Review article

Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis

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ABSTRACT

Rationale: Certifications for medical cannabis are generally restricted to a small number of specific medical conditions, yet patients frequently report symptoms of pain, anxiety, and depression as reasons for use. This is a critical concern for researchers, healthcare providers, and policymakers, yet research in this area is currently obstructed by the lack of a focused review or empirical synthesis on patient-reported reasons for medical cannabis use.

Objectives: AND METHOD: The first aim of this project was to conduct the first systematic review and meta-analysis of empirical studies of patient-reported symptoms of pain, anxiety, and depression as reasons for medical cannabis use. The second aim was to conduct an empirical assessment of the methodological quality of extant research, test for publication bias, and test sex composition and quality scores of individual studies as possible sources of observed heterogeneity.

Results: Meta-analytic results indicated that pain (64%), anxiety (50%), and depression/mood (34%) were common reasons for medical cannabis use. No evidence for publication bias was detected, despite heterogeneity in prevalence rates. A comprehensive assessment of study quality identified a number of specific methodological limitations of the existing research, including challenges in patient recruitment, use of restrictive sampling frames, and a lack of randomized recruitment methods and validated assessment measures.

Conclusion: Findings are discussed with regard to possible explanations for current results, clinical considerations, and areas of future research that are needed to move the field forward.

1. Introduction

The increasing utilization and legalization of medical cannabis has garnered attention from researchers, clinicians, and policy-makers across disciplines (Compton et al., 2017b). At least 30 countries (e.g., Israel, Canada, Australia) and the majority of U.S. states (*n* = 33) have established medical cannabis programs (Arcview, 2016). Additionally, over 60% of Americans now live in states with access to medical cannabis (Arcview, 2016), and the total number of medical cannabis users is estimated at over two million nationwide (Park and Wu, 2017). Patients frequently report using medical cannabis to manage symptoms of pain, anxiety, and depression (Sexton et al., 2016). Researchers have noted that medical cannabis is often advertised as an efficacious treatment for a wide range of health problems, despite only being state legal for a limited number of conditions and symptoms (Caulkins, 2018). For example, at least 30 states now specify pain as a qualifying reason to use medical cannabis, only New Jersey includes anxiety (if "intolerant" to other treatments), and no states include depression as a

qualifying condition for medical cannabis use. At least nine states defer to physician recommendation regarding the use of medical cannabis, often with the caveat that use be restricted to a chronic and/or debilitating medical condition (Bierut et al., 2017; Choo and Emery, 2017).

A critical need for healthcare providers and policy makers is to better understand the symptoms patients report using medical cannabis to assuage (e.g., anxiety, depression) in the context of limited legal conditions for use and evolving evidence for therapeutic effects. For example, data from the electronic medical records of physicians in California who reported the conditions for *approving medical cannabis* indicated that "back/spine/neck pain" and "anxiety/depression" were reported by 30.6% and 13% of patients, respectively. Notably, the patient-reported use of medical cannabis was nearly threefold greater for pain (82.6%) and five times greater for anxiety or depression (63.9%) than the data from the medical record would have predicted (Reinarman et al., 2011). In addition, amelioration of anxiety and depression are not yet medically indicated for prescribed cannabis, and a recent review of the clinical efficacy of cannabis for anxiety and mood

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┌─────────────────────────────────┐   ┌─────────────────────────────┐
│ Records identified through       │   │ Records identified through   │
│ database searching               │   │ reference searching          │
│                                  │   │                              │
│ (PsycINFO: k = 179) (Scopus:     │   │ (k = 2)                      │
│ k = 2,059)                       │   │                              │
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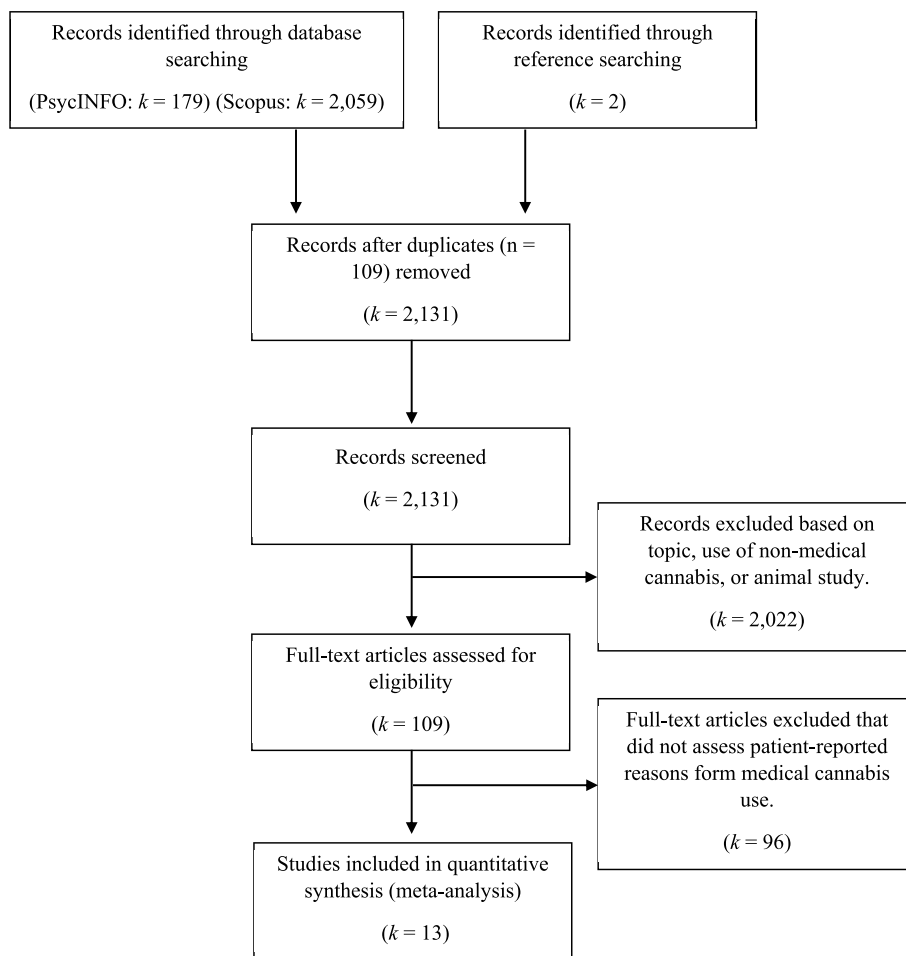
Fig. 1. Flow of studies into the quantitative synthesis (meta-analysis).

disorders highlighted the discrepancy between patients' positive expectations of the anxiolytic and antidepressant effects of cannabis, despite limited scientific support for such uses (Turna et al., 2017).

A related concern is that the current state of research examining patient-reported reasons for using medical cannabis (Nunberg et al., 2011) requires consumers to identify and interpret the results of individual studies, without consideration of factors such as study quality and the potential for bias in published work. A focused systematic review and quantitative synthesis of the literature is needed to pool results, estimate the magnitude of associations, and ultimately inform future research and clinical practice (e.g., Nugent et al., 2017). Indeed, primary care physicians are a primary source of medical cannabis certifications (Alexander-Scott, N., 2017), and pain, anxiety, and depression are among the most common reasons for visiting a physician in the United States (Mayo Clinic, 2001; Gaskin and Richard, 2011, Ûstùn and Sartorius, 1995). Pain, anxiety, and depression are also highly comorbid (Arnow et al., 2006). For example, individuals with chronic pain are up to four times more likely to meet diagnostic criteria for mood and anxiety disorders (relative to the general population), and depression has been reported by up to 54% of patients seeking treatment for pain (Arnow et al., 2006; Demyttenaere et al., 2007).

To our knowledge, there has been no systematic or quantitative synthesis of the literature examining *patient-reported use of medical cannabis for pain, anxiety, or depression symptoms*. Park and Wu (2017) conducted a broad review of the literature on prevalence, perceived effects, and correlates of medical cannabis use. They found that the reported use of medical cannabis was as high as 17.4% among U.S. healthcare patients, and that patients often reported that medical cannabis relieved symptoms of pain, anxiety, and related disorders. This review was limited to only two studies that assessed anxiety or depression as reasons for using medical cannabis and did not assess study quality (Park and Wu, 2017). Walsh et al. (2017) conducted a systematic review of the evidence for medical and recreational cannabis use in relation to psychological health conditions and concluded that, although cannabis may have therapeutic use for post-traumatic stress disorder, the clinical implications for mood disorders remain unclear. Furthermore, Walsh et al. did not systematically review patient-reported reasons for the use of medical cannabis. Both reviews noted mixed findings, the possibility of publication bias, and concerns regarding methodological rigor (Park and Wu, 2017; Walsh et al., 2017).

The current review and meta-analyses had three aims. The first aim was to quantify the percentage of medical cannabis patients reporting pain and symptoms of anxiety or depression as reasons for medical cannabis use. The second aim was to conduct a systematic analysis of study quality, assess for evidence of publication bias, and test for sources of heterogeneity. Finally, the third aim was to integrate evidence derived from the meta-analytic results and those of individual studies to identify limitations in the literature that can help inform future directions.

2. Method

2.1. Search strategy

The current meta-analysis and systematic review were completed using PRISMA guidelines (Liberati et al., 2009). A systematic literature search was conducted in both PsycINFO and Scopus databases to include the entire contents of MEDLINE. The literature search was limited

to full text papers published in English in peer-reviewed journals, available through July of 2017. A Boolean search strategy was developed and subsequently reviewed by a member of the university library sciences. For PsycINFO, the following search was conducted: [Tx ("medical marijuana" OR "medical cannabis" OR "cannabis for therapeutic purposes") AND (pain OR anxiety OR depression OR psychological OR "mental health" OR "chronic pain")]. For Scopus, the following search was conducted: [ALL ("medical marijuana" OR "medical cannabis" OR "cannabis for therapeutic purposes") AND (pain OR anxiety OR depression OR psychological OR "mental health" OR "chronic pain")]. The reference sections of identified articles were reviewed for additional relevant studies by the primary author.

A total of 2238 studies were identified using the designated search strategy, 109 duplicates were removed, 2131 records were screened, and 109 full texts were reviewed (see Fig. 1). A total of 96 articles were excluded because they did not assess self-reported reasons for using medical cannabis. Given that two studies appeared to be derived from an overlapping sample (Reinarman et al., 2011; Nunberg et al., 2011), we selected the study with the most inclusive sample (i.e., Reinarman et al., 2011). This process resulted in a final selection of 13 eligible studies and a total of 6759 participants. Two studies did not report participant sex, and four studies did not report mean age. Included samples were mostly male (range: 54.6%–74%), with a mean age ranging from 21.4 to 49.3 (see Table 1).

2.2. Study selection criteria

Studies were included if they met the following criteria: (1) assessed self-reported use of *medical* cannabis for symptoms of pain and either anxiety or depression, (2) published in a peer-reviewed journal, (3) available in English, and (4) provided data necessary for computation of the prevalence rate for each reason for using medical cannabis. The Institute of Medicine has stated that specific *symptoms,* not specific *diseases*, are the preferred categories for medical cannabis use, despite common current practice. Thus, we included studies that assessed *symptoms* of pain, anxiety, and depression (Institute of Medicine, 1999). A decision was made a-priori to include *chronic pain* as a reason for use, as it is commonly defined by the length of time pain symptoms have been present (Turk and Okifuji, 2001). Studies were excluded if samples were selected for a specific medical condition (e.g., HIV).

2.3. Study quality assessment

An assessment of study quality was performed for individual studies using a 10-item measure developed specifically for meta-analysis of prevalence studies (Hoy et al., 2012). This measure allows for concurrent evaluation of both external and internal validity factors. An example of an external validity item is "Was the likelihood of non-response bias minimal?" An example of an internal validity item is "Was an acceptable case criterion variable used?" Individual items were rated as either (0/"low risk") or (1/"high risk"), and total scores (0–10) were generated to reflect overall study quality. Hoy et al. (2012) reported that the measure demonstrated excellent interrater agreement (91%).

2.4. Data extraction and coding

Data extraction and coding from all identified studies ($k = 13$), as well as data pertaining to methodological quality and bias were conducted by two independent raters. Interrater reliability across items (Cohen's kappa) averaged 0.86 and ranged from 0.69 to 1.00. The pooled interrater agreement for all quality assessment items was excellent (93.3%). Consensus (100% agreement) on all items was obtained through further inspection and discussion.

2.5. Quantitative data analysis

All computations were performed using Comprehensive Meta-Analysis Version 3 (CMA v.3; Biostat, USA). Effect size was defined as the prevalence rate; a proportion based on number of people reporting a given reason for using cannabis (e.g., pain, anxiety, depression, insomnia) divided by the total sample size. A random-effects model was employed, as this approach makes fewer assumptions regarding the data and is recommended when included studies are not expected to be equivalent (i.e., variance in distribution of effects; Dersimonian and Laird, 2015). The 95% confidence intervals surrounding the weighted (inverse variance) mean effect sizes were calculated, which reflect the degree of precision of the estimate and corresponding statistical significance.

Studies with statistically significant results may be more likely to be published, resulting in publication bias. The possibility of publication bias was initially examined by visual inspection of funnel plot asymmetry. Funnel plots are created by plotting larger studies at the top and smaller ones at the bottom, and the possibility for publication bias is inferred if smaller studies cluster toward the right. The Begg-Mazumdar (Kendall's tau) rank correlation test and Egger's test were used to further probe for publication bias, by testing statistical significance of observed asymmetry in the relationship between study size and magnitude of the observed prevalence rate (Egger et al., 1997; Begg and Mazumdar, 1994).

Between-study heterogeneity was assessed using two measures. Specifically, the Q statistic assesses for the presence of heterogeneity, while the I^2 test assesses the magnitude of heterogeneity. The Q statistic is a measure of precision that provides a test of homogeneity between studies (i.e., a test of the null hypothesis that all studies in the analysis share a common prevalence rate). Based on conservative recommendations from Berman and Parker (2002), the significance level was set at 0.10 for Q statistics (Berman and Parker, 2002; Petitti, 2001). I^2 values range from 0 to 100 and indicate the proportion of heterogeneity that reflects true differences in prevalence rates across studies, and not variance due to sampling error. Higher values indicate greater heterogeneity, and the 95% confidence intervals around the I^2 statistic reflect the degree of uncertainty in the estimate. Values of I^2 can be characterized as follows: low heterogeneity = 25%; moderate heterogeneity = 50%; high heterogeneity = 75% (29). Comparisons made with a small number of studies (< 10) may disguise heterogeneity (Harwell and Maeda, 2008). Should results indicate heterogeneity, the decision was made to examine study quality and sex distribution as possible explanatory variables.

3. Results

3.1. Study characteristics

In terms of reasons for using medical cannabis, 12 studies assessed pain, 11 assessed anxiety, and 13 assessed depression. All included studies relied on self-report data, either collected via survey methods or indirectly via self-reported survey data that was imputed into the medical record. Nine studies used data gathered directly from participants, two employed retrospective chart review (Aggarwal et al., 2013; Reinarman et al., 2011), one employed in-person interview (Lankenau et al., 2017), and one used a mixed-methods collection strategy (Walsh et al., 2013). The majority of identified studies recruited within the United States ($k = 8$), including four from California (Grella et al., 2014; Lankenau et al., 2017; Reinarman et al., 2011; Bonn-Miller et al., 2014b), two from Washington state (Aggarwal et al., 2013; Sexton et al., 2016), one from Arizona (Troutt and Didonato, 2015), and one from Hawaii (Webb and Webb, 2014). One study was conducted in New Zealand (Pledger et al., 2016), one in Australia (Swift et al., 2005), and two recruited participants in Canada (Lucas and Walsh, 2017; Walsh et al., 2013). A final study recruited an international online sample that

Table 1
Study characteristics and reasons for using medical cannabis.

Study	Recruitment/Location	Study Method	Sample Size	Age and Sex Characteristics	Key Findings	Assessment Question about Reasons for Medical Cannabis Use
Aggarwal et al. (2013)	MC[1] Dispensary in Washington State, USA	Retrospective Chart Review	37	65% male M age = 41.4	25 (67.6%) used to reduce anxiety 24 (64.9%) used to improve mood Pain-related use was not assessed	"Thinking now about your qualifying condition, for which of the following symptom-relieving purposes do you use medical marijuana?"
Bonn-Miller et al. (2014a,b)	MC Dispensary in California, USA	In-Person Self-Report	217	73.3% male M age = 41.2	123 (56.7%) used for chronic pain 131 (60.4%) used for anxiety 95 (43.8%) used for depression	"What condition(s) have led you to seek out medical cannabis (i.e. 'what is it prescribed for')?"
Grella et al. (2014)	MC Dispensaries in Los Angeles County California, USA	In-Person Self-Report	181	74% male M age = 28.4	76 (42.0%) used for chronic pain 109 (60.2%) used for anxiety 60 (33.1%) used for depression	Participants were asked about the conditions that they used MM for.
Hazekamp et al. (2013)	IACM[2] Website	Online Survey	953	64% male M age = 40.7	278 (29.2%) used for chronic pain 175 (18.4%) used for anxiety 50 (5.2%) used for depression	Participants were asked to select the main symptoms for which they sought relief.
Lankenau et al. (2017)	Greater Los Angeles Area, California, USA	In-Person Interviews	210	68.1% male M age = 21.4	150 (71.4%) used for physical pain 117 (55.7%) used for anxiety 91 (43.3%) used for feeling depressed	"What are some of the reasons you used marijuana in the past 90 days?"
Lucas & Walsh (2017)	MC Dispensaries in Canada	Online Survey	271	73% male M age = 40	197 (72.7%) used for chronic pain 126 (46.5%) used for depression Anxiety-related use was not assessed	Respondents were asked to select the symptoms affected by the medical use of cannabis.
Pledger et al. (2016)	Nationwide Survey in New Zealand	Nationally Representative Survey	498	Sex and age data not provided	200 (40.2%) used for pain 135 (27.1%) used for anxiety/nerves 129 (25.9%) used for depression	Medicinal users were asked the reasons that they intentionally treated themselves with cannabis.
Reinarman et al. (2011)	MC Assessment Clinics in California, USA	Retrospective Chart Review	1746	72.9% male age data not provided	1442 (82.6%) used for pain 965 (55.3%) used for anxiety/panic 455 (26.1%) used for depression	"Which of the following best describe the therapeutic benefit you receive from medicinal cannabis?"
Sexton et al. (2016)	Social Media and MC Dispensaries in Washington State, USA	Online Survey	1429	54.6% male M age = 36.3	874 (61.2%) used for pain 830 (58.1%) used for anxiety	"Do you use cannabis for the management of any of the following conditions?"

(continued on next page)

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Table 1 (*continued*)

Study	Recruitment/Location	Study Method	Sample Size	Age and Sex Characteristics	Key Findings	Assessment Question about Reasons for Medical Cannabis Use
					719 (50.3%) used for depression	
Study	**Recruitment/Location**	**Study Method**	**Sample Size**	**Age and Sex Characteristics**	**Key Findings**	
Swift et al. (2005)	Diverse Media Advertisements in Australia	Mailed Questionnaire	128	63% male Median age = 45	73 (57.0%) used for chronic pain 72 (56.3%) used for depression Anxiety-related use was not assessed	Participants were asked to report the medical conditions and symptoms associated with their use of medical cannabis.
Troutt and Didonato (2015)	MC Dispensaries in Arizona, USA	In-Person Self-Report	367	63.8% male *M* age = 45.78	318 (86.6%) used for chronic pain 181 (49.3%) used for anxiety 106 (28.9%) used for depression	Participants were asked to select from an extensive list of conditions for which they use medical cannabis to control or treat.
Walsh et al. (2013)	MC Dispensary in Canada and Nationwide Survey	In-Person and Online Survey	628	71% male Modal age range: 25-34	486 (77.4%) used for pain 463 (73.7%) used for anxiety 394 (62.7%) used for depression	Participants were asked to check all applicable symptoms they treated with cannabis.
Webb & Webb (2014)	MC Patients Returning for Recertification in Hawaii, USA	In-Person Self-Report	94	Sex data not collected *M* age = 49.3	91 (97%) used for chronic pain 47 (50%) used for stress/anxiety 6 (6.4%) used for depression	"Does medical cannabis help you with any other problems? If so, what?"

Note. [1]MC = Medical Cannabis; [2]International Association for Cannabinoid Medicines.

Table 2
Study quality assessment.

Study	Quality Assessment Items										
	C1[1]	C2[2]	C3[3]	C4[4]	C5[5]	C6[6]	C7[7]	C8[8]	C9[9]	C10[10]	Total[11]
Aggarwal et al. (2013)	1	1	1	1	0	1	1	0	1	0	8/HR
Bonn-Miller et al. (2014a,b)	1	0	1	1	0	1	1	0	1	0	6/MR
Grella et al. (2014)	1	0	0	1	0	1	1	0	1	0	5/MR
Hazekamp et al. (2013)	1	1	1	1	0	1	1	0	1	0	7/HR
Lankenau et al. (2017)	1	1	1	1	1	1	1	0	1	0	8/HR
Lucas and Walsh (2017)	1	0	1	0	0	1	1	0	1	0	5/MR
Pledger et al. (2016)	0	0	0	0	0	1	1	0	0	0	2/LR
Reinarman et al. (2011)	1	0	1	0	0	1	1	0	1	0	5/MR
Sexton et al. (2016)	1	0	1	1	0	1	1	0	1	0	5/MR
Swift et al. (2005)	1	1	1	1	0	1	1	0	1	1	8/HR
Troutt and Didonato (2015)	0	0	1	1	0	1	1	0	1	0	5/MR
Walsh et al. (2013)	1	0	1	1	0	1	1	1	1	0	7/HR
Webb & Webb (2014)	1	1	1	0	0	1	1	0	1	0	6/MR

Notes. [1]Criterion 1: Was the study's target population was a close representation of the national population?; [2]Criterion 2: Was the sampling frame a true or close representation of the target population?; [3]Criterion 3: Was some form of random selection used to select the sample, or, was a census undertaken?; [4]Criterion 4: Was the likelihood of non-response bias minimal?; [5]Criterion 5: Were data collected directly from the subjects (as opposed to a proxy)?; [6]Criterion 6: Was an acceptable case definition used in the study?; [7]Criterion 7: Was the study instrument that measured the parameter of interest shown to have reliability and validity (if necessary)?; [8]Criterion 8: Was the same mode of data collection used for all subjects?; [9]Criterion 9: Was the length of the shortest prevalence period for the parameter of interest appropriate?; [10]Criterion 10: Were the numerator(s) and denominator(s) for the parameter of interest appropriate?; [11]Total = total score; LR = low risk; MR = moderate risk; HR = high risk.

included participants from 31 countries, including the United States (38.5%), Germany (16.6%), France (7.9%), Canada (7.5%), The Netherlands (5.5%), and Spain (5.1%) (Hazekamp et al., 2013). All identified studies allowed patients to indicate multiple symptoms/conditions as reasons for medical cannabis use (see Table 1).

3.2. Study quality

One study (7.7%) was deemed at low risk of bias (Pledger et al., 2016), seven (53.8%) were deemed at moderate risk of bias (Bonn-Miller et al., 2014b; Grella et al., 2014; Lucas and Walsh, 2017; Reinarman et al., 2011; Sexton et al., 2016, Troutt and Didonato, 2015; Webb and Webb, 2014), and five (38.4%) were deemed at high risk of bias (Aggarwal et al., 2013; Hazekamp et al., 2013; Swift et al., 2005; Walsh et al., 2013). The most common limitation noted was the absence of a psychometrically validated instrument for assessing reasons for using cannabis. To our knowledge, a psychometrically-sound measure of reasons for using cannabis has yet to be developed. The most common strength identified across studies was within-study consistency in the mode of data collection (typically assessed as either survey measure or an in-person interview; see Table 2).

3.3. Pain as a reason for medical cannabis use and tests of publication bias

The overall random-effects pooled prevalence of pain (often categorized as chronic or severe pain) as a reason for medical cannabis use was 67.2% (95% CI = 54.4%, 77.9%). There was evidence of statistically significant heterogeneity Q = 973.55; df = 11; p = < .001). The magnitude of heterogeneity could be characterized as high (I^2 = 98.87), indicating that the majority of observed variance was due to true differences between studies, not sampling error. The Begg-Mazumdar rank correlation test (Kendall's tau = 0.12, p = .58) and Egger's test (t = 0.37, p = .71) did not indicate evidence of publication bias.

3.4. Anxiety symptoms as a reason for medical cannabis use and tests of publication bias

The overall random-effects pooled prevalence of anxiety as a reason for medical cannabis use was 51.7% (95% CI = 40.8%, 62.4%). There was evidence of statistically significant heterogeneity Q = 619.95;

df = 10; p < .001). The magnitude of heterogeneity could be characterized as high (I^2 = 98.39), indicating that the majority of observed variance was due to true differences between studies, not sampling error. The Begg-Mazumdar rank correlation test (Kendall's tau = −0.09, p = .70) and Egger's test (t = 0.19, p = .85) did not indicate evidence of publication bias.
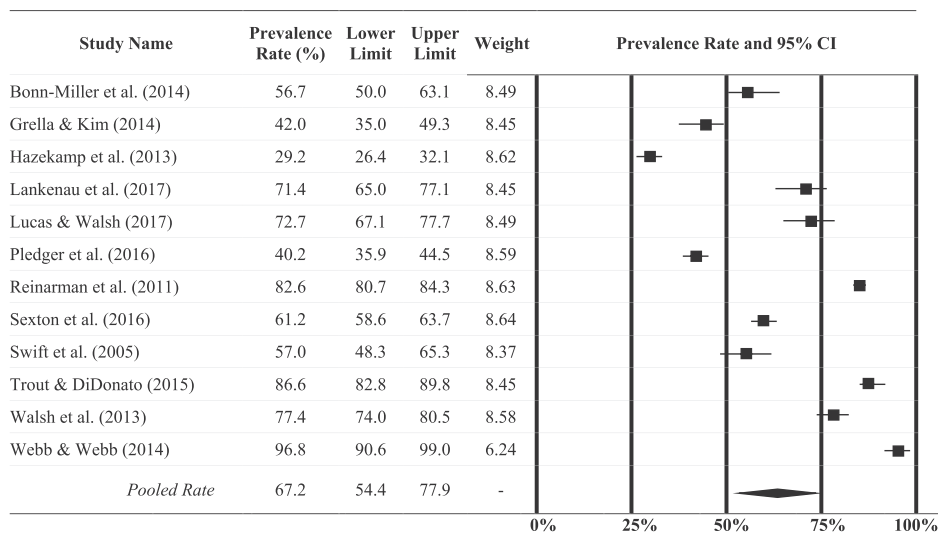
3.5. Depression symptoms as a reason for medical cannabis use and tests of publication bias

The overall random-effects pooled prevalence of depression as a reason for medical cannabis use was 34.7% (95% CI = 25.3%, 45.5%). There was evidence of statistically significant heterogeneity Q = 729.50; df = 12; p = < .001). The magnitude of heterogeneity could be characterized as high (I^2 = 98.35), indicating that the majority of observed variance was due to true differences between studies, not sampling error. The Begg-Mazumdar rank correlation test (Kendall's tau = −0.05, p = .81) and Egger's test (t = 0.51, p = .62) did not indicate evidence of publication bias.

3.6. Risk of bias, sex composition, and recruitment methodology

Meta-regression analyses were conducted in an attempt to explain some of the observed heterogeneity. Results indicated no association between either the percentage of male respondents ($coef$ = 0.016; SE = 0.05; 95% CI = −0.09, 0.12; Z = 0.29; p = .77), or risk of bias score ($coef$ = 0.13; SE = 0.18; 95% CI = −0.22, 0.48; Z = 0.71; p = .47) in relation to the prevalence of pain as a reason for medical cannabis use. No association was observed between either the percentage of male respondents ($coef$ = 0.03; SE = 0.05; 95% CI = −0.06, 0.12; Z = 0.63; p = .53) or risk of bias score ($coef$ = −0.14; SE = 0.14; 95% CI = −0.13, 0.42; Z = 1.04; p = .30) in terms of the prevalence of anxiety as a reason for medical cannabis use. Finally, results showed no association between either the percentage of male respondents ($coef$ = 0.00; SE = 0.05; 95% CI = −0.096 − 0.097; Z = 0.01; p = .99) nor risk of bias score ($coef$ = 0.14; SE = 0.14; 95% CI = −0.13, 0.42; Z = 1.00; p = .32) in terms of the prevalence of depression as a reason for medical cannabis use. It was not possible to assess recruitment location as a moderator of reasons for medical cannabis use. Specifically, is not recommended that moderation be tested with such a small number of studies per covariate (Borenstein et al., 2009), and most of

Table 3
Forest plot: Use of cannabis for pain Symptoms.

Study Name	Prevalence Rate (%)	Lower Limit	Upper Limit	Weight	Prevalence Rate and 95% CI
Bonn-Miller et al. (2014)	56.7	50.0	63.1	8.49	
Grella & Kim (2014)	42.0	35.0	49.3	8.45	
Hazekamp et al. (2013)	29.2	26.4	32.1	8.62	
Lankenau et al. (2017)	71.4	65.0	77.1	8.45	
Lucas & Walsh (2017)	72.7	67.1	77.7	8.49	
Pledger et al. (2016)	40.2	35.9	44.5	8.59	
Reinarman et al. (2011)	82.6	80.7	84.3	8.63	
Sexton et al. (2016)	61.2	58.6	63.7	8.64	
Swift et al. (2005)	57.0	48.3	65.3	8.37	
Trout & DiDonato (2015)	86.6	82.8	89.8	8.45	
Walsh et al. (2013)	77.4	74.0	80.5	8.58	
Webb & Webb (2014)	96.8	90.6	99.0	6.24	
Pooled Rate	67.2	54.4	77.9	-	
					0% 25% 50% 75% 100%

Note. Summary statistics were computed via random effects meta-analysis.

Note. Summary statistics were computed via random effects meta-analysis.

the included studies were recruited from multiple U.S. states and/or several countries.

4. Discussion

This study is the first systematic review and meta-analysis of patient-reported medical cannabis use for symptoms of pain, anxiety, and depression. Data were extracted from 13 studies that included 6665 participants from over 30 countries. Pooled statistics indicated that the mean prevalence of individuals who reported using medical cannabis for pain was 67%, for anxiety was 52%, and for depression was 35%. No evidence of publication bias was detected using several meta-analytic methods, and there was no support for a moderating role of study quality or sex distribution.

The high prevalence of patients who reported using medical cannabis for pain (see Table 3) in this analysis is consistent with recent conclusions by the National Academy of Sciences that there is "*substantial evidence*" supporting cannabis as an effective treatment for chronic pain (National Academies of Sciences, 2017). This finding is also consistent with evidence that cannabis may confer acute analgesic effects (Hill et al., 2017), and the results of two separate studies in which up to 80% of individuals with chronic pain endorsed pain-related benefit from medical cannabis (Troutt and Didonato, 2015; Bonn-Miller et al., 2014b). Although there is some experimental evidence that males may experience greater cannabis-induced analgesia than females (Cooper and Haney, 2016), the current results did not indicate sex differences in the reasons reported for using medical cannabis for pain.

Results of this review also indicated that approximately half of all patients report anxiety as a reason for using medical cannabis (See Table 4). The anxiolytic effects of medical cannabis have yet to be tested with randomized-controlled trials (National Academies of Sciences, 2017), and data on the associations between medical cannabis and anxiety has produced mixed results (Crippa et al., 2009). For example, a modest positive correlation between social anxiety and perceived helpfulness of medical cannabis was found among patients recruited from dispensaries in California ($r = 0.21$; 34). A recent study of 367 patients recruited from medical cannabis dispensaries in Arizona found that, among those who endorsed symptoms of anxiety, 83% reported "*a lot or almost complete relief*" of their anxiety when using medical cannabis (82.9%; Troutt and Didonato, 2015). However,
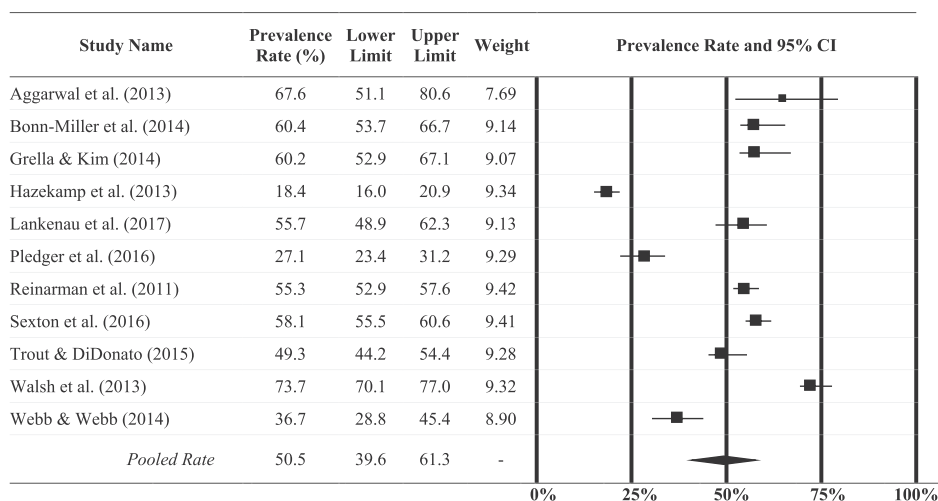
retrospective self-report data has also indicated that symptoms of anxiety may increase following the discontinuation of medical cannabis (Swift et al., 2005).

The use of medical cannabis for depression was endorsed by approximately 35% of participants in our pooled analysis (see Table 5). Troutt and Didonato (2015) found that 82% of patients with depression reported that medical cannabis resulted in "*a lot or almost complete relief*" of their depressive symptomatology (Turna et al., 2017). Poli et al. (2017) conducted a non-randomized trial of medical cannabis among 388 chronic pain patients. Results indicated a reduction in depressive symptoms at 12-month follow-up and a reduction in pain-related disability from baseline and 12-month follow-up (Poli et al., 2017). Pre-clinical findings have indicated that cannabidiol (CBD), a principal constituent of cannabis, may be a promising treatment for anxiety and depression (Zanelati et al., 2010; Linge et al., 2016; Blessing et al., 2015). However, we are not aware of any randomized-controlled, clinical trials of cannabidiol or medical cannabis for depression, and the National Academy of Sciences (2017) concluded there is no evidence yet to support the use of cannabis in the treatment of mood symptoms or disorders.

Collectively, these data indicate that pain, anxiety, and depression are common reasons that patients report as reasons for using medical cannabis. These conditions often present in comorbid fashion (Gureje et al., 2008; Arnow et al., 2006; Demyttenaere et al., 2007), and individuals may hold substance-related outcome expectancies that medical cannabis can ameliorate unpleasant physical and psychological states (Goldman, 1999). Indeed, cannabis users (vs. non-users) are more likely to endorse expectations that cannabis will reduce tension and physical discomfort (Schafer and Brown, 1991; Boden et al., 2013). In addition, among 1116 medical cannabis patients in Michigan, coping motives (e.g., forget your problems; to escape from your life) were the fifth most commonly endorsed reasons for using medical cannabis (Bohnert et al., 2018).

One possibility is that the reasons patients indicate for using medical cannabis differ from the actual degree of benefit experienced, and the reasons for which the prescription was written in the first place. For example, one study of 217 medical cannabis patients found that although anxiety (62%) and depression (45%) were commonly cited reasons for using medical cannabis, a much smaller percentage of the sample reported that cannabis actually helped in reducing their anxiety

Table 4

Forest plot: Use of cannabis for anxiety Symptoms.

Study Name	Prevalence Rate (%)	Lower Limit	Upper Limit	Weight	Prevalence Rate and 95% CI
Aggarwal et al. (2013)	67.6	51.1	80.6	7.69	
Bonn-Miller et al. (2014)	60.4	53.7	66.7	9.14	
Grella & Kim (2014)	60.2	52.9	67.1	9.07	
Hazekamp et al. (2013)	18.4	16.0	20.9	9.34	
Lankenau et al. (2017)	55.7	48.9	62.3	9.13	
Pledger et al. (2016)	27.1	23.4	31.2	9.29	
Reinarman et al. (2011)	55.3	52.9	57.6	9.42	
Sexton et al. (2016)	58.1	55.5	60.6	9.41	
Trout & DiDonato (2015)	49.3	44.2	54.4	9.28	
Walsh et al. (2013)	73.7	70.1	77.0	9.32	
Webb & Webb (2014)	36.7	28.8	45.4	8.90	
Pooled Rate	50.5	39.6	61.3	-	

Note. Summary statistics were computed via random effects meta-analysis.

Note. Summary statistics were computed via random effects meta-analysis.

(20%) and depression (10%) (Bonn-Miller et al., 2014b). In addition, among a sample of 1746 individuals who completed an assessment for medical cannabis in California, only 13% received a physician recommendation for medical cannabis to treat anxiety or depression, whereas 64% of the same sample reported using their prescription to help treat anxiety or depression (Reinarman et al., 2011).
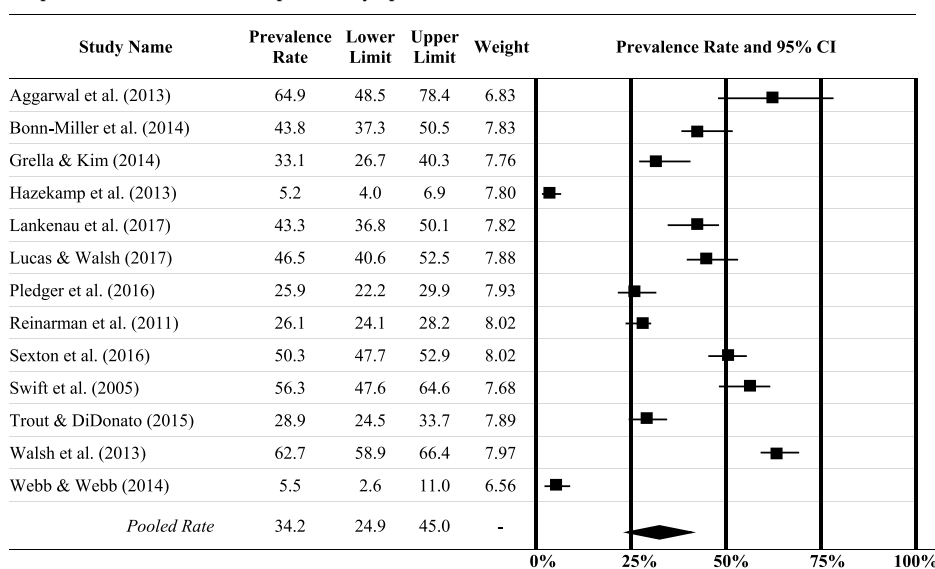
These data could also reflect the possibility that prolonged cannabis use might contribute to pain, anxiety, and depression. For example, results from longitudinal studies indicate a positive association between cannabis use and depression (Degenhardt et al., 2011, 2013; Lev-Ran et al., 2014). A recent meta-analysis of longitudinal studies found that cannabis use was associated with increased odds of anxiety ($OR = 1.15$; 95% $CI = 1.03, 1.29$). However, results were attenuated after adjusting

for publication bias and restricting to high quality studies, respectively (Twomey, 2017). A second meta-analysis pooled data from longitudinal, cohort studies of adults with anxiety and mood disorders ($k = 12$) to examine associations between baseline cannabis use with psychological symptoms (Mammen et al., 2018). Results indicated that past-6-month cannabis use was associated with greater mental health symptoms and lower treatment response (Mammen et al., 2018). Future research is needed that can examine both the short and long-term effects of medical cannabis in relation to pain, anxiety, and depression.

4.1. Conceptual and methodological considerations

Qualifying conditions for medical cannabis. High rates of

Table 5

Forest plot: Use of cannabis for depression Symptoms.

Study Name	Prevalence Rate	Lower Limit	Upper Limit	Weight	Prevalence Rate and 95% CI
Aggarwal et al. (2013)	64.9	48.5	78.4	6.83	
Bonn-Miller et al. (2014)	43.8	37.3	50.5	7.83	
Grella & Kim (2014)	33.1	26.7	40.3	7.76	
Hazekamp et al. (2013)	5.2	4.0	6.9	7.80	
Lankenau et al. (2017)	43.3	36.8	50.1	7.82	
Lucas & Walsh (2017)	46.5	40.6	52.5	7.88	
Pledger et al. (2016)	25.9	22.2	29.9	7.93	
Reinarman et al. (2011)	26.1	24.1	28.2	8.02	
Sexton et al. (2016)	50.3	47.7	52.9	8.02	
Swift et al. (2005)	56.3	47.6	64.6	7.68	
Trout & DiDonato (2015)	28.9	24.5	33.7	7.89	
Walsh et al. (2013)	62.7	58.9	66.4	7.97	
Webb & Webb (2014)	5.5	2.6	11.0	6.56	
Pooled Rate	34.2	24.9	45.0	-	

Note. Summary statistics were computed via random effects meta-analysis.

Note. Summary statistics were computed via random effects meta-analysis.

endorsing pain as a reason for use may be partly due to chronic pain being among the most common legally qualifying conditions for prescribing medical cannabis. Indeed, current chronic pain was reported by 53% of medical cannabis patients in Australia (Swift et al., 2005), and 58% in California (Nunberg et al., 2011). These findings are also consistent with state data indicating that severe/chronic pain is the most common condition for receiving medical cannabis (Park and Wu, 2017). For example, *severe pain* was the most frequent qualifying condition for medical cannabis prescriptions in Colorado as of January 31, 2014 (94%; Light and Lewandowski, 2014), and Oregon as of April 2017 (89%). Chronic pain was also reported by 84.12% of patients who were prescribed medical cannabis in Arizona, as of May 2017. In the United States, California provides the broadest range of conditions for which medical cannabis can be legally prescribed (Compassionate Use Act, 2003), and only a small minority of those patients (13%) received medical cannabis for anxiety or depression (Reinarman et al., 2011). As a result, it is useful to consider the current legal indications for medical cannabis when interpreting current findings.

Recruitment location/methods. The legal status of medical cannabis may influence patient-reported reasons for use. For example, pain was the most common reason reported for medical cannabis use among a sample of 94 patients returning for a refill of their prescription in Hawaii (91%; Webb and Webb, 2014), a state where pain is one of the only conditions for which medical cannabis is legally indicated. Recruitment methodology may also influence stated reasons for using medical cannabis. For example, four out of 13 (31%) of the studies identified in this review utilized patient samples recruited in California (see Table 1), which may not be representative of the general population of medical cannabis users (Troutt and Didonato, 2015). Additionally, the lowest rates of endorsing pain (29%), anxiety (18%), and depression (5%) as reasons for medical cannabis use were reported in the only international online sample, which required participants to have self-reported the use of two or more types of cannabinoid-based medicines (Müller-Vahl and Grotenhermen, 2017). Finally, depression was especially common as a reason for medical cannabis use (65%) among a sample of patients recruited from a dispensary in Washington state (Aggarwal et al., 2013). There patients were recruited based on having self-selected a high tetrahydrocannabinol (THC) strain called "plum", which might have influenced the findings (Aggarwal et al., 2013).

Methodological quality and publication bias. Convenience samples are often biased representations of the larger population (Jeong et al., 2018), and none of the studies included in the current meta-analysis utilized nationally-representative samples. Furthermore, researchers have raised concerns about potential methodological bias in published research examining reasons for using medical cannabis (Park and Wu, 2017). However, a recent investigation observed minimal selection and respondent bias among samples of medical cannabis users recruited from both dispensaries and online surveys in California (Thomas and Freisthler, 2017), and venue-based sampling is a recommended approach to understanding specific populations (Rothman et al., 2013), including medical cannabis users (Thomas and Freisthler, 2016). Results of the current study indicated that composition of the individual studies in terms of sex and risk of bias did not help explain the heterogeneity observed across studies. Excluding studies deemed at high risk of bias also did not significantly change the results. Common methodological limitations included infrequent use of randomized recruitment, restrictive sampling frames, and a general lack of standardized self-report measures (see Table 2). However, the current assessment of study quality was based on a single instrument that required some degree of subjectivity, and these ratings do not define the utility of individual studies. The single study that used a randomized recruitment strategy was also the only study that was classified as having a low risk of bias (Pledger et al., 2016). No evidence for publication bias was observed using meta-analytic methods.

4.2. Clinical implications

Pain, anxiety, and depression frequently co-occur and often go undiagnosed and undertreated (Meghani et al., 2012; Vermani et al., 2011). Healthcare providers are increasingly likely to encounter individuals seeking medical cannabis to self-medicate or cope with these symptoms (Walsh et al., 2017). This raises a number of clinical issues, including potentially unexpected consequences of cannabis use and the importance of ongoing education for both providers and patients.

Consequences of medical cannabis use. Medical cannabis patients appear to use cannabis in greater amounts and with greater frequency than recreational users (Compton et al., 2017a; Lankenau et al., 2017; Sznitman, 2017), and there is some evidence that cannabis use may worsen anxiety and depression over time. A recent systematic review concluded there is limited-to-moderate evidence implicating cannabis use in the development of anxiety and depressive disorders (National Academies of Sciences, 2017). Indeed, lifetime cannabis use has been associated with increased odds of being diagnosed with panic disorder (Zvolensky et al., 2006), and recent meta-analytic data indicate that cannabis users (OR: 1.17; 95% CI = 1.05, 1.30), and particularly heavy users (OR: 1.62; 95% CI = 1.21, 2.16), are at increased risk for developing depression (Lev-Ran et al., 2014). Thus, the long-term implications of using medical cannabis for anxiety and depression remain unclear.

Medical cannabis use may also result in unwanted physical health effects. Chronic exposure to THC can produce neurotoxic effects and cognitive impairment (Volkow et al., 2014). Regular, heavy use of medical cannabis may also result in tolerance to analgesic effects via downregulation of cannabinoid receptors (D'souza et al., 2016). Thus, one possibility is that patients who report pain as a motive for using medical cannabis may find that they increasingly require larger or more frequent doses to achieve the initial analgesic effect (Wakley et al., 2014). However, some research has also shown no increase in analgesic efficacy of medical cannabis over time (Ware et al., 2015, Maccallum and Russo, 2018).

Clinician knowledge, acceptance, and education. Research has only begun to examine attitudes of healthcare practitioners toward medical cannabis. For example, the majority of family physicians in Colorado reported that formal training should be a requisite to certifying patients for medical cannabis and that continuing education on medical cannabis should be readily available (Kondrad and Reid, 2013). A survey study in Canada indicated that 80% of physicians desired more information on medical cannabis (Charuvastra et al., 2005). Limited provider acceptance and education may contribute to variability in prescribing practices and acceptance of medical cannabis (Karanges et al., 2018). For example, providers often do not recommend a specific dose, THC-to-CBD ratio, or strain of medical cannabis to their patients (Fletcher, 2013), despite data indicating that medical cannabis may have a narrow therapeutic window for certain conditions (i.e., chronic pain; Wallace, 2007). Healthcare providers play an important role in educating patients on the therapeutic use of medical cannabis specific to the patient's reason for use. Providers might consider collaborating with patients to set specific and measurable treatment goals tailored to individual motivations for seeking medical cannabis.

5. Limitations

The current results must be interpreted in the context of the statistical and methodological limitations of the included studies and of the overall data-analytic approach. First, while some studies asked users to report reasons for their medical cannabis use based on a list of possible symptoms (e.g., Sexton et al., 2016), other studies did not report the exact phrasing of their response options (e.g., Hazekamp et al., 2013; Lucas and Walsh, 2017). For example, while many studies phrased questions to reflect the present tense (e.g., "Which of the

following symptom-relieving purposes do you use medical marijuana?"; Aggarwal et al., 2013), only one study explicitly asked participants to consider a specific timeframe regarding their reasons for using medical cannabis (past 90 days; Lankenau et al., 2017). In addition, most studies assessed symptoms (vs. disorders) as reasons for use, one study collected self-report data on mental health history (Bonn-Miller et al., 2014b), and one study extracted diagnostic data from electronic medical records (Reinarman et al., 2011). Future research should include a more fine-grained analysis of symptom endorsement and severity (including symptom count and duration), in relation to the initiation and maintenance of medical cannabis.

Second, although the current study focused on symptoms of pain, anxiety, and depression, some patients also reported other reasons for using medical cannabis (e.g., loss of appetite; post-traumatic stress; Troutt and Didonato, 2015). Given that the majority of studies allowed participants to report on a variety of reasons for using medical cannabis, future research would benefit from conducting a more comprehensive accounting of all reasons patients cite for using medical cannabis.

Individual studies were included in the present analyses if they reported the ratio of the percentage of persons indicating specific reason for using medical cannabis (numerator) within the specific study sample (denominator). These samples approximate the general population of medical cannabis users with varying degrees of accuracy and are subject to differences in terms of recruitment, definition of the numerator (i.e., reason for medical cannabis use), and parameters of individual study samples (Mccaffrey et al., 2000). For example, while some studies used recruitment and sampling strategies designed to help generate representative populations of medical cannabis users (Bonn-Miller et al., 2014b), others utilized convenience sampling (Webb and Webb, 2014). Thus, pooled estimates must be considered in the context of the methodological limitations of the included studies. The current meta-analysis did not identify enough studies to test associations between reasons for use of the strain and potency of the medical cannabis that was prescribed. Seven of the identified studies recruited from dispensaries and only one study validated medical cannabis prescriptions using chart review (Reinarman et al., 2011). Meta-analytic methods limited testing of between-study heterogeneity to study-level variables that were uniformly assessed (i.e., risk of bias score, sex distribution). It is likely that other sources of heterogeneity exist that we were not able to examine using meta-analytic methods among the available studies (e.g., length of medical cannabis use, prior use of recreational cannabis). Future research might use longitudinal cohort studies to examine the influence of individual-level variables such as a history of recreational cannabis use or cannabis use disorder (Boden et al., 2017).

5.1. Future research directions

Recruitment methodology. Future research designs should employ rigorous sampling strategies, including those that capture users regardless of their medical cannabis strain, prior history of medical cannabis use, and state residence. For example, random sampling procedures could be used to recruit patients from medical cannabis registries or assessment clinics that allow for verification of prescription data. In addition, standardized instruments could be used to assess patients' cannabis use history, including recreational use, initial motivation for seeking medical cannabis and continued use over time. Although the current study focused on medical cannabis users, we were not able to assess the potentially confounding influence of concomitant recreational cannabis use. Rapidly evolving legislation governing the use of medical cannabis has resulted in geographic differences in legality, availability, and acceptance of medical cannabis (Klieger et al., 2017). The most common recruitment location among identified studies was the state of California, which limits generalizability to other states. Future research might usefully consider associations between medical

cannabis legislation and patterns of use (e.g., Sarvet et al., 2018). For example, a sampling strategy and statistical approach that incorporates multi-level modeling may allow for testing differences in reasons for medical cannabis use across dispensaries/clinics, nested within states or regions (Keyes et al., 2016).

Assessment instruments. Self-report measures of cannabis use outcome expectancies (Bohnert et al., 2018; Connor et al., 2011), consumption patterns (Cuttler and Spradlin, 2017), and dependence (Bonn-Miller et al., 2016), have been developed and validated among recreational users. However, only one measure of cannabis use motives has been tested among medical users (Bohnert et al., 2018) and there are no validated self-report measures that assess reasons for medical cannabis use. Future research is needed to develop and validate measures that are more specific in terms of assessing expectancies, reasons for use, and therapeutic effects of medical cannabis. Measures that define symptoms in lay language, discriminate among specific symptoms as reasons for use (e.g., panic attacks vs. generalized worry), reference a specific timeframe (e.g., past two weeks), and follow established measurement development strategies would improve our understanding of reasons for medical cannabis use (Boateng et al., 2018). Furthermore, measures that identify between reasons for initially seeking medical cannabis as well as reasons for currently using medical cannabis could help inform empirically supported cannabis policy. Consistent and standardized assessment will enable more direct comparison of findings and replication across recruitment settings and locations.

Diagnostic assessment of pain, anxiety and mood. The current review did not identify a single study that reported complete diagnostic data regarding the psychological disorders/symptoms or physical health diagnosis that medical cannabis was being prescribed to treat. Further examination of a potential discrepancy between the diagnostic targets, relative to self-reported reasons for using medical cannabis is needed. This is especially relevant given that the percentage of patients reporting multiple reasons for use could be a function of the co-occurrence of pain with psychiatric symptoms including anxiety and depression (Arnow et al., 2006; Atkinson et al., 1991; Dersh et al., 2002a, 2002b). The current meta-analysis was unable to examine number of reasons for medical cannabis use given the nature of study-level data, and future research should assess for patterns in the number and combination of reasons for medical cannabis use (PATEL, 2017).

5.2. Post-traumatic stress disorder

The current study focused on pain and mental health symptoms of anxiety and depression as reasons for medical cannabis use. This decision was made a-priori given that patients frequently report using medical cannabis to manage these symptoms (Park and Wu, 2017), anxiety and depression are among the most common psychiatric problems encountered by physicians (Kroenke et al., 2007; Gaynes et al., 2007), and given that PTSD is a relatively recent addition to the legally-indicated reasons for medical cannabis use. Future research is needed to examine other mental health conditions as possible reasons for medical cannabis use (Walsh et al., 2017; Bonn-Miller et al., 2014a; Short et al., 2015). In particular, PTSD is now a qualifying condition for medical cannabis in at least 28 U.S. states (Shishko et al., 2018), is often co-morbid with anxiety and depression (Price et al., 2018), and is common among treatment-seeking chronic pain patients (Siqveland et al., 2017). A recent systematic review concluded that there is insufficient evidence regarding the benefits and harms of medical cannabis among those with post-traumatic stress disorder (PTSD; O'neil et al., 2017), but rigorous clinical trials are underway (Bonn-Miller and Paula, 2015). Unfortunately, only a minority ($n = 5$) of the studies identified in the current review assessed PTSD symptoms as a patient-reported reason for using medical cannabis (e.g., Bonn-Miller et al., 2014b), and many were conducted prior to the increase in PTSD as a qualifying condition. Across studies identified here, rates of medical

cannabis use for PTSD ranged from 1% to 18.9% (Bonn-Miller et al., 2014b; Swift et al., 2005).

Examination of sex and age differences. Studies included in the current quantitative synthesis were comprised mostly of male medical cannabis users (54.6%–74.0%). While we did not observe evidence of sex-based differences in reasons for medical cannabis use, our analysis was limited to examining between-study differences. Future meta-analytic research should examine sex differences in reasons for medical cannabis use, as they may have implications for recommending and monitoring the use of medical cannabis. For example, there is evidence that males (compared to females) tend to experience greater cannabis-induced analgesia (Cooper and Haney, 2016), use cannabis at a higher frequency (Cuttler and Spradlin, 2017), and are more likely to increase their dose of medical cannabis (Swift et al., 2005). Reasons for using medical cannabis may also differ as a function of age. For example, it is more common for middle-aged individuals to report insomnia as a reason for medical cannabis use, while older adults are more likely to endorse medical conditions such as cancer, glaucoma, and HIV/AIDS (Haug et al., 2017).

6. Summary

This meta-analytic review is the first to examine the prevalence of patient-reported use of medical cannabis for pain, anxiety, and depression symptoms. Results indicated that a substantial portion of patients reported pain (64%), anxiety (50%), and depression/mood (34%) as reasons for medical cannabis use, and there was no evidence for publication bias. These results highlight the multiple reasons patients seek and use medical cannabis, despite limited empirical data of its therapeutic efficacy for certain symptoms. The assessment of study quality and risk of bias identified several methodological and conceptual limitations that may help guide future research. Examples include the development of validated patient questionnaires that assess reasons for medical cannabis use, and utilization of randomized recruitment procedures.

Acknowledgments

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