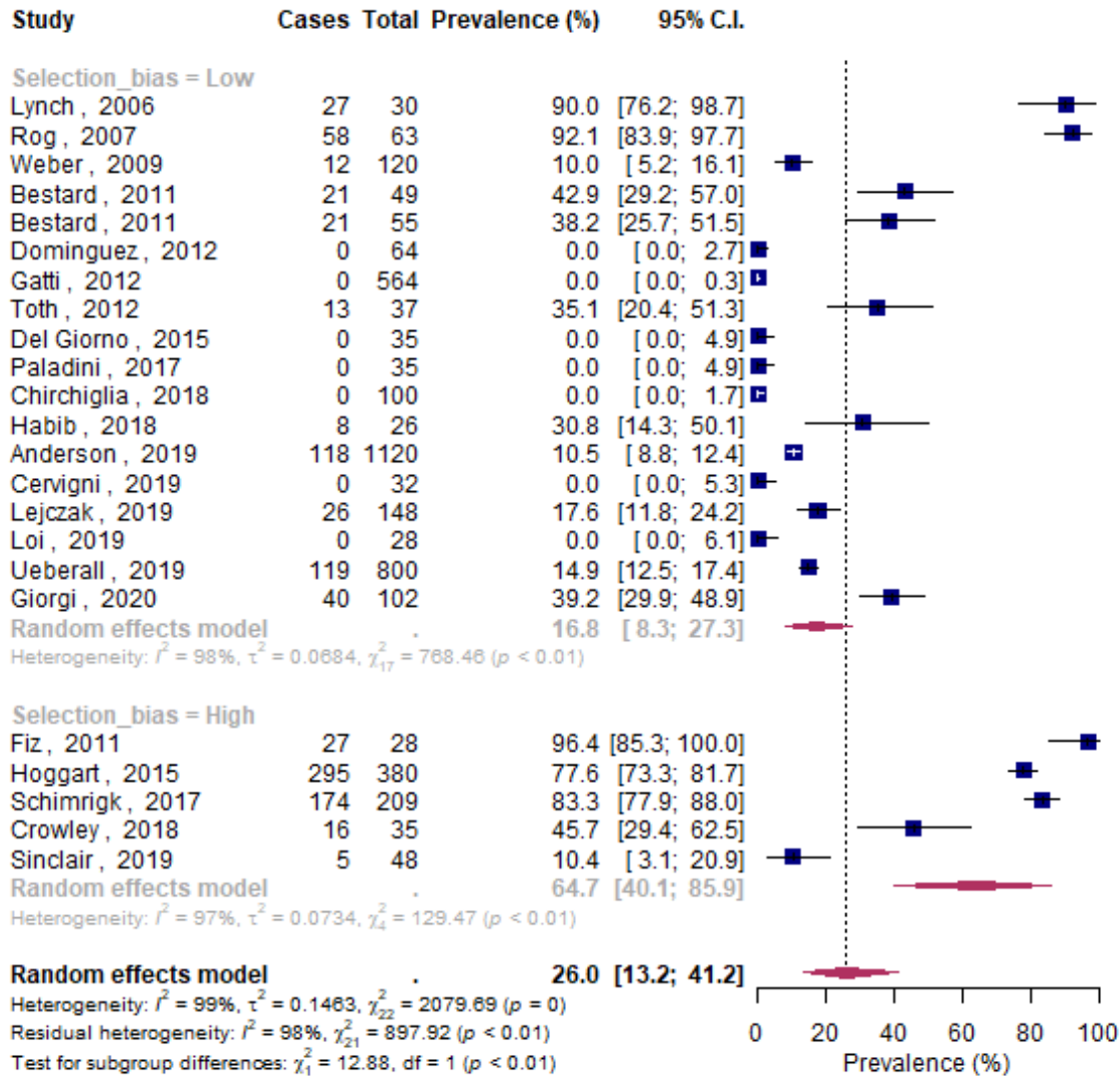
Appendix 7: Results for all adverse events (subgroup by duration)



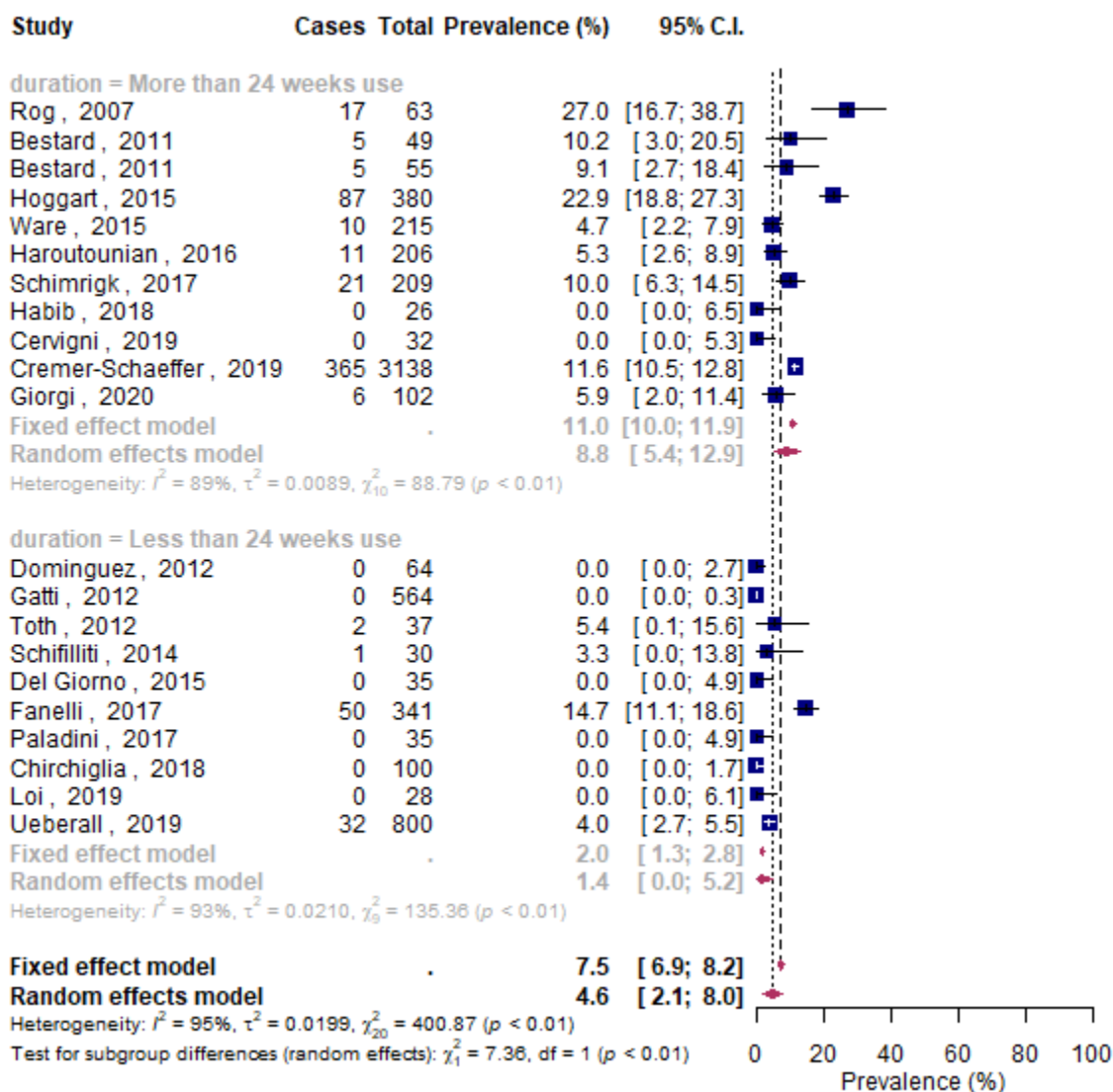
Appendix 8: Results for all adverse events (subgroup by cannabis)



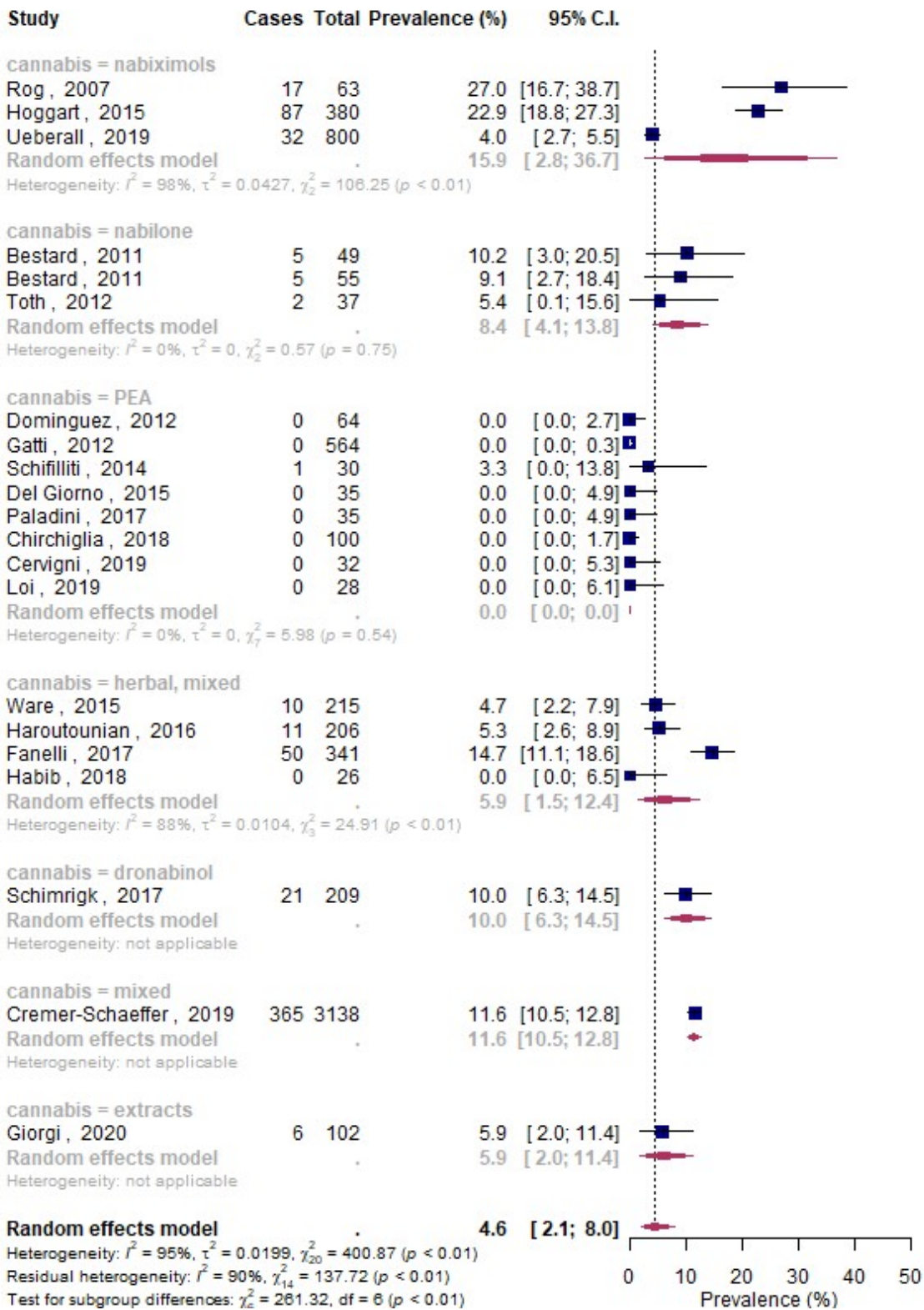
Appendix 9: Results for all adverse events (subgroup by selection bias)



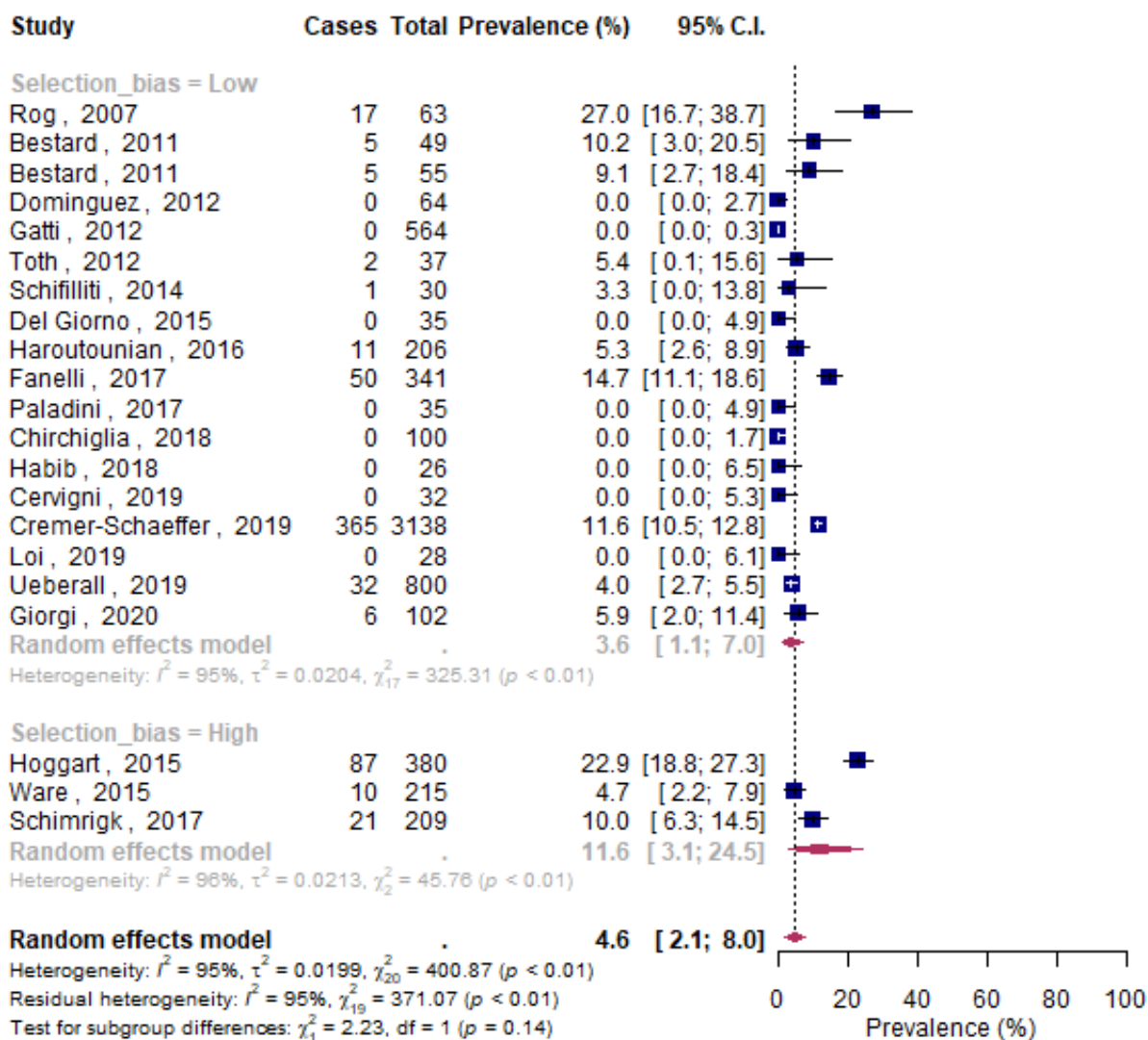
Appendix 10: Results for adverse events leading to discontinuation (subgroup by duration)



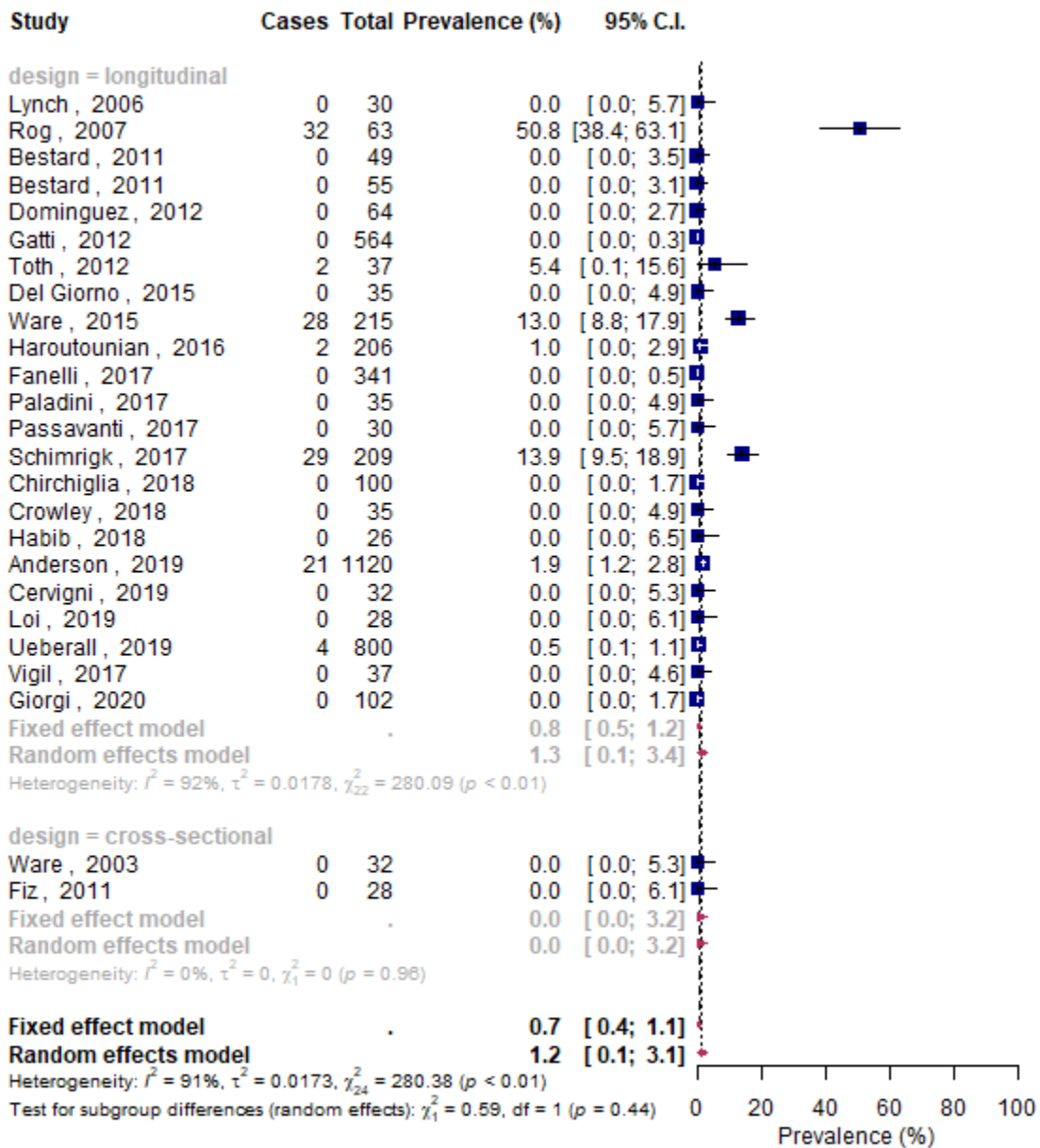
Appendix 11: Results for adverse events leading to discontinuation (subgroup by cannabis)



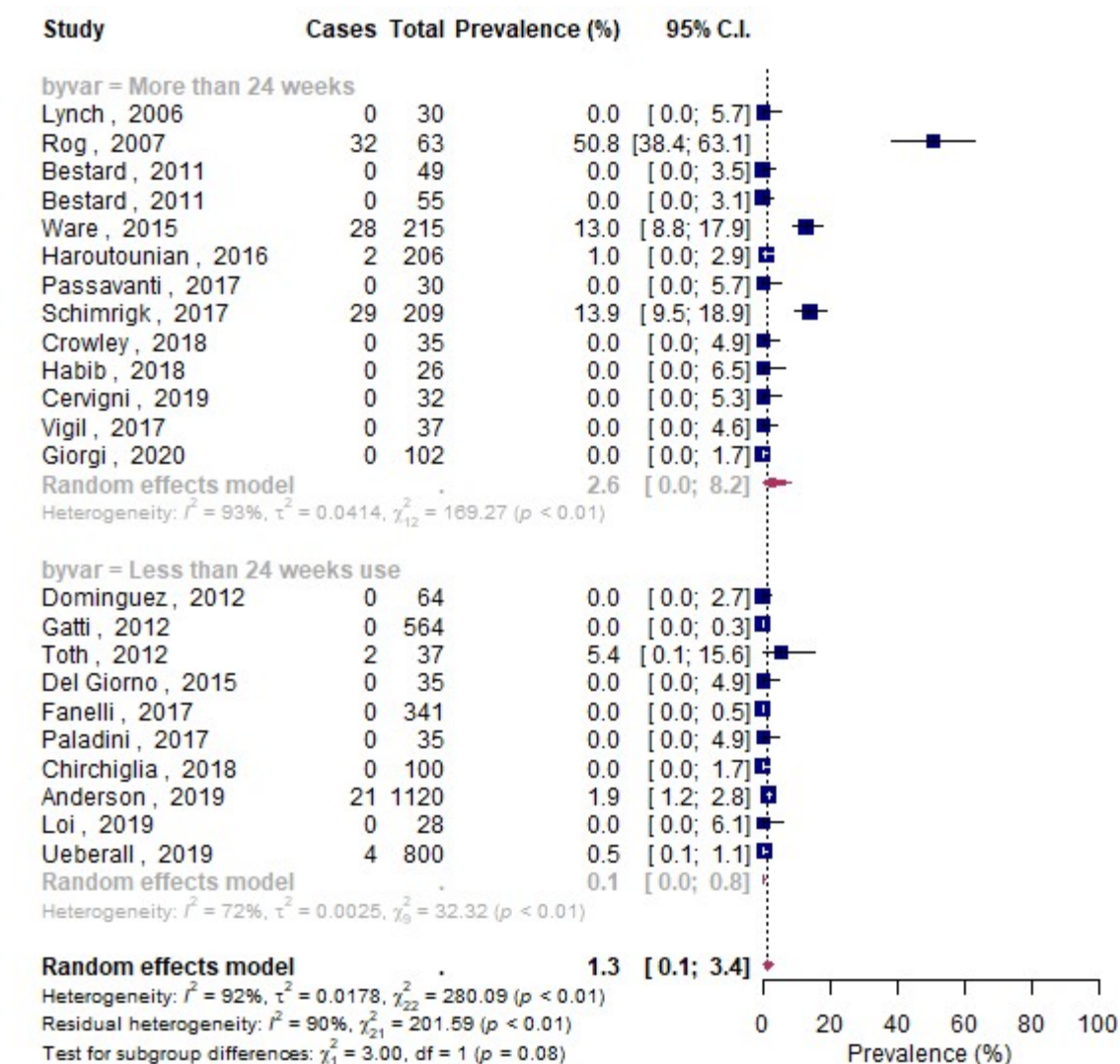
Appendix 12: Results for adverse events leading to discontinuation (subgroup by selection bias)



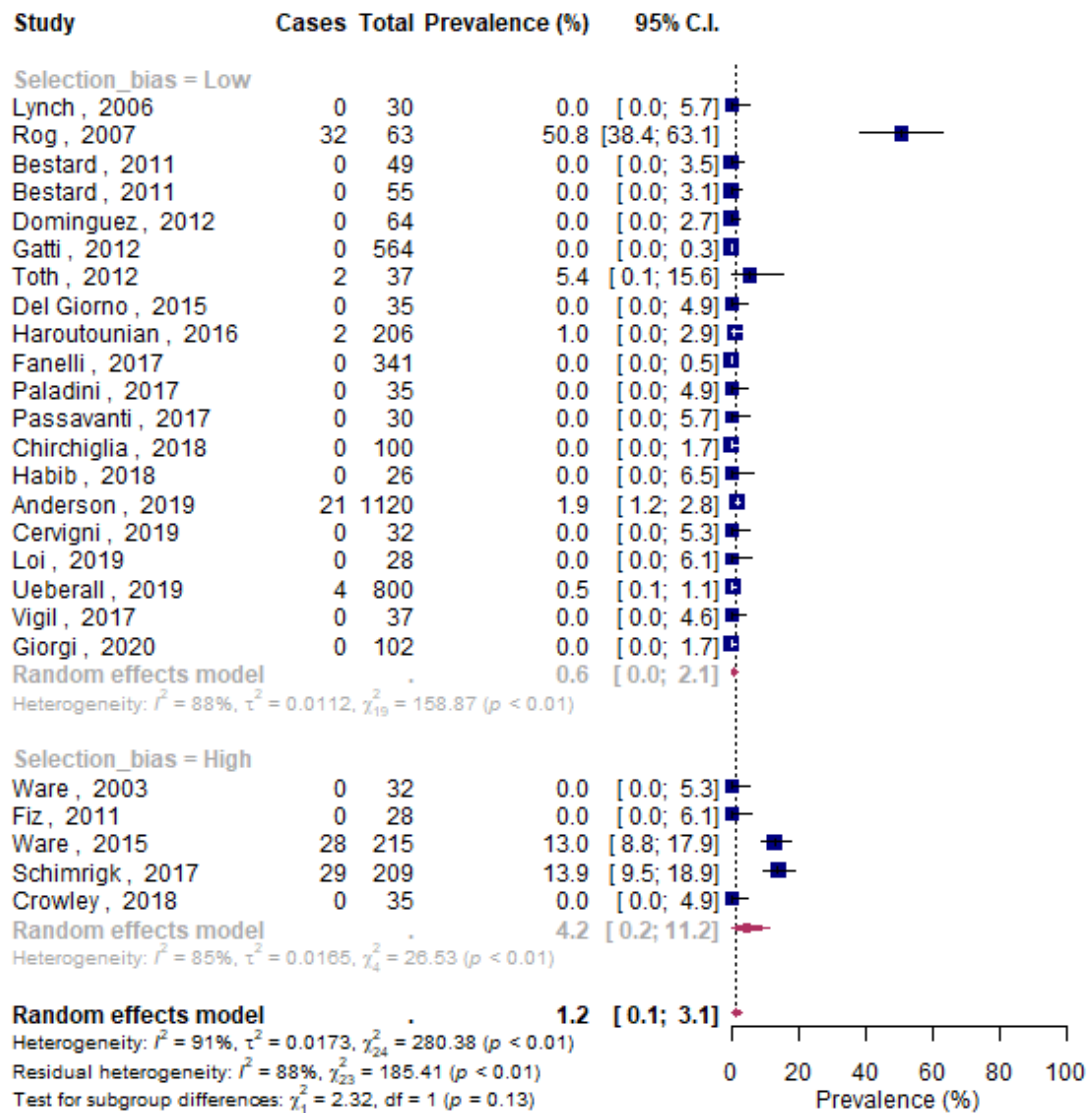
Appendix 13: Results for serious adverse events (subgroup by design)



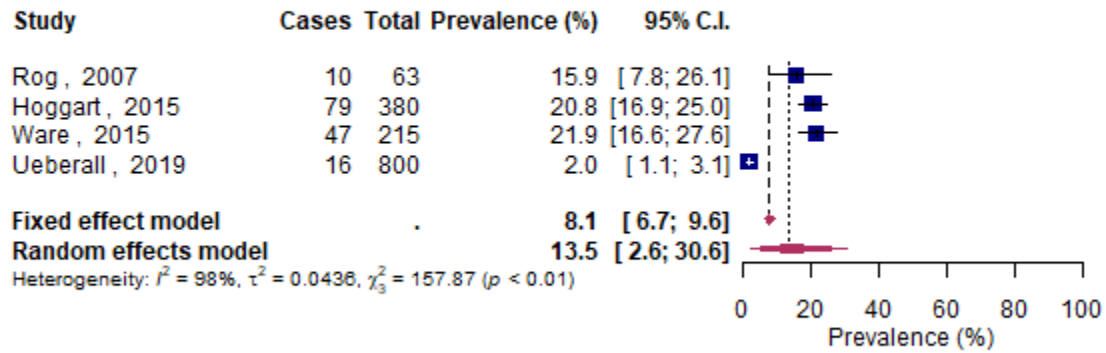
Appendix 14: Results for serious adverse events (subgroup by duration)



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

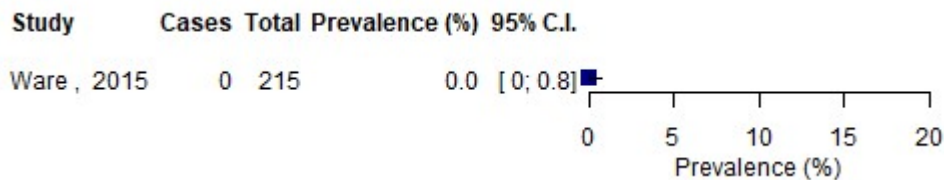


Appendix 16: Results for psychiatric adverse events



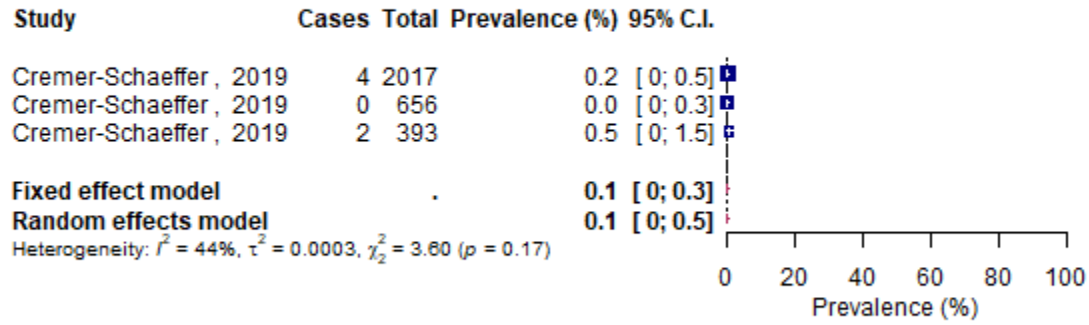
Peer review only

Appendix 17: Results for suicide



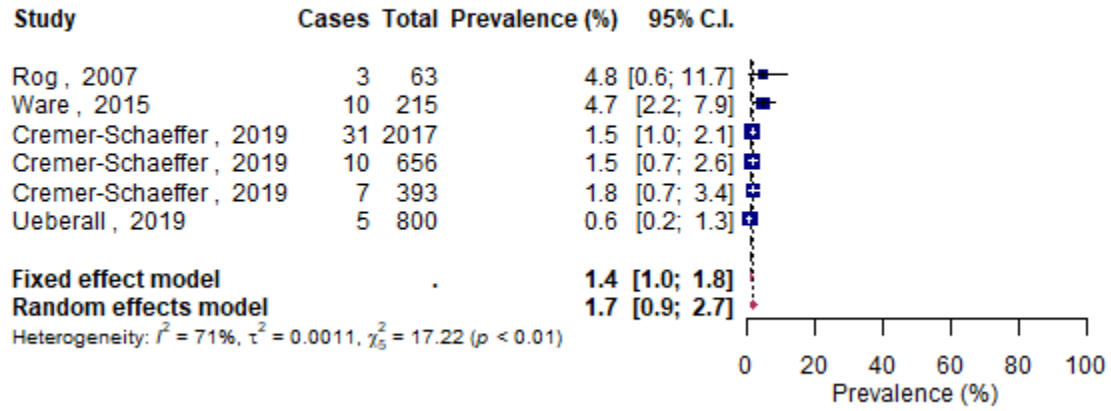
For peer review only

Appendix 18: Results for suicidal thoughts



For peer review only

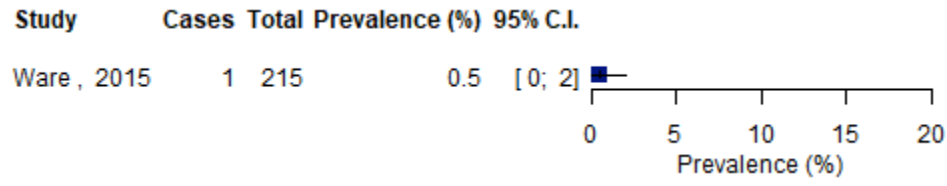
Appendix 19: Results for depression



Peer review only

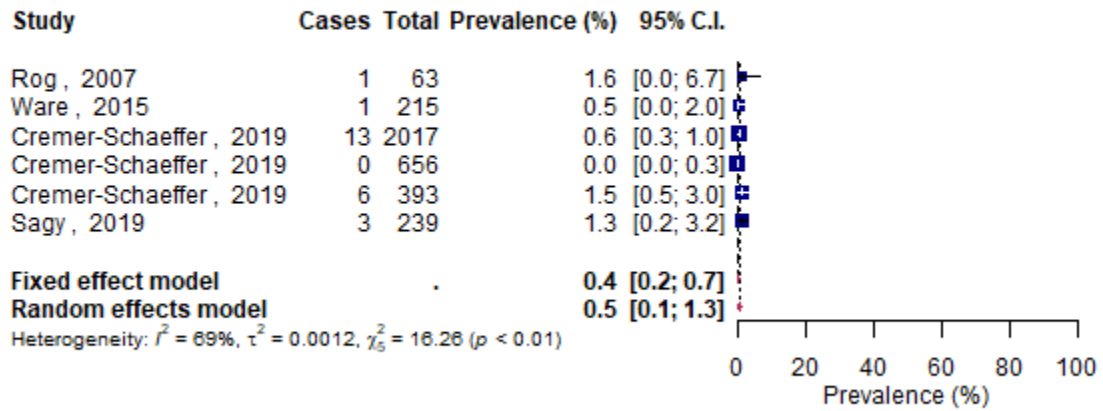
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Appendix 20: Results for mania



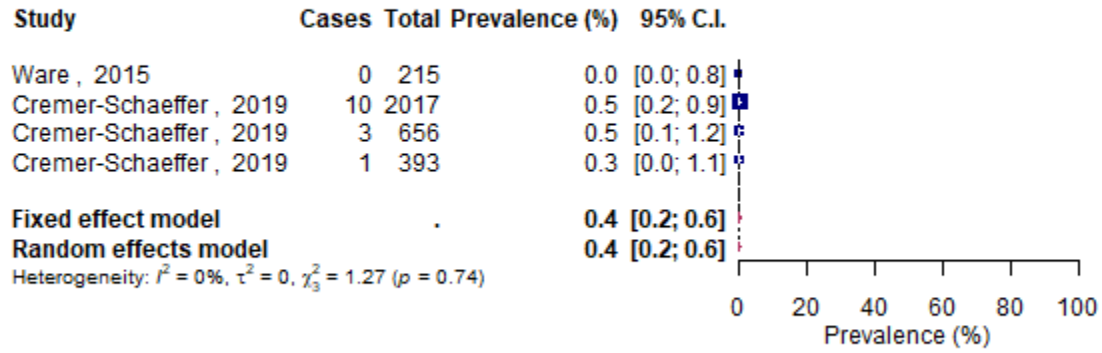
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Appendix 21: Results for hallucinations



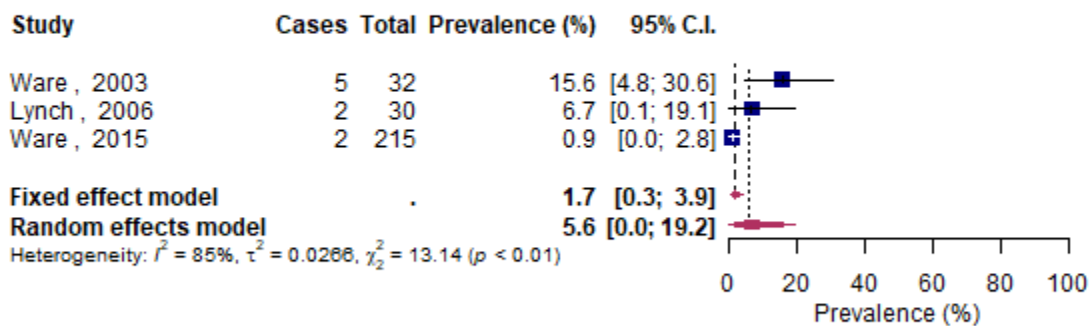
Peer review only

Appendix 22: Results for delusions



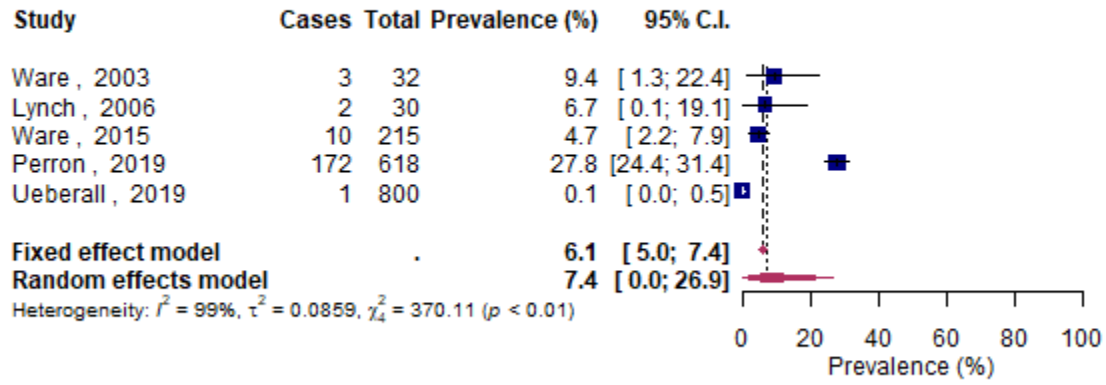
For peer review only

Appendix 23: Results for paranoia



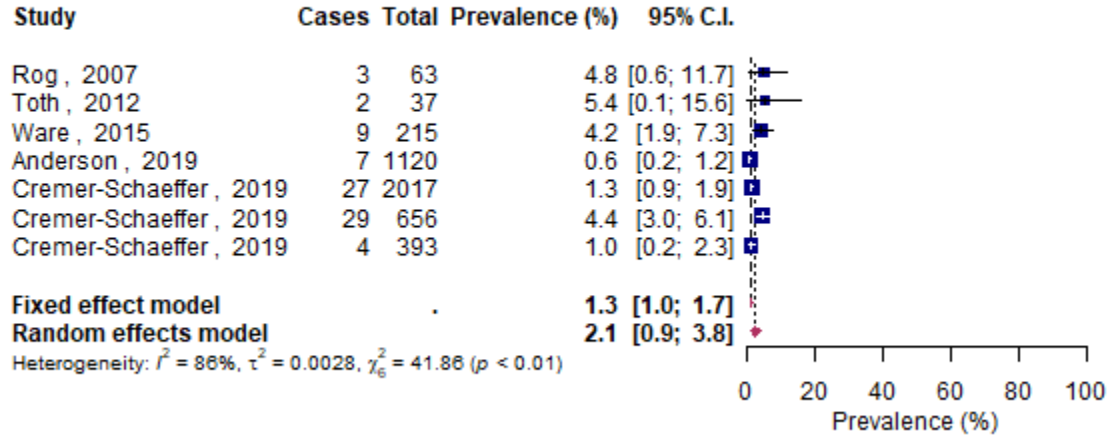
Peer review only

Appendix 24: Results for anxiety



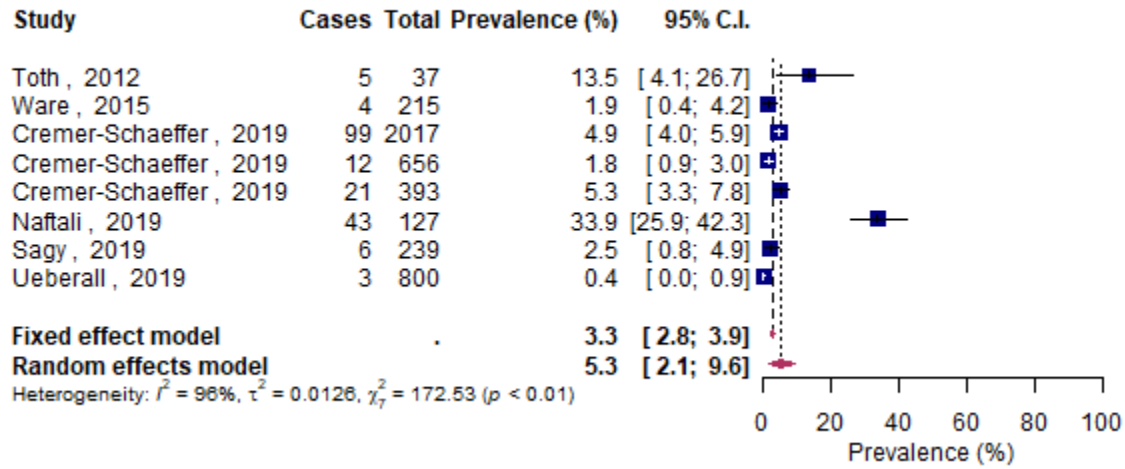
Peer review only

Appendix 25: Results for euphoria

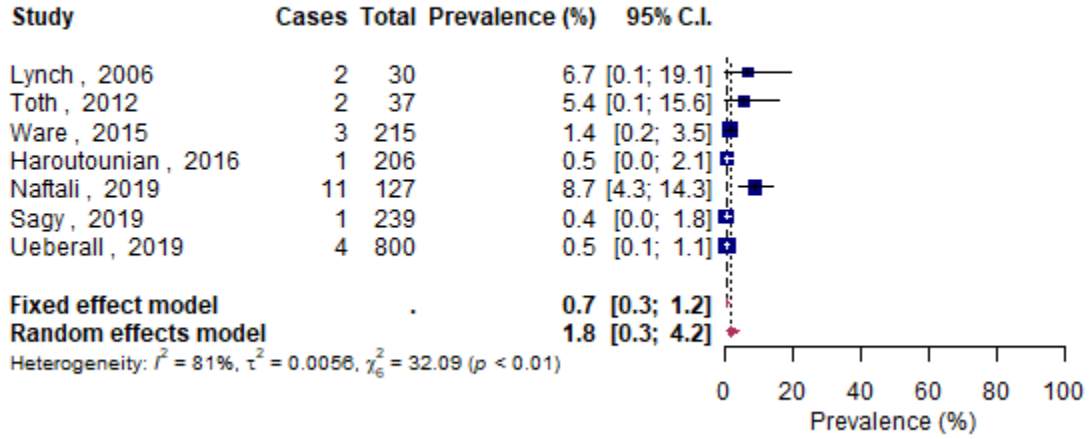


Peer review only

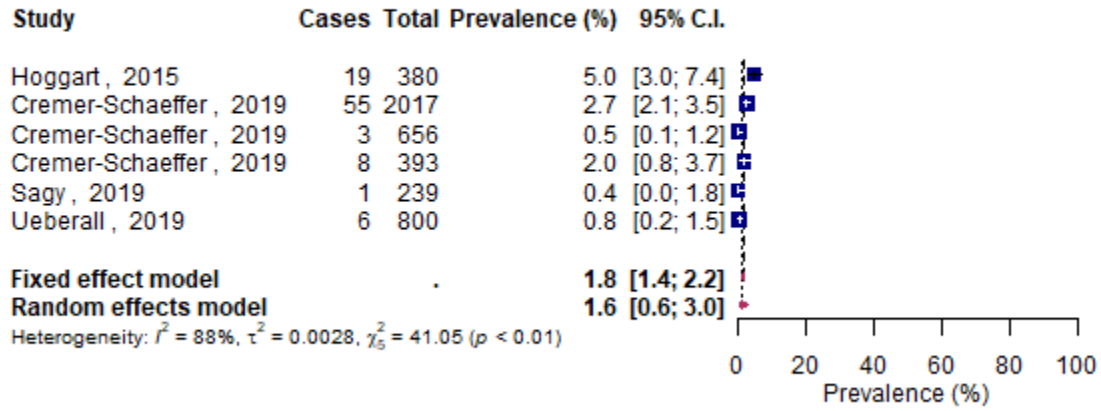
Appendix 26: Results for memory impairment



Appendix 27: Results for confusion

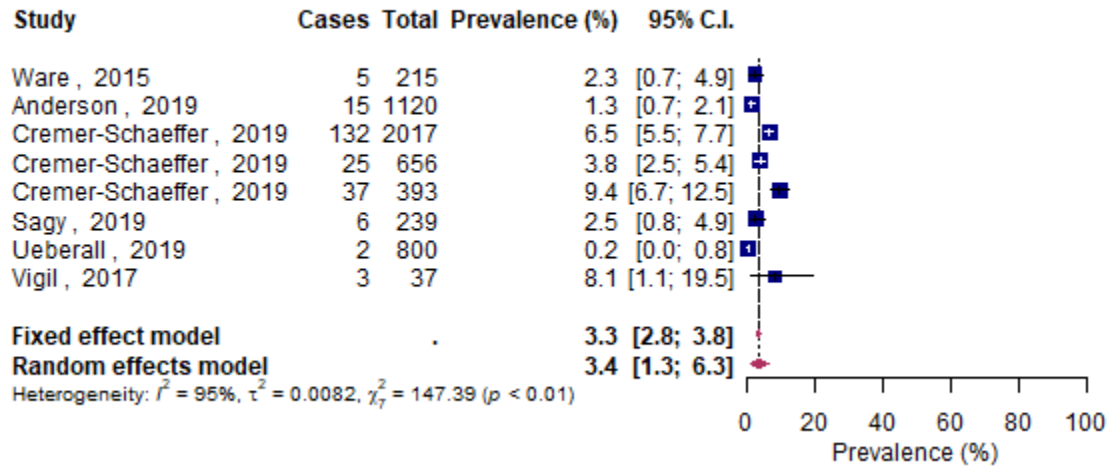


Appendix 28: Results for disorientation



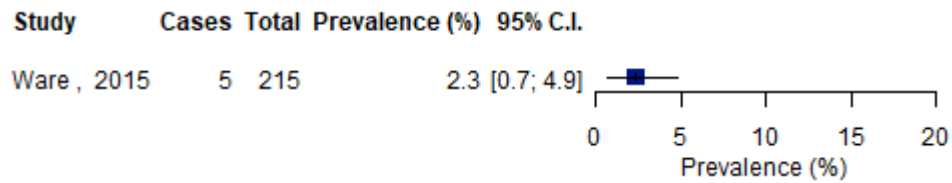
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Appendix 29: Results for impaired attention



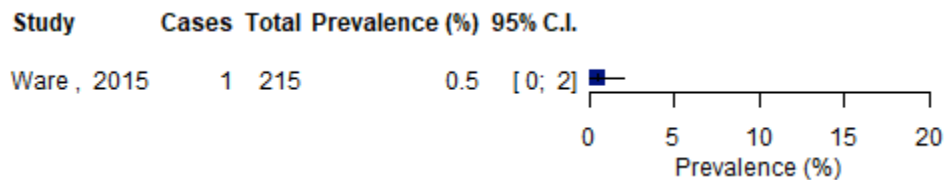
Peer review only

Appendix 30: Results for falls



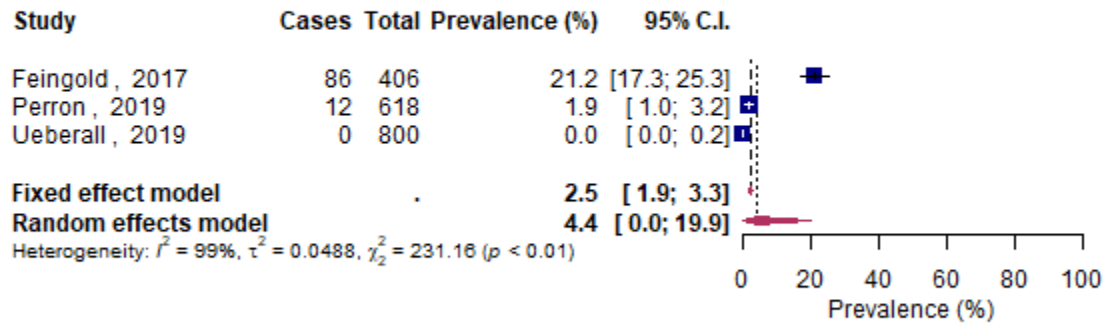
For peer review only

Appendix 31: Results for motor vehicle accidents



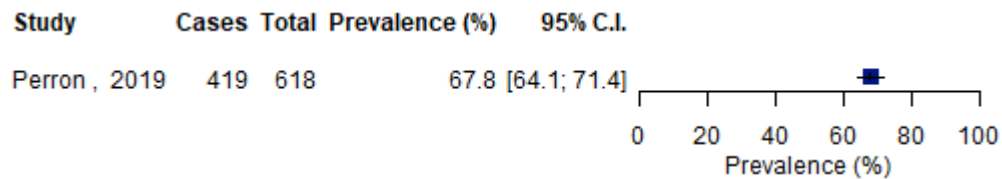
For peer review only

Appendix 32: Results for dependence



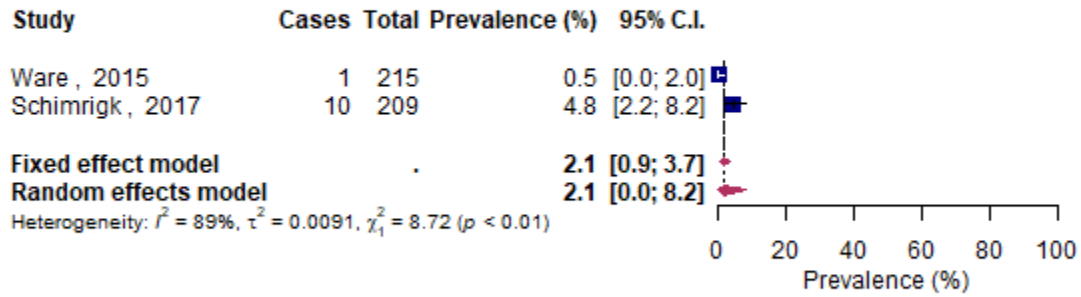
Peer review only

Appendix 33: Results for withdrawal symptoms



For peer review only

Appendix 34: Results for withdrawal syndrome



Peer review only

Section/top ic (page no)	Item	PRISMA checklist item	PRISMA harms (minimum)	Recommendations for reporting harms in systematic reviews (desirable)	Check if done
Title Title (3)	1	Identify the report as a systematic review, meta-analysis, or both.	Specifically mention “harms” or other related terms, or the harm of interest in the review.	—	X
Abstract Structured summary (4)	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	—	Abstracts should report any analysis of harms undertaken in the review, if harms are a primary or secondary outcome.	X
Introduction Rationale (5)	3	Describe the rationale for the review in the context of what is already known.	—	It should clearly describe in introduction or in methods section which events are considered harms and provide a clear rationale for the specific harm(s), condition(s), and patient group(s) included in the review.	X
Objectives (5)	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	—	PICOS format should be specified, although in systematic reviews of harms the selection criteria for P, C, and O may be very broad (same intervention may have been used for heterogeneous indications in a diverse range of patients)	X
Methods Protocol and registration (6)	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	—	No specific additional information is required for systematic reviews of harms.	X
Eligibility Criteria (6)	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	—	Report how handled relevant studies (based on population and intervention) when the outcomes of interest were not reported. Report choices for specific study designs and length of follow-up.	X
Information Sources (7)	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	—	Report if only searched for published data, or also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If includes unpublished data, provide the source and the process of obtaining it.	X
Search (7)	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	—	If additional searches were used specifically to identify adverse events, authors should present the full search process so it can be replicated.	X

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3	Study	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	—	If only included studies reporting on adverse events of interest, defined if screening was based on adverse event reporting in title/abstract or full text. If no harms reported in the text, report if any attempt was made to retrieve relevant data from authors.	X
4	Selection (8)					
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10	Data	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	—	No specific additional information is required for systematic reviews of harms.	X
11	collection					
12	process (9)					
13						
14	Data	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	—	Report the definition of the harm and seriousness used by each included study (if applicable). Report if multiple events occurred in the same individuals, if this information is available. Consider if the harm may be related to factors associated with participants (eg, age, sex, use of medications) or provider (eg, years of practice, level of training). Specify if information was extracted and how it was used in subsequent results. Specify if extracted details regarding the specific methods used to capture harms (active/passive and timing of adverse event).	X
15	items (9)					
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29	Risk of bias in	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	—	The risk of bias assessment should be considered separately for outcomes of benefit and harms.	X
30	individual					
31	studies (10)					
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35	Summary	13	State the principal summary measures (eg, risk ratio, difference in means).	—	No specific additional information is required for systematic reviews of harms.	X
36	measures (11)					
37						
38	Synthesis of	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	Specify how zero events were handled, if relevant.		
39	results (11)					
40						
41	Risk of bias	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	—	Present the extent of missing information (studies without harms outcomes), any factors that may account for their absence, and whether these reasons may be related to the results.	X
42	across studies					
43	(11)					
44						
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46	Additional	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	—	Sensitivity analyses may be affected by different definitions, grading, and attribution of adverse events, as adverse events are typically infrequent or reported using heterogeneous classifications. Report the number of participants and studies included in each subgroup.	X
47	analyses (12)					
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52	Results					
53	Study	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each	—	If a review addresses both efficacy and harms, display a flow diagram specific for each (efficacy and harm).	X
54	selection (13)					
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3		stage, ideally with a flow diagram.			
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6	Study characteristics (14)	18 For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Define each harm addressed, how it was ascertained (eg, patient report, active search), and over what time period.	Add additional characteristics to: “P” (population) patient risk factors that were considered as possibly affecting the risk of the harm outcome. “I” (intervention) professional expertise/skills if relevant (for example if the intervention is a procedure). “T” (time) timing of all harms assessments and the length of follow-up.	X
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13	Risk of bias within studies (15)	19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	—	Consider the possible sources of biases that could affect the specific harm under consideration within the review. Sample selection, dropouts and measurement of adverse events should be evaluated separately from the outcomes of benefit as described in item 12, above.	X
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20	Results of individual studies (16)	20 For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	—	Report the actual numbers of adverse events in each study, separately for each intervention.	X
21	Synthesis of results (17)	21 Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Describe any assessment of possible causality.	If included data from unpublished sources, report clearly the data source and the impact of these studies to the final systematic review.	X
22	Risk of bias across studies (18)	22 Present results of any assessment of risk of bias across studies (see item 15).	—	No specific additional information is required for systematic reviews of harms. See item 15 above.	X
23	Additional analysis (18)	23 Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression (see item 16)).	—	No specific additional information is required for systematic reviews of harms.	X
24	Discussion				
25	Summary of evidence (18)	24 Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	—	No specific additional information is required for systematic reviews of harms.	X
26	Limitations (18)	25 Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	—	Recognise possible limitations of meta-analysis for rare adverse events (ie, quality and quantity of data), issues noted previously related to collection and reporting.	X
27	Conclusions (18)	26 Provide a general interpretation of the results in the context of other evidence, and implications for future research.	—	State conclusions in coherence with the review findings. When adverse events were not identified we caution against the conclusion that the intervention is “safe,” when, in reality, its safety remains unknown.	X
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51	Funding (19)	27 Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	—	No specific additional information is required for systematic reviews of harms.	X
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