HARMS ASSOCIATED WITH INHALED CANNABIS FOR CHRONIC PAIN

HARMS ASSOCIATED WITH INHALED CANNABIS FOR MANAGEMENT OF CHRONIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

By JANE JOMY, BHSc

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

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TITLE: Harms Associated with Inhaled Cannabis for Management of Chronic Pain: A Systematic Review and Meta-analysis of Observational Studies

AUTHOR: Jane Jomy, BHSc (McMaster University)

SUPERVISOR: Dr. Jason Walter Busse

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Lay Abstract

Increasing recognition of harms associated with long-term opioid therapy for management of chronic pain has generated enthusiasm for alternatives, including medical cannabis which is often consumed through inhalation. This review assesses the harms associated with the use of inhaled cannabis for management of chronic pain. Among serious adverse events, we found that inhaled cannabis is likely associated with amnesia, disorientation, impaired coordination, hallucinations, confusion, dizziness, chronic wheeze, and shortness of breath. Inhaled cannabis may be associated with palpitations, paranoia, anxiety, and cannabis dependence. The effects of inhaled cannabis on lung cancer, depression, and psychosis were uncertain. Among less serious adverse events, we found that inhaled cannabis is likely associated with thirst, fatigue, increased appetite, nausea, mood changes, diarrhea, and dry mouth. Inhaled cannabis may be associated with red eyes, vomiting, phlegm, asthma, and cough. The effects of inhaled cannabis on euphoria and irritability were uncertain.

Abstract

Background: Cannabis is increasingly used for management of chronic pain; however, the benefits and harms of this therapy remain uncertain. We conducted a systematic review to inform harms associated with inhaled cannabis for chronic pain.

Methods: We searched MEDLINE, EMBASE, PsychInfo, and Web of Science for non-randomized studies reporting on harms associated with inhaled cannabis use, from inception to October 6, 2021. We used random-effects models for meta-analyses and assessed the certainty of evidence using the GRADE approach.

Results: We identified 29 eligible studies enrolling 174,562 participants that reported 145 adverse events. Moderate certainty evidence suggests inhaled cannabis use is probably associated with dry mouth (prevalence: 56%; 95%CI 49 to 64), thirst (prevalence: 44%; 95% CI 33 to 55), fatigue (prevalence: 38%; 95%CI 31 to 45), nausea (prevalence: 17%; 95%CI 8 to 27), increased appetite (prevalence: 13%; 95%CI 9 to 18), dizziness (prevalence: 10%; 95%CI 6 to 14), diarrhea (prevalence: 9%; 95%CI 3 to 18), confusion (prevalence: 9%; 95%CI 5 to 13), mood changes (prevalence: 8%; 95%CI 4 to 15), hallucinations (prevalence: 7%; 95%CI 4 to 10), amnesia (prevalence: 6%; 95%CI 3 to 11), impaired coordination (prevalence: 5%; 95%CI 4 to 6), and disorientation (prevalence: 3%; 95%CI 1 to 7). Moderate certainty evidence shows that, compared to non-users, inhaling cannabis is probably associated with increased risk of shortness of breath (risk difference [RD]: 7%; 95%CI 4 to 10).

Conclusions: Our review found moderate certainty evidence that dry mouth, thirst, and fatigue are probably frequently experienced with inhaled cannabis use. Several other

adverse events are also probable associated with inhaled cannabis use but were less common. Rigorously conducted cohort studies are needed to inform harms associated with inhaled medical cannabis for chronic pain.

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List of Abbreviations and Symbols

AIDS = acquired immunodeficiency syndrome

BMJ = British Medical Journal

CBD = cannabidiol

CLARITY = Clinical Advances through Research and Information Translation

GRADE = Grading of Recommendations Assessment, Development and Evaluation

HIV = human immunodeficiency virus

IBD = inflammatory bowel disease

ICD = International Classification of Diseases

MeSH = Medical Subject Heading terms

PRISMA-P = Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

PTSD = post-traumatic stress disorder

OR = odds ratio

RD = risk difference

ROBVIS = Risk-of-bias visualization

SOB = shortness of breath

THC = delta-9-tetrahydrocannabinol

Declaration of Academic Achievement

I, Jane Jomy, declare my thesis to be my own research work. I am the sole author of this thesis document and was involved in all stages of the research project under the supervision of Dr. Jason W. Busse. Dr. Li Wang and Dr. Behnam Sadeghirad contributed to the editing and refinement of my thesis and Dr. Dena Zeraatkar conducted all meta-analyses of proportions. To my knowledge, the content of this document does not infringe on any copyrights.

1.0 BACKGROUND

1.1 Chronic pain

Chronic pain is a common reason to seek medical treatment, producing a significant economic and social burden (1), affecting 20-30% of individuals worldwide (2). According to the International Classification of Diseases (ICD) of the World Health Organization, chronic pain is defined as pain that lasts or recurs for more than 3 to 6 months (3).

On an individual level, living with chronic pain interferes with physical functioning, daily activities, mental health, social and role functioning (4, 5). One review found this burden extends to over 30% of caregivers, who report an inability to cope with pain-related problems affecting family members. Further, that presenteeism secondary to chronic pain was responsible for up to a 43% loss in workplace productivity (6). In 2016, the incremental cost to manage chronic pain was $1,742 per patient in Ontario, which was 51% higher than matched patients without pain. The largest component of this cost was attributed to hospitalization (7). In Canada, the economic burden of chronic pain was estimated to be between $38.3 to $40.4 billion alone in 2019 (8).

Chronic pain can be managed with pharmacologic and nonpharmalogic therapies. Pharmacologic management includes opioids, nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen), antidepressants, antiseizure medications, and infusion therapies (e.g., ketamine and lidocaine infusion) (9). Nonpharmalogic management for chronic pain includes exercise, psychotherapy, complementary and integrative health therapies, and physical modalities (10).

1.2 Benefits and harms of treatments for chronic pain

Opioids are commonly used to manage chronic pain, particularly in North America (11). However, their use remains controversial, especially for longer treatment periods, due to safety concerns including addiction, overdose, and death. A systematic review found that among patients prescribed opioid therapy for chronic pain, rates of addiction were 8-12% (12). Rates of opioid use disorder and opioid-related deaths in Canada have multiple contributors, including over-prescription, diversion, and the rise in the production of illicit opioids (13-15). Since 2016, more than 17,000 opioid-related deaths and 21,000 opioid-related hospitalizations have been reported in Canada (16, 17).

Current opioid guidelines have highlighted the risks that accompany the use of opioids for chronic pain and recommend against use of opioids as first-line therapy (18). Evidence shows that alternatives to opioids may have similar effects on pain relief and improvements in physical function, including nonsteroidal anti-inflammatory drugs (NSAIDs), tricylic antidepressants, and nabilone (a synthetic cannabinoid). The increasing recognition of harms associated with long-term opioid use, and greater appreciation for the modest benefits of opioids for patients with chronic pain, have generated enthusiasm for alternative approaches, one of which is the use of medicinal cannabis (18, 19).

1.3 Cannabis

Cannabis is among the most common psychoactive substance used globally, and is derived from a genus of flowering plants in the Cannabaceae family (20). Evidence for cannabis use dates back at least 6000 years, yet most of its pharmacological attributes have been

elucidated since the nineteenth century. The cannabis plant contains over 400 distinct chemicals; 125 of which are classified as cannabinoids (21). Many of these cannabinoids exhibit antagonistic effects to other chemicals within this class. Three notable cannabinoids are cannabinol, cannabidiol (CBD), and delta-9-tetrahydrocannabinol (d-9-THC, or THC) (22). THC, the major psychotropic chemical in cannabis, is the primary determinant of cannabis potency and adverse effects following use. Unlike THC, CBD is not psychoactive; however, recent research suggests protective activity of CBD against negative effects from using THC in addition to its therapeutic properties (23).

Cannabis can be delivered via various routes, including oral ingestion, inhalation, oromucosally, sublingually, and transdermally. Thus, cannabis products take many forms such as extracts, oils, foods, topical creams and ointments, and cigarettes. Inhalation of cannabis presents the possibility of pulmonary risks that oral administration avoids (24). However, inhalation of cannabis in the form of cigarettes is the most popular choice among therapeutic users (25).

When cannabis is orally ingested, THC is metabolized by the liver. Comparatively, this step is skipped during inhalation and so cannabinoids are rapidly absorbed in the blood for effect. Despite the fast onset of action, possible adverse effects of the respiratory tract should be considered (26). Respiratory implications with inhalation cannabis may include increased risk for lung cancer, spontaneous pneumothorax, and complications consistent with chronic obstructive pulmonary disease (27).

1.4 Clinical evidence and guidelines for cannabis

A 2021 systematic review of randomized trials found 32 studies focused on medical cannabis for chronic non-cancer and cancer related pain. Of these, no trials focused on inhaled cannabis (28). Researchers found that non-inhaled cannabis probably results in a small increase in pain relief, improvements in physical functioning, and sleep quality. However, small increases in adverse event risks such as vomiting, drowsiness, impaired attention, and nausea were also associated with medical cannabis use.

Several guidelines have recently been published on cannabis and chronic pain, but are conflicting. The National Institute for Health and Care Excellence (NICE) guideline for cannabis-based medicinal products strongly recommend that THC and combinations of CBD with THC should not be used to manage chronic pain in adults (29). Alternately, a 2021 British Medical Journal (BMJ) Rapid Recommendation issued a weak recommendation to offer a trial of non-inhaled medical cannabis in addition to standard care for people living with chronic non-cancer or cancer related pain in whom their current management was insufficient (30).

1.5 Legalization and regulation

In 2020, upon recommendations from the World Health Organization, the United Nations voted for the removal of medicinal cannabis from Schedule IV of the 1961 Single Convention on Narcotic Drugs, which denotes highly dangerous drugs. While governments reserve jurisdiction for controlling the use of cannabis, this vote may accelerate cannabis research and further promote global legalization of related therapies (31). Now regarded as

a Schedule I drug by the Single Convention Treaty, cannabis is still noted to carry risk for addiction and abuse but regulating bodies may permit its medical use (32). Already since 2001, medicinal cannabis has been legally available in Canada, and some US States have passed laws encouraging cannabis as a substitute for opioids in managing chronic pain (33).

As of March 2021, approximately 300,000 Canadians were authorized to use an average of up to 2 grams per day of cannabis for medical purposes under the Cannabis Act (34). Comparatively, almost 40,000 Canadians were registered with Health Canada for cultivation of medical cannabis for personal use. Within 12 months prior to March 2021, 7,781 healthcare practitioners were linked to registrations made with federally licensed sellers of cannabis (35). On October 17, 2018, Canada modified the Cannabis Act to legalize the production, distribution, and sale of recreational cannabis for adult use; the second country in the world to do so after Uruguay.

In 2020, Statistics Canada reported that 20% of Canadians over the age of 15 had used cannabis within the past 3 months of survey, with comparable overall consumption between genders. Younger populations tended to have higher rates of cannabis consumption than older populations, with 36% of 18-to-24-year-olds having consumed cannabis within 3 months. Further, 8% of Canadians reported daily or almost daily use of cannabis. The most common routes of administration at the time of survey were smoking (58%), followed by oral consumption (19%), vaping (12%), and unspecified routes (11%) (36).

1.6 Objective and Rationale

A recent systematic review of randomized trials of cannabis for chronic pain that followed patients for at least 4 weeks failed to find any randomized studies of inhaled cannabis; however, inhalation or vaporization remain the most common mode of cannabis consumption (37). This systematic review and meta-analysis of non-randomized studies will explore the harms associated with inhaled cannabis for the management of chronic pain.

2.0 METHODS

2.1 Standardised reporting and protocol registration

Our protocol is registered on the Open Science Framework, an open-access database (DOI: 10.17605/OSF.IO/5Z8EG). We reported our systematic review results in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline (38).

2.2 Information sources and searches

A medical research librarian (RJC) performed systematic searches in MEDLINE, EMBASE, PsychInfo and Web of Science for non-randomized studies from inception to October 6, 2021, without language restrictions. We also scanned the reference lists of all eligible studies and relevant systematic reviews to identify any additional studies. Appendix A presents our search strategy.

2.3 Eligibility criteria

We included observational studies, specifically cross-sectional, prospective or retrospective cohort, and case-control studies reporting at least one patient-important adverse event associated with inhaled cannabis. We only considered studies with at least 1-month follow-up to allow for sufficient time for adverse events to become manifest. As there is limited literature available regarding medicinal cannabis in inhaled forms among clinical populations, we included studies of either medical or recreational cannabis users (37).

We included studies of any clinical (any medical condition) or non-clinical (community) populations of adults that report on medical and/or recreational use of inhaled cannabis (≥85% smoked and/or vaporized cannabis) or reported the results of inhaled cannabis separately. We defined adverse events as incidences of temporary or permanent impairment of physical or psychological body functions or structure. We excluded studies that only reported on surrogate measures of adverse events such as physiological markers (i.e., heart rate, skin conductance, cortisol levels, and pupil dilation).

2.4 Selection and data collection process

Six pairs of reviewers were trained and participated in calibration exercises using standardized forms, prior to starting screening of titles and abstracts in DistillerSR, an online systematic review software. Pairs of reviewers, independently, screened the titles and abstracts of all identified citations. All citations judged as potentially eligible by at least one reviewer was retrieved for full-text review. Reviewers resolved discrepancies through

discussion and involved a third reviewer (JJ) as adjudicator when needed. We reviewed all eligible articles for overlap in study populations, and in cases in which >50% of the population overlapped we only included the largest study.

2.5 Data extraction and outcomes

The same pairs of reviewers independently abstracted relevant data from eligible studies. We conducted consensus exercises with a standardized data extraction form prior to the reviewers abstracting data. We extracted: (1) study and patient demographic information (author, year of publication, country, funding, study design, length of follow-up, sample size, patient population, condition(s) studied); (2) intervention (type of cannabis/control, dose); and (3) all patient-important adverse events. Reviewers resolved discrepancies through discussion.

2.6 Risk of bias

We used criteria proposed by the Clinical Advances through Research and Information Translation (CLARITY) group at McMaster University to assess the risk of bias of observational studies, including selection bias, control for confounding variables, validity of outcome assessment(s), and infrequent missing data (<20%) (39). For example, a study was determined to have a low risk of selection bias when researchers selected a target population from a representative population roster such as a patient registry or used consecutive enrollment of all patients attending a group of clinics. Bias due to confounding variables was assessed by comprehensive matching or adjustment for all plausible

prognostic variables. Item responses of 'definitely yes' and 'probably yes' corresponds to low risk of bias. Responses of 'probably no' and 'definitely no' corresponds to high risk of bias (Appendix B). Risk of bias assessments are presented using robvis software in Appendices (https://mcguinlu.shinyapps.io/robvis/) (40).

2.7 Data synthesis

We reported adverse events as binary outcomes. We pooled the proportion of patients who experienced adverse events of interest by first applying a Freeman-Tukey arcsine transformation to stabilize the variance of individual studies (41). For comparative studies, we pooled the odds ratio (OR) of adverse events between inhaled cannabis users and non-users using DerSimonian and Laird random-effects model and calculated pooled risk differences (RD). We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots. We did not assess heterogeneity using the Q or I^2 statistic because large observational studies may provide very precise estimates of association and provide misleading results on these statistical tests of heterogeneity.

We explored heterogeneity of pooled estimates with five pre-defined subgroups, when we had at least two studies in each subgroup: (1) risk of bias, (2) length of follow-up, (3) type of cannabis use, (4) smoked vs. vaporized intake, and (5) greater vs. less THC content. Credibility of subgroup analyses was assessed using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool (42). When there were at least 10 contributing studies, we explored the association between adverse events and loss to follow-up, length of follow-up, and THC content with meta-regression. Meta-analyses

of proportions were conducted using R software (version 3.5.1, R Foundation for Statistical Computing) and meta-analyses of comparative studies were conducted using RevMan 5.4 (43, 44).

2.8 Certainty of evidence

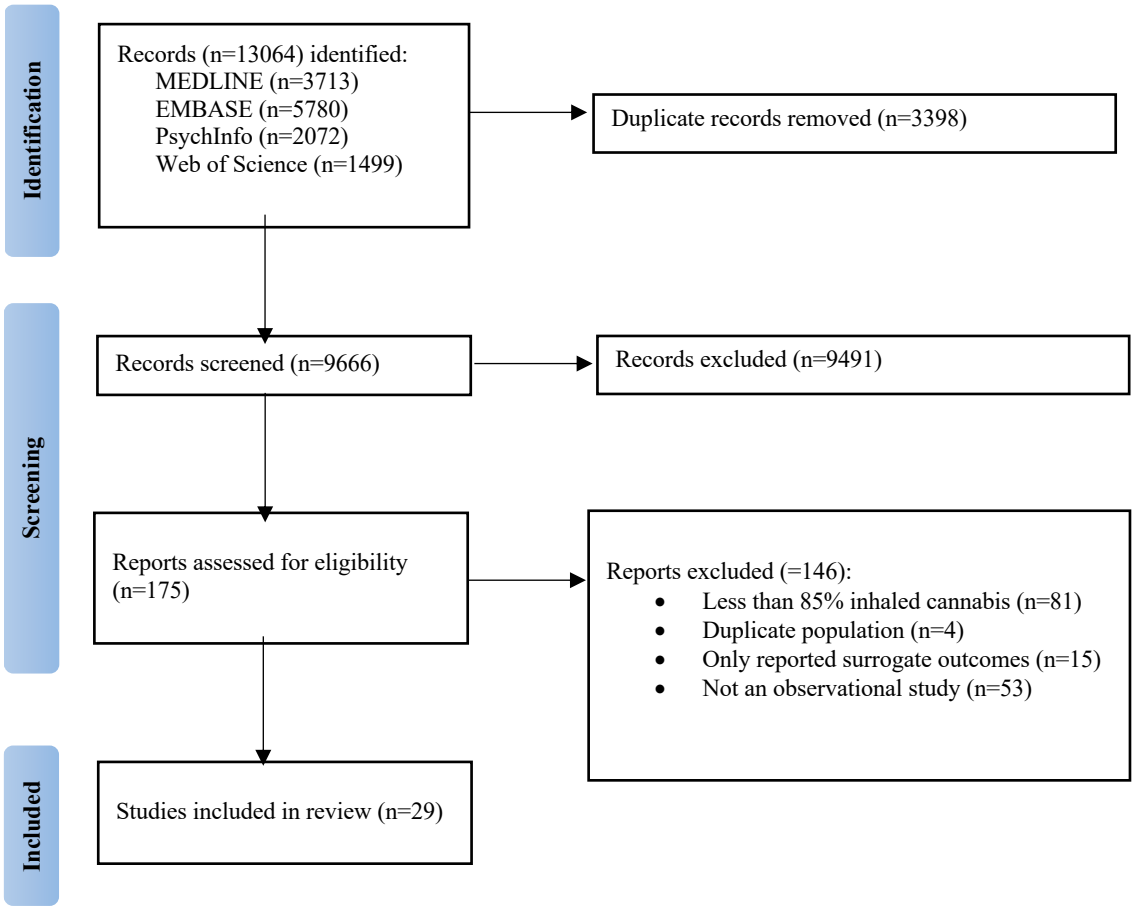
We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to appraise the certainty of evidence (45). With this approach, evidence begins as high certainty but can be rated down due to risk of bias, indirectness, imprecision, inconsistency, or publication bias. We considered measures of association for adverse events to be imprecise when their associated 95%CI included both trivial and important harms. The consideration of a trivial or important prevalence of adverse events depended on the severity of the adverse event; 5% prevalence of serious adverse events and 10% for less serious adverse events. We considered evidence to be indirect if contributing studies included ≥20% recreational cannabis users, who are more likely to prefer products with higher THC concentrations that medical users (46). However, if subgroup analyses found no credible evidence of systematic differences in adverse events based on risk of bias or indirectness, then we did not rate down for these issues. If both inconsistency and imprecision was present, we only rated down the certainty of evidence one level. We followed GRADE guidance for communicating our findings (45).

3.0 RESULTS

3.1 Study selection

Of the 9,666 unique records found in our search, 175 full-texts were retrieved and reviewed; 29 studies were eligible for review (47-75) (Figure 1, Appendix C). We excluded 146 studies for the following reasons: (1) less than 85% of enrolled participants consumed cannabis through inhalation (n=81); (2) overlapping populations (n=4); (3) reported only surrogate outcomes (n=15); and (4) not an observational study (n=53) (Appendix D).

Figure 1. PRISMA flow diagram of study selection



3.2 Description of studies

Eligible studies included 174,562 adults with a median sample size of 311 (interquartile range [IQR] 80 to 1998) (Table 1). Studies were cohort studies (14/29; 48%), cross-sectional designs (12/29; 41%), and case-control studies (3/29; 11%). Twelve studies (41%) were conducted in the United States, with the remaining studies in Israel (n=6), Canada or New Zealand (n=3, respectively), India (n=2), Germany, Sweden, or Tunisia (n=1, respectively). Most of the studies (21/29; 72%) enrolled participants that were only using inhaled cannabis products.

Of the 29 included studies, 15 focused only on recreational cannabis users and ten studies focused solely on medical cannabis users. Four studies enrolled mixed populations of recreational and medical users. Therapeutic use of cannabis was targeted at cancer-related chronic pain (n=1), mixed types of chronic non-cancer pain (n=3), fibromyalgia (n=2), pain associated with human immunodeficiency virus (HIV) (n=1), inflammatory bowel disease (IBD) (n=2), and pain associated with Parkinson's disease (n=2). Studies reported 145 unique adverse events.

Table 1. Study characteristics

Study	Design	Country	Mean age	% female	Recreational or medical	Condition	% inhaled cannabis	Dose	# of participants	Mean duration of use (months)
Aldington, 2008	Case control	New Zealand	NR	49	Recreational		100% smoked	mode: 1 joint/day	403	17
Aviram, 2021	Cohort	Israel	42	36	Medical	Chronic pain	100% smoked and/or vaporized	median: 40g/month	82	6
Balash, 2017	Cross-sectional	Israel	64	15	Medical	Parkinson disease	91.3% smoked	mean: 0.9g/day	47	19
Callaghan, 2013	Cohort	Sweden	42	NR	Recreational		100% smoked	NR	49321	NR

Chopra, 1973	Cross-sectional	India	27	NR	Recreational		100% smoked	40 to 350 mg THC/day	142	36
Feingold, 2020	Cross-sectional	Israel	NR	25	Medical	Chronic pain	100% smoked	mode: 21-40g/month	209	NR
Habib, 2018	Cohort	Israel	38	73	Medical	Fibromyalgia	92% smoked and/or vaporized	mean: 26g/month	26	10
Harris, 2000	Cross-sectional	United States	40	22	Medical	HIV	100% smoked	NR	100	288
Hashibe, 2006	Case control	United States	NR	39	Recreational		100% smoked	1 joint/day	2252	600
Ladha, 2021	Cross-sectional	United States	NR	50	Recreational		88.31% smoked or vaporized	NR	33173	1
Lal, 2011	Cross-sectional	Canada	33	59	Recreational, medical	IBD	99% smoked or vaporized	NR	284	84
Lorenz, 2021	Cohort	United States	41	0	Recreational, medical		100% smoked	NR	558	72
Mehndiratta, 1975	Cohort	India	NR	0	Recreational, medical		100% smoked	mean: 150mg THC/day	75	120
Mittleman, 2001	Cross-sectional	United States	61	32	Recreational		100% smoked	NR	3882	12
Moore, 2005	Cohort	Canada	36	58	Recreational		100% smoked	NR	6728	12
Mukamal, 2008	Cohort	United States	62	31	Recreational		100% smoked	NR	1913	46
Phatak, 2017	Cross-sectional	United States	19	40	Medical	IBD	91.8% smoked and/or vaporized	NR	53	NR
Reis, 2017	Cohort	United States	NR	NR	Recreational		100% smoked	NR	5113	6 to 12
Robson, 2021	Cohort	New Zealand	28	29	Recreational		100% smoked and/or vaporized	mean: 5.44g/day	113	84
Sexton, 2019a	Cross-sectional	United States	35	46	Medical		91.3% smoked	mode: 3-5g/week	891	NR
Sexton, 2019b	Cross-sectional	United States	35	46	Recreational		91.3% smoked	mode: 3-5g/week	1110	NR
Sherrill, 1991	Cohort	United States	NR	NR	Recreational		100% smoked	NR	1802	72
Sidney, 1997	Cohort	United States	33	NR	Recreational		100% smoked	NR	64855	NR
Tashkin, 1987	Cohort	United States	34	33	Recreational		100% smoked	NR	446	NR
Taylor, 2000	Cohort	New Zealand	21	NR	Recreational		100% smoked	NR	279	12
Voirin, 2006	Case control	Tunisia	57	0	Recreational		100% smoked	NR	337	NR
Waissengrin, 2015	Cross-sectional	Israel	60	57	Medical	Chronic cancer pain	91% smoked	NR	69	6

Ware, 2003	Cross-sectional	Canada	47	63	Medical	Chronic pain	90.6% smoked and/or vaporized	NR	209	96
Yassin, 2019	Cohort	Israel	33	90	Medical	Fibromyalgia	100% smoked and/or vaporized	20g/month	31	3
Yenilmez, 2021	Cross-sectional	Germany	72	45	Medical	Parkinson disease	100% smoked and/or vaporized	NR	59	NR

3.3 Risk of bias

Only seven studies were rated at low risk of bias with no concerns across all domains. The remaining 22 studies had at least one domain rated at high risk of bias (Appendix E).

Of the single-arm longitudinal studies (n=4), half were rated as low risk of bias for representativeness of our target population (i.e., chronic cancer or non-cancer pain patients), three studies were rated as low risk of bias for the validity of their assessment of adverse events, and all had <20% of missing data. Of the cross-sectional studies (n=13), eight were rated as high risk of bias for unrepresentativeness, and eight had <20% of missing data. Further, seven cross-sectional studies administered surveys that were clinically sensible, and six used questionnaires that were reliable and valid. Studies were rated as high risk of bias if authors provided no evidence that comprehensiveness, clarity, and face validity of the questionnaire had been assessed. All comparative cohort studies (n=9) had six or more domains rated at low risk of bias. Similarly, all case control studies (n=3) has three or more domains rated at low risk of bias.

3.4 Adverse events

Across 29 studies, the prevalence of adverse events ranged from 3% to 56%, and 29 adverse events were possible to pool. (Appendix F and G) We found no evidence for credible subgroup effects. (Appendix H)

3.4.1 The prevalence of adverse events

Amnesia

Amnesia was reported across four cohorts and 2,171 participants with follow-up ranging from 19 to 26 months (Figure A6.6.1). The pooled prevalence of amnesia was 6% (95% CI: 3 to 11). The certainty of evidence was moderate – rated down for risk of bias.

Anxiety

Anxiety was reported across eight cohorts and 2,423 participants with follow-up ranging from 6 to 288 months (Figure A6.6.2). The pooled prevalence of anxiety was 24% (95% CI: 17 to 33) – low certainty; one study was rated as low risk of bias, the remaining studies were rated as high risk of bias for at least one domain. We further rated down for indirectness because the majority of studies were not focused on chronic pain patients.

Confusion

Confusion was reported across five cohorts and 2,178 participants with a follow-up duration ranging from 6 to 36 months (Figure A6.6.3). The pooled prevalence of confusion was 9% (95% CI: 5 to 13) – moderate certainty; one study was rated as low risk of bias, the remaining studies were rated as high risk of bias for at least one domain.

Dependence

Cannabis dependence was reported across two cohorts and 213 patients with a follow-up duration ranging from 7 to 24 years (Figure A6.6.4). The pooled prevalence of dependence was 26% (95% CI: 20 to 32) – low certainty; both studies demonstrated high risk of bias in more than one domain, and indirectness, as neither study focused on chronic pain patients.

Diarrhea

Diarrhea was reported across two cohorts and 195 patients with a follow-up duration of 6 to 82 months (Figure A6.6.5). The pooled prevalence of diarrhea was 9% (95% CI: 3 to 18) – moderate certainty; both studies demonstrated high risk of bias in more than one domain.

Disorientation

Disorientation was reported across two cohorts and 130 patients with a follow-up duration of 6 to 36 months (Figure A6.6.6). The pooled prevalence of disorientation was 3% (95% CI: 1 to 7) – moderate certainty; both studies demonstrated high risk of bias in more than one domain.

Dizziness

Dizziness was reported across seven cohorts and 2,265 patients with a follow-up duration of 6 to 36 months (Figure A6.6.7). The pooled prevalence of dizziness was 10% (95% CI: 6 to 14) – moderate certainty; while one study was rated as low risk of bias, the remaining studies were rated as high risk of bias for at least one domain.

Dry mouth

Dry mouth was reported across six cohorts and 2,241 patients with a follow-up duration of 6 to 288 months (Figure A6.6.8). The pooled prevalence of dry mouth was 56% (95% CI: 49 to 64) – moderate certainty; while one study was rated as low risk of bias, the remaining studies were rated as high risk of bias for at least one domain.

Euphoria

Euphoria was reported across four cohorts and 338 patients with a follow-up duration of 6 to 288 months (Figure A6.6.9). The pooled prevalence of euphoria was 51% (95% CI: 21 to 81) – very low certainty. While one study was rated as low risk of bias, the remaining studies were rated as high risk of bias for at least one domain. We rated down for inconsistency using visual inspection.

Fatigue

Fatigue was reported across five cohorts and 2,186 patients with a follow-up duration of 6 months (Figure A6.6.10). The pooled prevalence of fatigue was 38% (95% CI: 31 to 45) – moderate certainty; while one study was rated as low risk of bias, the remaining studies were rated as high risk of bias for at least one domain.

Hallucinations

Hallucinations was reported across six cohorts and 2,289 patients with a follow-up duration of 6 to 36 months (Figure A6.6.11). The pooled prevalence of hallucinations was 7% (95%

CI: 4 to 10) – moderate certainty; all studies were rated as high risk of bias for at least one domain.

Impaired coordination

Impaired coordination was reported across four cohorts and 2,131 patients with a follow-up duration of 6 to 36 months (Figure A6.6.12). The pooled prevalence of impaired coordination was 5% (95% CI: 4 to 6) – moderate certainty; all studies were rated as high risk of bias for at least one domain.

Increased appetite

Increased appetite was reported across six cohorts and 2,174 patients with a follow-up duration of 3 to 288 months (Figure A6.6.13-14). The pooled prevalence of increased appetite was 13% (95% CI: 9 to 18) – moderate certainty; all studies except for one was rated as high risk of bias for at least one domain.

Irritability

Irritability was reported across two cohorts and 237 patients with a follow-up duration of 36 to 84 months. (Figure A6.6.15). The pooled prevalence of irritability was 12% (95% CI: 1 to 33) – very low certainty. Both studies were rated as high risk of bias for at least one domain and neither study focused on chronic pain patients. Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Mood changes

Mood changes was reported across two cohorts and 282 patients with a follow-up duration of 6 to 288 months (Figure A6.6.16). The pooled prevalence of mood changes was 8% (95% CI: 4 to 15) – moderate certainty; both studies were rated as high risk of bias for at least one domain.

Nausea

Nausea was reported across two cohorts and 195 patients with a follow-up duration of 6 to 19 months (Figure A6.6.17). The pooled prevalence of nausea was 17% (95% CI: 8 to 27) – moderate certainty; both studies were rated as high risk of bias for at least one domain.

Palpitations

Palpitations were reported across two cohorts and 114 patients with a follow-up duration of 6 to 96 months (Figure A6.6.18). The pooled prevalence of palpitations was 16% (95% CI: 1 to 41) – low certainty. One study was rated as low risk of bias, and both focused on chronic pain patients. Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Paranoia

Paranoia was reported across four cohorts and 2,081 patients with a follow-up duration of 36 to 96 months (Figure A6.6.19). The pooled prevalence of paranoia was 12% (95% CI: 5 to 21) – low certainty; all studies were rated as high risk of bias for at least one domain.

Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Psychosis

Psychosis was reported across four cohorts and 309 patients with a follow-up duration of 19 to 120 months (Figure A6.6.20). The pooled prevalence of paranoia was 5% (95% CI: 0 to 12) – very low certainty; all studies were rated as high risk of bias for at least one domain and no studies focused on chronic pain patients. Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Red eyes

Red eyes were reported across four cohorts and 239 patients with a follow-up duration of 6 to 288 months (Figure A6.6.21). The pooled prevalence of red eyes was 47% (95% CI: 22 to 74) – low certainty; all studies were rated as high risk of bias for at least one domain, and inconsistency, assessed by visual inspection. While the associated measure of precision includes both trivial and important harms, we did not rate down for imprecision as this is explained by the inconsistency.

Thirst

Thirst was reported across two cohorts and 182 patients with a follow-up duration of 6 to 288 months (Figure A6.6.22). The pooled prevalence of thirst was 43.6% (95% CI: 32.9 to

54.7) – moderate certainty; one study was rated as low risk of bias and both focused on chronic pain patients.

Vomiting

Vomiting was reported across two cohorts and 195 patients with a follow-up duration of 6 to 82 months (Figure A6.6.23). The pooled prevalence of vomiting was 6% (95% CI: 0 to 21) – low certainty; one study was rated as low risk of bias and both focused on chronic pain patients. Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

3.4.2. The risk difference of 7 adverse events between inhaled cannabis users and non-users

Asthma

Asthma was reported across two cohorts and 5,819 participants with a follow-up of 12 months (Figure A6.7.1). The odds ratio (OR) and risk difference (RD) associated with asthma between inhaled cannabis users and non-users was 1.6 (95% CI: 1.1 to 2.3) and 4% (95% CI: 1 to 9) – low certainty; neither study focused on chronic pain patients. Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Chronic wheeze

Chronic wheeze was reported across four cohorts and 8,997 participants with a follow-up duration of 12 to 72 months (Figure A6.7.2). The OR and RD associated with chronic wheeze between inhaled cannabis users and non-users was 2.3 (95% CI: 1.9 to 2.9) and 2% (95% CI: 2 to 3) – moderate certainty; no studies focused on chronic pain patients.

Cough

Cough was reported across five cohorts and 9,047 participants with a follow-up duration of 12 to 120 months (Figure A6.7.3). The OR and RD associated with cough between inhaled cannabis users and non-users was 2.9 (95% CI: 1.4 to 5.9) and 14% (95% CI: 3. to 29) – low certainty. No studies focused on chronic pain patients and the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Depression

Depression was reported across two cohorts and 334 participants with a follow-up duration of 84 to 120 months (Figure A6.7.4). The OR and RD associated with depression between inhaled cannabis users and non-users was 2.1 (95% CI: 1 to 4) and 7% (95% CI: 0 to 16) – very low certainty; both studies demonstrated high risk of bias in more than one domain, and neither study focused on chronic pain patients. Further, the associated measure of precision includes both trivial and important harms, and so we rated down one level for imprecision.

Lung cancer

Lung cancer was reported across four cohorts and 52,313 participants with a follow-up duration of 17 to 660 months (Figure A6.7.5). The OR and RD associated with lung cancer between inhaled cannabis users and non-users was 1.3 (95% CI: 0.7 to 2.7) and 2% (95% CI: -2 to 9) – very low certainty due to indirectness, risk of bias, and inconsistency. No studies focused on chronic pain patients and one of the two were rated as high risk of bias. While the associated measure of precision includes both trivial and important harms, we did not rate down for imprecision as this is explained by the inconsistency.

Phelgm

Phelgm was reported across two cohorts and 8,140 participants with a follow-up duration of 12 months (Figure A6.7.6). The OR and RD associated with phelgm between inhaled cannabis users and non-users was 1.7 (95% CI: 1.3 to 2.2) and 3% (95% CI: 1 to 5) – low certainty due to indirectness and risk of bias. No studies focused on chronic pain patients and one of the two were rated as high risk of bias.

Shortness of breath

Shortness of breath (SOB) was reported across three cohorts and 6,060 participants with a follow-up duration of 12 months (Figure A6.7.7), OR and RD associated with SOB between inhaled cannabis users and non-users was 1.8 (95% CI: 1.4 to 2.3) and 7% (95% CI: 4 to 10) – moderate certainty due to indirectness. Neither study focused on chronic pain patients.

3.4.3. Unpoolable data

A cross-sectional study of 209 chronic pain patients conducted by Feingold (2020) reported an association between inhaled cannabis consumption and mild depression (aOR= 2.07, 95% CI= 1.01-4.23) and moderate to severe depression (aOR= 2.58, 95% CI= 0.87 to 7.63) (52) – moderate certainty evidence due to high risk of bias.

Ladha (2021) conducted a cross-sectional study of 33,173 adults in the United States reported an association between cannabis use and a history of myocardial infarction (aOR= 2.07, 95% CI= 1.12-3.82). As frequency of cannabis use increases to greater than 4 times per month, the association increases (aOR= 2.31, 95% CI= 1.18-4.50) – low certainty evidence due to high risk of bias and indirectness (56). Mukamal (2008) conducted a cohort of adults with myocardial infarction and reported an association between death following infarction and less than weekly use (HR= 2.5, 95% CI= 0.9-7.3) and weekly use or more (HR= 4.2, 95% CI=1.2-14.3) (60) – moderate certainty evidence due to indirectness. A study by Reis (2017) found no association between cumulative lifetime cannabis use and total cardiovascular, stroke or transient ischemic attack, coronary heart disease, and cardiovascular disease mortality – moderate certainty evidence due to indirectness (64).

Lorenz (2017) conducted a prospective study of men with HIV found long-term heavy cannabis use was associated with increased cardiovascular events between ages 40 and 60 (aOR= 2.5, 95% CI= 1.3-5.1) – moderate certainty evidence due to indirectness (58). A retrospective study conducted by Sidney (1997) found that among nonsmokers of tobacco cigarettes, ever having used cannabis was associated with increased risk of prostate cancer (RR= 3.1, 95% CI= 1.0-9.5) and cervical cancer (RR = 1.4, 95% CI= 1.0-2.1) – low

certainty evidence due to high risk of bias and indirectness (68). Lastly, Phatak (2017), a study of patients with inflammatory bowel disease, reported 7 of 37 cannabis users experienced adverse events including fear, paranoia, light-headedness, laziness, drowsiness, loss of focus, poor diet, lethargy, and addiction – moderate certainty evidence due to indirectness (63).

4.0 DISCUSSION

4.1 Main findings

Our systematic review found that inhaled cannabis use is likely often associated with dry mouth, thirst, and fatigue (prevalence ranges from 38% to 56%). To a lesser extent, we also found nausea, increased appetite, dizziness, diarrhea, confusion, mood changes, hallucinations, amnesia, impaired coordination, and disorientation likely to be associated with inhaled cannabis consumption (prevalence ranges from 3% to 17%;). Compared to non-users, inhaled medical cannabis users are likely associated with modest increased risk of shortness of breath and chronic wheeze (range of RD: 2 to 4%).

Inhaled cannabis may be commonly associated be red eyes (prevalence: 47%). To a lesser extent, we also found cannabis dependence, anxiety, palpitations, vomiting, and paranoia may be associated with inhaled cannabis consumption (prevalence ranges from 5% to 26%). Compared to non-users, inhaled medical cannabis users may be associated with modest increased risk of asthma, phlegm, and cough (range of RD: 2% to 7%).

The evidence is uncertain about the impact of inhaled cannabis on irritability,

euphoria, psychosis (range of prevalence: 5% to 51%), depression, and lung cancer (range of RD: 2% to 14%).

4.2 Strengths and limitations

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 use of indirect evidence as a result of the lack of literature on inhaled cannabis among chronic pain patients. However, we conducted subgroup analyses for therapeutic vs. recreational cannabis use when possible (3 of the 29 outcomes) and found no credible subgroup effects. Small numbers of trials contributing to some subgroups may have obscured significant subgroup effects. Limitations of the data include a lack of consistent reporting of cannabis product information, which often precluded our prespecified subgroup analyses. The non-comparative design of most studies precludes confident inferences regarding the proportion of adverse events that can be attributed to inhaled cannabis and the magnitude by which inhaled cannabis may increase or decrease the risk of adverse events. Additionally, in comparative studies, the variables controlled for across adjusted odds ratios were inconsistent (presented in Appendix G).

4.3 Conclusion

Our systematic review and meta-analysis found moderate certainty evidence that dry mouth, thirst, and fatigue are probably frequently experienced with inhaled cannabis use.

We also found that nausea, increased appetite, dizziness, diarrhea, confusion, mood changes, hallucinations, amnesia, impaired coordination, disorientation, and shortness of breath are also probable associated with inhaled cannabis use but are less common. Rigorously conducted cohort studies are needed to inform our understanding of harms associated with inhaled medical cannabis for chronic pain.

5.0 REFERENCES

1. Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. Vital Health Stat 13. 2006(159):1-66.

2. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. (1474-547X (Electronic)).

3. Merskey HE. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Pain. 1986.

4. Hadi MA, McHugh GA, Closs SJ. Impact of chronic pain on patients' quality of life: a comparative mixed-methods study. Journal of Patient Experience. 2019;6(2):133-41.

5. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain. 2006;125(1-2):172-9.

6. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. Journal of pain research. 2016;9:457-67.

7. Hogan ME, Taddio A Fau - Katz J, Katz J Fau - Shah V, Shah V Fau - Krahn M, Krahn M. Incremental health care costs for chronic pain in Ontario, Canada: a population-based matched cohort study of adolescents and adults using administrative data. (1872-6623 (Electronic)).

8. Campbell F, Hudspith M, Choiniere M, El-Gabalawy H, Laliberte J, Sangster M, et al. Canadian Pain Task Force Report: October 2020 [Internet]. Government of Canada;

2020 [cited 2022 25 Jan]. Available from: https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/canadian-pain-task-force/report-2020.html#message.

9. Park HJ, Moon DE. Pharmacologic management of chronic pain. Korean J Pain. 2010;23(2):99-108.

10. Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. 2017;37(1):29-42.

11. Häuser W, Schubert T, Scherbaum N, Tölle T. Guideline-recommended vs high-dose long-term opioid therapy for chronic noncancer pain is associated with better health outcomes: data from a representative sample of the German population. Pain. 2018;159(1):85-91.

12. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.

13. Vojtila L, Ashfaq I, Ampofo A, Dawson D, Selby P. Engaging a person with lived experience of mental illness in a collaborative care model feasibility study. Res Involv Engagem. 2021;7(1):5.

14. Men F, Fischer B, Urquia ML, Tarasuk V. Food insecurity, chronic pain, and use of prescription opioids. SSM - Population Health. 2021;14:100768.

15. Gomes T, Khuu W, Martins D, Tadrous M, Mamdani MM, Paterson JM, et al. Contributions of prescribed and non-prescribed opioids to opioid related deaths: population based cohort study in Ontario, Canada. BMJ. 2018;362:k3207.

16. Gomes T, Greaves S, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. Measuring the Burden of Opioid-related Mortality in Ontario, Canada. J Addict Med. 2018;12(5):418-9.

17. Belzak L, Halverson J. The opioid crisis in Canada: a national perspective. Health Promot Chronic Dis Prev Can. 2018;38(6):224-33.

18. Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Cmaj. 2017;189(18):E659-e66.

19. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. Jama. 2018;320(23):2448-60.

20. Pollio A. The Name of Cannabis: A Short Guide for Nonbotanists. Cannabis and cannabinoid research. 2016;1(1):234-8.

21. Radwan MM, Chandra S, Gul S, ElSohly MA. Cannabinoids, Phenolics, Terpenes and Alkaloids of Cannabis. Molecules. 2021;26(9).

22. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Therapeutic advances in psychopharmacology. 2012;2(6):241-54.

23. Lafaye G, Karila L, Blecha L, Benyamina A. Cannabis, cannabinoids, and health. Dialogues in clinical neuroscience. 2017;19(3):309-16.

24. Vandrey R, Herrmann ES, Mitchell JM, Bigelow GE, Flegel R, LoDico C, et al. Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes. 2017;41(2):83-99.

25. Shiplo S, Asbridge M, Leatherdale ST, Hammond D. Medical cannabis use in Canada: vapourization and modes of delivery. Harm Reduction Journal. 2016;13(1):1-10.

26. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.

27. Turner A, Agrawal S. Marijuana [Internet]. Treasure Island (FL): StatPearls Publishing; [cited 2022 31 Jan]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430801/.

28. Wang L, Hong PJ, May C, Rehman Y, Oparin Y, Hong CJ, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 2021;374:n1034.

29. Chang-Douglass S, Mulvihill C, Pilling S. Cannabis-based medicinal products: summary of NICE guidance. Bmj. 2020;369:m1108.

30. Busse JW, Vankrunkelsven P, Zeng L, Heen AF, Merglen A, Campbell F, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ. 2021;374:n2040.

31. Asfaw A, Boden LI. Impact of workplace injury on opioid dependence, abuse, illicit use and overdose: a 36-month retrospective study of insurance claims. Occupational and Environmental Medicine. 2020;77(9):648-53.

32. Turner BJ, Liang Y, Louden CL, Ehler BR, Aung K. Intensity of opioid analgesic prescribing and urgent care services: A national cohort study. Journal of General Internal Medicine. 2013;28:S109.

33. Ault A. New Illinois Law Encourages Marijuana as Opioid Alternative 2018 [Available from: https://www.medscape.com/viewarticle/901763.

34. Canada Go. Data on cannabis for medical purposes 2022 [Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/medical-purpose.html.

35. Chou R. Long-acting opioids for chronic noncancer pain were linked to mortality. Annals of Internal Medicine. 2016;165(6):JC34.

36. Rotermann M. Looking back from 2020, how cannabis use and related behaviours changed in Canada [Internet]. Statistics Canada; 2021 [updated 21 Apr; cited 2022 31 Jan]. Available from: https://www150.statcan.gc.ca/n1/pub/82-003-x/2021004/article/00001-eng.htm.

37. Zeraatkar D, Cooper M, Agarwal A, Vernooij R, Leung G, Loniewski K, et al. Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A systematic review of non-randomized studies2021.

38. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA Surgery. 2021;156(8):787-8.

39. Tool to Assess Risk of Bias: Clarity group at McMaster University; 2020 [Available from: https://www.evidencepartners.com/resources.

40. McGuinness LA, Higgins JP. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Research synthesis methods. 2021;12(1):55-61.

41. Freeman MF, Tukey JW. Transformations related to the angular and the square root. The Annals of Mathematical Statistics. 1950:607-11.

42. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. Canadian Medical Association Journal. 2020;192(32):E901.

43. Schwarzer G. meta: An R package for meta-analysis. R news. 2007;7(3):40-5.

44. Collaboration TC. Review Manager
(RevMan) 5.4 ed2020.

45. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

46. Zeng L, Lytvyn L, Wang X, Kithulegoda N, Agterberg S, Shergill Y, et al. Values and preferences towards medical cannabis among people living with chronic pain: a mixed-methods systematic review. BMJ Open. 2021;11(9):e050831.

47. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, et al. Cannabis use and risk of lung cancer: a case-control study. Eur Respir J. 2008;31(2):280-6.

48. Aviram J, Lewitus GM, Vysotski Y, Yellin B, Berman P, Shapira A, et al. Prolonged Medical Cannabis Treatment is Associated With Quality of Life Improvement and Reduction of Analgesic Medication Consumption in Chronic Pain Patients. Frontiers in Pharmacology. 2021;12:613805.

49. Balash Y, Schleider LB-L, Korczyn AD, Shabtai H, Knaani J, Rosenberg A, et al. Medical cannabis in Parkinson disease: Real-life patients' experience. Clinical Neuropharmacology. 2017;40(6):268-72.

50. Callaghan RC, Allebeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control. 2013;24(10):1811-20.

51. Chopra GS. Studies on Psycho-Clinical Aspects of Long-Term Marihuana Use in 124 Cases. International Journal of the Addictions. 1973;8(6):1015-26.

52. Feingold D, Bril S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. Depression level, not pain severity, is associated with smoked medical marijuana dosage among chronic pain patients. Journal of Psychosomatic Research. 2020;135 (no pagination).

53. Habib G, Artul S. Medical Cannabis for the Treatment of Fibromyalgia. J Clin Rheumatol. 2018;24(5):255-8.

54. Harris D, Jones RT, Shank R, Nath R, Fernandez E, Goldstein K, et al. Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. Journal of Addictive Diseases. 2000;19(3):89-103.

55. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1829-34.

56. Ladha KS, Mistry N, Wijeysundera DN, Clarke H, Verma S, Hare GMT, et al. Recent cannabis use and myocardial infarction in young adults: a cross-sectional study. Canadian Medical Association Journal. 2021;193(35):E1377.

57. Lal S, Prasad N, Ryan M, Tangri S, Silverberg MS, Gordon A, et al. Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011;23(10):891-6.

58. Lorenz DR, Dutta A, Mukerji SS, Holman A, Uno H, Gabuzda D. Marijuana Use Impacts Midlife Cardiovascular Events in HIV-Infected Men. Clinical Infectious Diseases. 2017;65(4):626-35.

59. Mehndiratta SS, Wig NN. Psychosocial effects of longterm cannabis use in India. A study of fifty heavy users and controls. Drug Alcohol Depend. 1975;1(1):71-81.

60. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J. 2008;155(3):465-70.

61. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001;103(23):2805-9.

62. Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. J Gen Intern Med. 2005;20(1):33-7.

63. Phatak UP, Rojas-Velasquez D, Porto A, Pashankar DS. Prevalence and Patterns of Marijuana Use in Young Adults with Inflammatory Bowel Disease. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(2):261-4.

64. Reis JP, Auer R, Bancks MP, Goff DC, Jr., Lewis CE, Pletcher MJ, et al. Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Public Health. 2017;107(4):601-6.

65. Robson H, Braund R, Glass M, Ashton J, Tatley M. Synthetic cannabis: adverse events reported to the New Zealand Pharmacovigilance Centre. Clinical Toxicology. 2021;59(6):472-9.

66. Sexton M, Cuttler C, Mischley LK. A survey of cannabis acute effects and withdrawal symptoms: Differential responses across user types and age. The Journal of Alternative and Complementary Medicine. 2019;25(3):326-35.

67. Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD. Respiratory Effects of Non-Tobacco Cigarettes: A Longitudinal Study in General Population. International Journal of Epidemiology. 1991;20(1):132-7.

68. Sidney S, Quesenberry CP, Jr., Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). Cancer Causes Control. 1997;8(5):722-8.

69. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis. 1987;135(1):209-16.

70. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR. The respiratory effects of cannabis dependence in young adults. Addiction. 2000;95(11):1669-77.

71. Voirin N, Berthiller J, Benhaïm-Luzon V, Boniol M, Straif K, Ayoub WB, et al. Risk of lung cancer and past use of cannabis in Tunisia. J Thorac Oncol. 2006;1(6):577-9.

72. Waissengrin B, Urban D, Leshem Y, Garty M, Wolf I. Patterns of use of medical cannabis among Israeli cancer patients: A single institution experience. Journal of Pain and Symptom Management. 2015;49(2):223-30.

73. Yenilmez F, Fründt O, Hidding U, Buhmann C. Cannabis in Parkinson's Disease: The Patients' View. J Parkinsons Dis. 2021;11(1):309-21.

74. 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.

75. 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. Clin Exp Rheumatol. 2019;37 Suppl 116(1):13-20.

6.0 APPENDICES

6.1 APPENDIX A: Summary of search and strategy inhaled cannabis

MEDLINE	3713
EMBASE	5780
PsycInfo	2072
Web of Science	1499
Subtotal	13064
-dupes	-3398
Total	9666

Oct 6, 2021

MEDLINE

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 Cannabis/ (10632)

2 exp cannabinoids/ or cannabidiol/ or cannabinol/ or dronabinol/ (15659)

3 Endocannabinoids/ (6232)

4 exp Receptors, Cannabinoid/ (10060)

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*).mp. (62738)

6 or/1-5 (62738)

Annotation: strategy from 2020 cannabis review

7 "marijuana use"/ or marijuana smoking/ (6511)

8 Marijuana Abuse/ (6669)

9 (epidiolex or gwp 42003p or gwp42003p or nabidiolex or dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetrabinex or tetranabinex or cesamet or nabilone or deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726" or nabiximol? or "gw 1000" or gw1000 or "sab 378" or sab378 or sativex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (13208)

10 or/7-9 (23943)

Annotation: cannabis terms from Wolfe 2020

11 or/1-10 (64107)

12 (chronic adj4 pain*).mp. (79026)

13 Chronic Pain/ (17840)

14 exp Osteoarthritis/ (68825)

15 osteoarthrit*.mp. (99416)

16 osteo-arthrit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (492)

17 exp Arthritis, Rheumatoid/ (118053)

18 exp Neuralgia/ (22220)

19 Diabetic Neuropathies/ (15296)

20 (neuropath* adj5 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (27667)

21 neuralg*.mp. (30021)

22 zoster.mp. (22314)

23 Irritable Bowel Syndrome/ (8115)

24 IBS.mp. (10026)

25 Migraine Disorders/ (26916)

26 migraine*.mp. (42506)

27 Fibromyalgia/ (9033)

28 Fibromyalg*.mp. (12718)

29 complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/ (5735)

30 Pain, Intractable/ (6284)

31 Phantom Limb/ (1956)

32 Hyperalgesia/ (12679)

33 exp back pain/ or failed back surgery syndrome/ or low back pain/ (41585)

34 radiculopath*.mp. (10132)

35 Musculoskeletal Pain/ (3838)

36 Headache/ (29132)

37 exp Headache Disorders/ (36668)

38 headache*.mp. (101629)

39 exp Temporomandibular Joint Disorders/ (17933)

40 whiplash.mp. (4093)

41 Whiplash Injuries/ (3328)

42 exp Cumulative Trauma Disorders/ (14376)

43 exp Peripheral Nervous System Diseases/dt, rh, th [Drug Therapy, Rehabilitation, Therapy] (32298)

44 Pain Measurement/de [Drug Effects] (6860)

45 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).ti,ab. (179796)

46 ((cancer* or noncancer* or non-cancer* or back or discogen* or chronic* or recurrent or persist* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or non-malign* or shoulder* or knee* or hip or hips) adj3 pain).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (249553)

47 or/12-46 (814272)

Annotation: chronic pain and painful conditions

48 Muscle Spasticity/ or Muscle Hypertonia/ (10583)

49 (spasticity or spasm or spastic or hypertonia).mp. (55477)

50 or/12-49 (865549)

51 11 and 50 (3713)

EMBASE

Database: Embase <1974 to 2021 October 05>

Search Strategy:

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1 cannabis/ (37929)

2 medical cannabis/ (2962)

3 exp cannabinoid receptor/ (15900)

4 cannabis addiction/ (10586)

5 "cannabis use"/ or cannabis smoking/ (14178)

6 exp cannabinoid/ (74315)

7 (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* or epidiolex or gwp 42003p or gwp42003p or nabidiolex or dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetrabinex or tetranabinex or cesamet or nabilone or deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726" or nabiximol? or "gw 1000" or gw1000 or "sab 378" or sab378 or sativex).mp. (100464)

8 or/1-7 (101871)

Annotation: cannabis concept

9 chronic pain/ or exp osteoarthritis/ or exp rheumatoid arthritis/ or exp neuralgia/ or diabetic neuropathy/ or irritable colon/ or exp migraine/ or fibromyalgia/ or intractable pain/ or agnosia/ or exp radiculopathy/ or musculoskeletal pain/ or exp arthralgia/ or headache/ or temporomandibular joint disorder/ or whiplash injury/ or exp cumulative trauma disorder/ (920142)

Annotation: Emtree terms for painfil chronic conditions

10 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyni* or ischialgi* or crps or rachialgi*or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. (1543159)

11 ((irrita* or inflam*) adj4 (bowel or colon)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (136576)

12 ((cancer* or noncancer* or non-cancer* or back or discogen* or chronic* or recurrent or persist* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or non-malign* or shoulder* or knee* or hip or hips) adj3 pain).mp. (427899)

13 muscle hypertonia/ or spasticity/ (29212)

14 (spasticity or spasm or spastic or hypertonia).mp. (100116)

15 or/9-14 (1953636)

16 8 and 15 (10552)

17 clinical study/ (156268)

18 case control study/ (178523)

19 family study/ (25342)

20 longitudinal study/ (161757)

21 retrospective study/ (1140318)

22 prospective study/ (716633)

23 randomized controlled trials/ (212167)

24 22 not 23 (708374)

25 cohort analysis/ (758479)

26 (Cohort adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (368145)

27 (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 heading word, floating subheading word, candidate term word] (238463)

28 (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 heading word, floating subheading word, candidate term word] (70874)

29 (observational adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (305623)

30 (epidemiologic$ adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (118093)

31 (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 heading word, floating subheading word, candidate term word] (484877)

32 or/17-21,24-31 (3388258)

33 16 and 32 (1127)

34 (ae or si or to or co).fs. (3352838)

35 (safe or safety).ti,ab. (1329174)

36 side effect$.ti,ab. (393591)

37 ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab. (905523)

38 exp adverse drug reaction/ (563672)

39 exp drug toxicity/ (140059)

40 exp intoxication/ (387129)

41 exp drug safety/ (465580)

42 exp drug monitoring/ (56345)

43 exp drug hypersensitivity/ (59356)

44 exp postmarketing surveillance/ (37209)

45 exp drug surveillance program/ (26345)

46 exp phase iv clinical trial/ (4491)

47 (toxicity or complication$ or noxious or tolerability).ti,ab. (2086506)

48 or/34-47 (6541768)

49 16 and 48 (5693)

50 33 or 49 (6194)

51 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (29577189)

52 human/ or normal human/ or human cell/ (22886956)

53 51 and 52 (22819913)

54 51 not 53 (6757276)

55 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1123962)

56 Animal experiment/ not (human experiment/ or human/) (2358398)

57 54 or 55 or 56 (6821826)

58 50 not 57 (5780)

PsycInfo

Database: APA PsycInfo <1806 to September Week 4 2021>

Search Strategy:

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1 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ or marijuana usage/ or "cannabis use disorder"/ (17167)

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* or epidiolex or gwp 42003p or gwp42003p or nabidiolex or dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetrabinex or tetranabinex or cesamet or nabilone or deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726" or nabiximol? or "gw 1000" or gw1000 or "sab 378" or sab378 or sativex).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (29445)

3 1 or 2 (29445)

4 pain*.mp. or exp PAIN/ (138120)

5 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyni* or ischialgi* or crps or rachialgi*or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (72989)

6 muscle spasms/ (481)

7 (spasticity or spasm or spastic or hypertonia).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh] (5388)

8 or/4-7 (181756)

9 3 and 8 (2072)

Web of Science 1499

5

(ALL=(backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis* or spasticity or spasm or spastic or hypertonia)) AND #3

Edit

Add to Search

1,499

4

ALL=(backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi* or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis* or spasticity or spasm or spastic or hypertonia)

Edit

Add to Search

312,700

3

(#1) OR #2

Edit

Add to Search

91,641

2

ALL=(epidiolex or gwp 42003p or gwp42003p or nabidiolex or dronabinol or thc or tetrahydrocannabinol* or ea 1477 or ea1477 or marinol or qcd 84924 or syndros or tetrabinex or tetranabinex or cesamet or nabilone or deltanyne or "abbott 40566" or namisol or dronabinolum or "QCD 84924" or "CCRIS 4726" or nabiximol? or "gw 1000" or gw1000 or "sab 378" or sab378 or sativex)

Edit

Add to Search

20,973

1

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* (All Fields)

Edit

Add to Search

82,232

6.2 APPENDIX B: Detailed risk of bias assessment

Table A6.2.1. Tool to Assess Risk of Bias in Single-Arm Longitudinal Studies

Item	Examples of low risk of bias	Examples of high risk of bias
1. Is the source population (sampling frame) representative of the target population?	Selection of target population from a representative population roster such as a patient registry; Consecutive enrollment of all patients attending a group of clinics.	Studies where the source population cannot be defined (or enumerated), i.e., any volunteer studies using self-recruitment; Subgroups of the target population, i.e., those with more severe disease.
2. Is the assessment of adverse events accurate?	Repeated interview or other ascertainment asking about current adverse events; Use of patient diaries in which adverse events are recorded on a regular basis (e.g., daily)	Uncertain how information was obtained; Only collected AEs if patients happened to mention them, unprompted; Studies with non-standardised clinical interviews (including large administrative databases in which systematic collection of adverse events is unlikely)
3. Is there little missing data?	High response proportion (rate) at follow-up with little missing data. For instance, the proportion of responders was more than 75% at follow-up(s).	More than 50% missing data at follow-up(s).

Table A6.2.2. Tool to Assess Risk of Bias in Cross-sectional Studies

Item	Examples of low risk of bias	Examples of high risk of bias
1. Is the source population representative of the population of interest?	Selection of target population (either the entire population or a random sample) from a representative population roster such as a national association database	Studies where the source population cannot be defined (or enumerated), i.e. any volunteer studies using self-recruitment
2. Is the response rate adequate?	High enough response rate to ensure that any differences would be unlikely to affect results (>75%)	Response rate of <50% and no testing done to explore the differences between respondents and non-respondents, or testing indicates that important difference exist
3. Is there little missing data?	Less than 10% missing data within questionnaires	More than 15% missing data within questionnaires
4. Is the survey clinically sensible?	Formal assessment of the comprehensiveness, clarity, and face validity of the questionnaire in a similar population	No evidence that comprehensiveness, clarity, and face validity of the questionnaire have been assessed
5. Is there any evidence for the reliability and validity of the survey instrument?	Reliability and construct validity (i.e. convergent and discriminant validity) of the survey have been well-established in a similar population	No evidence that reliability and construct validity have been established for the instrument

Table A6.2.3. Tool to Assess Risk of Bias in Cohort Studies

Item	Examples of low risk of bias	Examples of high risk of bias
1. Was selection of exposed and non-exposed cohorts drawn from the same population?	Exposed and unexposed drawn for same administrative data base of patients presenting at same points of care over the same time frame	Exposed and unexposed presenting to different points of care over a different time frame
2. Can we be confident in the assessment of exposure?	- Secure record (e.g. surgical records, pharmacy records) - Repeated interview or other ascertainment asking about current use/exposure	Uncertain how exposure information obtained
3. Can we be confident that the outcome of interest was not present at start of study?		
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	Comprehensive matching or adjustment for all plausible prognostic variables	- Matching or adjustment for a minority of plausible prognostic variables - No matching or adjustment of plausible prognostic variables - Statements of no differences between groups - Statements that differences were not statistically significant are not sufficient for establishing comparability
5. Can we be confident in the assessment of the presence or absence of prognostic factors?	- Interview of all participants - Self-completed survey from all participants - Review of charts with reproducibility demonstrated - From data base with documentation of accuracy of abstraction of prognostic data	Prognostic information from data base with no available documentation of quality of abstraction of prognostic variables
6. Can we be confident in the assessment of outcome?	- Independent blind assessment - Record linkage - For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture	Uncertain
7. Was the follow up of cohorts adequate?	- No missing outcome data - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias) - Missing outcome data balanced in numbers across intervention	- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce important bias in intervention effect estimate

	groups, with similar reasons for missing data across groups - For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not large enough to have an important impact on the observed effect size - Missing data have been imputed using appropriated methods	- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is large enough to induce clinically relevant bias in the observed effect size
8. Were co-interventions similar between groups?	Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed	Few or no relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed

Table A6.2.4. Tool to Assess Risk of Bias in Case-control Studies

Item	Examples of low risk of bias	Examples of high risk of bias
1. Can we be confident in the assessment of exposure?	Evidence of exposure comes from previously created records and data abstractors are unaware of the study hypothesis	- Evidence of exposure is acquired by patient interview, data collectors are not blinded to patient status or the study hypothesis - Memory of exposure is likely to be influenced by the occurrence of the outcome
2. Can we be confident that cases had developed the outcome of interest and controls had not?	- Cases and controls undergo valid and reliable diagnostic procedures - Surveillance for the outcome of interest clearly unrelated to the exposure of interest	- No description - Cases are stablished with diagnostic procedures associated with high rates of false positive results - Controls are established with diagnostic procedures associated with high rates of false negative results - Surveillance for the outcome of interest clearly relate to the exposure of interest
3. Were the cases (those who were exposed and developed the outcome of interest) properly selected?	- All eligible cases are enrolled in a defined catchment area over a defined period of time during which diagnostic procedures would be unlikely to have changed - Random sample of those cases	Not reported
4. Were the controls (those who were exposed and did not develop the outcome of interest) properly selected?	Controls clearly selected from the same underlying population as the cases and equally at risk of exposure to the putative causal factor	Difference in sampling frame of cases and controls clearly related to the exposure of interest
5. Were cases and controls matched according to important prognostic variables or was statistical adjustment carried out for those variables?	Comprehensive matching or adjustment for all plausible prognostic variables	- Matching or adjustment for a minority of plausible prognostic variables - No matching or adjustment of plausible prognostic variables - Statements of no differences between groups - Statements that differences were not statistically significant are not sufficient for establishing comparability

6.3 APPENDIX C: List of included studies

1. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, et al. Cannabis use and risk of lung cancer: a case-control study. Eur Respir J. 2008;31(2):280-6.
2. Aviram J, Lewitus GM, Vysotski Y, Yellin B, Berman P, Shapira A, et al. Prolonged Medical Cannabis Treatment is Associated With Quality of Life Improvement and Reduction of Analgesic Medication Consumption in Chronic Pain Patients. Frontiers in Pharmacology. 2021;12:613805.
3. Balash Y, Bar-Lev Schleider L, Korczyn AD, Shabtai H, Knaani J, Rosenberg A, et al. Medical Cannabis in Parkinson Disease: Real-Life Patients' Experience. Clin Neuropharmacol. 2017;40(6):268-72.
4. Callaghan RC, Allebeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control. 2013;24(10):1811-20.
5. Chopra GS. Studies on Psycho-Clinical Aspects of Long-Term Marihuana Use in 124 Cases. International Journal of the Addictions. 1973;8(6):1015-26.
6. Feingold D, Bril S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. Depression level, not pain severity, is associated with smoked medical marijuana dosage among chronic pain patients. Journal of Psychosomatic Research. 2020;135 (no pagination).
7. Habib G, Artul S. Medical Cannabis for the Treatment of Fibromyalgia. J Clin Rheumatol. 2018;24(5):255-8.

8. Harris D, Jones RT, Shank R, Nath R, Fernandez E, Goldstein K, et al. Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. Journal of Addictive Diseases. 2000;19(3):89-103.
9. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1829-34.
10. Ladha KS, Mistry N, Wijeysundera DN, Clarke H, Verma S, Hare GMT, et al. Recent cannabis use and myocardial infarction in young adults: a cross-sectional study. Canadian Medical Association Journal. 2021;193(35):E1377.
11. Lal S, Prasad N, Ryan M, Tangri S, Silverberg MS, Gordon A, et al. Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011;23(10):891-6.
12. Lorenz DR, Dutta A, Mukerji SS, Holman A, Uno H, Gabuzda D. Marijuana Use Impacts Midlife Cardiovascular Events in HIV-Infected Men. Clinical Infectious Diseases. 2017;65(4):626-35.
13. Mehndiratta SS, Wig NN. Psychosocial effects of longterm cannabis use in India. A study of fifty heavy users and controls. Drug Alcohol Depend. 1975;1(1):71-81.
14. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation. 2001;103(23):2805-9.
15. Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. J Gen Intern Med. 2005;20(1):33-7.

16. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J. 2008;155(3):465-70.
17. Phatak UP, Rojas-Velasquez D, Porto A, Pashankar DS. Prevalence and Patterns of Marijuana Use in Young Adults with Inflammatory Bowel Disease. Journal of Pediatric Gastroenterology and Nutrition. 2017;64(2):261-4.
18. Reis JP, Auer R, Bancks MP, Goff DC, Jr., Lewis CE, Pletcher MJ, et al. Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Public Health. 2017;107(4):601-6.
19. Robson H, Braund R, Glass M, Ashton J, Tatley M. Synthetic cannabis: adverse events reported to the New Zealand Pharmacovigilance Centre. Clinical Toxicology. 2021;59(6):472-9.
20. Sexton M, Cuttler C, Mischley LK. A survey of cannabis acute effects and withdrawal symptoms: Differential responses across user types and age. The Journal of Alternative and Complementary Medicine. 2019;25(3):326-35.
21. Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD. Respiratory Effects of Non-Tobacco Cigarettes: A Longitudinal Study in General Population. International Journal of Epidemiology. 1991;20(1):132-7.
22. Sidney S, Quesenberry CP, Jr., Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). Cancer Causes Control. 1997;8(5):722-8.

23. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis. 1987;135(1):209-16.
24. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR. The respiratory effects of cannabis dependence in young adults. Addiction. 2000;95(11):1669-77.
25. Voirin N, Berthiller J, Benhaïm-Luzon V, Boniol M, Straif K, Ayoub WB, et al. Risk of lung cancer and past use of cannabis in Tunisia. J Thorac Oncol. 2006;1(6):577-9.
26. Waissengrin B, Urban D, Leshem Y, Garty M, Wolf I. Patterns of use of medical cannabis among Israeli cancer patients: A single institution experience. Journal of Pain and Symptom Management. 2015;49(2):223-30.
27. 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.
28. 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. Clin Exp Rheumatol. 2019;37 Suppl 116(1):13-20.
29. Yenilmez F, Frundt O, Hidding U, Buhmann C. Cannabis in Parkinson's Disease: The Patients' View. Journal of Parkinsons Disease Print. 2021;11(1):309-21.

6.4 APPENDIX D: List of excluded studies by exclusion reason

6.4.1 Inadequate intervention (i.e. <85% inhaled cannabis consumption)

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. 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.
3. 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.
4. Bellnier T, Brown G, Ortega T, Insull R. A preliminary evaluation of the effcacy, safety, and costs associated with the treatment of chronic pain with medical marijuana in the elderly. Consultant Pharmacist. 2017;32(10):597.
5. 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.
6. Bigand T, Anderson CL, Roberts ML, Shaw MR, Wilson M. Benefits and adverse effects of cannabis use among adults with persistent pain. Nursing Outlook. 2019;67(3):223-31.
7. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. Journal of Pain. 2016;17(6):739-44.

8. Cahill SP, Lunn SE, Diaz P, Page JE. Evaluation of Patient Reported Safety and Efficacy of Cannabis From a Survey of Medical Cannabis Patients in Canada. Frontiers in Public Health. 2021;9:626853.
9. Castelli L, Prosperini L, Pozzilli C. Balance worsening associated with nabiximols in multiple sclerosis. Multiple Sclerosis. 2019;25(1):113-7.
10. Choi NG, DiNitto DM, Marti C, Choi BY. Association between nonmedical marijuana and pain reliever uses among individuals aged 50+. Journal of Psychoactive Drugs. 2017;49(4):267-78.
11. Choi NG, DiNitto DM, Marti CN. Nonmedical versus medical marijuana use among three age groups of adults: Associations with mental and physical health status. American Journal on Addictions. 2017;26(7):697-706.
12. Chong MS, Wolff K, Wise K, Tanton C, Winstock A, Silber E. Cannabis use in patients with multiple sclerosis. Multiple Sclerosis Journal. 2006;12(5):646-51.
13. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. Neurology. 2004;62(11):2098-100.
14. Coates MD, Dalessio S, Walter V, Stuart A, Bernasko N, Tinsley A, et al. Symptoms and Extraintestinal Manifestations in Active Cannabis Users with Inflammatory Bowel Disease. Cannabis and Cannabinoid Research.
15. Cobb S, Bazargan M, Smith J, Del Pino HE, Dorrah K, Assari S. Marijuana Use among African American Older Adults in Economically Challenged Areas of South Los Angeles. Brain Sciences. 2019;9(7):16.

16. Cofield SS, Salter A, Tyry T, Crowe C, Cutter GR, Fox RJ, et al. Perspectives on marijuana use and effectiveness A survey of NARCOMS participants. Neurology-Clinical Practice. 2017;7(4):333-43.
17. Cogan PS. On healthcare by popular appeal: critical assessment of benefit and risk in cannabidiol based dietary supplements. Expert Review of Clinical Pharmacology. 2019;12(6):501-11.
18. Cooke A, Chavez L, Freisthler B. The relationships between chronic pain and changes in health with cannabis consumption patterns. International Journal of Drug Policy. 2020;76:102657.
19. Costales B, van Boemmel-Wegmann S, Winterstein A, Segal R. Clinical Conditions and Prescription Drug Utilization among Early Medical Marijuana Registrants in Florida. Journal of Psychoactive Drugs. 2021;53(3):185-94.
20. Crescioli G, Lombardi N, Bettiol A, Menniti-Ippolito F, Da Cas R, Parrilli M, et al. Adverse events following cannabis for medical use in Tuscany: An analysis of the Italian Phytovigilance database. British Journal of Clinical Pharmacology. 2020;86(1):106-20.
21. Croker Iii JA, Bobitt JL, Arora K, Kaskie B. Assessing health-related outcomes of medical cannabis use among older persons: Findings from colorado and illinois. Clinical Gerontologist: The Journal of Aging and Mental Health. 2020:No Pagination Specified.

22. Crowell TL. Therapeutic value of medical marijuana in New Jersey patients: A community partnership research endeavor. Journal of Allied Health. 2017;46(4):232-40.
23. Donovan KA, Chang YD, Oberoi-Jassal R, Rajasekhara S, Smith J, Haas M, et al. Relationship of Cannabis Use to Patient-Reported Symptoms in Cancer Patients Seeking Supportive/Palliative Care. Journal of Palliative Medicine. 2019;22(10):1191-5.
24. Elliott DA, Nabavizadeh N, Romer J, Chen Y, Holland J. Medical marijuana use in patients with history of head and neck squamous cell carcinoma treated with radiation therapy. International Journal of Radiation Oncology Biology Physics. 2014;1):S710.
25. Elliott DA, Nabavizadeh N, Romer JL, Chen Y, Holland JM. Medical marijuana use in head and neck squamous cell carcinoma patients treated with radiotherapy. Supportive Care in Cancer. 2016;24(8):3517-24.
26. Erridge S, Salazar O, Kawka M, Holvey C, Coomber R, Usmani A, et al. An initial analysis of the UK Medical Cannabis Registry: Outcomes analysis of first 129 patients. Neuropsychopharmacology Reports. 2021;41(3):362-70.
27. 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.
28. Fedorova EV, Wong CF, Ataiants J, Iverson E, Conn BM, Lankenau SE. Cannabidiol (CBD) and other drug use among young adults who use cannabis in

Los Angeles. Drug and Alcohol Dependence Vol 221 2021, ArtID 108648. 2021;221.

29. 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.
30. 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 [Electronic Resource]. 2011;6(4):e18440.
31. Fiz J, Duran M, Capella D, et al. Cannabis use in patients with Fibromyalgia: Effect on symptoms relief and health-related quality of life. PLoS ONE 2011;6 (4) (no pagination)(e18440) doi: http://dx.doi.org/10.1371/journal.pone.0018440
32. Frohe T, Beseler CL, Mendoza AM, Cottler LB, Leeman RF. Perceived health, medical, and psychiatric conditions in individual and dual-use of marijuana and nonprescription opioids. Journal of Consulting & Clinical Psychology. 2019;87(10):859-71.
33. Gallagher R, Best JA, Fyles G, Hawley P, Yeomans W. Attitudes and beliefs about the use of Cannabis for symptom control in a palliative population. Journal of Cannabis Therapeutics. 2003;3(2):41-50.
34. Gibson LP, Hitchcock LN, Bryan AD, Bidwell LC. Experience of migraine, its severity, and perceived efficacy of treatments among cannabis users. Complementary Therapies in Medicine. 2021;56:102619.

35. Guarnaccia JB, Khan A, Ayettey R, Treu JA, Comerford B, Njike VY. Patterns of Medical Cannabis Use among Patients Diagnosed with Multiple Sclerosis. Multiple Sclerosis and Related Disorders. 2021;50:102830.
36. 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.
37. Hawley LA, Ketchum JM, Morey C, Collins K, Charlifue S. Cannabis Use in Individuals With Spinal Cord Injury or Moderate to Severe Traumatic Brain Injury in Colorado. Archives of Physical Medicine & Rehabilitation. 2018;99(8):1584-90.
38. Leehey MA, Liu Y, Hart F, Epstein C, Cook M, Sillau S, et al. Safety and Tolerability of Cannabidiol in Parkinson Disease: An Open Label, Dose-Escalation Study. Cannabis and Cannabinoid Research. 2020;5(4):326-36.
39. Lintzeris N, Driels J, Elias N, Arnold JC, McGregor IS, Allsop DJ. Medicinal cannabis in Australia, 2016: the Cannabis as Medicine Survey (CAMS-16). Medical Journal of Australia. 2018;209(5):211-6.
40. Lum HD, Arora K, Croker JA, Qualls SH, Schuchman M, Bobitt J, et al. Patterns of Marijuana Use and Health Impact: A Survey Among Older Coloradans. Gerontology & Geriatric Medicine. 2019;5:2333721419843707.

41. Luque JS, Okere AN, Reyes-Ortiz CA, Williams PM. Mixed methods study of the potential therapeutic benefits from medical cannabis for patients in Florida. Complementary Therapies in Medicine. 2021;57:102669.
42. 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.
43. Macari DM, Gbadamosi B, Jaiyesimi I, Gaikazian S. Medical Cannabis in Cancer Patients: A Survey of a Community Hematology Oncology Population. American Journal of Clinical Oncology. 2020;43(9):636-9.
44. Ofir R, Bar-Sela G, Weyl Ben-Arush M, Postovsky S. Medical marijuana use for pediatric oncology patients: single institution experience. Pediatric Hematology and Oncology. 2019;36(5):255-66.
45. Rosenthal MS, Pipitone RN. Demographics, Perceptions, and Use of Medical Marijuana among Patients in Florida. Medical Cannabis and Cannabinoids. 2021;4(1):13-20.
46. Russo EB, Cuttler C, Cooper ZD, Stueber A, Whiteley VL, Sexton M. Survey of Patients Employing Cannabigerol-Predominant Cannabis Preparations: Perceived Medical Effects, Adverse Events, and Withdrawal Symptoms. Cannabis and Cannabinoid Research. 2021;27:27.
47. Sagy I, Bar-Lev Schleider L, Abu-Shakra M, Novack V. Safety and Efficacy of Medical Cannabis in Fibromyalgia. Journal of Clinical Medicine. 2019;8(6):05.

48. Stephen MJ, Chowdhury J, Tejada LA, Zanni R, Hadjiliadis D. Use of medical marijuana in cystic fibrosis patients. BMC Complementary Medicine and Therapies. 2020;20(1) (no pagination).
49. Stillman M, Capron M, Mallow M, Ransom T, Gustafson K, Bell A, et al. Utilization of medicinal cannabis for pain by individuals with spinal cord injury. Spinal Cord Series and Cases. 2019;5(1) (no pagination).
50. Tripp D, Nickel JC, Laura K, Ginting JV, Mark W, Santor D. Cannabis (marijuana) use in men with chronic prostatitis / chronic pelvic pain syndrome. Journal of Urology. 2012;1):e439-e40.
51. Tripp DA, Nickel JC, Katz L, Krsmanovic A, Ware MA, Santor D. A survey of cannabis (marijuana) use and self-reported benefit in men with chronic prostatitis/chronic pelvic pain syndrome. Canadian Urological Association Journal. 2014;8(11-12):E901-5.
52. Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. Best Practice & Research Clinical Anaesthesiology. 2020;34(3):463-77.
53. Ware MA, Wang T, Shapiro S, Collet JP. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015;16(12):1233-42.
54. Zeiger JS, Silvers WS, Fleegler EM, Zeiger RS. Age related differences in cannabis use and subjective effects in a large population-based survey of adult athletes. Journal of Cannabis Research. 2019;1(1) (no pagination).

55. Desai R, Patel U, Sharma S, Amin P, Bhuva R, Patel MS, et al. Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. Cureus. 2017;9(11):e1816.
56. Hemachandra D, McKetin R, Cherbuin N, Anstey KJ. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. Aust N Z J Public Health. 2016;40(3):226-30.
57. Li X, Vigil JM, Stith SS, Brockelman F, Keeling K, Hall B. The effectiveness of self-directed medical cannabis treatment for pain. Complementary Therapies in Medicine. 2019;46:123-30.
58. Moon AS, Smith W, Mullen S, Ponce BA, McGwin G, Shah A, et al. Marijuana use and mortality following orthopedic surgical procedures. Subst Abus. 2019;40(3):378-82.
59. Rumalla K, Reddy AY, Mittal MK. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. J Neurol Sci. 2016;364:191-6.
60. Stith SS, Li X, Diviant JP, Brockelman FC, Keeling KS, Hall B, et al. The effectiveness of inhaled Cannabis flower for the treatment of agitation/irritability, anxiety, and common stress. Journal of Cannabis Research. 2020;2(1) (no pagination).
61. 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.

62. Carrubba AR, Ebbert JO, Spaulding AC, DeStephano D, DeStephano CC. Use of Cannabis for Self-Management of Chronic Pelvic Pain. Journal of Women's Health. 2021;30(9):1344-51.
63. Gruber SA, Sagar KA, Dahlgren MK, Racine MT, Smith RT, Lukas SE. Splendor in the grass? A pilot study assessing the impact of medical marijuana on executive function. Frontiers in Pharmacology. 2016;7(OCT) (no pagination).
64. Hoffman KA, Ponce Terashima J, McCarty D, Muench J. Toward a Patient Registry for Cannabis Use: An Exploratory Study of Patient Use in an Outpatient Health-Care Clinic in Oregon. World Medical and Health Policy. 2017;9(3):307-17.
65. Lahat A, Lang A, Ben-Horin S. Impact of Cannabis Treatment on the Quality of Life, Weight and Clinical Disease Activity in Inflammatory Bowel Disease Patients: A Pilot Prospective Study. Digestion. 2011;85(1):1-8.
66. Liguori A, Gatto C, Robinson J. Effects of marijuana on equilibrium, psychomotor performance, and simulated driving. Behavioural Pharmacology. 1998;9(7):599-609.
67. Manning K, Rogers AH, Bakhshaie J, Hogan JB, Buckner JD, Ditre JW, et al. The association between perceived distress tolerance and cannabis use problems, cannabis withdrawal symptoms, and self-efficacy for quitting cannabis: The

explanatory role of pain-related affective distress. Addictive Behaviors. 2018;85:1-7.

68. Martin EL, Strickland JC, Schlienz NJ, Munson J, Jackson H, Bonn-Miller MO, et al. Antidepressant and Anxiolytic Effects of Medicinal Cannabis Use in an Observational Trial. Frontiers in psychiatry Frontiers Research Foundation. 2021;12:729800.
69. Martinez L, La Maida N, Papaseit E, Perez-Mana C, Poyatos L, Pellegrini M, et al. Acute Pharmacological Effects and Oral Fluid Concentrations of the Synthetic Cannabinoids JWH-122 and JWH-210 in Humans After Self-Administration: An Observational Study. Frontiers in Pharmacology. 2021;12 (no pagination).
70. Morean ME, Lederman IR. Prevalence and correlates of medical cannabis patients' use of cannabis for recreational purposes. Addictive Behaviors. 2019;93:233-9.
71. 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 and Hepatology. 2019;31(11):1376-81.
72. Napchan U, Buse DC, Loder EW. The use of marijuana or synthetic cannabinoids for the treatment of headache. Headache. 2011;51(3):502-5.
73. Neufeld T, Pfuhlmann K, Stock-Schroer B, Kairey L, Bauer N, Hauser W, et al. Cannabis use of patients with inflammatory bowel disease in Germany: a cross-sectional survey. Zeitschrift fur Gastroenterologie. 2021;22:22.

74. Ngan TYT, Litt M, Eguzo K, Thiel JA. Patient Outcomes Following Initiation of Medical Cannabis in Women with Chronic Pelvic Pain. Journal of Minimally Invasive Gynecology. 2019;26(7 Supplement):S89-S90.
75. Nielsen SW, Ruhlmann CH, Eckhoff L, Bronnum D, Herrstedt J, Dalton SO. Cannabis use among Danish patients with cancer: a cross-sectional survey of sociodemographic traits, quality of life, and patient experiences. Supportive Care in Cancer. 2021.
76. Piper BJ, Beals ML, Abess AT, Nichols SD, Martin MW, Cobb CM, et al. Chronic pain patients' perspectives of medical cannabis. Pain. 2017;158(7):1373-9.
77. Reynolds IR, Fixen DR, Parnes BL, Lum HD, Shanbhag P, Church S, et al. Characteristics and Patterns of Marijuana Use in Community-Dwelling Older Adults. Journal of the American Geriatrics Society. 2018;66(11):2167-71.
78. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2016;36(5):505-10.
79. Vaillancourt R, Moreno M, Pouliot A, Sell E. Cannabis Use for Therapeutic Purposes by Children and Youth at a Tertiary Teaching Hospital in Canada: A Retrospective Chart Review. Canadian Journal of Hospital Pharmacy. 2020;73(2):105-15.

80. Vin-Raviv N, Akinyemiju T, Meng Q, Sakhuja S, Hayward R. Marijuana use and inpatient outcomes among hospitalized patients: analysis of the nationwide inpatient sample database. Cancer Med. 2017;6(1):320-9.
81. Wiegand DM, Methner MM, Grimes GR, Couch JR, Wang L, Zhang L, et al. Occupational Exposure to Secondhand Cannabis Smoke Among Law Enforcement Officers Providing Security at Outdoor Concert Events. Annals of Work Exposures And Health. 2020;64(7):705-14.

6.4.2 Overlapping population

1. Aviram J, Lewitus GM, Vysotski Y, Berman P, Shapira A, Procaccia S, et al. Sex differences in medical cannabis-related adverse effects. Pain. 2021;26:26.
2. Bloom J W, Kaltenborn W T, Paoletti P, Camilli A, Lebowitz M D. Respiratory effects of non-tobacco cigarettes. Br Med J (Clin Res Ed) 1987; 295 :1516 doi:10.1136/bmj.295.6612.1516
3. Falkstedt D, Wolff V, Allebeck P, Hemmingsson T, Danielsson AK. Cannabis, Tobacco, Alcohol Use, and the Risk of Early Stroke: A Population-Based Cohort Study of 45 000 Swedish Men. Stroke. 2017;48(2):265-70.
4. Jouanjus E, Lapeyre-Mestre M, Micallef J. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc. 2014;3(2):e000638.

6.4.3 Only reported surrogate outcomes

1. Awad OGA. Impact of habitual marijuana and tobacco smoke on severity of chronic rhinosinusitis. American Journal of Otolaryngology. 2019;40(4):583-8.
2. Bouso JC, Jimenez-Garrido D, Ona G, Woznica D, os Santos RG, Hallak JEC, et al. Quality of Life, Mental Health, Personality and Patterns of Use in Self-Medicated Cannabis Users with Chronic Diseases: A 12-Month Longitudinal Study. Phytotherapy Research. 2020;34(7):1670-7.
3. Buckner JD, Zvolensky MJ, Mayorga NA, Abarno CN, Hopper K, Garey L. Cannabis use among dual electronic and combustible cigarette smokers: Relations with pain and hazardous drinking. Substance Use & Misuse. 2020:No Pagination Specified.
4. Fales JL, Ladd BO, Magnan RE. Pain Relief as a Motivation for Cannabis Use Among Young Adult Users With and Without Chronic Pain. Journal of Pain. 2019;20(8):908-16.
5. Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. Neurology. 2005;64(5):917-9.
6. Hansen TM, Sabourin BC, Oketola B, Bernstein CN, Singh H, Targownik LE. Cannabis Use in Persons With Inflammatory Bowel Disease and Vulnerability to Substance Misuse. Inflammatory Bowel Diseases. 2020;26(9):1401-6.
7. Honarmand K, Tierney MC, O'Connor P, Feinstein A. Effects of cannabis on cognitive function in patients with multiple sclerosis. Neurology. 2011;76(13):1153-60.

8. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer. 2012;118(21):5374-83.
9. Leroux E, Taifas I, Valade D, Donnet A, Chagnon M, Ducros A. Use of cannabis among 139 cluster headache sufferers. Cephalalgia. 2013;33(3):208-13.
10. Lev-Ran S, Imtiaz S, Taylor BJ, Shield KD, Rehm J, Le Foll B. Gender differences in health-related quality of life among cannabis users: Results from the national epidemiologic survey on alcohol and related conditions. Drug and Alcohol Dependence. 2012;123(1-3):190-200.
11. Lewis NM, Friedrichs M, Wagstaff SS, Nakashima AK, Dunn AC. Characteristics of Adults Who Use Both Marijuana and E-Cigarette, or Vaping, Products : A Cross-Sectional Study, Utah, 2018. Public Health Reports. 2021:333549211018679.
12. Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: an open-label observational study. Clinical Neuropharmacology. 2014;37(2):41-4.
13. Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. BMJ supportive & palliative care. 2020;10(4):415-20.
14. Wagner J, Salter A, Fox R, Cutter G, Nichol K, Steinerman J, et al. Cannabis Use for Symptom Management Among People with Multiple Sclerosis (PwMS): A

2020 NARCOMS Survey. Archives of Physical Medicine and Rehabilitation. 2021;102(10):e23-e4.

15. Zhang N, Woldeamanuel YW. Medication overuse headache in patients with chronic migraine using cannabis: A case-referent study. Headache. 2021;61(8):1234-44.

6.4.5 Ineligible study design (i.e. randomized studies, systematic reviews)

1. Aladag-Ciftdemir N, Yucel I, Duran R, Vatansever-Ozbek U, Acunas B. A new emerging problem in pediatric emergency units: Synthetic cannabinoids. Turkish Journal of Pediatrics. 2016;58(5):492-7.
2. Arias S, Leon M, Jaimes D, Bustos RH. Clinical Evidence of Magistral Preparations Based on Medicinal Cannabis. Pharmaceuticals. 2021;14(2):21.
3. Bagshaw SM, Hagen NA. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. Journal of Palliative Care. 2002;18(2):111-22.
4. Cameron EC, Hemingway SL. Cannabinoids for fibromyalgia pain: a critical review of recent studies (2015-2019). Journal of Cannabis Research. 2020;2(1):19.
5. Carvalho ACA, Souza GA, Marqui SV, Guiguer EL, Araujo AC, Rubira CJ, et al. Cannabis and Canabidinoids on the Inflammatory Bowel Diseases: Going Beyond Misuse. International Journal of Molecular Sciences. 2020;21(8):22.
6. Chetty K, Lavoie A, Deghani P. A Literature Review of Cannabis and Myocardial Infarction-What Clinicians May Not Be Aware Of. CJC Open. 2021;3(1):12-21.
7. Choi S, Huang BC, Gamaldo CE. Therapeutic Uses of Cannabis on Sleep Disorders and Related Conditions. Journal of Clinical Neurophysiology. 2020;37(1):39-49.
8. Ciccone CD. Medical Marijuana: Just the Beginning of a Long, Strange Trip? Physical Therapy. 2017;97(2):239-48.

9. Cinti S. Medical marijuana in HIV-positive patients: what do we know? Journal of the International Association of Physicians in AIDS Care: JIAPAC. 2009;8(6):342-6.
10. Clark AJ, Lynch ME, Ware M, Beaulieu P, McGilveray IJ, Gourlay D. Guidelines for the use of cannabinoid compounds in chronic pain. Pain Research & Management. 2005;10 Suppl A:44A-6A.
11. Clark WC. Hyperalgesia and response bias following chronic marihuana smoking. 1999. p. 541-52.
12. Corless IB, Lindgren T, Holzemer W, Robinson L, Moezzi S, Kirksey K, et al. Marijuana effectiveness as an HIV self-care strategy. Clinical Nursing Research. 2009;18(2):172-93.
13. Echeverria-Villalobos M, Todeschini AB, Stoicea N, Fiorda-Diaz J, Weaver T, Bergese SD. Perioperative care of cannabis users: A comprehensive review of pharmacological and anesthetic considerations. Journal of Clinical Anesthesia. 2019;57:41-9.
14. Finn K. Is Marijuana Use for Pain Driving Negative Societal Effects? Missouri Medicine. 2017;114(5):326-7.
15. First L, Douglas W, Habibi B, Singh JR, Sein MT. Cannabis Use and Low-Back Pain: A Systematic Review. Cannabis and Cannabinoid Research. 2020;5(4):283-9.
16. Franz CA, Frishman WH. Marijuana Use and Cardiovascular Disease. Cardiology in Review. 2016;24(4):158-62.

17. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. New England Journal of Medicine. 2015;373(11):1048-58.
18. Furrer D, Kroger E, Marcotte M, Jauvin N, Belanger R, Ware M, et al. Cannabis against chronic musculoskeletal pain: a scoping review on users and their perceptions. Journal of Cannabis Research. 2021;3(1):41.
19. Gamaoun R, Kasvis P, Patronidis F, Arboleda MF, Vigano A. Potential impact of medical cannabis treatment on pain control among cancer patients in Quebec-Canada: A pilot study. Supportive Care in Cancer. 2019;27(1 Supplement):S54-S5.
20. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. Journal of the International Neuropsychological Society. 2003;9(5):679-89.
21. Guillouard M, Authier N, Pereira B, Soubrier M, Mathieu S. Cannabis Use Assessment and Its Impact on Pain in Rheumatic Diseases: A Systematic Review and Meta-analysis. Arthritis and Rheumatology. 2020;72(SUPPL 10):2414-5.
22. Gusho CA, Court T. Cannabidiol: A Brief Review of Its Therapeutic and Pharmacologic Efficacy in the Management of Joint Disease. Cureus. 2020;12(3):e7375.
23. Gustavsen S, Sondergaard HB, Andresen SR, Sorensen PS, Sellebjerg FT, Oturai AB. Medical and recreational cannabis use in patients with multiple sclerosis in Denmark. Multiple Sclerosis Journal. 2018;24(2 Supplement):954-5.

24. Hauser W, Fitzcharles M-A, Radbruch L, Petzke F. Cannabinoids in pain management and palliative medicine: an overview of systematic reviews and prospective observational studies. Deutsches Arzteblatt International. 2017;114(38):627-34.
25. Karst M, Wippermann S, Ahrens J. Role of cannabinoids in the treatment of pain and (painful) spasticity. Drugs. 2010;70(18):2409-38.
26. Köstenberger M, Nahler G, Jones TM, Neuwersch S, Likar R. The Role of Cannabis, Cannabidiol and Other Cannabinoids in Chronic Pain. The Perspective of Physicians. J Neuroimmune Pharmacol. 2021.
27. Kramer JL. Medical marijuana for cancer. CA Cancer J Clin. 2015;65(2):109-22.
28. Kumar RN, Chambers WA, Pertwee RG. Pharmacological actions and therapeutic uses of cannabis and cannabinoids. Anaesthesia. 2001;56(11):1059-68.
29. Kurlyandchik I, Tiralongo E, Schloss J. Safety and Efficacy of Medicinal Cannabis in the Treatment of Fibromyalgia: A Systematic Review. Journal of Alternative & Complementary Medicine. 2021;27(3):198-213.
30. Lau N, Sales P, Averill S, Murphy F, Sato S-O, Murphy S. A safer alternative: Cannabis substitution as harm reduction. Drug and Alcohol Review. 2015;34(6):654-9.
31. Lavie-Ajayi M, Shvartzman P. Restored Self: A Phenomenological Study of Pain Relief by Cannabis. Pain Medicine. 2019;20(11):2086-93.
32. Lucas P. Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. Journal of Psychoactive Drugs. 2012;44(2):125-33.

33. Maayah ZH, Dyck JRB. The pharmacological effects of inhaled cannabis on pain in patients with multiple sclerosis: risks versus rewards. Inflammation Research. 2020;69(11):1073-6.
34. Maharajan MK, Yong YJ, Yip HY, Woon SS, Yeap KM, Yap KY, et al. Medical cannabis for chronic pain: can it make a difference in pain management? Journal of Anesthesia. 2020;34(1):95-103.
35. Maher DP, Carr DB, Hill K, McGeeney B, Weed V, Jackson WC, et al. Cannabis for the Treatment of Chronic Pain in the Era of an Opioid Epidemic: A Symposium-Based Review of Sociomedical Science. Pain Medicine. 2019;20(11):2311-23.
36. Modesto-Lowe V, Bojka R, Alvarado C. Cannabis for peripheral neuropathy: The good, the bad, and the unknown. Cleveland Clinic Journal of Medicine. 2018;85(12):943-9.
37. Mohiuddin M, Blyth FM, Degenhardt L, Di Forti M, Eccleston C, Haroutounian S, et al. General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews. Pain. 2021;162(Suppl 1):S80-S96.
38. Murff HJ. Review: Weak evidence of benefits of cannabis for chronic neuropathic pain; moderate to weak evidence of adverse effects. Annals of Internal Medicine. 2017;167(12):JC62.
39. Nugent SM, Kansagara D. The Effects of Cannabis Among Adults With Chronic Pain. Annals of Internal Medicine. 2018;168(7):525.

40. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, et al. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. Annals of Internal Medicine. 2017;167(5):319-31.
41. O'Brien M, McDougall JJ. Cannabis and joints: scientific evidence for the alleviation of osteoarthritis pain by cannabinoids. Current Opinion in Pharmacology. 2018;40:104-9.
42. Perisetti A, Rimu AH, Khan SA, Bansal P, Goyal H. Role of cannabis in inflammatory bowel diseases. Annals of Gastroenterology. 2020;33(2):134-44.
43. Porr CJ, Rios P, Bajaj HS, Egan AM, Huot C, Batten R, et al. The effects of recreational cannabis use on glycemic outcomes and self-management behaviours in people with type 1 and type 2 diabetes: A rapid review. Systematic Reviews. 2020;9(1) (no pagination).
44. Ribeiro L, Ind PW. Marijuana and the lung: Hysteria or cause for concern? Breathe. 2018;14(3):196-205.
45. Romero-Sandoval EA, Kolano AL, Alvarado-Vázquez PA. Cannabis and Cannabinoids for Chronic Pain. Curr Rheumatol Rep. 2017;19(11):67.
46. Taneja S, Hoogenes J, Slaven M, Kapoor A. Use of cannabis in urological cancer patients: A review to evaluate risk for cancer development, therapeutic use, and symptom management. Canadian Urological Association Journal. 2021;22:22.
47. Thanabalasingam SJ, Ranjith B, Jackson R, Wijeratne DT. Cannabis and its derivatives for the use of motor symptoms in Parkinson's disease: a systematic

review and meta-analysis. Therapeutic Advances in Neurological Disorders. 2021;14(no pagination).

48. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.
49. Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. Annals of Internal Medicine. 1997;126(10):791-8.
50. Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. Supportive Care in Cancer. 2003;11(3):137-43.
51. Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. Supportive Care in Cancer. 2003;11(3):137-43.
52. Ware MA, Jensen D, Barrette A, Vernec A, Derman W. Cannabis and the Health and Performance of the Elite Athlete. Clinical Journal of Sport Medicine. 2018;28(5):480-4.
53. Ware MA, Tawfik VL. Safety issues concerning the medical use of cannabis and cannabinoids. Pain Research and Management. 2005;10(SUPPL. A):31A-7A.

6.5 APPENDIX E: Risk of bias diagrams

Figure A6.5.1. Risk of Bias in Single-Arm Longitudinal Studies exploring Adverse Events

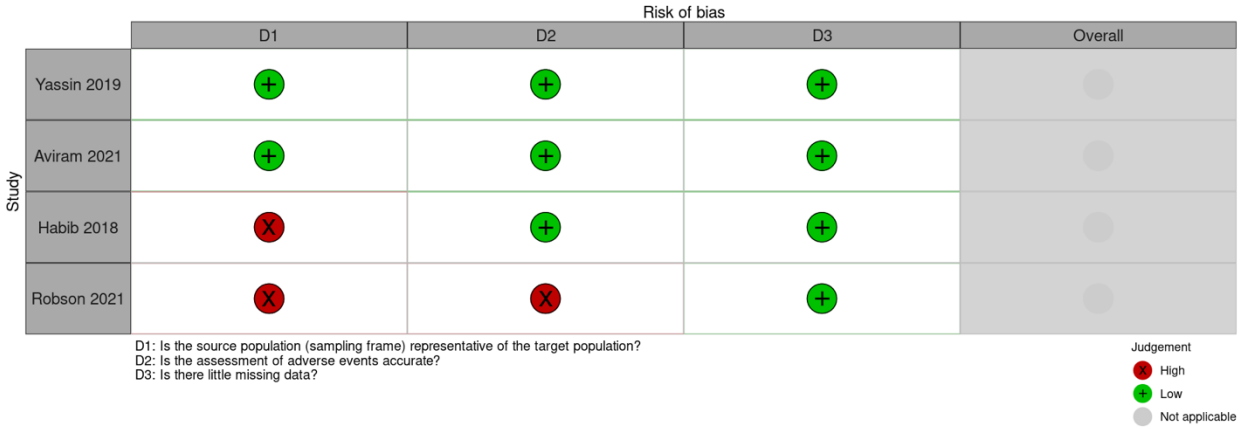


Figure A6.5.2. Risk of Bias in Cross-sectional Studies

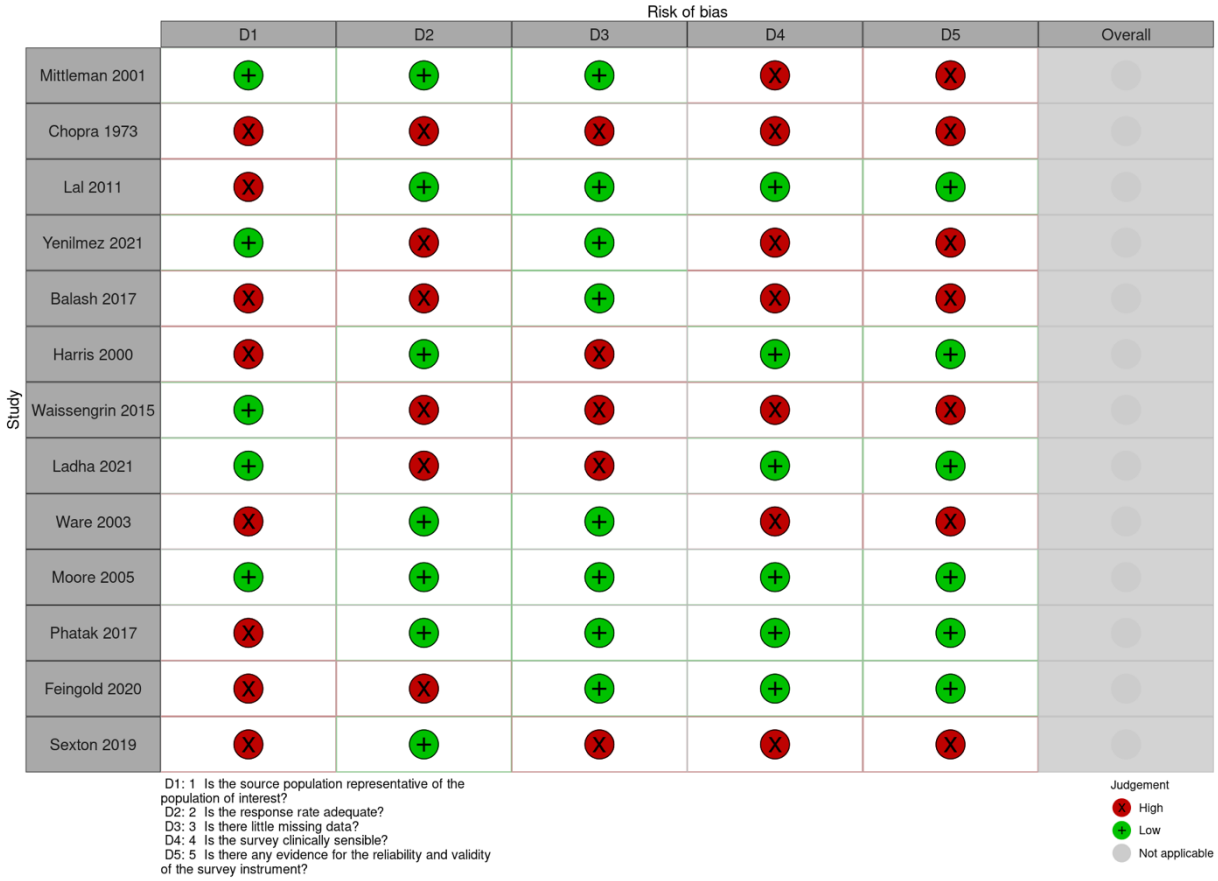


Figure A6.5.3. Risk of Bias in Cohort Studies

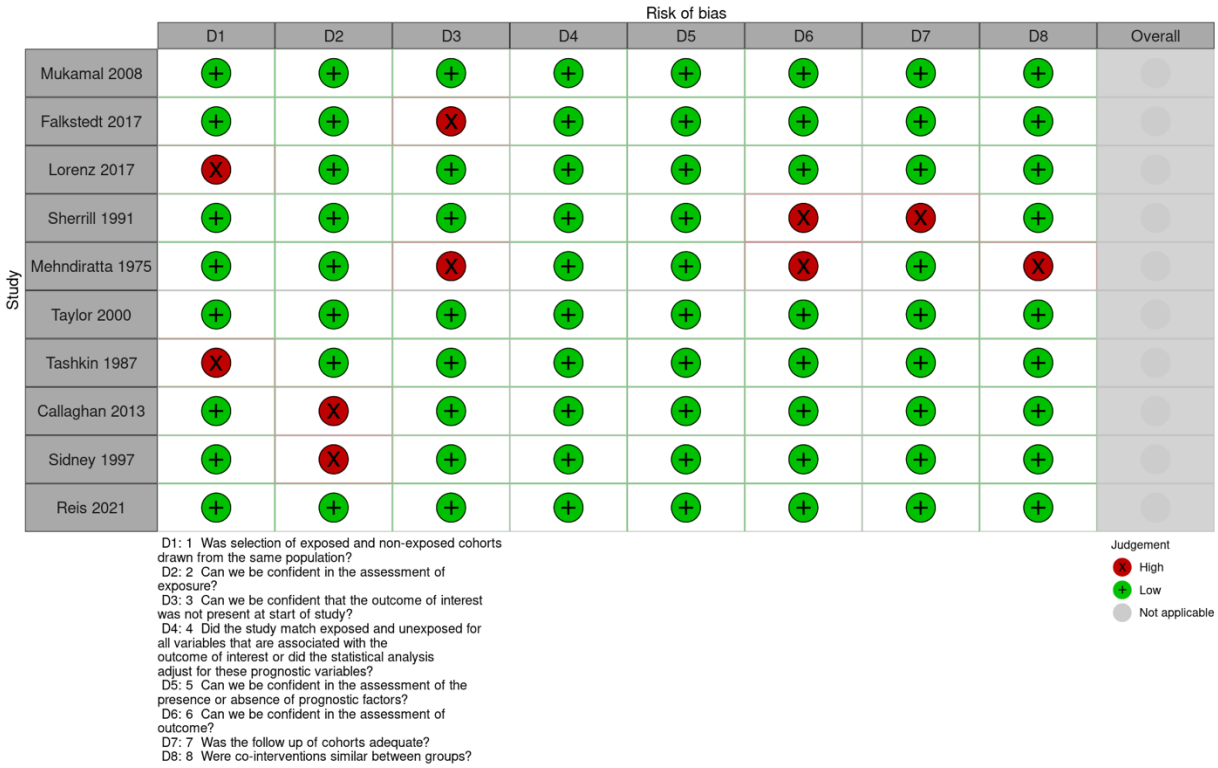
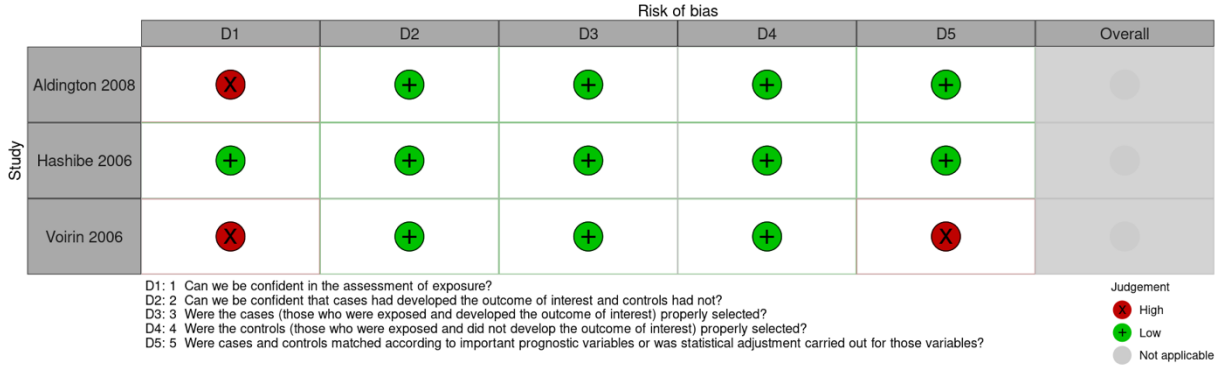


Figure A6.5.4. Risk of Bias in Case-control Studies



6.6 APPENDIX F: Meta-analysis of proportions forest plots

Table A6.6.1. Prevalence of adverse events from non-comparative studies

Outcome	# of studies	# of participants	Duration of follow-up (months)	Prevalence % (95% CI)	Certainty	Reasons for downgrading
Amnesia	4	2171	19 to 36	6.4% (2.9 to 11.1)	Moderate	risk of bias
Anxiety	8	2,423	6 to 288	24.4% (16.7 to 33.0)	Low	risk of bias, indirectness
Confusion	5	2178	6 to 36	8.5% (4.7 to 13.2)	Moderate	risk of bias
Dependence	2	213	84 to 288	25.8% (20.1 to 31.9).	Low	risk of bias, indirectness
Diarrhea	2	195	6 to 82	9.3% (3.4 to 17.5)	Moderate	risk of bias
Disorientation	2	130	6 to 36	3.0% (0.5 to 6.9)	Moderate	risk of bias
Dizziness	7	2265	6 to 96	9.5% (5.6 to 14.2)	Moderate	risk of bias
Dry mouth	6	2241	6 to 288	56.3% (48.7 to 63.9)	Moderate	risk of bias,
Euphoria	4	338	6 to 288	51% (20.6 to 81.0)	Very low	risk of bias, indirectness, inconsistency
Fatigue	5	2186	6	37.6% (30.8 to 44.7).	Moderate	risk of bias
Hallucinations	6	2289	6 to 36	6.7% (3.8 to 10.2)	Moderate	risk of bias
Impaired coordination	4	2131	6 to 36	5.0% (4.1 to 6.0)	Moderate	risk of bias
Increased appetite	6	2174	3 to 288	13.2% (9.0 to 18.0)	Moderate	risk of bias
Irritability	2	237	36 to 84	11.9% (0.6 to 32.6)	Very low	risk of bias, indirectness, imprecision
Mood changes	3	282	6 to 288	8.4% (3.7 to 14.7)	Moderate	risk of bias
Nausea	2	195	6 to 19	16.6% (8.3 to 27)	Moderate	risk of bias
Palpitations	2	114	6 to 96	15.7% (1 to 40.6)	Low	risk of bias, imprecision
Paranoia	4	2081	36 to 96	11.5% (4.6 to 20.8)	Low	risk of bias, imprecision

Psychosis	4	309	19 to 120	4.6% (0.3 to 12.1)	Very low	risk of bias, indirectness, imprecision
Red eyes	4	239	6 to 288	47.3% (21.8 to 73.5)	Low	risk of bias, inconsistency
Thirst	2	182	6 to 288	43.6% (32.9 to 54.7)	Moderate	risk of bias
Vomiting	2	195	6 to 82	5.7% (0 to 20.8)	Low	risk of bias, imprecision

Figure A6.6.1. Amnesia

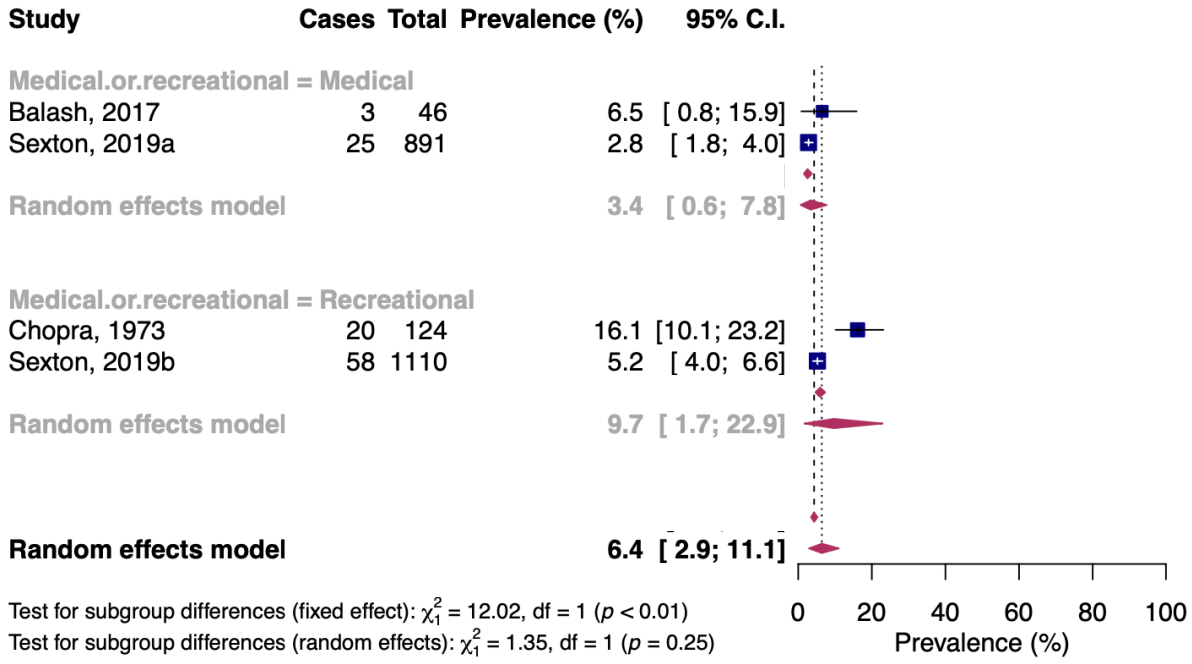


Figure A6.6.2. Anxiety

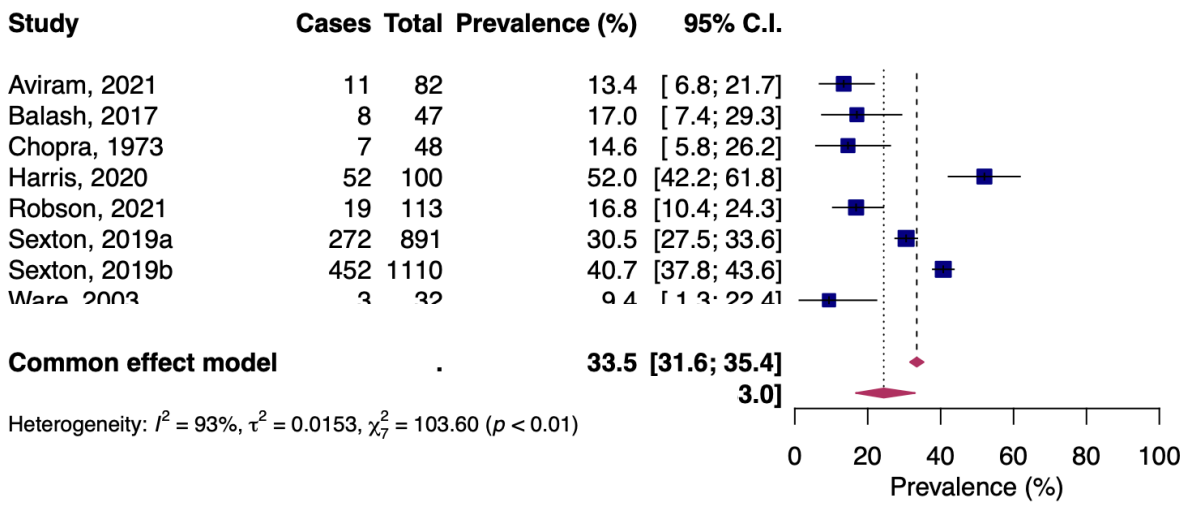


Figure A6.6.3. Confusion

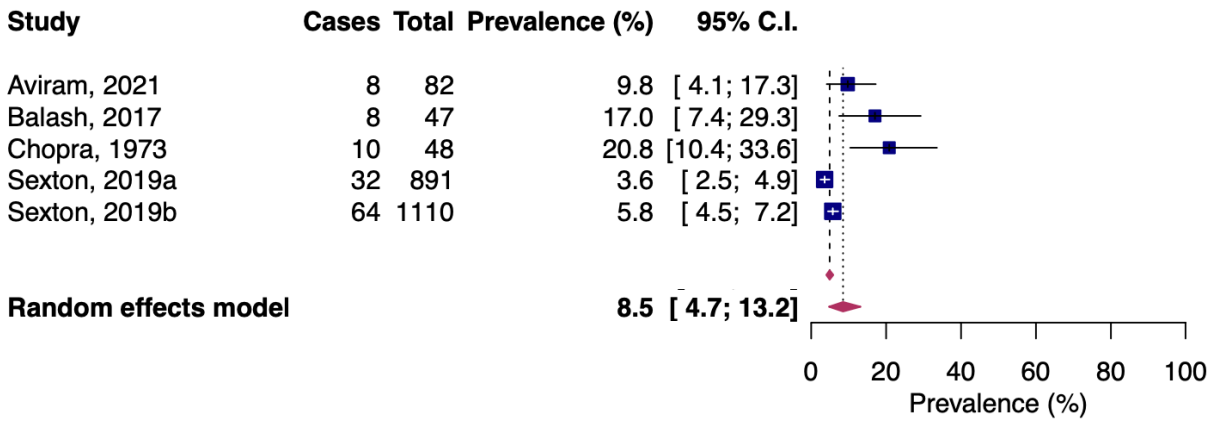


Figure A6.6.4. Dependence

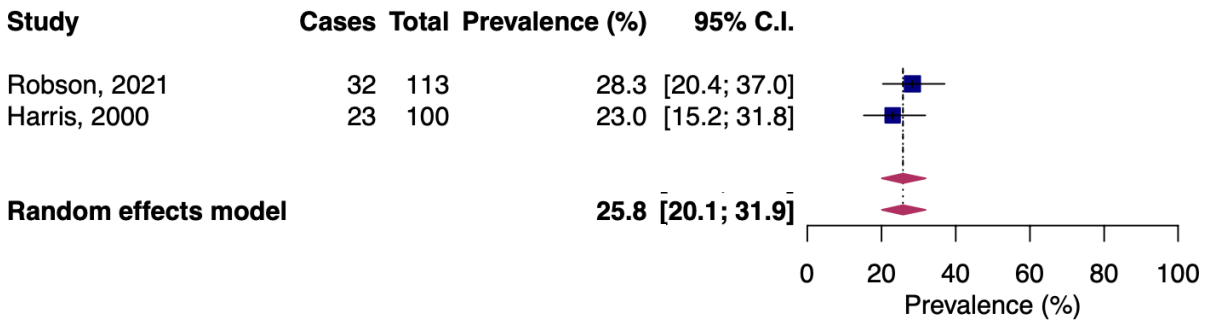


Figure A6.6.5. Diarrhea

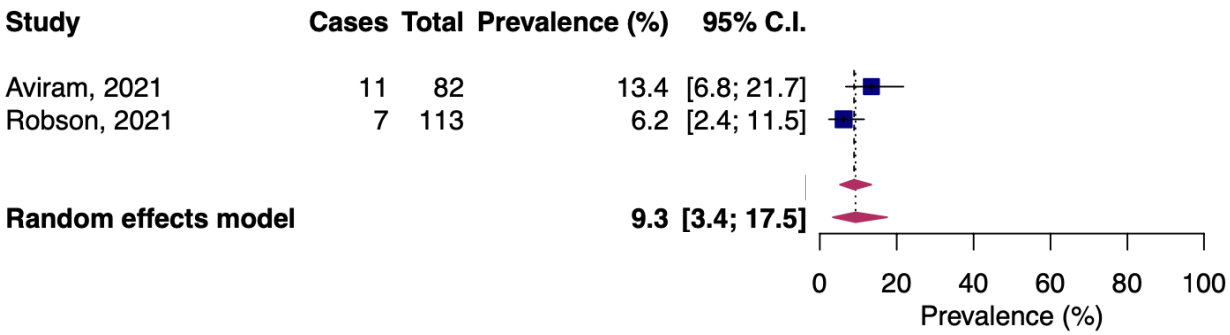


Figure A6.6.6. Disorientation

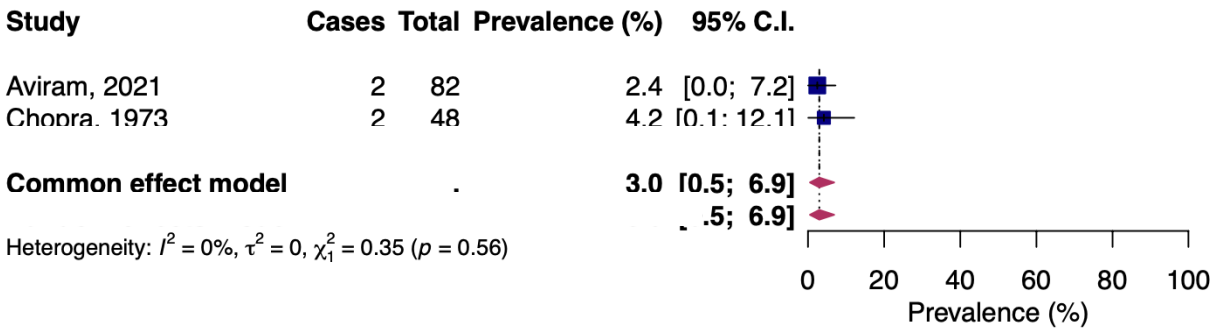


Figure A6.6.7. Dizziness

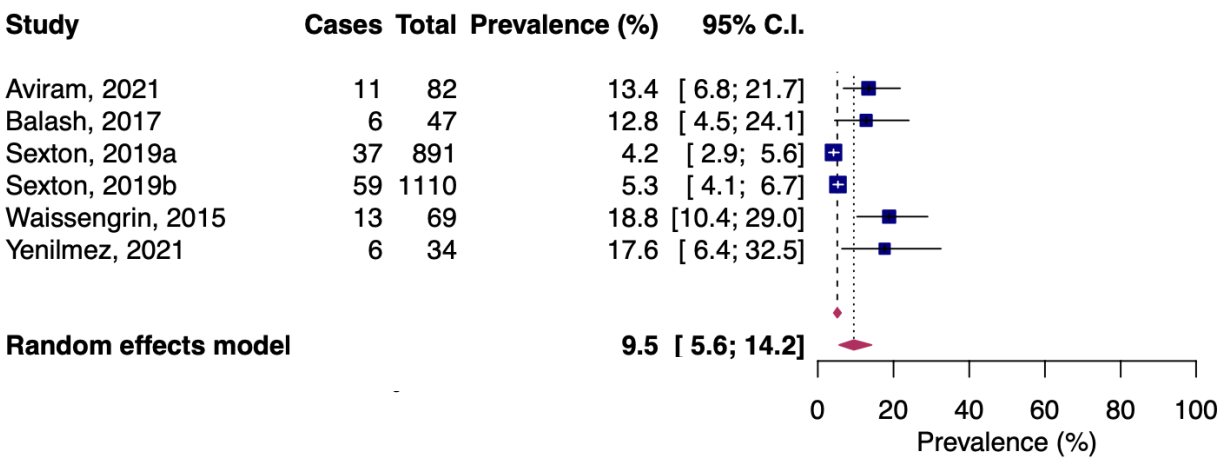


Figure A6.6.8. Dry mouth

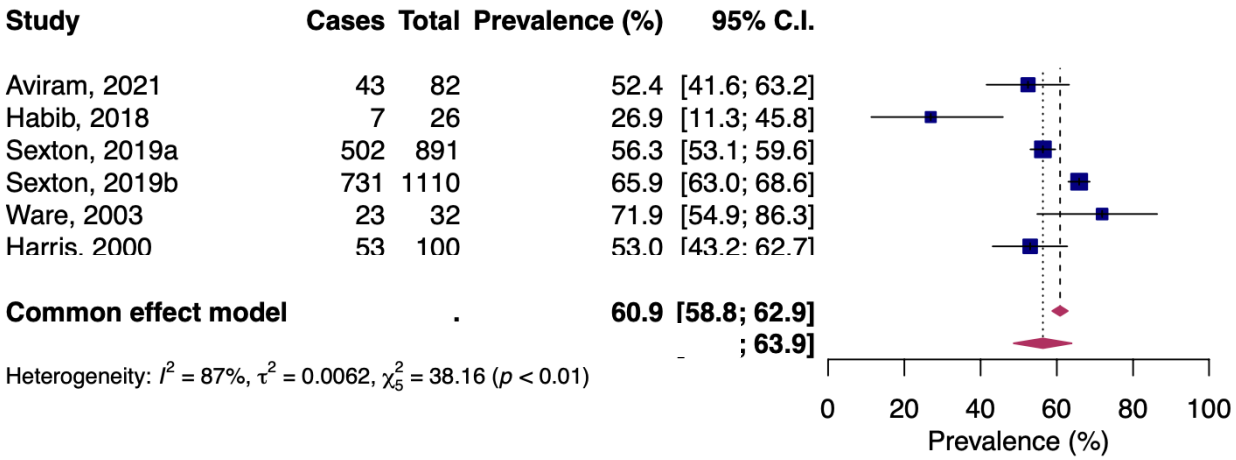


Figure A6.6.9. Euphoria

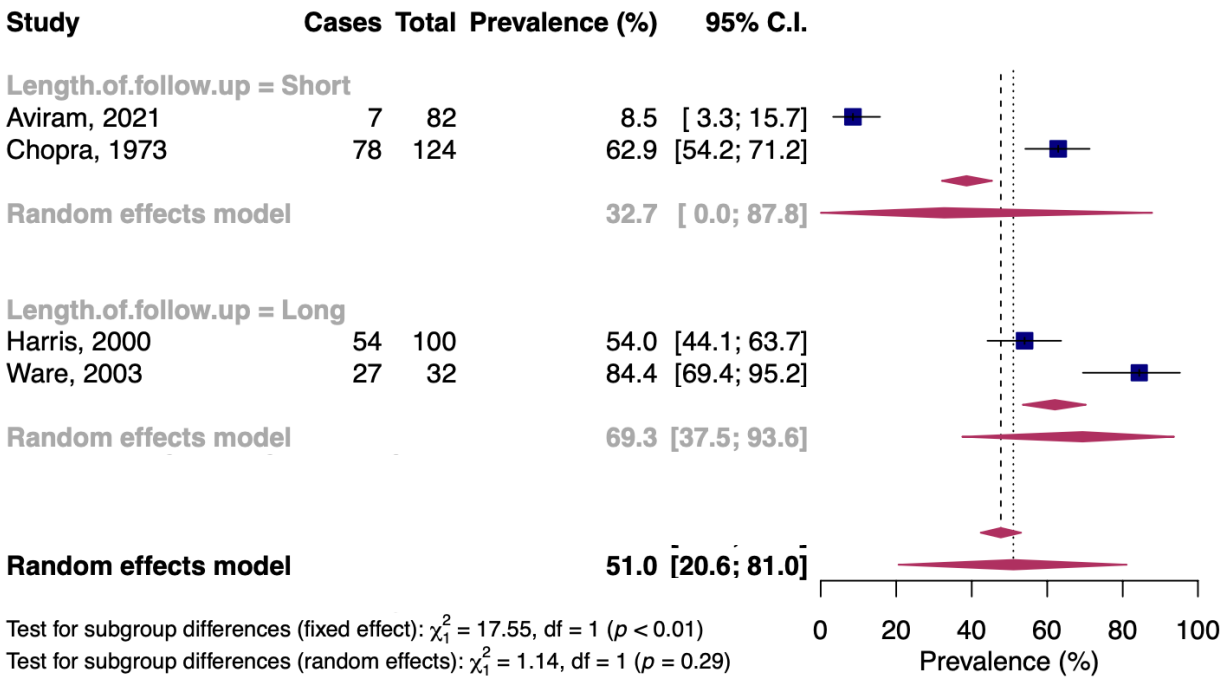


Figure A6.6.10. Fatigue

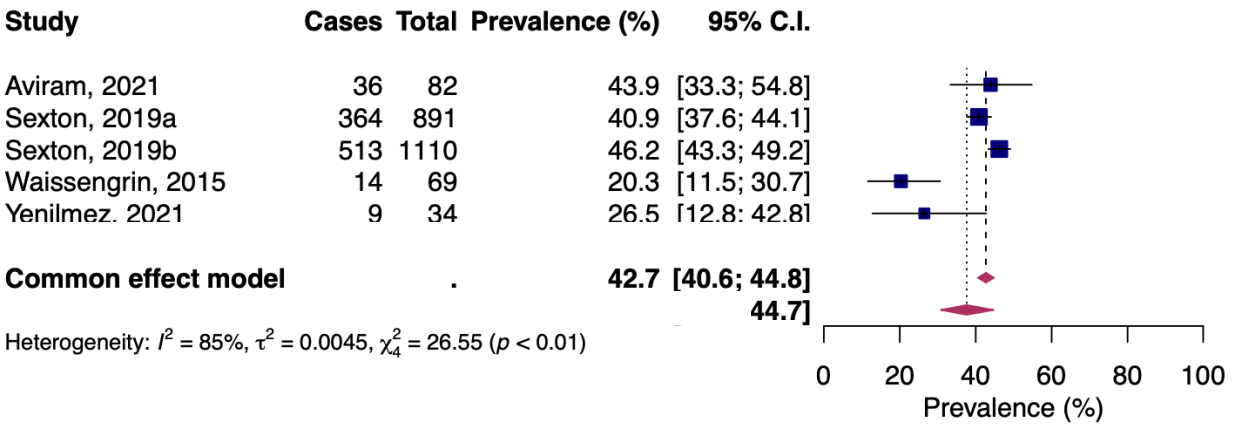


Figure A6.6.11. Hallucinations

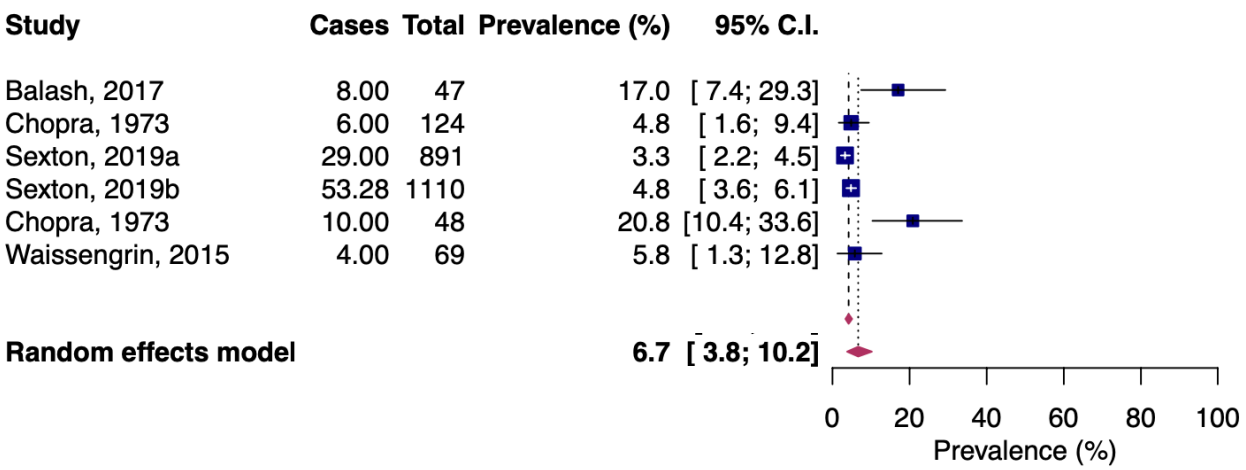


Figure A6.6.12. Impaired coordination

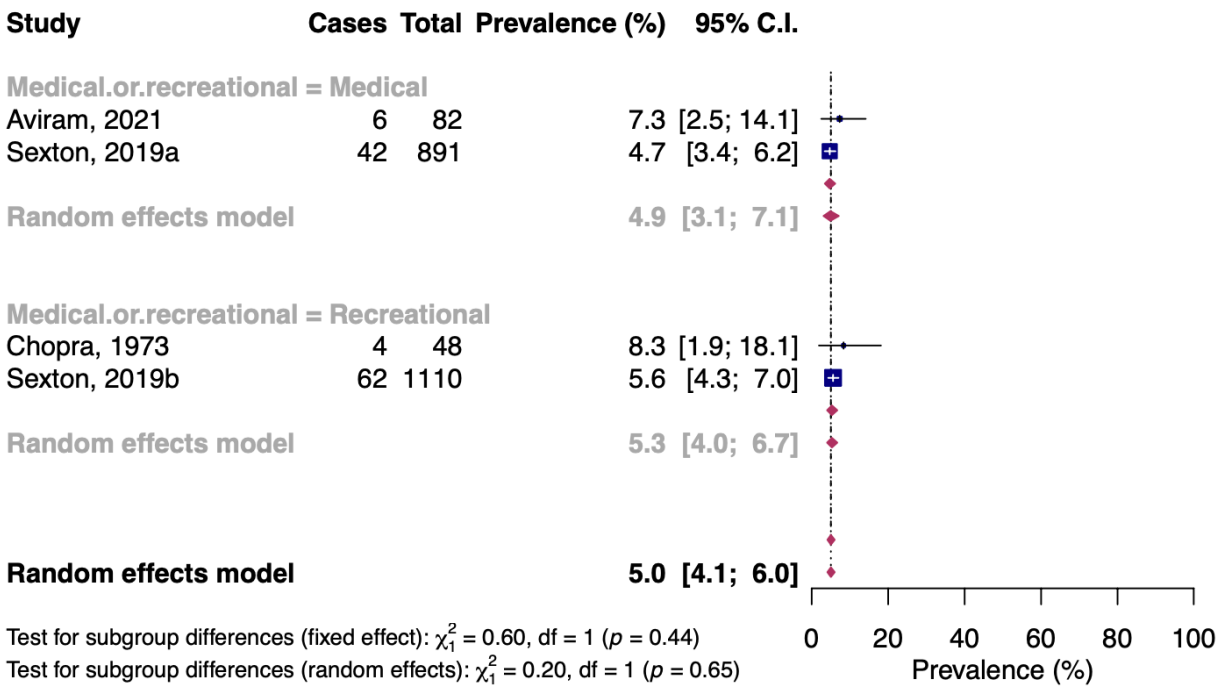
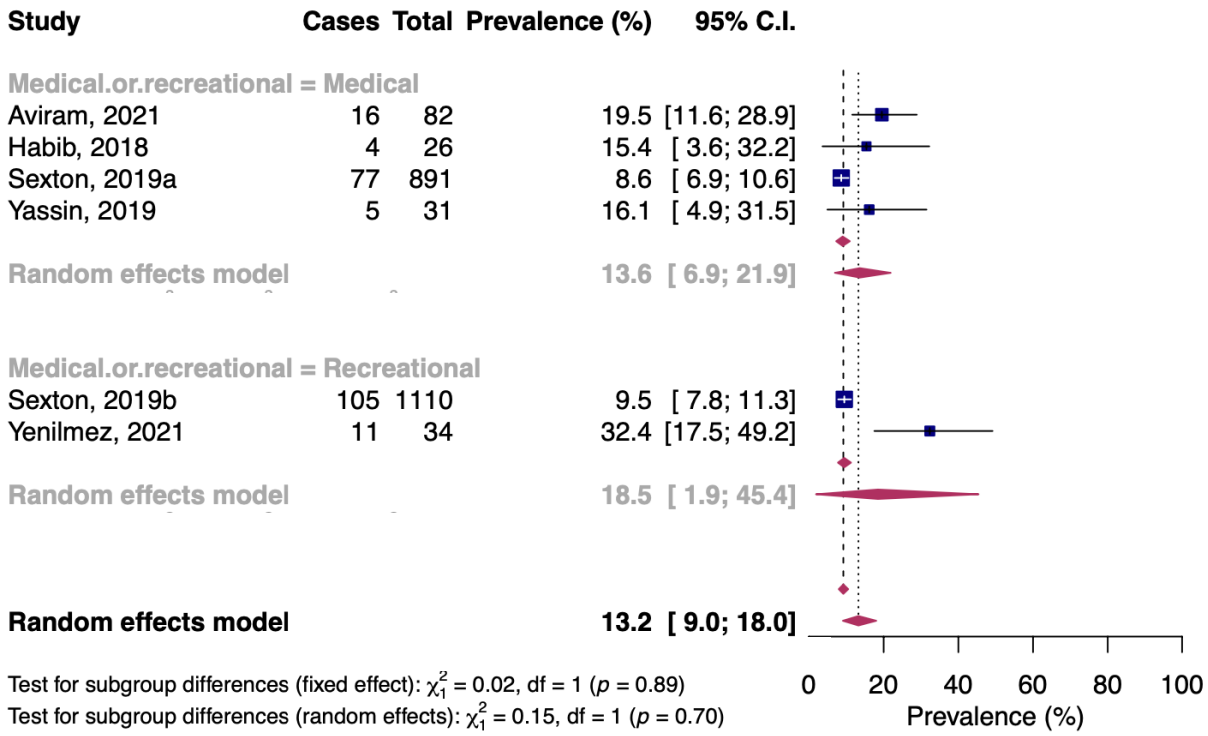


Figure A6.6.13-14. Increased appetite



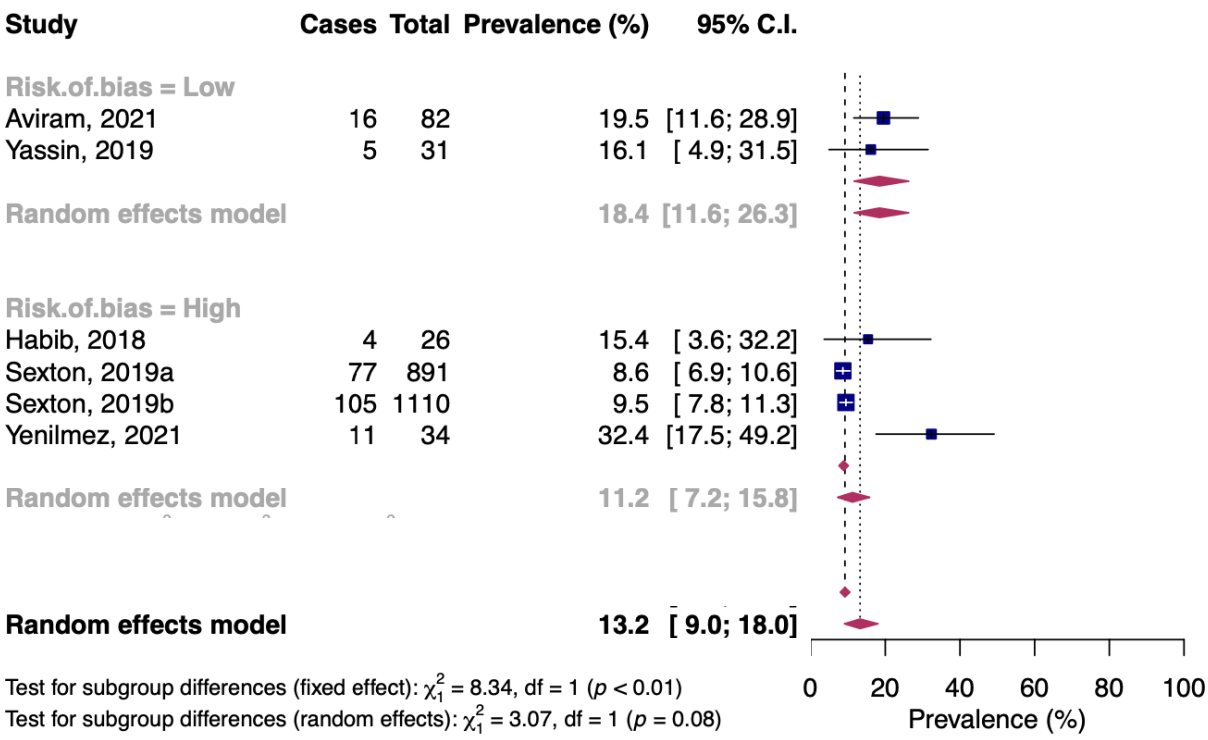


Figure A6.6.15. Irritability

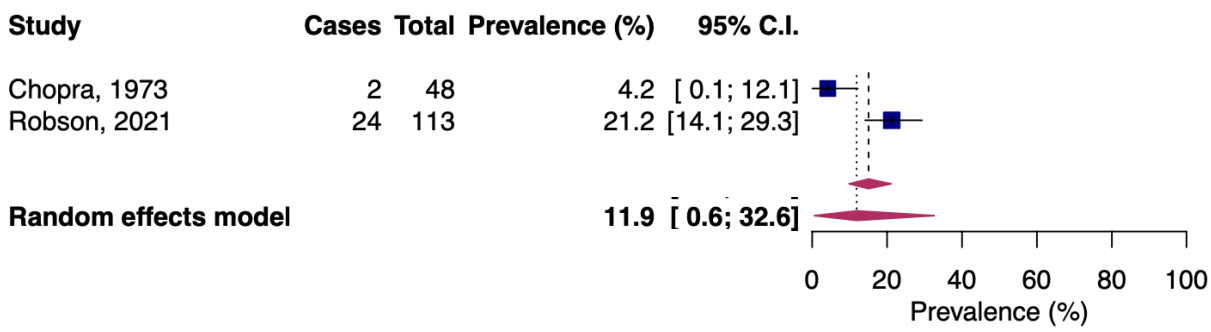


Figure A6.6.16. Mood changes

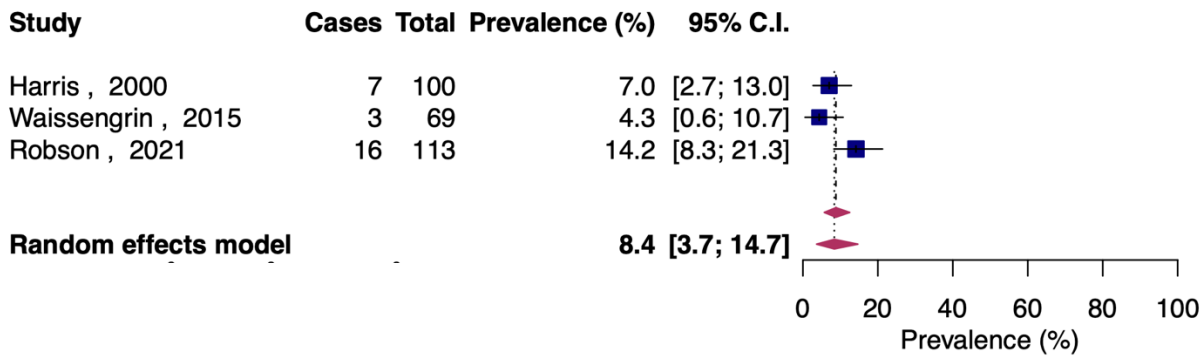


Figure A6.6.17. Nausea

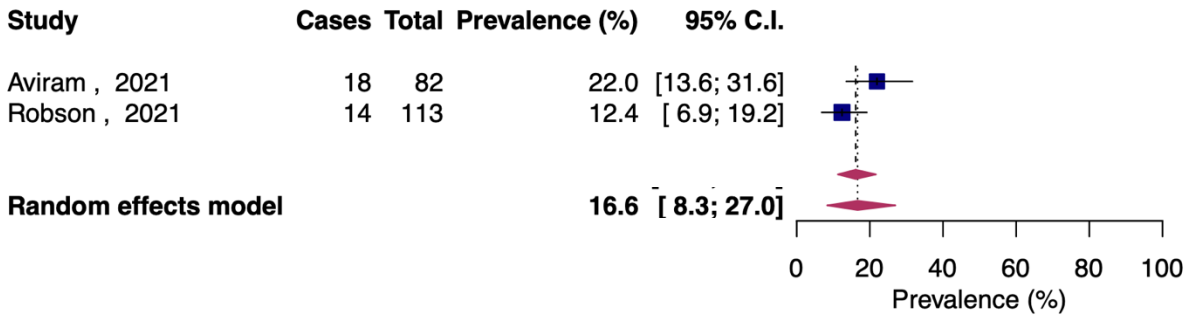


Figure A6.6.18. Palpitations

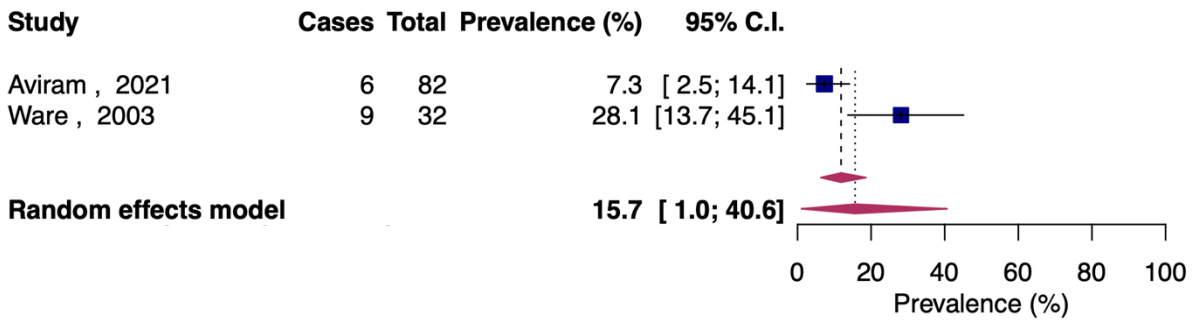


Figure A6.6.19. Paranoia

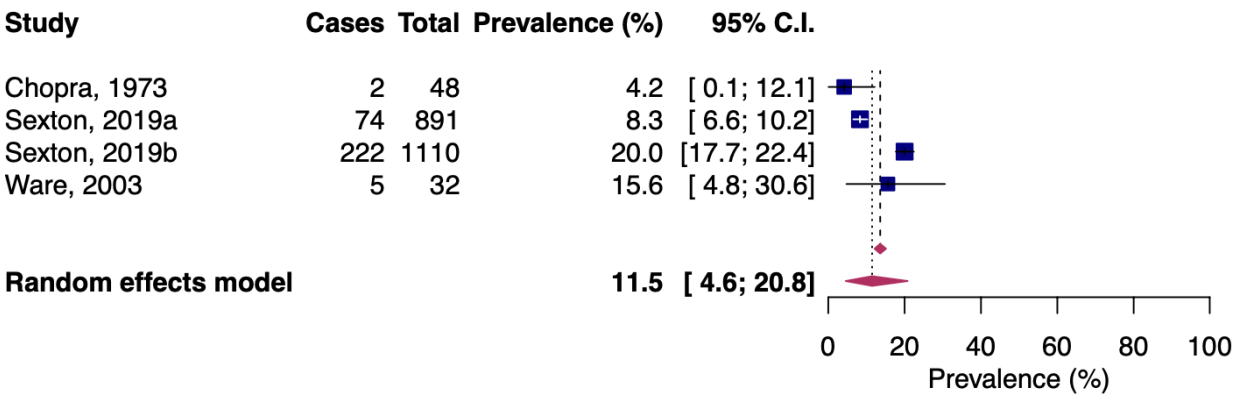


Figure A6.6.20. Psychosis

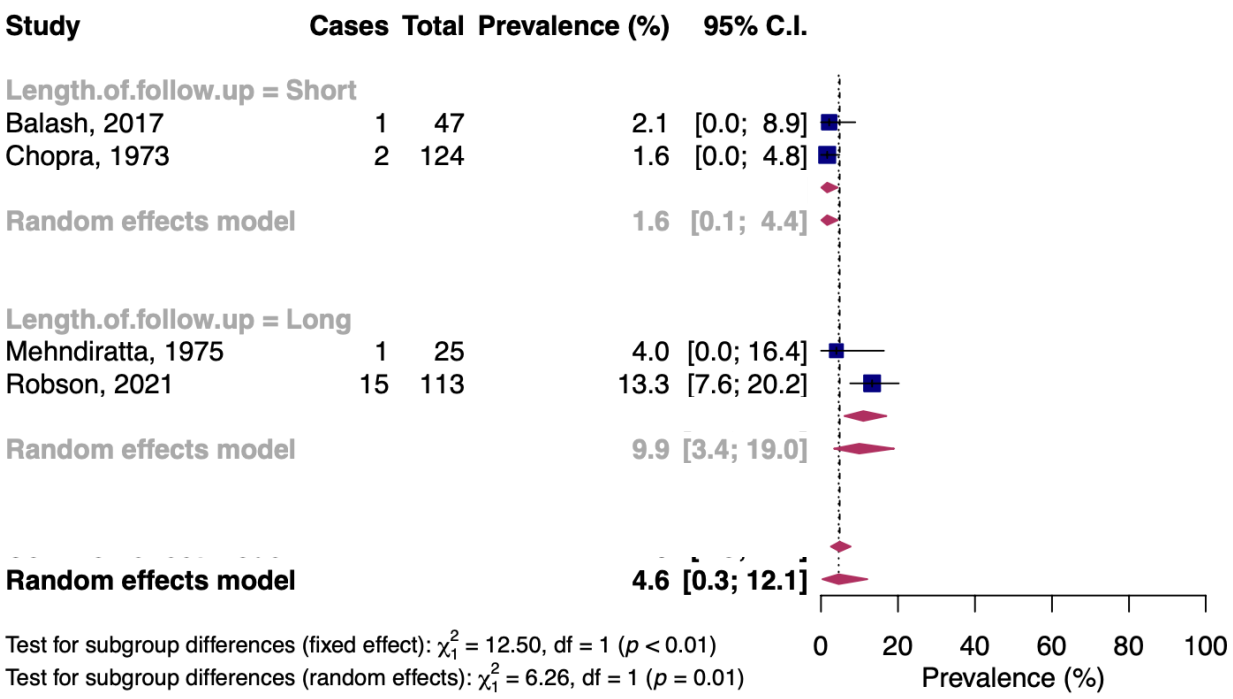


Figure A6.6.21. Red eyes

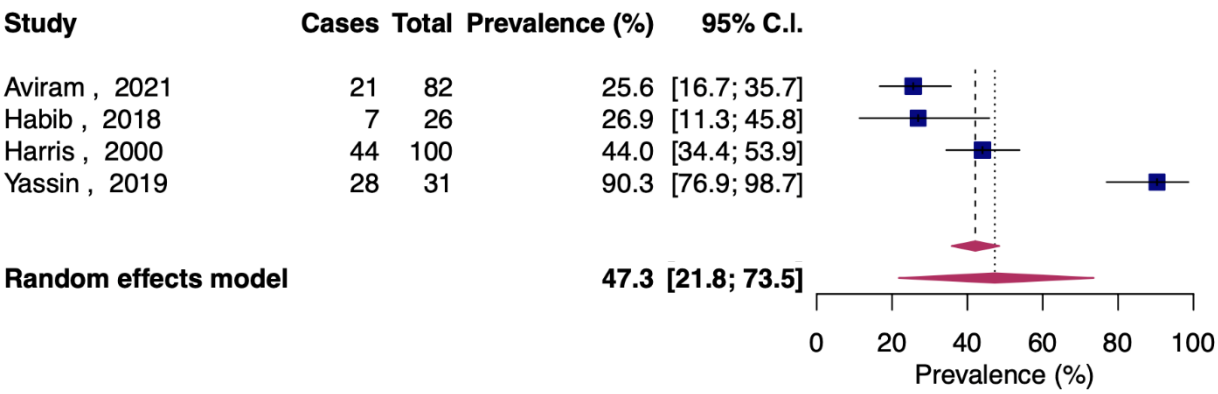


Figure A6.6.22. Thirst

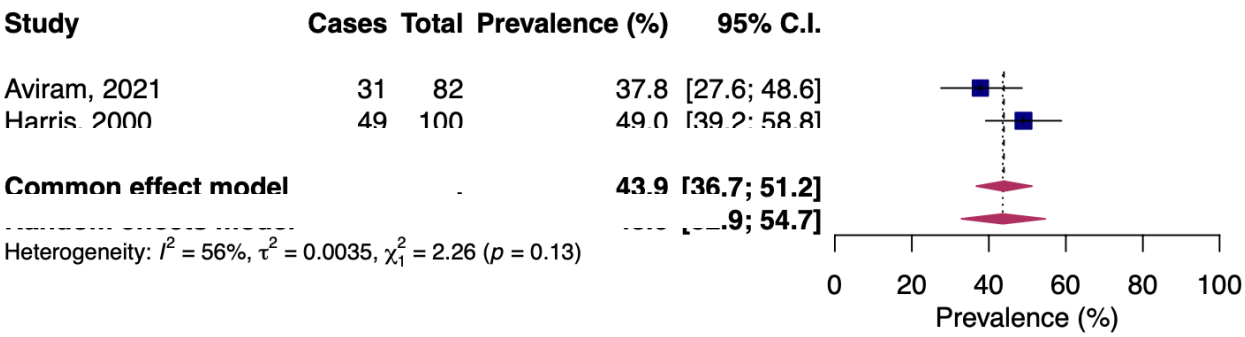
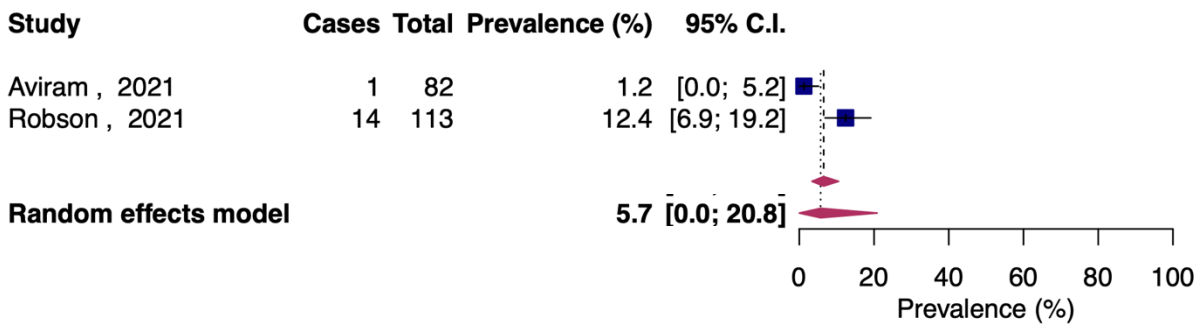


Figure A6.6.23. Vomiting



6.7 APPENDIX G: Dichotomous meta-analysis forest plots

Table A6.7.1. Risk differences for adverse events from comparative studies

Outcome	# of studies	# of participants	Follow-up (months)	Odds ratio (95% CI)	Risk difference (95% CI)	Certainty	Reasons for downgrading
Asthma	2	5819	12	1.58 (1.07 to 2.34)	3.9% (0.5 to 8.6)	Low	indirectness, imprecision
Chronic wheeze	4	8997	12 to 72	2.34 (1.89 to 2.90)	2.3% (1.5 to 3.2)	Moderate	indirectness
Cough	5	9047	12 to 120	2.87 (1.39 to 5.89)	13.8% (3.3 to 28.9)	Low	indirectness, inconsistency
Depression	2	334	84 to 120	2.09 (1.04 to 4.00)	6.7% (0.3 to 16.3)	Very low	risk of bias, indirectness, imprecision
Lung cancer	4	52313	17 to 600	1.32 (0.65 to 2.71)	1.8% (-2.1 to 9)	Very low	indirectness, risk of bias, inconsistency
Phlegm	2	8140	12	1.71 (1.34 to 2.17)	2.9% (1.4 to 4.7)	Low	indirectness, risk of bias
Shortness of breath	3	6060	12	1.81 (1.43 to 2.29)	6.6% (3.6 to 10.1)	Moderate	indirectness

Figure A6.7.1. Asthma

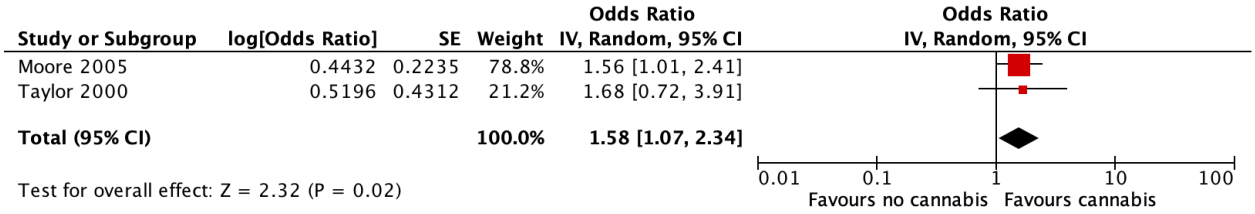


Figure A6.7.2. Chronic wheeze

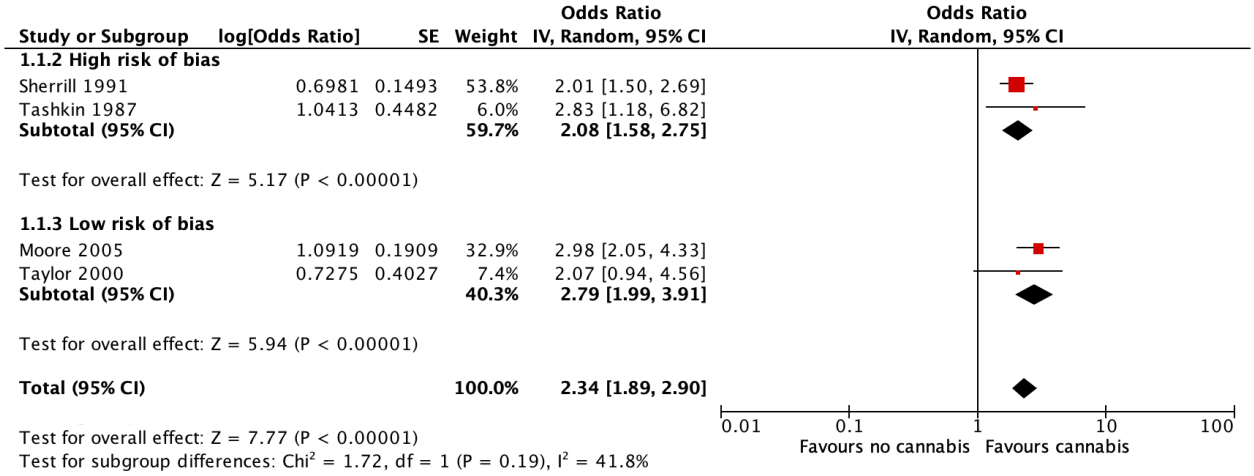


Figure A6.7.4.3 Cough

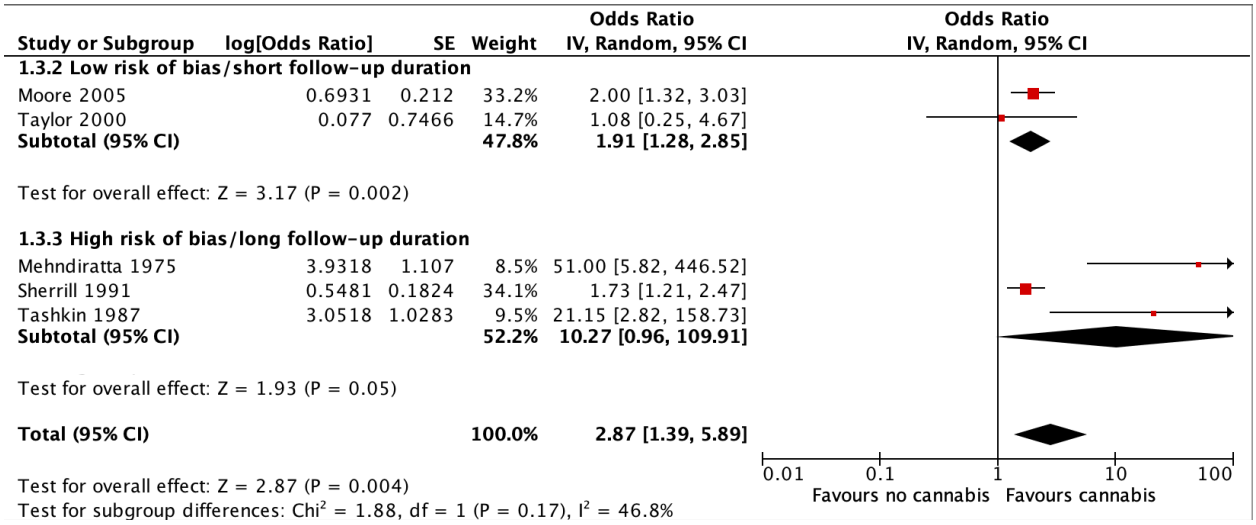


Figure A6.7.4. Depression

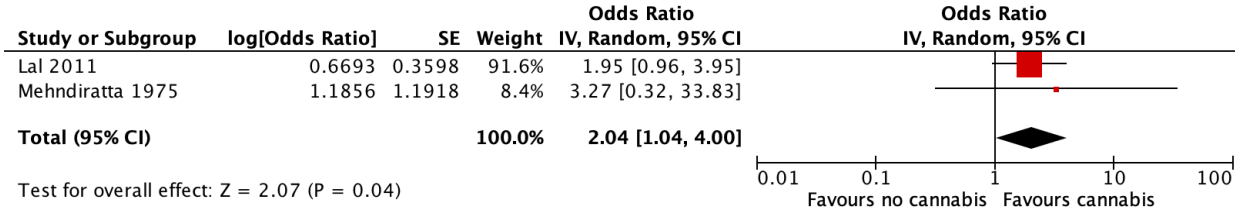


Figure A6.7.5. Lung cancer

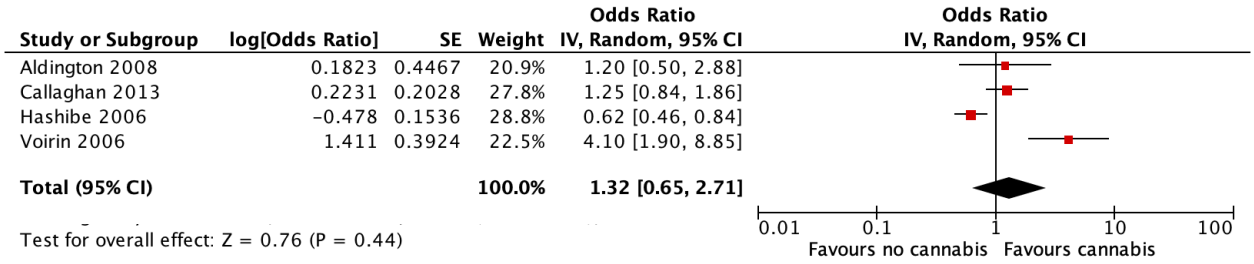


Figure A6.7.6. Phelgm

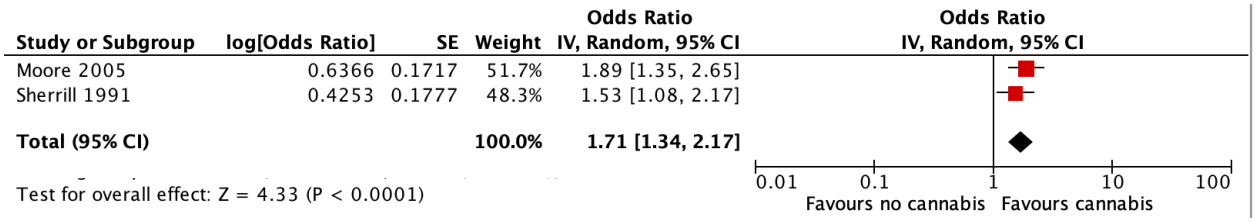


Figure A6.7.7. Shortness of breath

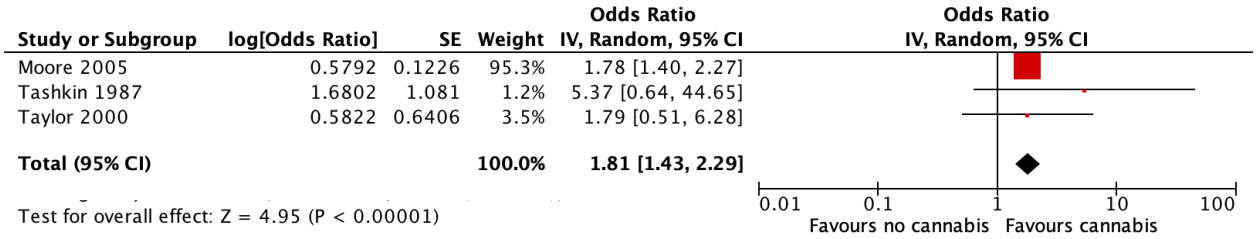


Table A6.7.2. Variables controlled for if adjusted odds ratio is used

Study	**Controlled variables**
Moore 2005	None
Taylor 2000	Cannabis dependence
Sherrill 1991	Age, tobacco smoking and previous occurrence of the adverse event
Taskin 1987	Concomitant tobacco smoking or other drug use
Aldington 2008	Age, joint-years of cannabis smoking and pack-years of cigarette smoking
Callaghan 2013	Baseline tobacco use, alcohol use, respiratory conditions, and socioeconomic status
Hashibe 2006	Age, gender, race/ethnicity, education, drink-years, tobacco use, pack-years
Voirin 2006	Age, tobacco use, and occupational exposures
Lal 2011	None
Mehndiratta 1975	None

6.8 APPENDIX H: Subgroup analyses

Table A6.8.1. Subgroup analyses

	Adverse event	Subgroup analyses conducted
1	Amnesia	Type of cannabis use[1]
2	Euphoria	Duration of study follow-up period[2]
3	Impaired coordination	Type of cannabis use
4	Increased appetite	Type of cannabis use; risk of bias[3]
5	Psychosis	Duration of study follow-up period
6	Chronic wheeze	Risk of bias
7	Cough	Risk of bias; duration of study follow-up period

[1]Type of cannabis use= medical vs recreational use; [2] Duration of study follow-up period= 5 years or greater vs less than 5 years follow-up; [3]Risk of bias= low vs high risk of bias

Table A6.8.2. ICEMAN Evaluation

Outcome	Amnesia	Euphoria	Impaired coordination	Increased appetite	Increased appetite	Psychosis	Chronic wheeze	Cough	Cough
Subgroup analysis	Type of cannabis	Length of follow up	Type of cannabis	Type of cannabis	Risk of bias	Length of follow up	Risk of bias	Risk of bias	Length of follow up
1: Is the analysis of effect modification based on comparison within rather than between trials?	Completely between	Completely between	Completely between	Completely between	Completely between	Completely between	Completely between	Completely between	Completely between
2: For within-trial comparisons, is the effect modification similar from trial to trial?	NA	NA	NA	NA	NA	NA	NA	NA	NA
3: For between-trial comparisons, is the number of trials large?	Very small	Very small	Very small	Very small	Very small	Very small	Very small	Very small	Very small
4: Was the direction of effect modification correctly hypothesized a priori?	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation	Chance a very likely explanation
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no	Definitely no
7: Did the authors use a random effects model?	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Definitely yes
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided?	Definitely yes	Probably no or unclear	Definitely yes	Definitely yes	NA	Probably no or unclear	NA	NA	Probably no or unclear
Overall credibility	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**