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Review

Medical cannabis and mental health: A guided systematic review

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HIGHLIGHTS

- Mental health conditions are prominent among the reasons for medical cannabis use.
- Cannabis has potential for the treatment of PTSD and substance use disorders.
- Cannabis use may influence cognitive assessment, particularly with regard to memory.
- Cannabis use does not appear to increase risk of harm to self or others.
- More research is needed to characterize the mental health impact of medical cannabis.

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ABSTRACT

This review considers the potential influences of the use of cannabis for therapeutic purposes (CTP) on areas of interest to mental health professionals, with foci on adult psychopathology and assessment. We identified 31 articles relating to the use of CTP and mental health, and 29 review articles on cannabis use and mental health that did not focus on use for therapeutic purposes. Results reflect the prominence of mental health conditions among the reasons for CTP use, and the relative dearth of high-quality evidence related to CTP in this context, thereby highlighting the need for further research into the harms and benefits of medical cannabis relative to other therapeutic options. Preliminary evidence suggests that CTP may have potential for the treatment of PTSD, and as a substitute for problematic use of other substances. Extrapolation from reviews of non-therapeutic cannabis use suggests that the use of CTP may be problematic among individuals with psychotic disorders. The clinical implications of CTP use among individuals with mood disorders are unclear. With regard to assessment, evidence suggests that CTP use does not increase risk of harm to self or others. Acute cannabis intoxication and recent CTP use may result in reversible deficits with the potential to influence cognitive assessment, particularly on tests of short-term memory.

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1. Background

The first decades of the 21st century have witnessed a dramatic resurgence of interest in the therapeutic potential of cannabis. In response, a growing number of countries and jurisdictions have initiated or expanded programs to allow legal access to cannabis for therapeutic purposes (CTP). Although the majority of CTP programs specifically focus on the use of cannabis for symptoms associated with physical health disorders (e.g. arthritis, cancer, chronic pain; see Belendiuk, Baldini, & Bonn-Miller, 2015 for a review), a substantial portion of CTP use aims to address mental health concerns, and CTP users evince substantial levels of psychiatric comorbidity (Bonn-Miller, Boden, Bucossi, & Babson, 2014; Walsh et al., 2013). As such, mental health practitioners are increasingly likely to encounter CTP use in the course of clinical practice.

Cannabis is among the world's most widely used psychoactive substances, and the associations between cannabis use, cognition, and mental health have been the subject of substantial research. Nonetheless, the implications of CTP use for mental health remain somewhat unclear as extant research has focused primarily on negative consequences associated with illicit, non-medical use of cannabis (NMC), and although this research can contribute to understanding the potential consequences of CTP use, differences in comorbidity, motivations, and patterns of use complicate generalizing from NMC to CTP. In order to provide a comprehensive review and synthesis of the literature regarding the impact of CTP on issues of concern to mental health practitioners, the current review integrates parallel reviews of the nascent research on CTP and the more developed research on NMC.

1.1. Cannabis strains and cannabinoids

User reports and pharmacological analyses unequivocally point to diversity across types - or strains - of herbal cannabis and understanding the diverse consequences of cannabis use may be furthered by the appreciation of the variety of agents that underlie the psychoactivity of cannabis. Herbal cannabis may contain over 100 distinct cannabinoid compounds that are unique to cannabis, several of which have proven, or potential, psychoactive effects. The most prominent and well-characterized cannabinoids are Δ^9 – THC (THC) and cannabidiol (CBD), with THC being the primary agent responsible for the psychoactivity of cannabis (Schier et al., 2012). The distinct influences of THC and CBD are particularly salient with regard to psychosis and anxiety where they may exert contradictory influences (Crippa et al., 2009; Zuardi, Crippa, Hallak, Moreira, & Guimarães, 2006). Strains of cannabis vary substantially with regard to concentrations of THC and CBD, and adding complexity to the unique and combined influences of THC and CBD are the still obscure influences of the many other cannabinoids and terpenes that are present to differing degrees across strains. These diverse constituents have been proposed to engage in interactions described as entourage effects (Russo, 2011), such that strains of cannabis with distinct profiles of THC, CBD, and other constituents may differ with regard to psychoactive and therapeutic effects (Russo & Guy, 2006; Russo & McPartland, 2003; Schier et al., 2012).

The phenomenological importance of strain-type is reflected in a recent study in which over 80% of CTP users reported variable effectiveness across strains (Walsh et al., 2013). Popular discourse and promotion of CTP also tout salutary features of distinct strains (e.g., Leafly.com), and federal health authorities have allowed for such distinctions to be included – with caveats - on product labelling (e.g. Health Canada). Percentages of THC and CBD content are prominent features of strain distinctions, as is the still-debated botanical distinction between *Cannabis sativa* and *Cannabis indica*, with the former reputed to have more stimulating effects and the later putatively more sedative. However, although there are clear pharmacological and morphological differences across strains, evidence germane to this topic is not strong, as few human studies have compared the effects of differing levels of cannabinoids (Ilan, Gevins, Coleman, ElSohly, & de Wit, 2005; Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002), and methodological factors complicate generalizing from the relatively limited range compared in these studies to the diverse strains and products available to many CTP users (Russo & McPartland, 2003). Estimating the relative effectiveness of different cannabis strains for diverse outcomes requires further research; nonetheless, strain-level differences are salient to CTP users and are promising candidates to help explain the apparently divergent effects of cannabis.

2. Methodology

To systematically review research elucidating the influence of CTP use on adult psychopathology and psychological assessment, we comprehensively review studies of CTP and meta-review studies of NMC. Throughout, we adopt an integrative approach that allows for review of diverse methodologies including longitudinal, cross-sectional, and lab-based studies (Whittemore & Knafl, 2005). The review is organized as mini-reviews of areas of interface between CTP and clinical practice, with discussion of implications, quality of evidence, and areas requiring further investigation. Topics reviewed include substance use, anxiety, affective, and psychotic disorders, cognitive functioning, and risk for harm to self and others.

2.1. Search strategy

Our inclusion of research from medical and nonmedical contexts involved a mixed search methodology. To identify research on CTP use we searched electronic databases (Psycinfo, Medline) for all published studies between 1960 and September 2015 on medical OR therapeutic cannabis OR marijuana AND anxiety disorder, posttraumatic stress disorder, social anxiety disorder, substance dependence, substance abuse, substance use disorder, tobacco, cocaine, alcohol, opiates, heroin, amphetamine, depression, bipolar, mania, mood disorder, psychosis, schizophrenia, neuropsychology, neurocognitive, IQ, intelligence, violence, intimate partner violence, suicide, suicide risk. Article titles and abstracts were reviewed and studies were included if they addressed the association of CTP use with these outcomes (Fig. 1). The literature on NMC and mental health is voluminous and diverse, thus we conducted a more guided and exclusive review focusing on meta-analytic and systematic reviews using a strategy parallel to that described above, but omitting the terms medical OR therapeutic, and adding the terms review OR meta-analysis OR meta-analytic (Fig. 2).

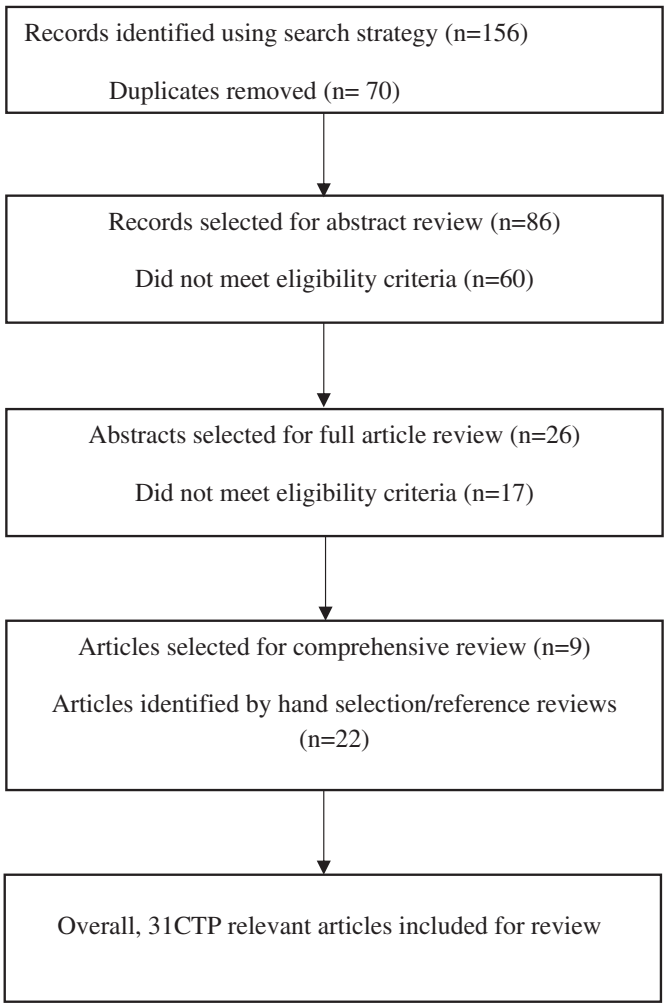

Fig. 1. Flowchart of CTP study selection.

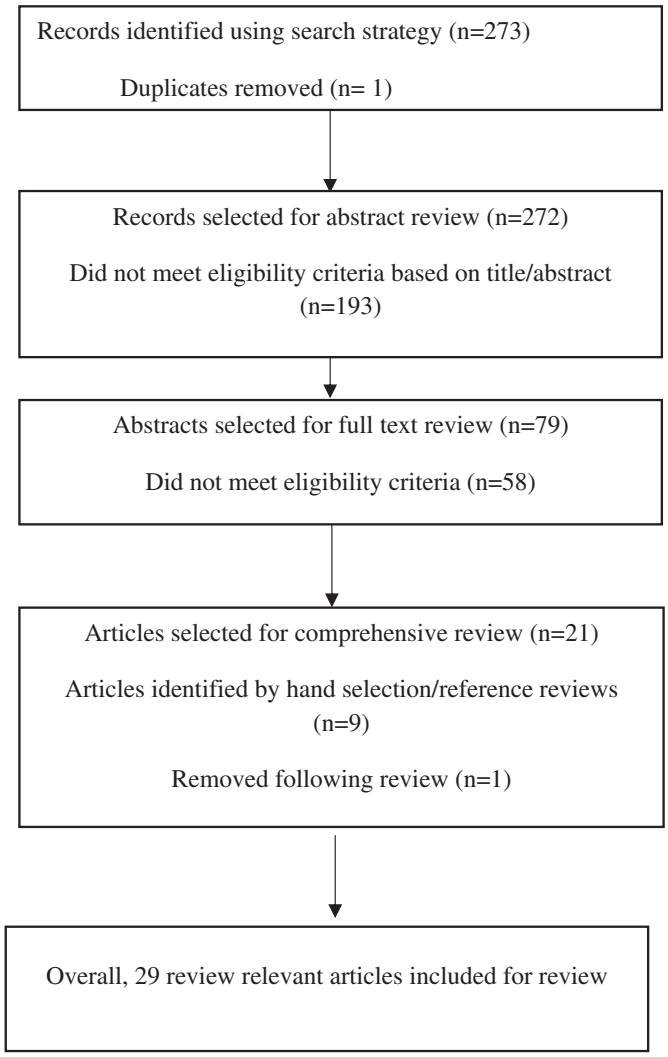

Fig. 2. Flowchart of review study selection.

2.2. Quality assessment

Studies of CTP were predominantly cross-sectional and we assessed the quality of these studies on a 10-point scale based on a version of the Newcastle-Ottawa Scale (Wells et al., 2000) adapted to evaluate cross-sectional studies (Herzog et al., 2013). Assessment was based on dimensions including measurement of outcome, sample selection, and comparability of groups. Reviews of NMC were assessed using the AMSTAR checklist which evaluates the quality of reviews along 11 face-valid criteria (Shea et al., 2007). For both measures higher scores indicate better quality of evidence.

3. Results

Our CTP search identified 31 studies, with a total of 23,850 participants. Of these studies 87% (27) were cross-sectional and 68% (21) were US samples. Recruitment from medical cannabis dispensaries was the most frequent method of data collection (42% (13)), followed by recruitment from clinics that specialize in disorders for which CPT use is prominent (e.g. pain, M.S.) (19% (6)), and reviews of records from clinics that focus on providing assessments for eligibility to access CTP (19% (6)). Evaluation of the quality of the CTP studies indicated that most were not of methodologically high quality (Table 1); ratings ranged from 3 to 7 of a possible 10 points and with a median rating of 4. Preliminary review of our NMC search identified several reviews related to cannabis and psychosis, including recent meta-reviews; therefore, to avoid redundancy we limited our review of psychosis to reviews published after 2010. This search identified 29 reviews germane to the impact of NMC on mental health, of which 38% (11) were meta-analyses, 31% (9) were systematic reviews, and 31% (9) were narrative reviews (Table 2). The quality of these reviews were variable ranging from 1 (narrative reviews) to 8 of a possible 11 points, with a median score of 4. We supplemented areas in which reviews were absent or incomprehensive with studies identified through manual search.

3.1. Adult psychopathology

3.1.1. Problematic substance use

Addiction treatment is a prominent context in which mental health care providers might encounter the use of cannabis. In this context, NMC may be a primary focus of treatment or a potentially complicating factor in the treatment of problematic use of another substance (Roffman & Stephens, 2006). These conceptualizations are qualified by the use of CTP; the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) notes, with regard to the assessment of cannabis use disorder, that "Although medical uses of cannabis remain controversial and equivocal, use for medical circumstances should be considered when a diagnosis is being made." (pp. 512), and further suggests that medical use should be considered in establishing the clinical significance of tolerance and withdrawal symptoms. In contrast, prior editions of the DSM (e.g.,

Table 1
Study characteristics - cannabis for therapeutic purposes.

	N (% female)	Location	Recruitment	Conditions	Design & quality	Key relevant findings
Aggarwal et al., 2012	37 (35)	Washington, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	Prominent reasons for using CTP included anxiety (71%), mood (69%), and depression (12%).
Ashrafioun et al., 2015	433 (31)	Midwestern US	Patients from a specialized clinic	Pain	Cross-sectional (7)	Using of CTP for pain reported by 15% of patients in addictions treatment. Use of CTP for pain was associated with higher levels of past year substance use.
Babson et al., 2013	162 (22)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (6)	Participants with higher level of depressive symptoms reported more problematic cannabis use. This relation was moderated by sleep quality.
Bedi et al., 2010	7 (0)	New York, US	Self-identified from the community	HIV	Laboratory	Dronabinol enhanced mood among cannabis using participants across the 16 day study period.
Boden, Babson et al., 2013	153 (22)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	The combination of cognitive reappraisal and emotional clarity was associated with problematic cannabis use among CTP users.
Bohnert et al., 2014	186 (38)	Michigan, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (5)	Twenty -three percent of patients seeking CTP for the first time screened positive for PTSD. Those with PTSD had higher rates of substance use relative to CTP seeking patients without PTSD.
Bonn-Miller et al., 2014a	170 (22)	California, US	Medical cannabis dispensary	PTSD and sleep	Cross-sectional (6)	Greater severity of PTSD was associated with more frequent cannabis use, and with use to help with sleep and to cope with negative affect.
Bonn-Miller, Boden et al., 2014	217 (27)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	Reported benefits of CTP include reductions of stress (24%), anxiety (20%), depression (10%), and PTSD symptoms (4%). CTP was reported to be particularly helpful among participants with greater levels of traumatic intrusions and lower levels of well-being.
Boyd, Veliz, & McCabe, 2015	4394 (47)	US	National surveillance survey	Other substance use	Cross-sectional (5)	Adolescent medical cannabis users were approximately 2 times more likely to report the nonmedical use of prescription drugs and illicit substances other than cannabis.
Grella et al., 2014	182 (26)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (3)	Primary reasons for CTP use included anxiety (60%), insomnia (56%), chronic pain (42%), depression (33%), and ADHD (17%).
Greer et al., 2014	80 (20)	New Mexico, US	Medical evaluations of patients seeking CTP	PTSD	Cross-sectional (5)	Patients who used CTP reported reductions of 75% in symptoms of trauma related re-experiencing, avoidance, and hyperarousal.
Harris et al., 2000	100 (16)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	Mental health conditions were cited as the primary reason for CTP use among 15% of respondents. Patients reported that CTP was more effective than other treatments for psychiatric problems.
Lucas et al., 2015	404 (33)	British Columbia, Canada	Medical cannabis dispensary	Substance use disorders	Cross-sectional (4)	Cannabis use to substitute for medications was reported by 67%, substitution for alcohol reported by 41%, and substitution for illicit drugs reported by 36%.
Mikuriya, 2004	92 (9)	California, US	Medical evaluations of patients seeking CTP	Alcohol use disorder	Cross-sectional (3)	All participants reported cannabis use as effective for reducing drinking, 28% reported cannabis as effective for depression, and 20% reported cannabis as effective for anxiety
Nunberg et al., 2011	1655 (27)	California, US	Medical evaluations of patients seeking CTP	Diverse medical conditions	Cross-sectional (6)	Reported mental health benefits CTP included relief of anxiety (38%), depression (26%), anger (23%), and panic (17%), as well as substitution for alcohol (13%).
O'Connell & Bou-Matar, 2007	4117 (23)	California, US	Medical evaluations of patients seeking CTP	Diverse medical conditions	Cross-sectional (3)	Participants reported high levels of past substance use, and subsequent substitution with cannabis. Male respondents reported high levels of adolescent ADHD, suggesting CTP use to address inattention.
Ogborne et al., 2000	50 (34)	Ontario, Canada	Self-identified from the community	Diverse medical conditions	Cross-sectional (6)	Reported mental health benefits of CTP included relief of depression (24%), anxiety (22%), and heroin craving (4%).
Page & Verhoef, 2006	14 (57)	Alberta, Canada	Patients from a specialized clinic	Multiple Sclerosis	Cross-sectional (3)	Patients reported that the perceived benefits included general relaxation and decreased stress.
Reiman, 2007	130 (25)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (3)	History of treatment for problematic alcohol use was reported by 19%, and slightly fewer than 50% of CTP users reported using cannabis as a substitute for alcohol and illicit drugs.

Table 1 (*continued*)

	N (% female)	Location	Recruitment	Conditions	Design & quality	Key relevant findings
Reiman, 2009	350 (32)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (3)	Using CTP to address mental health concerns was reported by 75% of respondents. Substituting cannabis for alcohol was reported by 40% of respondents, and 26% reported substituting cannabis for illicit drugs.
Reinarman et al., 2011	1746 (27)	California, US	Medical evaluations of patients seeking CTP	Diverse medical conditions	Cross-sectional (3)	Reported mental health benefits CTP included relief of anxiety (38%), depression (26%), anger (23%), and panic (17%), as well as substitution for alcohol (13%).
Richmond et al., 2015	7875 (49)	Colorado, US	Patients from a general clinic	Diverse medical conditions	Cross-sectional (7)	Relative to nonmedical cannabis users, CTP users engaged in lower levels of high risk use of alcohol and use of other substances, including tobacco.
Roitman et al., 2014	10 (30)	Jerusalem, Israel	Patients from a specialized clinic	PTSD	Open-label trial	Use of oral THC was associated with reduced symptom severity, improved sleep quality, reduced frequency of nightmares, and reduced symptoms of hyperarousal.
Short, Babson, Boden, & Bonn-Miller, 2015	151 (23)	California, US	Medical cannabis dispensary	PTSD	Cross-sectional (6)	Among patients with problematic cannabis use, poor sleep quality is associated with greater severity of PTSD symptoms. Sleep quality is not associated with increased severity of symptoms among those without problematic cannabis use.
Swift et al., 2005	128 (37)	New South Wales, Australia	Self-identified from the community	Diverse medical conditions	Cross-sectional (3)	Reported mental health benefits included relief of depression (56%), and general relaxation (75%). Depression or anxiety symptoms were reported to return with cessation of CTP use among 30% of respondents.
Swartz, 2010	13 (15)	California, US	Patients from a specialized clinic	Substance use disorder	Cross-sectional (6)	Participants who used CTP demonstrated outcomes for treatment completion and progress at discharge (69%) that were comparable or superior to a comparison groups of non-CTP users in treatment (41%).
Ware et al., 2015	431 (57)	Canada	Patients from a specialized clinic	Neurocognition	Prospective cohort study	CTP users did not differ from controls with regard to neurocognitive functioning at one-year follow-up.
Ware et al., 2010	23 (52)	Quebec, Canada	Patients from a specialized clinic	Chronic neuropathic pain	Randomized controlled trial	Participants receiving the highest dose of THC demonstrated improvements in anxiety and depression relative to those receiving cannabis with no THC.
Walsh et al., 2013	628 (29)	Canada, National	Self-identified from community, and dispensary	Diverse medical conditions	Cross-sectional (3)	Reported mental health benefits of CTP use included relief of anxiety (56%), and depression (67%).
Webb & Webb, 2014	94 (no data)	Hawaii, US	Medical evaluations of patients seeking CTP	Diverse medical conditions	Cross-sectional (3)	Reported mental health benefits of CTP use included relief from anxiety and stress (50%), and relief from depression (7%).
Woolridge et al., 2005	523 (8)	London, UK	Patients from a general clinic	HIV	Cross-sectional (4)	Reported mental health benefits of CTP use included relief from anxiety (61%), and relief from depression (45%).

Note: Ratings provided for cross-sectional studies (/10).

DSM-IV; APA, 2000) make no comment on the diagnostic impact of CTP, thus highlighting changing perspectives on cannabis use. Nonetheless, the caution related to CTP differs from the caution regarding opiate-related disorders, where medical use explicitly precludes assessment of tolerance and dependence symptoms (APA, 2013).

We identified two cross-sectional studies of CTP users that explicitly examined use of other psychoactive substances (Ashrafioun, Bohnert, Jannausch, & Ilgen, 2015; O'Connell & Bou-Matar, 2007). Among clients in an abstinence-based addictions treatment program, approximately 15% used CTP to treat pain, and these individuals reported higher rates of past alcohol, cannabis, cocaine, and opiate use than did the non-CTP group (Ashrafioun et al., 2015). Similarly, a methodologically lower quality study of self-selected CTP program applicants in California identified high levels of lifetime substance use. That study also reported reduced use from adolescence to adulthood, which led the authors to suggest that CTP use may have been protective against the development of problematic use of other substances (O'Connell & Bou-Matar, 2007). However, the results of these cross-sectional studies do not directly speak to the extent to which cannabis is being used as a substitute for other substances or whether prior substance use leads to increased acceptability of and interest in CTP.

Risk for addiction and misuse are prominent concerns among clinicians considering recommending CTP. However, evidence regarding transition from therapeutic to problematic use is scant. The two cross-sectional studies that have examined problematic cannabis use among CTP users identify depression, sleep disturbance, and cognitive style as risk factors for problematic use (Babson, Boden, & Bonn-Miller, 2013; Boden, Gross, Babson, & Bonn-Miller, 2013), which is similar to the patterns of risk evidenced for problematic cannabis use among non-medical users (e.g., Degenhardt, Hall, & Lynskey, 2003). In light of increasing uptake of CTP, the further specification of risk and protective factors for transition to problematic use is a research priority. Longitudinal examinations of the association between therapeutic and problematic cannabis use are required to elucidate this issue and thereby facilitate informed comparison of the risks and benefits of CTP relative to other treatments.

Table 2
Study characteristics – reviews of nonmedical cannabis use and mental health.

	Study type (# studies)	Conditions	Quality	Conclusions
Abel, 1977	Narrative review	Interpersonal violence	1	Cannabis use does not increase risk for violence among adults.
Ashton et al., 2005	Narrative review	Bi-polar disorder	1	Both THC and CBD have pharmacological properties that could reduce bipolar symptoms due to sedative, anxiolytic, and antidepressant effects.
Bally et al., 2014	Narrative review	Bi-polar/manic episodes	2	Approximately 30% of patients with bipolar disorder have concurrent cannabis abuse or dependence. Younger age of first-episode mania is related to cannabis use. The causal nature of the relation between CU and bipolar disorder has not been determined.
Calabria et al., 2010	Systematic review (19)	Suicide	6	Extant literature is unclear regarding whether cannabis use is associated with increased risk of suicide.
Cairns et al., 2014	Systematic review and meta-analysis (113)	Depression	7	Cannabis use in adolescence is associated with higher levels of depression.
Carrà et al., 2014	Systematic review and meta-analysis (29)	Bipolar disorder/Suicide attempts	7	A lifetime cannabis use disorder was associated with increased odds of suicide attempts in individuals with bipolar disorder.
Crane et al., 2013	Narrative review	Neurocognitive effects	2	Cannabis use is associated with acute and non-acute cognitive deficits in episodic memory. Evidence of broader deficits relating to attention and concentration is mixed and effects may be moderated by sex and by developmental period of cannabis use initiation.
Crean et al., 2011	Narrative review	Neurocognitive effects	2	Cannabis use has acute negative effects on attention, memory, and information processing that are primarily acute and generally remit after a month of abstinence. Frequent use beginning in adolescence may be associated with more persistent executive function deficits.
Crippa et al., 2009	Systematic review	Anxiety	3	Cannabis use and anxiety disorders commonly co-occur. Evidence exists for the anxiogenic effect of THC and the anxiolytic effect of CBD. Evidence regarding a causal relation between herbal cannabis use and anxiety is inconclusive.
Degenhardt et al., 2003	Systematic review	Depression	2	Cannabis use is associated with depression. Findings from cross-sectional and longitudinal data are mixed on the nature of this association.
Gage et al., 2015	Narrative review	Psychosis	1	Longitudinal studies generally support the association between cannabis use and later development of psychotic symptoms and schizophrenia
Gibbs et al., 2015	Systematic review and meta-analysis (6)	Mania	7	Cannabis use appears to exacerbate manic symptoms in individuals with biopolar disorders, and is associated with more new symptoms.
Gonzalez, 2007	Narrative review	Neurocognitive effects	1	Cannabis use has acute, transient negative effects on diverse areas of cognitive functioning. Long term effects are poorly characterized and most consistently identified among heavy cannabis users.
Grant et al., 2003	Meta-analysis (11)	Neurocognitive effects	5	Deficits in learning and memory are evident among heavy cannabis users.
Kedzior & Laeber, 2014	Meta-analysis (31)	Anxiety	6	Cannabis use evinces a small relation with anxiety disorders with and without comorbid depression. Evidence is insufficient to determine causality.
Lev-Ran et al., 2014	Systematic review and meta-analysis (14)	Depression	8	Risk for developing depressive disorders in increased among frequent cannabis users, relative to non-users or light users.
Macleod et al., 2004	Systematic review (16)	Substance use among adolescents and young adults	7	Cannabis use among adolescents and young adults is consistently associated with other substance use. No causal associations were identified between cannabis use and other substance use, poor psychological health, or other psychosocial problems.
Malchow et al., 2013	Systematic review (16)	Schizophrenia	4	Cannabis use does not appear to alter brain morphology prior to first episode psychosis, but may be involved in subsequent alterations.
Matheson et al., 2011	Systematic review (24)	Schizophrenia	8	Cannabis use has a medium-sized, dose-dependent effect on development of schizophrenia
Minozzi et al., 2010	Meta-review (5)	Psychosis	7	Analysis of five systematic reviews suggest a generally consistent association between cannabis use and psychotic symptoms; however causality cannot be established.
Moore & Stuart, 2005	Narrative review	Violence	1	There is insufficient laboratory evidence to suggest that acute cannabis intoxication can lead to interpersonal violence. Cross-sectional studies and longitudinal studies suggest a link between cannabis use and interpersonal violence.
Moore et al., 2008	Meta-analysis (96)	Intimate partner violence	5	Cannabis has a modest positive association with intimate partner aggression and violence.
Moore et al., 2007	Systematic review and meta-analysis (35)	Psychotic and affective disorders	8	Individuals with a history of cannabis use are at 40% increased risk of psychosis and related outcomes. Less evidence for increased risk of affective outcomes (i.e., depression, anxiety, suicidal ideation/attempts) with generally small effect sizes reported.
Peters et al., 2012	Systematic review (28)	Tobacco use	2	Cannabis use was not associated with tobacco use disorder or poor cessation outcomes
Rapp et al., 2012	Systematic review (19)	Psychosis	4	Evidence for brain structural abnormalities associated with cannabis use in individuals with psychosis and at risk for psychosis.
Schreiner & Dunn, 2012	Meta-analysis (33)	Neurocognitive effects	4	Cannabis use is acutely associated with poor performance on a variety of neuropsychological domains. These deficits resolve following 1 month abstinence.
Serafini et al., 2012	Systematic review (45)	Suicide	4	Cannabis use is associated with suicidal risk in psychotic and non-psychotic samples. However, studies are equivocal on the nature of the association.
Subbaraman, 2014	Narrative review	Alcohol use	2	All criteria were satisfied or partially satisfied for cannabis to serve as a substitute for alcohol.
Wilcox et al., 2004	Systematic review and meta-analysis (42)	Suicide	3	No cohort studies of cannabis use disorders and completed suicide met eligibility criteria, and were therefore not the subject of review. Inconclusive evidence to support an association.

The association between NMC and elevated levels of concurrent use of other substances is robust, although evidence regarding the direction of the association is equivocal. A systematic review of longitudinal outcomes among youth reported that CU is associated with the self-reported use of other drugs (Macleod et al., 2004). Several studies have suggested that NMC precedes use of other illicit drugs (Lynskey et al., 2012; Swift et al., 2012), leading to proposals that cannabis acts as a "gateway" to the use of other substances (Kandel, 2003). However,

the available evidence does not provide consistent support for this pattern. Results from a large cross-national study suggest that the gateway archetype manifests indirectly through common factors, and that hypothesized patterns of gateway NMC do not generalize across contexts (Degenhardt et al., 2010). Similarly, other studies indicate that apparent gateway effects reflect underlying propensities and environmental factors (Tarter, Vanyukov, Kirisci, Reynolds, & Clark, 2006; Tarter et al., 2012; Morral, McCaffrey, & Paddock, 2002). With regard to tobacco use, a recent review concluded that whereas tobacco use was associated with worse outcomes among cannabis users, NMC did not contribute to negative outcomes among tobacco users (Peters, Budney, & Carroll, 2012).

In contrast to the proposition that cannabis may serve as a gateway is an emerging stream of research which suggests that cannabis may serve as an "exit drug", with the potential to facilitate reductions in the use of other substances (Lucas et al., 2013; Reiman, 2009). According to this perspective, cannabis serves a harm-reducing role by substituting for potentially more dangerous substances such as alcohol (Mikuriya, 2004) and opiates (Lucas, 2012; Ramesh, Owens, Kinsey, Cravatt, Sim-Selley & Lichtman, 2011). Four quantitative cross-sectional studies of CTP have reported the use of cannabis as a substitute for prescription drugs, alcohol, and other substances (Lucas et al., 2015; Reiman, 2007, 2009; Reinarman, Nunberg, Lanthier, & Heddleston, 2011), and a study of cannabis using individuals drawn from a lower-SES urban clinic reported that who are authorized to use CTP demonstrate lower rates of risky use of alcohol, tobacco, and other substances (Richmond et al., 2015). Cannabis substitution has also been identified in community samples (Model, 1993), and among opiate users (Scavone, Sterling, Weinstein, & Van Bockstaele, 2013). Users of CTP note fewer side-effects, less withdrawal, and greater effectiveness as reasons for substituting for prescription medications such as opiates (Lucas et al., 2015; Reiman, 2009). Cannabis substitution may underlie reduced opioid overdose and alcohol-related traffic fatalities in districts that have adopted regulations to facilitate use of CTP (Anderson, Hanson, & Rees, 2013; Bachhuber, Saloner, Cunningham, & Barry, 2014). A recent examination of cannabis substitution for alcohol noted that cannabis met nearly all of the criteria required for consideration as a substitute therapy (Subbaraman, 2014). However, the effectiveness of CTP for problematic substance use has not been tested. Clinical trials in this area will be informative, as will the results of naturalistic examinations of the impact of ongoing expansions of CTP legalization on rates of use of other substances. Pending such findings, extant evidence appears sufficient to suggest that the consideration of the impact of CTP on the broader penumbra of addiction should entertain the potential for positive outcomes related to substitution of cannabis for potentially more dangerous substances.

The impact of CTP use on treatment for addictions is of concern to clinicians, as CTP use may continue during treatment for problematic use of other substances. Although some health care providers and organizations have established policies to accommodate CTP use (Coutts, 2014), norms in this area have yet to be established, and CTP may conflict with approaches that maintain a strict prohibition on NMC (e.g., Alcoholics Anonymous; Barcella, 2013). Evidence pertaining to this important issue is not robust. A study of co-use of tobacco and cannabis in adolescents and young adults reported indeterminate associations with quit attempts/relapse (Ramo, Liu, & Prochaska, 2012), and a small, low-quality study of a substance use treatment sample reported that CTP did not interfere with treatment effectiveness, and was associated with completion or satisfactory progress at discharge and generally good outcomes (Swartz, 2010).

Research on the influence of NMC on substance use treatment is complicated by traditional prohibitions on such use during treatment for other substances, and we did not identify any reviews of this subject. The results of the few studies to have undertaken such an examination are equivocal; two clinical trials of opiate maintenance therapy (Epstein & Preston, 2003; Hill et al., 2013) have concluded that NMC was not associated with treatment retention or compliance, whereas other studies have reported a negative association between NMC and maintenance of abstinence from other substances (Mojarrad, Samet, Cheng, Winter, & Saitz, 2014; Wasserman, Weinstein, Havassy, & Hall, 1998). In general, findings regarding the influence of NMC on addictions treatment are equivocal and substantial contextual differences complicate generalizing to CTP.

In sum, diverse cross-sectional studies have identified cannabis as a potential substitute for other psychoactive substances, and preliminary results suggest that CTP may not interfere with substance use treatment. Indeed, substitution effects suggest that, in some circumstances, CTP may be protective for the problematic use of other substances. Ultimately, longitudinal studies and clinical trials are required to specify the impact of CTP on addiction and treatment. Pending such research, clinicians should consider both harms and benefits of CTP so as to not unnecessarily add CTP to the barriers to accessing treatment for problematic substance use.

3.1.2. Anxiety

Relaxation and relief of anxiety are among the most widely reported motives for both CTP and NMC. Evidence from cross-sectional studies is consistent regarding the anxiolytic effects of CTP. Our search identified 8 cross-sectional studies reporting relief of anxiety as a primary or secondary benefit of CTP (Bonn-Miller, Babson and Vandrey, 2014; Grella, Rodriguez, & Kim, 2014; Nunberg, Kilmer, Pacula, & Burgdorf, 2011; Ogborne, Smart, Weber, & Birchmore-Timney, 2000; Swift, Gates, & Dillon, 2005; Walsh et al., 2013; Webb & Webb, 2014; Woolridge et al., 2005). Notably, one cross-sectional study reported retrospective reports that symptoms of anxiety returned upon cessation of use (Swift et al., 2005).

The search identified two reviews of NMC and anxiety. A narrative review highlights the complexity of the association, noting that cannabis is characterized by both anxiogenic and anxiolytic properties (Crippa et al., 2009), and attributes anxiogenic effects to THC given the demonstrated anxiolytic effects of CBD (Crippa et al., 2009; Zuardi et al., 2006). A more recent meta-analysis identified a small positive association between anxiety and NMC (Kedzior & Laeber, 2014). These relations are likely due to underlying associations between anxiety-specific vulnerability factors and NMC (e.g., Johnson, Mullin, Marshall, Bonn-Miller, & Zvolensky, 2010; Zvolensky et al., 2009). Indeed, evidence pertaining to the direction of these associations is equivocal, as some longitudinal studies report that frequent NMC use precedes anxiety disorders (Hayatbakhsh et al., 2007; Zvolensky et al., 2008), others show precedence of anxiety (Wittchen et al., 2007), and others report no association (McGee, Williams, Poulton, & Moffitt, 2000; Windle & Wiesner, 2004). Anxiety may also manifest as a component of the cannabis withdrawal syndrome, which includes nervousness, restlessness, irritability, and sleep difficulties that typically begin 1–3 days post-cessation, peak in a week, and last up to 28 days (Budney, Moore, Vandrey, & Hughes, 2003; Budney, Hughes, Moore, & Vandrey, 2004). Awareness of the anxiogenic effect of cannabis withdrawal may be important when evaluating or treating anxiety among CTP users, as symptoms may be associated with emergent symptoms of withdrawal association with fluctuations in levels and frequency of use.

The significance of NMC for understanding pathological anxiety appears to vary across disorders, and considerable attention has been directed at Social Anxiety Disorder (SAD) and Posttraumatic Stress Disorder (PTSD). With regard to SAD, socially anxious individuals are more likely than individuals with other anxiety disorders to use cannabis to relieve anxiety symptoms (Buckner et al., 2008). We found no research that specifically examined social anxiety among CTP users. Studies of NMC among nonclinical samples suggest that cannabis use among the socially anxious may be associated with cannabis-related problems (Buckner, Bonn-Miller, Zvolensky, & Schmidt, 2007; Buckner, Heimberg, Matthews, & Silgado, 2012; Buckner, Mallott, Schmidt, & Taylor, 2006; Buckner & Schmidt, 2008; Buckner, Schmidt,

Bobadilla, & Taylor, 2006; Buckner, Zvolensky, & Schmidt, 2012). A large epidemiological study found that SAD typically preceded the development of a cannabis use disorder (CUD) and that the co-occurrence of the disorders resulted in poorer outcomes relative to either SAD or CUD on their own (Buckner, Heimberg et al., 2012). However, a recent study indicated that psychiatric outpatients with comorbid SAD and CUD reported better physical functioning than did those with SAD alone (Tepe, Dalrymple, & Zimmerman, 2012).

Recent research suggests a potential therapeutic application for cannabinoids in SAD (Schier et al., 2012); administration of CBD is associated with decreased subjective anxiety among SAD patients (Crippa, Zuardi, & Hallak, 2010; Crippa et al., 2011), and with decreased cognitive impairment, negative evaluations, and anxiety in a simulated public speaking task (Bergamaschi et al., 2011). In sum, research on cannabis use and SAD reports both benefits and harms, complicating the evaluation of the potential impact of CTP on social anxiety.

Although recent nosology distinguishes PTSD from anxiety disorders (APA, 2013), PTSD has traditionally been conceptualized as an anxious condition (APA, 2000). Increasingly, CTP is being recognized as an approved indication for the treatment of symptoms associated with PTSD. Search identified four studies of CTP in the context of PTSD (Bonn-Miller, Babson et al., 2014; Bohnert et al., 2014; Greer, Grob, & Halberstadt, 2014). These studies suggest that a substantial portion (19%) of CTP users report use to manage PTSD (Bonn-Miller, Boden et al., 2014), and that this use is associated with facilitation of sleep, and coping with negative affect (Bonn-Miller, Babson et al., 2014). Similarly, a study of first-time CTP patients seeking treatment for non-PTSD conditions reported that nearly 25% screened positive for a lifetime diagnosis of PTSD (Bohnert et al., 2014). The relations between cannabis use and PTSD have not been the subject of review; however, epidemiological work indicates positive associations between PTSD and NMC among general (Cougle, Bonn-Miller, Vujanovic, Zvolensky, & Hawkins, 2011; Kevorkian et al., 2015) and specialty populations (Bonn-Miller, Harris, & Trafton, 2012). Studies of NMC also indicate that individuals with PTSD symptoms use cannabis to cope with hyperarousal (Bremner, Southwick, Darnell, & Charney, 1996; Bonn-Miller, Vujanovic, & Drescher, 2011) and sleep difficulties (Vandrey, Babson, Herrmann, & Bonn-Miller, 2014). A PET study identified increased cannabinoid receptor availability among individuals with PTSD, suggesting a mechanism for the benefits of CU for some PTSD symptoms (Neumeister et al., 2013).

Research on the efficacy of cannabis for the treatment of PTSD is still in its infancy; however preliminary results are promising. Oral THC and synthetic cannabinoids have demonstrated effectiveness for improving sleep duration and quality, and reducing nightmares and daytime flashbacks among treatment-resistant patients (Fraser, 2009; Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014). A recent observational study reported that among a sample of combat veterans, cannabis use was associated with a retrospective self-reported 75% reduction in re-experiencing, avoidance, and arousal symptoms of PTSD (Greer et al., 2014), and a case report and review of treatment called for further research into the therapeutic effectiveness of CTP for PTSD (Passie, Emrich, Karst, Brandt, & Halpern, 2012). Conversely, a recent observational study of PTSD veterans in treatment reported that cannabis use was associated with worse PTSD symptoms following discharge from treatment (Wilkinson, Stefanovics, & Rosenheck, 2015). Notably, there are a number of limitations associated with extant studies, including small samples, retrospective reporting, cross-sectional design, and lack of placebo control. At the time of this writing, researchers in Canada and the US are preparing randomized placebo-controlled clinical trials to evaluate this psychiatric application of CTP (Golgowski, 2014; Leung, 2014). Importantly, evidence also cautions that individuals with PTSD who develop CUDs may later experience diminished benefit from traditional PTSD treatments (Bonn-Miller, Boden, Vujanovic, & Drescher, 2013), heightened withdrawal during a quit attempt (Boden, Babson, Vujanovic, Short, & Bonn-Miller, 2013), and poor short-term cessation outcomes (Bonn-Miller, Moos, Boden, Kimerling, & Trafton, 2015). Given these potential consequences, individuals with PTSD who are interested in or already using cannabis should be monitored for development of CUDs.

3.1.3. Depression

Relief of negative mood is a prominent motive for cannabis use (Simons, Correia, Carey, & Borsari, 1998), and early European accounts of CTP highlight antidepressant effects (Moreau, 1845). We identified 9 cross-sectional studies of CTP and depressed mood, 7 of which noted mood improvement among the salutary effects of CTP. These effects appear to be consistent across condition and were evident in studies that examined specific patient groups such as pain (Ware et al., 2010), HIV (Bedi et al., 2010), and multiple sclerosis (Page & Verhoef, 2006), and in studies that examined CTP use across diverse conditions (Aggarwal et al., 2012; Bonn-Miller et al., 2013; Harris et al., 2000; Nunberg et al., 2011; Ogborne et al., 2000; Walsh et al., 2013). One study reported a positive association between depression severity and problematic CTP use, and suggested that this association might reflect increased CTP use to address depression-related sleep disturbance (Babson et al., 2013).

We identified 4 reviews of NMC and depression, including a recent methodologically high-quality systematic review and meta-analysis which indicated that cannabis users are at a modestly increased risk of developing depression compared to controls (Lev-Ran et al., 2014). Earlier reviews drew similar conclusions, reporting that NMC was associated with increased risk of depression and depressive symptoms (Degenhardt et al., 2003; Moore et al., 2007). Similarly, a review of depression in adolescents reported a small association between cannabis use and depression severity (Cairns, Yap, Pilkington, & Jorn, 2014). Cohort studies also suggests that risk is increased for more frequent users, and that NMC is associated with depression after controlling for potential confounding variables (Bovasso, 2001; Degenhardt et al., 2003; Horwood et al., 2012). However, authors note that these findings do not indicate a causal pathway, and do not preclude alternative explanations such as social factors (Degenhardt et al., 2003; Lev-Ran et al., 2014), and adverse psychosocial consequences (e.g., less education, unemployment, criminal activity) that often co-occur with NMC (Marmorstein & Iacono, 2011). Although reviews generally indicate a positive relationship between NMC and depression, a few cross-sectional studies report the opposite pattern of association; cannabis users report less negative affect than non-users (Denson & Earleywine, 2006), and frequent use is associated with a decreased likelihood of experiencing a major depressive event among those experiencing social pain (Deckman, DeWall, Way, Gilman, & Richman, 2013).

In addition to research suggestive of depressogenic effects of NMC, the development of a distinct depression-like "amotivational syndrome" characterized by lethargy, apathy, and decreased productivity has long been a proposed consequence of NMC (McGlothlin & West, 1968). However, despite generating considerable research interest, concerted efforts have failed to identify a cannabis-specific motivational syndrome (Campbell, 1976; Kupfer, Detre, Koral, & Fajans, 1973), although recent findings of attenuated dopamine synthesis and reactivity suggest a mechanism by which NMC may be associated with behavioral hypoactivity (Bloomfield, Morgan, Kapur, Curran, & Howese, 2014; Volkow et al., 2014).

Anecdotal reports suggest that some individuals use cannabis to effectively treat symptoms of bipolar disorder (BD) (Grinspoon & Bakalar, 1998) and a narrative review suggested therapeutic potential of cannabis and its constituents for managing both manic and depressive symptoms (Ashton, Gallagher, Moore, & Young, 2005). In addition, two studies of individuals with BD, report better neurocognitive functioning in cannabis users relative to non-users (Braga, Burdick, DeRosse & Malhotra, 2012; Ringen et al., 2010). The association between NMC and BD has been subject to three reviews which concluded that NMC may prolong or worsen manic states (Gibbs et al., 2015), is

associated with increased odds of suicide attempts (Carrà, Bartoli, Crocamo, Brady, & Clerici, 2014) and with earlier age of BD onset (Bally, Zullino, & Aubry, 2014). Studies also suggest that CUDs in BD patients are associated with a number of poor treatment outcomes, including psychosis (van Rossum, Boomsma, Tenback, Reed, & van Os, 2009), mixed episodes (Agrawal, Nurnberger, & Lynskey, 2011), and a more severe course of illness (Lev-Ran, Le Foll, McKenzie, George, & Rehm, 2013; van Rossum et al., 2009).

In sum, the literature germane to use of CTP and mood disorders is equivocal. Several cross-sectional surveys suggest that CTP is used to improve mood and well-being among individuals with medical conditions. In contrast, NMC research reports small positive associations between use and depression, with unclear directionality of effects. Research related to BD is scant and similarly inconclusive. However, evidence of associations between non-therapeutic use and negative outcomes in BD suggests that caution may be warranted among CTP-users with BD.

3.1.4. Psychosis

Search revealed no systematic examinations of the association between CTP use and psychosis, and one case study in which CTP use appeared to induce psychosis in an individual with chronic pain and PTSD (Pierre, 2010). In contrast to the dearth of literature on CTP, the association between NMC and psychosis is the subject of a robust literature that has been extensively reviewed, including recent meta-reviews; therefore, to avoid redundancy we limited our review of psychosis to articles published after 2010. Meta-analysis suggests that CUDs are common among individuals with schizophrenia, and in particular, in young males experiencing first-episode psychosis (Koskinen, Löhönen, Koponen, Isohanni, & Miettunen, 2010). A synthesis of five previous reviews reported a consistent association between cannabis use and psychotic symptoms (Minozzi et al., 2010). This finding was highlighted in another meta-review of risk factors of schizophrenia, confirming the association between NMC and psychosis (Matheson, Shepherd, Laurens, & Carr, 2011). A recent epidemiological review noted that evidence from case-control, cross-sectional, and cohort studies supports an association between NMC and development of later psychosis and schizophrenia (Gage, Hickman, & Zammit, 2015). Meta-analyses also suggest an earlier onset of psychosis for cannabis users relative to non-users (Large, Sharma, Compton, Slade, & Nielssen, 2011). Longitudinal studies of NMC and schizophrenia have demonstrated heightened risk of developing schizophrenia among frequent users (Shapiro & Buckley-Hunter, 2010; Malone, Hill, & Rubino, 2010) and other studies demonstrated that these association were generally consistent after controlling for other substance use and prior psychiatric illness (Kristensen & Cadenhead, 2007; Radhakrishnan, Wilkinson, & D'Souza, 2014). Two systematic reviews reported that cannabis use may alter brain structure in schizophrenia (Malchow et al., 2013; Rapp, Bugra, Riecher-Rossler, Tamagni, & Borgwardt, 2012), although the influence of use on psychotic disorders is strongest among individuals with genetic vulnerability to psychosis (McLaren, Silins, Hutchinson, Mattick, & Hall, 2010; Malone et al., 2010; Proal, Fleming, Galvez-Buccollini, & Delisi, 2014).

Studies that have directly administered THC have provided further evidence of psychotogenic effects. Intravenous administration of THC induces transient psychotic symptoms among healthy individuals (D'Souza et al., 2004), and transiently exacerbates symptoms among individuals with schizophrenia (D'Souza et al., 2005; Morgan & Curran, 2008). However, studies that administer THC in isolation may not accurately mirror the effects of the diverse cannabinoid profiles that characterize the products favored by CTP users. Indeed, whereas THC is psychotomimetic, CBD has demonstrated antipsychotic properties which may counteract or attenuate THC effects (Schubart et al., 2014). Indeed, a recent systematic review of human studies suggested that CBD counteracts symptoms of psychosis and the cognitive impairment associated with THC administration, and notes the potential safety and efficacy of CBD as an antipsychotic compound (Iseger & Bossong, 2015).

Although evidence of an association between cannabis and psychosis is robust, the extent to which cannabis use plays a causal role in the development of psychotic disorders has not been definitively determined (McLaren et al., 2010). Specifically, evidence of a casual relation is obscured by plausible third factors such as polydrug use and socioeconomic status (Cantor-Graae, 2007; Matheson et al., 2011), and by possible reverse causation whereby individuals at risk for developing schizophrenia use cannabis to alleviate prodromal symptoms (Moore et al., 2007). Indeed, the observation over the past several decades that rates of schizophrenia have remained constant despite dramatic increases in cannabis use presents a compelling counter to causal models of cannabis use and schizophrenia (Rajapakse & Rodrigo, 2009). Nonetheless, the available evidence suggests that CTP users with psychotic disorders, and those at increased genetic risk of developing such disorders, should be cautioned regarding the use of cannabis. At-risk users of CTP who are reluctant to discontinue cannabis use should be counseled regarding the potential increase of risk associated with high THC strains of cannabis, and monitored closely for the development or exacerbation of psychotic symptoms.

3.2. Psychological assessment

3.2.1. Neurocognition

The psychoactive effects of cannabis are primarily attributable to THC binding to cannabinoid receptors concentrated in brain regions important for cognition (e.g., hippocampus, striatum, and cingulate; Herkenham et al., 1990); thus, it is not surprising that alterations in neurocognitive functioning are among the most well-documented side-effects of regular cannabis use (Gonzalez, 2007; Hall, 2015). One high-quality prospective cohort study of CTP for management of non-cancer chronic pain included detailed assessment of neurocognitive performance. That study, which followed over 200 participants using a median of 2.5 g daily, reported no significant differences in neurocognitive functioning between cannabis users and controls at one year post-study (Ware, Wang, Shapiro, & Collet, 2015). Although these results represent the best evidence to date regarding the cognitive effects of CTP, patient populations who already suffer from neurocognitive deficits (e.g., multiple sclerosis, HIV, epilepsy) may experience more pronounced effects. Specifically, several lab-based studies report that administration of THC or a history of cannabis use, are associated with salient neurocognitive deficits among individuals with HIV (Gonzalez, Schuster, Vassileva, & Martin, 2011), multiple sclerosis (Honarmand, Tierney, O'Connor, & Feinstein, 2011), and schizophrenia (D'Souza, Sewell, & Ranganathan, 2009).

With regard to NMC, four reviews have summarized lab-based administration studies of the acute neurocognitive effects of THC and cannabis (reviewed in Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crean, Crane, & Mason, 2011; Gonzalez, 2007; Ranganathan & D'Souza, 2006). It is important to consider that studies reviewed often differ with regard to dosing, cannabis strain, route of administration, and whether THC or herbal cannabis was administered. This complicates generalizability, as these factors may influence the degree of neurocognitive deficits experienced during the approximately 4 h of acute intoxication that follow cannabis administration. With that in mind, evidence suggests acute deficits in memory, with more mixed findings for decision-making and inhibitory control, and some individual studies reporting deficits in attention and working memory (Curran, Brignell, Fletcher, Middleton, & Henry, 2002; D'Souza et al., 2004). These findings suggest that regular CTP use may have a measurable impact on everyday neurocognitive functioning. However, there is evidence that frequent cannabis use, which characterizes many CTP users, may result in the development of tolerance to acute effects, and as such experimental findings might overestimate functional impairment (Hart, van Gorp, Haney, Foltin, & Fischman, 2001).

The potential for non-acute, longer-lasting, or permanent changes in neurocognitive functioning resulting from cannabis use are of

considerable concern to CTP users and health care providers. Two meta-analyses of NMC have addressed this issue, the first of which concluded that statistically significant deficits of approximately ¼ of a standard deviation were evident in episodic memory, but no differences emerged in other neurocognitive ability areas (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). A more recent meta-analysis found poorer performance among cannabis users in terms of abstraction/executive functioning, attention, memory (forgetting, retrieval), learning, verbal abilities, and motor skills, but reported no impact on reaction time, or perceptual-motor abilities (Schreiner & Dunn, 2012). Importantly, when only studies that compared cannabis users to non-users after 25 days or more of supervised abstinence were considered, there were no lasting residual effects on performance. This recovery of neurocognitive functions after abstinence mirrors studies showing reversibility of cannabinoid receptor downregulation from chronic cannabis exposure (Hirvonen et al., 2012).

Although the aforementioned studies suggest no evidence of long-term, persistent neurocognitive deficits after cessation of regular cannabis use among adults, the characterization of neurcognitive consequences of use in adolescence remains an area of active research and debate. For example, recent reports from a longitudinal study that identified global declines in IQ and neurocognitive functioning associated with regular and persistent cannabis use beginning during adolescence (Meier et al., 2012) garnered extensive attention, and a substantial literature suggests that adolescent-onset use may exacerbate NMC- related neurocognitive dysfunction (Ehrenreich et al., 1999; Fontes et al., 2011; Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Pope et al., 2003). However, two recent high-quality studies suggest that prior epidemiological studies may have overstated the negative cognitive impact of adolescent NMC. A prospective cohort study of over 2000 adolescents reported that after adjusting for confounds such as tobacco use, adolescents who has used cannabis >50 times did not differ from never -users with regard to IQ or academic achievement (Mokrysz et al., 2016). Similarly, a quasi-experimental examination of two longitudinal twin studies with a combined sample of over 3000 adolescents found no differences in IQ change between ages 9–12 and 17–20 among twins discordant for NMC and no evidence of a dose-response relationship between frequency of use and IQ decline, leading the authors to conclude that apparent differences between cannabis users and non-users are attributable to genetic and familial factors (Jackson et al., 2016).

In sum, acute deficits present during intoxication are likely to significantly impair performance on cognitive assessment. When not acutely intoxicated, the magnitude of these neurocognitive decrements range from about ¼ to ½ of a standard-deviation (e.g., about 4 to 8 IQ points) with recovery approximately one month following cessation. Although the magnitude of these transient deficits is modest, they may be sufficient to impact functioning. However, tolerance may attenuate these effects among CTP populations. Nonetheless, in light of potential CTP-related memory deficits clinicians should consider the use of memory aids to maximize compliance with co-occurring treatments. In addition, although some evidence appears to indicate that regular cannabis use beginning in adolescence may be associated with mild, but significant, neurocognitive decline, recent high-quality evidence suggests that the assertion of accentuated risk associated with adolescent use remains debatable. As with other medications with neurocognitive side-effects (e.g., opiates, benzodiazepines, some antipsychotics and anti-convulsives) clinicians and patients should weigh potential benefits with possible neurocognitive impact. In this respect, CTP is not unique, and providers should reference experiences with patients with mild neurocognitive deficits when working with patients using CTP.

3.2.2. Risk of harm to self

In addition to the assessment of cognitive functioning mental health clinicians are regularly called on to assess risk of harm to self (i.e. suicide, self-injury) or to others (i.e. interpersonal violence). With regard to risk for self-harm the association between CTP and suicide risk has not been examined. However, preliminary evidence from US states that allow CTP indicates no association between the number of medical cannabis registrants and rates of completed suicide, and tentatively suggests that CTP is associated with a decreased suicide among young adult men (Anderson, Rees, & Sabia, 2014; Rylander, Valdez, & Nussbaum, 2014).

We identified four reviews of NMC and suicide risk. These reviews report conflicting findings, and evidence for a relation between NMC and suicide is inconclusive (Calabria, Degenhardt, Hall, & Lynskey, 2010; Moore et al., 2007; Serafini et al., 2012; Wilcox, Conner, & Caine, 2004). Many studies do not control for confounding variables (Calabria et al., 2010; Moore et al., 2007). The conclusions of studies that consider potential confounds are equivocal; some report that NMC is not associated with risk of suicidal ideation or attempts (Price, Hemmingsson, Lewis, Zammit, & Allebeck, 2009; Rasic, Weerasinghe, Asbridge, & Langille, 2013), whereas other studies indicate an association between NMC and subsequent suicidal ideation and attempts even after controlling for potential confounds (Beautrais, Joyce, & Mulder, 1999; Chabrol, Chauchard, & Girabet, 2008; Fergusson, Horwood, & Swain-Campbell, 2002; van Ours, Williams, Fergusson, & Horwood, 2013). Accordingly, the most recent of these reviews concluded that further research is required to delineate the distinct contribution of NMC across a complex web of risk factors (Serafini et al., 2012).

3.2.3. Risk of harm to others

With regard to harm to others, cultural lore suggests a positive relation between cannabis and aggression (e.g. Reefer Madness; Hirlman & Gasnier, 1936); however, evidence bearing on this association is inconclusive. Our search identified no studies of CTP and violence, and 3 reviews of NMC and violence (Abel, 1977; Moore & Stuart, 2005; Moore et al., 2008). These reviews highlight discrepancies in the literature; whereas some research has suggested that NMC is positively associated with violence due to alterations in cognitive functioning (Moore & Stuart, 2005), negative consequences of withdrawal (Kouri, Pope, & Lukas, 1999), or associations with deviance and risk-taking behavior (Harrison, Erickson, Adlaf, & Freeman, 2001), other research has concluded that cannabis is not associated with violence because of its sedative and quieting nature, reducing irritability and hostility (Salzman, Van der Kolk, & Shader, 1976), and nonviolent expectancies (Alfonso & Dunn, 2007). Directionality and potential confounds further obscure the nature of the association, as cannabis users report use to attenuate aggression (Arendt et al., 2007), and use was unrelated to violence after controlling for other factors among patients in substance use treatment (Macdonald, Erickson, Wells, Hathaway, & Pakula, 2008).

The results of longitudinal studies of NMC and violence are also inconsistent. A study of consecutive births reported that cannabis dependence was uniquely associated with increased violence (Arseneault, Moffitt, Caspi, Taylor, & Silva, 2000). However, a comparable study reported no association between NMC and violence when controlling for other factors (Pedersen & Skardhamar, 2009). A longitudinal study of inpatient PTSD veterans reported that initiation of cannabis use while in treatment was associated with increased violent behavior following discharge (Wilkinson et al., 2015). A laboratory-based study found that long-term users are more aggressive during a period of abstinence (Kouri et al., 1999) which is consistent with proposals that cannabis withdrawal may underlie the associations with aggression (Hoaken & Stewart, 2003; Moore & Stuart, 2005; Moore et al., 2008). In contrast to evidence of a positive association between NMC and violence, a large longitudinal cohort study of married couples reported that frequent NMC use was associated with less intimate partner violence, with co-using couples exhibiting the lowest rates of violence (Smith et al., 2014). In sum, the association between cannabis use and violence remains obscure, is likely small when present, and may vary according to types of violent behavior. As such, although no research has

examined CTP and violence, it appears unlikely that CTP use represents a notable risk factor for harm to others.

4. Summary

The reemergence of the therapeutic use of cannabis leads to several points of interface with domains related to clinical psychology and other mental health professions. Our review focused on what we feel are the most central areas in which CTP presents an issue of interest to clinical judgment or practice; implications for clinical disorders of adulthood (i.e. DSM-V, Axis I), assessment of cognitive functioning, and of risk of harm to self and others. The literature on CTP and mental health is generally underdeveloped. Research focusing on non-medical use is better developed but remains equivocal with regard to many clinical implications, and extension to CTP is problematic. In sum, further research directed explicitly at the mental health consequences of CTP is required to make more definitive statements. Nonetheless, the extant literature does allow for some informed, if preliminary, observations.

Substance use disorders are the category of psychopathology with the most robust literature relevant to CTP. Users of CTP report that cannabis may serve as a substitute for both pharmaceutical and recreational drugs, and that it may be preferred due to its perceived lack of harm, more acceptable side effect profile, and relative effectiveness. Moreover, population-level analyses suggest that cannabis substitution may have public health benefits. In contrast, research on NMC has largely focused on increased risk for the use of other substances and influences addiction treatment outcomes. However, research on the influence of NMC on the use of other substances is equivocal, as are findings regarding the influence of NMC on addictions treatment. Taken as a whole, the literature suggests that evaluating the influence of CTP use on use of other substances should consider potential for harm reduction and thereby extend beyond traditional conceptualization of cannabis use as inherently unhealthy and maladaptive.

Anxiety disorders are another area in which the emergence of CTP requires re-evaluation of cannabis use consequences. Users of CTP report anxiolytic motives, and an emerging literature suggest potential for treating SAD and PTSD. However, research on other anxiety disorders is scant and the comparative effectiveness of cannabis relative to other pharmacological treatments for anxiety has yet to be determined. Evidence bearing on the association between CTP use and mood disorders is also underdeveloped. Although CTP users widely report using CTP to improve mood and alleviate negative affect, the effectiveness of CTP in that regard remains obscure. In general, further research is needed to assess the effects of CTP on anxiety and affective disorders, as the relative harms and benefits likely vary across disorders and according to individual differences.

In contrast to areas where research suggests the potential for both attenuation and exacerbation of psychopathology, evidence on cannabis and psychosis largely indicates that use is associated with negative outcomes. This is particularly true with regard to cannabis that contains high concentrations of THC. However, pre-clinical evidence suggests that the cannabinoid CBD may have antipsychotic properties, and future research that focuses more specifically on isolated CBD, or on herbal cannabis strains that are characterized by high levels of CBD and lower THC, may elucidate the medicinal potential of CTP for psychotic disorders. Indeed, the therapeutic implications of variability in cannabinoid content across strains of cannabis may have implication beyond psychosis, and further research in this area is expected in the near future. However, pending such increased specificity, CTP use may represent a risk for patients who exhibit psychotic symptoms or are otherwise vulnerable.

With regard to assessment, evidence does not suggest that CTP is a distinct risk factor for harm to self or others. The influence of CTP use on cognitive assessment, however, is somewhat more complex. Intensity and duration of the acute neurocognitive effects of CTP use vary widely due to factors such as mode of administration, user tolerance, dosage, and cannabinoid content. However, research has generally converged to document acute and non-acute deficits in learning and memory as well as varied deficits in other neurocognitive domains, and as such frequent CTP users may experience these deficits for a considerable proportion of their daily life. However, tolerance may attenuate these deficits, and with regard to longer-term outcomes, research suggests that deficits appear to recover following a period of abstinence.

In sum, the implications of CTP for mental health care appear to vary across conditions with potential for both benefits and harms. In this regard cannabis is similar to other psychoactive medicines. Health care providers should work to maximize positive outcomes by pursuing strategies to increase medication adherence, such as psychoeducation, ongoing assessment of motivations and barriers to adherence, and attention to the therapeutic alliance (Julius, Novitsky, & Dubin, 2009). Maintenance of alliance during CTP-related interactions may be particularly important as poor patient - caregiver communication has been identified as a potential barrier to safe access to CTP (Belle-Isle et al., 2014).

Our confidence in the conclusions of this review is constrained by the limitations of the literature we reviewed. Nearly all studies that directly examined CTP were cross-sectional studies of low to medium methodological quality, and extrapolation from the more developed literature on NMC is problematic. The more robust elucidation of the consequences of CTP for psychopathology will require focused longitudinal cohort studies of CTP users and clinical trials using well-characterized cannabis. Our conclusions are further limited by our decisions to not include examination of the grey literature in our review, and our exclusive reliance on published reports makes our interpretations vulnerable to the influence of publication bias (Shea et al., 2007). Furthermore, the diversity of approaches we surveyed did not facilitate estimates of effect size and thus limited our ability to empirically compare results across studies.

There are also several topics which we do not address but which nonetheless fall within the purview of mental health, and merit the attention of future investigations. Notable among these are the potential impacts of CTP use on disorders of eating and sleep. Given the centrality of the endogenous cannabinoid system in the regulation of appetite and sleep (Babson & Bonn-Miller, 2014; Watkins & Kim, 2015), it is likely that CTP use might have implications for these aspects of mental health. The influence of CTP use in behavioral medicine, particularly with regard to the treatment of chronic pain, also warrants systematic examination (Ilgen et al., 2013). Finally, the influence of CTP use on disorders that frequently emerge in youth, such as ADHD and autism, as well disorders of old age, including dementia, demand further attention. In general, the study of the mental health implications of the medicinal use of cannabis is in its infancy. We expect that increasing interest, accompanied by a more conducive research environment, will soon lead to the elucidation of outstanding issues, and thus facilitate the more informed assessment of the benefits and risks of using cannabis for therapeutic purposes.

Conflict of interest

Zach Walsh is Coordinating Principal Investigator on a clinical trial of cannabis that is sponsored by Tilray, a licensed producer of medical cannabis. Kim Crosby and Michelle Thiessen are paid by Tilray as graduate research assistants to Dr. Walsh in running that trial. Marcel Bonn-Miller has been a paid consultant for CW Botanicals, Tilray, and Aphria within the past 12 months, all of whom are producers of medical cannabis. Within the past 12 months, he has also served as a consultant for Insys Therapeutics and Zynerba Pharmaceuticals. Dr. Bonn-Miller also serves on the boards of the International Cannabis and Cannabinoids Institute, Institute for Research on Cannabinoids, Realm of Caring Foundation, The Medical Cannabis Institute, and the Thomas Jefferson University Center for Medical

Cannabis Education and Research. All other authors declare that they have no conflicts of interest.

Contributors

Zach Walsh designed and initiated the review, and wrote the first draft. Raul Gonzalez wrote portions of the first draft and provided several editorial reviews of the manuscript. Kim Crosby and Chris Carroll conducted literature searches, provided summaries of previous research studies and contributed to the writing of the first draft. Michelle Thiessen and Kim Crosby conducted literature searches and rated the studies for quality. Marcel Bonn-Miller provided several editorial reviews of the manuscript and contributed to writing of the first draft. All authors contributed to and have approved the final manuscript.

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