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Arizona researcher stubborn in fight to study pot as PTSD treatment

Ken Alltucker, The Republic | azcentral.com Published 3:07 p.m. MT June 8, 2017 | Updated 1:03 p.m. MT June 9, 2017



(Photo: Nick Oza/The Republic)

Two major research universities have cut ties with a Valley doctor's efforts to answer this question: Does smoking marijuana help veterans struggling with post-traumatic stress disorder?

Dr. Sue Sisley, who was fired by the University of Arizona ([/story/news/arizona/2014/07/17/marijuana-researcher-appeals-uas-firing/12821261/](https://www.azcentral.com/story/news/arizona/2014/07/17/marijuana-researcher-appeals-uas-firing/12821261/)) in 2013 after her study was underway, learned in March that Baltimore-based Johns Hopkins University has dropped plans to partner on the first-ever study of cannabis for veterans.

Beyond Sisley losing a prestigious research partner, the Johns Hopkins departure means study backers won't have access to Baltimore-area veterans and must recruit study participants from Arizona.



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Dr. Sue Sisley heads a medical study of marijuana as a treatment for veterans with post-traumatic stress disorder. Sisley's study has encountered a series of roadblocks. (Photo: Nick Oza/The Republic)

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However, Sisley's efforts to tap veterans seeking treatment at the U.S. Department of Veterans Affairs hospital in Phoenix have gone nowhere.

"We still haven't been allowed to get in the VA hospital," Sisley said. "This study is actually enrolling patients after seven years of being stonewalled at all levels. A lot of people (veterans) aren't even aware that it is underway."

Phoenix VA Health Care System administrators told Sisley two years ago that referring veterans to her study would violate the VA's national policy and federal law.

A Phoenix VA spokesman said this week that hasn't changed over the past two years.

"We are not permitted to prescribe, promote or discuss the use of medical marijuana with our veterans," said Paul Coupaud, a Phoenix VA public affairs officer.

Recruitment barriers

Sisley began her study at UA, but the university declined to renew her contract for unspecified reasons. She alleged she was let go because of political pressure from some state lawmakers, whom she had lobbied as she sought funding for the study from the Arizona Department of Health Services.

Sisley's study is still moving ahead, for now, without the help of Johns Hopkins or the VA.

The study is sponsored by Santa Cruz, Calif.-based Multidisciplinary Association for Psychedelic Studies (MAPS) and funded with a \$2.1 million grant from the Colorado Department of Public Health and Environment.

Sisley said the main challenge is screening hundreds of veterans to find those who fit the study's criteria.

Possible candidates must have a service-connected disability with chronic post-traumatic stress disorder. And they must be willing to commit themselves to the randomized, placebo-controlled study for 14 weeks and a six-month follow-up.

So far, the study has signed up 16 veterans with a goal of enrolling 76 veterans by August 2018. Sisley's Scottsdale Research Institute research team is conducting the study in a small industrial space near the Deer Valley Airport. She doesn't have a large budget and her research team had to recruit more staffers because Johns Hopkins dropped out.

"We don't have any budget for advertising," Sisley said. "I'm worried we will not get all 76."

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Sisley and Rick Doblin, founder and executive director of MAPS, acknowledged that Johns Hopkins' departure and a lack of cooperation from the VA have both been barriers.

Doblin pointed to VA Secretary David Shulkin's remarks last month during a press briefing that medical marijuana "may be helpful" for veterans and "everything that could help veterans should be debated by Congress and by medical experts."

However, Shulkin also stressed that the VA is unable to prescribe marijuana under federal law.

Sisley has appealed to the American Legion, with the goal of arranging a meeting with Shulkin to discuss her study and the lack of access to the Phoenix VA.



The veterans organization has advocated for medical marijuana research as a possible treatment for veterans with PTSD. The American Legion has requested a meeting with the Trump administration to seek loosened restrictions on federal research of marijuana, which the U.S. government groups with other Schedule 1 drugs such as LSD and heroin that have a potential for abuse.

Doblin said the inability to inform Phoenix VA veterans — particularly those with PTSD that has resisted pharmaceutical therapies — is a large barrier to his group's study.

"Recruitment is the key issue for us," Doblin said. "They will not let veterans know about the study. They say they do this because of federal law. That is absolutely absurd."

Johns Hopkins' departure

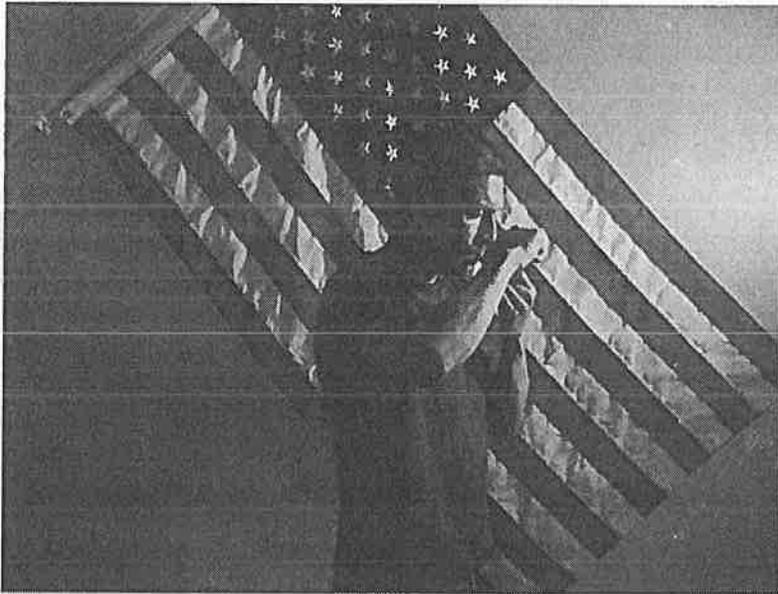
Johns Hopkins officials said the university's goals for the study did not align with MAPS'.

Ryan Vandrey, the Johns Hopkins researcher who was paired with MAPS, declined to discuss why he left the study. He deferred to the university's media relations department, which issued a statement.

"Johns Hopkins elected to withdraw from the MAPS study of cannabis in veterans with PTSD prior to any participant enrollment because our goals for this study weren't in alignment," the university's statement read. "Johns Hopkins remains dedicated to helping military veterans, finding improved treatments for PTSD, and conducting innovative research to enhance our understanding of both the risks and benefits of cannabis/cannabinoids."

Johns Hopkins dropped out of the study after Sisley, in a media interview, criticized the quality of the marijuana used in the study. The federal government's only approved source of marijuana for clinical trials is a National Institute on Drug Abuse-run farm at the University of Mississippi.

The Obama administration signaled that it would expand the number of federally-approved marijuana manufacturers, but it is unclear whether President Donald Trump's administration will continue with that policy.



Roberto Pickering, 36, uses marijuana for post-traumatic stress disorder. Pickering was a U.S. Marine Corps sniper in 2003 and 2004, and is a founder of Battlefield Foundation. Dr. Sue Sisley is heading a medical study of marijuana as a treatment for veterans with post-traumatic stress disorder. (Photo: Nick Oza/The Republic)

In an interview with PBS in March, Sisley complained that the government's marijuana contained mold, lead and inconsistent potency levels. Within days of that interview, Johns Hopkins dropped out of the study.

MAPS officials and veterans groups suspect that the public criticism prompted Johns Hopkins to leave the study.

In a progress report to the Colorado state agency that is funding the study, MAPS said that it felt it was necessary to "focus both on the science and on the politics of the quality of marijuana," but Johns Hopkins wanted to exclusively focus on the science.

Veterans groups were critical of Johns Hopkins' decision to leave the study.

"I think they took the easy route out and decided to keep their federal relationships for money," said Ricardo Pickering, founder of the Battlefield Foundation.

Sisley said that she, too, is focused on the science.

She said she publicly criticized the quality of government-provided cannabis because she wanted to be transparent about her group's study.

"I grind every day to make sure this study is successful," Sisley said. "I want people to understand I am not an activist. I am a scientist. The only thing I care about is collecting objective data and getting that data in the public domain."

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The American Legion



OFFICE OF THE
NATIONAL COMMANDER

★ WASHINGTON OFFICE ★ 1608 "K" STREET, N.W. ★ WASHINGTON, D.C. 20006 ★
(202) 263-2986 ★

July 10, 2017

The Honorable Matt Gaetz
United States House of Representatives
507 Cannon House Office Building
Washington, DC 20515

Dear Representative Gaetz:

On behalf of the more than 2.2 million members of The American Legion, we express support for the H.R. 2020 entitled *To provide for the rescheduling of marijuana into schedule III of the Controlled Substances Act*. This draft bill, as currently written, would direct the Attorney General of the United States to transfer marijuana from Schedule I to Schedule III of the Controlled Substances Act. This would greatly enable medical research into the efficacy of cannabis in treating post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), chronic pain, and other afflictions that veterans face every day as a result of their combat service.

Despite advances in diagnostics and interventions, PTSD and TBI remain a leading causes of death and disability within the veteran community. Many Afghanistan and Iraq veterans have contacted The American Legion to share their personal stories about the efficacy of cannabis in significantly improving their quality of life by enabling sleep, decreasing the prevalence of night terrors, mitigating hyper-alertness, reducing chronic pain, and more. This is why our 2.2 million members, through American Legion Resolution 11 titled *Medical Marijuana Research*, are calling on Congress and the President to instruct the Drug Enforcement Agency to change how it classifies cannabis, release the monopoly on cultivation for research purposes, and immediately allow highly regulated, privately funded medical marijuana production operations in the United States to enable safe and efficient cannabis drug development research.

With 90 percent of Americans supporting legalization of medical marijuana today, it is time for Congress to act so that scientists are free to conduct advanced research into cannabis and PTSD/TBI, and enable the American people to have a fact-based discussion about the therapeutic value of cannabis. The lives of our veterans depend on it.

The American Legion unequivocally supports H.R. 2020 as currently written and we thank you for your leadership in addressing this critical issue facing our nation's veterans and their families.

Sincerely,

A handwritten signature in cursive script, appearing to read "Charles E. Schmidt".

CHARLES E. SCHMIDT
National Commander
The American Legion



Office of Government Relations

215 South Monroe Street
Suite 110
Tallahassee, FL 32301
850-488-2447
850-488-5808 Fax

March 17, 2014

The Honorable Matt Gaetz
Chair, Criminal Justice Subcommittee
Florida House of Representatives
Tallahassee, FL 32399-1300

Dear Rep. Gaetz:

President Bernie Machen asked me to deliver the enclosed letter from Hogan Lovells regarding medical marijuana.

The letter is authored by Lynn Mehler, a partner in the international law firm of Hogan Lovells, which is headquartered in Washington, DC. Prior to joining Hogan Lovells, she was senior counsel of the U.S. Food and Drug Administration and had responsibility for advising the agency on controlled substances and liaising with the Drug Enforcement Administration. Her practice at the firm covers these issues as well.

I hope this information is helpful. Please contact us if you have any questions.

Sincerely,

A handwritten signature in cursive script that reads 'Jane Adams'.

Jane Adams
Vice President, University Relations

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March 14, 2014

J. Bernard Machen, President
University of Florida
Office of the President
226 Tigert Hall
Gainesville, Florida 32611-3125

Re: Proposed State Legislation Regarding Medical Marijuana

Dear President Machen:

As requested, this letter analyzes whether the University of Florida (the "University") would be in violation of federal law if it cultivates, manufactures, possesses or distributes marijuana or supervises or participates in such activities, including by growing marijuana for research, creation of marijuana seedlings, or provision of plant material to other entities in the state of Florida, consistent with, or at the direction of, Florida state law.¹ The basis for your inquiry is proposed legislation in the state of Florida that may permit or require the University to undertake certain marijuana-related activities, including cultivating, manufacturing, possessing and distributing marijuana, or supervising or participating in such activities and marijuana-related research.² For the reasons described in detail below, such activities would violate federal law, conflict with the University's obligations under federal controlled substances law, and jeopardize the University's continued receipt of federal funds through research grants and contracts and student financial assistance programs. The University could do purely data-based research if complying with human subject protection requirements, protocol approvals and the Health Insurance Portability and Accountability Act (HIPAA), or using marijuana grown and supplied by the single permitted national research facility, if the proper Drug Enforcement Administration ("DEA") registrations were granted. However, the University could not grow marijuana, even for research.

With only extremely limited exceptions, which would not bear on the proposed Florida legislation, the Federal Controlled Substances Act (the "CSA")³ prohibits cultivation, manufacture, possession, and distribution of marijuana and marijuana derivatives in the United

¹ In providing this analysis, in addition to legal research, I have relied on my expertise with federal regulation of controlled substances, including marijuana, gained during more than a decade of employment with the U.S. Food and Drug Administration, most recently as Senior Counsel for Drugs advising the agency on all controlled substances matters and liaising with the Drug Enforcement Administration, and my experience as a Hogan Lovells partner advising clients on controlled substances issues. I have also drawn on Hogan Lovells' extensive experience advising higher education institutions regarding regulatory compliance matters pertinent to federally funded research and participation in the federal student financial assistance programs.

² S.B. 1030, 2014 Leg., Reg. Sess. (Fla. 2014); H.B. 843, 2014 Leg., Reg. Sess. (Fla. 2014).

³ 21 U.S.C. § 801 et seq.

States. Moreover, the U.S. Supreme Court has considered the application of the CSA to state law that permits marijuana-related activities and has found that federal law "unambiguously" trumps any conflicting provision of state law.⁴ Thus, an entity that possesses, grows or distributes marijuana in the United States is in violation of federal law, even if state law permits or authorizes such activity. This is true even if the activity is for research-related purposes only, because the only marijuana that can be used for research-related purposes is marijuana that the federal government supplies through the National Institute on Drug Abuse ("NIDA").

In addition, as explained below, federal law requires recipients of federal grants and contracts and participants in the federal student financial assistance programs under the Higher Education Act of 1965, as amended ("HEA"), to maintain a drug-free workplace and to have a drug abuse prevention program that includes standards of conduct that prohibit, at a minimum, the unlawful possession, use, or distribution of drugs by students and employees on the institution's property or as part of the institution's activities. The University is a leading research institution with approximately \$423M in federal research grants and contracts during FY2012-2013,⁵ and, as one of the largest universities in the United States, it disbursed over \$300M in HEA student financial assistance in FY2012-2013.⁶ The University would be in violation of its drug-free workplace and drug prevention program obligations if it cultivates, manufactures, possesses or distributes marijuana or otherwise participates in such activities.

I. **The Controlled Substances Act**

A. **Marijuana is a Schedule I Substance under the Federal Controlled Substances Act**

The CSA lists both marijuana and the psychotropic components of marijuana, called tetrahydrocannabinols ("THC"), as Schedule I substances.⁷ Schedule I is the most restrictive CSA schedule.⁸

Under the CSA, a Schedule I substance is one for which there is "no currently accepted medical use in treatment in the United States," "a lack of accepted safety for use of the drug or other substance under medical supervision," and a "high potential for abuse."⁹ Except as otherwise provided for in the CSA, there are both criminal and civil penalties for cultivating, manufacturing, distributing or possessing any amount of a controlled substance.¹⁰

⁴ See *Gonzales v. Raich*, 545 U.S. 1, 29 (2005).

⁵ See University of Florida, Office of Research, 2012 Annual Report.

⁶ See University of Florida, 2012-2013 Annual Financial Report.

⁷ 21 U.S.C. § 812(c). The CSA defines marijuana as "all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin." 21 U.S.C. § 802(16). The Schedule I listing also applies to "any material, compound, mixture, or preparation, which contains any quantity of" marijuana or THC, including "any of their salts, isomers, and salts of isomers." 21 U.S.C. § 812(c).

⁸ See 21 U.S.C. § 812(b).

⁹ 21 U.S.C. § 812(b)(1).

¹⁰ See 21 U.S.C. § 844, 844a.

Since the original categorization of marijuana as a Schedule I substance by Congress in 1970, there have been many requests to change its schedule through the administrative process set forth in the CSA.¹¹ To move a substance to a different schedule, or out of the schedules entirely, the DEA must initiate a rulemaking process.¹² If a rescheduling petition is filed with DEA, the DEA must request a scientific and medical evaluation and a scheduling recommendation from the U.S. Department of Health and Human Services ("HHS").¹³ Such an evaluation and scheduling recommendation requires HHS to perform a substantial and in-depth review of available data and information on the substance that touches on all facets of abuse, medical use, and public health effects.¹⁴

Since the original classification of marijuana as a Schedule I substance, there have been a number of requests to reschedule marijuana that have triggered an evaluation and scheduling recommendation from HHS. HHS has consistently recommended that marijuana remain on Schedule I and DEA has agreed and denied the rescheduling requests after its own analysis of available data. At least six of these decisions were appealed to the U.S. Court of Appeals for the D.C. Circuit, and in no case did the court overturn the DEA's ruling.¹⁵

B. Possessing, Cultivating, Manufacturing or Distributing Marijuana without a DEA Registration Violates the CSA

The CSA prohibits possessing, cultivating, manufacturing or distributing any controlled substance without annually registering with the DEA.¹⁶ However, DEA does not provide a registration for marijuana for non-research uses such as for medical treatment and obtaining a registration from DEA to cultivate, manufacture or distribute marijuana, even for research purposes only, does not appear to be a viable option for the University.

Since 1968, DEA has registered only a single manufacturer of marijuana for use in research activities only – the National Center for Natural Products Research (the "Center") at the University of Mississippi operating under contract with NIDA.

¹¹ The CSA grants authority to the U.S. Attorney General to make changes to the schedules through a single specified procedure. See 21 U.S.C. § 811(a). The Attorney General has delegated this authority to the U.S. Drug Enforcement Administration ("DEA"). See 28 C.F.R. § 0.100(b); 28 C.F.R. § 0.104.

¹² See 21 U.S.C. § 811(a).

¹³ See 21 U.S.C. § 811(b).

¹⁴ When assessing the scheduling of a substance, HHS and DEA are required to consider the following factors before making findings related to potential for abuse, currently accepted medical use in the U.S., and safety or dependence liability: (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significance of abuse; (6) what, if any, risk there is to public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. See 21 U.S.C. § 811(c).

¹⁵ See, e.g., *Doe v. DEA*, 484 F.3d 561 (D.C. Cir. 2007); *Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131 (D.C. Cir. 1994); *Alliance for Cannabis Therapeutics v. DEA*, 930 F.2d 936 (D.C. Cir. 1991); *NORML v. DEA*, No. 79-1660 (D.C. Cir. Oct. 16, 1980); *NORML v. DEA*, 559 F.2d 735 (D.C. Cir. 1977); *NORML v. Ingersol*, 497 F.2d 654 (D.C. Cir. 1974).

¹⁶ See 21 U.S.C. § 822(a).

The University of Massachusetts at Amherst applied to DEA for a registration to manufacture research-grade marijuana for purposes of clinical studies in 2001. In 2009 DEA denied the application on the basis that NIDA (through the University of Mississippi) was capable of manufacturing an adequate quantity and quality of marijuana for meritorious scientific research. The applicant's appeal to the U.S. Court of Appeals for the First Circuit was unsuccessful inasmuch as the Court of Appeals held that DEA's decision to deny registration was entitled to deference and the applicant failed to demonstrate that the current supply of marijuana for research was inadequate.¹⁷

C. The Federal Government Interprets an International Treaty as Permitting Only One Source for Legal Cultivation of Marijuana in the United States

The United States is a signatory to the Single Convention on Narcotic Drugs, as amended by the 1972 Protocol,¹⁸ ("Single Convention"). DEA interprets the Single Convention to require each nation to designate a single official source of marijuana for research.¹⁹ In the United States, NIDA has been designated as the responsible agency, and, as noted above, it contracts with the Center to grow marijuana as necessary for research in the United States.²⁰

The Center is required to supply its product to meet the United States' entire need for marijuana-related research and, as noted above, DEA has consistently found the supply to be "adequate and uninterrupted."²¹

D. While the University May Be Registered to do Research on Marijuana, it would Be Unable to Satisfy Conditions for Growing Marijuana for Research

Federal law permits research on marijuana, but only if certain conditions are met.²² To conduct research on marijuana, the researcher must first obtain a registration under the CSA from DEA.²³ To receive such a registration, HHS must determine that the researcher is qualified and competent and the proposed research must be determined to have merit.²⁴ Applying for such a registration requires submission of a detailed protocol to the DEA describing, among other things, the location where the research will take place and the security provisions for storing and dispensing the controlled substance to prevent diversion.²⁵ Certain research may also require an Investigational New Drug Application under the Federal Food, Drug, and Cosmetic Act ("FDCA").²⁶ Researchers using Schedule I substances, including marijuana, are required to

¹⁷ See *Craker v. DEA*, 714 F.3d 17 (1st Cir. 2013).

¹⁸ 18 U.S.T. 1407.

¹⁹ See Brief for the Drug Enforcement Agency at 11, *Craker v. Drug Enforcement Administration*, 714 F.3d 17 (2013) (No. 09-1220).

²⁰ *Id.* at 7.

²¹ See, e.g., *Craker v. Drug Enforcement Administration*, 714 F.3d 17, 29 (2013).

²² See HHS Guidance on the Provision of Marijuana for Research (May 21, 1999), available at <http://grants.nih.gov/grants/guide/notice-files/not99-091.html>; see also NIH Grants Policy Statement at IIA-15 (Oct. 2013 ed.).

²³ 21 U.S.C. § 823(f).

²⁴ *Id.*; 21 C.F.R. § 1301.32.

²⁵ 21 C.F.R. § 1301.18.

²⁶ 21 U.S.C. § 355(i).

comply with DEA regulations regarding security, record-keeping and reporting (including reports of any theft or significant loss within one business day), and proper disposal of unwanted or unneeded controlled substances.²⁷ Failure to comply with federal requirements regarding research with a Schedule I controlled substance subjects the researcher and the research institution to civil and/or criminal penalties.

If all necessary conditions are met, DEA will authorize NIDA to provide research-grade marijuana. As discussed above, however, because NIDA is the only legal source for marijuana-related research in the United States, the University will not be permitted by federal law to participate in the cultivation of marijuana for any purpose, including research.²⁸

E. The Controlled Substances Act Requirements and Prohibitions are Unchanged by Any Contrary State Law

A 2005 Supreme Court decision makes clear that the CSA prohibitions related to marijuana are unaffected by contrary state laws. California residents challenged the reach of the CSA to regulate marijuana that was legal under California state law and that was grown, shipped, dispensed and used entirely in the state of California.²⁹ In addition to finding that the Commerce Clause permitted the CSA to reach even those who grew and consumed their own marijuana,³⁰ the Supreme Court found that CSA "unambiguously" trumps any conflicting provision of state law.³¹ The Court found that state laws governing marijuana could not in any way diminish the federal power to regulate drugs as exercised in the CSA.³² As a result, the provisions of the CSA unquestionably apply over any contrary provision of state law, even for marijuana that is grown and used entirely within the state. Indeed, these provisions apply even if the marijuana at issue were to be grown and consumed by the same person.³³

F. Statements from the U.S. Department of Justice Concerning its Enforcement Priorities Do Not Change Marijuana's Status as a Schedule I Substance

In 2009,³⁴ 2011,³⁵ and 2013³⁶ the U.S. Department of Justice ("DOJ") sent memoranda to U.S. Attorneys outlining its CSA enforcement priorities regarding marijuana in light of changes in state laws related to marijuana. The 2009 and 2011 memoranda draw a distinction between, on

²⁷ 21 C.F.R. § 1301.71; 21 C.F.R. § 1301.75; 21 C.F.R. § 1301.76; 21 C.F.R. § 1304; 21 C.F.R. § 1307.21; and 21 C.F.R. § 1307.22.

²⁸ HHS Guidance on the Provision of Marijuana for Research (May 21, 1999).

²⁹ *Gonzales v. Raich*, 545 U.S. 1 (2005).

³⁰ *Id.* at 15-33.

³¹ *Id.* at 29.

³² *Id.*

³³ *See id.* at 7 ("Respondent Monson cultivates her own marijuana, and ingests the drug in a variety of ways").

³⁴ Memorandum from James M. Cole, Deputy Attorney General, to Selected United States Attorneys (Oct. 19, 2009), available at <http://www.justice.gov/opa/documents/medical-marijuana.pdf>.

³⁵ Memorandum from James M. Cole, Deputy Attorney General, to United States Attorneys (June 29, 2011), available at <http://www.justice.gov/oip/docs/dag-guidance-2011-for-medical-marijuana-use.pdf>.

³⁶ Memorandum from James M. Cole, Deputy Attorney General, to All United States Attorneys (Aug. 29, 2013), available at <http://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf>.

the one hand, patients and their caregivers using marijuana in a manner consistent with state law as part of treatment regime for a serious disease and, on the other hand, commercial entities engaged in the cultivation, sale, and distribution of marijuana. The 2013 memorandum outlines the current enforcement priorities that are particularly important to the federal government and notes that they are listed in general terms and "each encompasses a variety of conduct that may merit civil or criminal enforcement of the CSA":

- Preventing the distribution of marijuana to minors;
- Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels;
- Preventing the diversion of marijuana from states where it is legal under state law in some form to other states;
- Preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking or other illegal drugs or other illegal activity;
- Preventing violence and the use of firearms in the cultivation and distribution of marijuana;
- Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use;
- Preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands;
- Preventing marijuana possession or use on federal property.³⁷

The 2013 DOJ memorandum also notes that it rests on DOJ's expectation that states that have enacted marijuana legislation "will implement strong and effective regulatory and enforcement systems that will address the threat those state laws could pose to public safety, public health, and other law enforcement interests."³⁸ Even if the state of Florida and the University are able to develop a robust system to oversee marijuana-related activities that are permitted under state law, the University faces a heavy burden in ensuring that its and its collaborators' activities avoid triggering any of the enforcement priorities set out by DOJ (e.g., preventing distribution to minors, diversion to other states, and other illegal diversion) and the challenges in doing so could expose the University to potential civil or criminal enforcement efforts by the federal government.

Furthermore, the exercise of investigative and prosecutorial discretion is subject to change. Notably, the 2013 Memorandum states: "This memorandum does not alter in any way the Department's authority to enforce federal law, including federal laws relating to marijuana, regardless of state law. Neither the guidance herein nor any state or local law provides a legal defense to a violation of federal law, including any civil or criminal violation of the CSA."³⁹

For the foregoing reasons, federal law prohibits the cultivation, manufacture and distribution of marijuana in the United States, even if authorized or required by state law and even if such activity is for research purposes only. The only marijuana that can be possessed and used for research-related purposes is marijuana that the federal government supplies through the NIDA. Thus, the University would be in violation of the CSA if it participates in the cultivation,

³⁷ *Id.* at 1-2.

³⁸ *Id.* at 2.

³⁹ *Id.* at 4.

manufacture or distribution of marijuana for research, medical treatment, or any other purpose. Violations of the CSA can result in civil and criminal penalties that can range from suspension or revocation of controlled substance registrations, to civil money penalties, property forfeiture and imprisonment.

II. Federal Drug-Related Regulation Pertinent to Recipients of Federal Funds

In addition to federal criminal and civil exposure under the CSA, the University would also risk loss of federal research and student financial assistance funds if it cultivates, manufactures, possesses (other than for DEA registered research) or distributes marijuana or otherwise participates in such activities, because such activities would violate the University's obligations as a recipient of federal grants and contracts and as a participant in the HEA student financial assistance programs.

A. **The University Must Maintain a Drug-Free Workplace under the Drug-Free Workplace Act**

The Drug-Free Workplace Act ("DFWA") requires the University to maintain a drug-free workplace.⁴⁰ The DFWA applies to the University through the University's receipt of federal grants and contracts, predominantly for research, and its participation in the Federal Supplemental Educational Opportunity Grant program, Federal Work-Study program, and Federal Perkins Loan program, three HEA student financial assistance programs that are collectively referred to as the campus-based programs.⁴¹ Although DFWA requirements generally apply only to federal grant and contract worksites, the University's participation in the campus-based programs makes DFWA requirements applicable to all University offices and departments,⁴² and the University's research activities are, in any event, so extensive that DFWA likely captures a substantial proportion of the University's campuses.

The University would violate the DFWA if it possesses, cultivates, manufactures or distributes marijuana pursuant to Florida law (other than possessing marijuana provided by NIDA for research purposes under a DEA registration) because it would be unable to satisfy all of its obligations under the DFWA. Under the DFWA, the University must:

- Publish a statement notifying employees that the unlawful manufacture, distribution, dispensation, possession or use of a controlled substance is prohibited in the person's workplace and specifying the consequences of violations of this prohibition;
- Establish a drug-free awareness program;
- Give employees engaged in performance of the federal award/contract a copy of the statement described above;

⁴⁰ See 41 U.S.C. §§ 8102-8103.

⁴¹ The University's grants and contracts funded by HHS also require certification of compliance with provisions of annual appropriations bills that limit the use of HHS appropriated funds for purposes relating to controlled substances. Although the specific language may change from year-to-year, generally speaking, contractors and grantees are prohibited from knowingly using HHS appropriated funds to support activities that promote the legalization of any drug or other substance included in Schedule I under the CSA. See Consolidated Appropriations Act, 2012, Pub. L. No 112-74, § 810. As stated above, marijuana is a Schedule I drug. 21 U.S.C. § 812(c)(Schedule I)(c)(10).

⁴² See U.S. DEPT OF EDUCATION, FEDERAL STUDENT AID HANDBOOK 2-147 (2013-14).

- Notify the employee that a condition of employment on the federal grant/contract is for the employee to comply with the statement described above and require that the employee notify the University of any criminal drug statute conviction for a violation occurring in the workplace no later than five days after conviction;
- Notify the contracting agency of any employee conviction as described above no later than ten days after receiving notice from the employee;
- For any employee who is convicted as described above, impose a sanction on that employee or require participation in drug assistance or rehabilitation program; and
- Make a good faith effort to maintain a drug-free workplace.⁴³

The University must certify its compliance with the DFWA in its program participation agreement ("PPA"), which is the agreement an institution must sign in order to participate in HEA student financial assistance programs.⁴⁴ The University must also certify compliance with the DFWA through receipt of its federal research grants and contracts.⁴⁵ DFWA violations could result in (a) suspension of payments under the grant/contract; (b) suspension or termination of the award/contract; or (c) suspension or debarment of the University for a period of time not to exceed five years.⁴⁶

B. The University Must Have a Drug Abuse Prevention Program that Prohibits Unlawful Possession, Use or Distribution of Illicit Drugs on University Property

In order for an institution to receive funds under any HEA student financial assistance program,⁴⁷ including the Federal Direct Loan program and the Federal Pell Grant program, an institution must adopt and implement a program to prevent the use of illicit drugs and alcohol.⁴⁸ The University would be unable to satisfy all of its obligations with respect to a drug abuse program if it cultivates, manufactures, possesses or distributes marijuana or otherwise participates in such activities. In particular, the program must require, among other elements, that the institution will distribute annually to each student and employee standards of conduct that prohibit the unlawful possession, use or distribution of illicit drugs and alcohol by students and employees on the institution's property or as part of the institution's activities.⁴⁹ The institution must issue a clear statement that it will impose sanctions on students and employees for violations of the standards of conduct (consistent with local, state, and federal law) and a description of those sanctions, up to and including expulsion, termination of employment, and referral for prosecution.⁵⁰ An institution must certify its compliance with these provisions in its PPA.⁵¹

⁴³ 41 U.S.C. §§ 8102(a)(1), 8103(a)(1).

⁴⁴ See U.S. DEP'T OF EDUCATION, FEDERAL STUDENT AID HANDBOOK 2-14 (2013-14).

⁴⁵ 41 U.S.C. §§ 8102-8103; 2 C.F.R. § 182.200(a); 48 C.F.R. § 23.504; 48 C.F.R. § 52.223-6.

⁴⁶ See 41 U.S.C. §§ 8102(b), 8103(b).

⁴⁷ The University is responsible not only for its own compliance with federal drug law, but it also must not award HEA student financial assistance to any student who was convicted of an offense involving possession or sale of a controlled substance for conduct that occurred during a period of enrollment for which the student was receiving HEA student financial assistance. See 20 U.S.C. § 1091(r).

⁴⁸ See 20 U.S.C. § 1011i(a); 34 C.F.R. § 86.3.

⁴⁹ See 20 U.S.C. § 1011i(a)(1); 34 C.F.R. § 86.100(a)(1)

⁵⁰ See 20 U.S.C. § 1011i(a)(1)(E).

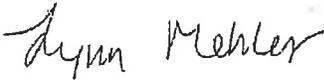
⁵¹ See 34 C.F.R. § 668.14(c)(1).

If an institution does not certify that it has a drug abuse prevention program or if it fails to implement a drug abuse prevention program, the U.S. Department of Education ("ED") may terminate any or all forms of HEA student financial assistance and may require the institution to repay any or all federal student financial assistance that it received while not in compliance.⁵² ED may also provide information and technical assistance to the institution and formulate a compliance agreement for the institution.⁵³

As discussed above, the CSA governs the possession, cultivation, manufacture, distribution and research of marijuana and marijuana derivatives in the United States. The University of Florida would be in violation of such federal law if it participates in the cultivation, manufacture or distribution of marijuana for any purpose, including for medical treatment or research, and as a result would be exposed to criminal and civil penalties (possession of federally-provided marijuana for research, registered and approved by the DEA and in compliance with the restrictions of the registration, is permitted). Furthermore, the University is obligated as a matter of law and certifications to the federal government to maintain a drug-free workplace and to have a drug abuse prevention program. It would be unable to satisfy those obligations if it cultivates, manufactures, possesses (except for limited permitted research on federally-provided marijuana) or distributes marijuana and would consequently risk loss of hundreds of millions of dollars in federal funding through research grants and contracts and federal student financial assistance.

I am available to respond to any questions.

Sincerely,



Lynn W. Mehler
Partner
lynn.mehler@hoqanlovells.com
D 2026376419

cc: Jamie Lewis Keith, Vice President and General Counsel

⁵² See 34 C.F.R. § 86.301(b); U.S. DEP'T OF EDUCATION, FEDERAL STUDENT AID HANDBOOK 2-147 (2013-14).

⁵³ See 34 C.F.R. § 86.301(a).

MATT GAETZ
1ST DISTRICT, FLORIDA

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August 23, 2017

The Honorable Jefferson Sessions
Attorney General
U.S. Department of Justice
950 Pennsylvania Avenue, NW
Washington, DC 20530-0001

Dear Attorney General Sessions:

We write to express our concern regarding an August 15th article from the Washington Post, "Justice Department at odds with DEA on marijuana research, MS-13," which asserts that the Justice Department has prevented the DEA from moving forward in its permitting process for marijuana research. The purpose of our letter is threefold: first, we wish to establish the veracity of this article's claims. Second, if the article's claims are true, we would like to know the rationale behind the Department of Justice's decision. Finally, we would like to encourage you to proceed with rapidity on the DEA's permitting process, as we believe it is in keeping with President Trump's campaign promises, and the best interests of the American people.

On August 11, 2016, Chuck Rosenberg, Acting Administrator of the Drug Enforcement Administration, stated in a letter to Governors Gina Raimondo of Rhode Island and Jay Inslee of Washington that the DEA "fully support[s] legitimate medical and scientific research on marijuana and its constituent parts," and that the DEA "will continue to seek ways to make the process for those researchers more efficient and effective." The following day, on August 12th, the DEA established a new rule (21 CFR Part 1301, Docket No. DEA-447) that it would begin accepting applications to grow cannabis for the purposes of medical and scientific research.

According to the Post story of August 15, as well as a July 24 report from Scientific American, over two dozen applications have been completed. These applicants, however, have received neither an approval nor a denial — they are in limbo. The Post claims this is because the Justice Department will not give the "sign-off to move forward" on processing these applications. Quite simply, we would like to know whether this is true, and, if so, we would like to know the rationale for this decision.

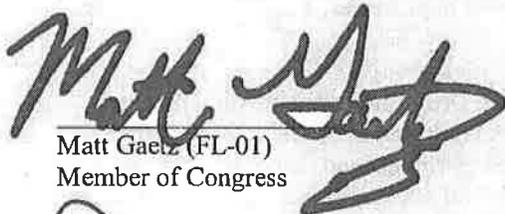
Over eighty percent of Americans believe that doctor-prescribed marijuana should be legal, according to recent polls. Yet despite widespread public support, health care professionals are understandably cautious about prescribing medical marijuana. Further research into its safety and efficacy is necessary. Only rigorous scientific research can ascertain the medical potential of cannabis, if any, but the rules and regulations surrounding cannabis make such research extremely challenging. The cumbersome and lengthy permitting process, as well as the difficulty of obtaining different types and "strains" of cannabis with which to perform research, have thwarted researchers' ability to study the pharmacology and potential medical usage of cannabis. The DEA's new permitting process of August 2016 does not attempt to change marijuana laws, except for the acquisition of research material. Such a change is small, but will

greatly enhance scientists' ability to perform research, and, as such, it should not be hindered unnecessarily.

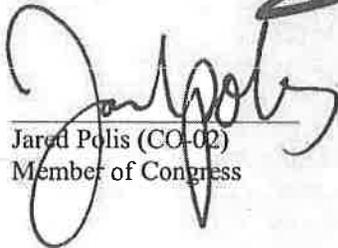
A "tough-on-crime" position is important to this administration, and your efforts to curb the importation of drugs into America are laudable. While we must continue our fight against organized crime and drug-related violence, it is our opinion that medical marijuana research falls outside of those categories, and does not pose a pressing danger to American society. This view, it seems, is supported by President Trump: in an October 29, 2015 campaign rally in Sparks, NV, Mr. Trump stated that he believed in the efficacy of medical cannabis for certain patients — a position he expressed several times at many other campaign stops. Indeed, as you surely know, many patients and patients' advocacy groups nationwide have attested to the potential benefits of medical marijuana — including its usage as a treatment for PTSD, which has afflicted many of the heroic men and women of our armed forces.

These groups' claims for medical marijuana's efficacy can only be determined through scientific research, which will be expedited and enhanced by the DEA's new permitting process. It is worrisome to think that the Department of Justice, the cornerstone of American civil society, would limit new and potentially groundbreaking research simply because it does not want to follow a rule. We write to inquire whether the allegations raised by the Post are true, and, if so, to understand the Department of Justice's rationale in refusing to process these applications. Finally, because we know you to be a man with unwavering commitment to the rule of law, we ask with respect for the DEA's rule to be followed, and for the permitting process to move forward with all possible expeditiousness.

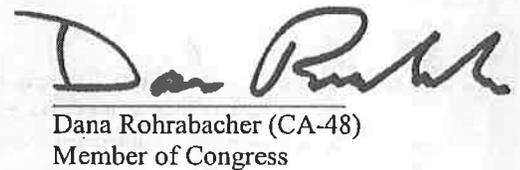
Sincerely,



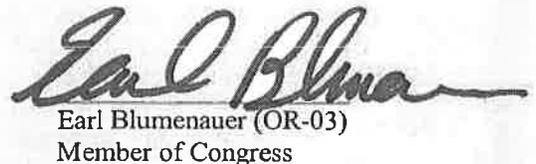
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Member of Congress



Jared Polis (CO-02)
Member of Congress



Dana Rohrabacher (CA-48)
Member of Congress



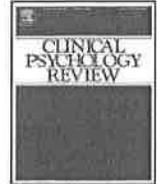
Earl Blumenauer (OR-03)
Member of Congress



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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 & Knafel, 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).

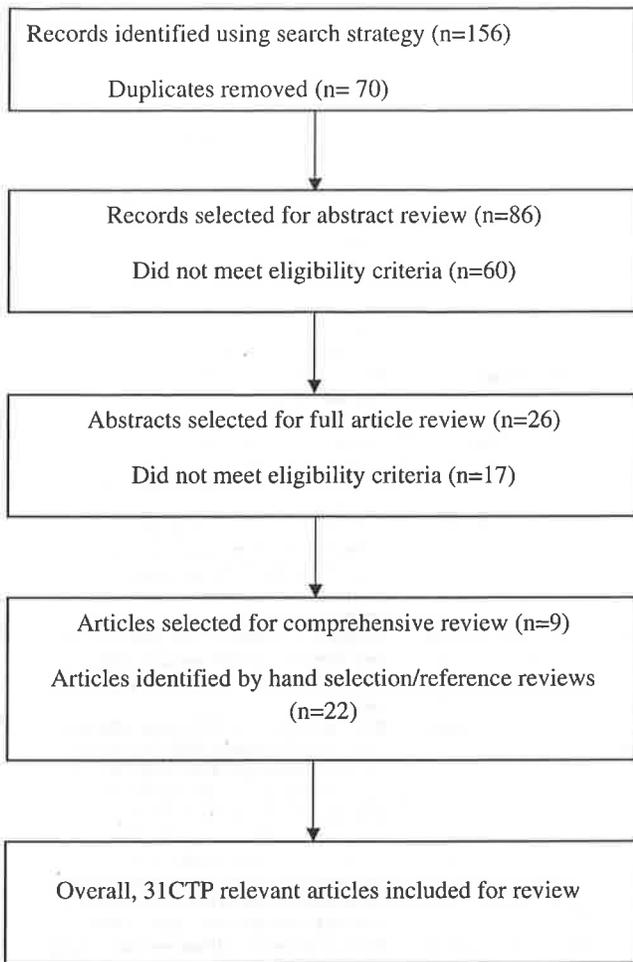


Fig. 1. Flowchart of CTP study selection.

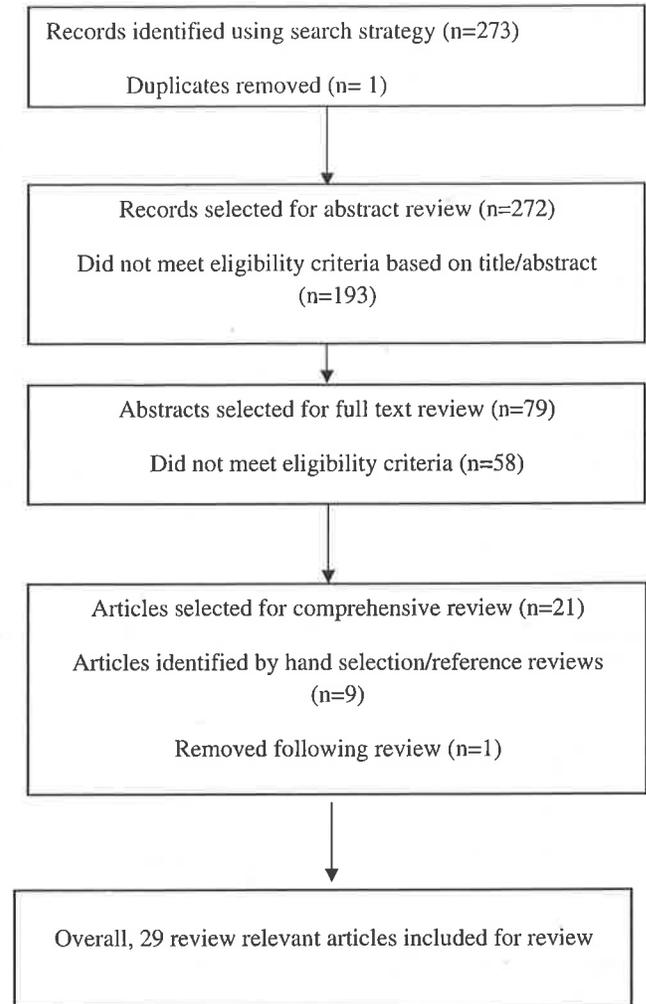


Fig. 2. Flowchart of review study selection.

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)	<p>Prominent reasons for using CTP included anxiety (71%), mood (69%), and depression (12%).</p> <p>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.</p> <p>Participants with higher level of depressive symptoms reported more problematic cannabis use. This relation was moderated by sleep quality.</p> <p>Dronabinol enhanced mood among cannabis using participants across the 16 day study period.</p> <p>The combination of cognitive reappraisal and emotional clarity was associated with problematic cannabis use among CTP users.</p> <p>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.</p> <p>Greater severity of PTSD was associated with more frequent cannabis use, and with use to help with sleep and to cope with negative affect.</p> <p>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.</p> <p>Adolescent medical cannabis users were approximately 2 times more likely to report the nonmedical use of prescription drugs and illicit substances other than cannabis.</p> <p>Primary reasons for CTP use included anxiety (60%), insomnia (56%), chronic pain (42%), depression (33%), and ADHD (17%).</p> <p>Patients who used CTP reported reductions of 75% in symptoms of trauma related re-experiencing, avoidance, and hyperarousal.</p> <p>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.</p> <p>Cannabis use to substitute for medications was reported by 67%, substitution for alcohol reported by 41%, and substitution for illicit drugs reported by 36%.</p> <p>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</p> <p>Reported mental health benefits CTP included relief of anxiety (38%), depression (26%), anger (23%), and panic (17%), as well as substitution for alcohol (13%).</p> <p>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.</p> <p>Reported mental health benefits of CTP included relief of depression (24%), anxiety (22%), and heroin craving (4%).</p> <p>Patients reported that the perceived benefits included general relaxation and decreased stress.</p> <p>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.</p>
Ashrafioun et al., 2015	433 (31)	Midwestern US	Patients from a specialized clinic	Pain	Cross-sectional (7)	
Babson et al., 2013	162 (22)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (6)	
Bedi et al., 2010	7 (0)	New York, US	Self-identified from the community	HIV	Laboratory	
Boden, Babson et al., 2013	153 (22)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	
Bohnert et al., 2014	186 (38)	Michigan, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (5)	
Bonn-Miller et al., 2014a	170 (22)	California, US	Medical cannabis dispensary	PTSD and sleep	Cross-sectional (6)	
Bonn-Miller, Boden et al., 2014	217 (27)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	
Boyd, Veliz, & McCabe, 2015	4394 (47)	US	National surveillance survey	Other substance use	Cross-sectional (5)	
Grella et al., 2014	182 (26)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (3)	
Greer et al., 2014	80 (20)	New Mexico, US	Medical evaluations of patients seeking CTP	PTSD	Cross-sectional (5)	
Harris et al., 2000	100 (16)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (4)	
Lucas et al., 2015	404 (33)	British Columbia, Canada	Medical cannabis dispensary	Substance use disorders	Cross-sectional (4)	
Mikuriya, 2004	92 (9)	California, US	Medical evaluations of patients seeking CTP	Alcohol use disorder	Cross-sectional (3)	
Nunberg et al., 2011	1655 (27)	California, US	Medical evaluations of patients seeking CTP	Diverse medical conditions	Cross-sectional (6)	
O'Connell & Bou-Matar, 2007	4117 (23)	California, US	Medical evaluations of patients seeking CTP	Diverse medical conditions	Cross-sectional (3)	
Ogborne et al., 2000	50 (34)	Ontario, Canada	Self-identified from the community	Diverse medical conditions	Cross-sectional (6)	
Page & Verhoef, 2006	14 (57)	Alberta, Canada	Patients from a specialized clinic	Multiple Sclerosis	Cross-sectional (3)	
Reiman, 2007	130 (25)	California, US	Medical cannabis dispensary	Diverse medical conditions	Cross-sectional (3)	

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 bipolar 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 is 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; Reinerman, 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 (Witcher 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 (Cogle, 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, & Jorm, 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, & Nielsen, 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 causal 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 $\frac{1}{4}$ 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 neurocognitive 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 $\frac{1}{4}$ to $\frac{1}{2}$ 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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