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A Mapping Literature Review of Medical Cannabis Clinical Outcomes and Quality of Evidence in Approved Conditions in the USA from 2016 to 2019

Sebastian Jugl[a, b] Aimalohi Okpeku[a, b] Brianna Costales[a, b] Earl J. Morris[a, b] Golnoosh Alipour-Haris[a, b] Juan M. Hincapie-Castillo[a, b] Nichole E. Stetten[c] Ruba Sajdeya[d] Shailina Keshwani[a, b] Verlin Joseph[d] Yahan Zhang[a, b] Yun Shen[a, b] Lauren Adkins[e] Almut G. Winterstein[a, b] Amie Goodin[a, b]

[a]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [b]Center for Drug Evaluation and Safety (CoDES), University of Florida, Gainesville, FL, USA; [c]Occupational Therapy, University of Florida, Gainesville, FL, USA; [d]Epidemiology, University of Florida, Gainesville, FL, USA; [e]Health Sciences Center Libraries, University of Florida, Gainesville, FL, USA

Keywords

Medical marijuana · Cannabis · Cannabinoids · Cannabidiol · Marijuana efficacy · Commonly recommended conditions for marijuana treatment · Marijuana clinical outcomes

Abstract

In 2017, a National Academies of Sciences, Engineering, and Medicine (NASEM) report comprehensively evaluated the body of evidence regarding cannabis health effects through the year 2016. The objectives of this study are to identify and map the most recently (2016–2019) published literature across approved conditions for medical cannabis and to evaluate the quality of identified recent systematic reviews, published following the NASEM report. Following the literature search from 5 databases and consultation with experts, 11 conditions were identified for evidence compilation and evaluation: amyotrophic lateral sclerosis, autism, cancer, chronic noncancer pain, Crohn's disease, epilepsy, glaucoma, human immunodeficiency virus/AIDS, multiple sclerosis (MS), Parkinson's disease, and posttraumatic stress disorder. A total of 198 studies were included after screening for condition-specific relevance and after imposing the following exclusion criteria: preclinical focus, non-English language, abstracts only, editorials/commentary, case studies/series, and non-U.S. study setting. Data extracted from studies included: study design type, outcome definition, intervention definition, sample size, study setting, and reported effect size. Few completed randomized controlled trials (RCTs) were identified. Studies classified as systematic reviews were graded using the Assessing the Methodological Quality of Systematic Reviews-2 tool to evaluate the quality of evidence. Few high-quality systematic reviews were available for most conditions, with the exceptions of MS (9 of 9 graded moderate/high quality; evidence for 2/9 indicating cannabis improved outcomes; evidence for 7/9 indicating cannabis inconclusive), epilepsy (3 of 4 graded moderate/high quality; 3 indicating cannabis improved outcomes; 1 indicating cannabis inconclusive), and chronic noncancer pain (12 of 13 graded moderate/high quality; evidence for 7/13 indicating cannabis improved outcomes; evidence from 6/7 indicating cannabis inconclusive). Among RCTs, we identified few studies of substantial rigor and quality to contribute to the evidence base. However, there are some conditions for which significant evidence suggests that select dosage forms and routes of administration likely have favorable risk-benefit ra-

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Amie Goodin
Pharmaceutical Outcomes and Policy, University of Florida
1225 Center Dr
Gainesville, FL 32610 (USA)
amie.goodin@ufl.edu

tios (i.e., epilepsy and chronic noncancer pain). The body of evidence for medical cannabis requires more rigorous evaluation before consideration as a treatment option for many conditions, and evidence necessary to inform policy and treatment guidelines is currently insufficient for many conditions.

Introduction

Medical cannabis is available to patients by physician order in 33 states and territories in the USA as of 2020. However, at the federal level, cannabis remains classified as a schedule I controlled substance, which limits efficacy and safety investigations [1]. Collectively, "medical cannabis" encompasses various terms used in reference to medical marijuana, cannabis-derived products from the cannabis plant (including cannabinoids), and synthetic cannabinoids (e.g., synthetic delta-9-tetrahydrocannabinol (THC) or dronabinol). States that permit physician-ordered medical cannabis typically require a diagnosed medical condition that is considered qualifying by respective state law permitting its use as treatment or adjuvant. Currently, over 50 medical conditions have been granted a qualifying medical condition status by individual state laws, though there is significant variation between each state's approved conditions [2]. The most frequent medical conditions for approved medical cannabis use nationally are chronic noncancer pain, multiple sclerosis (MS) and other motor neuron disorders, epilepsy, cancer and cancer symptoms, mental health disorders (primarily anxiety disorders such as posttraumatic stress disorder [PTSD]), glaucoma, and symptoms related to irritable bowel diseases [3, 4].

Approximately 12.9% of Americans report past-year cannabis use, with 90.2% using for nonmedical purposes only, 6.2% for medical purposes only, and 3.6% for both purposes [5]. The amount of medical-only cannabis users is higher in states that have enacted medical marijuana laws, where around 17% of cannabis users consumed cannabis for medical reasons in those states [6]. The most common routes of administration of cannabis use in the USA are oral/peroral (e.g., edibles), pulmonary (e.g., smoking, or vaping), and topical [7].

In 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) published a comprehensive scientific review on the effects of cannabis and cannabinoids in the treatment of medical conditions frequently cited for medical cannabis use [8]. The NASEM report included an evidence review of studies evaluating the efficacy and safety of cannabis for selected conditions based on the frequency of use, hypothesized effectiveness, and/or eligibility of the condition for medical cannabis certification across several states. The NASEM report evaluated the body of evidence published in the literature through the year 2016, and the objective of this study is to further expand this work by examining the most recently available evidence. Therefore, the objectives of this review are to (1) identify and map the most recently published clinical and scientific evidence across approved conditions for medical cannabis and (2) evaluate the quality of identified recent systematic reviews.

Methods

Topic Selection

Clinical conditions were selected based on inclusion within the NASEM report, relevance to current trends in medical cannabis-eligible diagnoses, and consultation with subject matter experts and relevant stakeholders (e.g., physicians, patients, and community input). Relevant stakeholders perceived needs in research priorities, and evidence gaps as related to clinical outcomes were assessed via preliminary surveys, interviews, and open-ended discussion. Stakeholders recommended including medical conditions approved in the US state jurisdiction of the study team, in addition to emerging trends in use of medical cannabis applications based on discussion with physicians who were certified to order medical cannabis in this locale. Based on this process, the clinical conditions determined for inclusion for this review were amyotrophic lateral sclerosis (ALS), autism, cancer, chronic noncancer pain, Crohn's disease, epilepsy, glaucoma, human immunodeficiency virus (HIV)/AIDS, MS, Parkinson's disease, and PTSD.

Literature Search and Identification

The search strategy was developed in collaboration with the University of Florida Health Sciences Center Library. For this mapping review, we conducted a systematic search using the following databases: PubMed, Embase, Web of Science, the Cochrane Library, and clinicaltrials.gov. We restricted our search to studies that were published after the NASEM report's inclusion period, between May 2016 and October 2019. Search strings from the NASEM report were replicated, and additional keywords and Medical Subject Headings terms were identified in collaboration with subject matter experts and through literature cross-referencing. Since autism was the only included condition that was not evaluated by NASEM, we employed rapid review strategies and adjusted our date restriction inclusion period from the year 2000 to October 2019 for this condition. We limited our search to English language literature only. Complete search strings are available for all conditions in the see online suppl. files. (For all online suppl. material, see www.karger.com/doi/10.1159/000515069.)

Literature Screening

Screening for eligible studies was conducted in 2 phases. In each phase, publications were either classified as include, exclude,

or uncertain. In the first phase, for each clinical indication, one reviewer screened the identified abstracts for eligibility. Abstracts that were classified as "uncertain" were then screened by a second reviewer. If the second abstract reviewer also classified the abstract as uncertain, the publication was advanced for full-text screening. In the second phase, full-text publications were screened for eligibility for each clinical indication. Publications classified as "uncertain" during full-text screening were then screened by a second reviewer. If the publication was still classified as "uncertain" following a second full-text screening, group review and discussion were required until consensus regarding eligibility was achieved. Other discrepancies between reviewers were resolved via discussion and by a third reviewer, when necessary. Publications were included in qualitative synthesis if they were published between 27 May 2016 and 22 September 2019 and investigated the therapeutic effect, a patient or provider perspective, or utilization of medical cannabis in any form in one of the identified 11 indications or conditions. Additionally, the study had to be conducted in humans. Publications were excluded if they included only preclinical data, if the primary research was conducted exclusively outside the USA, clinical case studies, abstracts-only, letters to the editors, opinion pieces, or editorials.

Data Extraction

The study team created a standardized data extraction tool in Microsoft Excel to capture elements from all included studies. An initial pilot run with the underlying data extraction table was performed in a group setting for training purposes and to ensure consistency. Afterward, for each condition, one reviewer extracted the following data from the eligible studies into the tool: study design, study setting, cannabis intervention type, study period, inclusion and exclusion criteria, indicators for whether special populations were included (e.g., pediatrics and geriatrics), outcomes assessed, outcome definition, change in outcome, and summary of findings. Reviewers presented uncertainties in data extraction in a group discussion meeting for resolution. In instances where a single study was identified as eligible for data extraction for multiple conditions, data were independently extracted as relevant for each condition covered within the study; however, these studies were not counted more than once in overall counts of assessed studies.

Quality of Evidence Assessment

Studies that were classified as systematic reviews with or without meta-analysis were evaluated using the Assessing the Methodological Quality of Systematic Reviews-2 (AMSTAR-2) instrument. The Assessing the Methodological Quality of Systematic Reviews-2 tool was developed to grade the quality of evidence reviewed, organized, and presented within systematic reviews [9]. It consists of 16 items that evaluate the methodological quality of systematic reviews and the risk of bias via a checklist, and each item can be answered with "yes," "partial yes," "no," or "no meta-analysis conducted." Based on weaknesses in critical domains, systematic reviews are then rated as a high-, moderate-, low-, or critically low-quality review. Two reviewers for each condition conducted the evidence grading independently. Disagreements were resolved by a third reviewer, and when necessary, classifications of study design were re-evaluated. Additional reviewers examined studies when needed until the majority consensus on both study design classification and quality of evidence rating was achieved.

Evidence Synthesis

Findings from identified studies were reported in accordance with PRISMA guidelines. Search, screening, and evaluation were conducted in accordance with systematic literature review best practices; however, the structure of this review is more appropriately classified as a mapping review to allow for its broad scope [10].

Studies in each condition were classified according to whether they assessed efficacy and/or safety outcomes. (See online suppl. Tables for outcome definitions.) Studies assessing relevant efficacy outcomes were classified into 1 of 5 categories based on the following classification scheme. Studies were classified as "outcome improved" when the condition improved following medical cannabis treatment; as "outcome worsened" when the condition worsened; as "none" when there was no significant observable change; as "inconclusive" if they specifically indicated that results were inconclusive in their results and discussion section and/or there were multiple outcomes assessed but not all reported in findings; or as "mixed" in cases where multiple outcomes were assessed, but some indicated improvement and others indicated no change or worsening. Study outcome definitions for efficacy by condition were summarized (online suppl. Table 1).

Studies reporting safety outcomes were classified into 4 different categories. Studies were classified as "worsening" when an increase in adverse events as compared to placebo, active comparator, or both groups were reported, or single-arm studies reported side effects or adverse events that might be associated with exposure; as "mixed" when different safety outcomes were assessed, but some indicated no change, while others indicated worsening; as "no change" when no significant changes in safety outcomes when measured against the comparator group were reported, or in the case of single-arm studies, studies not reporting any side effects that might be associated with exposure; or as "inconclusive" when studies specifically described results as inconclusive in the results and discussion section and/or if there were multiple outcomes assessed, but not all reported in findings were classified analogous to the efficacy outcome.

Studies that did not fit into the presented classification scheme assessed outcomes unrelated to efficacy and safety, employed a cross-sectional design, or were utilization studies, all of which were summarized separately. Cross-sectional studies were not included in the classification scheme due to their lack of longitudinal assessment, thus limiting the interpretability of findings for quantifying the evidence base in regard to efficacy and safety. Studies that were classified as "other nonsystematic reviews" (e.g., clinical, narrative, scoping, or undefined) were captured in our search strategy but were not evaluated using the classification schemes described herein.

For visualization purposes, all systematic reviews assessing safety or efficacy outcomes were compiled into an evidence map figure consisting of 5 different dimensions (Fig. 1). The bubble size is proportional to the number of included studies within each condition topic area. The bubble color represents the underlying medical condition. The *x*-axis describes the effect of cannabis in each condition. The *y*-axis represents the quality of evidence assessment score, and notations within the bubbles indicate whether the systematic reviews included meta-analysis. For a more comprehensive insight into the efficacy and safety-related findings of eligible studies, studies were finally organized by the condition-specific outcome, study design type, and directions of findings.

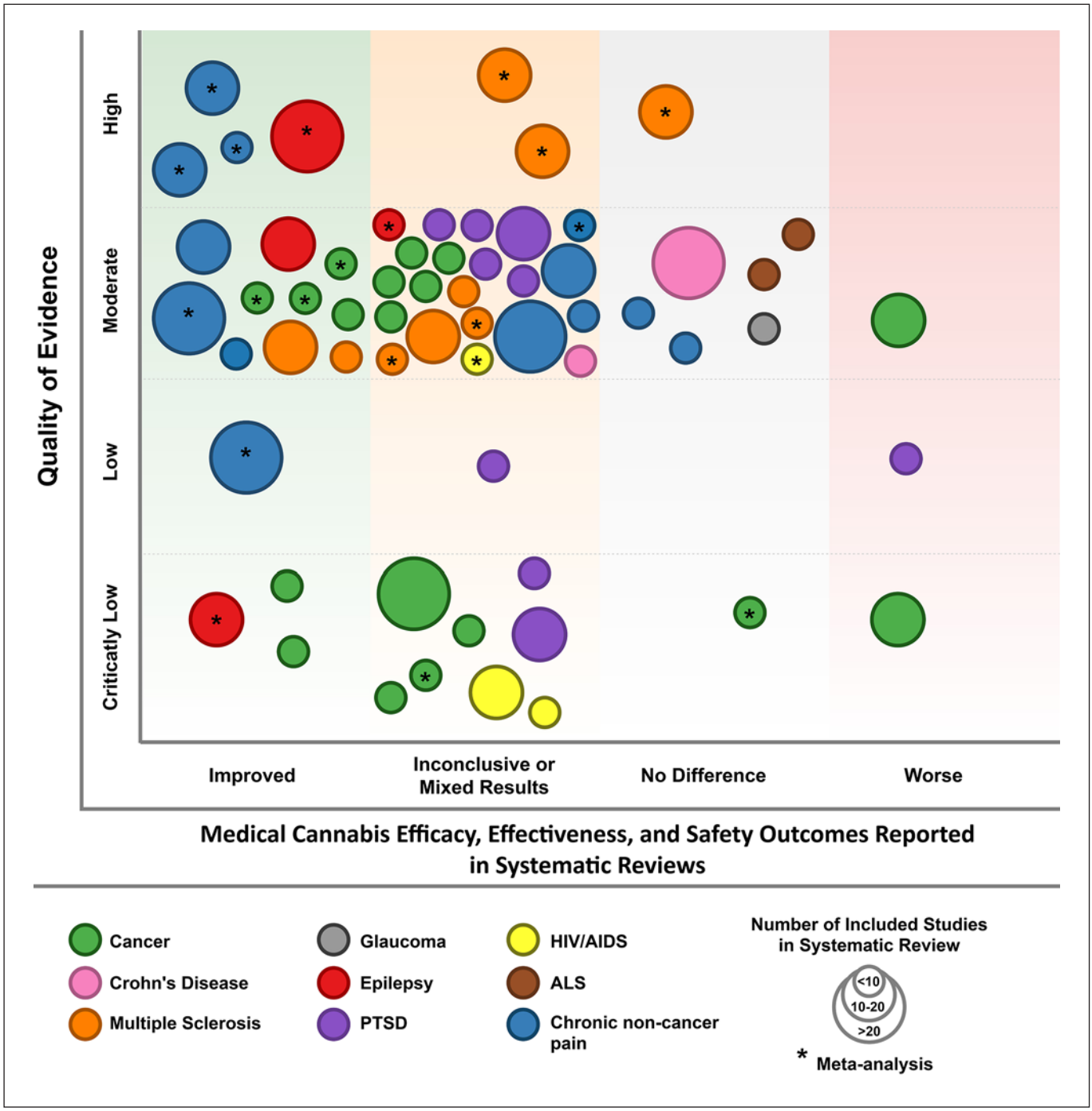

Fig. 1. Quality of evidence among systematic reviews assessing medical cannabis efficacy, effectiveness, and safety outcomes in selected conditions. MS, multiple sclerosis; ALS, amyotrophic lateral sclerosis; PTSD, posttraumatic stress disorder; HIV, human immunodeficiency virus.

Table 1. Medical cannabis study efficacy outcome findings,[1] by condition and study design type

	Total studies	Improvement	Worsening	Mixed	No change	Inconclusive
ALS						
Outcomes: cramp intensity and cramp frequency	2	–	–	–	1	1
Systematic reviews	2	–	–	–	1 [11]	1 [12]
Autism						
Outcome: symptom mitigation	3	2	–	–	1	–
Observational or quasi-experimental studies	3	2 [16, 17]	–	–	1 [15]	–
Cancer						
Outcome: pain	13	5	–	–	2	6
Systematic reviews with meta-analysis	4	2 [24, 25]	–	–	–	2 [220, 221]
Systematic reviews	6	2 [28, 222]	–	–	–	4 [32, 33, 223, 224]
RCTs	2	–	–	–	2 [34, 225]	–
Observational or quasi-experimental studies	1	1 [36]	–	–	–	–
Outcome: nausea and vomiting	2	1	–	–	–	1
Systematic reviews with meta-analysis	1	–	–	–	–	1 [221]
Observational or quasi-experimental studies	1	1 [36]	–	–	–	–
Outcome: cachexia	3	1	–	–	–	2
Systematic reviews with meta-analysis	2	–	–	–	–	2 [37, 221]
Observational or quasi-experimental studies	1	1 [36]	–	–	–	–
Chronic noncancer pain						
Outcomes: pain reduction/quality of life	17	10	–	1	3	3
Systematic reviews with meta-analysis	6	6 [25, 111, 113–115, 226]	–	–	–	–
Systematic reviews	8	2 [121, 122]	–	1 [42]	2 [116, 117]	3 [119, 120, 223]
Observational or quasi-experimental studies	3	2 [227, 228]	–	–	1 [118]	–
Crohn's disease						
Outcome: symptom mitigation	3	1	–	1	–	1
Systematic reviews	1	–	–	–	–	1 [131]
Observational or quasi-experimental studies	2	1 [229]	–	1 [61]	–	–
Epilepsy						
Outcomes: frequency/duration of seizures	19	13	–	–	4	2
Meta-analysis only	3	2 [137, 138]	–	–	1 [230]	–
Systematic reviews	2	2 [116, 143]	–	–	–	–
RCTs	2	2 [136, 145]	–	–	–	–
Observational or quasi-experimental studies	12	7 [134, 135, 139–142, 144]	–	–	3 [144, 146, 147]	2 [149, 150]
Outcomes: health-related quality of life	2	2	–	–	–	–
Observational or quasi-experimental studies	2	2 [144, 146]	–	–	–	–
Glaucoma						
Outcome: intraocular pressure	1	–	–	–	1	–
Systematic reviews	1	–	–	–	1 [116]	–
HIV/AIDS						
Outcome: symptom mitigation	2	1	–	–	–	1
Systematic reviews with meta-analysis	2	1 [120]	–	–	–	1 [115]

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Table 1 (continued)

	Total studies	Improvement	Worsening	Mixed	No change	Inconclusive
Outcome: adherence to ART	5	–	2	–	2	1
Systematic reviews	1	–	–	–	–	1 [231]
Observational or quasi-experimental studies	4	–	2 [172, 232]	–	2 [160, 173]	–
Outcome: viral suppression	2	–	–	–	1	1
Systematic reviews	1	–	–	–	–	1 [231]
Observational or quasi-experimental studies	1	–	–	–	1 [173]	–
MS						
Outcome: spasticity and spasm frequency	6	3	–	1	1	1
Systematic reviews with meta-analysis	3	1 [179]	–	1 [233]	1 [183]	–
Systematic reviews	3	2 [180, 181]	–	–	–	1 [223]
Outcome: pain	4	1	–	–	1	2
Systematic reviews with meta-analysis	2	–	–	–	1 [183]	1 [115]
Systematic reviews	2	1 [180]	–	–	–	1 [223]
Outcome: bladder function	3	2	–	–	1	–
Systematic reviews with meta-analysis	2	1 [184]	–	–	1 [183]	–
Systematic reviews	1	1 [180]	–	–	–	–
Outcome: gait and physical functioning	1	–	–	–	–	1
Systematic reviews	1	–	–	–	–	1 [185]
Parkinson's disease						
Outcome: none assessed	–	–	–	–	–	–
PTSD						
Outcome: symptom mitigation	8	–	–	2	–	6
Systematic reviews	8	–	–	2 [192, 193]	–	6 [12, 122, 194, 195, 197, 234]

ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; MS, multiple sclerosis. [1] Findings for efficacy outcomes were classified for cannabis/cannabinoid treatment relative to placebo or active comparator according to the following: "improvement" if outcome improved, "worsening" if outcome worsened, "mixed" if multiple efficacy outcomes were assessed with divergent findings for each, "no change" if no change observed, and "inconclusive" if outcomes were unable to be assessed.

Results

A total of 15,917 studies were identified across all searched databases during the study period, where searches were conducted for each of the included clinical conditions. Following stratification by clinical condition relevance and screening for eligibility, 438 studies remained (see online suppl. materials for PRISMA flow diagrams for individual clinical conditions). We then further restricted qualitative synthesis to studies that reported primary results or systematically reviewed prior work (n = 198), meaning that 240 studies were narrative reviews or other types of nonsystematic reviews. Table 1 summarizes efficacy findings as stratified by study design type and condition, and Table 2 summarizes the same for safety findings. Table 3 summarizes cannabis agents administered or observed in randomized controlled trials (RCTs) and observational studies by agent and route of administration for each condition. Below, we summarize condition-specific findings.

Amyotrophic Lateral Sclerosis

As depicted in the flow diagrams (online suppl. files), the use of medical cannabis in patients with ALS was investigated in 9 eligible publications. Among those were 2 systematic reviews without meta-analysis, 2 observational/quasi-experimental studies, and 5 other types of reviews. Of all studies investigating medical cannabis and ALS, 2 studies used cramp intensity/frequency as the primary outcome [11, 12] and 2 investigated other outcomes or used a cross-sectional design [13, 14]. Among those studies that investigated cramp intensity/frequency, one indicated no change [11] and one study indicated inconclusive findings [11, 12]. (More detailed information about each study type and summary of findings can be found in Tables 1 and 2 and in the online suppl. files.) Other outcomes assessed in this condition included an examination of trajectories of ALS cases [13], and one cross-sectional study assessed patient characteristics in a dispensary and dispensary staff recommendations [14].

Autism

Medical cannabis in patients with autism was investigated in 17 eligible publications. Among those were one systematic review with meta-analysis, 8 observational/quasi-experimental studies, and 8 other types of reviews. Of all studies investigating medical cannabis and autism, 3 studies used symptom mitigation (see online suppl. Table 1 for outcome definitions) as the primary outcome [15–17] and 6 investigated other outcomes or used a cross-sectional design [18–23]. The latter studies and other types of reviews are summarized in the online suppl. files. Among those studies that investigated symptom mitigation, 2 indicated an improvement [16, 17] and one study indicated no change in symptoms [15]. Other outcomes assessed in this condition were assessed in 6 studies, of which one used a cross-sectional study design. Among those outcomes that were assessed by more than 1 study, 2 studies assessed the brain activity in response to CBD with functional magnetic resonance imaging and magnetic resonance spectroscopy [22, 23].

Cancer

Medical cannabis in patients with cancer was investigated in 138 eligible publications. Among those were 6 systematic reviews with meta-analysis, 10 systematic reviews without meta-analysis, 4 RCTs, 31 observational/quasi-experimental studies, and 86 other types of reviews. Of all studies investigating medical cannabis and cancer, 13 studies investigated cancer-related pain reduction as the primary outcome [24–36]; 2 studies investigated cancer-related nausea and vomiting [27, 36]; 3 studies investigated weight change, appetite increase, or caloric intake [27, 37]; 17 studies investigated safety outcomes [24, 26–32, 34–36, 38–43]; and 31 studies investigated other outcomes or used a cross-sectional design [3, 44–73]. Among studies that investigated cancer-related pain, 5 indicated an improvement [24, 25, 28, 29, 36], 2 studies indicated no change [34, 35], and 6 were inconclusive [26, 27, 30, 32, 74, 75]. Among studies that investigated cancer-related nausea and vomiting, one indicated an improvement [36] and one was inconclusive [27]. In studies that investigated weight change, appetite increase, or caloric intake, one indicated an improvement [36] and 2 were inconclusive [27, 37]. Of the 17 studies assessing safety outcomes of medical cannabis in cancer patients, 11 studies indicated worsening [24, 26, 28, 29, 34–36, 38–40, 43], one indicated mixed findings [41], and 5 studies were inconclusive [27, 30, 32, 42, 74]. For 2 RCTs, results are still pending at this time [76, 77]. Other outcomes assessed in this condition were assessed in 31 studies, of which 24 used a cross-sectional study design. Among those outcomes that were assessed by more than one study, 10 studies investigated patients or provider perceptions of cannabis benefits and side effects [47, 52, 53, 56, 60, 62, 64, 67–69] and 7 investigated patterns of cannabis consumption [48, 49, 55, 57, 63, 71, 72].

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Table 2. Medical cannabis safety outcome findings,[1] by condition and study design type

	Total studies	Worsening	Mixed	No change	Inconclusive
ALS	–	–	–	–	–
Autism	–	–	–	–	–
Cancer	17	11	1	–	5
Systematic reviews with meta-analysis	4	3 [24, 220, 235]	–	–	1 [221]
Systematic reviews	9	4 [28, 39, 222, 236]	1 [41]	–	4 [32, 42, 223, 237]
RCTs	2	2 [34, 225]	–	–	–
Observational or quasi-experimental studies	2	2 [36, 43]	–	–	–
Chronic noncancer pain	9	6	1	–	2
Systematic reviews with meta-analysis	4	2 [111, 226]	1 [25]	–	1 [114]
Systematic reviews	5	4 [117, 119, 121, 122]	–	–	1 [223]
Crohn's disease	1	1	–	–	–
Observational or quasi-experimental studies	1 [132]	1 [132]	–	–	–
Epilepsy	18	10	1	5	2
Systematic reviews with meta-analysis	1	1 [138]	–	–	–
RCTs	3	3[2] [136, 145, 153]	–	–	–
Observational or quasi-experimental studies	14	6 [134, 140, 142, 151, 152, 154]	1 [155]	5 [135, 141, 144, 146, 238]	2 [149, 150]
Glaucoma	–	–	–	–	–
HIV/AIDS	5	3	–	2	–
Systematic reviews with meta-analysis	1	1 [120]	–	–	–
Observational or quasi-experimental studies	4	2 [175, 239]	–	2 [176, 177]	–
MS	6	3	–	2	1
Systematic reviews with meta-analysis	3	2 [183, 184]	–	1 [233]	–
Systematic reviews	3	1 [180]	–	1 [181]	1 [223]
Parkinson's disease	1	–	–	1	–
Observational or quasi-experimental studies	1	–	–	1 [186]	–
PTSD	3	–	1	–	2
Systematic reviews	3 [195, 198, 199]	–	1 [198]	–	2 [195, 199]

ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; MS, multiple sclerosis. [1] Safety outcomes were defined in all studies as proportion of adverse events relative to placebo/active comparator, frequency of adverse events, or severity of adverse events relative to placebo/active comparator. Findings for safety outcomes were classified for cannabis/cannabinoid treatment according to the following: "worsening" if outcome worsened, "mixed" if multiple safety outcomes were assessed with divergent findings for each, "no change" if no change observed, and "inconclusive" if outcomes were unable to be assessed. [2]A secondary endpoint from one RCT, was deemed appropriate for inclusion in safety outcomes [136].

Table 3. Counts of agents in reviewed studies by routes of administration and condition

Medical cannabis product/ route of administration	Autism	Cancer	Chronic noncancer pain	Crohn's disease	Epilepsy	HIV/ AIDS	Parkinson's disease	PTSD
Agent not specified	–	1 [59]	–	–	–	–	–	–
THC (including dronabinol and nabilone)	–	3 [43, 59, 67]	1 [228]	–	–	–	–	3 [200, 202, 204]
Not specified	–	1 [59]	–	–	–	–	–	–
Peroral	–	1 [43]	–	–	–	–	–	3 [200, 202, 204]
Other[1]	–	–	1 [228]	–	–	–	–	–
Multiple roa[2]	–	1 [67]	–	–	–	–	–	–
CBD	2 [22, 23]	4 [59, 62, 67, 76]	2 [124, 228]	1 [133]	16 [134–136, 139–142, 144, 145, 149–151, 153, 154, 157, 240]	1 [170]	2 [186, 187]	1 [203]
Not specified	–	2 [59, 62]	2 [124, 228]	–	–	–	–	1 [203]
Peroral	2 [22, 23]	–	–	1 [133]	16 [134–136, 139–142, 144, 145, 149–151, 153, 154, 157, 240]	–	2 [186, 187]	–
Sublingual	–	1 [76]	1 [124]	–	–	–	–	–
Other	–	–	1 [228]	–	–	–	–	–
Multiple routes of administration[2]	–	1 [67]	–	–	–	1 [170]	–	–
THC/CBD	2 [16, [241]	5 [34, 35, 59, 67, 242]	3 [123, 227, 243]	1 [126]	1 [152]	–	–	–
Not specified	–	1 [59]	–	–	–	–	–	–
Peroral or oral	1 [16]	–	1 [123]	1 [126]	1 [152]	–	–	–
Sublingual	1 [241]	–	–	1 [126]	–	–	–	–
Pulmonary (vaping)	–	–	1 [227]	–	–	–	–	–
Other[3]	–	2 [34, 35]	1 [243]	1 [126]	–	–	–	–
Multiple routes of administration[2]	–	2 [67, 242]	–	–	–	–	–	–
Cannabis and whole plant	–	–	1 [98]	–	1 [146]	1 [170]	–	2 [201, 202]
Peroral	–	–	–	–	1 [146]	–	–	–
Pulmonary (smoking)	–	–	–	–	–	–	–	2 [201, 202]
Multiple routes of administration[2]	–	–	1 [98]	–	–	1 [170]	–	–
Cannabis/marijuana not specified	4 [15, 18–20]	12 [48, 58, 61–63, 68, 70, 71, 77, 244–246]	20 [68, 83–85, 91, 92, 96–98, 101–103, 107, 110, 118, 227, 247–250]	3 [61, 129, 251]	–	18 [161–170, 172, 173, 175, 176, 178, 232, 239, 252]	2 [83, 189]	–
Not specified	4 [15, 18–20]	6 [58, 61, 70, 71, 244, 246]	12 [84, 85, 92, 96, 101, 103, 107, 118, 247–250]	2 [61, 251]	–	14 [161, 163–169, 172, 173, 176, 178, 232, 252]	–	–
Peroral or oral	–	6 [48, 62, 63, 68, 77, 245]	8 [68, 83–85, 97, 102, 110, 227]	1 [129]	–	1 [162]	2 [83, 189]	–
Pulmonary (unspecified)	–	1 [48]	1 [97]	1 [129]	–	–	–	–
Pulmonary (vaping)	–	3 [63, 68, 245]	5 [68, 83, 84, 102, 110]	1 [129]	–	1 [162]	1 [83]	–
Pulmonary (smoking)	–	4 [62, 63, 68, 245]	7 [68, 83–85, 91, 102, 110]	1 [129]	–	3 [162, 175, 239]	2 [83, 189]	–
Topical	–	2 [63, 68]	4 [68, 83, 84, 110]	–	–	–	1 [83]	–
Multiple routes of administration[2]	–	–	1 [98]	–	–	1 [170]	–	–
Other[1]	–	2 [63, 245]	3 [83, 97, 110]	1 [129]	–	–	–	–

Table 3 (continued)

Medical cannabis product/ route of administration	Autism	Cancer	Chronic noncancer pain	Crohn's disease	Epilepsy	HIV/ AIDS	Parkinson's disease	PTSD
Other compound[3]	–	1 [59, 67]	–	–	–	–	–	–
Not specified	–	1 [59]	–	–	–	–	–	–
Multiple routes of administration[2]	–	1 [67]	–	–	–	–	–	–

No studies were eligible in the area of ALS, glaucoma, and MS. THCA, tetrahydrocannabinolic acid; ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; PTSD, posttraumatic stress disorder; THC, tetrahydrocannabinol. [1] Buccal, tincture, oromucosal, rectal, and other not specified. [2] When more than one agent was investigated, but the route of administration was not distinguished between the agents. [3] THCA oil.

Chronic Noncancer Pain

Medical cannabis in patients with chronic noncancer pain was investigated in 120 publications. Among those were 8 systematic reviews with meta-analysis, 8 systematic reviews without meta-analysis, 3 RCTs, 36 observational/quasi-experimental studies, and 63 other types of reviews. Of all studies investigating medical cannabis and chronic noncancer pain, 17 studies investigated pain reduction or quality of life as the primary outcome, 9 studies investigated safety outcomes, and 35 investigated other outcomes or used a cross-sectional design [14, 68, 78–110]. Among those studies that investigated pain reduction or quality of life, 10 indicated an improvement [25, 111–115], one study indicated mixed findings [42], 3 studies indicated no change [116–118], and 3 were inconclusive [30, 119, 120]. Of the 9 studies investigating safety outcomes of medical cannabis in patients with chronic noncancer pain, 6 studies indicated a worsening [111, 112, 117, 119, 121, 122], 1 indicated mixed findings [25], and 2 were inconclusive [30, 114]. For 3 RCTs, results are still pending (see online suppl. Table 2) [123–125]. Thirty-five eligible studies, including 27 cross-sectional studies, investigated other outcomes. Among those outcomes that were assessed by more than 1 study, 9 studies investigated patients or provider perceptions of cannabis benefits and side effects [84, 85, 88, 92, 100, 102, 103, 106, 107], 8 studies investigated different relationships between cannabis use and opioid use [79, 81, 87, 96, 101, 105, 108, 109], 6 studies investigated cannabis use patterns [78, 82, 83, 90, 97, 110], 2 examined consumer characteristics [89, 93], and 2 explored reasons for medical cannabis use [68, 99].

Crohn's Disease

Twenty-five publications investigated medical cannabis in patients with Crohn's disease. Among those were 2 systematic reviews without meta-analysis, 1 RCT, and 8 observational/quasi-experimental studies. Of all studies investigating medical cannabis in patients with Crohn's disease, 3 studies investigated symptom mitigation as the primary outcome, 1 study investigated safety outcomes, and 6 investigated other outcomes or used a cross-sectional design [14, 116, 126–129]. In studies that investigated symptom mitigation, 1 study indicated an improvement [130], 1 study indicated mixed findings [61], and one was inconclusive [131]. Safety outcomes were reported by one study, which indicated worsening safety outcomes [132]. The RCT has recently been withdrawn due to inadequate funding [133]. Six eligible studies, including 3 cross-sectional studies, investigated other outcomes.

Outcomes that were assessed by more than one study included patient perceptions of cannabis benefits and side effects, which was assessed by 2 studies [127, 128], and cannabis use patterns, which was investigated by 2 studies [126, 129].

Epilepsy

Medical cannabis in patients with epilepsy was investigated in 72 eligible publications. Among those were 3 systematic reviews with meta-analysis, 2 systematic reviews without meta-analysis, 3 RCTs, 17 observational/quasi-experimental studies, and 47 other types of reviews. Of all studies investigating medical cannabis and epilepsy, 19 studies investigated the effect on seizures (i.e., reductions in number of seizures and seizure frequency) as the primary outcome, 2 studies assessed health-related quality of life, 18 studies investigated safety outcomes, and 3 studies investigated other outcomes or used a cross-sectional design. Among those studies that investigated the effect on seizures as outcomes, 13 studies indicated an improvement [116, 134–145], 4 studies indicated no change [144, 146–148], and 2 studies were inconclusive [149, 150]. In those studies that investigated health-related quality of life or quality of life as the primary outcome, both studies indicated an improvement [144, 146] and one study indicated no change [146]. Among those 18 studies that investigated safety outcomes, 10 studies indicated worsening [134, 136, 138, 140, 142, 145, 151–154], 1 indicated mixed findings [155], 5 indicated no change [135, 141, 144, 156], and 2 were inconclusive [149, 150]. Three eligible studies, including 1 cross-sectional study, investigated other outcomes. One study assessed potential pharmacokinetic interactions [157], one investigated perception about cannabis use and benefits [158], and the third assessed doses of cannabidiol [116].

Glaucoma

Medical cannabis in patients with glaucoma was investigated in 14 eligible publications, including one systematic review without meta-analysis and one book section. (Detailed information about the latter and the 12 other types of reviews can be found in the online suppl. files.) Of all studies, one investigated the effect of medical cannabis on intraocular pressure, and this study indicated no change in the outcome [116].

Human Immunodeficiency Virus/AIDS

Medical cannabis in patients with HIV/AIDS was investigated in 25 eligible publications, among those were 3 systematic reviews with meta-analysis, 19 observational/quasi-experimental studies, and 3 other types of reviews. Of all studies within this section, 2 studies investigated symptom mitigation (see online suppl. material) as the primary outcome, 4 studies investigated the effect on adherence to antiretroviral therapy, 2 studies investigated the effect on viral suppression, 5 studies investigated safety outcomes, and 12 studies investigated other outcomes or used a cross-sectional design [159–170]. Among the 2 studies that investigated symptom mitigation, one indicated an improvement [120] and one was inconclusive [115]. Among the 5 studies examining the effect of cannabis use on adherence to antiretroviral therapy, 2 indicated worsening [171, 172], 2 reported no change [160, 173], and 1 reported inconclusive findings [174]. One study examining the effect on viral suppression indicated no change [173], and 1 study indicated inconclusive findings [174]. Of the 5 studies investigating safety outcomes, 3 studies indicated worsening [120, 175, 176] and 2 studies indicated no change [176, 177]. Twelve eligible studies, including 6 cross-sectional studies, investigated other outcomes. Among those outcomes that were assessed by more than one study, 5 studies assessed aspects of HIV care continuum measures [160–163, 168] and 2 studies assessed the prevalence and correlates of substance use [165, 178].

Multiple Sclerosis

Medical cannabis in patients with MS or related motor neuron disorders was investigated in 25 eligible publications. Among those were 5 systematic reviews with meta-analysis, 4 systematic reviews without meta-analysis, and 16 other types of reviews. Of all studies within this section, 6 studies investigated spasticity and spasm as the primary outcome, 4 studies investigated efficacy on MS-related pain, 3 studies investigated bladder function, 1 study examined the effect on gait function, and 6 studies investigated safety outcomes. (More information about the 17 other types of reviews can be found in the online suppl. files.) Among the 6 studies investigating spasticity and spasm, 3 indicated an improvement [179–181], one indicated mixed findings [182], one study reported no change [183], and one was inconclusive [30]. Among the 4 studies examining MS-related pain, one indicated improvement [180], one reported no change [183], and 2 reported inconclusive findings [30, 115]. Of studies examining the effect on bladder function, 2 indicated improvement [180, 184] and one reported no change [183]. One study investigating gait function reported inconclusive findings [185]. In studies investigating safety outcomes, 3 studies indicated worsening [180, 183, 184], 2

studies indicated no change [181, 182], and 1 study reported inconclusive findings [30].

Parkinson's Disease

Medical cannabis in patients with Parkinson's disease was investigated in 17 eligible publications. Among those were one RCT and 4 observational/quasi-experimental studies. Of all studies, one study investigated the effect of medical cannabis on safety outcomes and indicated no change in the outcome [186]. For one RCT, results are still forthcoming [187]. Other outcomes were investigated by 3 cross-sectional studies. All of these studies investigated physicians or patient expectations or perceived benefits of cannabis on Parkinson's disease-related symptoms [83, 188, 189]. (More information about the studies that assessed other outcomes and the 12 other types of reviews can be found in the online suppl. files.)

Posttraumatic Stress Disorder

Medical cannabis in patients with PTSD was investigated in 50 eligible publications. Among those were 10 systematic reviews without meta-analysis, 5 RCTs, 3 observational/quasi-experimental studies, and 31 other types of reviews. Of all studies investigating medical cannabis in patients with PTSD, 8 studies investigated symptom mitigation (e.g., sleep disturbances, dissociative reactions or flashbacks, and hyperarousal) as the primary outcome, 3 studies investigated safety outcomes, and 3 assessed other outcomes or used a cross-sectional design [14, 190, 191]. Among those studies that investigated symptom mitigation, 2 indicated mixed findings [192, 193] and 6 were inconclusive [12, 122, 194–197]. One study investigating safety outcomes indicated mixed findings [198], and 2 studies reported inconclusive findings [195, 199]. Among those 5 RCTs, 1 study has been terminated, 2 were completed, but publications were not available at the time of literature search, and for 2, results are still pending. For 5 RCTs, results are still pending [200–204]. Three eligible studies, including 2 cross-sectional studies, investigated other outcomes. Two of 3 investigated cannabis dispensary staff or healthcare provider practices [14, 191] and 1 study investigated cannabis use patterns and associated problems [190].

Cannabis Agents

The vast majority of RCTs and observational studies (including cross-sectional studies) that investigated the safety or efficacy of cannabis did not further specify the type of cannabis product that was investigated. A specific route of administration was also often not reported. Among those publications that specified the cannabis product, CBD was the most frequent investigated agent and mostly for investigations related to epilepsy or other seizure disorders. Whole plant cannabis was the least investigated drug. With respect to route of administration, studies investigating THC, CBD, or THC and CBD combinations typically employed oral/peroral, buccal, or sublingual administration. This is in contrast to those studies assessing unspecified agents, in which pulmonary and oral/peroral administrations were most common. We encountered only one study that assessed minor cannabinoids, namely, tetrahydrocannabinolic acid.

Evidence Map

The majority of identified systematic reviews were conducted on the topic areas of chronic noncancer pain, cancer, MS, epilepsy, and PTSD. The evidence map includes indications for conditions that were determined to have scarce recent evidence available. The quality of evidence varied widely among all eligible systematic reviews and differed between each condition. Reviews graded as either critically low or low quality, indicating serious risks of biases and/or methodological limitations, were mainly conducted in the areas of cancer, PTSD, and HIV/AIDS. Moderate-quality systematic reviews were represented in all conditions. Only the areas of chronic noncancer pain, epilepsy, and MS included systematic reviews graded as high quality. In terms of safety and efficacy outcomes, only a few systematic reviews in the area of ALS, cancer, chronic noncancer pain, Crohn's disease, glaucoma, and MS indicated worsening or no difference. The majority of included reviews reported inconclusive or mixed results, and only publications in the area of chronic noncancer pain, cancer, epilepsy, and MS reported improved outcomes. Furthermore, among high-quality reviews, only chronic noncancer pain and epilepsy reported improved outcomes (see Fig. 1).

Discussion

Referring to the 11 investigated conditions, the NASEM report in 2017 concluded that there is conclusive or substantial evidence for cannabis in treating chronic noncancer pain, chemotherapy-induced nausea and vomiting (oral cannabinoids), and MS spasticity symptoms (via oral cannabinoids). In addition, limited evidence was reported for the efficacy of cannabis and cannabinoids for the purposes of increasing appetite and decreasing weight loss in patients with HIV/AIDS, im-

proving clinician measures of MS spasticity symptoms (specifically, via oral cannabinoids), and improving symptoms of PTSD (specifically, with nabilone). NASEM also concluded that limited evidence was available that cannabis and cannabinoids were ineffective in improving intraocular pressure associated with glaucoma (specifically via cannabinoids). Furthermore, insufficient or no evidence existed to support or refute the effectiveness of cannabis or cannabinoids for a majority of examined indications. Those indications included cancer (cannabinoids), cancer-associated anorexia-cachexia syndrome and anorexia nervosa (cannabinoids), symptoms of irritable bowel syndrome (dronabinol), epilepsy (cannabinoids), symptoms associated with ALS, or Parkinson's disease-related symptoms or levodopa-induced dyskinesia (cannabinoids).

In the 4 years since the NASEM report, much has been published in the clinical and scientific literature regarding the safety and efficacy of cannabis and cannabinoids, but we identified few recent studies conducted within US populations and were of substantial rigor and quality to move the evidence base forward for many clinical conditions. In fact, across all condition topic areas, the most frequently identified study design was clinical/narrative review with a nonsystematic approach, and these reviews only recounted and compiled previous RCT and observational study findings. Many other identified studies, particularly observational studies, also had significant limitations when assessing the safety and efficacy of cannabis that potentially affected validity. Detailed information about the history of cannabis use, other substance use, concomitant medications, comorbidities, types of cannabis product (THC, CBD, THC/CBD, and whole plant), route of administration, and dosage was not captured in the majority of observational studies due to unavailable data or limited subject knowledge. Thus, confounding was a recurring threat to validity in many identified studies. Several observational studies, for example, suggest that cancer patients using medical cannabis tend to have more severe symptoms than those who did not consume medical or recreational cannabis [57, 60, 71]. However, it is unclear if cannabis is contributing to more severe symptoms or if the presence of severe symptoms prompted increases in cannabis utilization. In addition, patient-reported outcomes and behaviors may be more susceptible to recall bias and/or inaccurate reporting of dosage, duration, and frequency of use [205, 206]. Patients also might not report nonmedical cannabis use due to perceived social norms.

Quality of Evidence

Our assessment of the quality of systematic reviews determined that high-quality systematic reviews were conducted only among the conditions of chronic noncancer pain, epilepsy, and MS. In the area of chronic noncancer pain, the most recent systematic reviews are in alignment with findings of the NASEM report, which reported substantial evidence for the use of cannabis as a treatment for chronic pain in adults.

In the area of epilepsy, one recently published high-quality systematic review included several newly published RCTs focusing on pediatrics and found significantly reduced seizure frequency with adjunctive CBD use in pediatric drug-resistant Dravet and Lennox-Gastaut syndromes, aligning with the FDA approval of Epidiolex. High-quality systematic reviews in the field of MS did not include any RCT results following the publication of the NASEM report and are, therefore, not expanding the evidence base.

Only 7 systematic reviews were graded as high quality, whereas almost one-third were graded as low- or critically low-quality systematic reviews. Common reasons for being rated as a moderate- or low-quality review were due to the absence of a prior established protocol, lack of a comprehensive literature search strategy, failing to report the source of funding of included studies, missing an adequate detailed description of excluded studies, inadequate accounting for the risk of bias assessment within result interpretation and discussion, absence of adequate discussion of heterogeneity, and absence of a quantitative synthesis or meta-analysis. In addition to these limitations, many identified systematic reviews also consisted of few RCTs.

Despite the limited evidence available from recent high-quality systematic reviews, it is promising that we identified 12 RCTs with registered protocols and trial registrations. The studies are covering the field of Crohn's disease, chronic noncancer pain, cancer, Parkinson's disease, and PTSD [76, 77, 123–125, 133, 187, 200–204], and 2 of them have recently been withdrawn or terminated [133, 202]. However, the remaining 10 RCTs have the potential to expand the evidence base. In addition, our review identified many studies that reported an increase in adverse events relative to placebo or an active comparator, which was consistent across most of the assessed medical conditions. Nevertheless, the vast majority of the reviewed studies reported that adverse event severity ranged from mild to moderate, and most adverse events were reversible with dose reduction or discontinuation. Medical cannabis was often referred to as "generally well

tolerated." However, information about long-term safety outcomes was scarce.

Gaps in Literature

We identified several persistent gaps in the literature during this review. Recent observational studies often lacked specific information about the route of administration, dosage, frequency, and cannabis product used. Clinical trials were mainly limited to peroral, oral, or sublingual administration and represented few formulations of available cannabis products. Studies investigating whole-plant cannabis products are needed to better understand the risks and benefits of cannabis in real-world settings as patients receiving medical cannabis in practice are typically receiving whole-plant products. In order to provide valuable information about the effectiveness and safety of medical cannabis, real-world studies must define cannabis products, the route of administration, and dosage precisely. In addition, it is unclear whether or not standardized products provided in RCTs are comparable to those products offered by dispensaries, where consistency in product dosing, concentrations, and even routes of administration offered are not necessarily guaranteed and are subject to variations in state regulations [207]. Furthermore, there remain other questions about the generalizability of existing evidence raised. For example, patients with substance use disorder histories were often excluded from randomized studies across several conditions, even though use by patients with these or similar underlying conditions is common (e.g., PTSD and chronic noncancer pain) [208].

Implications for Research, Clinicians, and Policy

The prevalence of medical cannabis and cannabis use for nonmedical reasons is increasing [209], while perceived risks associated with cannabis use are decreasing, particularly among younger persons [210]. Therefore, it is important to evaluate and disseminate the evidence widely to both clinicians and patients. Interestingly, there is also some evidence suggesting that the legalization of cannabis might not necessarily affect the compliance rate of primary therapies in patients with chronic noncancer pain under opioid therapy [211], so it is unclear whether the changing availability of licit nonmedical cannabis will impact clinical outcomes in patients receiving medical cannabis.

There remains a need for well-designed and conducted RCTs for most of the assessed medical conditions. However, there are several methodological and practical challenges in conducting RCTs specific to investigating efficacy and safety of cannabis and cannabinoids, including placebo effects, practical limitations in conducting blinding for cannabis products, and regulatory barriers. Expense and complicated implementation, meanwhile, render it difficult to design and perform high-quality RCTs even in the absence of cannabis-related regulatory barriers [212, 213]. Studies assessing cannabis efficacy and safety for these conditions, or any condition, must consider the effect that different routes of administration can have on systemic exposure and ultimately on study outcomes. Studies must also clearly and precisely quantify active metabolites and ratio of metabolites (i.e., THC:CBD) with the same rigor as applied to other medication studies.

Questions also remain about medical cannabis safety, especially in terms of rare adverse drug events, long-term effects, the effects on patients with comorbidities (e.g., people with history of substance abuse), and the potential for interactions with prescription medications and other substances, particularly among patients most susceptible to adverse events from drug-drug interactions (e.g., geriatric populations). Future research will require the utilization of a combination of approaches and techniques to overcome the barriers associated with capturing these rare or long-term outcomes, including the use of real-world data and sophisticated pharmacoepidemiologic methods to overcome current limitations in reported studies for ascertaining exposures and outcomes.

The evolving and challenging legal status of cannabis remains a significant obstacle to the expansion of cannabis research in the USA. The schedule I controlled substance designation of whole-plant cannabis restricts research in this area due to regulatory barriers and limited feasibility, along with scarce federal research funding allocated to the investigation of constituent compounds [214]. Furthermore, only a minority of the National Institute of Health's budget is earmarked for therapeutic cannabis research, while more is available for investigations of problematic uses and/or abuse potential, making it challenging to get US funding for investigation of therapeutic potential [215, 216]. The complicated legal status of cannabis in the USA restricts cultivation and production to a single federally permitted institution; thus, a narrow amount of cannabis products can be tested, and these may not mirror constituents and concentrations of products available to consumers on the market [217, 218]. Thus, policies would need revision to permit handling or production of dispensary-available cannabis products for research purposes and expand funding mechanism to support urgently needed research on clinical outcomes of medical cannabis.

Limitations and Strengths

Our review has several limitations that should be considered in the interpretation of the findings. First, we restricted our search strategy to studies published between July 2016 and October 2019 and for our rapid review to studies published between 2000 and October 2019. Therefore, we assessed only a narrow period of the most recently available literature. Second, we excluded articles reporting primary research conducted exclusively outside the USA, in order to account for differences in cannabis product availability internationally as well as differences in regulatory barriers and access. We, therefore, have excluded potentially relevant recent literature conducted in countries with robust scientific and clinical research programs evaluating cannabis efficacy and safety. However, studies originating from the USA accounted for almost 2/3 of all publications between 2000 and 2017 [219]. Third, even though we conducted pilot runs and training with reviewers on the use of the data extraction tool, the data extraction step was only conducted by one reviewer with review by a second reviewer in cases of uncertainty. In addition, the screening process for each topic area was only conducted by a second reviewer for those articles categorized as "uncertain"; thus, selection bias might have been introduced during both stages. However, weekly meetings throughout the review process were used to clarify any questions and uncertainties throughout the screening and extraction process. Fourth, systematic reviews and meta-analyses were not excluded if they partially included studies that were not matching our criteria (e.g., a systematic review consisting of studies that were conducted between 2016 and 2019 but also prior to 2016 was still considered as eligible, since it was not feasible to disentangle the evidence synthesis without examining the underlying primary study). Therefore, our findings based on systematic reviews and meta-analyses might not be restricted to our country and time criteria. In order to account for this limitation, we stratified our findings by study design and also restricted our summary of cannabis agents to RCTs and observational studies. Fifth, we did not assess whether medical cannabis was used as adjuvant treatment or primary therapy. Subsequently, different directions of findings might be based on variation in co-medications. However, the regulatory environment in the US mainly restricts the use of medical cannabis products to adjuvants, and the objective of this study was not to assess safety and efficacy of medical cannabis. Last, although a standardized classification scheme was applied to categorize the outcomes, inter-rater variability might have introduced misclassification of the outcomes.

There are also several strengths of this review to consider, including the broad scope of assessed medical conditions, comprehensive search strategy that extended beyond RCTs, and adherence to the PRISMA statement for gathering and reporting findings. Furthermore, this review highlights recent research efforts by medical condition, and directions of findings, thus creating a comprehensive picture of the scientific landscape of clinical studies about cannabis. Moreover, we also identified several literature gaps that could be addressed in future research, and we assessed the quality of evidence available, which is essential information for policymaking. Additionally, input from an external expert panel ensured a wide range in scope of the literature covered, and this review gives an up-to-date overview about the current state of evidence quality in a readily interpretable map.

Conclusion

The large body of the literature recently published regarding medical cannabis masks a paucity of evidence related to efficacy and safety as treatment options for several conditions for which it is commonly prescribed. Across 11 conditions, we identified few studies of substantial rigor and quality to contribute to the evidence base. However, there are some conditions for which significant evidence suggests that certain dosage forms and routes of medical cannabis products likely have favorable risk-benefit ratios (i.e., epilepsy and chronic noncancer pain). Gaps in the evidence remain significant for most examined conditions, but the identification of several registered forthcoming RCTs suggests that improved evidence will be available in the coming years.

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Conflict of Interest Statement

The Consortium for Medical Marijuana Clinical Outcomes Research provided funding support for 4 contributors to this study, where S.J. and B.C. received graduate student stipend support in

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Author Contributions

S.J. prepared protocols for literature search, screening, and data extraction and drafted the manuscript. A.G. designed the study, supervised contributors, and critically revised the manuscript. L.A. performed literature searches and curated the reference library. The following contributors were topic lead reviewers for the following conditions: A.G. in amyotrophic lateral sclerosis, A.O. in human immunodeficiency virus (HIV)/AIDS, B.C. in Crohn's disease and posttraumatic stress disorder, E.J.M. in Parkinson's disease, G.A.H. in epilepsy, S.K. and S.J. in cancer, S.J. in chronic noncancer pain, Y.S. in autism and multiple sclerosis, and Y.Z. in glaucoma. R.S. developed figures. All other contributors were positioned in various roles as screeners, in data extraction, in reviewer resolutions, and in qualitative synthesis. All contributors critically revised and approved the manuscript.

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