Systematic Review and Meta-Analysis

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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

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Abstract

The growing demand for improved pain treatments together with expanding legalization of, and access to, cannabinoids, cannabis, and cannabis-based medicines has intensified the focus on risk–benefit considerations in pain management. Given limited harms data from analgesic clinical trials, we conducted an overview of systematic reviews focused on all harms possibly relevant to patients receiving cannabinoids for pain management. This PROSPERO-registered, PRISMA-compliant systematic overview identified 79 reviews, encompassing over 2200 individual reports about psychiatric and psychosocial harms, cognitive/behavioral effects, motor vehicle accidents, cardiovascular, respiratory, cancer-related, maternal/fetal, and general harms. Reviews, and their included studies, were of variable quality. Available evidence suggests variable associations between cannabis exposure (ranging from monthly to daily use based largely on self-report) and psychosis, motor vehicle accidents, respiratory problems, and other harms. Most evidence comes from settings other than that of pain management (eg, nonmedicinal and experimental) but does signal a need for caution and more robust harms evaluation in future studies. Given partial overlap between patients receiving cannabinoids for pain management and individuals using cannabinoids for other reasons, lessons from the crisis of oversupply and overuse of opioids in some parts of the world emphasize the need to broadly consider harms evidence from real-world settings. The advancement of research on cannabinoid harms will serve to guide optimal approaches to the use of cannabinoids for pain management. In the meantime, this evidence should be carefully examined when making risk–benefit considerations about the use of cannabinoids, cannabis, and cannabis-based medicine for chronic pain.

Keywords: Cannabis, Cannabinoids, Risk, Harm, Adverse effects, Systematic review

1. Introduction

Chronic pain is highly prevalent, affecting 11% to 40% of the population[11,24,33,61,67,108] and causing suffering, disability, and mortality,[119] and increasing burden to caregivers, health care, and providers.[90,122] The *International Classification of Diseases* (*ICD-11*) recognized chronic pain as a disease in its own right.[97] Chronic pain is rarely managed effectively with monotherapy[48] necessitating a multimodal approach.[26,37] Analgesic drugs such as acetaminophen, NSAIDs, opioids, anticonvulsants, and antidepressants are often ineffective,[35,93] and have potential harms and risks.[29,62,72,87]

Interest has emerged in cannabinoids, cannabis, and cannabis-based medicine as treatments for chronic pain.[36,121,123,129,131] Cannabis refers to all or part of the plant,

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including products such as *Cannabis sativa* and hashish.[95] Cannabinoids are constituents of cannabis or synthetic compounds acting at cannabinoid receptors, including products such as tetrahydrocannabinol (THC), cannabidiol (CBD), and nabilone. Cannabis-based medicines refer to medicinal cannabis extracts developed as a therapeutic with a defined THC/CBD content and ratio and include products such as nabiximols and dronabinol. Cannabis legislation is evolving, with increasing availability in various jurisdictions and increasing use for chronic pain. Consequently, there is a global need to intensify risk–benefit considerations for this group of interventions. Thus, in 2018, the International Association for the Study of Pain Presidential Taskforce on Cannabis and Cannabinoid Analgesia was established (https://www.iasp-pain.org/About/Content.aspx?ItemNumber=7917) and includes 4 work packages (WP) to address the following topics: WP1—preclinical evidence for analgesic efficacy; WP2—evidence of clinical analgesic efficacy; WP3—harms (this review); and WP4—societal and policy issues.

The most direct and unbiased harms evidence is expected to come from randomized, placebo-controlled trials (RCTs) of cannabinoids in treating chronic pain. However, limitations of this evidence base include: (1) relatively few and often low quality RCTs; (2) limited assessment and reporting of adverse events (AEs) in these RCTs; (3) brief duration of treatment exposure; (4) limited generalizability to broader populations; and (5) inadequate information about dose–response relationships.[91] Therefore, risk–benefit consideration requires broader examination of all relevant evidence. Evidence relevant to patients receiving cannabinoids for pain may come from different settings. In addition to high-quality reviews[1,5,110] and studies[7,58] about harms of medicinal cannabis, this review also explores reviews of nonmedical cannabis. This is because an appreciable proportion of individuals receiving cannabinoids for nonmedical purposes may, in part, be attempting to also treat pain—even if not explicitly prescribed for this purpose. Using opioids as an example, pain RCTs would never have predicted the public health harms seen in the crisis of opioid oversupply and overuse in some parts of the world. These harms were only realized after studying population safety patterns in real-world settings. In attempting to collect and synthesize harms evidence, systematic reviews are very likely to have searched widely for available evidence and may also include diverse sources, including large cohort and administrative database studies that may identify harms not otherwise recognized from smaller RCTs. With this rationale, we conducted an overview of systematic reviews that are focused on harms of cannabinoids.

2. Methods

The protocol for this overview has been previously published,[47] follows PRISMA-P guidelines,[103] and has been registered on the PROSPERO register (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=124600).

2.1. Sources of evidence

The search strategy for this overview was designed to identify systematic reviews where harms were the primary focus. We defined systematic reviews as reviews that undertook a systematic search of the literature, through screening, extraction, and analysis. We searched for systematic reviews in PubMed, EMBASE, and the Cochrane Database of Systematic Reviews. The literature search strategy is shown in Supplementary Appendix 1 (available at http://links.lww.com/PAIN/B116) and was developed with careful consideration of previous reviews of cannabinoid-related harms, as well as previous generic approaches to harms reviews.[50] In addition to the reviews identified by this search strategy, additional reviews identified by hand searching of the reviewed articles, and other literature were also considered for inclusion.

2.2. Review selection

To be included in this overview, reports were required to be a systematic review (with or without meta-analysis) focusing on one or more harms related to cannabinoids, cannabis, and cannabis-based medicine in any setting that was considered relevant to patients receiving these for pain management. The search strategy for this overview concentrated on reviews where cannabinoid harms were the focus and did not necessarily include efficacy and safety reviews where harms were not the main focus. Two authors (M.M. and R.P.) independently reviewed identified citation titles and abstracts for inclusion and a third author (I.G.) had served as an adjudicator for any disagreements.

2.3. Data extraction

Data extracted from each report included type(s) of cannabinoid(s) evaluated, type(s) of harm(s) evaluated, type(s) of studies (eg, randomized controlled trials of nonpain conditions, case series, epidemiological studies [including prospective cohort studies], large database studies, and epidemiological studies etc.), numbers of studies and subjects/participants included in each review, patient population and/or clinical setting, specific harm(s) reported and methods for their assessment/quantification, cannabinoid studied (eg, nonmedicinal, medicinal, pharmaceutical, smoked, and ingested), and reported dosage/duration. Frequency, prevalence, and/or estimated risk of specific harms were reported where available as well as the results of any reported meta-analyses. Where available, 95% confidence intervals were reported for estimates of risk.

2.4. Quality assessment

For each review included in the overview, methodological quality was assessed using AMSTAR-2[115] and compliance with items included in the PRISMA harms checklist.[133] Other elements of evidence quality were evaluated including the use of control groups/comparators, study size, precision/accuracy of cannabinoid exposure, and methodology for the measurement of harm.

3. Results

3.1. Characteristics of included reviews

The initial literature search identified 2582 articles with 11 additional articles found through hand searching of other literature (**Fig. 1**). After excluding duplicates (837), 1745 articles remained for abstract review. After excluding articles based on abstract review (1622), 135 articles remained for full-text review from which 56 were excluded (Supplementary Appendix 2, available at http://links.lww.com/PAIN/B116). Overall, 79 reviews were included in the overview (Supplementary Appendix 3, available at http://links.lww.com/PAIN/B116). Key characteristics of included reviews are shown in **Tables 1–3** and Supplementary Appendices 4 to 7 (available at http://links.lww.com/PAIN/B116). Included harms reviews were categorized broadly as harms from studies of: (1) administration of cannabis,

and (2) administration of cannabinoids. Studied harms were categorized as psychiatric, behavioral, and psychosocial harms, neurocognitive harms, motor vehicle accidents, cardiovascular, respiratory, cancer-related, maternal/fetal, and general harms. The reviews in this overview included, in total, over 2200 individual studies/reports (Supplementary Appendix 8, available at http://links.lww.com/PAIN/B117) of various types (case reports, case series, cross-sectional, longitudinal, case-control, and clinical trials) and widely varying in numbers of subjects/participants involved (single case report to cohort study of 172,718 participants).

3.2. Quality of included reviews

According to quality assessments using AMSTAR-2,[115] 76 of the 79 included reviews received a "critically low" score and 3 received a "low" score (Supplementary appendix 9, available at http://links.lww.com/PAIN/B118). Very common critical domain deficiencies include failure to preregister the review protocol, listing of excluded studies, and reasons for exclusion. Problems with risk of bias assessment and consideration of bias when interpreting results were not as common but still quite frequent. Reviews were also evaluated based on PRISMA Harms reporting standards (Supplementary appendix 10, available at http://links.lww.com/PAIN/B119). Areas consistently unmet included: protocol not registered, failing to outline methods of risk of bias in individual studies and across studies, and presenting results on risk of bias.

3.3. General harms

Meta-analyses of harms in RCTs indicate increased incidence of AEs with cannabis (risk ratio [RR] = 1.86 [1.57, 2.21]), oromucosal-THC (RR = 1.88 [1.48, 2.39]), and oral-THC (2.18 [1.59-2.99])[128] (Supplementary Appendix 5, available at http://links.lww.com/PAIN/B116). However, no significant association was found with rates of serious AEs or death. From included reviews on general harms with no meta-analyses (Supplementary appendix 5, available at http://links.lww.com/PAIN/B116), there were various harms associated with cannabis. First, cannabis has been identified as a potential cause of acute pancreatitis with numerous cases in the literature where development correlated strongly with recent cannabis use, and resolved after its cessation.[6] Cannabis use co-occurring with tobacco was also

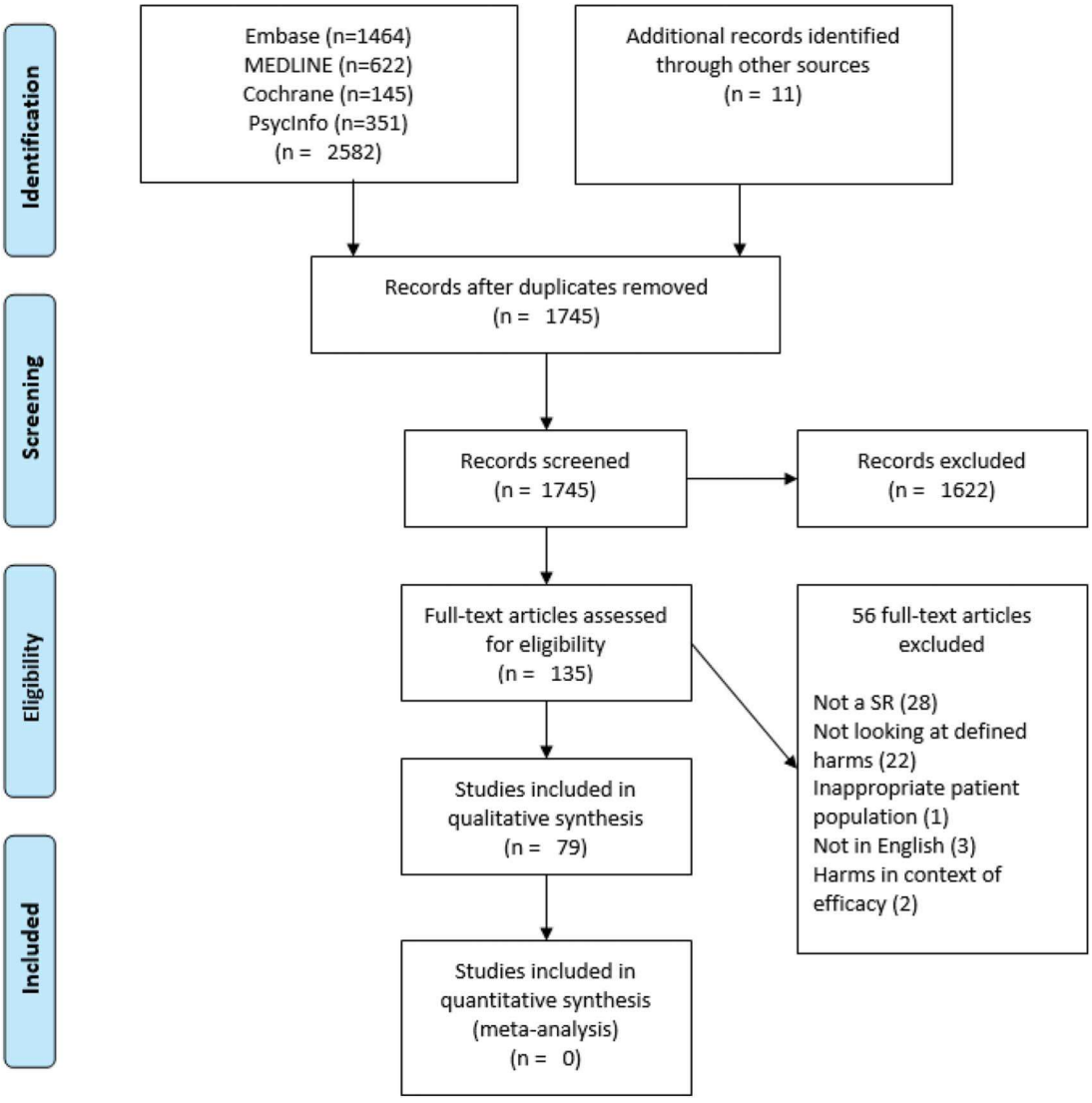

Figure 1. Overview of review flow diagram.

Table 1

Reviews (with meta-analyses)[1] of mental health and psychosocial harms associated with cannabis use.

Author	# Of included studies and designs	Participants/subjects (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
Mental health outcomes						
Borges 2016	19—Longitudinal, case series, toxicology reports	NR	Cases of suicide attempts	Self-reports, toxicology reports, attribution by Emergency Department personnel	Funnel plot for publication bias	Increased odds of: death by suicide with chronic cannabis use (OR = 2.56 [1.25, 5.27]), suicidal ideation with any cannabis use (OR = 1.43 [1.13, 1.83]), suicide attempt and any cannabis use (OR = 2.23 [1.24, 4.00]), and suicide attempt with heavy cannabis use (OR = 3.20 [1.72, 5.94]). Control(s) not specified.
Burns 2012	9—NR	1726	Patients diagnosed with psychosis	Self-reports	Funnel plot for publication bias	No increased risk of longer duration of untreated psychosis in cannabis users compared to nonusers
Esmaeelzadeh 2018	16—cross-sectional, longitudinal	10,519—cannabis and depression, 5144—cannabis and anxiety	Adolescents and young adults in the United States and Canada using cannabis	Self-reports	Modified Newcastle–Ottawa quality scale; funnel plot for publication bias	Increased odds of: depression with cannabis use (OR = 1.29 [1.10, 1.51]), anxiety and cannabis use (OR = 1.36 [1.02, 1.81]). Cannabis use at baseline resulted in depression at follow-up (OR = 1.33 [1.19, 1.49]). Adjusted analysis resulted in increased odds with cannabis use and depression (OR = 1.31 [1.17, 1.46]), depression symptoms (1.20 [1.01, 1.42]), diagnosis of depression (1.41 [1.21, 1.65]), and in adolescents (1.34 [1.17, 1.54]). Controls were nonusers.
Foglia 2017	15—Longitudinal (11), prospective (6)	3678	Participants diagnosed with schizophrenia or psychotic disorder, on antipsychotic medication	Self-reports, ratings by clinicians, combination of assessments	Funnel plot for publication bias	Increased odds of medication nonadherence when comparing any cannabis use to nonuse (OR = 2.46 [1.97, 3.07]), comparing current cannabis users to nonusers (OR = 5.79 [2.86, 11.76]), and comparing former users to nonusers (OR = 1.12 [1.12, 2.07]).
Gibbs 2015	6—Prospective cohort	14,918	General and clinical populations	NR	Cochrane Risk of Bias Tool	Increased odds of onset of mania symptoms with cannabis use (OR = 2.97 [1.80-4.90]). Control(s) not specified.
Gobbi 2019	35—Qualitative (35), meta-analysis (11)	23,317	General population	Self-reports	Research Triangle Institute item bank on risk of bias and precision of observational studies	Meta-analysis: cannabis in adolescence and depression in young adulthood (OR = 1.37 [1.16, 1.62]), suicidal ideation (OR = 1.50 [1.11, 2.03]), and suicide attempts (3.46 [1.53,7.84]) Controls: nonusers
Kedzior 2014	31 cross-sectional(16), longitudinal(15)	173,575	General population	Self-reports	Predefined study quality exclusion criteria; funnel plot for publication bias	Increased odds with cannabis use of: anxiety (OR = 1.24 [1.06, 1.45]), comorbid anxiety and depression (OR = 1.68 [1.17, 2.40]), baseline cannabis use and anxiety at follow-up (OR = 1.28 [1.06, 1.54]) Control(s): nonusers of cannabis.

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Table 1 (*continued*)

Author	# Of included studies and designs	Participants/subjects (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
Kraan 2016	7—prospective cohort	1171	Ultrahigh risk for psychosis	Clinical ratings	Funnel plot for publication bias	No increased odds of transition to psychosis in ultrahigh risk cannabis users compared to nonusers.
Large 2011	7—NR	8167 users, 14,352 controls	Patients experiencing psychosis after substance use	Not reported	Funnel plot for publication bias	Age at onset of psychosis 2.70 y earlier in cannabis users ($z = -7.18$; $P < 0.001$). Controls: nonusers.
Lev-ran 2014	14—longitudinal		Patients experiencing depression	Self-reports	Newcastle–Ottawa quality scale; funnel plot for publication bias	Increased odds of depression with cannabis use (OR = 1.17 [1.05, 1.30]) compared to nonusers. Dose–response effects found with heavy use and depression (OR = 1.62 [1.21, 2.16]) compared to occasional users.
Marconi 2016	16—prospective cohort, cross-sectional, case-control	66,816	Patients experiencing psychosis	Self-reports	Funnel plot for publication bias	With severe cannabis user, increased odds of schizophrenia and other psychoses (OR = 3.90 (2.84, 5.34)), psychotic symptoms (OR = 3.59 (2.42, 5.32)), and diagnosis of schizophrenia/psychotic disorder (OR = 5.07 (3.62, 7.09)). Controls: nonusers.
Moore 2007	32—cohort studies	NR	Patients experiencing psychosis	Self-reports	Predefined study quality inclusion criteria; funnel plot for publication bias	Increased adjusted odds of: psychotic outcomes with ever-use of cannabis (OR = 1.41 [1.20, 1.65]), psychotic outcomes with frequent cannabis use (OR = 2.09 (1.54, 2.84)), ever-use and psychotic disorder (OR = 2.58 [1.08, 6.13]), and most frequent cannabis use and depression (OR = 1.49 [1.15, 1.94]). Controls: nonusers.
Myles 2012	42—cohort	3199 users, 5715 nonusers	General and psychiatric populations	Self-reports with clinical interview	Predefined study quality inclusion criteria; funnel plot for publication bias	The age at onset of psychosis (SMD = −0.399 [−0.493, −0.306]) equivalent to 32 mo earlier in cannabis users compared to nonusers.
Myles 2016	39—Cohort	10,762	Patients with first episode psychosis	Self-reports	Funnel plot for publication bias	Cannabis use begins approximately 5.3 y before age at onset psychosis (SMD = 1.56 [1.40, 1.72]) compared to nonusers. A proportion of 33.7% (33.7% [29%-38%]) used cannabis at the time of first psychosis compared to nonusers.
Schoeler 2016b	24	5849 users, 10,308 nonusers	Patients with psychosis	Self-reports	Funnel plot for publication bias	Meta-analysis: continued cannabis use after onset of psychosis and risk of psychosis relapse compared with nonusers (d = 0.36 [0.22, 0.50]), and discontinued use (0.28 [0.12, 0.44]). Continued vs nonuse and hospital length (0.36 [0.13, 0.58]), positive symptoms (0.15 [0.01, 0.29]). For functioning, discontinued use vs nonuse (−0.49 [−0.81, −0.17]).
Semple 2005	11—Prospective cohort, cross-sectional, case-control	113,802	Various cohorts	Self-reports with clinical interview	Funnel plot for publication bias	Increased odds of psychosis with cannabis use (OR = 2.9 [2.3, 3.6]). Controls: nonusers.

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Table 1 (*continued*)

Author	# Of included studies and designs	Participants/subjects (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
Cognitive outcomes						
Bogaty 2018	14—NR	1430	Young psychosis patients with cannabis use	NR	Funnel plot for publication bias	In cannabis users, deficits in premorbid IQ (g = −0.40 [−0.59, −0.20]), working memory (g = −0.76 [−1.30, −0.22]), and verbal language (g = −0.47 [−1.22, −0.28]). No significant deficits in current IQ, processing speed, cognitive flexibility, sustained attention, verbal learning, verbal memory, conceptual set-shifting, and motor inhibition. Controls: never-users.
Ganzer 2016	38—cross-sectional (30), repeated measures (6), longitudinal (2)	NR	General population	Self-reports	Funnel plot for publication bias	Deficits in neurocognitive performance (r = 0.305 [0.254, 0.358]), attention (r = 0.273 [0.109, 0.423]), executive function (r = 0.294 [0.109, 0.423]), memory and learning (r = 0.229 [0.130, 0.323]). Controls: nonusers.
Grant 2003	15—NR	704 users, 484 control	General population	Self-reports	No details provided	Deficits in learning (ES = −0.21 [−0.39, −0.040]), forgetting/retrieval (ES = −0.27 [−0.49, −0.044]), and neurocognitive performance (ES = −0.15 [−0.29, −0.019]). No significant deficits in executive function, attention, motor, perceptual-motor, simple reaction time, and language. Controls: nonusers.
Platt 2019	6—NR	205	General population	NR	Cochrane Risk of Bias Tool	Deficits in event-based prospective memory (ES = −0.49 [−0.90, −0.08]) and time-based prospective memory (ES = −0.70 [−0.80, −0.61]). Control: nonusing or infrequent users.
Rabin 2011	8—cross-sectional	942	Patients with schizophrenia	NR	No details provided	Deficits in selective, sustained, and divided attention (d = 0.35 [0.23]) and visuospatial and constructional abilities (0.33 [0.27]). No significant deficits in general cognitive ability and intelligence, executive function, retrieval, and language. Controls: nonusers
Schoeler 2016	88—NR	7697	Nonpsychotic cannabis users	NR	Funnel plot for publication bias	Deficits in prospective memory (d = 0.61 [0.38, 0.65]), working memory (0.11 [0.04, 0.17]), verbal immediate recall (0.40 [0.27, 0.53]), verbal learning (0.36 [0.24, 0.48]), visual learning (0.09 [0.11, 0.28]), verbal delayed recall (0.36 [0.22, 0.49]), visual recognition (0.41 [0.10, 0.72]), verbal recognition (0.27 [0.11, 0.42]), and total memory (0.27 [0.22, 0.32]). Light user (0.02 [−0.09, 0.14]), regular user (0.20 [0.10, 0.30]), heavy user (0.32 [0.25, 0.39]), short-

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Table 1 (*continued*)

Author	# Of included studies and designs	Participants/subjects (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
						term user (0.26 [0.20, 0.33]), and long-term user (0.49 [0.26, 0.72]). No significant deficits in visual memory and visual recall. Control: nonusers
Schreiner 2012	46—NR	1010 cases, 839 controls	General population	Self-reports	No details provided	Overall residual deficits in: abstraction/executive function (ES = −0.21 [−0.38, −0.05]), attention (−0.36 [−0.56, −0.16]), forgetting/retrieval (−0.25 [−0.47, −0.02]), learning (−0.35 [−0.55, −0.15]), motor (−0.34 [−0.57, −0.11), and verbal/language (−0.23 [−0.47, −0.001]). No significant association for perceptual-motor and reaction time. Controls: never-use or limited use history.
Scott 2018	69—cross-sectional	8727—2152 users, 6575 controls	General population—adolescents and young adults using cannabis	NR	Funnel plot for publication bias	Deficits in: overall neurocognition (d = −0.247 [−0.32, −0.17]), learning (−0.33 [−0.42, −0.24]), executive functioning-abstraction/shifting(−0.30 [−0.40, −0.20]), speed of information processing (−0.26 [−0.38, −0.15]), delayed memory (−0.26 [−0.35 to −0.16]), executive functioning-inhibition (−0.25 [−0.38, −0.13]), executive functioning-updating/working memory (−0.22 [−0.31, −0.12]), and attention (−0.21 [−0.31 to −0.12]). No significant deficits in language, visuospatial or motor functioning. Controls: Minimal exposure to cannabis.
Smith 2014	11—NR	462 controls, 277 users	Cannabis users	NR	No details provided	No significant deficits in inhibition control, attention, or reaction time. Controls: nonusers.
Psychosocial outcomes						
Bennett 2008	10—cohort	NR	Population arrested, committed crime	Self-reports, urinalysis	Maryland Scientific methods Scale	Increased odds of crime with cannabis use (OR = 1.51 [1.31, 1.74]). Control: never-users.
Dellazizzo 2019	12—cross-sectional (8), prospective (2), retrospective (2)	3873	Patients with severe mental illness	Self-reports, urine tox/drug screen	Funnel plot for publication bias; GRADE	Increased odds of committing violence with cannabis use (OR = 3.02 [2.01, 4.54]), with increased adjusted odds (OR = 2.82 [1.89, 4.23]). Controls: not reported.
Johnson 2017	16 cross-sectional, longitudinal	NR	Adolescents	Self-reports	Funnel plot for publication bias	Increased odds of physical dating violence victimization (OR = 1.54 [1.22, 1.93]) and physical dating violence perpetration (OR = 1.45 [1.20, 1.76]) with cannabis use. Controls: not reported.

Note that reviews that did not undertake meta-analyses across studies are summarised in supplementary appendix 4, http://links.lww.com/PAIN/B116.
OR, odds ratio; SMD, standardized mean difference.

Table 2

Reviews (with meta-analyses)[1] of physical health outcomes associated with cannabis.

Author	# Of included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
Pulmonary outcomes						
Ghasemiesfe 2018	22—cross-sectional (12), prospective cohort (10)	NR	Adolescents and adults using cannabis	Self-reports	Cochrane Risk of Bias Tool (for trials); Newcastle–Ottawa Scale (for observational studies)	In prospective cohort studies, with current cannabis use, increased odds of chronic cough (OR = 1.73 [1.21, 2.47]), chronic sputum production (1.53 [1.08, 2.18]), wheezing (2.01 [1.50, 2.70]), and bronchitis. In cannabis users, increased risks for cough (RR = 2.04 [1.02, 4.26]), sputum production (RR = 3.84 [1.62, 9.07]), wheezing (OR = 1.55 [1.23, 1.94]), and shortness of breath (OR = 1.23 [0.97, 1.56]). In cross-sectional studies, with cannabis use, increased risks for cough (RR = 4.37 [1.71, 11.19]), sputum production (RR = 3.40 [1.99, 5.79]), wheezing (RR = 2.83 [1.89-4.23]), and shortness of breath (RR = 1.56 [1.33-1.83]). Prospective cohort cannabis use and bronchitis episodes (OR = 2.3 [1.2, 4.4]), cross-sectional and bronchitis use (RR = 2.28 [0.68, 7.72]). Controls: nonusers
Cancer outcomes						
deCarvalho 2015	10 -case-control studies	5732 cases, 8199 controls	Cancer patients	NR	CONSORT statement	No increased risk of head and neck cancer compared to nonusers.
Ghasemiesfe 2019	25-case-control (19), cohort (5), cross-sectional (1)	NR	Cancer patients	NR	Newcastle–Ottawa	With >10 y of cannabis use, increased risk of testicular germ cell tumors (TGCT) (OR = 1.36 [1.03, 1.81]), and nonseminoma (1.85 [1.10, 3.11]). Controls: nonusers.
Gurney 2015	3—case-control	719 cases, 1419 controls	Patients with testicular cancer	Self-reports/survey	Newcastle–Ottawa quality scale	Increased risks of TGCT with ever-use of cannabis (OR = 1.19 [0.72, 1.95]), former use (1.54 [0.84, 2.85]), current use (1.62 [1.13, 2.31), weekly use (1.92 [1.25, 2.72]), and >10 y of use (1.50 [1.08, 2.09]). Increased risks of nonseminoma development with current use (OR = 2.09 [1.29, 3.37]), weekly use (2.59 [1.60, 4.19]), and >10 y use (2.40 [1.52, 3.80]). No association found between ever-use or former use and TGCT. Controls: never-users
Maternal and foetal outcomes						
Conner 2016	31—Retrospective cohort (13), prospective cohort (13), case-control (5)	7851 cases 124, 867 controls	Pregnant women using cannabis during pregnancy who experienced in utero exposure to cannabis	Self-reports, urine, meconium, oral fluid, umbilical cord	Funnel plot for publication bias; + 6 quality indices	With cannabis use in pregnancy, increases risks of low birth weight (LBW) (RR = 1.43 [1.27, 1.62]) and preterm delivery (1.32 [1.14, 1.54]), small for gestational age (SGA) (1.96

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Table 2 (*continued*)

Author	# Of included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
						[1.57, 2.45]), and placental abruption (1.60 [1.29, 2.02]). With weekly cannabis use, increased risks of LBW (RR = 1.90 [1.44, 2.45]) and preterm delivery (2.04 [1.32, 3.17]). Controls: women who did not use cannabis during pregnancy.
Gunn 2016	25—cohort (22), cross-sectional (1), case-control (1)	NR	Pregnant women using cannabis during pregnancy who experienced in utero exposure to cannabis	NR	"National Collaborating Centre for Environmental Health's tool" (for cross-sectional studies); "Critical Appraisal Skills Programmes making sense of evidence" (for cohort studies)	With smoking cannabis use pregnancy, increased risks of anemia (OR = 1.36 [1.10, 1.69]), low birth weight (P = 1.77 [1.04, 3.01]), and NICU stay (OR = 2.02 [1.27, 3.21]). Control: women who did not use cannabis during pregnancy.
English 1997	5—cohort	32, 483	Women using cannabis giving birth to live-born infants	Self-reports, urine	No details provided	No significant association with low birth weight in mothers using cannabis during pregnancy. Control: women who did not use cannabis during pregnancy.

Note that reviews that did not undertake meta-analyses across studies are summarised in supplementary appendix 5, http://links.lww.com/PAIN/B116.
OR, odds ratio; TGCT, testicular germ cell tumor.

associated with a greater likelihood of developing a cannabis use disorder, more psychosocial problems, and poorer cannabis-cessation outcomes relative to using cannabis alone.[100] Cannabis has been reported to have an overall negative impact on male fertility with decreased sperm motility, morphology, and count.[106] In one review of cannabis and all-cause mortality, it was concluded that there were too few studies to draw a clear relationship, but from the limited available evidence, there does not seem to be an increased risk of mortality due to motor vehicle collisions (MVC) for cannabis users in the general population.[18] Finally, one review found an inconsistent association between cannabis use and psychological problems and antisocial behaviors. However, the extent and strength of these associations were much less than conventionally assumed in society. Review authors concluded that although there is no strong evidence for or against the effects of cannabis, there is a trend to suggest cannabis use and its negative association for psychological and social health.[82]

3.4. Psychiatric harms

3.4.1. Suicidality

From the included systematic reviews on suicidality (**Table 1**), available meta-analyses have suggested increased risks of suicidal ideation with any use (odds ratio [OR] = 1.43 [1.13, 1.83]),[14] (OR = 1.50 [1.11, 2.03]),[49] and heavy use (OR = 2.53 [1.00, 6.39])[14] of cannabinoids. Risk of suicide attempt for any use was—OR = 2.23 [1.24, 4.00],[14] OR = 3.46 [1.53, 7.84],[49] and for heavy use—OR = 3.20 [1.72, 5.94].[14] Risk for death by suicide with chronic use was—OR = 2.56 [1.25, 5.27].[14] In one review without meta-analysis, there was an increased risk of suicidal ideation behavior in cannabis users, with a greater risk in males.[16]

3.4.2. Psychosis outcome

Cannabis and cannabinoids were associated with nonadherence to antipsychotic medication with any use (OR = 2.46 [1.97, 3.07]),[38] or current use vs nonusers (OR = 5.79 [2.86, 11.76])[38] (**Table 1**). For onset of psychosis, adjusted odds of ever-use of cannabis and psychotic outcome were OR = 1.41 [1.20, 1.65],[94] ever-use and psychotic disorders (OR = 2.58 [1.08, 6.13]),[94] lifetime use and transition to psychosis (OR = 1.13 [0.856, 1.524]),[74] heavy use and psychotic/schizophrenia outcome (OR = 2.09 [1.54, 2.84]),[94] (OR = 3.90 [2.84, 5.34]),[85] psychotic symptoms (pooled OR = 3.59 [2.42, 5.32]),[85] and diagnosis of schizophrenia/psychotic disorders (OR = 5.07 [3.62, 7.09]).[85] For relapse of psychosis, there was an increased risk with continued cannabis use vs nonusers (effect size d = 0.36 [0.22, 0.50]), and continued vs discontinued use (d = 0.28 [0.12, 0.44]).[111] There was no increased risk for length of stay in a psychiatric facility when comparing continued use to non-use of cannabis (d = 0.36 [0.13, 0.58]).[111] Two reviews estimated that cannabis use reduced age at onset of psychosis by approximately 2.7 years.[75,96] There were also several reviews without meta-analysis that explored the association between cannabis and psychosis outcomes. Cannabis use was found to increase the risk of psychosis,[3] with early and frequent use associated with developing psychosis.[88] Cannabis use was also found to be associated with "psychotic-like events" in a dose–response manner, with more frequent cannabis use increasing the risk of developing schizophrenia.[105] In individuals diagnosed with psychosis who used cannabis, there was an increased rate of relapse, rehospitalization, and decreased treatment adherence

Table 3

Reviews of motor vehicle accident risk associated with cannabis.

Author	# Of included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
Asbridge 2012	9—observational (case-control, culpability designs)	49, 411	Drivers under influence of cannabis	Blood analysis	Newcastle–Ottawa quality scale	Increased risks with cannabis use of motor vehicle collisions (MVC) (OR = 1.92 [1.35, 2.73]) and fatal collisions (OR = 2.10 [1.31, 3.36]). Control: unimpaired drivers
Calabria 2010	19—cohort, case-control	47, 578	Drivers under influence of cannabis	Self-reports, laboratory analysis	"McGrath–Saha Quality Index" score	Only modest associations found when comparing THC-positive drivers to drug and alcohol-free drivers. Drivers with higher THC levels (>5 ng/ML), had greater risk of culpable driving, with a dose–response effect of heavy cannabis use associated with greater risk of culpable driving than light use.
Elvik 2013	28	NR	Drivers at fault in accident	Self-reports, laboratory analysis	Funnel plot for publication bias; customized quality score	Increased risks of property damage (OR = 1.48 [1.28, 1.72]). No significant associations for fatal collisions, crash risk, or injury. Controls: unimpaired drivers.
Hartman 2013	29—case-control, experimental data, simulator experiments, on-road studies	NR	Drivers with cannabis intake	Blood levels	No details provided	Increased crash risk, cannabis driving even without alcohol associated with substantial morbidity and mortality on roadways.
Hostiuc 2018	24—16 (case control), 3 (surveys), 4 (retrospective cohort), 1 (cross-sectional)	245, 779 drivers	Drivers involved in collisions, or drivers taking cannabis	Self-reports, blood, urine	Predefined study quality inclusion criteria; funnel plot for publication bias	In unadjusted analysis, increased risks of MVC when driving under influence of cannabis (OR = 1.889 [1.580, 2.258]). Using cannabis-blood analysis increased risks of MVCs (1.97 [1.35, 2.87]), and increased risks with chronic cannabis use (1.75 [1.21, 2.53]) and with self-reports (1.94 [1.26, 2.99]). After adjustment, no significant association with collisions or injury remained. Increased adjusted odds of death with driving under influence of cannabis (1.43 [1.12, 1.83]). Controls: unimpaired drivers.
Li 2012	9—case control (5), cross-sectional (2), cohort (2)	4207 drivers in crash, 88, 993 not involved	Drivers involved in collisions, or drivers taking cannabis	Self-reports, blood, urine	"Centre for Occupational and Environmental Health, University of Manchester critical appraisal checklist"; funnel plot for publication bias	Increased risks of MVC with cannabis users (OR = 2.66 [2.07, 3.41]). Controls: unimpaired drivers.

(*continued on next page*)

Table 3 (*continued*)

Author	# Of included studies and designs	Participants (n)	Population	Assessment of cannabinoid exposure	Assessment of study quality/risk of bias	Results of meta-analysis
Rogeberg 2019	13—case-control, culpability	78, 023	Drivers involved in MVA at fault	NR	No details provided (review limited to culpability studies)	Increased risks of MVC with cannabis use (OR = 1.28 [1.16, 1.40]). Controls: unimpaired drivers

THC, tetrahydrocannabinol.

compared to individuals with psychosis not using cannabis.[94] Finally, although one review found no association between cannabis use and transition to psychosis, they did find a trend towards cannabis provoking and enhancing subclinical symptoms of psychosis in high-risk individuals.[81]

3.4.3. Depression, mania, and phobia

For included systematic reviews on depression (**Table 1**), meta-analyses have suggested increased risks for any cannabis use and depression (OR = 1.17 [1.05, 1.30]),[78] (OR = 1.33 [1.19, 1.49]),[32] use in adolescence and depression in young adulthood (OR = 1.37 [1.16, 1.62]),[49] and any use and depression in adolescents (OR = 1.34 [1.17, 1.54][32]) and young adults (OR = 1.22 [0.99, 1.51]).[32] Risks were also increased for any use and depressive symptoms (OR = 1.20 [1.01, 1.42]),[32] diagnosis of depression (OR = 1.41 [1.21, 1.65]),[32] comorbid anxiety and depression (OR = 1.68 [1.17, 2.40]),[70] as well as for heavy use and depression (OR = 1.49 [1.15, 1.94]),[94] (OR = 1.62 [1.21, 2.16]).[78] In individuals without a diagnosis of bipolar disorder, any cannabis use was associated with increased risks of the onset of mania (OR = 2.97 [1.80-4.90])[46] (**Table 1**). One review found evidence for an association between cannabis use and greater symptom severity, number of symptoms, and less occurrence of remission for mania and depression compared to nonuse.[83] One review without meta-analysis found no evidence for cannabis being associated with symptoms of panic or social phobia.[83]

3.4.4. Anxiety and post-traumatic stress disorder

For outcomes of anxiety (**Table 1**), any use was associated with increased risk of anxiety (OR = 1.28 [1.06, 1.54]),[70] (OR = 1.36 [1.02, 1.81]).[32] In one review exploring the relationship between cannabis and post-traumatic stress disorder, cannabis use within the past month was associated with negative course, worse outcomes, and greater symptom severity at follow-up compared to abstinence.[83] Cessation of cannabis use was associated with less severe symptoms and greater response to treatment.

3.4.5. Crime and violence

Meta-analyses of other psychosocial harms indicate higher risks of crime (OR = 1.51 [1.31, 1.74]),[8] intimate partner violence victimization (OR = 1.54 [1.22, 1.93]),[68] and violence in cannabis users with severe mental illness (adjusted OR = 2.82 [1.89, 4.23]).[25]

3.5. Neurocognitive harms

In reviews of cognitive and behavioral outcomes (**Table 1**, Supplementary index 4, available at http://links.lww.com/PAIN/B116), meta-analyses and systematic reviews suggested impairment of cognitive flexibility,[12] reasoning,[99] association,[99] speed of information processing,[12,113] attention,[43,51,52,104,112,113] verbal memory,[12] verbal immediate recall,[111] verbal delayed recall,[111] verbal recognition,[111] working memory,[10,12,51,99,111,113] prospective event-based memory,[101] prospective time-based memory,[101] prospective memory,[111] total memory,[111] and language.[12,52,104,112,113] Impairments were found for learning,[10,43,52,112,113] visual learning,[111] verbal learning,[12,111] and forgetting/retrieval.[52,104,112] Reviews also found impairments in visuospatial abilities,[104,113] motor functioning,[52,112,113] perceptual-motor,[52,112] motor inhibition,[12,120] reaction time,[52,112,120] conceptual set-shifting,[12] executive function/abstraction,[43,52,104,112,113] and overall neurocognitive abilities.[43,52,104,113]

3.6. Cardiovascular harms

Available reviews of cardiovascular harms (**Table 2**, Supplementary appendix 6, available at http://links.lww.com/PAIN/B116) provided insufficient evidence to suggest that cannabis use was associated with adverse cardiovascular outcomes, such as hyperlipidemia, acute myocardial infarction, and stroke.[107] There was inconsistent evidence to suggest that weekly cannabis use may be associated with an increased risk for cardiovascular mortality,[69,107] and no evidence for an increase in all-cause mortality. When assessing for dose–response effects, lifetime cannabis use was not found to be associated with cardiovascular mortality, stroke, and coronary heart disease.[107] There was some evidence to suggest that cannabis use can be associated with an increased risk for multifocal intracranial stenosis and acute ischemic stroke requiring hospitalization.[69]

There is a rare form of arteritis known as Buerger disease thought to be linked to cannabis use, with young patients presenting with distal ischemia in their extremities.[21] Although a significant proportion of these patients used cannabis, reviews have concluded that cannabis is not associated with arteritis as concurrent tobacco use is a significant and more likely contributing factor.[53,69] Cases of atrial fibrillation taking place after cannabis smoking have also been reported.[73] Finally, cannabinoid exposure seemed to induce several cardiovascular harms, with tachycardia and hypertension the most frequent symptoms experienced by patients.[107]

3.7. Pulmonary harms

In reviews of prospective cohort studies (**Table 2**), increased risks were found for cough (RR = 2.04 [1.02, 4.26]),[45] sputum production (RR = 3.84 [1.62, 9.07]), wheezing (OR = 1.55 [1.23, 1.94]), dyspnea (OR = 1.23 [0.97, 1.56]), and bronchitis (OR = 2.3 [1.2, 4.4]).Across cross-sectional studies, increased risks were found for cough (RR = 4.37 [1.71, 11.19]),[45] sputum production (RR = 3.40 [1.99, 5.79]), wheezing (RR = 2.83 [1.89-4.23]), and dyspnea (RR = 1.56 [1.33-

1.83]). Numerous cases of COPD, emphysema, and lung hyperinflation were also identified in cannabis smokers.[86]

There was some evidence to suggest a relationship between COPD and inhalational cannabis (Supplementary appendix 6, available at http://links.lww.com/PAIN/B116), but insufficient evidence for airflow obstruction.[86] Cannabis smoking was associated with common symptoms including wheezing, dyspnea, phlegm production, chest tightness, and also with pulmonary infections such as aspergillosis, Legionnaires disease, tuberculosis, and other opportunistic infections.[45,86]

There was some evidence to indicate precancerous lung changes with cannabis because bronchial biopsy of non–tobacco-smoking cannabis smokers identified changes such as squamous cell metaplasia, increased mitotic figures, and columnar cells.[89] There was no evidence of lung bullae in cannabis smokers.[125] There was also no consistent association between long-term cannabis smoking and lung function or airway hyperactivity.[126]

3.8. Cancer-related harms

Across systematic reviews of cancer-related outcomes (**Table 2**, Supplementary appendix 6, available at http://links.lww.com/PAIN/B116), the available meta-analyses showed increased harms with both any-use and current use of cannabis and testicular germ cell tumor (TGCT) (OR = 1.62 [1.13, 2.31]),[55] as well as >10 years use and TGCT (OR = 1.50 [1.08, 2.09]),[55] (OR = 1.36 [1.03, 1.81])[44] and nonseminoma TGCT (OR = 1.85 [1.10, 3.11]).[44] There was no increased risk of non-Hodgkin lymphoma,[66] lung, head and neck cancer, anal, penile, seminoma-TGCT, colorectal or overall cancer,[18,60,66] with one review reporting insufficient evidence to assess risk for lung, oral, pharyngeal, and esophageal cancers.[44] reported with cannabis use. However, in non–tobacco-smoking cannabis users, there does seem to be increased risks for primary glioma, and prostate, cervical, testicular, bladder, and oropharyngeal cancer.[18,60,66] In pediatric cancers, parental use of cannabis was weakly associated with increased risks of childhood leukemia, astrocytoma, rhabdomyosarcoma, and neuroblastoma.[60,66]

3.9. Maternal and fetal harms

For maternal and fetal health outcomes with cannabis during pregnancy (**Table 2**), one meta-analysis indicated risk of low birth weight (RR = 1.43 [1.27, 1.62]).[20] Also, cannabis use during pregnancy was associated with reduced neonatal length, smaller head circumference, longer neonatal intensive care unit stay, shorter gestational age, and maternal anemia[54] (supplementary table 6, available at http://links.lww.com/PAIN/B116). In reviews without meta-analysis, one review found that the relationship between prenatal cannabis exposure and effects is unclear but there are potential harms to neuropsychological functioning. These include deficits in attention, perceptive abilities, cognitive function, memory, impulse control, IQ, and reading comprehension in children aged >6 years.[114] Similarly, another review found infants prenatally exposed to cannabis had poorer attention skills, increased depressive symptoms, and future delinquency seen into adolescence.[130]

3.10. Motor vehicle collisions

Risks of MVC with cannabis use (**Table 3**) were (OR = 1.92 [1.35, 2.73]),[4] (OR = 1.22 [0.82, 1.81]),[65] (OR = 2.66 [2.07, 3.41]),[79] (OR = 1.28 [1.16, 1.40]),[109] fatal collisions (OR = 2.10 [1.31, 3.36]),[4] and property damage due to MVC (OR = 1.48 [1.28, 1.72]).[31]

3.11. Harms associated with cannabinoids

Reviews of cannabinoids have identified various harms associated with intoxication (Supplementary Appendix 7, available at http://links.lww.com/PAIN/B116). These included tachycardia, agitation, drowsiness, nausea/vomiting, hallucinations, irritability, hypertension, psychosis, palpitations, loss of consciousness, chest pain, anxiety, and hallucinations.[2,23,57] There have been various case reports of acute kidney injury with cannabinoid use, such as acute tubular necrosis, acute interstitial nephritis, rhabdomyolysis, extreme hypovolemia, and prerenal azotemia.[84] Individuals with cannabinoid intoxication presented differently than cannabis intoxication, experiencing higher levels of psychotic symptoms, agitation, aggression, longer hospital admission,[64] and requiring more urgent clinical attention.[124]

3.12. Harms not addressed by included reviews

Although this overview addresses most of the prominent cannabinoid harms for which there are multiple studies, our literature searches identified some harms that were not addressed in any systematic reviews but for which there is emerging evidence.

3.12.1. Harms in immunocompromised patients

There are various studies exploring harms in immunocompromised patients with HIV. First, daily cannabis use was associated with increased risk of developing fibrosis in individuals with chronic hepatitis C (OR = 3.4 [1.5, 7.4]),[63] and was an independent predictor of severe fibrosis even after accounting for alcohol and tobacco use (OR = 2.3 [1.1, 4.8]).[63] However, daily cannabis use was not associated with progression to significant liver fibrosis in patients infected with both HIV and hepatitis C virus (hazard ratio = 1.02 [0.93, 1.12]).[17]

Cannabis use was associated with statistically significant reductions in $CD4^+$ and $CD8^+$ T cells in populations with and without HIV, but there were no AEs and no clinically meaningful associations with these T-cell counts.[19] In other instances, varying frequencies of cannabis use were not associated with significant differences in $CD4^+$ T-cell count.[15,127] There was inconsistent evidence regarding cannabis exposure and adherence to antiretroviral therapy.[27] Cannabis exposure was not found to be associated with an increased rate of progression to AIDS,[27,118] or increased risks of oral HPV infection in both patients with and without HIV. Finally, daily cannabis users experienced more severe HIV symptoms and medication side effects than less frequent users.[13]

3.12.2. Maternal and fetal harms

For fetal harms with cannabis use in pregnancy not addressed by included reviews, one case-control study found no association between sudden infant death syndrome and maternal cannabis exposure at conception (adjusted OR = 1.1 [0.6, 2.0]),[71] during pregnancy (adjusted odds ratio OR = 0.6 [0.3, 1.6]), or postnatally (adjusted odds-ratio [aOR] = 0.6 [0.2, 1.8]). However, an increased risk of sudden infant death syndrome with paternal cannabis use at conception (aOR = 2.2 [1.2, 4.2]),[71] during pregnancy (aOR = 2.0 [1.0, 4.1]), and postnatally (aOR = 2.8 [1.1, 7.3]) was found. In one study of postnatal growth, a dose–response relationship between head circumference and cannabis exposure was found,[40,41] with heavy maternal exposure (6 or more joints per week) associated with the smallest head

circumference, persisting until 12 years of age,[42] but not seen at 13 to 16 years of age.[39] Infants of heavy cannabis users were also lightest at birth, but no differences in height, weight, ponderal index, or onset of puberty were seen at 13 to 16 years of age. There were also mild developmental abnormalities reported in children born to women who used cannabis during pregnancy, such as delay in visual system development shortly after birth, increased tremor, and startle.[39] None of these effects were seen at 1 month, or on ability tests at 6 and 12 months. Behavioral effects were subsequently reported at 36 and 48 months but not at 60 and 72 months.[39] At 12 years of age, children exposed to cannabis in utero did not differ in IQ scores, but did have small differences in certain higher cognitive processes (perceptual organization and planning).[39]

3.13. Occupational injuries and unemployment

Reports of associations between cannabis use in the previous year and occupational injuries have been investigated, but risks of minor occupational injuries (OR = 1.17 [0.74, 1.86]),[30] work-related accidents at work requiring medical attention (OR = 0.91 [0.43, 1.89]), or work-related traffic accidents (OR = 3.01 [0.89, 10.17]) did not remain significant after adjusting for confounders.[30] In a cross-sectional study of high school students, those who reported using cannabis 1 to 9 times in the previous 30 days reported a significantly increased risk of occupational injury (OR = 1.37 [1.06, 1.77])[116] even after adjusting for confounders, with heaviest use (40 or more times in the last 30 days) conferring a significantly higher risk (OR = 2.47 [1.64, 3.71])[116] compared to nonuse.[8,9] However, in another study of youth, lifetime cannabis use on 1 to 10 occasions (OR = 1.04 [0.94, 1.15])[28] or 11 or more occasions (OR = 1.10 [0.99, 1.21]) was not associated with incidence of occupation injury.[28] In a study investigating cannabis use and unemployment, no significant association was found for men (OR = 0.81 [0.23, 2.79])[102] or women (OR = 0.78 [0.27, 2.24]).[102] These findings were consistent with another study that also found cannabis use unrelated to unemployment (OR = 0.96 [0.91, 1.01]).[77] In one study of chronic cannabis users who started in adolescence, a statistically significant association was found with unemployment 3 decades later, at 43 years of age, (aOR = 3.51 [1.13, 10.91]).[132] However, low socioeconomic status has been reported to be a major confounding factor and difficult to account for within these studies.

3.13.1. Cannabis addiction, illicit drug use, and overdose injuries

In one study of cannabis use leading to problematic cannabis use or addiction, current use was reported to be significantly associated with cannabis use disorder at follow-up (aOR = 9.5 [6.4, 14.1]).[9] In a prospective analysis, an increased frequency of daily cannabis use was weakly associated with progression to cannabis use disorder (OR = 1.08 [1.04, 1.13]).[22] In one longitudinal study, cannabis users were most likely to use heroin and cocaine at follow-up, with earlier age of cannabis use associated with greater odds of using heroin and cocaine.[34] In overdose injuries within pediatric populations, one study found that over a 3.5-year period, 7 children aged 11 to 33 months were admitted to a pediatric intensive care unit with accidental cannabis poisoning, symptoms of drowsiness, and coma, sometimes requiring mechanical ventilation.[76] In another study of calls to an Arizona poison control center, 49 calls were reported for accidental ingestions in children aged 7 years and younger, with most common symptoms being lethargy, inability to walk, coma, and vomiting, and occasional respiratory depression and aspiration pneumonia.[80]

3.14. Dose–response effects across reviews

There were several reviews that reported doses of cannabis, cannabinoids, or THC consumed by patients and correlated them with harms experienced. Here, we present an overview of the associations from these reviews.

Five reviews reported dose–response effects for the effects of cannabis on driving (accidents or driving skills). Calabria et al.[18] and found modest associations between THC blood levels and driving culpability, with THC levels greater than 5 ng/mL correlating with a higher risk of culpable driving. Hostiuc et al.[65] found 3 studies indicating that a THC blood level above 0.5 ng/mL was associated with an increased risk of unfavorable traffic events (OR = 2.08, [0.35-12.43]). Li et al.[79] did not report specific doses, but found that the risk of crash involvement increased in a dose-dependent manner with increasing concentrations of 11-nor-9-carbody-THC (THC-COOH), categorizing risks for low (OR = 1.1, [0.5-2.6]), medium (OR = 1.8, [1.0-3.5]), and high (OR = 3.3, [1.9-5.9]). Asbridge et al.[4] found higher amounts of THC in blood analysis of studies of fatally injured drivers than those of studies investigating nonfatal injuries to drivers. They also found 3 studies showing that raised THC concentrations were associated with an increased crash risk but did not have enough data to examine dose–response effects. Hartman et al.[59] reported dose–response effects of THC on driving performance, with low (13 mg13 mg) and moderate (17 mg17 mg) doses of THC.

Four reviews reported dose–response effects of cannabis, cannabinoids, or THC on psychological functioning and cognition. Blithikioti et al.[10] found that individuals administered intravenous THC, vaporized cannabis, and oral nabilone had deficits in verbal learning and memory, with greater deficits in attention in individuals with lower CBD/THC ratios. They also reported that smoked or vaporized cannabis impaired reaction times and motor control in a dose-dependent manner but did not state the dose amounts. Oomen et al.[99] found that pulmonary administration of THC is associated with the greatest inhibition, with the mean dose showing impairment being significantly higher than that which did not show an effect (21.8 ± 14.9 vs 11.1 ± 7.8 mg; $P = 0.036$). They also reported that the pulmonary dose of THC that impaired reasoning tasks was not significantly different from that which was not associated with an impairment (13.8 ± 6.0 vs 14.0 ± 9.2 mg; $P = 0.952$). Furthermore, the study found that the pulmonary dose of THC in assessments that showed an impairment on memory was not significantly different from assessments that did not show an impairment (25.0 ± 36.3 vs 35.7 ± 37.9 mg; $P = 0.275$). Akram et al.[2] reported the doses of cannabinoids and compared the psychological effects 2 mg and 3 mg of cannabinoids compared to placebo. They reported significant differences between placebo and 2 mg, but very few differences between the 2 mg and 3 mg doses. Skalski et al.[117] found the strongest effects on cognitive deficits for pulmonary administration and higher doses of THC, but did not report on specific doses administered.

Finally, there were several reviews reporting dose–response effects that could not be analyzed. Some of these reviews reported dose–response effects based on frequency and duration of administration as opposed to the physical quantity of cannabis,[43,44,52,85,94,126] whereas others were unable to correlate doses with effects due to a lack of studies reporting dose information.[10,51,57]

4. Discussion

This overview encompasses evidence of harms associated with cannabis and cannabinoids generally relevant to individuals being treated for pain. As an overview, we included 79 systematic reviews of cannabinoid-related harms including psychiatric and psychosocial harms, cognitive/behavioral effects, motor vehicle accidents, cardiovascular, respiratory, cancer-related, maternal/fetal, and general harms. Most included reviews (n = 72) addressed cannabis (smoked, vaporized, or ingested), whereas only 7 reviews addressed other cannabinoids. Included reviews covered, in total, over 2200 studies/reports each involving a wide range of participants (single case reports to cohort study of 172,718). Evidence sources included uncontrolled cohort studies, health database studies, case reports, toxicology reports, analytical surveys, simulator experiments, and some RCTs. Available evidence suggests variable associations between cannabis exposure (ranging from monthly to daily use based largely on self-report) and the following harms: psychosis (lifetime occurrence, earlier onset, and transition), motor vehicle accidents, respiratory problems (coughing, wheezing, increased sputum, and bronchitis), low birth weight (in infants of cannabis exposed mothers), and short-term AEs.

Integrating this large and diverse body of evidence into a rational risk–benefit perspective on the use of cannabinoids for pain management is extremely challenging and requires a thorough evaluation of study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias.[56] Previous efforts to contextualize harms associated with medicines include the development of a "multicriteria decision analysis" framework that considers physical, psychological, and social harms both to the recipient of the drug and also to others.[98] Such an approach has been applied to over-the-counter analgesic drugs[92] and could be beneficial here but for cannabinoids, this would be much more difficult and complex. Multicriteria decision analysis of cannabinoids for chronic pain could include multidisciplinary panels of experts from diverse stakeholder perspectives. Such a project is beyond the scope of this overview but should be considered a future research priority.

Several limitations of this overview should be acknowledged. Regarding directness of evidence, there may be differences in cannabinoid dose exposure between studies represented in this overview and that which might occur during carefully supervised chronic pain management. For example, if cannabinoid analgesia reported at low doses (Wallace et al., *In Press*) generalizes to real-world settings, carefully supervised cannabinoid administration could provide meaningful efficacy at doses low enough to avoid important harms. Threats to validity in many studies incorporated within this overview include lack of a control group and potential for confounding. However, carefully interpreted observational studies can provide insights in the absence of stronger evidence and/or for identification of rare and important harms. The majority of evidence in this review is derived from reviews of nonmedicinal cannabis use thus challenging the directness of evidence to individuals receiving cannabinoids to treat pain. However, it is important to recognize that some proportion of nonmedicinal cannabis use may include self-treatment of pain. Therefore, harms evidence related to nonmedicinal cannabis use should not be entirely disregarded when developing general risk–benefit considerations. Until more high-quality studies and studies involving longer-term administration of cannabinoids are available, the data provided in this overview should at least be considered when making risk–benefit decisions in the setting of pain management. Another challenge relates to the cannabinoid of exposure because most reviews reported interventions broadly as "cannabis" or "cannabinoids" and did not always specify route of administration. Furthermore, evidence on some cannabinoids, particularly cannabis-based medicines and phytocannabinoids, was lacking.

Thus, we have identified several needs for this area including: (1) better assessment and reporting of cannabinoid harms in pain RCTs; (2) expanded population research methods to track nonmedicinal cannabis use specific to pain treatment; (3) additional epidemiological studies correlating cannabinoid harms to dose and duration of exposure; and (4) more population studies about synthetic cannabinoids.

In conclusion, the public health impact of harms associated with cannabis and cannabis-based medicine is a growing area of investigation, given the expanding legalization and widespread availability of cannabis around the world. Current evidence, mostly from the setting of nonmedicinal use, suggests that cannabis exposure is associated with higher risks of psychosis, motor vehicle accidents, respiratory problems, testicular cancer, low birth weight, and short-term AEs. Expanded research in this area is sorely needed to better determine causality and to describe any other as yet unreported harms. In the meantime, this evidence and the safety signals it suggests should be carefully considered when making risk–benefit considerations about the use of cannabinoids to treat chronic pain.

Conflict of interest statement

L. Degenhardt has received untied educational grants from Reckitt Benckiser, Indivior, Munipharma, and Seqirus for the conduct of postmarketing surveillance studies of opioid medications. M. Di Forti reports grants from MRC and personal fees from Janssen, outside the submitted work. A. Moore has nothing to report. S. Haroutounian has received research support from Pfizer Inc (ASPIRE neuropathic pain grant program) and DISARM therapeutics, and consulting fees from Medoc Ltd and Rafa Laboratories. A.S.C. Rice is Chair of the Presidential Task Force of the IASP, during the conduct of the study; A.S.C. Rice also reports, during the conduct of the study; personal fees from Imperial College Consultants; and other from Spinifex/Novartis, outside the submitted work. In addition, A.S.C. Rice has a patent null pending. M. Wallace reports personal fees from Insys, outside the submitted work. I. Gilron reports personal fees from Adynxx, Biogen, Eupraxia, Novaremed, and Teva, and nonfinancial support from Canopy Health, Toronto Poly Clinic, and CannTrust, outside the submitted work. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B116, http://links.lww.com/PAIN/B117, http://links.lww.com/PAIN/B118, and http://links.lww.com/PAIN/B119.

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