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ORIGINAL ARTICLE

A Scoping Review of the Use of Cannabis and Its Extracts as Potential Harm Reduction Strategies: Insights from Preclinical and Clinical Research

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Abstract
Cannabis as a harm reduction strategy (HRS) is supported by evidence demonstrating its efficacy for pain relief and as a substitution for alcohol, illicit drugs, and pharmaceuticals. Animal models show cannabinoids reduce the effects of opiate withdrawal, which contribute to drug-seeking behavior. This scoping review assessed cannabis and its extracts as HRS while identifying critical gaps in preclinical and clinical research. Halas et al.'s (*British Medical Journal Open, 5*, e006643, 2015) five-stage scoping review methodology was used focusing primarily on "harm reduction" and "harm reduction strategies" related to "cannabis" or "marijuana" and its derivatives "THC" and "cannabidiol." Across 33 countries, 57 articles were identified demonstrating that cannabinoids (i) enhance opioid analgesia while reducing tolerance and dependence, (ii) interrupt dependence on cocaine, alcohol, and nicotine, and (iii) can be vaporized or eaten to reduce harms associated with smoking. Critical gaps in research include (i) discrepancies due to species and route of administration differences and (ii) the legal status of cannabis. Future research on HRS should examine access to cannabis and its extracts, the effects of varying cannabinoid concentrations, limiting selection bias by recruiting more authorized medicinal and recreational cannabis users, and the various methods cannabis is consumed in humans and animal models of drug dependence.

Keywords Harm reduction strategies (HRS) · Cannabis · Tetrahydrocannabinol (THC) · Opiate withdrawal · Substitution treatments

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Introduction

Cannabis (marijuana), one of the most commonly used drugs worldwide, is derived from the *Cannabis* plant in the Cannabaceae family and is used in various forms (Baker et al. 2003; Small et al. 2003). For example, cannabis, which contains a large amount of the psychoactive cannabinoid Δ9-tetrahydrocannabinol (THC), can be used for medicinal as well as recreational purposes (Sawler et al. 2015). In addition, hemp, which contains a low amount of THC, can be used to produce seeds, food, and fiber for textiles, industrial products, paper, and thousands of other products (Bouloc 2013; Sawler et al. 2015; Sumner 2018). Although the primary route of administration of THC in humans is pulmonary, by smoking or vaporizing dried cannabis, the vast majority of animal models administer THC through a parenteral route (injection) with only a few exceptions that mimic inhalation in humans (Naef et al. 2004; Wilson et al. 2006; Niyuhire et al. 2007; Manwell et al. 2014a, b; Manwell and Mallet 2015; Nguyen et al. 2016). THC is structurally similar to anandamide (AEA), which is an endogenous cannabinoid that acts as a retrograde synaptic neuromodulator in the brain (Joy et al. 1999; Castillo et al. 2012). THC, which binds to cannabinoid CB1 receptors in brain regions involved in memory and motor function, produces various effects, including disruption of short-term memory, and either stimulation or inhibition of movement by low and high doses of THC, respectively (Joy et al. 1999). Although there are some adverse psychological and physiological effects associated with the use of cannabis, clinical research also demonstrates its medicinal benefits (Voth and Schwartz 1997; Baker et al. 2003). There is growing evidence that cannabis and its extracts, such as THC and the non-psychoactive cannabidiol (CBD), can serve as effective harm reduction strategies for individuals with substance abuse and addictions (Andre et al. 2016).

Efficacy of Medical Cannabis

There is currently mixed evidence on a wide range of medical treatments supporting the efficacy of medical cannabis within the healthcare field. Medicinal cannabis is well known for its efficacy in stimulating the appetite for patients with AIDS or cancer-related anorexia (Voth and Schwartz 1997; Lucas et al. 2013; Bruni et al. 2018) and its efficacy in treating rheumatoid arthritis by acting as an analgesic and reducing inflammation (Blake et al. 2006; Rea et al. 2019). Cannabis extracts, such as nabiximols containing both THC and CBD, have been shown to be effective in the treatment of painful spasms and sleep disturbances in patients with multiple sclerosis (MS) (Luessink et al. 2012) and to greatly reduce the number of days of illicit cannabis use compared with placebo (Lintzeris et al. 2019). Cannabinoid medicines are demonstrated to be effective as a mono-therapy or an add-on to other therapies (Borgelt et al. 2013). Nevertheless, it is important to recognize that research indicates that many of the benefits could be partially or completely offset by serious risks or harms (Martin-Sanchez et al. 2009). The adverse effects of cannabis use are largely influenced by the route of delivery, duration of exposure, age of the patient, and immunologic status (Voth and Schwartz 1997). Short and long-term use affects the central nervous system and can affect concentration, motor coordination, and the ability to sort important information (Voth and Schwartz 1997; Huestis et al. 2011). The major downfall to cannabis use is that for patients using it for treatment of glaucoma, AIDS appetite-enhancement, and MS, there is added risk due to short and long-term exposure to the drug (Hall and Degenhardt 2009; Volkow et al. 2014).

Cannabis as a Harm Reduction Strategy

Harm reduction strategies (HRS) are broadly defined as "any policy or program designed to reduce drug-related harm without requiring the cessation of drug use. Interventions may be targeted at the individual, the family, community, or society" (Erickson et al. 2002, p. 1). Examples of effective HRS include the use of methadone to reduce withdrawal symptoms in individuals with heroin dependency (Oviedo-Joekes et al. 2008, 2014) and the use of naltrexone paired with an alcohol treatment program (Sinclair 2001). Another form of HRS currently being implemented for injection drug users is a needle exchange program for heroin users as well as bleach kits (MacMaster 2004). The use of cannabis as a HRS is a growing field with clinically established evidence showing that it is an effective treatment method for a wide range of illnesses, diseases, addictions, pains, and discomforts. For instance, patients with neuropathic pain who use opioids for pain relief tend to see benefits from cannabis use (Collen 2012). Patients who use cannabis for neuropathic pain relief report higher pain tolerance, increased positive mood, improved sleeping patterns, and an overall improvement in quality of life compared with patients in the placebo condition (Collen 2012). There is also evidence of the efficacy of cannabis as an adjunct or substitution for alcohol, illicit drugs, and pharmaceuticals for individuals unwilling or unable to abstain from drug use (Lau et al. 2015; Lucas 2012, Lucas et al. 2016). Animal models of drug-seeking behavior indicate that cannabinoids may be important in interventions aimed at reducing both the unconditioned (e.g., somatic signs) and conditioned (e.g., negative affect) effects of opiate withdrawal syndrome, which contribute to drug-craving/seeking behavior in opioid addiction and relapse (Bechara et al. 1995; Koob 1996; Bechara et al. 1998; Manwell and Mallet 2015).

Currently, there are various harm reduction strategies being implemented that involve the use of medical cannabis. In the USA and Canada, several types of cannabinoid medicines are available; however, medical cannabis is considered to be a Schedule I drug federally in the USA, meaning that patients can only obtain it through a doctor's prescription depending on the state. Similarly, the extracts of cannabis such as dronabinol (Schedule III), nabilone (Schedule II), and nabiximols are cannabis-derived pharmaceuticals, which are used for treatments such as anorexia or nausea/vomiting associated with cancer chemotherapy and are also heavily restricted (Borgelt et al. 2013). Due to the fact that the US Federal Drug Administration (FDA) classifies cannabis as a Schedule I drug, it is very difficult to obtain consent for researchers to study its therapeutic effects, and limited information is available about specific drug interactions and contraindications with pharmaceuticals derived from cannabis (Borgelt et al. 2013).

Purpose of Scoping Review

With the changing laws pertaining to the legalization of medical and recreational cannabis, particularly in Western countries such Canada and the USA, more emphasis in research must be placed on the therapeutic effects of cannabis and its extracts. The purpose of this scoping review is to characterize the various uses of cannabis and its extracts specifically as an HRS for individuals with substance use disorders and identify critical gaps in preclinical and clinical research.

Methods

This review followed the five stages of the scoping review created by Halas et al. (2015), which were modified for the purposes of the current study.

Stage 1: Identifying the Research Question

An iterative search process, as developed by Arksey and O'Malley (2005) and adapted by Halas et al. (2015), was used to formulate a series of guiding questions in order to frame a research question. The specificity of the research question was driven by an increase in the literature on the topic of cannabis and/or its extracts as an HRS and the need to identify any gaps in preclinical and clinical research. In order to narrow a research question, we have identified six guiding questions (Table 1) (Halas et al. 2015).

Stage 2: Identifying Relevant Studies

The main goal of a scoping review is to broadly address a wide range of research questions. There are, however, specific parameters that should be used to guide the search strategy. The search strategy, selected key terms, and the eligibility criteria for this review are as follows:

Table 1 List of research questions and operational definitions

Research questions	Operational definitions
1. What are the main harm reduction targets?	Main harm reduction targets to reduce or prevent include: •Transmission of infectious diseases (e.g., HIV, Hepatitis) •Prevention of overdose death •Non-prescription related drug use for pain reduction (e.g., alcohol, illicit drugs, etc.) •Arrests and incarceration •Hospital visits
2. What are the main harm reduction strategies discussed in the literature?	Main harm reduction strategies: •Methadone maintenance •Naloxone injection (e.g., opioid overdose reversal) •Reduction of pharmaceutical and illicit substance use
3. What are the specific harm reduction strategies employing cannabis and/or its extracts (e.g., cannabinoids such as THC and cannabidiol)?	Specific harm reduction strategies using cannabinoids for: •Neuropathic pain management •Decrease hyperalgesia •Chemotherapy side effects •Spasticity from MS, Epilepsy, Parkinson's disease, etc.
4. What are the specific harm reduction strategies employing cannabis and/or its extracts for opioid users?	Specific harm reduction strategies using cannabinoids for opioid users: •Synergistic effects and cross-tolerance between use of cannabinoids and opioids
5. What are the side effects associated with cannabis and/or its extracts (e.g., cannabinoids such as THC and cannabidiol) compared to the side effects of opioids?	Side effects associated with cannabinoids: •Psychotic disorders •Memory disorders •Motor effects •Cardiovascular damage (method of consumption effects this) •Cannabis use disorder •Depression and mood disorders
6. What barriers and gaps in research are addressed with reference the control of administration of medical cannabis?	Barriers and gaps in research: •Dosage and concentration control •Self-medication and report •Selection and recruiter bias •Laws and public education •Effect with other illicit drugs •Method of consumption

Eligibility Criteria

The following inclusion criteria were used to guide the search and when reviewing articles:

- Published in the English language
- Human and animal subjects
- January 1997–December 2019
- All age groups
- Original preclinical and clinical research
- Review articles including systematic reviews, meta-analyses, meta-syntheses, scoping reviews, narrative reviews, rapid reviews, critical reviews, integrative reviews, and brief review-based expert commentaries.
- Research reviews are limited to Western countries including Canada, USA, UK, Europe, Australia, and New Zealand where rates of smoking, culture, income, standard of living, and infrastructures may be comparable and influence the perception of and access to medical cannabis.

Explicit Exclusion Criteria

Explicit exclusion criteria identified are articles that are not academic- or expert-based (i.e., outside of those defined in the inclusion list), such as book reviews, opinion articles, commentaries, or editorial reviews.

Databases

The following electronic databases were searched: Google Scholar, PubMed, MedLine, Scopus, the Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycInfo, and the Educational Resources Information Centre (ERIC).

Search Strategy

Our research team determined primary search terms and a multitude of secondary search terms as well as filtering methods. The primary search terms focused on a broad definition of "harm reduction" and "harm reduction strategies." The secondary search terms included more specific definitions such as "cannabis" or "marijuana" and its derivatives such as "tetrahydrocannabinol" or "THC" and "cannabidiol" or "CBD." The filtering methods included the date range (within a 22-year span) and English in order to narrow the results of the search.

It is important to be mindful of search terms that produce irrelevant outputs but need to be included as they may otherwise eliminate relevant articles. For example, many of the search results targeted a particular disease, such as psychotic disorders, and are therefore outside the domain of opioid use. Multiple searches to account for all the words that may possibly be substituted for medical cannabis (particularly its derivatives) are necessary in order to include human and animal studies. Appropriate keywords, Medical Subject Headings (MeSH) terms, and filters were determined, discussed, and tested to maximize sensitivity and specificity within the search. Further search strategy details across bibliographic databases are available upon request from the first author. Upon completion, the searches from each database were

documented, and references were imported into database-specific folders in Dropbox, where duplicates were eliminated.

Stage 3: Study Selection

This paper was designed with a two-part study selection process. First, titles were reviewed by a single reviewer to determine eligibility based on the defined inclusion and exclusion criteria and by using the defined key terms. The second part of the selection process involved two independent reviewers examining the titles and abstracts using the eligibility criteria. The two reviewers assessed the systematic approach as well as the results that are reported in the abstract. Given that abstracts commonly contain less specific details, the research group developed specific criteria to determine the acceptable level of rigor based on a preliminary review of the abstracts and an inductive approach drawing on Gough (2013) and Gough et al.'s (2012) observations of varied review methods (Table 2). While scoping review methodology does not specify a process for evaluating study quality, this paper only included abstracts that demonstrated sufficient evidence of the use of cannabis and/or its extracts as a harm reduction strategy.

Stage 4: Charting the Data

In order to collect key findings, we conducted a scan of the abstracts in the selected literature (Table 3). Data extracted from the journal articles was analyzed and summarized into tables and included standard information such as author, year of publication, and study objectives. In order to ensure the consistency of the questions and the data that is presented within these tables, a study by Daudt et al. (2013) suggested a "trial charting exercise and team consultation" (Halas et al. 2015, p. 4). The abstracts of the articles explained the necessary data such as the focus, main findings, harm reduction strategies, and information necessary to conduct a scoping review. If pertinent information was missing from within the abstracts, then the research team consulted to report the findings and discuss the papers' relevance to the review.

Stage 5: Collating, Summarizing, and Reporting the Results

The findings were presented as a broad overview of guiding questions that revealed the gaps that were identified within the current literature, rather than a narrow scope. This allows researchers to better identify where specific research is necessary and what population(s) must be targeted when examining HRS.

Table 2 Inclusion and exclusion criteria determining acceptable articles

Criteria for inclusion	Criteria for exclusion
At least one of the following minimum criterion required in the abstract: • Harm reduction • Cannabis and/or its extracts (e.g., cannabinoids, such as THC and CBD)	•Non-academic sources such as websites, book reviews, opinion articles, commentaries, or editorial reviews

Table 3 Data extraction framework

Bibliometrics	Characteristic of the article	Coding the characteristics
Authors Title Source Year of publication Country Language Type of article Number of included studies Time frame	Objective(s) and methods	Action areas: • Harm reduction • Harm reduction programs • Education pertaining to benefits of utilizing cannabis and its extracts as harm reduction strategies • Promotion to decrease use of opioids

Results

Using the outlined search strategy, a total of 293 documents were screened through database searching and other sources; of these publications, 57 articles were eligible for inclusion in this qualitative synthesis (refer to Table 4). Once selected, articles were separated into three tables based on relevance to each: clinical research, preclinical research, or literature reviews. Table 5 includes articles investigating pre-clinical animal research ($n = 5$), Table 6 explores clinical studies ($n = 26$), and Table 7 examines literature reviews ($n = 26$). Each table includes the author, year of publication, participant number, location, research method, major findings, and harm reduction recommendations.

The methods used to investigate the effects and harm reduction strategies involving cannabis varied widely. Of the chosen journal articles, forty-four (77%) demonstrated substituting cannabis or its derivatives for opioids or other substances yielded positive health benefits. The vast majority of these studies (90%) suggest that cannabis and its derivatives have a significant role to play in a wide variety of medical treatments and harm reduction strategies. Of these positive articles, thirty focused on or mentioned opiates (52%). The remaining twenty-six articles touch on a wider variety of substances (e.g., crack and alcohol) and medical conditions (epilepsy, multiple sclerosis, MS, Parkinson's disease, and cancer).

Discussion

The scoping review findings clearly show that cannabis and its extracts can be effective as a harm reduction strategy for a wide range of substance use disorders, including abuse of alcohol, opioids, cocaine, and prescription medications. For example, Karst & Wipperman's (2009) review of pre-

Table 4 Flow diagram

Identification	Records identified through database searching: ($n = 125, 922$)	Additional records identified through other sources ($n = 29$)
Screening	Records screened ($n = 293$)	Records excluded ($n = 125,645$)
Eligibility	Review abstracts assessed for Eligibility ($n = 73$)	Review abstracts excluded with Reasons ($n = 20$)
Included	Studies included in qualitative Synthesis ($n = 57$)	

Table 5 Summary of primary source pre-clinical articles identified through primary and secondary search terms

Articles and locations	Objectives, animals, and methods	Main findings	Harm reduction implications
Ramesh et al. (2011), USA	-Preclinical animal experiment using in vivo and in vitro models of morphine dependence - Mice	-Endocannabinoid inhibitors (FAAH & MAGL) improve naloxone-precipitated withdrawal symptoms in both in vivo and in vitro opioid dependence models	-The endocannabinoid system can be manipulated to improve opioid withdrawal symptoms -Indicates a potential use in opioid addiction treatment
Valverde et al. (2001), France	-Preclinical animal experiments using place preference paradigm, antinociception, and in vivo binding paradigms -Mice, Rats	-THC interacts with opiates and increases the antinociceptive and anti-depressant effects -A neurochemical interaction between cannabinoid and opiate systems is demonstrated in in vivo experiment -Pre-treatment with THC lessened opioid withdrawal symptoms and did not increase opiate-rewarding effect	-More evidence suggests a strong interaction between opiates and cannabinoids in how they impact behavior and addiction. -Combinations of these two substances could prove beneficial for treatment and therapy
Yamaguchi et al. (2001), Japan	-Preclinical animal experiment using in vivo model of morphine dependence - Mice	-Endogenous cannabinoids: $\triangle^8$THC, HU-210 (a synthetic CB1 receptor agonist), and 2-arachidonoylglycerol all mimic $\triangle^9$THC and anandamide in their ability to alleviate morphine withdrawal behavior in naloxone precipitated opiate dependent mice.	-There are many components of cannabis and the endocannabinoid system that can be beneficial in the treatment of opioid withdrawal symptoms. -Non-psychoactive CB1 receptor agonists demonstrate this ability allowing patients who cannot take psychoactive medication to benefit from this treatment method
Manwell et al. (2009, Experiments 2–3), Canada	-Preclinical animal experiment using operant and classical conditioning procedures - Rats	-Extinction of naloxone-precipitated withdrawal-induced behavior in the conditioned floor aversion procedure was promoted with FAAH inhibitors and indirect CB1 agonist (URB-597). These did not affect extinction of morphine-induced conditioned preference or sucrose-motivated operant responding	-The endocannabinoid system is an important aspect of behavior extinction and learning in general. -This system could be a useful tool in the treatment of opioid withdrawal and addiction under specific circumstances. -Animal research like this warrants further study on human participants.
Manwell and Mallet (2015) Canada	-Preclinical animal experiment using operant and classical conditioning procedures - Rats	-THC did not impact recall memory of rats -Vaporized THC facilitated extinction learning whereas injected THC impeded extinction learning -Higher doses of vaporized THC (5&10 mg) facilitated extinction more than lower doses (1 mg). The inverse was true for injected THC with lower doses impairing extinction more than higher doses.	-Both method of ingestion and dose size appear to play an important role in learning and extinction of behaviors. -Future studies should attempt to recognize the importance of these variables and recognize the limitation or control them accordingly. -Manipulation of the endocannabinoid system with THC can have benefits to opioid addiction and treatment

Articles identified by primary/secondary search terms ($N = 125{,}922$); articles meeting inclusion criteria ($N = 5$) for analysis

POM prescription opioid medication, *FAAH* fatty acid amide hydrolase, *MAGL* monoacylglycerol lipase

Table 6 Summary of primary source clinical (human) study articles identified through primary and secondary search terms

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
Labigalini et al. (1999), Brazil	-Case study of crack addicted patients using cannabis as a substitute ($N = 25$)	-68% of patients ceased crack use in an average of 5.2 weeks and reported reduced cravings with cannabis use -Patients reported a decline in anxiety, withdrawal symptoms, more weight gain, and better sleep	-Crack is one of the most addictive substances and cannabis has shown some effectiveness in treatment -Lessening crack withdrawal symptoms can greatly increase chances of successfully treating substance abuse
Reiman (2009), Berkeley, California, USA	-Anonymous survey ($N = 350$)	-Cannabis as a substitute: 65% report less unfavorable side effects & 57.4% improved symptom management -40% reported substituting for alcohol, 26% for illicit drugs & 65.8% for prescription drug	-Medical cannabis is used as a substitute for alcohol, prescription and illicit drugs to diminish addiction potential and effectiveness of symptom relief
Swartz (2010), California, USA	-Exploratory study of medical cannabis users referred to SUD treatment by criminal court ($N = 18$)	-Cannabis did not compromise SUD program completion, medical concerns, or criminal justice involvement; other improvements	-Replacing other drug use with cannabis in addiction treatment as HRS may have considerable social/economic savings
Earleywine and Van Dam (2010), New York, USA	-Case study of cannabis and tobacco users trying vaporizers for 1 month ($N = 4$)	-Cannabis vaporization reduced cannabis and tobacco use. -Measures of lung health such as forced expiratory volume and forced vital capacity showed modest improvement.	-Vaporization of cannabis is not only a less harmful method of consumption but may also result in the reduction of tobacco and cannabis use thus reducing the risk and harm even more.
Lucas et al. (2012) BC, Canada	-Community-based survey of B.C. medicinal cannabis users ($N = 404$)	-Over 75% reported substituting cannabis for alcohol, illicit drugs, or prescription medication	-Cannabis substitution identified as safer adjunct / alternative to licit / illicit drug use
Lucas et al. (2013), B.C., Canada	-Self report survey of medical cannabis users ($N = 404$)	-75.5% reported substituting cannabis for other substances like alcohol (>41%), illicit substances (36.1%), and prescription medication (67.8%)	-Cannabis can be an effective tool in weaning patients off of more harmful and risky substances -Transmission of diseases like HIV/AIDS, hepatitis C etc., are less likely with the use of cannabis
Cameron et al. (2014) Brockville, Ontario, Canada	-Controlled before and after study of PTSD patients treated with Nabilone ($N = 104$ men)	-101 patients reported increased hours slept, 90 reported fewer nightmares, 86% reported less pain, and 90 patients ended prescriptions in favor of Nabilone	-Cannabis and its derivatives like nabilone show promise in PTSD treatment and harm reduction their pain management
Malouff et al. (2014) USA, UK, Canada, Australia, etc.	-Self report online survey of cannabis users on vaporizers ($N = 96$)	-Vaporizers have a positive perception and are seen as harm reducing products for cannabis users - Cannabis vaporizers report smoking less tobacco as well	-Cannabis users recognize that vaporizers are a harm reduction tool to limit the damage that smoking cannabis and tobacco have on the cardiovascular system among others.
Mojarrad et al. (2014) Boston MA., USA	- RCT secondary analysis: Addiction Health Evaluation and Disease	- Cannabis associated with 27% reduction in odds of subsequent abstinence from drug (opioid, stimulant)	- Cannabis contraindicated for abstinence

Table 6 (continued)

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
	Management (AHEAD) study ($N = 535$) California, USA	and heavy alcohol use among SUD individuals across time	- Subjects mostly male, homeless, with recent incarceration history, smokers, and had comorbid depression and anxiety did not benefit from cannabis use
Lau et al. (2015) San Francisco, California, USA	- Community-based survey of S.F. medicinal cannabis users ($N = 97$)	- Cannabis substituted for licit / illicit drugs -10% reported physical/mental health concerns	- Cannabis substitution is an effective HRS when substance abstinence not possible
Manini et al. (2015) Mount Sinai, New York City, USA	-Double-blind, placebo-controlled cross-over study of CBD & fentanyl intravenous in humans ($N = 17$)	-There was no pharmacokinetic changes with up to 800 mg of CBD co-administered with fentanyl -Adds to the growing body of evidence that CBD is safe in humans	-CBD has the potential to be an effective treatment for many health issues including opioid addiction -This research suggests that CBD is not harmful when paired with opioids and can/should be studied together
Borodovsky et al. (2016), USA	-Self report study of cannabis use methods in states with MML vs. states without ($N = 2838$)	-Participants from States with MML ingest cannabis in multiple methods that are less harmful than smoking -Vaping and edibles were the most common methods -Non-MML's preferred smoking over other methods	-MML are not only important for medical treatments, but also reducing the harm in ingestion of cannabis -More research is required on the impact of the various methods of cannabis consumption and which methods is best
Boehnke et al. (2016), Ann Arbor, Michigan, USA	-Online self report survey of medical cannabis users ($N = 244$)	-64% reported a decrease in opioid use -Reduction of opioid use was least drastic in those who had the highest fibromyalgia pain -Mean medication number lowered with cannabis use	-By decreasing the number and dose of medications when using cannabis patients can mitigate some of the risks involved in treatment
Lucas et al. (2016) B.C. Canada	-Self report survey- People who use cannabis for therapeutic purposes ($N = 473$)	- 87% reported substitution alcohol (52%), illicit drugs (33%) or prescription drugs (80%) for cannabis -It is reported to have less adverse side effects (51%) or better symptom management (49%)	-By substituting cannabis for other more harmful substance the risk of addiction, overdose, and loss of pain management becomes greater.
Corroon et al. (2017) USA, Canada, etc.	-Self report online survey ($N = 2774$)	- 46% reported substituting prescriptions medication for cannabis, most commonly narcotics/opioids (35.8%)	-If cannabis can be used as a substitute or in a synergistic manner it can help alleviate the negative consequences of opioids and pharmaceuticals like addiction and overdose
Franklyn et al. (2017) Ontario, Canada	-Examined electronic medical records from 58 opioid agonist clinics ($N = 644$)	-Baseline cannabis users were 38.9% more likely to drop out of OAT than non-users -Patients with 75% or more cannabis positive urine samples were 48.1% more likely to drop out	-Physicians should closely monitor patients who use cannabis as they may require a more complex opioid treatment

Table 6 (continued)

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
Piper et al. (2017) Maine, USA	-Online cross-sectional self report survey ($N = 1513$)	-Patients reported lowering opioid (76.7%), antidepressant (37.6%), alcohol (42%), and other medication (>66%) use slightly or a lot with medical cannabis use	-Due to its myriad benefits and relatively low costs cannabis can be used to reduce the dependence on harmful medications and substances while also assisting in pain management
Socías et al. (2017) Vancouver, B.C., Canada	-Interviews and questionnaires from people who use drugs ($N = 820$)	-Daily users of cannabis were 21% more likely to be retained in a OAT at 6 months after controlling for several confounding variables	-Cannabis use may have some adjunct benefits to OAT and could help curtail addiction and overdose
Reiman et al. (2017) California, USA	-A cross sectional survey of medical cannabis users ($N = 2897$)	-63% of patients reported using cannabis for pain -Of the 513 patients who use cannabis with opioids 97% reported using less opioids, 81% agreed it was more effective than with opioids, and 71% agreed it was as effective as opioids	-Self-administered cannabis use for pain management could reduce opioid abuse and overdose -Cannabis alone could be a sufficient analgesic substitute for other medications
Socías et al. (2017) Vancouver, B.C. Canada	-Interviews and questionnaires of crack users over time (3 semi-annually) ($N = 120$)	-Patients who reported using cannabis to curtail crack use subsequently reduced crack use	-Cannabis can and should be examined as a harm reduction strategy for many substances not just opioids -The use of cannabis to reduce crack use demonstrates its versatility as a harm reducing substance
Vigil et al. (2017), New Mexico, USA	-21-month medical cannabis as a substitute for prescription opioid use in humans ($N = 37$)	-Self report surveys indicated improvement in quality of life, social life, activity levels, concentration, and with fewer side effects from the opioids when using cannabis	-Medical cannabis could be an alternative to opioids for some patients and to lower opioid dose size in others
Wilson et al. (2018),Washington, USA	-Self report survey of patients undergoing opioid addiction treatment ($N = 150$)	-Higher cannabis use was associated with greater symptoms of depression, anxiety, and pain - Self-efficacy may be affected by cannabis making links between these symptoms stronger	-Frequent cannabis use may exasperate symptoms like depression & anxiety making it difficult to treat opioid addiction
Schipper et al. (2018), Apeldoorn, Netherlands	-Case study on seven psychotic patients with comorbid substance use and abuse ($N = 7$)	-Patients used regular high THC cannabis after the first week of Bedrolite prescription (low THC, high CBD) -Nurses did not see any improvement in any patients	-Low THC high CBD cannabis may have little to no effect in these extreme cases -Future research on larger populations is necessary for more robust data
Blake et al. (2006), UK	-Self report of patients with rheumatoid arthritis pain using CBMs a THC & CBD mixture ($N = 58$)	-Measures like: pain at movement & rest, sleep quality, DAS28 & SF-MPQ questionnaires were improved with CBM oromucosal spray compared to placebo -Inflammation was reduced in treatment group	-CBMs can be a useful tool in pain management strategies for Rheumatoid arthritis and potentially other inflammation pains -Oromucosal sprays reduce harms of cigarette smoke

Table 6 (continued)

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
		-No adverse effects were seen in treatment group	-CBMs can be an alternative to other medication and potentially addicted substances like opioids
Abrams et al. (2007), USA, San Francisco	-Plasma concentrations and self report data of medical cannabis consumption via cigarette and vaporization ($N = 18$)	-THC was found in higher concentrations at 30 min & 1 h with vaporization compared to cigarette suggesting absorption of THC was faster with vaporization -Vaporization demonstrated lower CO levels -Self report measures suggest no difference in experience of "high" between two methods	-Even within cannabis use there are harm reduction techniques -Faster absorption of THC suggests faster pain relief and better pain management ability -Lower CO levels means fewer toxins in the blood stream increasing the medical benefits while reducing the harms -The experience or "high" was the same across methods
Abrams et al. (2011) USA, San Francisco	-Self report of patients using vaporized cannabis with opioids for pain relief ($N = 21$) (morphine = 10; oxycodone = 11)	-Patients who inhaled vaporized cannabis combined with opioid treatments exhibited a 27% reduction of pain response on average -Cannabis use did not alter blood opioid levels	-Combined cannabis and opioid use allow for lower doses of opioids without affecting pain management -reduced opioid prescriptions lowers risk of addiction, opioid abuse, and overdose

Articles identified by primary/secondary search terms ($N = 125{,}922$); articles meeting inclusion criteria ($N = 26$) for analysis

RCT randomized controlled trial, *POM* prescription opioid medication, *OAT* opioid agonist therapy, *SUD* substance use disorder, *PTSD* posttraumatic stress disorder, *HRS* harm reduction strategy, *CBM* cannabis-based medication, *MML* medical marijuana laws; *CO* carbon monoxide

Table 7 Summary of literature review articles identified through primary and secondary search terms

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
Joy et al. (1999) USA, Europe, Canada	Literature review of cannabis in medicine	-Cannabis has very broad medical applications: analgesia to nausea, Parkinson's, glaucoma, etc. -In contrast cannabis use presents some risks like mild withdrawal, CUD, depression, respiratory damage, etc.	-The benefits and uses of medical cannabis are vast, however the risks also numerous if improperly administered -Risks are under explored and evidence is inconclusive -More research is required to determine the safety of cannabis
Mathre (2002)	-Literature review of human and animal research	-Cannabis has demonstrated that it is remarkably safe and effective when compared to many accepted medications	-Humans cannot overdose on cannabis compared to >32,000 a year with prescription medications -Cannabis shows promise as an analgesia and/or in combination with other medications at lower doses
Hathaway and Erickson (2003), Canada	-Literature and policy review of cannabis and harm reduction strategies in Canada	-Evidence suggests that criminalization of cannabis is harmful to public health, the economy, and society -Research suggests cannabis is relatively safe substance compared to other legal substances	-Medical and cannabis laws are an important factor in Canada's harm reduction strategy and health care policies -Many harm reduction strategies exist in cannabis consumption itself with vaporization and concentrates
Baker et al. (2003)	-Literature review of therapeutic uses for cannabis	-Cannabis use helps: spasticity (Multiple Sclerosis, Huntington disease, Parkinson disease), bladder dysfunction, pain management with opioids -There are also several potential harms from cannabis	-Cannabis has a broad role in treating medical conditions and reducing the harmful side effects of those treatments -To further this harm reduction future studies should look at dosage, new consumption methods, cannabis abuse, etc.
Melamede (2005) USA, Canada, & Europe	- Critical review - Human and animal trials ($N = 137$)	- Endocannabinoid system homeostatically regulates all body system, acting as a natural, evolutionary, biological HRS	- Need for dose-dependent, disease-dependent, state-dependent, individually-tailored cannabis-based therapeutics
Hall and Degenhardt (2009), Australia	-Literature review of adverse health effects of non-medical cannabis use	-Compared to tobacco, alcohol, and other illicit substances cannabis has a relatively modest impact, but similar risks like cardiovascular harms, respiratory impact, anxiety paranoia in new users, psychotic symptoms, pregnancy concerns, etc.	-Non-medical cannabis use is increasing and has many health risks that need to be addressed and studies -Risks/harms including: driving accidents, pregnancy, behavioral disorders, abuse, suicide, educational obtainment, mental health, psychotic disorders, etc
Karst and Wippermann (2009)	- Literature review ($N = 100$) - Human and animal trials	- Combination of low, non-psychoactive doses of THC with opioids has synergistic effect and reduces opioid tolerance effects	- Efficacy of *combination therapy:* THC used to enhance opioid analgesia and reduce tolerance and dependence

Table 7 (continued)

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
Martin-Sanchez et al. (2009)	-Literature review and meta-analysis of cannabis vs placebo ($N = 18$)	-A significant amount of research suggests a strong analgesic effect of cannabis -The same research warns about short term negative effects on the CNS, perception, motor function, etc.	-Therapeutic properties of cannabis are broad and have implications for many harm reduction strategies -Cannabis can be ingested in different ways to reduce harm -It is not consequence free and involves risks like abuse
Bushlin et al. (2010), USA	-Literature review of animals (mice & rats) and humans on opioids and cannabinoids	-Opioids and cannabinoids share common features -These substances interact to increase anti-nociception and reduce chronic pain	-A combination of opioid and low doses of cannabinoid agonists increases analgesia while reducing undesirable effects of both drugs and mitigating risk
Carter et al. (2011) USA	- Literature review ($N = 104$) - Human and animal trials	- Palliative medicine needs to improve care for patients with "life-limiting" conditions that is distinct from hospice-focused care	- Reclassify cannabis as Schedule III - Use for pain, inflammation and to reduce opioid dependence, morbidity
Scavone et al. (2013), Philadelphia, Pennsylvania, USA	-Literature review on cannabinoids and opioid interaction	-There is a large amount of data suggesting the benefits of cannabinoids in treating opioid withdrawal symptoms and addiction -Cannabinoid use does not come without issues itself and misuse or abuse is also possible which requires further investigation	-Cannabinoids have beneficial effects in the treatment of nausea, anorexia, neurodegeneration, CNS injury, pain management, epilepsy, spasticity, Parkinson's disease, Amyotrophic lateral sclerosis, inflammation, addiction, excito-toxicity, chemotherapy and AIDS patients, etc. -Cannabinoids play a role in reducing risk and harm in the treatment of opioid addiction and many other disorders.
Collen (2012) Canada, USA	-Literature review -($N = 9$) RCT papers	-Significant decrease in pain compared to placebo and adverse events tolerable by majority participants -Physicians should prescribe cannabis to treat neuropathic pain before opioids.	-Medical cannabis prescriptions for pain management instead of opioid prescriptions may reduce opiate addiction and overdose mortality rates -Cannabis in conjunction with opioids is an effective HRS
Borgelt et al. (2013), USA, Canada	-Literature review of medical cannabis use benefits and risks	-Cannabis and cannabinoid-derived pharmaceuticals improves muscle spasticity, pain, nausea, etc. -Risks include schizophrenia and accidental ingestion in adolescents, memory and cognitive impairments, suicide and depression, etc.	-Medical cannabis and cannabinoid based pharmaceuticals have an important role to play in many different treatments -Benefits from these products also come with health risks when used improperly or abused outside medicinal use -Education & research is required to improve benefit/cost ratio
Thielman and Daeninck 2013	-Literature review of research on medical cannabis and cancer in humans	-Cannabis can be used to treat inflammation, pain, nausea, -It can be used as a antiemetic, anti-ischemic, and antiepileptiform.	-There are many comorbid conditions with cancer such as pain, nausea, and vomiting all of which have been

Table 7 (continued)

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
			shown to be effectively treatable with cannabis or cannabis products
Gates et al. (2014), Australia	Literature review of cannabis use on respiratory health and harm reduction education	-Cannabis smoke may have similar harms and health outcomes as tobacco smoke (lung damage, etc.) -Other methods of consumption reduce harms	-Cannabis consumption comes with some risk -Many harm reduction strategies exist that reduce respiratory harms, however they are not fully understood or researched
Budney et al. (2015)	-Literature review of vaporized cannabis risks	-Vaping has benefits in reducing ingestion of toxins, increased dose concentration, dose efficiency, etc. -Vaping risks include parallels of tobacco vaporization: proliferation of discreet, easy to use, and highly concentrated cannabis which could increase addiction, abuse, counterfeit or untested products, etc.	-There is relatively little research on vaping cannabis and its various manifestations though some parallels with e-cigs -Research suggests both positive and negative health impacts of vaporization of cannabis and cannabis products -More research into vaporization and other methods of cannabis consumption is needed to better understand the risks
Subbaraman (2014)	-Literature review of cannabis as a substitute for alcohol ($N = 7$)	-Most papers demonstrate that cannabis is safer than alcohol especially in cases of overdoses -There are mixed results when looking at cannabis a substitute, however there are some promising results	-Cannabis is certainly less harmful than alcohol and could be a potential substitute to help reduce alcohol use -Not only is cannabis less risky it also holds multiple economic and health benefits
Fischer et al. (2015)	-Literature review and commentary	-Cannabis and its derivatives are useful in curtailing opioid, crack-cocaine, ketamine, nicotine abuse as well as improving cognitive function in schizophrenic patients	-Cannabis and its derivatives could prove to be an effective harm reduction tool for crack-cocaine users -CBD, a non-psychoactive cannabinoid in cannabis, may have many other harm reducing properties
Basu and Basu (2017) New Zealand, Australia, Canada, USA	-Literature review on human cannabis use research ($N = 48$) 16 showed negative impacts 43 showed positive impacts	-Many cannabis users report positive effects like improved mood, alleviated pain, nausea, etc. -Due to low methodological standards of research it is still difficult to determine if the risks outweigh the benefits	-In many studies cannabis users report the benefits of cannabis as a substitute for other more harmful addictive substances like alcohol and opiates
Lake and Kerr (2017) Canada	-Literature review/Commentary on human research and health policy -Meta-analysis and systematic review	-Despite common misconception and media reports much of the research on cannabis displays its myriad benefits to health and harm reduction	-Cannabis research is relatively new, but promising -In order to quell misconceptions, health policy must be based on sound research

Table 7 (continued)

Articles and locations	Objectives and methods	Main findings	Harm reduction implications
Nielsen et al. (2017) Canada & Australia	-19 pre-clinical animal studies -9 clinical human studies ($N = 18$)	-17/19 pre-clinical animal studies demonstrated lower pain when combining opioids and cannabis than when alone -Clinical studies show mixed results with the highest quality studies showing no opioid sparring effects	-More in-depth clinical research is required to determine the effectiveness of cannabis as a harm reducing strategy -There is both evidence for and against cannabis' effectiveness as a synergistic analgesia with opioids
Wiese and Wilson-Poe (2018)	-Scoping review of cannabis and opioid use in humans and animals	-Growing pre-clinical and clinical research suggests that cannabis is useful for treating opioid addiction, withdrawal symptoms, pain, etc.	-Cannabis shows promise as a first line analgesic -Cannabis is also useful when dealing with opioid withdrawal symptoms
Bruni et al. (2018)	-Scoping review of different methods of cannabinoid delivery	-Cannabis has been shown to have significant health benefits in many areas -The methods of intake could impact how cannabis is metabolized and its health implications	-By examining the different methods of cannabis intake researchers can uncover the best means of delivering cannabinoids in the least harmful way to treat medical conditions as safely as possible
Subritzky (2018) Perth, Australia	-Literature review applying the spectrum of wellness rather than a public health perspective	-Cannabis literature has ignored the therapeutic medical nexus of non-problematic and recreational use	-Research has ignored the fact that most cannabis users never reach dependence (90%) and that many use it both medically and recreationally which can be beneficial in and of itself
Vyas et al. (2018), USA	-Literature review of medical cannabis use and prescription opioid use ($N = 10$)	-States with medical cannabis programs demonstrate a decrease in opioid use, overdose, hospital admissions, addiction rates, impaired driving, and increased quality of life.	-Multiple harm reduction strategies are required to mitigate the risk and harm in opioid addiction treatment -More in-depth, novel, and integrative strategies are required to tackle the growing issue of POM overdoes and addiction.
Chan et al. (2019), USA	-Difference-in-difference approach to analyze how medical and recreational cannabis laws effect opioid deaths in the USA	-Cannabis laws reduce annual opioid deaths by 20–35% with greater effects for synthetic opioids when controlling for many different variables -There is a larger reduction for white people vs non-whites also for women compared to men	-When comparing the various states based on cannabis laws and opioid deaths the data suggests a clear reduction of opioid deaths when controlling for many different variables like medical spending, population size, income, etc.

Articles identified by primary/secondary search terms ($N = 125{,}922$); articles meeting inclusion criteria ($N = 26$) for analysis

POM prescription opioid medication, *FAAH* fatty acid amide hydrolase, *MAGL* monoacylglycerol lipase, *HRS* harm reduction strategy, *CUD* cannabis use disorder, *CNS* central nervous system

clinical and clinical trials concluded that a combination of low, non-psychoactive doses of THC with opioids has a synergistic effect and reduces opioid tolerance effects thereby reducing dependence on opioids. Evidence shows THC is effective in reducing pain that is associated with heat, cold, inflammation, pressure, electrical pain, sunburn pain, and spasticity-induced pain (Baker et al. 2003; Karst and Wippermann 2009; Rea et al. 2019). Though there are benefits to cannabis use, there are also important negative side effects of ranging from mild to moderate to severe on the central nervous system (e.g., vertigo, dizziness, cognitive impairment, anxiety, and acute psychosis) and the cardiovascular system (e.g. tachycardia, hypotension, and vasovagal syncope) (Hall and Degenhardt 2009; Karst and Wippermann 2009; Volkow et al. 2014). Researchers concluded that small doses of cannabinoid receptor subtype 1 (CB1) agonists, which do not produce these adverse effects or analgesic effects on their own, can enhance analgesic effects of opioids and reduce risk of drug tolerance (Karst and Wippermann 2009). Although cannabinoids are promising for harm reduction treatment, more comparative research is required as "the discrepancy between absent or mild analgesic effects of THC in human trials and data from animal models may be the result of species-related differences" (Karst and Wippermann 2009, p. 127).

Both survey and case study research demonstrated that people who use cannabis vaporizers are more likely to report that they have quit or reduced their amount of tobacco intake (Earleywine and Van Dam 2010; Malouff et al. 2014; Gartner 2015). This is due to the fact that there are less adverse effects of vaporization (e.g., absence of combustion and unpleasant taste) compared with smoking. Vaporization of cannabis also encourages current tobacco smokers to withhold from participating in "mulling," which is the act of mixing cannabis and tobacco (Gartner 2015). Thus, for cannabis users who are interested in quitting tobacco, cannabis vaporizers could act as a harm reduction strategy (Earleywine and Van Dam 2010; Malouff et al. 2014; Gartner 2015). Vaporization of cannabis is also a less harmful way of cannabis consumption (Abrams et al. 2007; Moir et al. 2007; Gates et al. 2014; Budney et al. 2015).

Melamede's (2005) critical theoretical review argues that the endocannabinoid system, which homeostatically regulates all body systems, acts as a natural harm reduction apparatus within the body. Therefore, humans have a built-in mechanism that counteracts biochemical imbalances that are characteristic of numerous damaged or diseased states, in particular those associated with aging (Melamede 2005). Accordingly, Melamede (2005) advocates for a "personalized treatment" approach that tailors cannabinoid use in terms of "dose-dependent, disease-dependent, state-dependent, and individually-tailored approaches to cannabis therapeutics" (p. 5). The concept of cannabis and its synergistic effects, particularly its interaction with the endocannabinoid system, must be further explored in order to fully determine the efficacy of marijuana as a harm reduction strategy.

It is important to note that there are serious contraindications for using cannabis as HRS. One study by Mojarrad et al. (2014) measured the rate of abstinence from substances such as alcohol, opioids, and stimulant use in patients who also used cannabis. Although the authors conceded that there may be some benefits of using cannabis to decrease the overall consumption of alcohol and other drugs, there is a significant risk associated with it; specifically, the use of cannabis was associated with lower odds of subsequent abstinence from opioid, stimulant, and heavy alcohol use among substance dependent people across time (Mojarrad et al. 2014). Thus, cannabis may be useful for harm reduction but detrimental to the success of abstinence-focused treatments.

While the majority of these studies present promising findings, there is a need for more clinical and pre-clinical research on the effects of cannabis and its substituents, particularly in relation to opioid and substance abuse. A significant limitation that researchers currently face is determining the ideal dosage and potency of cannabis as a medical treatment. This is due to

the fact that individuals who engage in self-medicating practices are often enrolled in studies where they are asked to document the perceived efficacy of the drug (Corroon et al. 2017; Reiman et al. 2017; Socías et al. 2017; Vyas et al. 2018). This exposes many studies to recall and reporting biases. Therefore researchers must recruit more authorized medicinal cannabis users for harm reduction studies in order to systematically monitor confounding factors. In addition, many countries classify cannabis as an illegal substance, ultimately limiting the quality of research on its therapeutic efficacy and adverse effects (Hathaway and Erickson 2003; Gruber and Sagar 2017; Cox 2018). The greatest challenges will arise in balancing legal access for recreational and medical purposes with education and restrictions for populations most vulnerable to the effects of cannabis such as adolescents, young adults, and individuals with mental illness and/or substance use disorders. Resources need to be better allocated to properly educate people, particularly healthcare professionals, on the scientifically valid and reliable research demonstrating the therapeutic benefits as well as the serious risks of cannabis as treatment for some medical conditions. More importantly, there are critical gaps in preclinical and clinical research that need to be addressed to further our understanding of the effects of cannabis on the brain, addiction, physical, and mental health.

Although there are policy guidelines for prescribing and accessing medical cannabis, in practice, there exists significant inequality in patient access.[1] Approximately 369,614 Canadians are licensed to use medical marijuana, and this patient population is estimated to reach 450,000 by 2024 with an annual revenue of $1.3 billion (Posadzki 2015; Health Canada 2019; Statistics Canada 2019). For patients who would benefit from medical cannabis, there needs to be greater education on the risks associated with various routes of administration and greater research and education on emerging vaporization technology. Vaporization and other forms of ingestion (edibles, sprays, lotions, etc.) have the potential to reduce health risks associated with smoking marijuana. "Vaping" and e-cigarettes are becoming more popular and may lead to reduced smoking in general and possibly a cessation of smoking altogether (Hindocha et al. 2015). Various methods of cannabis consumption should also be examined more thoroughly (e.g., smoking, vaporization, and ingested) in clinical and preclinical research. There is evidence to suggest that the route of cannabis administration greatly affects cannabinoid metabolism in the body, which has important implications for the behavioral and neurobiological effects on the brain, which are implicated in physical and mental health and risk of addiction (Law et al. 1984; Samaha and Robinson 2005; Manwell et al. 2014a, b; Manwell and Mallet 2015; Borodovsky et al. 2016). Future research should examine edible cannabis (baked goods, sprays, beverages, gummies, etc.) as well as its many concentrated forms (hash, oils, distillate, etc.), which also could have important harm reduction properties as well as varied effects on the brain, addiction, and physical and mental health[2] (Smoker et al. 2019). This is

[1] For example, whereas some physicians are opposed or reluctant to prescribe medical cannabis, others actively and publicly promote it (Nussbaum et al. 2011). Legal gray areas also create "backdoor" legal access through memberships in medical cannabis dispensaries. For example, in Vancouver, one can typically obtain a membership in less than an hour and in one case just 65 s (Hager 2014; Kelley 2015). There are also many illegal dispensaries around Canada and online that do not require any membership at all and customers with a valid ID can purchase legal and illegal cannabis products within seconds. Individuals who may be more likely to access cannabis through such dispensaries may also be those in which medical cannabis is contraindicated or with substance use disorders (Kahan and Srivastava 2014).

[2] There is also a growing field of research on cannabis and exercise that could also help uncover how cannabis impacts motivation, obesity, wellbeing, and mental and physical health (Fuss et al. 2015; Gillman et al. 2015; Le Strat and Le Foll 2011; Lorente et al. 2005; Muguruza et al. 2019; Renaud and Cormier 1986; York-Williams et al. 2019). More research on cannabis and motor vehicle incidents/impairment is also required as there is conflicting evidence (Brands et al. 2019; Drummer et al. 2003; Ramaekers et al. 2004, 2009).

especially important with recreational legalization 2.0, which permits the purchase of concentrates like distillate, hash, shatter, etc. along with edibles and topicals like skin cream and bath bombs (Arsenault 2019). Another area for research concerns the ratio of THC and CBD in cannabis and how different ratios of each affect the brain, addiction, and physical and mental health (Hammond 2019). The THC content of illicit cannabis as well as legal cannabis has been rising over the years, and with the rising interest in high CBD content cannabis and CBD concentrates, there needs to be more clinical research to uncover how these two cannabinoids interact and how they work separately (Licata et al. 2005; Cascini et al. 2012; Dorbian 2019).

Conclusions

The goal of harm reduction approaches is to mitigate various harms associated with substance abuse for the individual as well as their family, community, and society in general. The implementation of cannabis treatment programs for individuals with substance use disorders has the potential to increase their quality of life as well as improve overall economic and social outcomes (Corroon et al. 2017; Lake and Kerr 2017). The findings of this scoping review support the use of cannabis as an effective harm reduction strategy and call for more preclinical and clinical research. Future research on harm reduction should examine access to cannabis and its extracts, the effects of varying cannabinoid concentrations, limiting selection bias by recruiting more authorized medicinal and recreational cannabis users, and the various methods cannabis is consumed in humans and animal models of drug dependence. These future directions for research assessing alternative approaches to the treatment of substance use disorders can lead to more informed and effective public policies that include both abstinence-focused and harm reduction programs.

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Compliance with Ethical Standards

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*Indicates articles included in qualitative analysis of scoping review results

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