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

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Running head: Harms of medical cannabis

Abbreviations: Cochrane Central Register of Controlled Trials (CENTRAL), Palmitoylethanolamide (PEA), tetrahydrocannabinol (THC)

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Authors' Contributions: JWB and TA conceived the idea. RC designed and conducted the search. DZ, MAC, AA, GL, KL, JD, BYH, CH, and PJH screened search records, extracted data, and assessed the risk of bias of the eligible studies. DZ conducted analyses. DZ, JWB, and TA interpreted the data. DZ wrote the first draft of the manuscript. JWB and TA critically revised the manuscript. All authors reviewed and approved the final version. DZ and JWB are the guarantors.

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Abstract

Objective: To establish the risk and prevalence of long-term and serious harms of medical cannabis and cannabinoids for chronic pain.

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, EMBASE, PsycInfo, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to April 1, 2020.

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

Data extraction and synthesis: A parallel guideline panel provided input on the design and interpretation of the systematic review, including selection of adverse events for consideration. Two reviewers, working independently and in duplicate, screened the search results, extracted data, and assessed risk of bias. We used random-effects models for all meta-analyses and the GRADE approach to evaluate the certainty of evidence.

Results: We identified 39 eligible studies that enrolled 12,143 adult patients with chronic pain. Very low certainty evidence suggests that adverse events are common (prevalence: 26.0%; 95% CI 13.2 to 41.2) among users of medical cannabis or cannabinoids for chronic pain, particularly any psychiatric adverse events (prevalence: 13.5%; 95% CI 2.6 to 30.6). Very low certainty evidence, however, indicates serious adverse events, adverse events leading to discontinuation, cognitive adverse events, accidents and injuries, and dependence and withdrawal syndrome are uncommon and each typically occur in fewer than one in 20 patients. We compared studies with <24 weeks and ≥24 weeks of cannabis use and found more adverse events reported among studies with longer follow-up (test for interaction $p < 0.01$). Palmitoylethanolamide was usually associated with few to no adverse events. We found insufficient evidence addressing the harms of medical cannabis compared to other pain management options, such as opioids.

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

Systematic review registration https://osf.io/25bxf

What is already known on this topic

- Medical cannabis and cannabinoids are increasingly used for the management of chronic pain.
- Clinicians and patients considering medical cannabis or cannabinoids as a treatment option for chronic pain require evidence on benefits and harms, including long-term and serious adverse events to make informed decisions.

What this study adds

- Very low certainty evidence suggests that adverse events are common among people living with chronic pain who use medical cannabis or cannabinoids, including psychiatric adverse events, though serious adverse events, adverse events leading to discontinuation, cognitive adverse events, accidents and injuries, and dependence and withdrawal syndrome are uncommon.
- There is insufficient evidence comparing the harms of medical cannabis or cannabinoids to other pain management options, such as opioids.

Background

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

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

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

and dependence and withdrawal. It is one of four systematic reviews that together informed a parallel guideline.[11 18 20 21] A parallel systematic review addressed evidence from randomized trials.[11]

Methods

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

Guideline panel involvement

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

Patient and public involvement

Three patient partners were included as part of the guideline panel and contributed to the selection and prioritization of outcomes, protocol, and interpretation of review findings, and provided insight on values and preferences.

Search

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

Study selection

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

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

Data extraction and risk of bias

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

duration), and (4) number of patients that experienced adverse events, including all adverse events, serious adverse events, and withdrawal due to adverse events. Reviewers resolved disagreements by discussion or by adjudication with a third party (DZ). We classified adverse events as serious based on the classification used in primary studies. For comparative studies, we collected results from models adjusted for confounders, when reported, and unadjusted models when results for adjusted models were not reported.

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

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

Data synthesis

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

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

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

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

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

medical cannabis before the inception of the study) or were preceded by a run-in period or clinical trial during which patients that experienced adverse events or found medical cannabis intolerable could discontinue would report fewer adverse events because prevalent of medical cannabis are likely to represent populations that have self-selected for tolerance to cannabis. We performed tests for interaction to establish whether subgroups differed significantly from one another. We assessed the credibility of significant subgroup effects (test for interaction $p < .05$) using published criteria.[29 30]

We performed all analyses using the 'meta' package in R (version 3.5.1, R Foundation for Statistical Computing).[31]

Certainty of evidence

We used the GRADE approach to rate the certainty of evidence.[32 33] Based on GRADE guidance for using the ROBINS-I tool, evidence starts at high certainty and is downgraded by one level when the majority of the evidence comes from studies at moderate risk of bias, two levels when the majority of the evidence comes from studies at high risk of bias, and three levels when the majority of the evidence comes from studies rated at critical risk of bias.[32] We additionally considered potential limitations due to indirectness if the population, intervention, or adverse events assessed in studies did not reflect the populations, interventions, or adverse events of interest, inconsistency if there was important unexplained differences in the results of studies, and imprecision if the upper and lower bounds of confidence intervals indicated appreciably different rates of adverse events. For assessing inconsistency and imprecision for the outcome all adverse events, based on feedback from the guideline panel, we deemed a 20% difference in the prevalence of all adverse evidence to be patient-important; a 10% difference for adverse events leading to discontinuation, serious adverse events, and psychiatric, cognitive, withdrawal and dependence, injuries; and a 3% difference for potentially fatal adverse events, such as suicides and motor vehicle accidents. We followed GRADE guidance for communicating our findings.[34] Guideline panel members interpreted the magnitude of adverse events and decided whether the observed prevalence of adverse events was sufficient to affect patients' decisions to use medical cannabis or cannabinoids for chronic pain.

Results

Study selection

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

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

Description of studies

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

Thirty studies (76.9%) reported on people living with chronic non-cancer pain, eight (n=20.5%) with mixed cancer and non-cancer chronic pain, and one (2.6%) with chronic cancer pain. All studies reported on adults. Sixteen studies reported on mixed types of herbal cannabis (e.g., buds for smoking, vaporizing, and ingesting, hashish, oils, extracts, edibles), nine on palmitoylethanolamide (PEA), four each on nabiximols and dronabinol, two on nabilone, one each on Trokie lozenges and extracts, and four did not report the type of medical cannabis used. One study reported on three types of medical cannabis (dronabinol, nabiximols, and mixed herbal) separately. The median duration of medical cannabis use was 24 weeks (IQR 12.0 to 33.8 weeks). Two studies were comparative: one study compared nabilone with gabapentin and another compared herbal cannabis with standard care.[39 48] Studies reported a total of 525 unique adverse events.

Risk of bias

Appendix 5 presents the risk of bias of included studies. We rated all results at critical risk of bias except for the comparative results from two studies,[39 48] which were rated at serious and moderate risk of bias. The primary limitation across studies was inadequate control for potential confounding either due to the absence of a control group or inadequate adjustment for confounders. A third of studies were rated at serious risk of bias for selection bias, primarily because they included prevalent users of medical cannabis. Such studies may underestimate the incidence of adverse events since patients that experience adverse

events are more likely to discontinue medical cannabis early. Such studies may also include adverse events that may have been present at inception and that are unrelated to medical cannabis use.

All adverse events

Twenty longitudinal and two cross-sectional studies, including 4,108 patients, reported the number of patients experiencing one or more adverse events.[36-43 46 47 54 56-60 62 64 65 69 70 73] Seven studies reported on PEA, five on mixed herbal cannabis, three each on nabilone and nabiximols, two on dronabinol, and one each on extracts and Trokie lozenges. The median duration of medical cannabis use was 24 weeks [IQR 12 to 32]. We observed substantial unexplained heterogeneity and so summarize the results descriptively (Appendices 6 to 9). The prevalence of any adverse event ranged between 0% to 92.1%. Studies with less than 24 weeks of cannabis use (the median duration of cannabis) 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.

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

Adverse events leading to discontinuation

Twenty longitudinal studies, including 6,509 patients, reported on the number of patients that 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] Eight studies reported on PEA, four studies on mixed herbal cannabis, three on nabiximols, two on nabilone, and one each on dronabinol and extracts, and one study did not report the type of medical cannabis used by patients. The median duration of cannabis use was 24 weeks [IQR 8.6 to 32]. We observed substantial unexplained heterogeneity and so summarize the results descriptively (Appendices 10 to 12). 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.

One study suggested herbal cannabis may increase the risk of adverse events leading to discontinuation compared to standard care without cannabis (4.7%; 95% CI 1.8 to 7.5). Another study suggested that nabilone may reduce the risk of adverse events leading to discontinuation compared to gabapentin (-

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

Serious adverse events

Twenty-two longitudinal and two cross-sectional studies, including 4,273 patients, reported on the 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 studies reported on mixed herbal cannabis, eight on PEA, two each on nabilone and nabiximols each, and one study each on dronabinol, extracts, and Trokie lozenges, and one study did not report the type of cannabis used. The median duration of medical cannabis or cannabinoid use was 24 weeks (IQR 12 to 32), and few patients experienced serious adverse events (1.2%; 95% CI 0.1 to 3.1; I^2=91%) (Figure 2) (Appendices 13 to 15). There was a statistically significant subgroup effect across different types of medical cannabis though serious adverse events appeared consistently uncommon among different types (low credibility). The certainty of evidence was very low overall due to serious risk of bias.

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

Psychiatric adverse events

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

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

Cognitive and attentional adverse events

Eleven longitudinal studies, including 6,257 patients, reported on cognitive adverse events, including memory impairment, confusion, disorientation, and impaired attention (Appendices 26 to 29).[35-37 43 47 48 60 63 67 68 70] Five studies reported on herbal cannabis, three on nabiximols, three on mixed types of cannabis, and one each on dronabinol and nabilone. The median duration of cannabis use was 52 weeks (IQR 24 to 52). The prevalence of cognitive adverse events ranged from 1.6% (95% CI 0.6 to 3.0; I^2=88%) to 5.3% (95% CI 2.1 to 9.6; I^2=96%) for disorientation and memory impairment, respectively. The certainty of evidence was very low due to risk of bias.

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

Accidents and injuries

One longitudinal study, including 431 patients, reported on accidents and injuries in patients using mixed herbal cannabis for 52 weeks (Appendices 30 & 31).[48] This study suggests herbal cannabis used for medical purposes may slightly increase the risk of motor vehicle accidents (0.5%; 95% CI -0.4 to 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 to risk of bias.

Dependence and withdrawal

Four longitudinal and one cross-sectional study, including 2,248 patients, reported on dependence-related adverse events, including dependence (one study reported on 'abuse' based on unspecified criteria, one study reported on 'problematic use' using the Alcohol Use Disorder and Associated Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (AUDADIS-IV)[74], and one study reported on 'dependence' using the Alcohol, Smoking, and Substance Involvement Screening Test[75]), withdrawal symptoms (defined as one or moderate or severe withdrawal symptoms including sleep difficulties, anxiety, irritability, and appetite disturbance), and withdrawal syndrome (two studies that used unspecified criteria) (Appendices 32 to 34).[48 53 56 67 70] Two studies

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

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

Discussion

Main findings

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

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

associated with longer durations of cannabis use.[10 76-80] A parallel systematic review of evidence from randomized controlled trials found no evidence to inform long-term harms of medical cannabis as no eligible trial followed patients for more than 5.5 months.[11] One previously published review that included non-randomized studies searched the literature until 2007, included studies exploring medical cannabis for any indication (excluding synthetic cannabinoids) of which only two enrolled people living with chronic pain.[12] The review also did not synthesize adverse event data from non-randomized studies.[12] Unlike previous reviews, we focused exclusively on medical cannabis for chronic pain and excluded recreational cannabis, because cannabis used for recreational purposes often contains higher concentrations of tetrahydrocannabinol (THC) than medical cannabis. We also focused on chronic pain because this patient population may be susceptible to different adverse events. Depression and anxiety, for example, are commonly occurring comorbidities of chronic pain, which may be exacerbated by cannabis.[15-17]

Strengths and limitations

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

Our review is limited by the non-comparative design of most studies, which precludes confident inferences regarding the proportion of adverse events that can be attributed to medical cannabis or cannabinoids and the magnitude by which medical cannabis may increase or decrease the risk of adverse events compared to other pain management options. Though adverse events appear common among medical cannabis users, it is possible that other management options for chronic pain, particularly opioids, may be associated with more (and more severe) adverse events.[81] Partly due to the non-comparative design of most studies, nearly all results included in our review were at serious or critical risk of bias for confounding and Simpson's paradox,[82] either due to the absence of a control group or due to insufficient adjustment for important confounders. Further, a third of studies were at high risk of selection bias, primarily because they included prevalent cannabis users. In such studies, the prevalence of adverse events may be underestimated. Our review provides limited evidence on the harms of medical cannabis beyond one year of use since most studies reported adverse events for less than one year of follow-up.

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

adverse events and adverse events leading to discontinuation due to substantial inconsistency. Further, some analyses included too few studies or participants, due to which estimates were imprecise.

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

Clinicians and patients may be more inclined to use medical cannabis or cannabinoids for pain relief if adverse events are mild; however, the evidence on whether adverse events are transient, life threatening, or the extent to which they impact quality of life is limited. While more than half of studies reported on the proportion of adverse events that were serious, criteria for ascertaining severity were rarely reported. None of the included studies reported the duration for which patients experienced adverse events. Further, most primary studies did not report adequate details on methods for the ascertainment of adverse events, including definitions or diagnostic criteria. The two studies that reported on withdrawal syndrome, for example, did not provide diagnostic criteria.[48 56] However, the DSM-5 requires ≥3 of 7 withdrawal symptoms to be present within a week of stopping cannabis use to meet a diagnosis of cannabis withdrawal syndrome.[83] It is therefore reasonable that people living with chronic pain that use medical cannabis would be more likely to experience withdrawal symptoms vs. withdrawal syndrome.

While children and youth account for approximately 15% of all chronic pain patients, we did not identify any evidence addressing the harms of medical cannabis in this population.[84] As such, the extent to which our findings are generalizable to pediatric populations is uncertain. Although there is evidence that cannabis use during youth is associated with increased risk of acute psychotic disorders, particularly acute psychosis,[85] such studies have explored use of recreational cannabis that contains greater amounts of THC than is typically seen in medical preparations. Further, the population of patients with chronic pain on which the studies report may not be representative of all patients with chronic pain—particularly rare conditions that cause chronic pain.

We used the DerSimonian and Laird method for meta-analysis.[26] A growing body of evidence, however, suggests that this model has important limitations that may be addressed by alternative models[86]—though there is limited evidence on the performance of these models for meta-analyses of proportions and prevalence.

Finally, we excluded studies from meta-analyses when they did not explicitly report the adverse events of interest to our panel members. This may have overestimated the prevalence of adverse events if the adverse events of interest were not observed in the studies in which they were not reported. This was, however, not possible to confirm because methods for the collection and reporting of adverse event data across studies were variable (e.g., active monitoring vs. passive surveillance; collecting data on specific adverse events vs. all adverse events) and poorly described in study reports.

Implications

Our systematic review and meta-analysis shows that evidence regarding long-term and serious harms of medical cannabis or cannabinoids is insufficient—an issue with important implications for patients and clinicians considering this management option for chronic pain. While the evidence suggests that adverse events are common in patients using medical cannabis for chronic pain, serious adverse events appear uncommon, which suggests that the potential benefits of medical cannabis or cannabinoids (although very modest) may outweigh potential harms for some patients.[11 18]

Clinicians and patients considering medical cannabis should be aware that more adverse events were reported among studies with longer follow-up, necessitating long term follow-up of patients and re-evaluation of pain treatment options. Our findings also have implications for the choice of medical cannabis. We found PEA, for example, to consistently be associated with few or no adverse events across studies, though the evidence on the efficacy of PEA is limited.[11]

We found very limited evidence comparing medical cannabis or cannabinoids with other pain management options. Other pharmacological treatments for chronic pain, such as gabapentinoids, antidepressants, and opioids, may be associated with more (and more serious) adverse events.[87-89] To guide patients' and clinicians' decisions on medical cannabis for chronic pain, future research should compare the harms of medical cannabis and cannabinoids with other pain management options, including opioids, ideally beyond one year of use, and adjust results for confounders. Comparative studies may be synthesized by way of network meta-analysis, which would allow indirect comparisons across formulations of medical cannabis. Future research could also explore whether the harms of medical cannabis vary depending on the type of chronic pain.

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

harms. To enhance the interpretability of adverse event data, future studies should also report the duration and severity of adverse events, since these factors are important to patients' decisions.

A valuable output of our systematic review is an open-source database of over 500 unique adverse events reported to date in non-randomized studies of medical cannabis or cannabinoids for chronic pain with corresponding assessments of risk of bias. This database was compiled in duplicate by trained and calibrated data extractors and is freely available to those interested in further analyzing the prevalence of different types of adverse events or to those interested in expanding the database to include adverse events in patients using medical cannabis or cannabinoids for other indications.

Conclusion

Our systematic review and meta-analysis found very low certainty evidence that suggests ~~that~~ adverse events are common among people living with chronic pain using medical cannabis or cannabinoids, but that serious adverse events, adverse events causing discontinuation, cognitive adverse events, motor vehicle accidents, falls, and dependence and withdrawal syndrome are uncommon. We also found very low certainty evidence that longer duration of use was associated more adverse events and that PEA, compared with other types of medical cannabis, may result in few or no adverse events. Future research should compare the risks of adverse events of medical cannabis and cannabinoids with alternative pain 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

				standard care		216	
Haroutounian, 2016 [49]	longitudinal*	Israel	mixed cancer and non-cancer pain	mixed herbal	mean: 43.2 g/month	206	30
Bellnier, 2017 [50]	longitudinal*	US	mixed cancer and non-cancer pain	mixed herbal	Capsule: 10 mg /8 to 10 hours 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
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
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
Feingold, 2017 [53]	cross-sectional*	Israel	mixed cancer and non-cancer pain	mixed herbal	NR	406	NR
Paladini, 2017 [54]	longitudinal††	Italy	failed back surgery syndrome	PEA	600 mg bid for one month; 600 mg/day for one month	35	8
Passavanti, 2017 [55]	longitudinal††	Italy	lower back pain	PEA	600 mg bid	30	24
Schimrigk, 2017 [56]	longitudinal*†	Germany, Austria	multiple sclerosis	dronabinol	range: 7.5 to 15 mg/day	209	32
Chirchiglia, 2018 [57]	longitudinal††	Italy	lower back pain	PEA	1.2 g/day	100	4
Crowley, 2018 [58]	longitudinal*	US	mixed non-cancer pain	Trokie lozenges	NR	35	4 to 60
Habib, 2018 [59]	longitudinal*	Israel	fibromyalgia	mixed herbal	mean: 26 g/month	26	mean: 41.6
Anderson, 2019 [60]	longitudinal*	US	cancer pain	mixed herbal	NR	1120	16
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
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
Cremer-Schaeffer, 2019 [63]	longitudinal††	Germany	mixed cancer and non-cancer pain	dronabinol	NR	2017	52
				mixed herbal	NR	656	
				nabiximols	NR	393	
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
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

Naftali, 2019 [66]	longitudinal*	Israel	inflammatory bowel disease	mixed herbal	mean: 31 g/month mean: 21 g/day THC; 170 g/day CBD	127	median: 176
Perron, 2019 [67]	cross-sectional*	US	mixed non-cancer pain	NR	daily (n=580), weekly (n=85)	618	≥12
Sagy, 2019 [68]	longitudinal††	Israel	mixed cancer and non-cancer pain	mixed herbal	median: 1000 mg/day cannabis median: 140 mg/day THC; 39 mg/day CBD	239	24
Sinclair, 2019 [69]	cross-sectional*	Australia	endometriosis	mixed herbal	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)	48	NR
Ueberall, 2019 [70]	longitudinal*	Germany	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)	nabiximols	mean: 7.1 sprays/day	800	12
Vigil, 2017 [71]	longitudinal*	US	mixed non-cancer pain	NR	NR	37	mean: 82.4
Yassin, 2019 [72]	longitudinal††	Israel	fibromyalgia	mixed herbal	20 to 30 g/month	31	24
Giorgi, 2020 [73]	longitudinal††	Italy	fibromyalgia	extracts	10 to 30 drops/day; no more than 120 drops/day	102	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)

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.

Figures

Figure 1: Study selection process

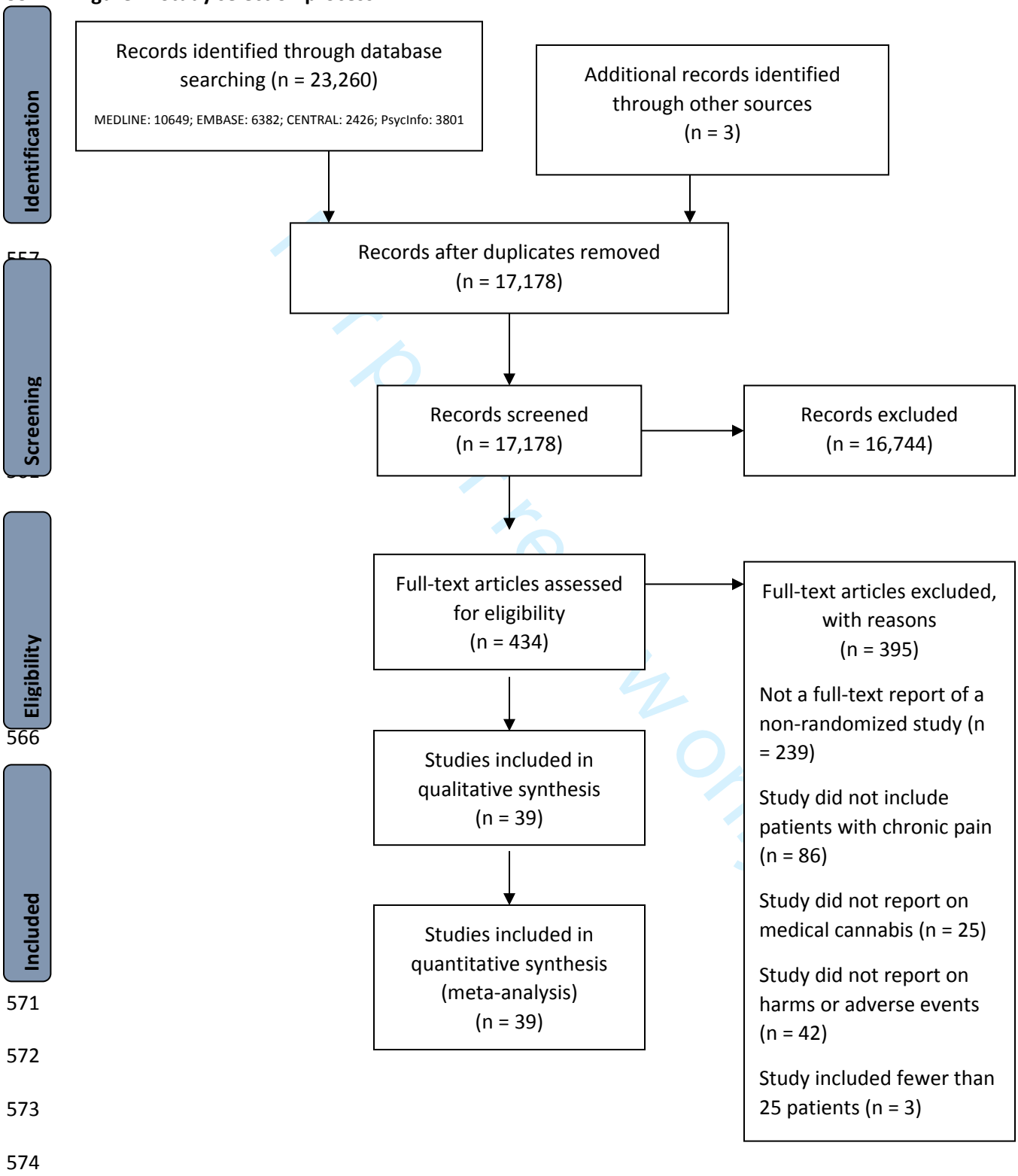

Figure 2: Forest plot of the meta-analysis for all adverse events stratified by type of medical cannabis

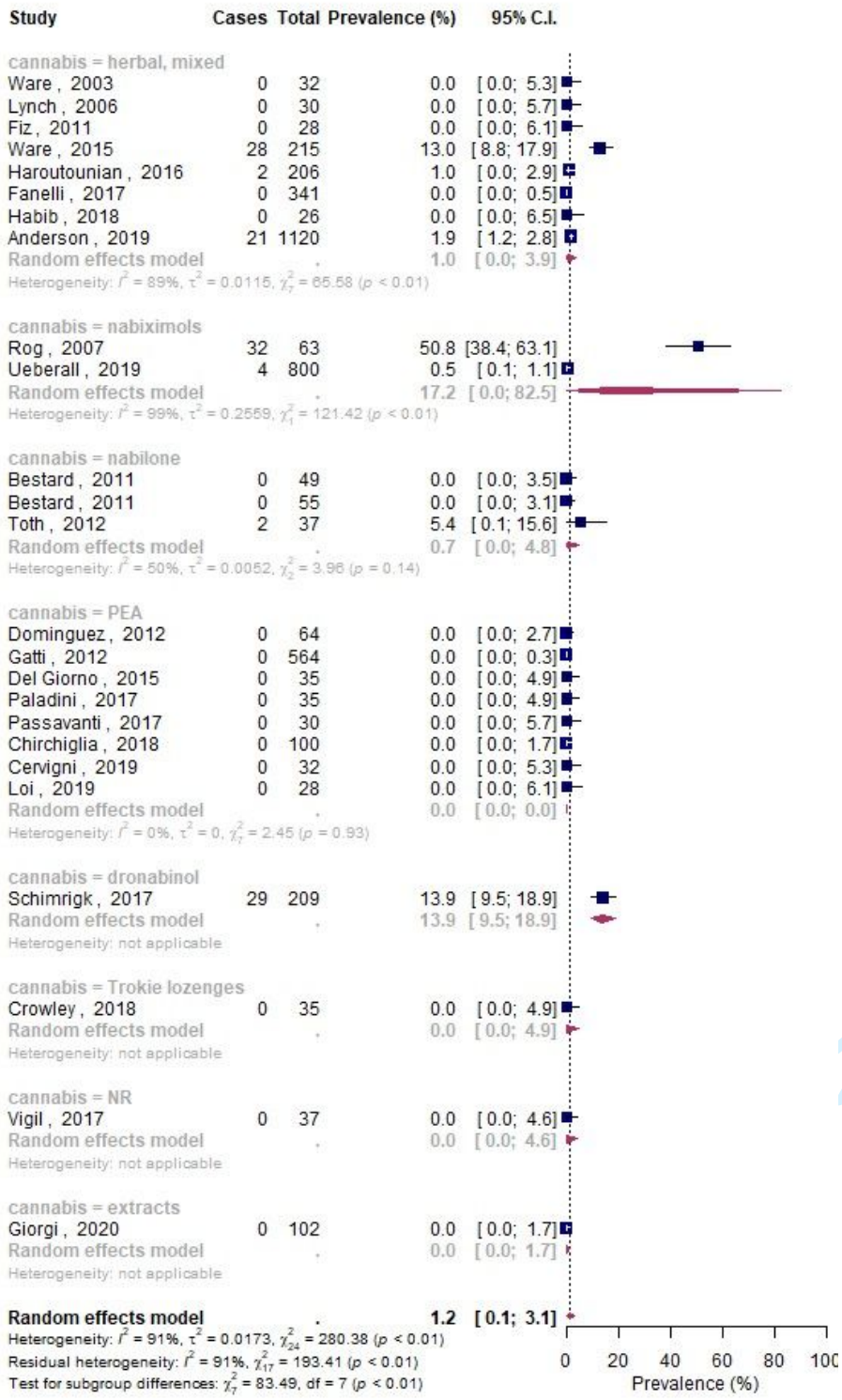

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Figure 1: Study selection process

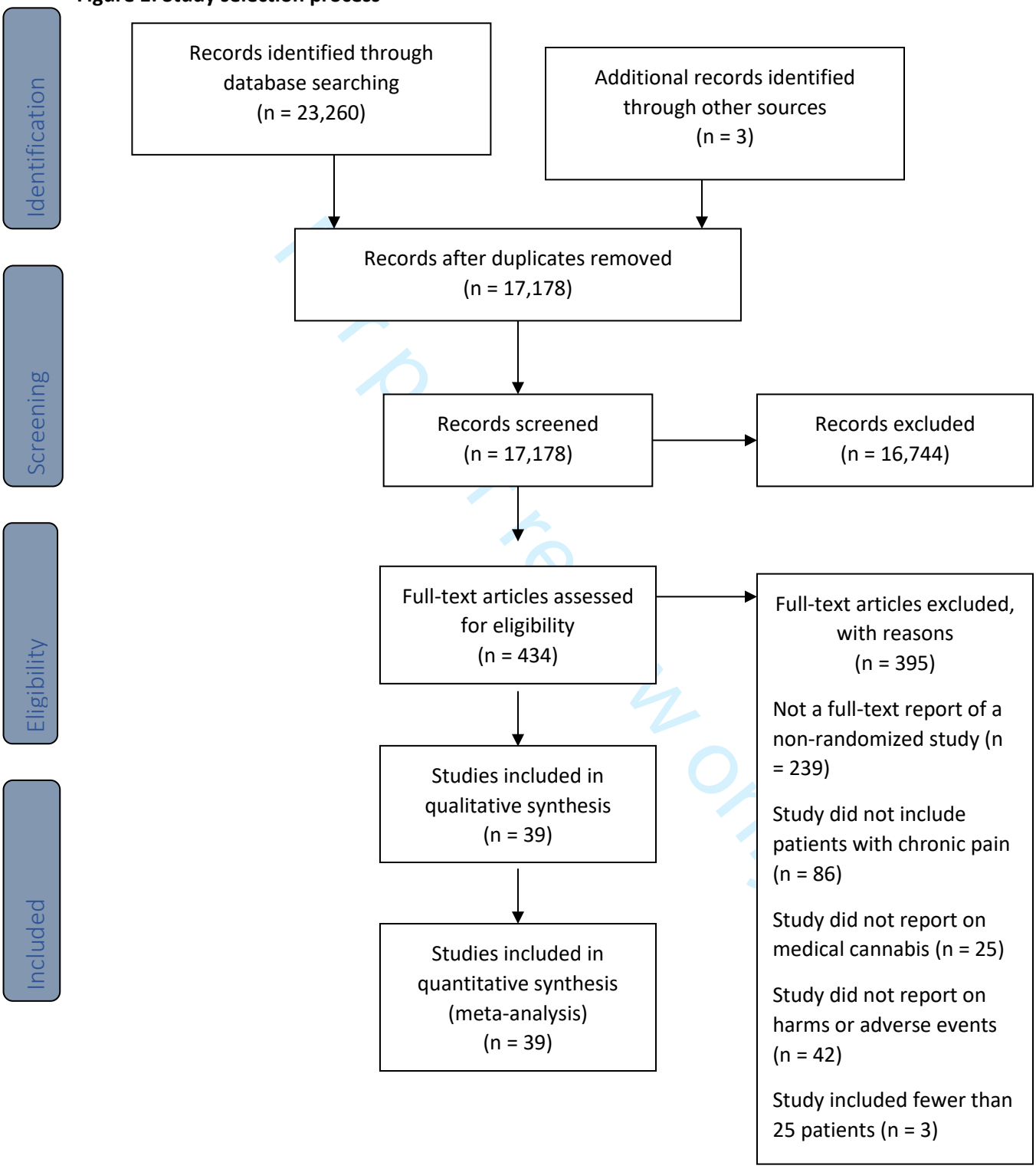
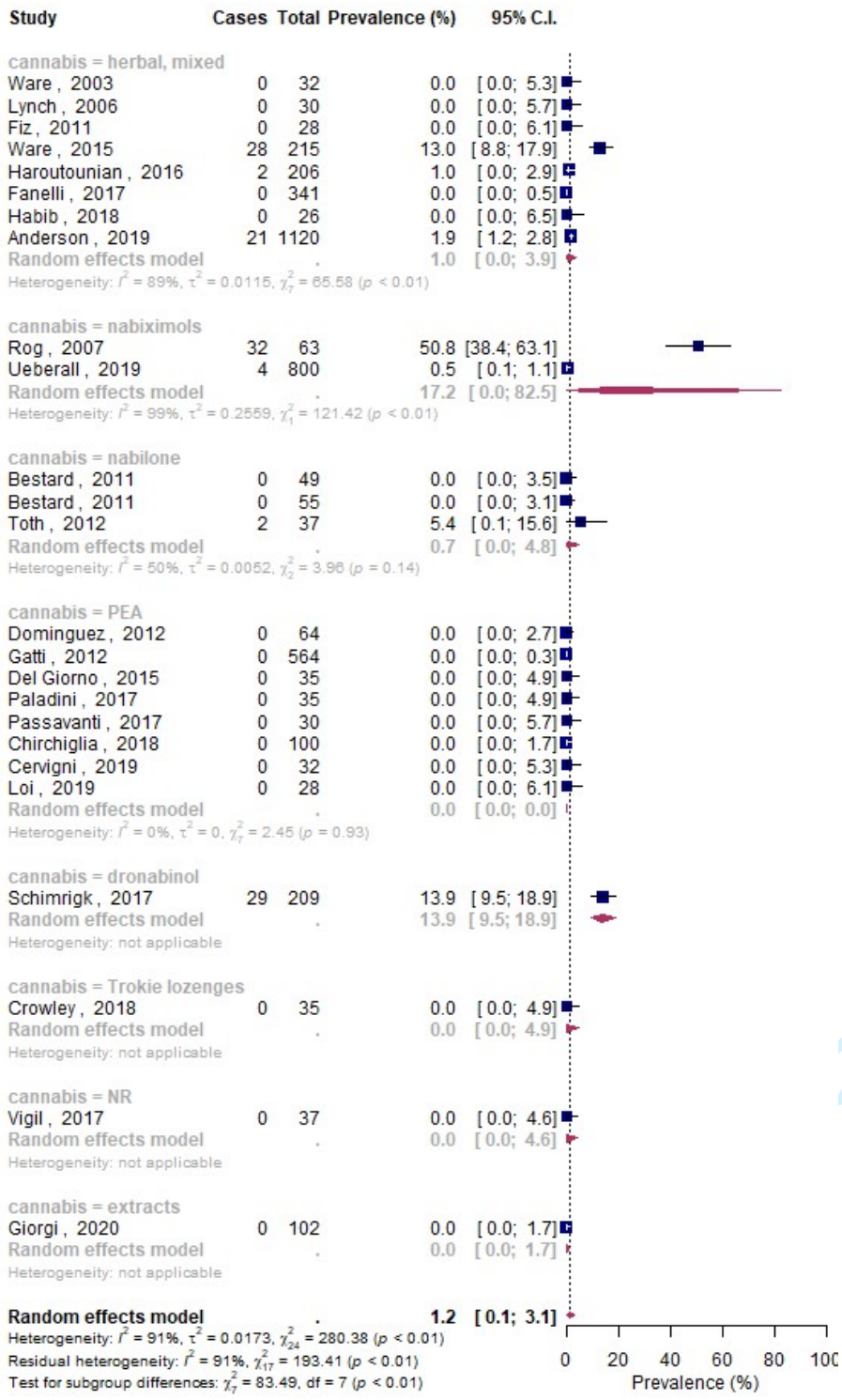


Figure 2: Forest plot of the meta-analysis for all adverse events stratified by type of medical cannabis



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

Appendix

Dr. Jason Busse

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Contents

Appendix 1: Search strategy

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

April 1, 2020

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

Search Strategy:

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1 Epidemiologic Studies/ (8256)

2 exp Case-Control Studies/ (1067341)

3 exp Cohort Studies/ (1974212)

4 Case control.tw. (123081)

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

6 Cohort analy$.tw. (7799)

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

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

9 Longitudinal.tw. (239715)

10 Retrospective.tw. (515751)

11 Cross sectional.tw. (342224)

12 Cross-sectional studies/ (322752)

13 or/1-12 (2953281)

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

15 13 not 14 (2889789)

Annotation: SIGN observational studies filter

16 randomized controlled trial.pt. (503041)

17 controlled clinical trial.pt. (93591)

18 randomized.ab. (474985)

19 placebo.ab. (206552)

20 drug therapy.fs. (2191450)

21 randomly.ab. (330409)

22 trial.ab. (500400)

23 groups.ab. (2028909)

24 or/16-23 (4670111)

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

26 24 not 25 (4048339)

Annotation: Cochrane HSSS RCT filter

27 15 or 26 (6033576)

Annotation: study design filter broad

28 Cannabis/ (8968)

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

30 Endocannabinoids/ (5630)

31 exp Receptors, Cannabinoid/ (9240)

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

33 or/28-32 (54925)

Annotation: strategy from 2020 cannabis review

34 27 and 33 (16307)

Annotation: cannabis AND study design filter

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

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

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

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

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

40 exp Product Surveillance, Postmarketing/ (15237)

41 adverse drug reaction reporting systems/ (7463)

42 clinical trials, phase iv/ (295)

43 exp Poisoning/ (156177)

44 exp Substance-Related Disorders/ (274845)

45 Abnormalities, Drug-Induced/ (14514)

46 Drug Monitoring/ (20599)

47 exp Drug Hypersensitivity/ (45642)

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

49 or/35-48 (5596308)

Annotation: OVID AE filter

50 34 and 49 (10649)

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

Database: Embase <1974 to 2020 March 31>

Search Strategy:

---

1 cannabis/ (33859)

2 exp cannabinoid/ (65694)

3 medical cannabis/ (2104)

4 exp cannabinoid receptor/ (14557)

5 exp endocannabinoid/ (8589)

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

7 or/1-6 (87843)

Annotation: cannabis

8 clinical study/ (154879)

9 case control study/ (153658)

10 family study/ (26012)

11 longitudinal study/ (137463)

12 retrospective study/ (897628)

13 prospective study/ (590879)

14 randomized controlled trials/ (176633)

15 13 not 14 (584662)

16 cohort analysis/ (564001)

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

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

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

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

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

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

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

Annotation: SIGN observational studies filter

24 7 and 23 (9720)

Annotation: cannabis AND observational studies

25 randomized controlled trial/ (597702)

26 Controlled clinical study/ (463832)

27 random$.ti,ab. (1518977)

28 randomization/ (86491)

29 intermethod comparison/ (258334)

30 placebo.ti,ab. (303428)

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

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

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

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

35 double blind procedure/ (171048)

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

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

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

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

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

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

42 human experiment/ (490389)

43 trial.ti. (295850)

44 or/25-43 (4952112)

Annotation: Cochrane RCT filter

45 7 and 44 (14036)

Annotation: cannabis AND RCTs

46 24 or 45 (21357)

Annotation: cannabis AND (Obs studies OR RCTs)

47 7 and (23 or 44) (21357)

Annotation: logic check

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

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

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

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

52 exp adverse drug reaction/ (522775)

53 exp drug toxicity/ (125051)

54 exp intoxication/ (366563)

55 exp drug safety/ (393912)

56 exp drug monitoring/ (53058)

57 exp drug hypersensitivity/ (56248)

58 exp postmarketing surveillance/ (35831)

59 exp drug surveillance program/ (26017)

60 exp phase iv clinical trial/ (3822)

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

62 or/48-61 (6002309)

Annotation: OVID AE filter 1-14

63 47 and 62 (6382)

Cannabis AEs

Search Name: cannabis AEs

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

Comment:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#22 #6 and #21 in Trials 2426

PsycInfo

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

Search Strategy:

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

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

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

3 1 or 2 (26466)

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

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

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

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

8 toxic disorders/ (1433)

9 exp "substance use disorder"/ (127742)

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

11 or/4-10 (310848)

12 3 and 11 (10984)

13 epidemiology/ (49562)

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

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

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

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

18 Case control.mp. (10736)

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

20 Cohort analy$.mp. (2099)

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

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

23 or/13-22 (561443)

24 12 and 23 (3801)

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

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

Appendix 3: List of included studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21. Bulbul A, Mino EA, Khorsand-Sahbaie M, Lentkowski L. Opioid dose reduction and pain control with medical cannabis. Journal of Clinical Oncology Conference. 2018;36(34 Supplement).

22. Caulley L, Caplan B, Ross E. Medical Marijuana for Chronic Pain. New England Journal of Medicine. 2018;379(16):1575-7.

23. Clements-Nolle K, Lensch T, Larson S, Yang W. Prevalence and correlates of any and frequent synthetic cannabinoid use in a representative sample of high school students. Substance Use & Misuse. 2016;51(9):1139-46.

24. Costales B, Van Boemmel-Wegmann S, Segal R. A descriptive analysis of Florida medical marijuana registry patients from 2016-2017. Pharmacoepidemiology and Drug Safety. 2019;28 (Supplement 2):268.

25. Cuestas E. [Cannabis for chronic neuropathic pain.]. Revista de la Facultad de Ciencias Medicas de Cordoba. 2019;76(1):1-2.

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27. De Trane S, Buchanan K, Keenan L, Valentine C, Liddicut M, Stevenson V, et al. Thc:cbd (nabiximols) has a beneficial effect on multiple sclerosis (MS) related spasticity and delays or negates the need for intrathecal baclofen pump implantation. Neurology Conference: 69th American Academy of Neurology Annual Meeting, AAN. 2017;88(16 Supplement 1).

28. Degenhardt L, Hall WD. The adverse effects of cannabinoids: implications for use of medical marijuana. CMAJ Canadian Medical Association Journal. 2008;178(13):1685-6.

29. Di Francesco A, Pizzigallo D. Use of micronized palmitoylethanolamide and trans-polydatin in chronic pelvic pain associated with endometriosis. An open-label study. Giornale Italiano di Ostetricia e Ginecologia. 2014;36(2):353-8.

30. Dimou T, Spanomanoli A, Michelis S. The use of palmitoylethinolamide (PEA) in FBSS for chronic pain management. Regional Anesthesia and Pain Medicine. 2019;44 (10 Supplement 1):A168.

31. Donato F, Turri M, Zanette G, Tugnoli V, Deotto L, Teatini F, et al. A study of cortical and spinal excitability in patients affected by multiple sclerosis and spasticity after oromucosal cannabinoid spray (THC/CBD). Clinical Neurophysiology. 2016;127 (4):e147.

32. Donovan KA. Age-related differences in cannabis use by cancer patients referred for supportive care. Diane Portman. Journal of Clinical Oncology Conference. 2019;37(31 Supplement 1).

33. Dow GJ, Meyers FH, Stanton W, Devine ML. Serious reactions to oral delta-9-tetrahydrocannabinol in cancer chemotherapy patients. Clinical Pharmacy. 1984;3(1):14.

34. Dusi V, Attili SVS, Singaraju M. Observational study on role of crude cannabis in pain control and quality of life in terminally ill cancer patients: An Indian perspective. Annals of Oncology. 2019;30 (Supplement 9):ix119.

35. Eltayb A, Etges T, Wright S. An observational post-approval registry study of patients prescribed Sativex. Results from clinical practice. Multiple Sclerosis. 2013;1):480.

36. Erbe B. [Cannabis - medicinal use]. Deutsche Medizinische Wochenschrift. 2014;139(3):74-5.

37. Euctr AT. SATIVEX® AS ADD-ON THERAPY VS. FURTHER OPTIMIZED FIRST-LINE ANTISPASTICS. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2015-004451-40-AT. 2016.

38. Euctr BE. An investigational study to assess the effect of GS-5745 on adult patients with Cystic Fibrosis. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2015-002192-23-BE. 2016.

39. Euctr DE. A cannabis preparation for neuropathic pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2014-005344-17-DE. 2015.

40. Euctr DK. Effect of Sativex on pain and spasticity following spinal cord injury. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2012-005328-14-DK. 2013.

41. Euctr DK. The effect of cannabis products on nerve pain and muscle stiffness in patients with multiple sclerosis and in patients with spinal cord injury. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2018-002315-98-DK. 2018.

42. Euctr GB. Study of Sativex for the Treatment of Cancer Related Pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2009-016065-29-GB. 2010.

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44. Euctr NL. ?9-THC (Namisol®) in persistent postsurgical pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2012-000812-27-NL. 2012.

45. Euctr NL. Perioperative ?9-THC for postsurgical pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2012-005808-17-NL. 2013.

46. Euctr NL. Interaction between opioids and cannabinoids in the treatment of fibromyalgia pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2019-001861-33-NL. 2019.

47. Fernandez O. Advances in the management of multiple sclerosis spasticity: Recent clinical trials. European Neurology. 2014;72:9-11.

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49. Ferre L, Nuara A, Pavan G, Radaelli M, Moiola L, Rodegher M, et al. Medium and long term efficacy of nabiximols for the treatment of multiple sclerosis related spasticity: An Italian monocentric study. Multiple Sclerosis. 2015;1):728-9.

50. Ferre L, Pavan G, Nuara A, Radaelli M, Liberatore G, Guaschino C, et al. Efficacy, safety and response rate to Nabiximol for the treatment of MS-related spasticity in an Italian monocentric cohort. Multiple Sclerosis. 2015;21 (4):501-2.

51. Ferre L, Sorosina M, Santoro S, Moiola L, Rodegher M, Colombo B, et al. Efficacy, safety and response rate of nabiximols assessed in an Italian monocentric cohort. Multiple Sclerosis. 2014;1):469-70.

52. Fitzcharles MA, McDougall J, Ste-Marie PA, Padjen I. Clinical implications for cannabinoid use in the rheumatic diseases: potential for help or harm? Arthritis & Rheumatism. 2012;64(8):2417-25.

53. Flachenecker P, Zettl U, Henze T. THC:CBD oromucosal spray (nabiximols) in the long term treatment of multiple sclerosis spasticity. The MOVE 2 long-term study. Multiple Sclerosis. 2013;1):527.

54. Flank J, Lavoratore S, Vol H, Taylor T, Zelunka E, Nathan P, et al. Chemotherapy-induced nausea and vomiting in children receiving high dose methotrexate with or without vincristine: Preliminary results. Canadian Journal of Hospital Pharmacy. 2014;67 (1):61.

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Study did not report on harms or adverse events

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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	Critical	Serious	Low	Low	Low	Moderate	Low
Lynch, 2006	Critical	Low	Low	Low	Low	Moderate	Low
Rog, 2007	Critical	Low	Low	Serious	Low	Moderate	Low
Weber, 2009	Critical	Low	Low	Serious	Low	Moderate	Moderate
Bestard, 2011*	Critical	Low	Low	Moderate	Low	Moderate	Low
Fiz, 2011	Critical	Serious	Low	Low	Low	Moderate	Low
Dominguez, 2012	Critical	Low	Low	Moderate	Low	Moderate	Low
Gatti, 2012	Critical	Low	Low	Low	Low	Moderate	Low
Toth, 2012	Critical	Low	Low	Low	Low	Moderate	Low
Schifilliti, 2014	Critical	Low	Low	Low	Low	Moderate	Moderate
Storr, 2014	Critical	Serious	Low	Low	Low	Moderate	Moderate
Del Giorno, 2015	Critical	Low	Low	Low	Low	Moderate	Low
Hoggart, 2015	Critical	Serious	Low	Moderate	Low	Moderate	Low
Ware, 2015†	Critical	Serious	Low	Moderate	Low	Moderate	Low
Haroutounian, 2016	Critical	Low	Low	Low	Low	Moderate	Low
Bellnier, 2017	Critical	Low	Low	Low	Low	Moderate	Moderate
Cranford, 2017	Critical	Serious	Low	Low	Low	Moderate	Low
Fanelli, 2017	Critical	Low	Low	Serious	Critical	Moderate	Low
Feingold, 2017	Critical	Serious	Low	Low	Low	Moderate	Moderate
Paladini, 2017	Critical	Low	Low	Low	Low	Moderate	Low
Passavanti, 2017	Critical	Low	Low	Low	Low	Moderate	Low
Schimrigk, 2017	Critical	Serious	Low	Low	Low	Moderate	Low
Chirchiglia, 2018	Critical	Low	Low	Low	Low	Serious	Low
Crowley, 2018	Critical	Serious	Low	Low	Low	Moderate	Low
Habib, 2018	Critical	Low	Low	Low	Low	Moderate	Low
Anderson, 2019	Critical	Low	Low	Low	Serious	Moderate	Low
Bonar, 2019	Critical	Serious	Low	Low	Low	Serious	Moderate
Cervigni, 2019	Critical	Low	Low	Low	Serious	Moderate	Low
Cremer-Schaeffer, 2019 ‡	Critical	Low	Low	Serious	Low	Moderate	Moderate
Lejczak, 2019	Critical	Low	Low	Critical	Serious	Moderate	Moderate
Loi, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Naftali, 2019	Critical	Serious	Low	Low	Moderate	Moderate	Low
Perron, 2019	Critical	Serious	Low	Low	Low	Moderate	Low
Sagy, 2019	Critical	Low	Low	Moderate	Serious	Moderate	Moderate
Sinclair, 2019	Critical	Serious	Low	Low	Low	Moderate	Moderate
Ueberall, 2019	Critical	Low	Low	Moderate	Low	Moderate	Low
Vigil, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Yassin, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Giorgi, 2020	Critical	Low	Low	Serious	Low	Moderate	Low

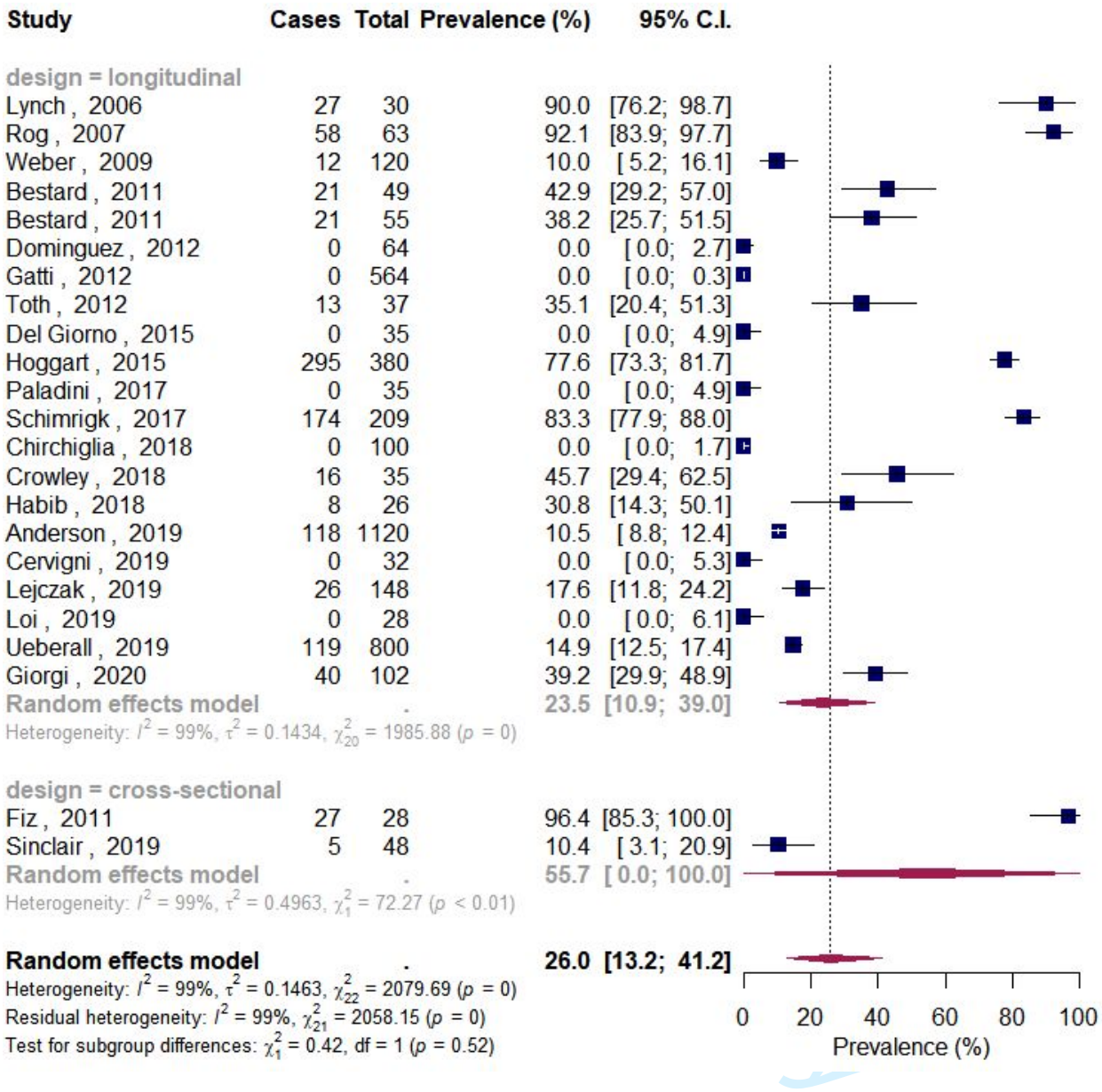
Low risk of bias	Low
Moderate risk of bias	Moderate
Serious risk of bias	Serious
Critical risk of bias	Critical

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

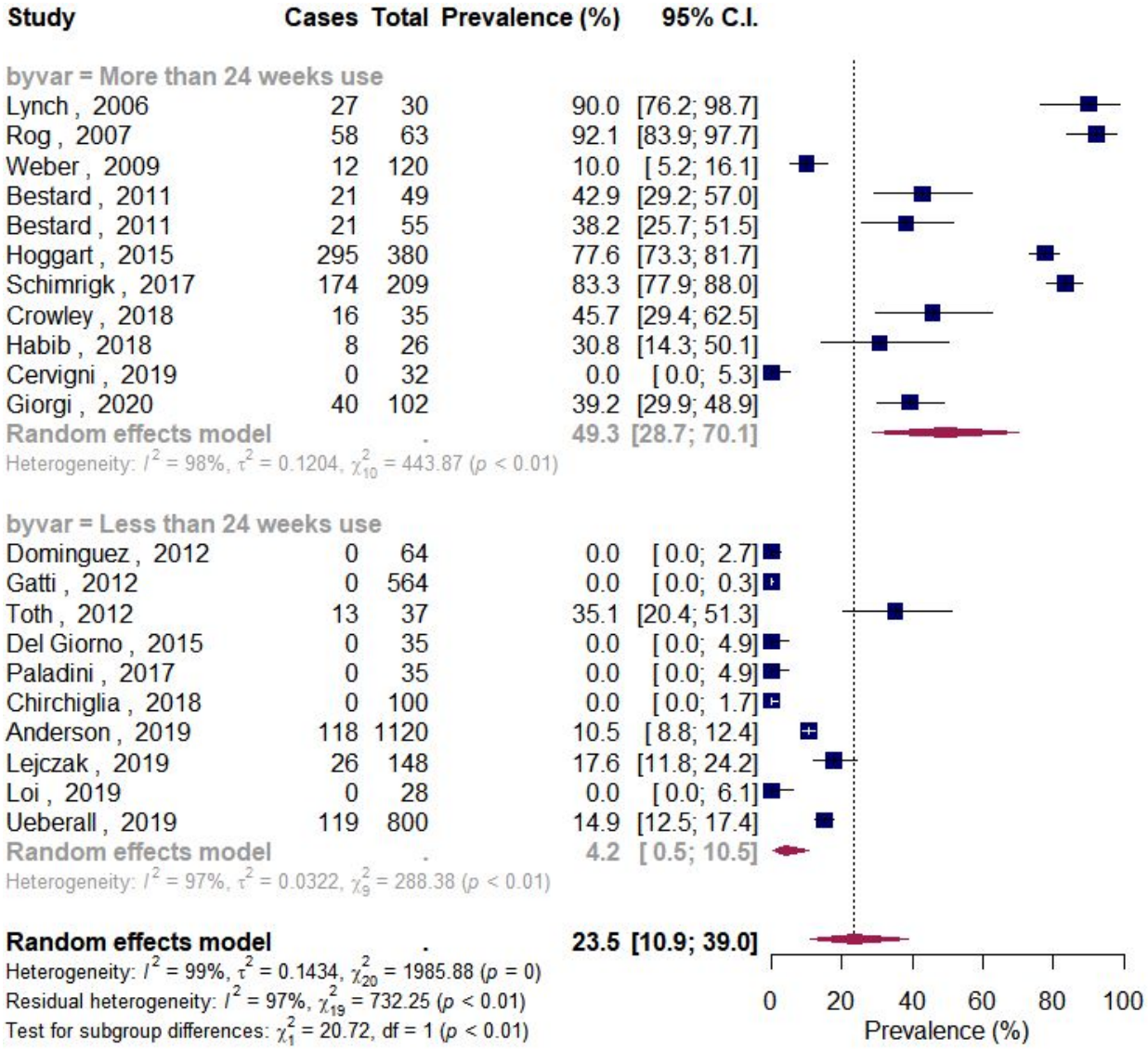
† Risk of bias for confounding for unadjusted comparative comparative results were rated as serious. Adjusted comparative results were rated as moderate.

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

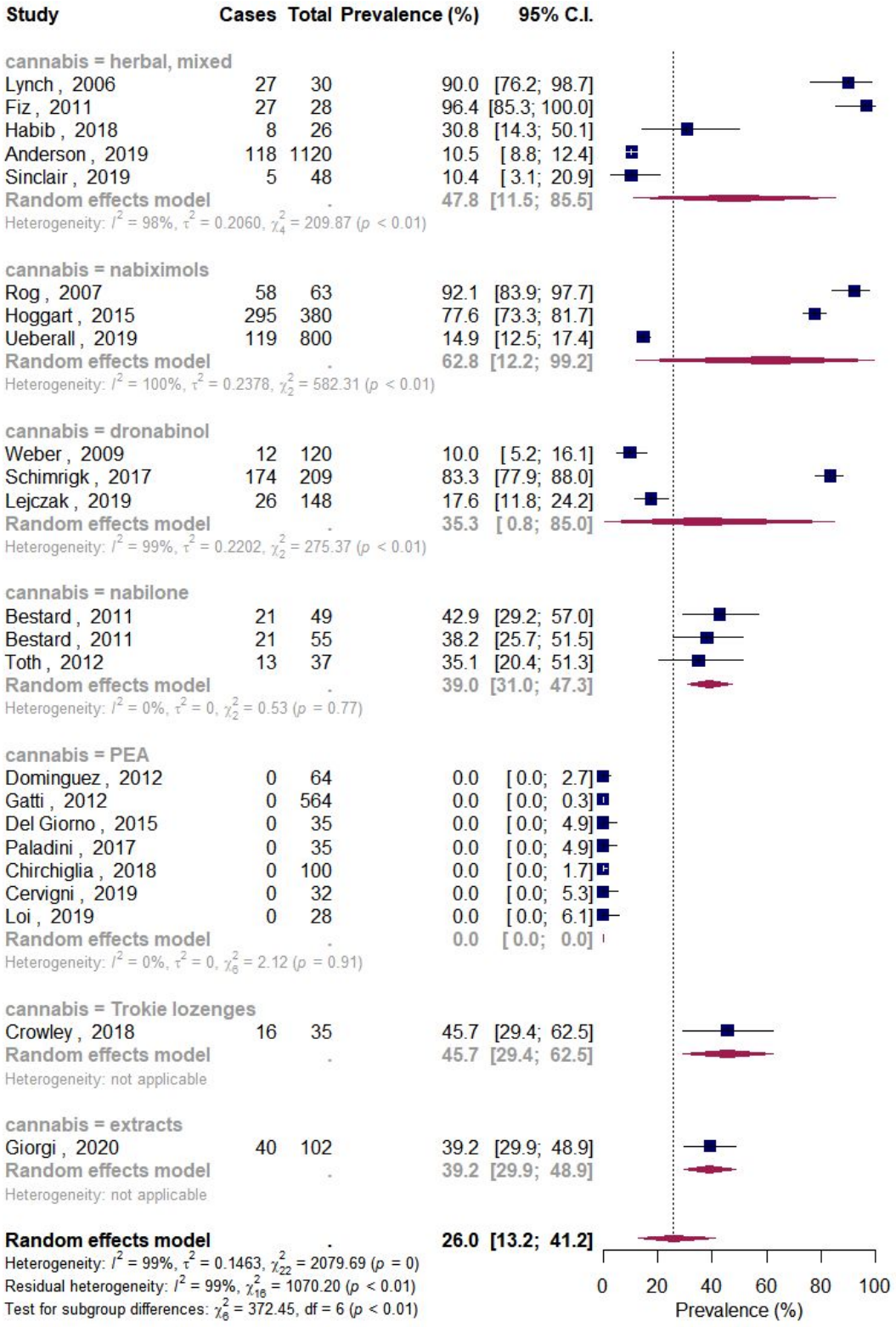
Appendix 6: Results for all adverse events (subgroup by design)



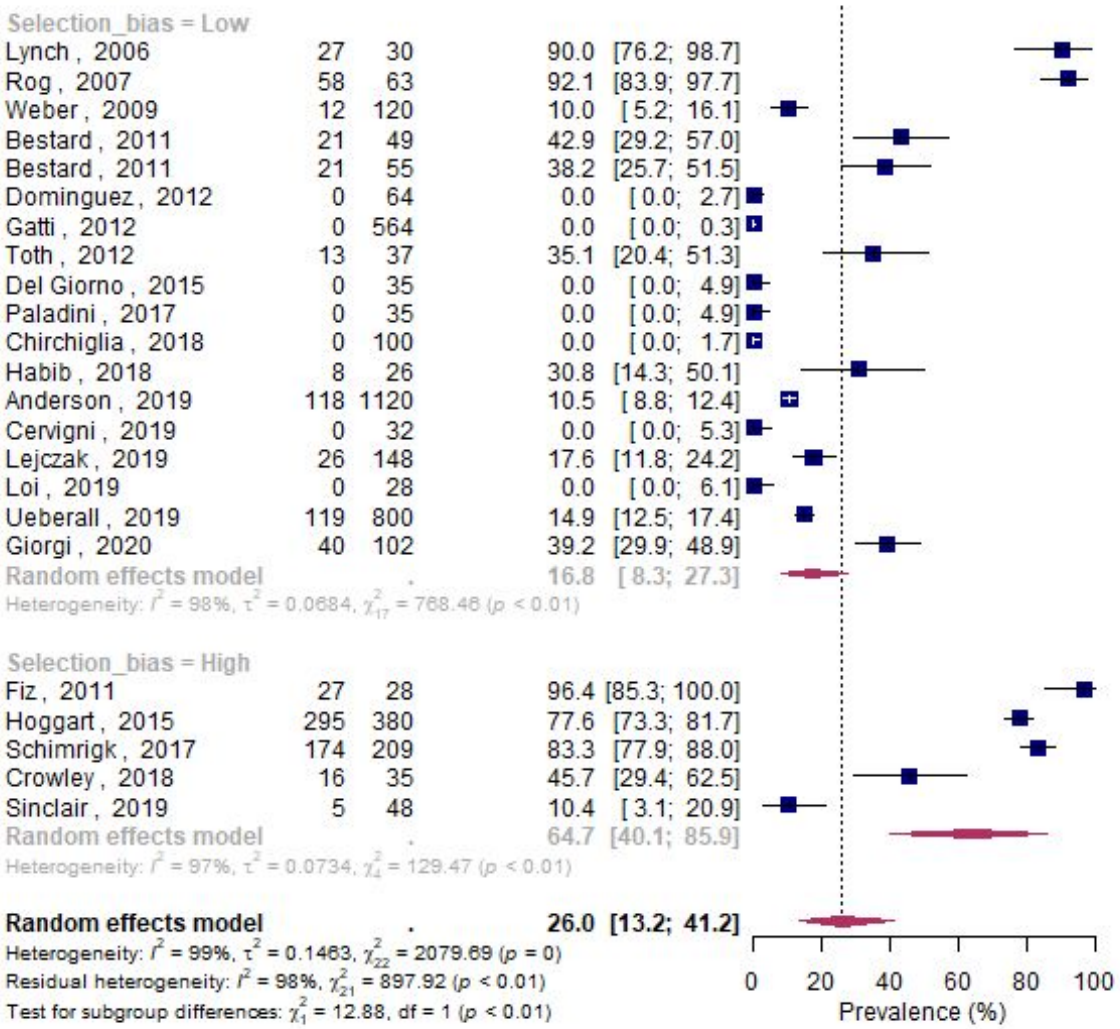
Appendix 7: Results for all adverse events (subgroup by duration)



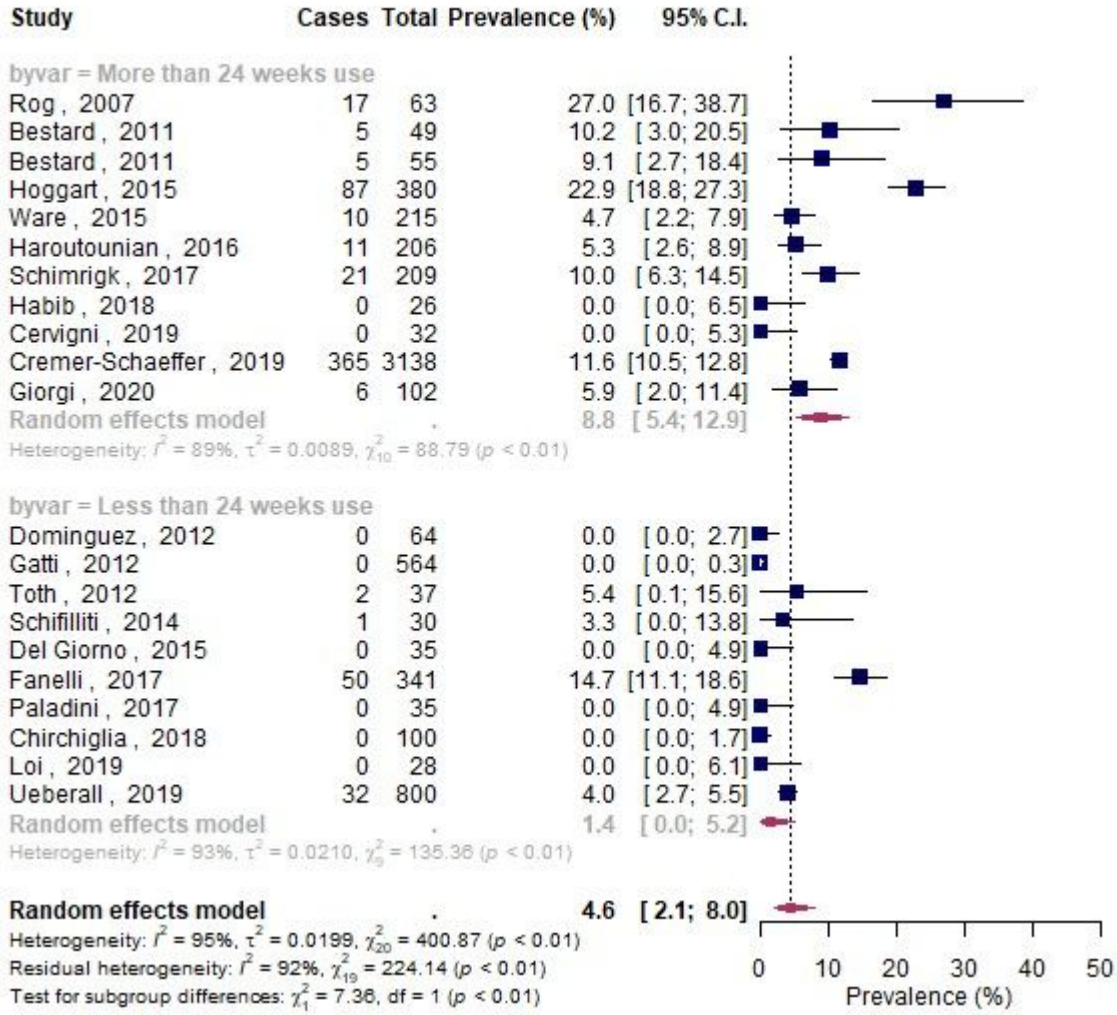
Appendix 8: Results for all adverse events (subgroup by cannabis)



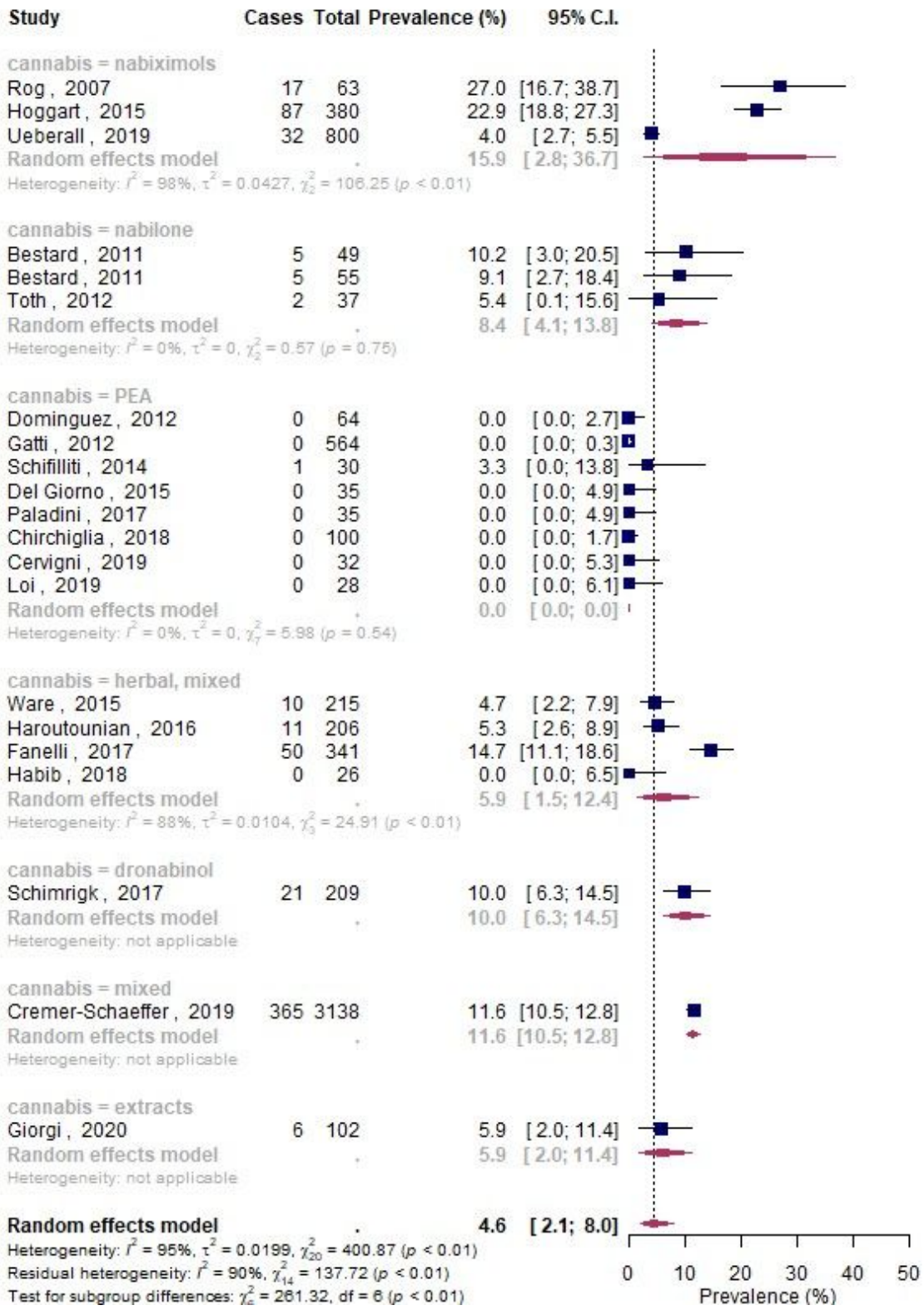
Appendix 9: Results for all adverse events (subgroup by selection bias)



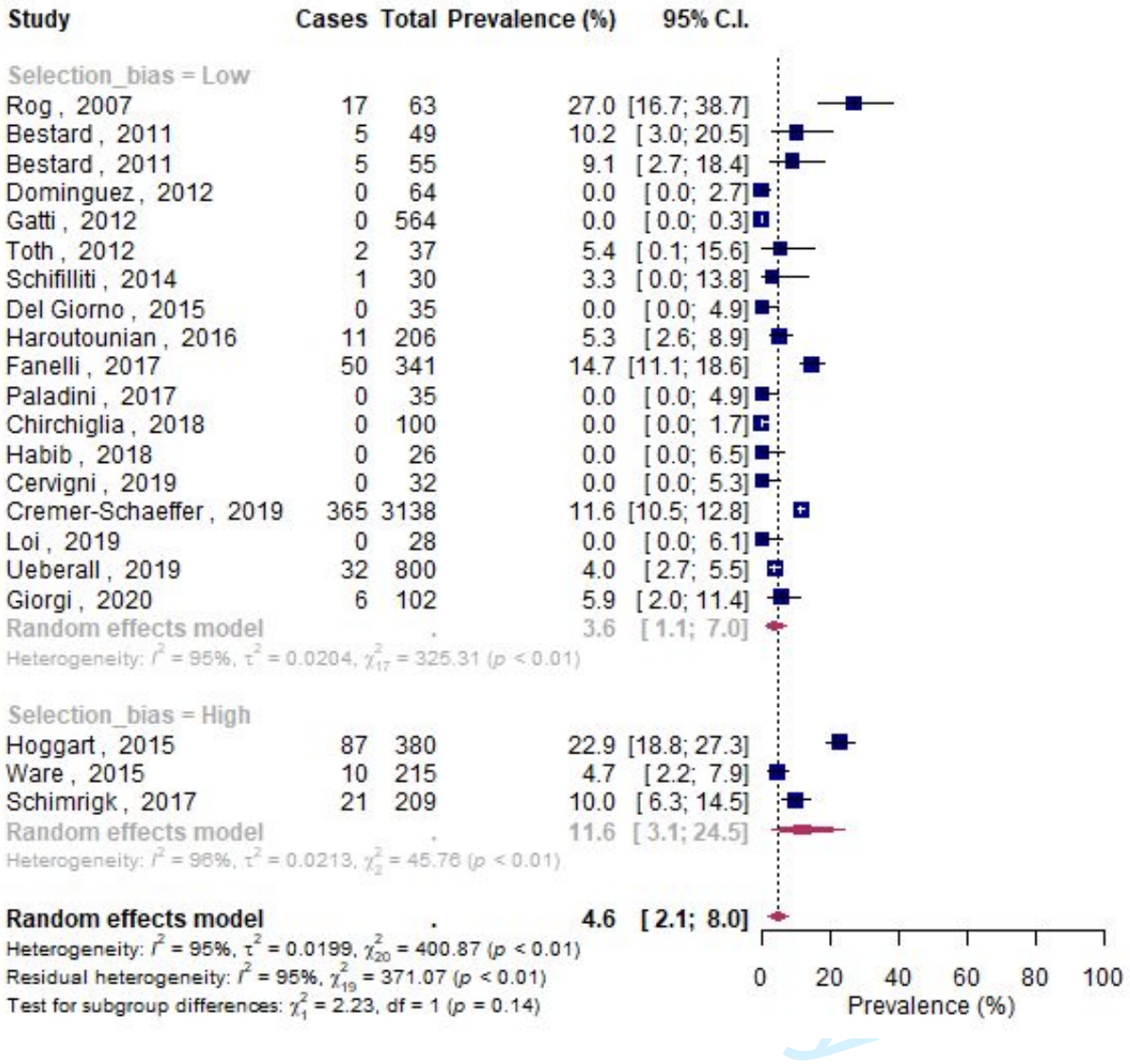
Appendix 10: Results for adverse events leading to discontinuation (subgroup by duration)



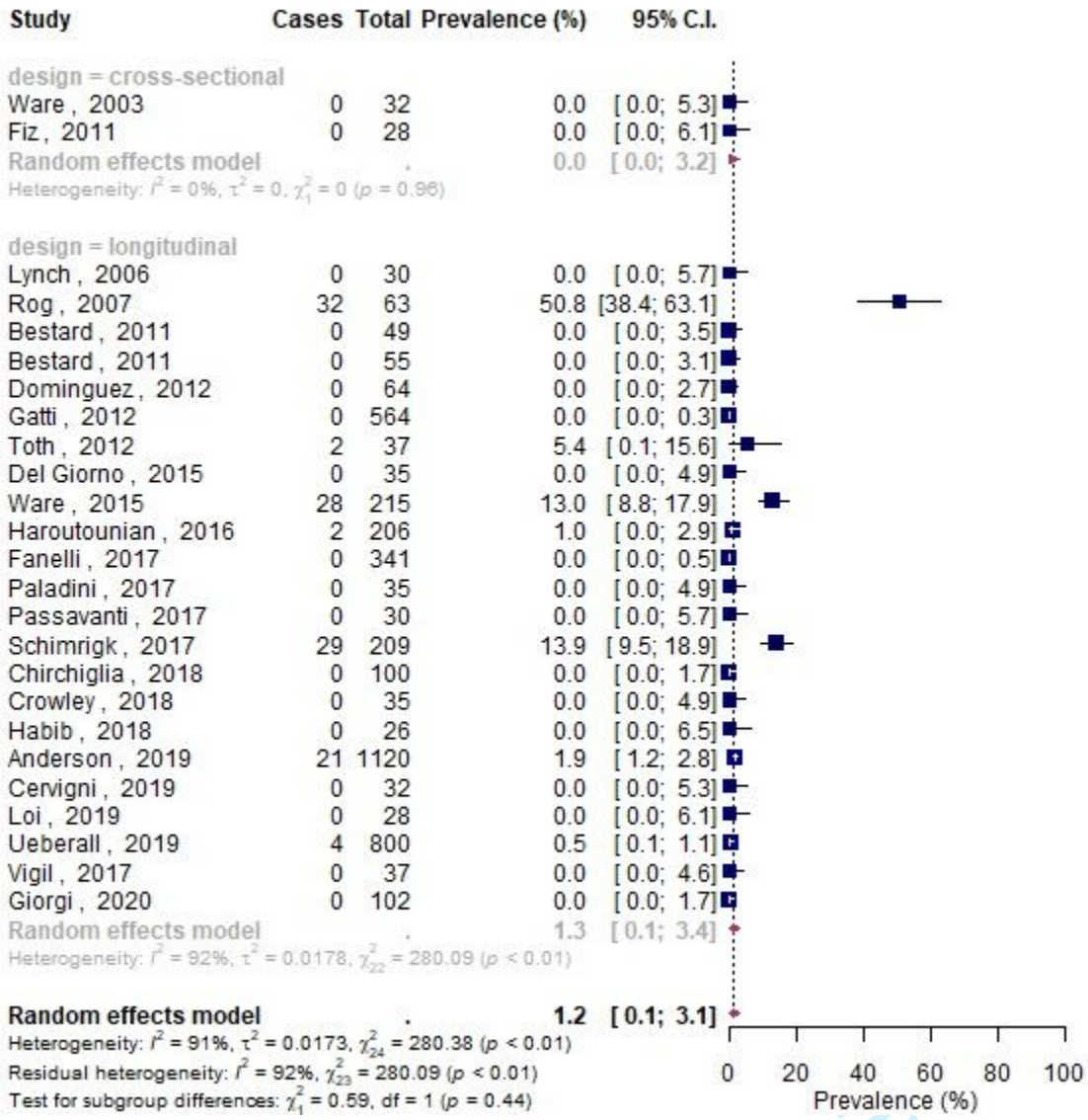
Appendix 11: Results for adverse events leading to discontinuation (subgroup by cannabis)



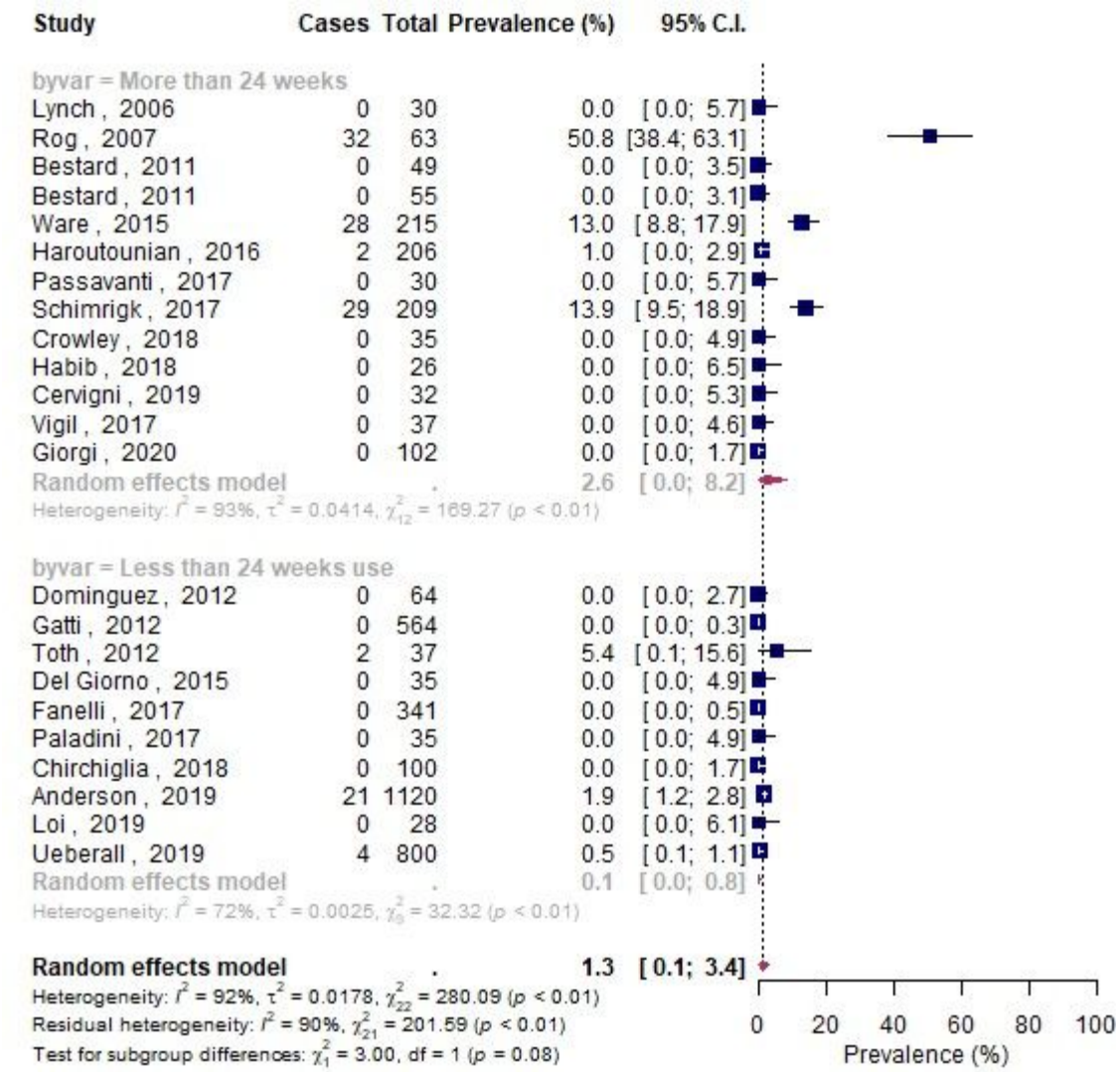
Appendix 12: Results for adverse events leading to discontinuation (subgroup by selection bias)



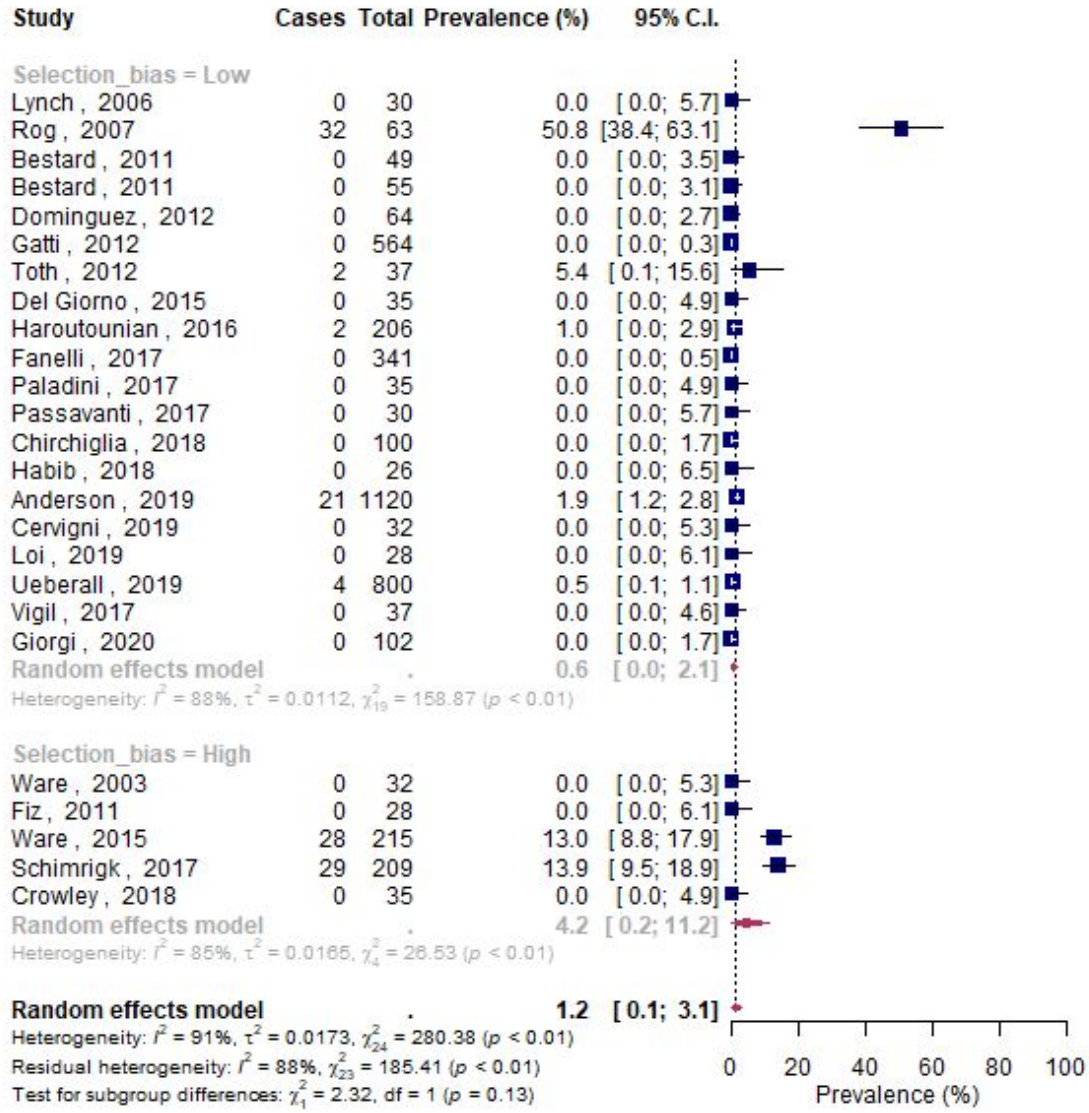
Appendix 13: Results for serious adverse events (subgroup by design)



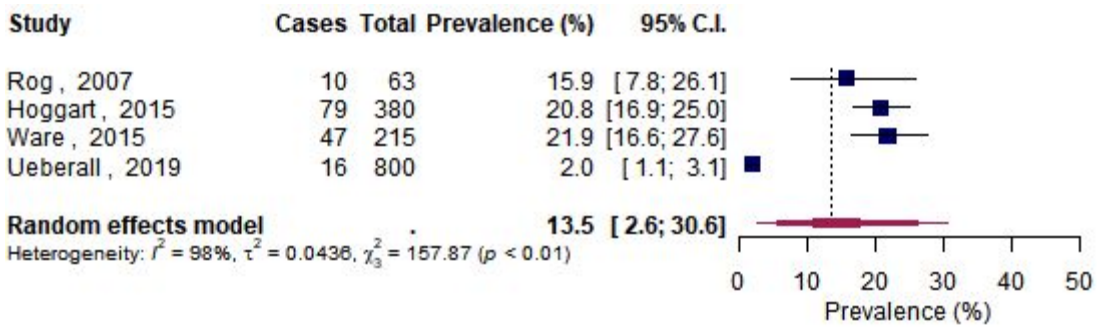
Appendix 14: Results for serious adverse events (subgroup by duration)



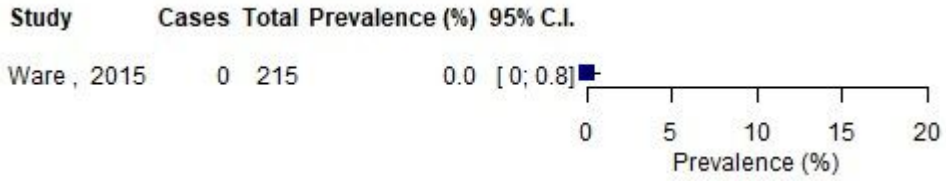
Appendix 15: Results for serious adverse events (subgroup by selection bias)



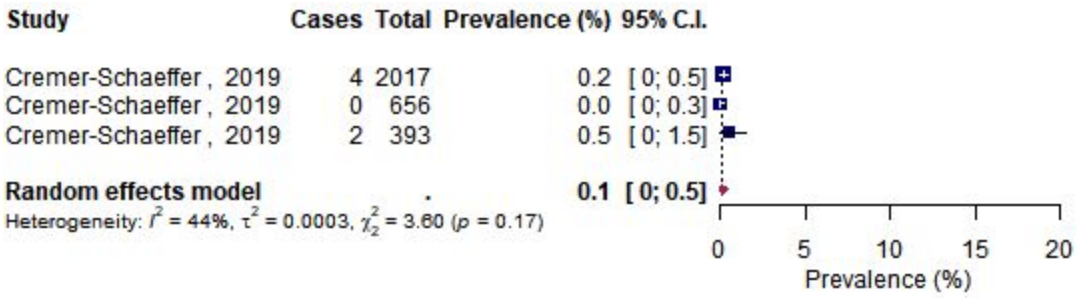
Appendix 16: Results for psychiatric adverse events



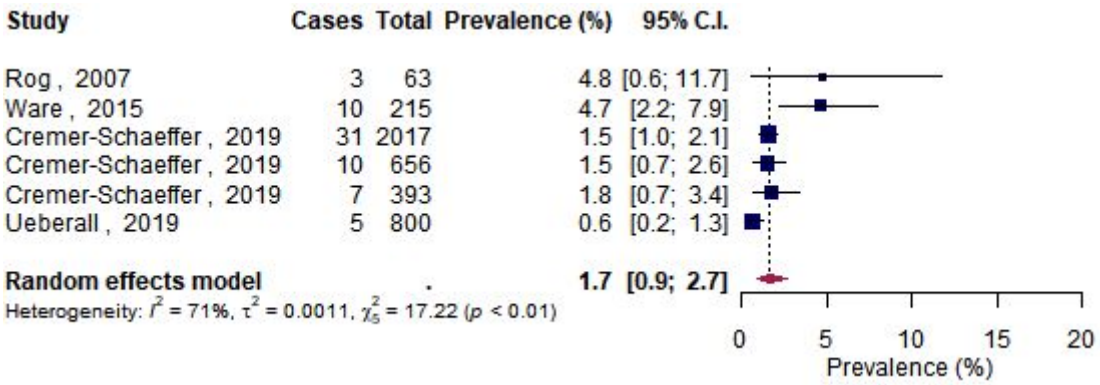
Appendix 17: Results for suicide



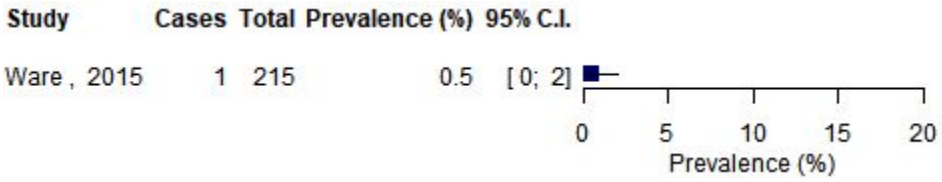
Appendix 18: Results for suicidal thoughts



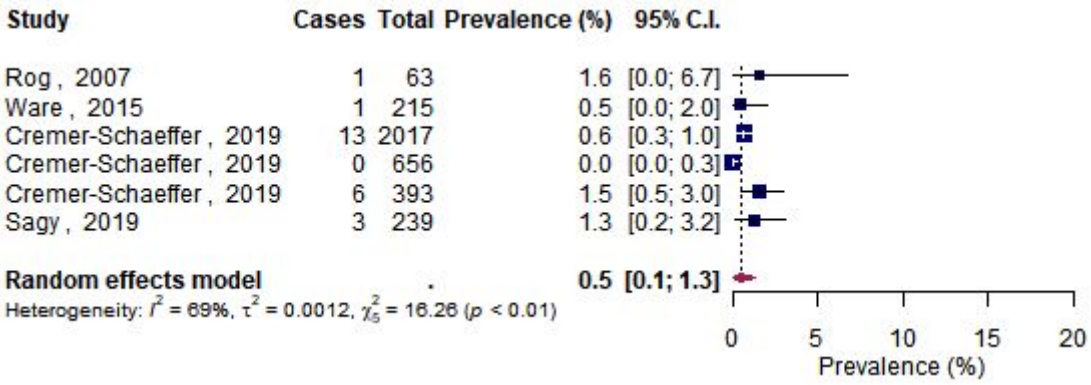
Appendix 19: Results for depression



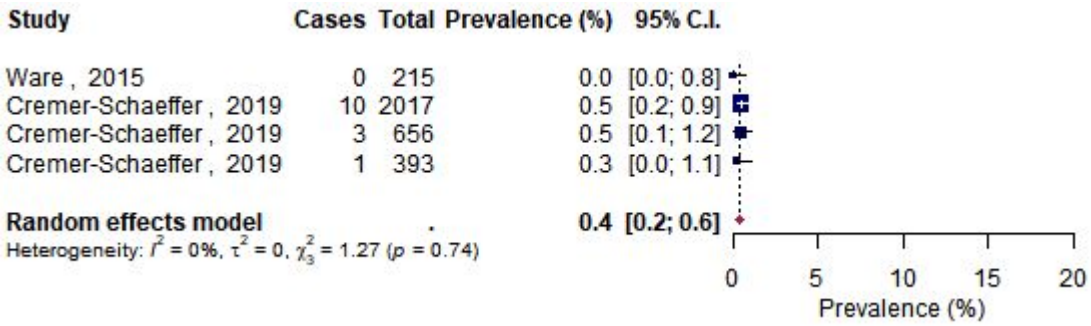
Appendix 20: Results for mania



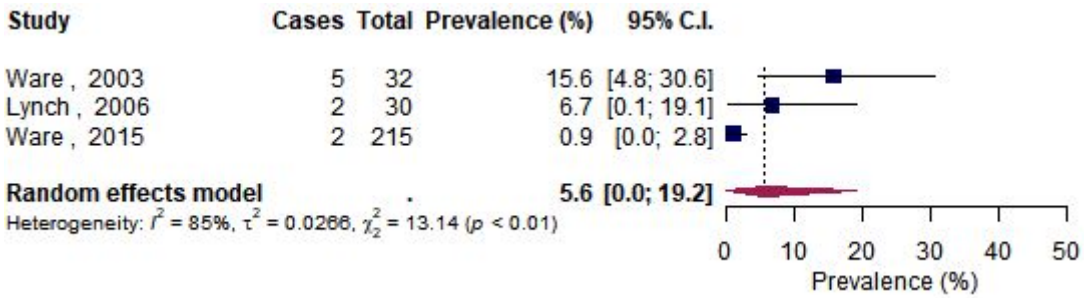
Appendix 21: Results for hallucinations



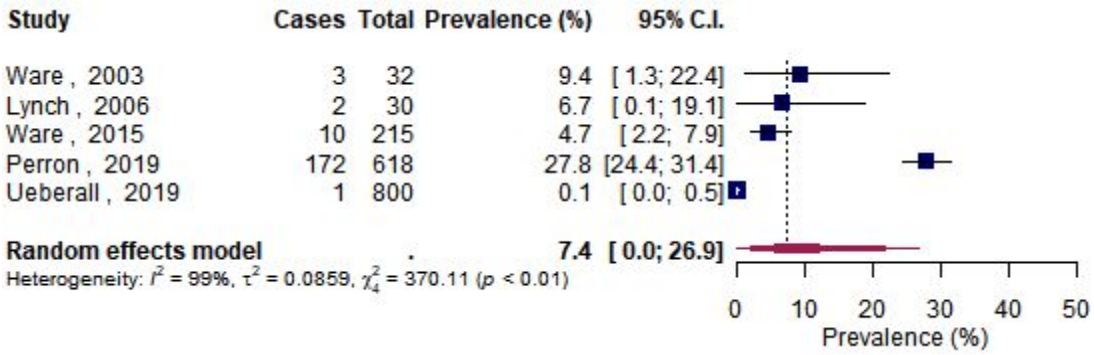
Appendix 22: Results for delusions



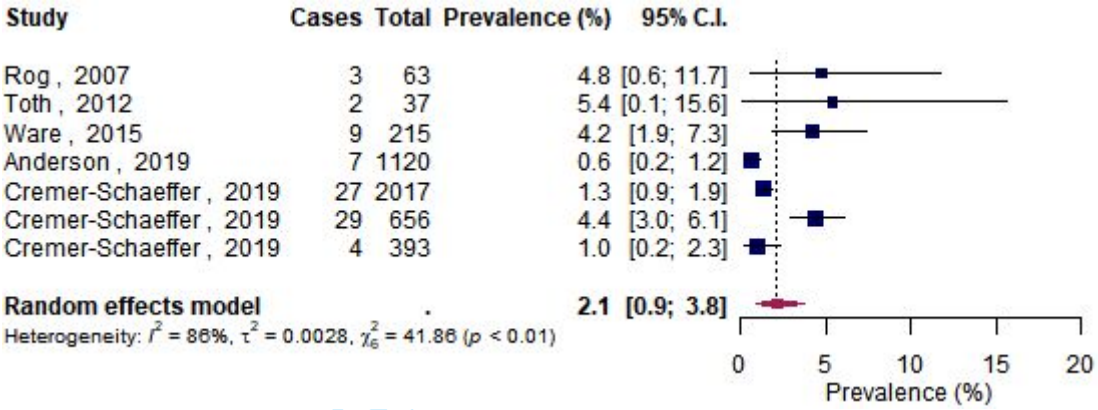
Appendix 23: Results for paranoia



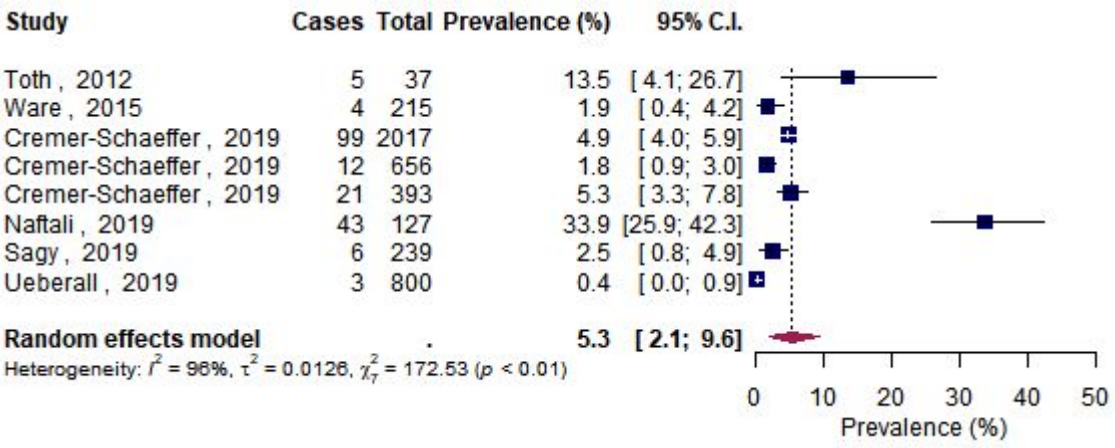
Appendix 24: Results for anxiety



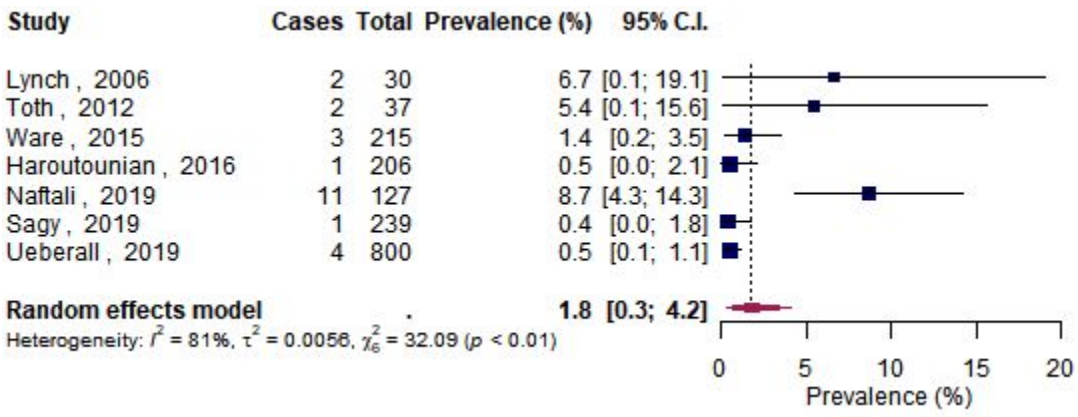
Appendix 25: Results for euphoria



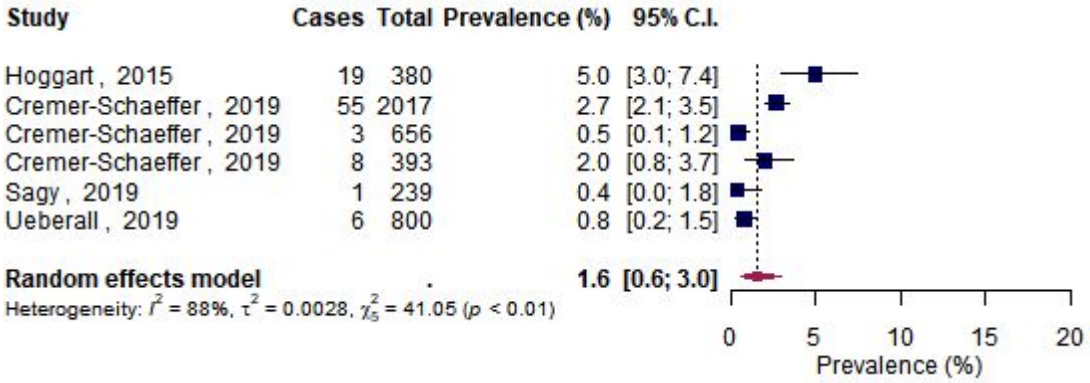
Appendix 26: Results for memory impairment



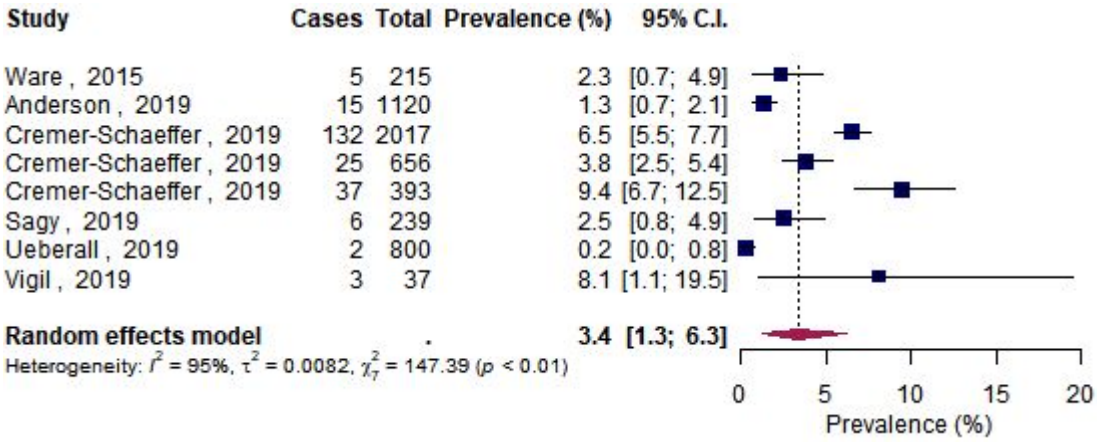
Appendix 27: Results for confusion



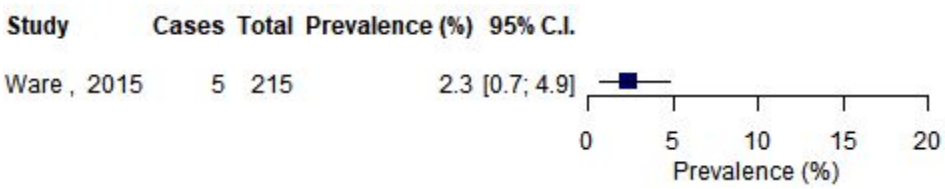
Appendix 28: Results for disorientation



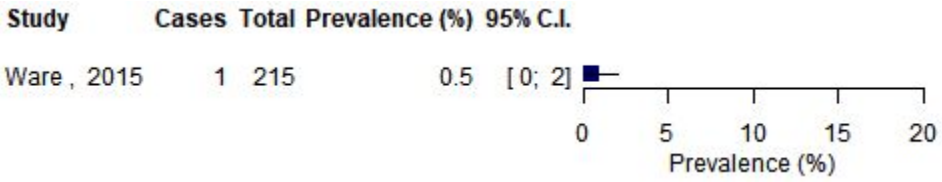
Appendix 29: Results for impaired attention



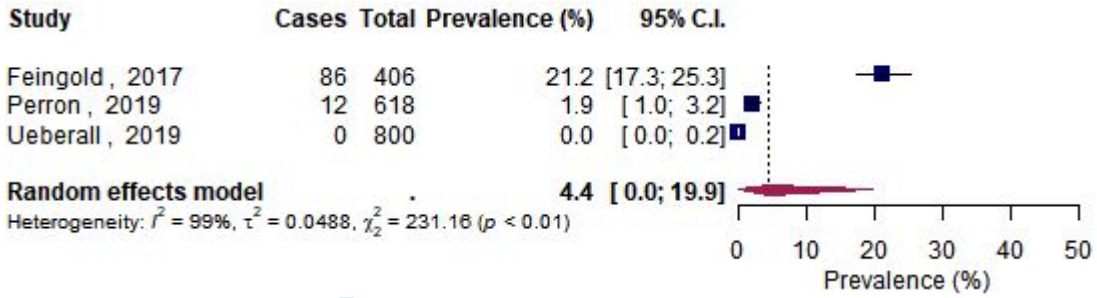
Appendix 30: Results for falls



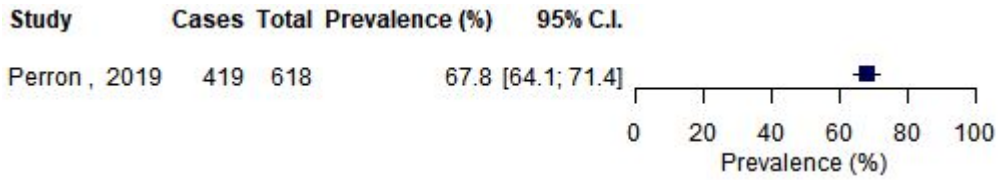
Appendix 31: Results for motor vehicle accidents



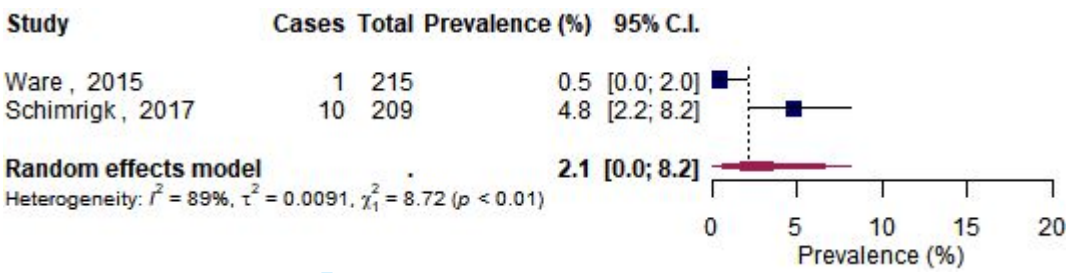
Appendix 32: Results for dependence



Appendix 33: Results for withdrawal symptoms



Appendix 34: Results for withdrawal syndrome



Section/topic (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

Study selection (8)	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
Data collection process (9)	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
Data items (9)	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
Risk of bias in individual studies (10)	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
Summary measures (11)	13	State the principal summary measures (eg, risk ratio, difference in means).	—	No specific additional information is required for systematic reviews of harms.	X
Synthesis of results (11)	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.		
Risk of bias across studies (11)	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
Additional analyses (12)	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
Results					
Study selection (13)	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

		stage, ideally with a flow diagram.			
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
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
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
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
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
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
Discussion					
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
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
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
Funding					
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

BMJ Open

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

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Secondary Subject Heading:	Anaesthesia, Medical management
Keywords:	Pain management < ANAESTHETICS, PAIN MANAGEMENT, PRIMARY CARE

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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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Running head: Harms of medical cannabis

Abbreviations: Cochrane Central Register of Controlled Trials (CENTRAL), Palmitoylethanolamide (PEA), tetrahydrocannabinol (THC)

Keywords: Medical cannabis, chronic pain, adverse events, harms, non-randomized studies, observational, systematic review, meta-analysis

Competing Interests: There are no competing interests for any author

Funding: DZ is supported by a Banting Postdoctoral Fellowship.

Ethics approval: The systematic review is exempt from ethics approval.

Data: Data are available in a public, open access repository: https://osf.io/ut36z/

Acknowledgements: We thank the members of the Rapid Recommendations panel for critical feedback on the selection of the adverse events of interest. We thank James MacKillop, PhD, for his guidance regarding the interpretation of problematic cannabis use, abuse, dependance and withdrawal syndrome within studies included in our review.

Data Sharing: Data on all other adverse events not included in our review, but reported in primary studies, are available in an open-access database (https://osf.io/ut36z/).

Authors' Contributions: JWB and TA conceived the idea. RC designed and conducted the search. DZ, MAC, AA, RWMV, GL, KL, JED, MMA, BYH, CH, and PJH screened search records, extracted data, and assessed the risk of bias of the eligible studies. DZ conducted all analyses. DZ, JWB, and TA interpreted the data. DZ wrote the first draft of the manuscript. JWB and TA critically revised the manuscript. All authors reviewed and approved the final version. DZ and JWB are the guarantors.

Word count: 5,811

Abstract

Objective: To establish the prevalence of long-term and serious harms of medical cannabis for chronic pain.

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, EMBASE, PsycInfo, and CENTRAL from inception to April 1, 2020.

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

Data extraction and synthesis: A parallel guideline panel provided input on the design and interpretation of the systematic review, including selection of adverse events for consideration. Two reviewers, working independently and in duplicate, screened the search results, extracted data, and assessed risk of bias. We used random-effects models for all meta-analyses and the GRADE approach to evaluate the certainty of evidence.

Results: We identified 39 eligible studies that enrolled 12,143 adult patients with chronic pain. Very low certainty evidence suggests that adverse events are common (prevalence: 26.0%; 95% CI 13.2 to 41.2) among users of medical cannabis for chronic pain, particularly any psychiatric adverse events (prevalence: 13.5%; 95% CI 2.6 to 30.6). Very low certainty evidence, however, indicates serious adverse events, adverse events leading to discontinuation, cognitive adverse events, accidents and injuries, and dependence and withdrawal syndrome are less common and each typically occur in fewer than one in 20 patients. We compared studies with <24 weeks and ≥24 weeks of cannabis use and found more adverse events reported among studies with longer follow-up (test for interaction $p < 0.01$). Palmitoylethanolamide was usually associated with few to no adverse events. We found insufficient evidence addressing the harms of medical cannabis compared to other pain management options, such as opioids.

Conclusions: There is very low certainty evidence that adverse events are common among people living with chronic pain who use medical cannabis or cannabinoids, but that few patients experience serious adverse events.

Systematic review registration https://osf.io/25bxf

Strengths and limitations of this study

- Strengths of this systematic review include a comprehensive search for non-randomized studies, explicit eligibility criteria, screening of studies and collection of data in duplicate to increase reliability, and use of the GRADE approach to evaluate the certainty of evidence.
- Our review is limited by the non-comparative design of most studies, which precludes confident inferences regarding the proportion of adverse events that can be attributed to medical cannabis or cannabinoids.
- A third of studies were at high risk of selection bias, primarily because they included prevalent cannabis users. In such studies, the prevalence of adverse events may be underestimated.
- Our review provides limited evidence on the harms of prolonged medical cannabis use since most studies reported adverse events for less than one year of follow-up.
- Some studies reported on smoked or vaporized medical cannabis, which may be associated with different adverse events (e.g. respiratory) than oral or topical formulations. We performed subgroup analyses based on the type of medical cannabis, but our findings were of low credibility due to inconsistency and/or imprecision.

Background

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

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

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

Methods

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

Guideline panel involvement

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

Patient and public involvement

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

Search

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

Study selection

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

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

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

Data extraction and risk of bias

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

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

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

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

Data synthesis

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

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

comparative studies, each with different comparators, we did not perform meta-analysis. For single-arm studies, we pooled the proportion of patients experiencing adverse events of interest by first applying a Freeman-Tukey type arcsine square root transformation to stabilize the variance. Without this transformation, very high or very low prevalence estimates can produce confidence intervals that contain values lower than 0% or higher than 100%. All meta-analyses used DerSimonian-Laird random-effects models, which are conservative as they consider both within- and between-study variability.[26-28] We also pooled all effect estimates using fixed-effects models as a sensitivity analysis. We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots and calculation of tau-squared (τ^2), because some statistical tests of heterogeneity (I^2 and Cochrane's Q) can be misleading when sample sizes are large and CIs are therefore narrow.[29] Higher values of τ^2, I^2, and Cochrane's Q indicate higher statistical heterogeneity. For studies that reported estimates for all-cause adverse events and those deemed to be potentially related to cannabis use, we preferentially synthesized results for all adverse events.

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

In consultation with the parallel BMJ Rapid Recommendations guideline panel, we also prespecified six subgroup hypotheses to explain heterogeneity between studies: (1) study design (longitudinal vs. cross-sectional), (2) type of medical cannabis, (3) cancer vs. non-cancer pain, (4) children vs. adults, (5) duration of medical cannabis use (shorter or longer than the median duration of follow-up across studies), and (6) risk of bias (low/moderate vs. serious/critical). We also performed two post-hoc subgroup analyses: (1) duration of follow-up (shorter or longer than the median duration of follow-up across studies) and (2) selection bias (studies at moderate, serious, or critical risk of selection bias vs. studies at low risk of selection bias). We anticipated that studies reporting on shorter use of medical cannabis, as well as cross-sectional studies, studies on cancer patients, studies including adults, studies with active comparators, studies at high risk of bias would report fewer adverse events. We anticipated that studies at moderate, serious, or critical risk of selection bias that included prevalent cannabis users (i.e., people who were using medical cannabis before the inception of the study) or were preceded by a run-in period or clinical trial during which patients that experienced adverse events or found medical cannabis intolerable could discontinue would report fewer adverse events because prevalent of medical cannabis are likely to represent populations that have self-selected for tolerance to cannabis. We performed tests for

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

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

Certainty of evidence

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

Results

Study selection

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

Description of studies

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

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

Risk of bias

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

All adverse events

Twenty longitudinal and two cross-sectional studies, including 4,108 patients, reported the number of patients experiencing one or more adverse events.[37-44 47 48 55 57-61 63 65 66 70 71 74] Seven studies reported on PEA, five on mixed herbal cannabis, three each on nabilone and nabiximols, two on dronabinol, and one each on extracts and Trokie lozenges. The median duration of medical cannabis use was 24 weeks [IQR 12 to 32]. We observed substantial unexplained heterogeneity and so summarize the results descriptively (Table 2; Supplement Appendices 6 to 9). The prevalence of any adverse event ranged between 0% to 92.1%. Studies with less than 24 weeks of cannabis use (the median duration of cannabis) 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.

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

Adverse events leading to discontinuation

Twenty longitudinal studies, including 6,509 patients, reported on the number of patients that 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] Eight studies reported on PEA, four studies on mixed herbal cannabis, three on nabiximols, two on nabilone, and one each on dronabinol and extracts, and one study did not report the type of medical cannabis used by patients. The median duration of cannabis use was 24 weeks [IQR 8.6 to 32]. We observed substantial unexplained heterogeneity and so summarize the results descriptively (Supplement Appendices 10 to 12). 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.

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

Serious adverse events

Twenty-two longitudinal and two cross-sectional studies, including 4,273 patients, reported on the 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 studies reported on mixed herbal cannabis, eight on PEA, two each on nabilone and nabiximols each, and one study each on dronabinol, extracts, and Trokie lozenges, and one study did not report the type of cannabis used. The median duration of medical cannabis or cannabinoid use was 24 weeks (IQR 12 to 32), and few patients experienced serious adverse events (1.2%; 95% CI 0.1 to 3.1; I^2=91%) (Figure 2) (Supplement Appendices 13 to 15). There was a statistically significant subgroup effect across different types of medical cannabis though serious adverse events appeared consistently uncommon (low credibility). The certainty of evidence was very low overall due to serious risk of bias.

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

Psychiatric adverse events

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

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

Cognitive and attentional adverse events

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

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

Accidents and injuries

One longitudinal study, including 431 patients, reported on accidents and injuries in patients using mixed herbal cannabis for 52 weeks (Supplement Appendices 30 & 31).[49] This study suggested herbal cannabis used for medical purposes may slightly increase the risk of motor vehicle accidents (0.5%; 95% CI -0.4 to 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 to risk of bias.

Dependence and withdrawal

Four longitudinal and one cross-sectional study, including 2,248 patients, reported on dependence-related adverse events, including dependence (one study reported on 'abuse' based on unspecified criteria, one study reported on 'problematic use' using the Alcohol Use Disorder and Associated Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition [AUDADIS-IV][75], and one study reported on 'dependence' using the Alcohol, Smoking, and Substance Involvement Screening Test[76]), withdrawal symptoms (defined as one or moderate or severe withdrawal symptoms including sleep difficulties, anxiety, irritability, and appetite disturbance), and withdrawal syndrome (two studies that used unspecified criteria) (Supplement Appendices 32 to 34).[49 54 57 68 71] Two studies reported on herbal cannabis, one each on nabiximols and nabilone, and one did not specify type of medical cannabis used by patients. Follow-up ranged from 12 to 52 weeks. The pooled prevalence of 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

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

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

Discussion

Main findings

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

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

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

Strengths and limitations

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

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

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

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

Clinicians and patients may be more inclined to use medical cannabis or cannabinoids for pain relief if adverse events are mild; however, the evidence on whether adverse events are transient, life threatening, or the extent to which they impact quality of life is limited. While more than half of studies reported on the proportion of adverse events that were serious, criteria for ascertaining severity were rarely reported. None of the included studies reported the duration for which patients experienced adverse events. Further, most primary studies did not report adequate details on methods for the ascertainment of adverse events, including definitions or diagnostic criteria. The two studies that reported on withdrawal syndrome, for example, did not provide diagnostic criteria.[49 57] However, the DSM-5 requires ≥3 of 7 withdrawal symptoms to be present within a week of stopping cannabis use to meet a diagnosis of cannabis withdrawal syndrome.[84] It is therefore reasonable that people living with chronic pain that use medical cannabis would be more likely to experience withdrawal symptoms vs. withdrawal syndrome.

While children and youth account for approximately 15% of all chronic pain patients, we did not identify any evidence addressing the harms of medical cannabis in this population.[85] As such, the extent to which our findings are generalizable to pediatric populations is uncertain. Although there is evidence that cannabis use during youth is associated with increased risk of acute psychotic disorders, particularly acute psychosis,[86] such studies have focussed on use of recreational cannabis that contains greater amounts of THC than is typically seen in medical preparations. Further, the population of patients with chronic pain included in the studies we reviewed may not be representative of all patients with chronic pain—particularly rare conditions that cause chronic pain.

We used the DerSimonian and Laird method for meta-analysis.[27] A growing body of evidence, however, suggests that this model has important limitations that may be addressed by alternative models[87]—though there is limited evidence on the performance of these models for meta-analyses of proportions and prevalence.

Finally, we excluded studies from meta-analyses when they did not explicitly report the adverse events of interest to our panel members. This may have overestimated the prevalence of adverse events if the adverse events of interest were not observed in the studies in which they were not reported. This was,

however, not possible to confirm because methods for the collection and reporting of adverse event data across studies were variable (e.g., active monitoring vs. passive surveillance; collecting data on specific adverse events vs. all adverse events) and poorly described in study reports.

Implications

Our systematic review and meta-analysis shows that evidence regarding long-term and serious harms of medical cannabis or cannabinoids is insufficient—an issue with important implications for patients and clinicians considering this management option for chronic pain. While the evidence suggests that adverse events are common in patients using medical cannabis for chronic pain, serious adverse events appear less common, which suggests that the potential benefits of medical cannabis or cannabinoids (although modest) may outweigh potential harms for some patients.[11 18]

Clinicians and patients considering medical cannabis should be aware that more adverse events were reported among studies with longer follow-up, necessitating long term follow-up of patients and re-evaluation of pain treatment options. Our findings also have implications for the choice of medical cannabis. We found PEA, for example, to consistently be associated with few or no adverse events across studies, though the evidence on the efficacy of PEA is limited.[11]

We found very limited evidence comparing medical cannabis or cannabinoids with other pain management options. Other pharmacological treatments for chronic pain, such as gabapentinoids, antidepressants, and opioids, may be associated with more (and more serious) adverse events.[88-90] To guide patients' and clinicians' decisions on medical cannabis for chronic pain, future research should compare the harms of medical cannabis and cannabinoids with other pain management options, including opioids, ideally beyond one year of use, and adjust results for confounders.

Our review highlights the need for standardization of reporting of adverse events in non-randomized studies since such studies represent a critical source of data on long-term and infrequently occurring harms. To enhance the interpretability of adverse event data, future studies should also report the duration and severity of adverse events and whether adverse events are life-threatening, since these factors are critical to patients' decisions.

A valuable output of our systematic review is an open-source database of over 500 unique adverse events reported to date in non-randomized studies of medical cannabis or cannabinoids for chronic pain with corresponding assessments of risk of bias (https://osf.io/ut36z/). This database was compiled in duplicate

by trained and calibrated data extractors and is freely available to those interested in further analyzing the prevalence of different types of adverse events or to those interested in expanding the database to include adverse events in patients using medical cannabis or cannabinoids for other indications.

Conclusion

Our systematic review and meta-analysis found very low certainty evidence that suggests adverse events are common among people living with chronic pain using medical cannabis or cannabinoids, but that serious adverse events, adverse events causing discontinuation, cognitive adverse events, motor vehicle accidents, falls, and dependence and withdrawal syndrome are less common. We also found very low certainty evidence that longer duration of use was associated more adverse events and that PEA, compared with other types of medical cannabis, may result in few or no adverse events. Future research should compare the risks of adverse events of medical cannabis and cannabinoids with alternative pain management options, including opioids, and adjust for potential confounders.

Figure Legends

Figure 1: Study selection process

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

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
Bellnier, 2017 [50]	longitudinal*	US	mixed cancer and non-cancer pain	mixed herbal (CBD + THC)	Capsule: 10 mg /8 to 10 hours 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

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
Feingold, 2017 [53]	cross-sectional*	Israel	mixed cancer and non-cancer pain	Mixed herbal (CBD + THC)	NR	406	NR
Paladini, 2017 [54]	longitudinal††	Italy	failed back surgery syndrome	PEA	600 mg bid for one month; 600 mg/day for one month	35	8
Passavanti, 2017 [55]	longitudinal††	Italy	lower back pain	PEA	600 mg bid	30	24
Schimrigk, 2017 [56]	longitudinal*†	Germany, Austria	multiple sclerosis	dronabinol (THC)	range: 7.5 to 15 mg/day	209	32
Chirchiglia, 2018 [57]	longitudinal††	Italy	lower back pain	PEA	1.2 g/day	100	4
Crowley, 2018 [58]	longitudinal*	US	mixed non-cancer pain	Trokie lozenges (CBD + THC)	NR	35	4 to 60
Habib, 2018 [59]	longitudinal*	Israel	fibromyalgia	mixed herbal (CBD + THC)	mean: 26 g/month	26	mean: 41.6
Anderson, 2019 [60]	longitudinal*	US	cancer pain	mixed herbal (CBD + THC)	NR	1120	16
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
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
Cremer-Schaeffer, 2019 [63]	longitudinal††	Germany	mixed cancer and non-cancer pain	dronabinol (THC)	NR	2017	52
				mixed herbal	NR	656	
				nabiximols	NR	393	
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
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
Naftali, 2019 [66]	longitudinal*	Israel	inflammatory bowel disease	mixed herbal (CBD + THC)	mean: 31 g/month mean: 21 g/day THC; 170 g/day CBD	127	median: 176
Perron, 2019 [67]	cross-sectional*	US	mixed non-cancer pain	NR	daily (n=580), weekly (n=85)	618	≥12
Sagy, 2019 [68]	longitudinal††	Israel	mixed cancer and non-cancer pain	mixed herbal (CBD + THC)	median: 1000 mg/day cannabis median: 140 mg/day THC; 39 mg/day CBD	239	24
Sinclair, 2019 [69]	cross-sectional*	Australia	endometriosis	mixed herbal (CBD + THC)	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)	48	NR
Ueberall, 2019 [70]	longitudinal*	Germany	mixed cancer and non-cancer pain	nabiximols (CBD + THC)	mean: 7.1 sprays/day	800	12
Vigil, 2017 [71]	longitudinal*	US	mixed non-cancer pain	NR	NR	37	mean: 82.4
Yassin, 2019 [72]	longitudinal††	Israel	fibromyalgia	mixed herbal (CBD + THC)	20 to 30 g/month	31	24
Giorgi, 2020 [73]	longitudinal††	Italy	fibromyalgia	extracts (CBD + THC)	10 to 30 drops/day; no more than 120 drops/day	102	24

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

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)

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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Figure 1: Study selection process

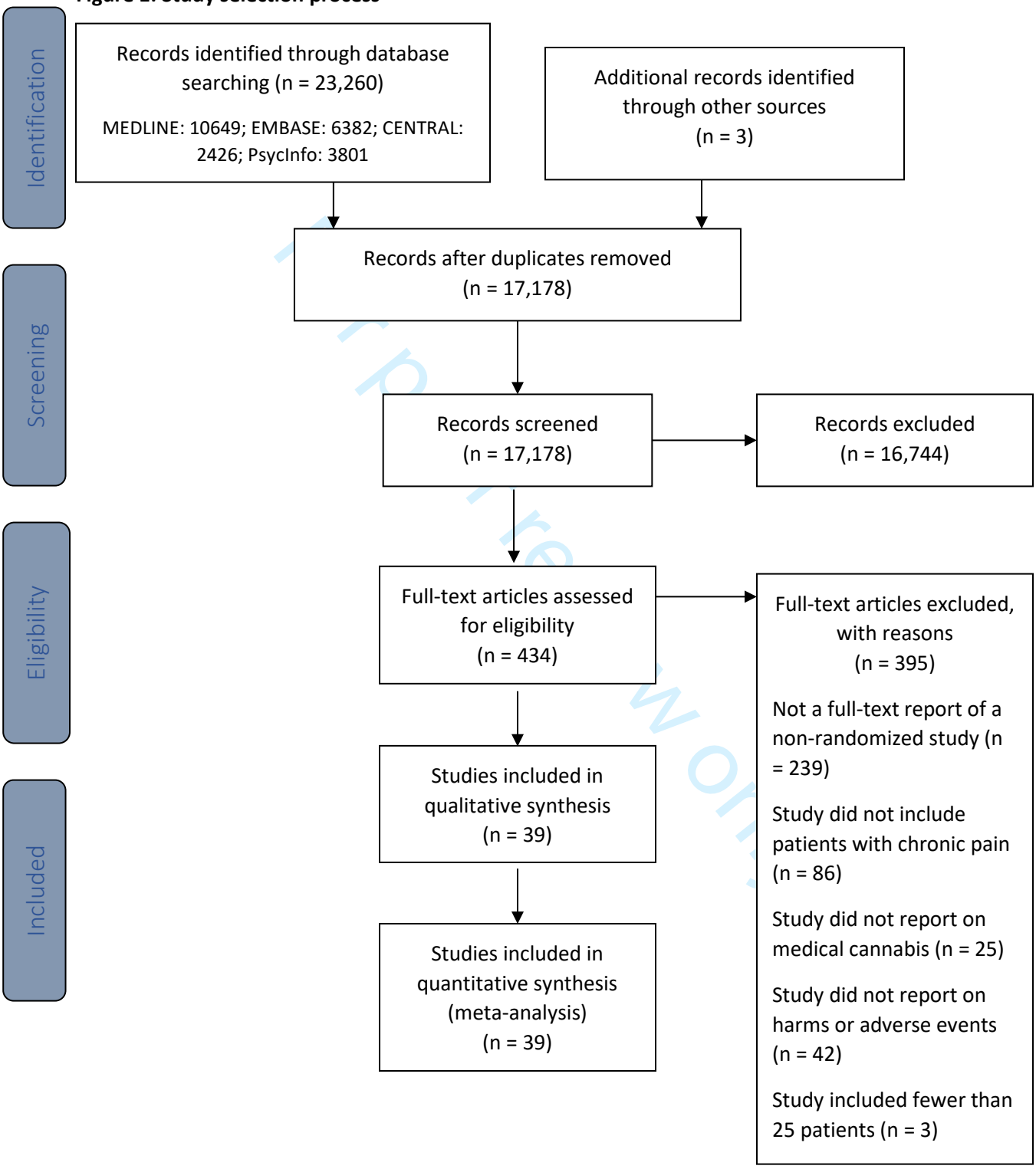
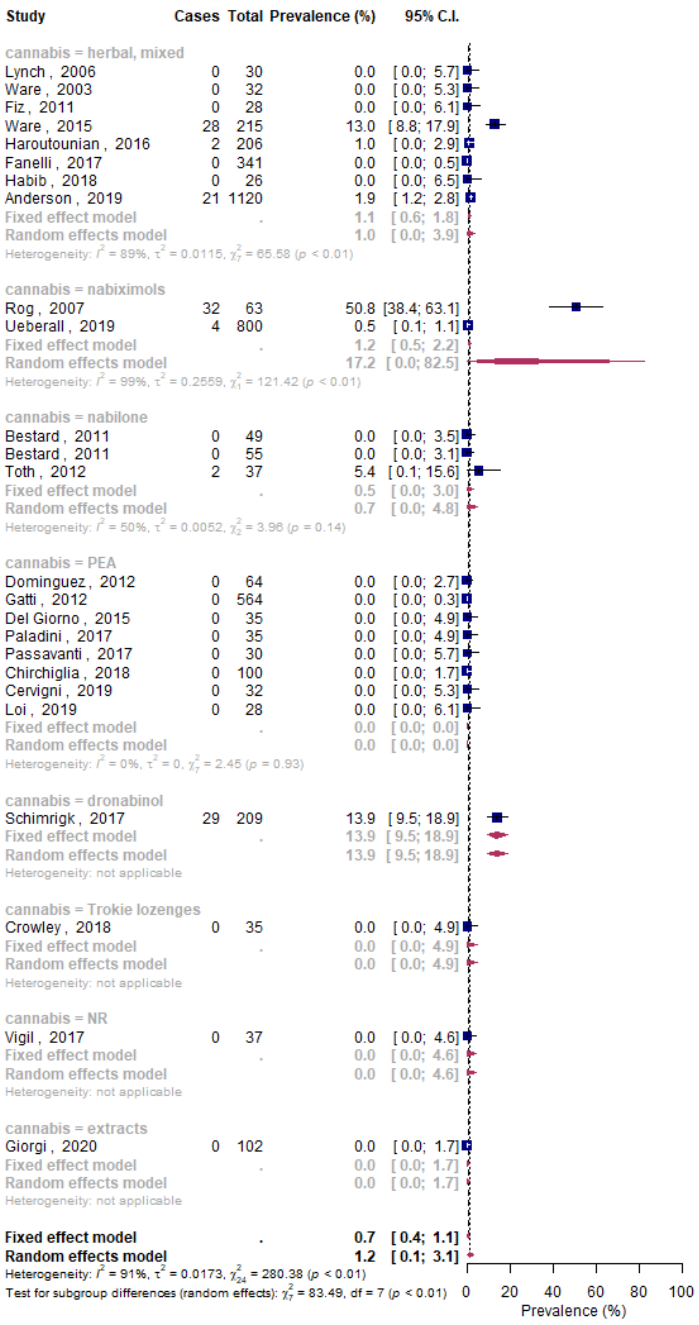


Figure 2: Forest plot of the meta-analysis for serious adverse events stratified by type of medical cannabis



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

Appendix

Dr. Jason Busse

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Contents

Appendix 1: Search strategy

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

April 1, 2020

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

Search Strategy:

---

1 Epidemiologic Studies/ (8256)

2 exp Case-Control Studies/ (1067341)

3 exp Cohort Studies/ (1974212)

4 Case control.tw. (123081)

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

6 Cohort analy$.tw. (7799)

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

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

9 Longitudinal.tw. (239715)

10 Retrospective.tw. (515751)

11 Cross sectional.tw. (342224)

12 Cross-sectional studies/ (322752)

13 or/1-12 (2953281)

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

15 13 not 14 (2889789)

Annotation: SIGN observational studies filter

16 randomized controlled trial.pt. (503041)

17 controlled clinical trial.pt. (93591)

18 randomized.ab. (474985)

19 placebo.ab. (206552)

20 drug therapy.fs. (2191450)

21 randomly.ab. (330409)

22 trial.ab. (500400)

23 groups.ab. (2028909)

24 or/16-23 (4670111)

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

26 24 not 25 (4048339)

Annotation: Cochrane HSSS RCT filter

27 15 or 26 (6033576)

Annotation: study design filter broad

28 Cannabis/ (8968)

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

30 Endocannabinoids/ (5630)

31 exp Receptors, Cannabinoid/ (9240)

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

33 or/28-32 (54925)

Annotation: strategy from 2020 cannabis review

34 27 and 33 (16307)

Annotation: cannabis AND study design filter

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

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

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

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

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

40 exp Product Surveillance, Postmarketing/ (15237)

41 adverse drug reaction reporting systems/ (7463)

42 clinical trials, phase iv/ (295)

43 exp Poisoning/ (156177)

44 exp Substance-Related Disorders/ (274845)

45 Abnormalities, Drug-Induced/ (14514)

46 Drug Monitoring/ (20599)

47 exp Drug Hypersensitivity/ (45642)

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

49 or/35-48 (5596308)

Annotation: OVID AE filter

50 34 and 49 (10649)

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

Database: Embase <1974 to 2020 March 31>

Search Strategy:

---

1 cannabis/ (33859)

2 exp cannabinoid/ (65694)

3 medical cannabis/ (2104)

4 exp cannabinoid receptor/ (14557)

5 exp endocannabinoid/ (8589)

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

7 or/1-6 (87843)

Annotation: cannabis

8 clinical study/ (154879)

9 case control study/ (153658)

10 family study/ (26012)

11 longitudinal study/ (137463)

12 retrospective study/ (897628)

13 prospective study/ (590879)

14 randomized controlled trials/ (176633)

15 13 not 14 (584662)

16 cohort analysis/ (564001)

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

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

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

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

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

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

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

Annotation: SIGN observational studies filter

24 7 and 23 (9720)

Annotation: cannabis AND observational studies

25 randomized controlled trial/ (597702)

26 Controlled clinical study/ (463832)

27 random$.ti,ab. (1518977)

28 randomization/ (86491)

29 intermethod comparison/ (258334)

30 placebo.ti,ab. (303428)

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

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

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

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

35 double blind procedure/ (171048)

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

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

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

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

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

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

42 human experiment/ (490389)

43 trial.ti. (295850)

44 or/25-43 (4952112)

Annotation: Cochrane RCT filter

45 7 and 44 (14036)

Annotation: cannabis AND RCTs

46 24 or 45 (21357)

Annotation: cannabis AND (Obs studies OR RCTs)

47 7 and (23 or 44) (21357)

Annotation: logic check

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

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

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

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

52 exp adverse drug reaction/ (522775)

53 exp drug toxicity/ (125051)

54 exp intoxication/ (366563)

55 exp drug safety/ (393912)

56 exp drug monitoring/ (53058)

57 exp drug hypersensitivity/ (56248)

58 exp postmarketing surveillance/ (35831)

59 exp drug surveillance program/ (26017)

60 exp phase iv clinical trial/ (3822)

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

62 or/48-61 (6002309)

Annotation: OVID AE filter 1-14

63 47 and 62 (6382)

Cannabis AEs

Search Name: cannabis AEs

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

Comment:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#22 #6 and #21 in Trials 2426

PsycInfo

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

Search Strategy:

---

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

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

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

3 1 or 2 (26466)

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

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

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

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

8 toxic disorders/ (1433)

9 exp "substance use disorder"/ (127742)

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

11 or/4-10 (310848)

12 3 and 11 (10984)

13 epidemiology/ (49562)

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

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

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

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

18 Case control.mp. (10736)

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

20 Cohort analy$.mp. (2099)

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

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

23 or/13-22 (561443)

24 12 and 23 (3801)

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

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

Appendix 3: List of included studies

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

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

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

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

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

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

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

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

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

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

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

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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	Critical	Serious	Low	Low	Low	Moderate	Low
Lynch, 2006	Critical	Low	Low	Low	Low	Moderate	Low
Rog, 2007	Critical	Low	Low	Serious	Low	Moderate	Low
Weber, 2009	Critical	Low	Low	Serious	Low	Moderate	Moderate
Bestard, 2011*	Critical	Low	Low	Moderate	Low	Moderate	Low
Fiz, 2011	Critical	Serious	Low	Low	Low	Moderate	Low
Dominguez, 2012	Critical	Low	Low	Moderate	Low	Moderate	Low
Gatti, 2012	Critical	Low	Low	Low	Low	Moderate	Low
Toth, 2012	Critical	Low	Low	Low	Low	Moderate	Low
Schifilliti, 2014	Critical	Low	Low	Low	Low	Moderate	Moderate
Storr, 2014	Critical	Serious	Low	Low	Low	Moderate	Moderate
Del Giorno, 2015	Critical	Low	Low	Low	Low	Moderate	Low
Hoggart, 2015	Critical	Serious	Low	Moderate	Low	Moderate	Low
Ware, 2015†	Critical	Serious	Low	Moderate	Low	Moderate	Low
Haroutounian, 2016	Critical	Low	Low	Low	Low	Moderate	Low
Bellnier, 2017	Critical	Low	Low	Low	Low	Moderate	Moderate
Cranford, 2017	Critical	Serious	Low	Low	Low	Moderate	Low
Fanelli, 2017	Critical	Low	Low	Serious	Critical	Moderate	Low
Feingold, 2017	Critical	Serious	Low	Low	Low	Moderate	Moderate
Paladini, 2017	Critical	Low	Low	Low	Low	Moderate	Low
Passavanti, 2017	Critical	Low	Low	Low	Low	Moderate	Low
Schimrigk, 2017	Critical	Serious	Low	Low	Low	Moderate	Low
Chirchiglia, 2018	Critical	Low	Low	Low	Low	Serious	Low
Crowley, 2018	Critical	Serious	Low	Low	Low	Moderate	Low
Habib, 2018	Critical	Low	Low	Low	Low	Moderate	Low
Anderson, 2019	Critical	Low	Low	Low	Serious	Moderate	Low
Bonar, 2019	Critical	Serious	Low	Low	Low	Serious	Moderate
Cervigni, 2019	Critical	Low	Low	Low	Serious	Moderate	Low
Cremer-Schaeffer, 2019 ‡	Critical	Low	Low	Serious	Low	Moderate	Moderate
Lejczak, 2019	Critical	Low	Low	Critical	Serious	Moderate	Moderate
Loi, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Naftali, 2019	Critical	Serious	Low	Low	Moderate	Moderate	Low
Perron, 2019	Critical	Serious	Low	Low	Low	Moderate	Low
Sagy, 2019	Critical	Low	Low	Moderate	Serious	Moderate	Moderate
Sinclair, 2019	Critical	Serious	Low	Low	Low	Moderate	Moderate
Ueberall, 2019	Critical	Low	Low	Moderate	Low	Moderate	Low
Vigil, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Yassin, 2019	Critical	Low	Low	Low	Low	Moderate	Low
Giorgi, 2020	Critical	Low	Low	Serious	Low	Moderate	Low

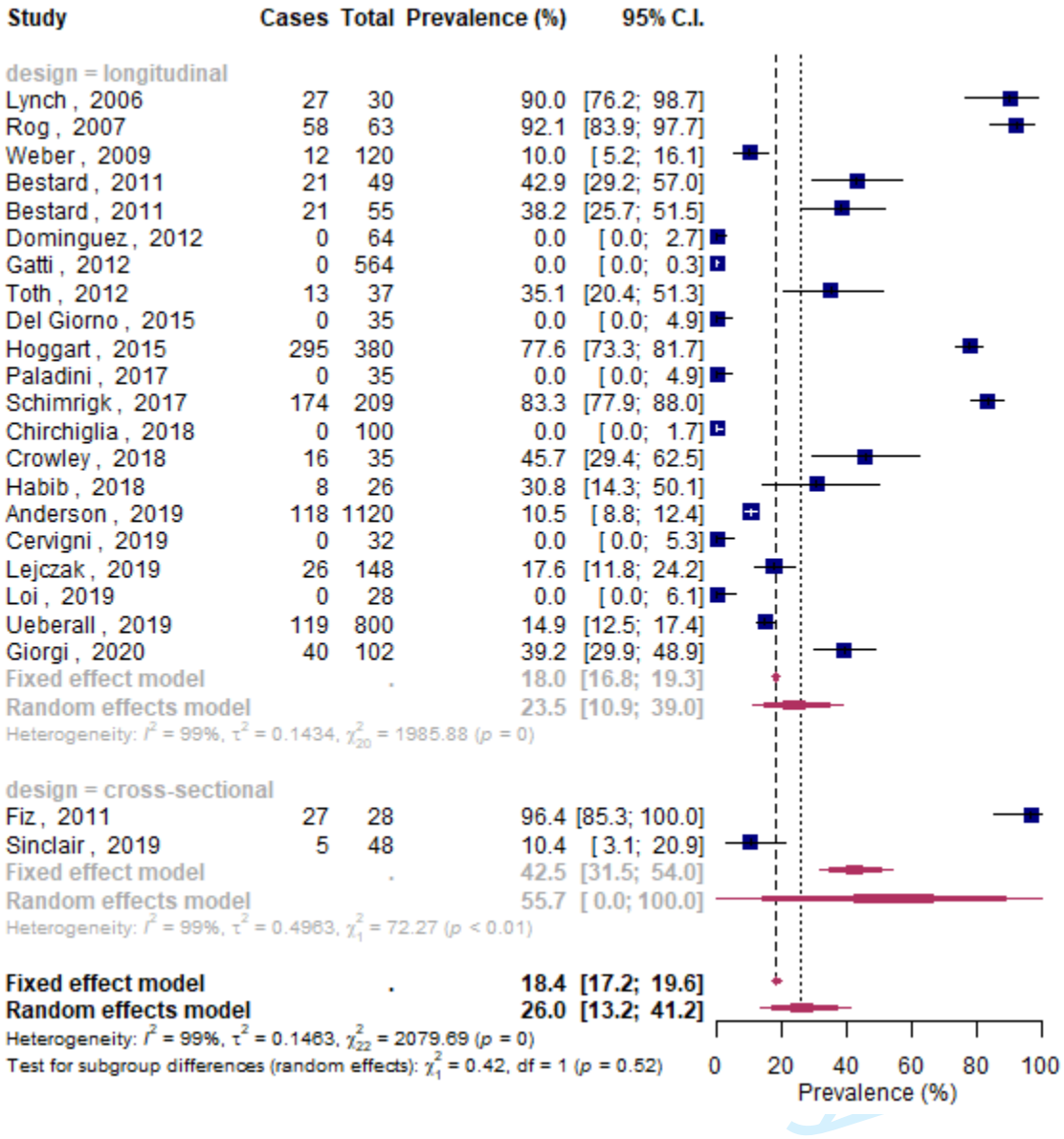
Low risk of bias	Low
Moderate risk of bias	Moderate
Serious risk of bias	Serious
Critical risk of bias	Critical

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

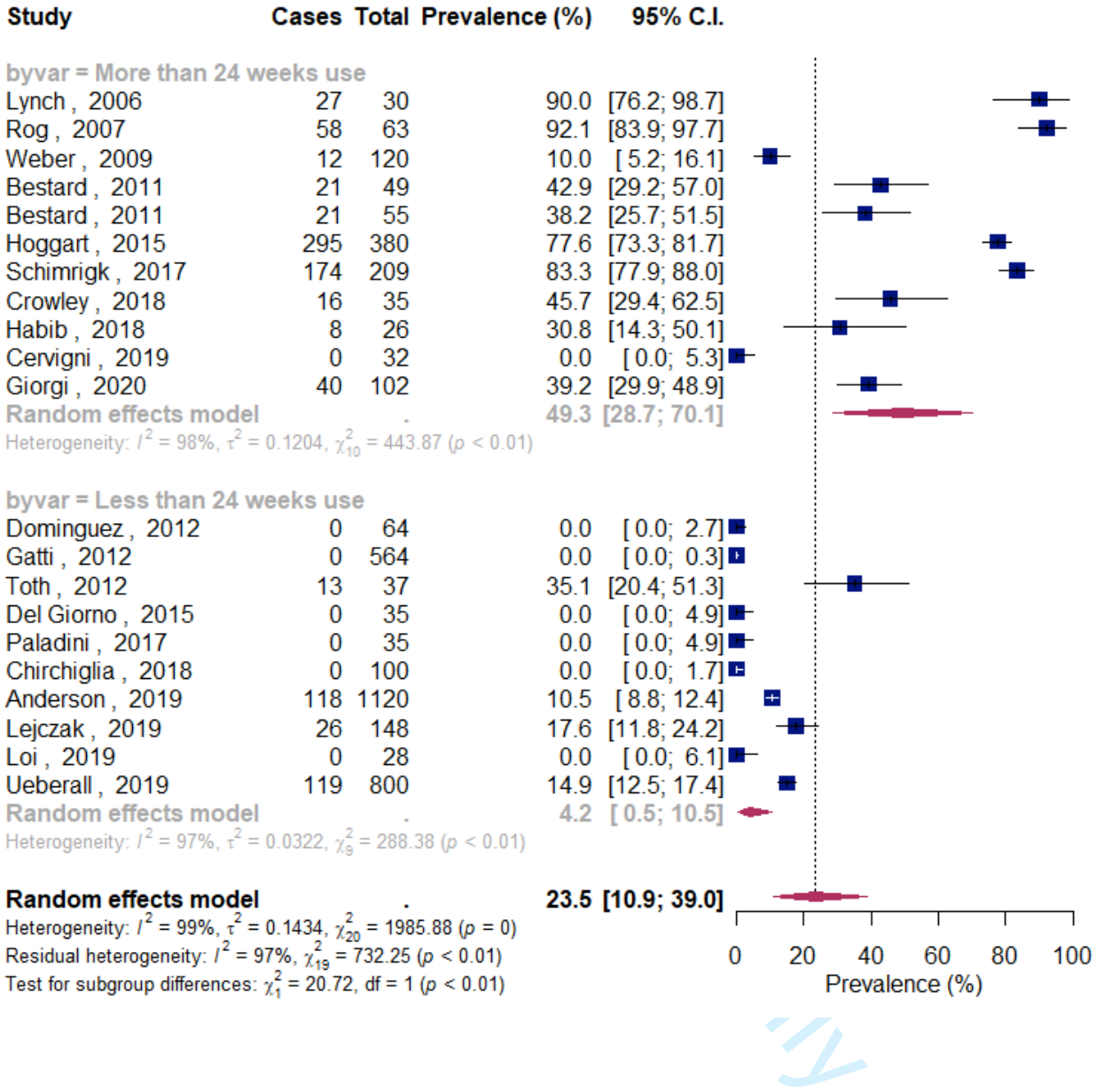
† Risk of bias for confounding for unadjusted comparative comparative results were rated as serious. Adjusted comparative results were rated as moderate.

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

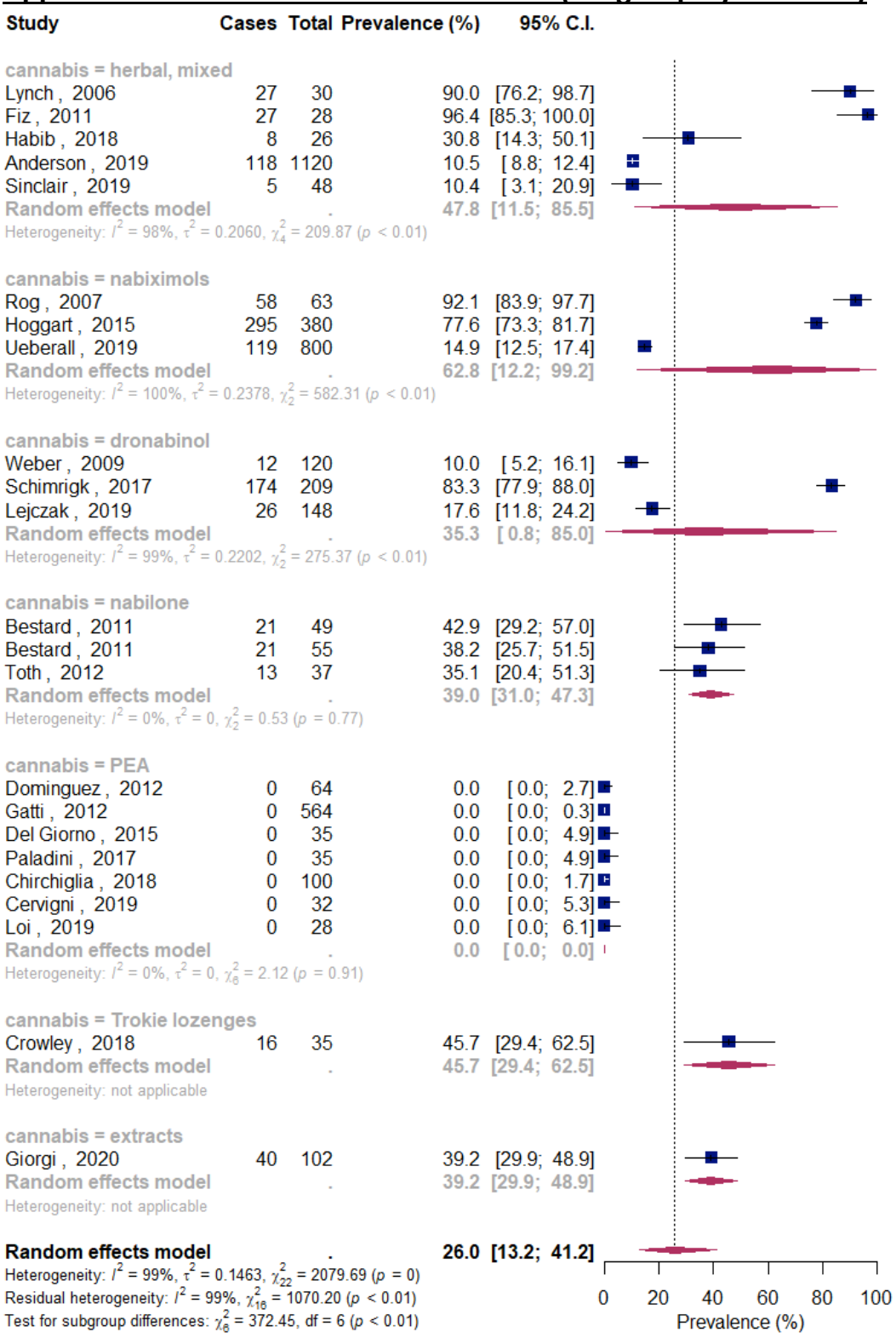
Appendix 6: Results for all adverse events (subgroup by design)



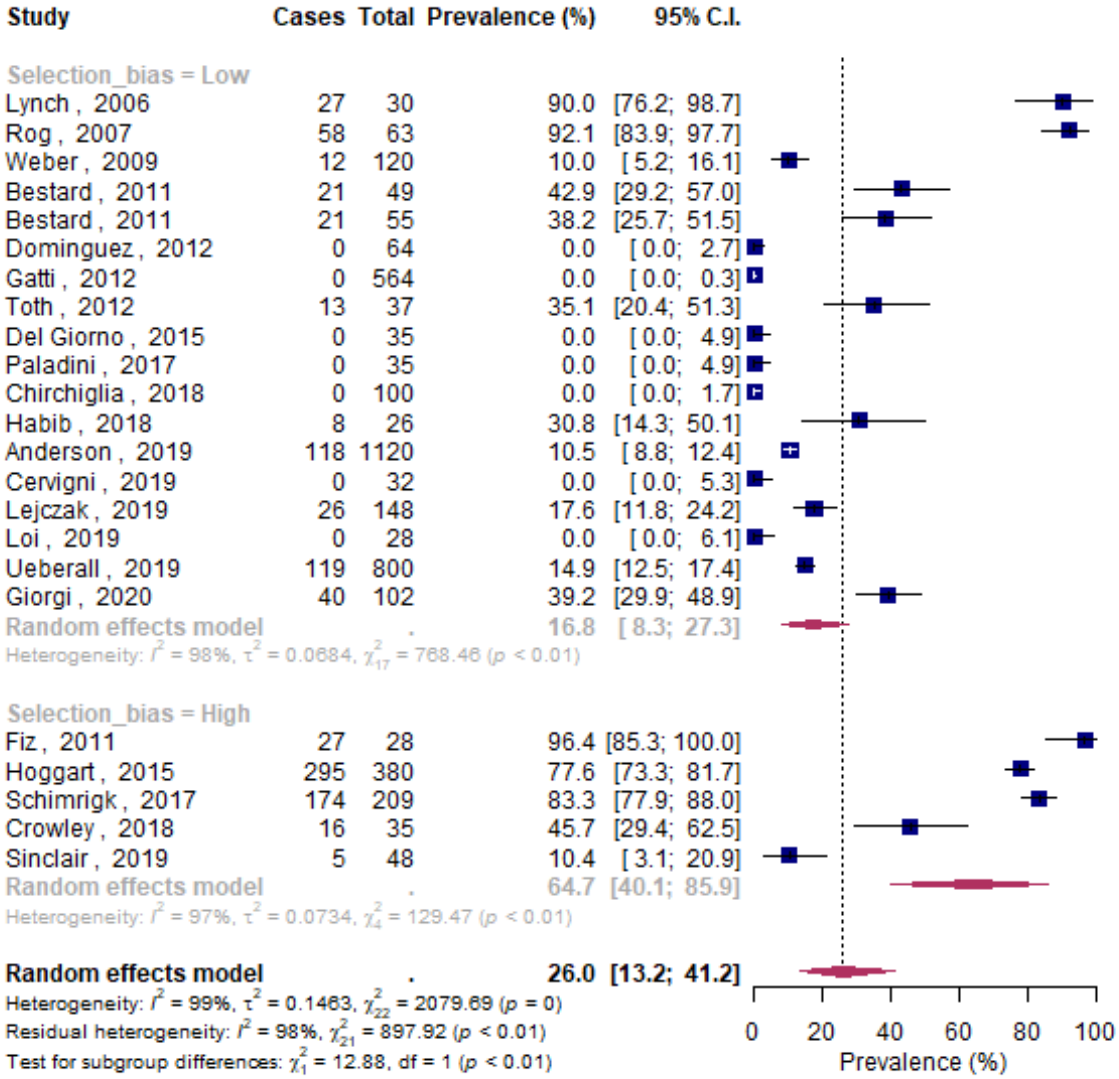
Appendix 7: Results for all adverse events (subgroup by duration)



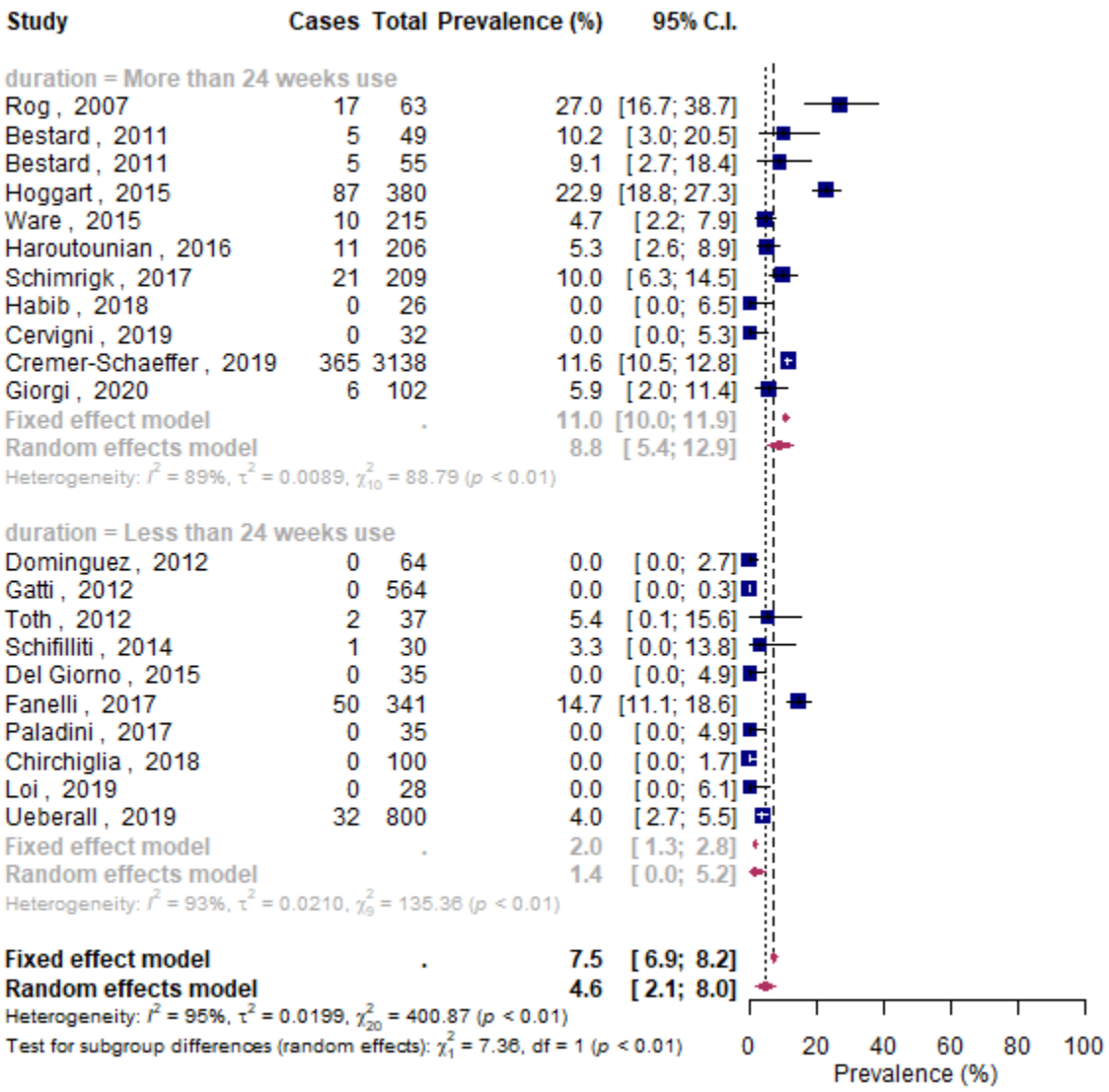
Appendix 8: Results for all adverse events (subgroup by cannabis)



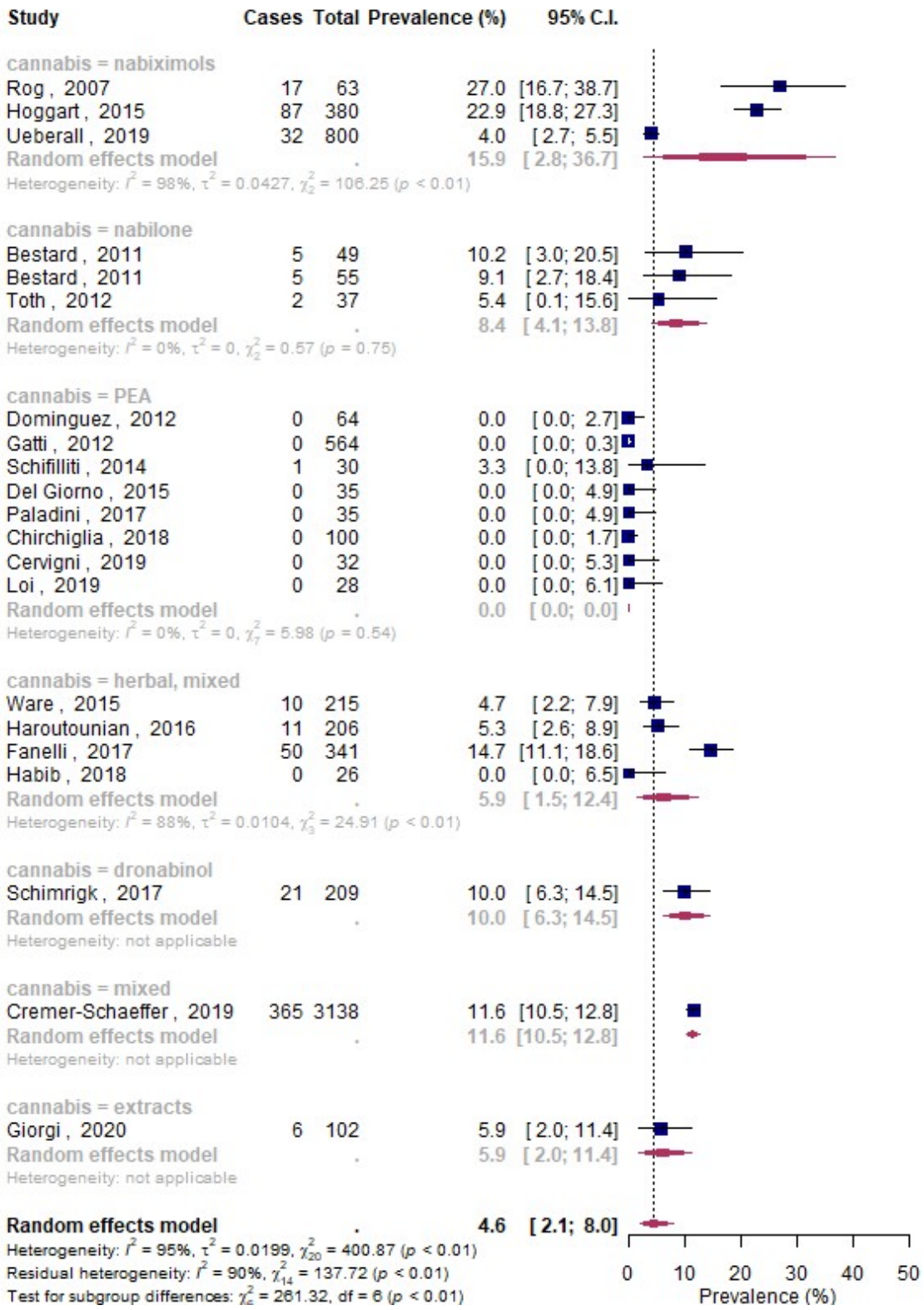
Appendix 9: Results for all adverse events (subgroup by selection bias)



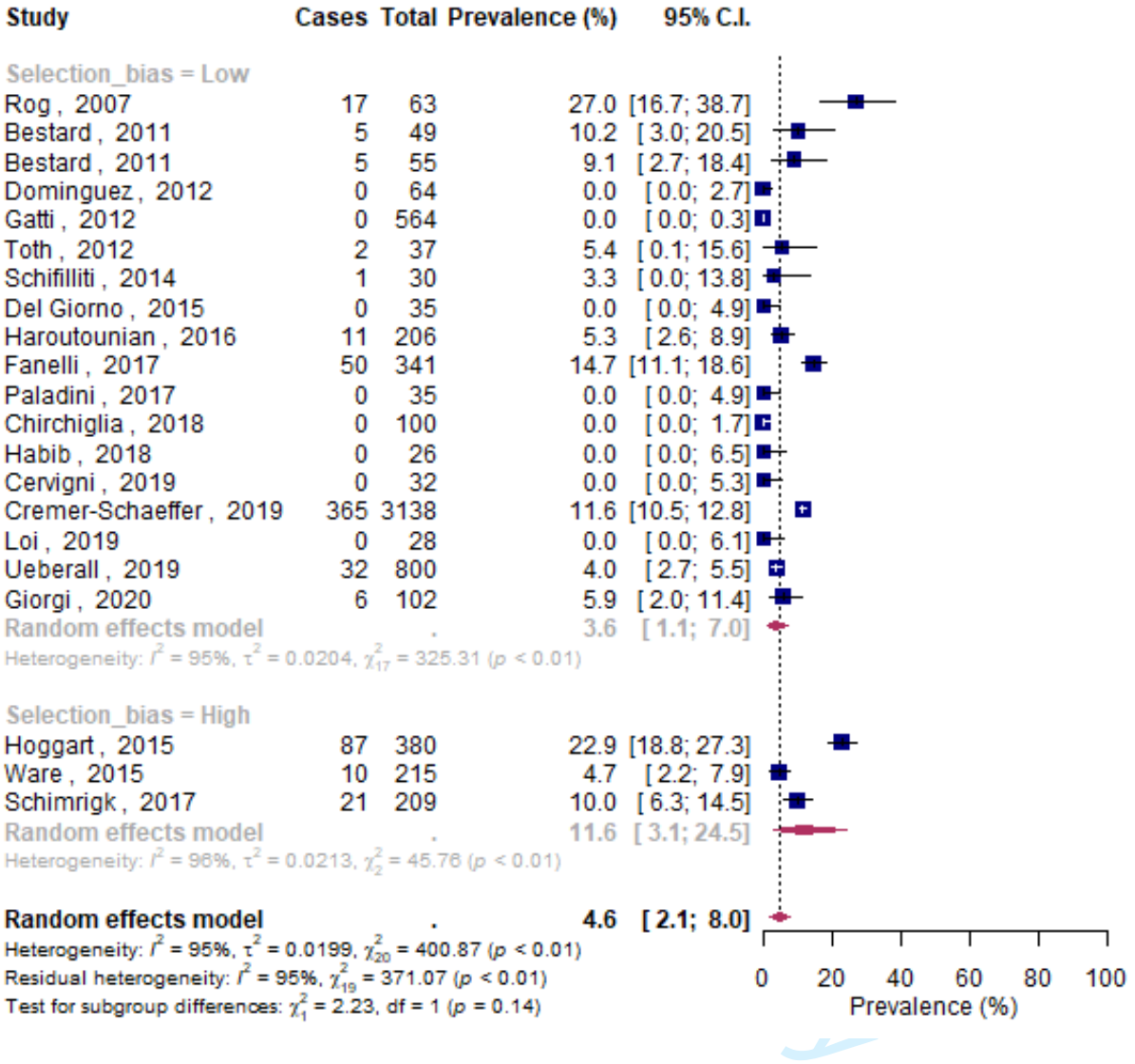
Appendix 10: Results for adverse events leading to discontinuation (subgroup by duration)



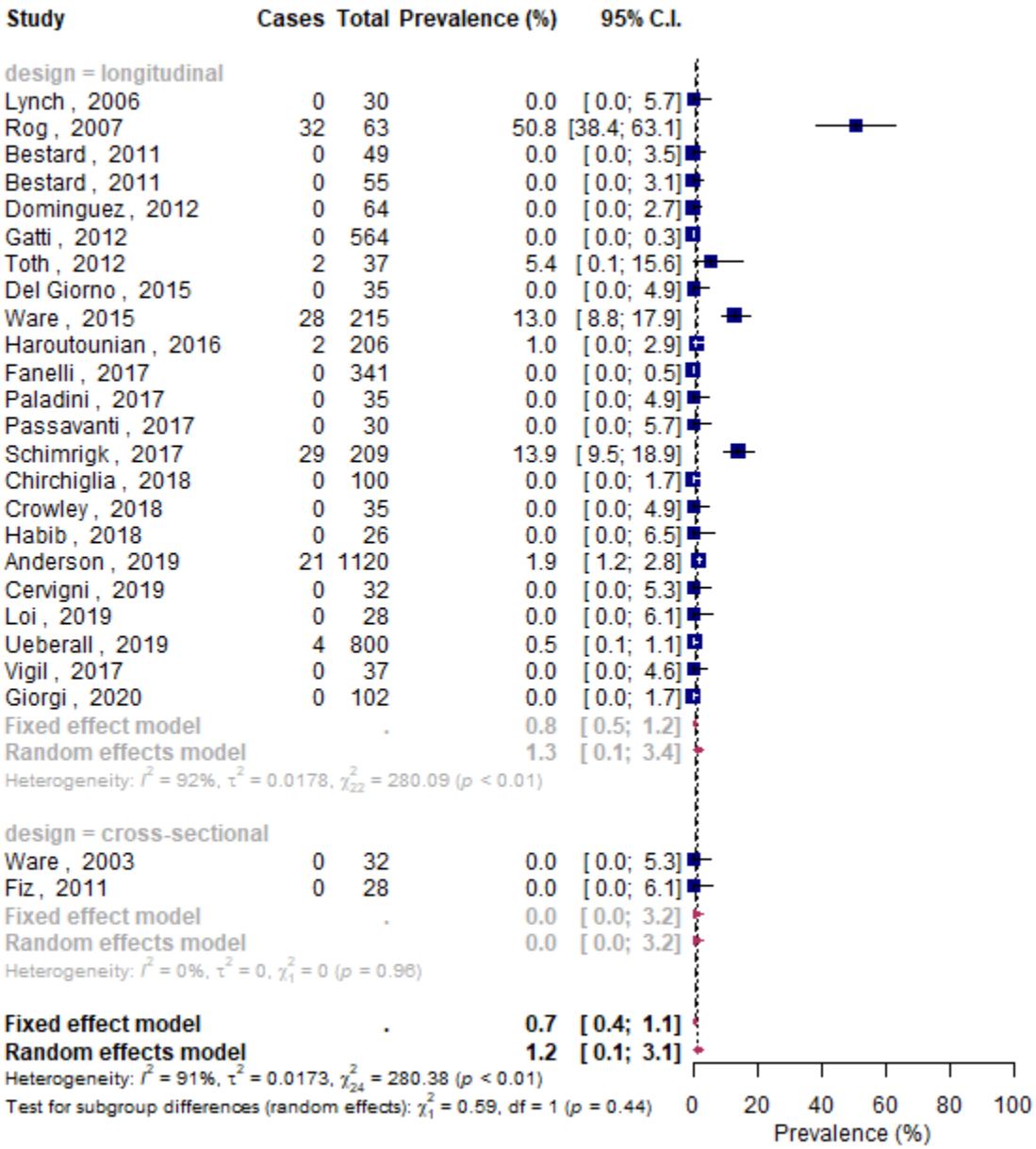
Appendix 11: Results for adverse events leading to discontinuation (subgroup by cannabis)



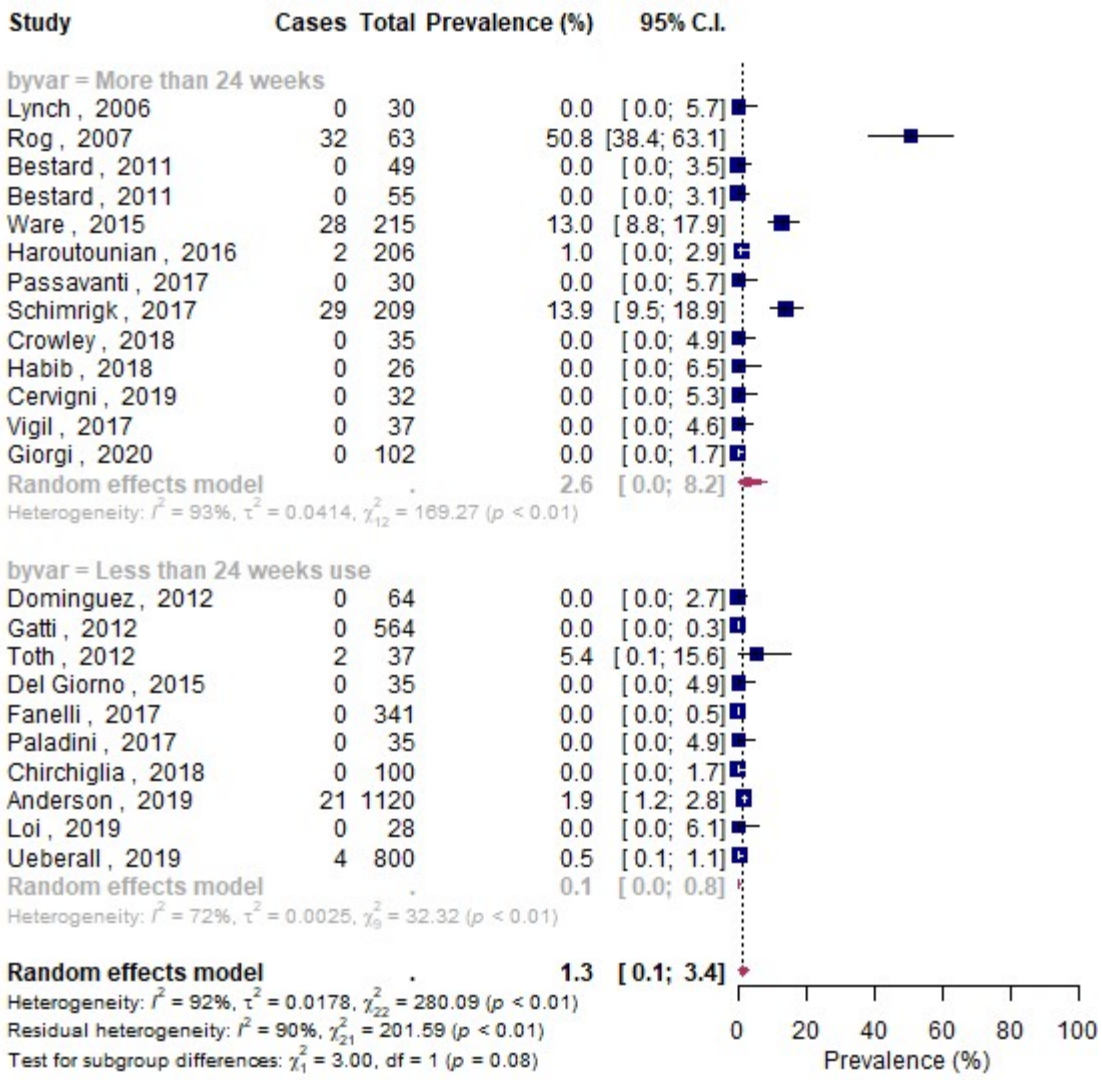
Appendix 12: Results for adverse events leading to discontinuation (subgroup by selection bias)



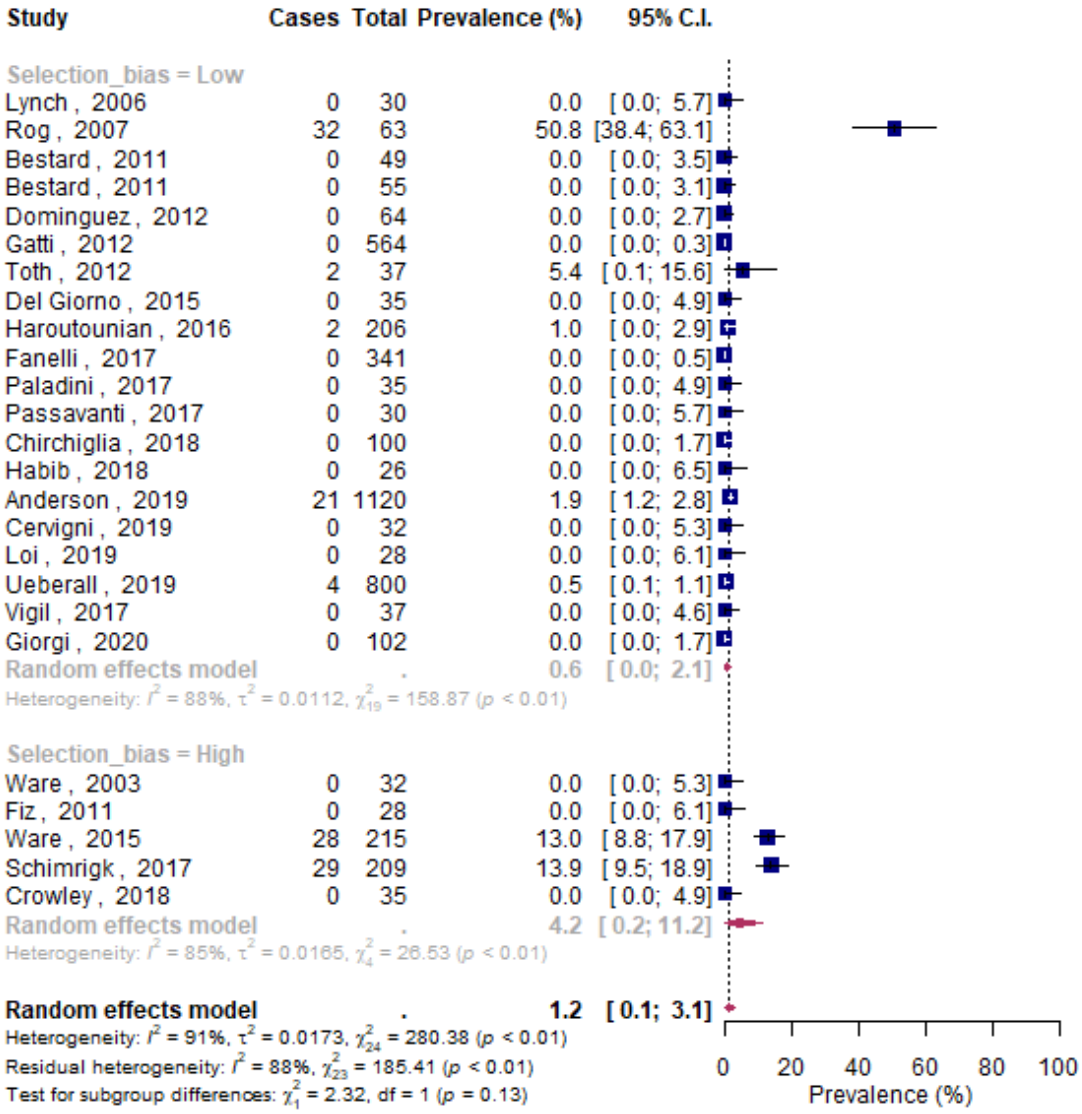
Appendix 13: Results for serious adverse events (subgroup by design)



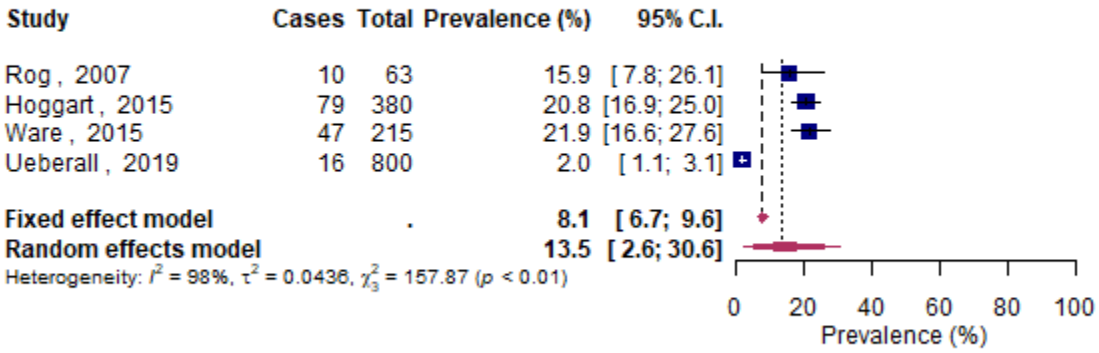
Appendix 14: Results for serious adverse events (subgroup by duration)



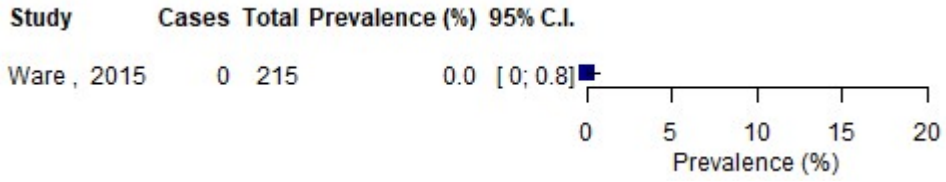
Appendix 15: Results for serious adverse events (subgroup by selection bias)



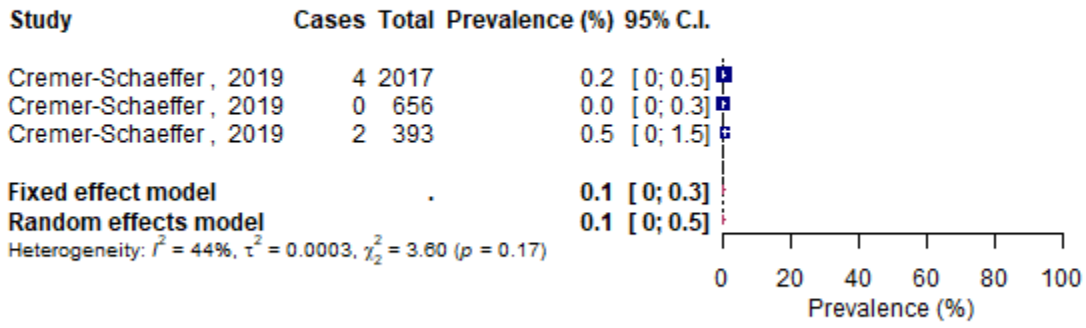
Appendix 16: Results for psychiatric adverse events



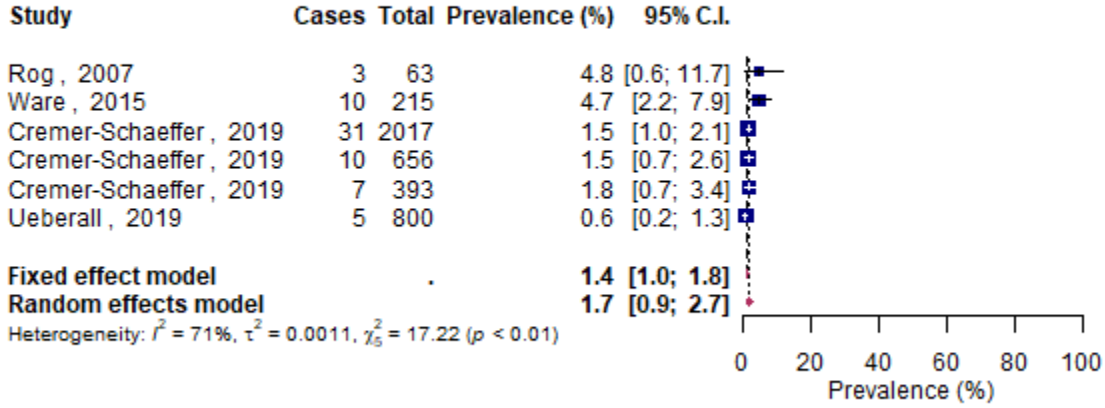
Appendix 17: Results for suicide



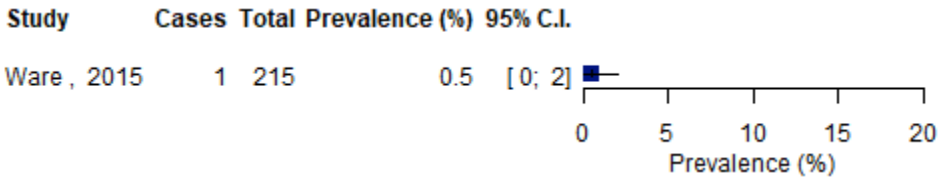
Appendix 18: Results for suicidal thoughts



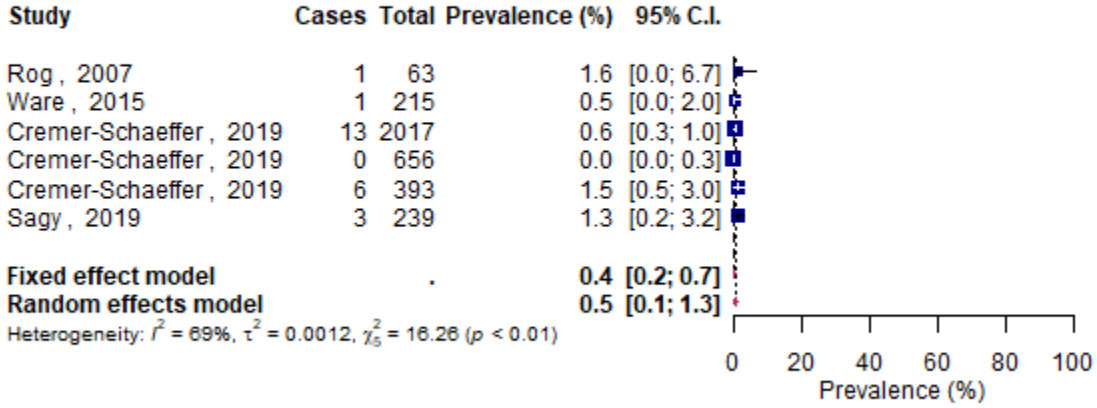
Appendix 19: Results for depression



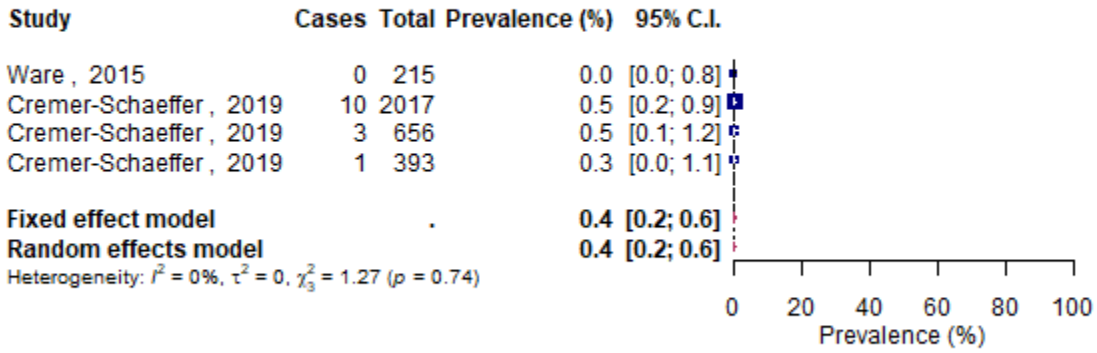
Appendix 20: Results for mania



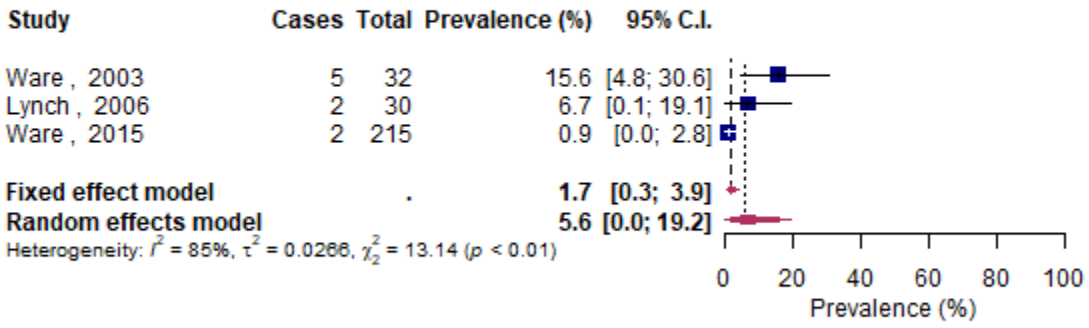
Appendix 21: Results for hallucinations



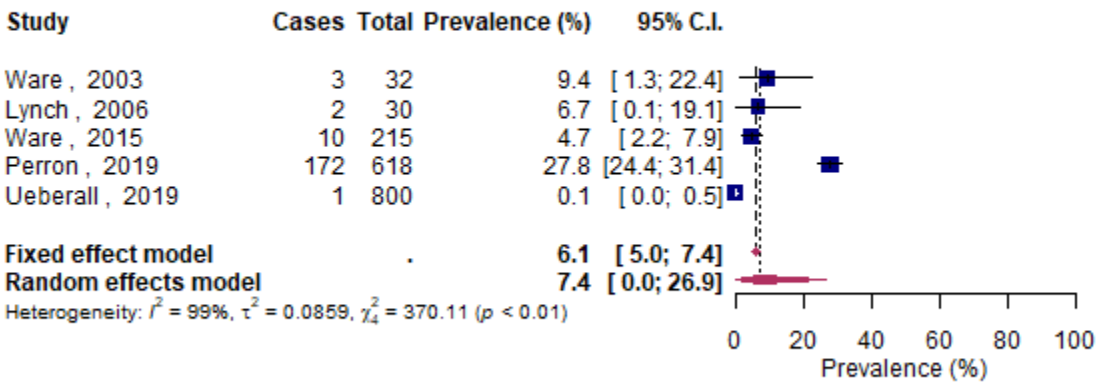
Appendix 22: Results for delusions



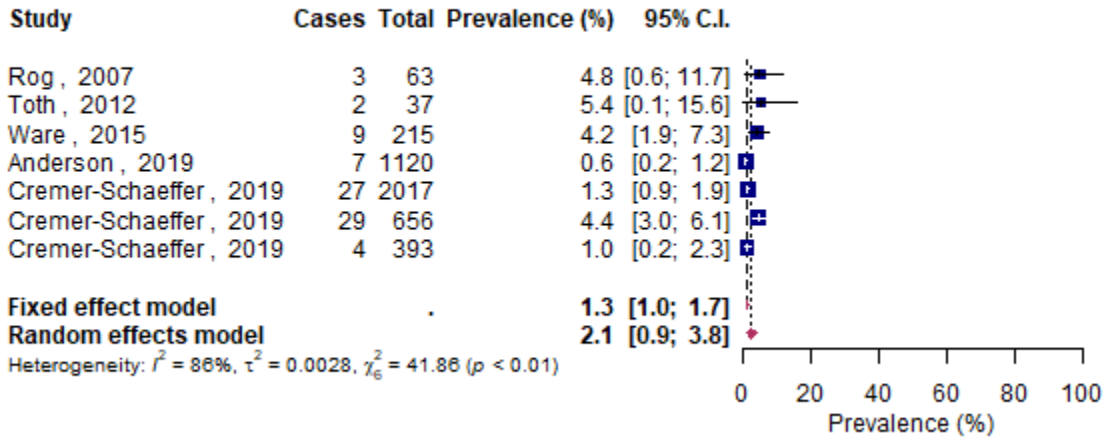
Appendix 23: Results for paranoia



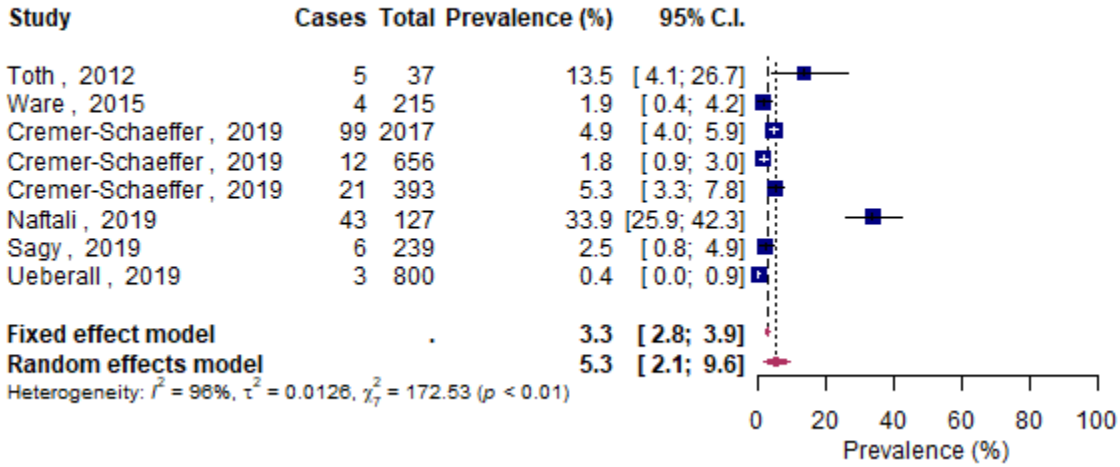
Appendix 24: Results for anxiety



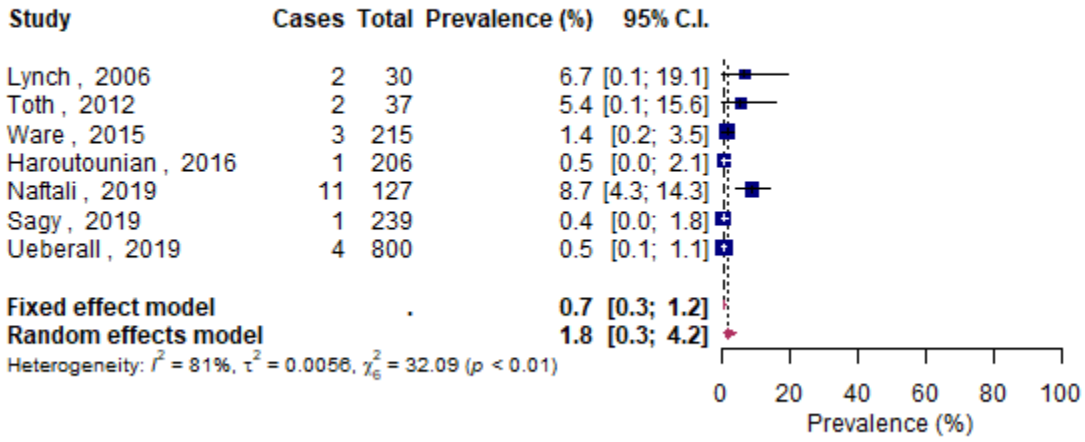
Appendix 25: Results for euphoria



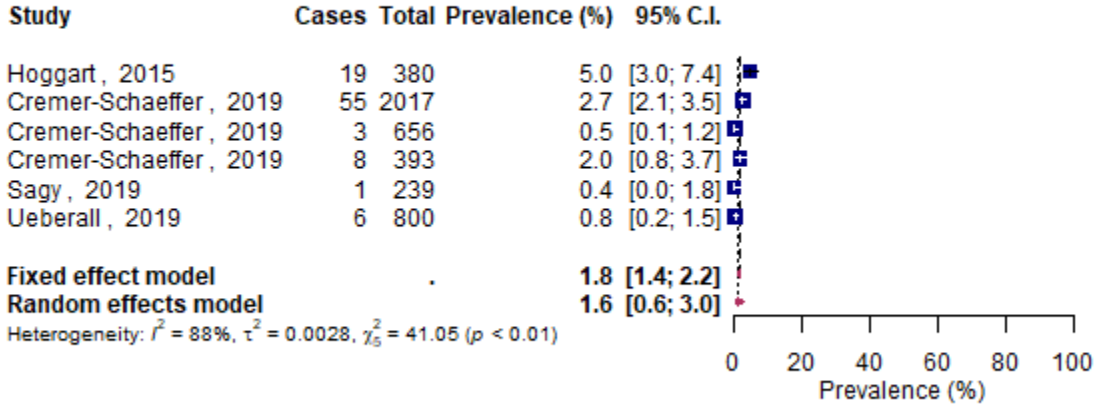
Appendix 26: Results for memory impairment



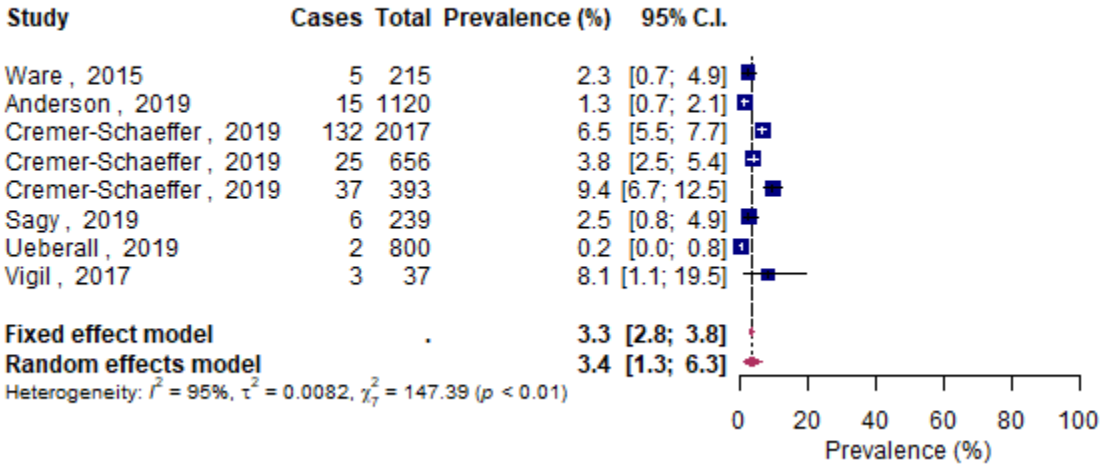
Appendix 27: Results for confusion



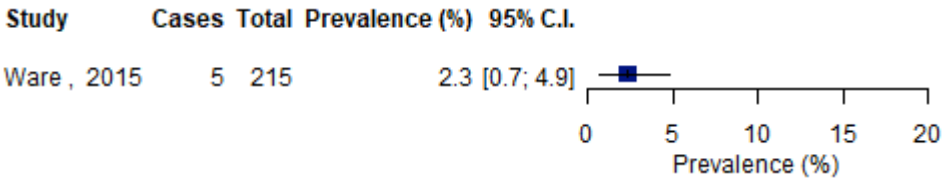
Appendix 28: Results for disorientation



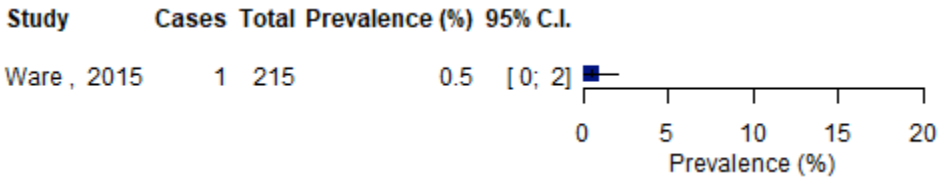
Appendix 29: Results for impaired attention



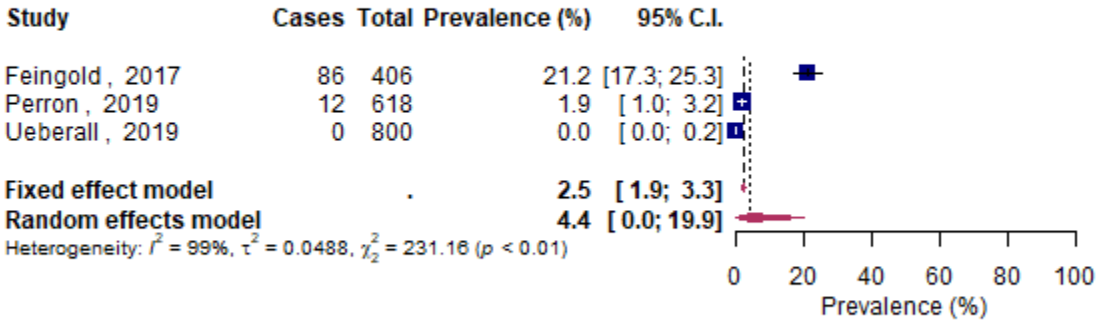
Appendix 30: Results for falls



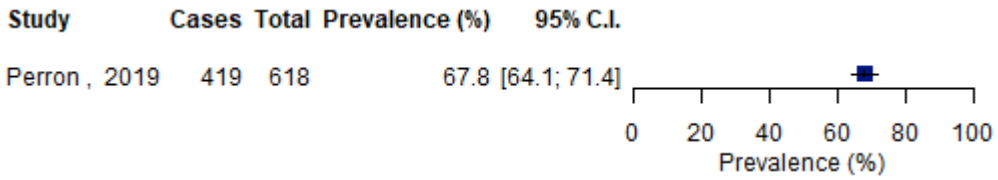
Appendix 31: Results for motor vehicle accidents



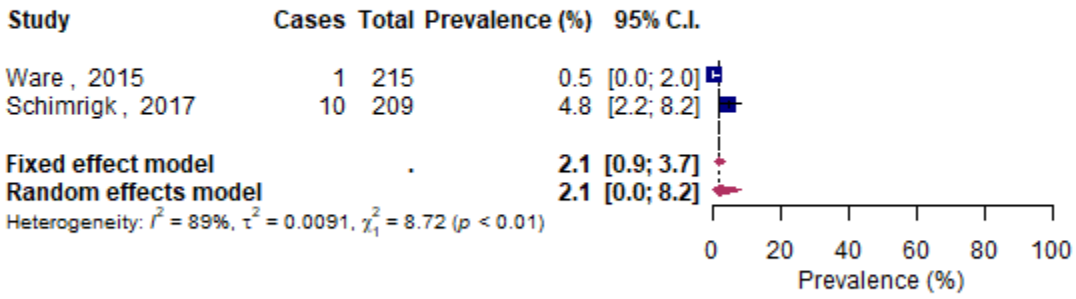
Appendix 32: Results for dependence



Appendix 33: Results for withdrawal symptoms



Appendix 34: Results for withdrawal syndrome



Section/topic (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

Study selection (8)	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
Data collection process (9)	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
Data items (9)	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
Risk of bias in individual studies (10)	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
Summary measures (11)	13	State the principal summary measures (eg, risk ratio, difference in means).	—	No specific additional information is required for systematic reviews of harms.	X
Synthesis of results (11)	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.		
Risk of bias across studies (11)	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
Additional analyses (12)	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
Results					
Study selection (13)	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

		stage, ideally with a flow diagram.			
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
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
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
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
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
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
Discussion					
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
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
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
Funding					
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