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REVIEW

The Role of Medicinal Cannabis as an Emerging Therapy for Opioid Use Disorder

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ABSTRACT

This narrative review explores current insights into the potential use of medicinal cannabis-related products as an emerging therapy for opioid use disorder in the landscape of increasing knowledge about medicinal cannabis-based products, commercialisation and global legalisation. Preclinical studies have provided preliminary insight into the putative neurobiological mechanisms that underpin the potential for medicinal cannabis to be considered a therapeutic in opioid use disorder and addiction. With the progressive legalisation of cannabis in many jurisdictions worldwide, contemporary research has highlighted further evidence that medicinal cannabis may have efficacy in reducing cravings and withdrawal effects, and therefore may be considered as an adjunct or standalone to current medications for opioid use disorder. Despite this potential, the landscape of research in this space draws from a large number of observational studies, with a paucity of rigorous randomised controlled trials to ascertain a true understanding of effect size and safety profile. With current

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challenges in implementation that arise from political and legal qualms about adopting medicinal cannabis on the background of associated social stigma, significant hurdles remain to be addressed by government, policy-makers, healthcare providers and researchers before medical cannabis can be introduced globally for the treatment of opioid use disorder.

PLAIN LANGUAGE SUMMARY

The aim of this review was to synthesise current evidence to understand how medicinal cannabis products may be able to tackle the signs, symptoms and outcomes related to opioid dependence. At the present time, opioid dependence is associated with a significant burden of disease and death in the community. Current treatment for opioid dependence includes supplying controlled-release opioids in a regulated (and often observed) manner in the community. However, despite the implementation of this strategy, the outcomes related to opioid use and dependence remain relatively unchanged, indicating that the current gold standard treatment is not as effective as it should be. Following the legalisation and commercialisation of medicinal cannabis, there has been increased research into the ways these products can be leveraged for different conditions and indications, including in opioid dependence. Given this context, in this narrative we explore this preliminary evidence and evaluate the steps required in further research and policy changes before more widespread implementation of medical cannabis can be considered.

Keywords: Medicinal cannabis; Cannabis; Cannabinoids; THC; Cannabidiol; Opioid use disorder; Opioid replacement therapy; Medications for opioid use disorder; Tetrahydrocannabinol

Key Summary Points

Why carry out the study?

The prescription and demand for medicinal cannabis-based products is ever increasing in modern society due to claims that these products may be able to remedy a variety of medical ailments

Cannabis-based therapies have been reported to be able to alleviate opioid withdrawal and addiction symptoms, with the potential to become a new standard of treatment or adjunct to treatment in opioid use disorder

Despite this, we hypothesise that there is lack of robust evidence to support the use of cannabis for this purpose

This review aims to summarise current evidence behind the potential for cannabis to adopt this role in the management of opioid use disorder and highlights challenges, limitations and considerations for stakeholders involved in the development and translation of these research findings into practice.

What was learnt from this study?

Evidence-based findings for the use of cannabis-based products in the management of opioid use disorder is highly heterogeneous, with abundant cases of disparate results supporting and refuting the role of cannabis-based products for this purpose.

This review identifies that important confounders must be accounted in future rigorous trials aimed at examining the efficacy of cannabis-based products for this purpose, including diversity of populations, the context and timeframe within which the research is being conducted, socioecological factors that influence opioid use and the impact of deeply ingrained habits on human behaviour.

INTRODUCTION

Excessive opioid prescribing has led to a crisis which has often been referred to as the opioid crisis or opioid epidemic [1]. Central to this has been the increasing incidence of opioid-related morbidity in the form of dependence and overdose, as well as opioid-related deaths worldwide [2–4]. Based on US Centers for Disease Control and Prevention data, an estimated 26–36 million individuals misuse opioids, with the trajectory continuing to move upwards [1, 5]. Pharmacological approaches to address opioid use disorder (OUD) aim to provide controlled opioid prescribing, dispensing and use. Currently, these therapies include medications such as buprenorphine or methadone, which have been shown to suppress licit and illicit opioid use, improve retention to safe treatment guidelines and reduce mortality attributed to overdose by up to 70% [6–8]. However, these strategies are not without limitations, with a high prevalence of patients discontinuing such therapies and relapsing into substance use [9–11]. Therefore, there is a significant demand for research into more efficacious alternative approaches to addressing the opioid epidemic.

Medicinal cannabis, cannabinoids and cannabinoid analogues (medicinal cannabis-related products [MCRPs]) have recently amassed interest as potential non-opioid therapeutics for treating OUD. Cannabis (or *Cannabis sativa*) is the most widely used illicit recreational drug in the world that has simultaneously been medicinally purposed as an established analgesic [5, 12, 13]. The main bioactive constituents of cannabis are cannabinoids. Although over 100 cannabinoids that have been isolated from cannabis, the two most abundant cannabinoids are cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) [7, 8]. Comparatively, the main difference between CBD and THC is the degree of psychotomimetic activity. CBD is a non-psychotomimetic compound, while THC is the main psychoactive compound found in the cannabis plant [7]. Medicinal cannabis is itself a heterogenous entity, encompassing a variety of available products, with varying concentrations of THC, CBD and other cannabinoids (ranging from > 98% CBD to > 98% THC). These products exist in numerous different forms (including capsules, oils, tinctures, gels, oral liquids and dried herb) and have differing methods of administration (including oral, inhaled and topical.).

A growing field of evidence has highlighted the role of the endocannabinoid system—and therefore medicinal cannabis—in substance use disorders [14]. Interestingly, in certain states of the Unites States (US) that have legalised medicinal cannabis, there is a reported 25% reduction in mean annual opioid overdose mortality [15]. The legalisation of cannabis in many jurisdictions has led to the exciting possibility of harnessing medicinal cannabinoids as a non-opioid alternative in addressing OUD. In this review, we provide an up-to-date overview of the current landscape of research surrounding the use of MCRPs in OUD and explore the potential for their implementation.

Ethics approval was not required for the generation of this review given that the data and findings reported were derived from open-access and freely accessible literature from medical databases. In addition, this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the authors.

THE CURRENT LANDSCAPE OF MEDICATIONS FOR OPIOID USE DISORDER

A major health challenge that modern society faces is substance use disorder (SUD), an umbrella term for the spectrum of chronic diseases characterised by an excessive and uncontrolled intake of licit and illicit psychoactive substances [16, 17]. Koob and Volkow describe three distinct phases associated with this cycle: 'binge/intoxication', 'withdrawal/negative affect' and 'preoccupation/anticipation' [18]. Patients who have SUD often present with an intense focus on the drive to reach an altered state of consciousness, development of cravings, tolerance to the substance and the resultant loss of control of drug intake irrespective of potential consequences [17]. This affliction

involves the rampant misuse of prescription opioids and heroin; henceforth referred to here as OUD. Prescription opioids in Australia can be obtained from registered health practitioners for certain chronic pain conditions; in contrast, heroin, although it was legally prescribed up until 1953, is now a highly restricted substance without an approved therapeutic use [19]. Despite the highly regulated and restricted nature of opioids both licit and illicit, a disproportionate burden of disease exists in the Australian public health system, with a staggering 3.1 million people dispensed a prescription opioid under the Pharmaceutical Benefits Scheme (PBS) in 2016–2017 and an estimated 735,000 people using opioids for illicit or non-medical purposes, which taken together represents a significant area of concern [19].

Prior to 1960, treatment for OUD was ineffective and did not provide meaningful pharmacologic support, with those who were suffering being sent to 'farms' for a period of forced abstinence, only to be reintroduced to the community and subsequently relapse [12]. Hence, the introduction of long-acting opioids, albeit highly regulated, was peddled as a revolutionary treatment that would reduce feelings of euphoria while concurrently avoiding the effects of withdrawal [12]. In the current landscape, harm reduction through the use of medications for opioid use disorder (MOUD)—also known as opioid substitution therapy or opioid maintenance therapy—is a well-established and pragmatic approach to the treatment of OUD [17, 19, 20]. Treatments with MOUD involve the use of opioid agonists, such as methadone and buprenorphine, and less commonly opioid antagonists, such as naltrexone, to reduce or stop the inappropriate use of opioids [19, 21]. Of these drugs, the latter is beginning to be phased out of clinical addiction medicine and therefore less widely used in current standard practice. Nonetheless, the therapeutic aim is to target all three stages of the proposed model put forth by Koob and Volkow [18]. There is considerable long-term data supporting MOUD; withdrawal is mitigated with use of opioid agonists to occupy the opioid receptors. Regular use of full or partial opioid agonists can block or reduce the euphoria derived from the use of additional illicit opioids and the prescription of MOUD has been shown to have anti-craving effects [16, 17, 22]. Furthermore, the implementation of these regimens has led to far-reaching societal benefits, including a significant reduction in opioid-related mortality as well as a reduction in social adversity in the form of reduced crime and incarceration rates (8, 12).

Methadone is a synthetic long-acting, selective μ-opioid receptor agonist. Its' use in OUD originated with the hypothesis that an opioid with a long half-life (20–36 h) administered in a scheduled manner would occupy the opioid receptor sufficiently to reduce cravings and eliminate withdrawal symptoms [12, 16, 23]. Contemporary evidence shows that treatment outcomes are significantly enhanced with higher doses of methadone, with the literature describing a range between 60 and 120 mg per day as an acceptable usual maintenance dose [16, 21, 24]. The benefits do not come without barriers, as the safe and effective prescribing of methadone mandates a slow up-titration to avoid potentially fatal overdose, a strategy which can be frustrating for some patients [23]. In Australia, methadone liquid is the only approved formulation for MOUD, and the strict regulations that govern the prescription and dispensing of methadone mandate regular attendance and engagement with methadone prescribers and pharmacies. This poses a problem for adherence as patients may be reluctant to engage. Additionally, a wide variety of drug–drug interactions are associated with methadone use, including prolongation of the QT interval on an electrocardiograph, which is of particular concern for patients with electrolyte abnormalities, comorbid heart, kidney or liver conditions, or those taking concomitant QT interval-prolonging drugs [17].

Buprenorphine is another option available to prescribers. Buprenorphine displays unique pharmacologic characteristics due to its' weak activity but high affinity for the μ-opioid receptor, offering both a reduced sensation of euphoria but also mitigation of withdrawal symptoms while retaining a receptor blocking effect [12]. It has been shown to be as effective as methadone in suppressing illicit opioid use, but less effective for retaining individuals on treatment [7, 21, 24].

Treatment with buprenorphine is available in sublingual films or tablets taken on consecutive days or alternate days, or as a modified-release subcutaneous injection injected weekly or monthly; as such, buprenorphine allows for more flexible dosing schedules when compared with methadone, which may be desirable to patients [17]. Despite these apparent benefits, there are drawbacks as buprenorphine has minimal oral absorption and must be absorbed sublingually for an effect (10% compared with 30–55% bioavailability). These sublingual formulations may take up to 10 min to dissolve completely, resulting in an impractical system of directly supervised dosing at the local pharmacy, opening the door to drug diversion if improperly done [17]. Nonetheless, these drawbacks have inspired innovative solutions to potential diversions; for example, the oral films adhere to the oral mucosa quite rapidly making them difficult to remove and therefore be diverted. Additionally, the films are formulated with naloxone, a μ-opioid receptor antagonist, to diminish the euphoric effects if the films are manipulated and injected [12, 20]. Furthermore, buprenorphine claims advantages over methadone with its ability to achieve a quicker therapeutic effect when titrating doses, fewer drug interactions and a lesser tendency for overdose [17, 21, 23].

The literature supports both buprenorphine and methadone as effective drugs for treating opioid dependence. Evidence for alternate approaches with use of μ-opioid receptor antagonists, such as naltrexone, shows limited benefits in the treatment of OUD due to very poor adherence to the prerequisite minimum 5- to 7-day period of abstinence prior to beginning therapy [12, 21].

MEDICINAL CANNABIS AS AN EMERGING THERAPY FOR OPIOID USE DISORDER

The Endocannabinoid System

The endocannabinoid system has been a key novel target for managing opioid addiction and is simultaneously involved in pain modulation [25, 26]. Importantly, the use of cannabinoids as an alternative for pain relief in the context of OUD may significantly reduce opioid harm. In this context, the authors of a retrospective cohort study observed high rates of chronic pain in patients with OUD (64.4%; $n = 5307$), most of whom had chronic pain symptoms prior to their OUD diagnosis (61.8%; $n = 5307$) [27]. Although extrapolating from a sample cohort, this study gives an indication of the potential importance of non-opioid analgesic alternatives in preventing and tackling OUD. Most of the physiological and pharmacological effects of cannabinoids are related to activation of the endocannabinoid system [28]. The endocannabinoid system includes the receptors CB1R and CB2R, which modulate the release of neurotransmitters (including dopamine) upon stimulation by endogenous cannabinoids such as *N*-arachidonylethanolamine (AEA) and 2-arachidonylglycerol (2AG), or exogenous cannabinoids found in cannabis [16, 29–31]. CB1Rs are primarily distributed centrally within the brain and the dorsal horn of the spinal cord, while CB2Rs can be found peripherally and lesser so in central regions [26, 30]. Physiologically, the endocannabinoid system is involved in various functions, including the development of drug addiction through neuroplastic changes and pain modulation [32]. In SUD, the activation of the mesolimbic dopamine system is purported to stimulate centrally located CB1Rs in key areas such as the ventral tegmental area [29]. This stimulation continually feeds forward to exacerbate dopaminergic signalling by the mesolimbic dopamine system [29]. Continual perturbation is posited to induce adaptive neurocircuitry changes, resulting in the development of drug reward signalling, motivation, emotional responses towards and memory of drug-related cues and addiction [29, 31]. Additionally, the endocannabinoid system is involved in pain sensation and modulation through activation of peripheral and central CB1R and CB2R [26].

Other Pathways

Although the endocannabinoid system elicits most of the physiological and pharmacological actions of cannabinoids, it is important to appreciate that cannabinoids influence many interconnected and complex signalling pathways to modulate opioid addiction and provide pain relief. In terms of mediating opioid dependence and addiction, other signalling pathways involved include the serotonergic and opioid systems [29, 33, 34]. It has been noted in studies that the co-localisation of CB1R and μ-opioid receptors in key central areas involved in reward signalling include the nucleus accumbens. Cannabinoid-induced modulation of the μ-opioid receptor has been purported to attenuate opioid dependence and addiction development [29, 34]. Furthermore, activation of the serotoninergic (5-HT1A) receptor by CBD has also been purported to have anti-craving and anxiolytic effects [29, 33, 35]. Regarding pain regulation, interactions with the opioid, serotonergic, proinflammatory and nociceptor systems have been documented [26, 36]. Firstly, similar co-localisation and cross-over interactions between CB1R and μ-opioid receptors may be involved in pain management [34]. Secondly, CBD activation of the 5-HT1A receptor is proposed to induce analgesic effects [35]. Finally, CBD activation of the capsaicin receptor (TRPV1) has been shown to induce anti-nociceptive effects (35).

Observational Studies

Recent observational studies have exhibited the potential of medicinal cannabis in addressing the opioid misuse. Bachhuber et al. observed that US states with implemented medicinal cannabis laws had a 24.8% reduction (95% confidence interval [CI] − 37.5% to − 9.5%; $P = 0.003$) in annual mean opioid overdose-related mortality rates compared to unregulated states between 1999 and 2010 [15]. Although this study only provides a generalised trend due to the nature of an epidemiological comparison, this association introduces a potential inverse correlation between the use of regulated medicinal cannabis and adverse opioid-related outcomes. More recent modelling by Shover et al. has raised the question about the ways such state-level data can be interpreted and whether individual-level analysis is warranted in the consideration of the research landscape in this space [37]. Specifically, when Shover et al. extended the modelling of the comparative analysis of state-based data between legalised and non-legalised states, similar findings were found between 2008 and 2012; however, using an additional 7 years of data up until 2017, the authors found a paradoxical increase in overdose deaths by a magnitude of 22.7% [37]. These findings support the discussion regarding the ecological fallacy and whether more considerations need to be emphasised on individual-level factors that account for the findings of such models, including transition from cannabis to opioids for euphoria, analgesia or intoxication. Overall, it is clear that at the present time, time- and context-dependent factors heavily influence the trajectory of health outcomes related to regulation laws behind medicinal cannabis. Despite this, our thorough search of the literature reveals two main avenues of interest for the use of medicinal cannabis in targeting the opioid crisis. Firstly, medicinal cannabis has been reported to be a potentially effective therapeutic in the management of opioid withdrawal. Secondly, as medicinal cannabis is an established first-line analgesic, it is posited that it has the potential to act as an adjunctive non-opioid pain medication to reduce prescription opioid use.

Medicinal Cannabis as a Potential Therapeutic for the Management of Opioid Addiction

Medicinal cannabis has been identified as a potential effective non-opioid therapeutic for management of the acute withdrawal and maintenance phases of treatment for established OUD. A review of non-opioid neurotransmitter contributions to opioid addiction and withdrawal evaluated evidence from preclinical and human studies, including analysis of the endocannabinoid system [38]. The authors reported mixed results, but overall concluded that the endocannabinoid system is

implicated in withdrawal severity, conveying a theoretical potential for existing cannabinoids to be leveraged to improve opioid withdrawal management. The first documented evidence of cannabis being prescribed to manage opioid addiction was found in a case report published by Birch in 1889, in which whole-plant cannabis use was documented to reduce opioid withdrawal symptom severity in an individual withdrawn from the opioid laudanum [39]. This case report notes specific improvements in sleep, nausea/vomiting and appetite. Since then, many studies have highlighted the role of cannabis in managing opioid addiction. In an exploratory analysis of an online forum, Meacham et al. showed that common self-reported motivations for cannabis use were to manage opioid withdrawal symptoms, as well as to enhance the "high" when used in combination with opioids [40]. However, when interpreting these findings it is important to consider the unregulated nature of online forums, including the lack of demographic or geographic information, unclear formulations of cannabis used, inability to generalise population subsets and the potential for skewed reporting biases of 'success stories'. Using data collected in a survey, Rosic et al. highlighted that some individuals currently on MOUD self-reported suppression of opioid craving (6.9%; $n = 1178$) and withdrawal symptoms (8.9%; $n = 1178$) with cannabis use [41]. This is congruent with the findings of Lucas et al. who found in a survey that 11.4% of participants ($n = 61$) experienced reduced withdrawal symptoms when substituting prescription drugs for cannabis [13]. A key strength of this latter study is the large cohort representative of individuals on MOUD, but again the results must be interpreted in the context of the inevitable risk of reporting biases. Finally, in a 2015 trial, Bisaga et al. found in their post-hoc analysis that among participants who were started on naltrexone for management of OUD, cannabis use was associated with statistically significant reductions in withdrawal-related insomnia and anxiety [42].

Cannabis has also been shown to improve retention rates to MOUD for opioid addiction management. A longitudinal analysis between 1996 and 2016 ($n = 820$) demonstrated that at least daily cannabis use (adjusted odds ratio [AOR] 1.20, 95% CI 1.02–1.43) increased the propensity of MOUD retention by 21% compared to non-daily users (AOR 1.00, 95% CI 0.87–1.14) [43]. Since these datasets were extracted from two community-recruited prospective cohorts of people using illicit drugs, the participants were not randomly selected, which may have resulted in skewed bias of a particular population subset and limit generalisability.

Although many of these observational studies show positive trends of cannabis in managing OUD, this effect is not reflected in all studies. Epstein and Preston found in a questionnaire that smoked cannabis did not influence opioid withdrawal scores between users ($n = 46$) and non-users ($n = 70$) currently on the methadone-taper phase of a clinical trial [44]. Key limitations of this study include a smaller sample size and, importantly, that opioid withdrawal severity measurements were limited to once per 2 weeks, noting that withdrawal symptoms can manifest within hours. Due to this latter limitation, there is potential for missed opioid-sparing effects. Further, a study conducted by Rosic et al. on participants receiving treatment for OUD ($n = 2315$) found that cannabis use in the past month was not associated with more or less opioid use during treatment (when compared to no cannabis use), although the study did identify that among cannabis users, daily users had lower odds of opioid use than occasional users [41]. Hermann et al. also demonstrated that in individuals diagnosed with OUD and treated with MOUD ($n = 89$), approximately 50% showed a beneficial effect, 15% showed no effect and 37.5% showed exacerbations of opioid withdrawals based on a Likert scale [45]. Bergeria et al. additionally demonstrated in a questionnaire that although most participants reported benefits of cannabis use, 6% of participants ($n = 125$) found that cannabis exacerbated withdrawal symptoms based on a subjective opioid withdrawal symptom scale (SOWS) [46]. Despite this, the overall trend was a beneficial effect of cannabis use (mean 16.2, standard error of the mean [SEM] 1.4) compared to non-cannabis use

(mean 27.8, SEM 1.3) for management of opioid withdrawal symptoms during statistical comparisons of SOWS ($P < 0.05$). Specifically, participants most frequently reported improvement in opioid-related anxiety, tremors and insomnia with cannabis use. However, this study used an online platform, limiting in-person validation of opioid use [46]. The conflicting findings from these studies highlight flaws with existing evidence, and underline the need for further rigorous research in this area.

Medicinal Cannabis as an Analgesic with Potential in Reducing Prescription Opioid Use

A significant proportion of opioid-related harms are attributable to prescription opioid use. In recent years, medicinal cannabis has increasingly been used for the management of chronic pain, with an approximately 65% approval rate for medicinal cannabis use in Australia (as of July 2021) for this indication [47]. A 2017 National Academies of Science, Engineering and Medicine (NASEM) report supports the effectiveness of cannabis as treatment for chronic non-cancer pain in adults [48]. Extensive research has focussed on the potential for cannabinoids to prevent opioid misuse and associated harms, both as an alternative to opioid introduction and as an adjunct to limit opioid dosages required to adequately manage pain.

Survey data identifies medicinal cannabis as a potentially effective and preferred analgesic agent when compared to prescription opioids among respondents, for reasons including personal preference, greater satisfaction and fewer adverse effects. A survey conducted by Reiman et al. on participants currently using medicinal cannabis ($n = 2897$) demonstrated that cannabis use was associated with self-reported reduction of opioid use in 97% of participants, with approximately 81% of participants reporting higher satisfaction with cannabis use alone compared to combined cannabis and opioid use [49]. These findings are congruent with those from a survey performed by Lucas et al. in which 51.2% of participants ($n = 419$) perceived medicinal cannabis as a safer alternative to prescription opioid use, with 39.7% ($n = 207$) and 19.5% ($n = 124$) reporting fewer adverse effects and better symptom management, respectively [13]. These views on medicinal cannabis as a preferred analgesic do seem to translate to a reduction in prescription opioid use, with 69% of respondents reporting a decrease in prescription medication use with medicinal cannabis. Opioids made up 35% of substituted medications, and within this group 59% were able to cease opioid use altogether [13]. Similarly, Boenhke et al. found that for participants recruited from a medicinal cannabis dispensary ($n = 118$), medicinal cannabis use was associated with decreased opioid use (64%), with self-reports of improved quality of life (45%) [50, 51]. Finally, a cross-sectional survey conducted by Lucas and Walsh found that 30% of patients registered to purchase medicinal cannabis ($n = 271$) substituted prescription opioids with medicinal cannabis for conditions including chronic pain, although this study was limited by a low survey-response rate of 21% [52]. While the amalgamation of this data is promising, it is important to note that participants for these surveys were recruited as a result of their medicinal cannabis use, leading to sampling error and likely biased results. Furthermore, survey data are inevitably limited by methodological constraints, including the cross-sectional nature of data (preventing cause and effect determination), subjective outcomes (e.g. quality of life) and potential for response bias.

Research evaluating epidemiological data suggests that increasing regulated access to cannabis (through the legalisation of recreational and/or medicinal cannabis use) can be associated with decreased opioid use and associated harms in the community [13, 52]. US states with medicinal cannabis laws have been found to have 25% lower mortality from opioid overdoses when compared to those without [53]. The authors of a US study using state-level opioid prescription records between 1993 and 2014 concluded that medicinal cannabis legalisation correlated with a 29.6% ($P = 0.03$) decrease in the number of Schedule III opioid prescriptions and a 29.9% ($P = 0.02$) reduction in the prescribed dose of Schedule III prescription opioids [54]. Correspondingly, a 2016

study analysing data on prescriptions filled between 2010 and 2013 found a significant drop in prescriptions for pain medications (including opioids) following the introduction of medical cannabis laws, suggesting cannabis may be being prescribed as an alternative to opioid analgesia [55]. Lucas and Walsh propose that this phenomenon is in part attributable to the "substitution effect", whereby the availability of one substance affects the use of another [52]. When it comes to illicit substances, this "substitution effect" can be harnessed by regulators as a harm-reduction strategy to reduce the use of more toxic substances. In this case, providing individuals with an alternative to opioid introduction can prevent the development of OUD. However, correlation studies have significant limitations, and alternate population-level data have shown that this association is not consistently reproducible. In Colorado, increasing use of cannabinoids following legalisation has in fact been associated with an increase in opioid use [56]. Moreover, Olfson et al. compared retrospective associations between cannabis use at time 1 (2001–2002) and OUD at time 2 (2004–2005) using logistic regression and found that at an individual level, cannabis use was associated with an increased risk of developing OUD [57].

These conflicting results may be in part attributable to limitations in study design. Epidemiological data can identify correlations, but causation cannot reliably be inferred as there is a high potential for confounding factors to influence results. Surveys fall prey to response and sample biases, particularly when conducted online and in limited populations. The latter are also limited by an absence of standardised outcome measurements, making it difficult to compare data between studies, and even between participants of any given survey. It is also worth noting that the majority of pre-existing studies were conducted in North America, thereby encompassing only a small demographic of the global population and consequently reducing the generalisability of the results. Clearly, due to methodological constraints and the ecological fallacy, observational studies are intrinsically insufficient to draw reliable conclusions regarding the impact of cannabinoids on opioid-related harms. Additionally, with changing context and individual-level factors driving reliance or dependence on opioids over time, the relationships noted by such observational studies further put into spotlight the role of the ecological fallacy in driving the way such findings are interpreted or may change [37]. Given the recency of regulatory laws in this space, the influence of medicinal cannabis, regulatory laws and opioid dependence has yet to be interrogated deeply at the individual, state, national or international level over a satisfactory period of time for robust correlations to be derived. It is likely that the factors which drive the relationships between these laws and health outcomes will be governed by various factors depending on the jurisdiction and context at play and therefore nuanced. When it comes to policy, guidelines and governmental regulation must be strongly context dependent and not solely reliant on the observational data that have been reported.

Clinical Trials

As already noted in this review, epidemiological and observational studies have highlighted the potential of medicinal cannabis as a therapeutic for opioid addiction, or as an adjuvant analgesic with prescription opioid to reduce dosage, and by extension, minimising the propensity of developing OUD. Although limited, our search of the literature highlighted key MCRPs of interest in clinical trials for this two-pronged potential in ameliorating the opioid crisis. These include whole-plant cannabis (referred to further as whole cannabis), dronabinol (a synthetic THC analogue, acting as a partial agonist for CB1R) and CBD [42].

The Role of Medicinal and Recreational Cannabis, Cannabinoids and Cannabinoid Analogues in the Management of Opioid Addiction

Medicinal and Recreational Cannabis

Although numerous epidemiological and observational studies have demonstrated the potential for cannabis-based products in managing opioid addiction and increasing

retention rates to MOUD, there is a paucity of randomised clinical trials that have investigated the whole cannabis effect to date. In a 2023 study analysing data from a 24-week, open-label randomised controlled trial on participants with OUD ($n = 272$) randomly assigned to either buprenorphine/naloxone ($n = 138$) or methadone ($n = 134$), measurements at 2-week intervals were taken of cannabis and opioid use, cravings and withdrawal [58]. This study found recent (recreational) cannabis use was not associated with opioid use, craving or withdrawal symptoms in individuals with prescription-type OUD [58]. However, a number of other studies have highlighted the role of cannabis in improving retention rates to MOUD, which is a crucial factor in preventing further opioid abuse. For example, Raby et al. showed in a clinical trial that in opioid-dependent patients initiated on naltrexone ($n = 63$), intermittent cannabis use (based on urine toxicology; 1–79% cannabis-positive samples) had greater retention to MOUD (median days retained: 133; mean 112.8, SE 17.5) compared to abstinent patients (median days retained: 35; mean 47.3, SE 9.2) or consistent cannabis users (median days retained: 35; mean 68.3, SE 14.1) ($P = 0.002$) [59]. However, although providing rigorous statistical evidence, these researchers posit that retention to MOUD may be influenced by unmeasured confounding factors rather than a direct effect of cannabis use [59]. This is reaffirmed by Lake et al. who based on their results from two prospective cohort studies, argue that addressing other external factors including incarceration, has higher precedence in promoting MOUD retention than does medicinal cannabis use [60]. Again, this raises the emphasis when it comes to considering medicinal cannabis-based interventions, on the role of individual-level factors in the context of the time and space the individual finds themselves in, as key contributors to the effectiveness of interventions. Overall, the reported effects of whole cannabis in clinical trials are limited and conflicting, which may highlight flaws or discrepancies in the current literature and demonstrate the need for further research with sustained durations of follow-up and across multiple spectrums of cultures and contexts.

Dronabinol Dronabinol is a synthetic THC analogue that elicits actions through stimulation of CB1R receptors. The efficacy of dronabinol for opioid addiction management has been demonstrated by two main studies. In the first of these studies, Bisaga et al. conducted a double-blinded randomised placebo-controlled trial between opioid-dependent participants taking 30 mg dronabinol per day ($n = 40$) or placebo ($n = 20$) for 5 weeks after buprenorphine detoxification and while undergoing naltrexone induction [42]. These authors found that dronabinol reduced the severity of opioid withdrawal symptoms in the acute detoxification stage ($P = 0.006$), as measured by the SOWS. In the contrary, there were no significant impacts on successful transition to extended-release naltrexone treatment. In the second study, Lofwall et al. conducted a double-blinded randomised placebo-controlled trial on opioid-dependent patients who received four oral doses daily of 30 mg oxycodone to induce stable opioid physical dependence [25]. These participants were randomly allocated placebo, oxycodone at 30 mg and 60 mg and dronabinol at 5 mg, 10 mg, 20 mg and 30 mg (for each condition $n = 12$, except for 30 mg dronabinol, where $n = 9$). Dronabinol (20 mg and 30 mg) was shown to produce modest withdrawal suppression effects when used as an alternative to opioid agonists in acute withdrawal, which was an improvement of up to 40% when compared to placebo ($P < 0.05$). However, lower doses of dronabinol (5 mg and 10 mg) showed no significant effects.

Altogether, both studies demonstrated positive effects of dronabinol in managing withdrawal using similar assessment measurements, including SOWS. However, a key limitation of both studies is the small sample sizes with high numbers of excluded patients due to external reasons (including violating protocol rules), which reduces generalisability. Furthermore, these studies cannot address the effect of long-term dronabinol use in withdrawal suppression, highlighting the need for future longitudinal clinical trials. Particularly for individuals with habitual dependence on opioids that has been developed over years and decades of fixed and firm behaviours, the emphasis for greater

duration of longitudinal follow-up and other jurisdictions and cultures is imperative to characterise the durability of such effects across time. Nonetheless, although dronabinol shows beneficial outcomes, a number of adverse effects have been documented with its use. Lofwall et al. found that significant adverse effects (including sedation and dose-dependent tachycardia) were reported with higher doses of dronabinol (20–30 mg) [25]. Additionally, with the same study design, Jicha et al. showed that higher doses of dronabinol (20–30 mg) induced dose-dependent tachycardia compared to the placebo 1 h after administration, lasting for 2 h ($P < 0.05$) [61]. The authors of this latter study also attempted to test 40 mg of dronabinol, but found that this dosage induced sinus tachycardia, anxiety and panic resulting in discontinuation. Interestingly, further research has suggested a potential biphasic effect of THC, with lower doses producing anxiolysis and analgesia and conversely, higher doses able to increase pain sensitivity and anxiety [62]. De Aquino et al. investigated the effect of varying doses of dronabinol (10 mg and 20 mg) on pain sensitivity among participants receiving methadone therapy for OUD and found that while both doses lead to lower total pain scores than placebo, 10 mg was more effective than 20 mg in this regard [62]. It may be that dronabinol has a narrow therapeutic window for mediating withdrawal symptoms without producing troublesome adverse effects. These negative side effects may limit the clinical potential of dronabinol in managing opioid withdrawal symptoms; alternative cannabinoid formulations might be more suitable for this indication.

Cannabidiol Cannabidiol (CBD) has a theoretical role in mediating addiction and has been shown to have therapeutic properties relevant to opioid withdrawal, including anxiolysis, analgesia and reduced cue-induced opioid cravings due to actions at the CB1R, CB2R, μ-opioid receptor, 5-HT1A receptor and TRPV1 [29, 34, 35, 63–65]. Results from animal studies suggest that CBD can decrease opioid reward effects and opioid-seeking behaviours and a recent systematic review of existing evidence found that CBD might have therapeutic benefit in substance use disorders, including OUD [56, 66–68]. However, there remains a scarcity of human studies evaluating the effects of CBD use in opioid-dependent individuals [28, 66].

The role of CBD in managing opioid addiction has been shown in two main studies. In the first of these studies, Hurd et al. conducted a double-blind randomised placebo-controlled trial on abstinent participants with heroin use disorder ($n = 42$) who were randomly allocated to either CBD (400 mg, $n = 14$; 800 mg, $n = 13$) or placebo ($n = 15$) [64]. Participants were then exposed to either neutral or drug-related cues either immediately after CBD administration, 24 h after initial administration and 7 days after a short-term repeated CBD administration (3 times) [69]. Overall, this study found that CBD attenuated cue-induced cravings for both 400 mg CBD and 800 mg CBD compared to placebo following administration ($P = 0.0105$), which persisted 7 days after short-term repeated CBD administration ($P = 0.0167$), when using the visual analogue scale for craving [69]. Furthermore, CBD reduced cue-induced anxiety for both 400 mg CBD and 800 mg CBD compared to placebo 7 days after short-term repeated CBD administration ($P = 0.0363$) when using the visual analogue scale for anxiety [69]. In the second study, Suzuki et al. conducted a double-blind randomised placebo-controlled trial on participants ($n = 10$) with OUD receiving either methadone or buprenorphine. Participants were randomly given a single 600 mg dose of CBD or placebo [70]. Overall, the study found that CBD attenuated cue-induced craving ($P = 0.04$) and reduced attentional bias to these drug-related cues ($P = 0.041$) compared to placebo [70]. Although both of these studies showed beneficial results of CBD, it should be noted that the measures were subjective and susceptible to bias. Additionally, it is unclear whether the effects demonstrated in these clinical trials maintain their durability when extended across durations spanning years; therefore, more robust clinical trials are warranted.

From a safety perspective, a key benefit of CBD compared to dronabinol is the safety profile at high doses or when given alongside potent opioid agonists [63]. In particular, in these two studies [69, 70], vital signs including

temperature, systolic and diastolic blood pressure, heart rate, respiratory rate and oxygen saturation were measured, with no significant serious adverse events identified. Furthermore, CBD is non-addictive and already available in approved medication formulations, making it a practical option for early implementation [66]. Overall, CBD is one area that upcoming research should aim to target given its favourable characteristics and encouraging findings to date.

Medicinal Cannabis, Cannabinoids and Cannabinoid Analogues as Analgesics with Potential in Reducing Prescription Opioid Use

Medicinal and Recreational Cannabis Clinical trials have additionally demonstrated the potential of cannabis as an adjunct treatment to reduce prescription opioid use, which may reduce the incidence of OUD. In a double-blind randomised placebo-controlled trial, Cooper et al. tested the analgesic effects of 2.5 mg oxycodone, smoked cannabis and cannabis-oxycodone combination treatment in healthy cannabis smokers ($n = 18$) [71]. In this study, 5 mg oxycodone was sufficient to produce analgesic effects ($P \leq 0.05$). Interestingly, although the 2.5 mg oxycodone or smoked cannabis treatments yielded no significant analgesic effects, the combination oxycodone-cannabis treatment showed increased pain threshold and tolerance ($P \leq 0.05$) [44]. While these results suggest a synergistic role of whole cannabis and prescription opioids, it should be noted that this study used experimental models with healthy individuals from a specific demographic and cultural system, which reduces generalisability. Furthermore, the study used smoked cannabis, which may be therapeutically limited by respiratory risks, including chronic bronchitis and exacerbation of opioid-related respiratory depression. Nevertheless, these findings are supported by additional research. Wiese and Wilson-Poe propose that cannabis is able to produce synergistic analgesia with opioids, therefore decreasing the dose required of both substances to achieve pain control [5]. This is additionally supported by Rodriguez-Arias et al. who report that cannabinoid receptor agonists enhance the analgesic effects of μ-opioid receptor agonists [72].

It is important to note that the literature for whole medicinal cannabis is conflicting. In a double-blind, randomised, placebo-controlled trial, Fallon et al. assessed the efficacy of Nabiximols (Sativex; a whole cannabis extract containing THC 27 mg/ml:CBD 25 mg/ml; $n = 136$) as an analgesic in comparison to placebo ($n = 158$) in participants with advanced cancer currently on opioid therapy with a stable dose of < 500 mg [73]. The authors concluded that Nabiximols had no significant adjuvant effect in comparison to the placebo treatment based on numerical rating scale (NRS) scores. The NRS scale is a subjective indicator reliant on self-reporting, which limits result validity given that participants had advanced cancer which can influence mood on a day-to-day basis. While existing data are incomplete, it appears that cannabinoids could be used as an alternative and/or adjunct to limit the development of OUD.

Dronabinol Dronabinol has been extensively studied for its analgesic properties, with emerging studies investigating its role as an adjunct therapeutic to reduce prescription opioid use. Narang et al. conducted a double-blinded, randomised, placebo-controlled, single-dose study in which chronic non-cancer pain participants currently taking stable doses of opioids ($n = 30$) were additionally given 10 mg dronabinol, 20 mg dronabinol or placebo [74]. Analgesic effects were significantly greater in both the 10 mg ($P < 0.05$) and 20 mg ($P < 0.01$) dronabinol treatment groups compared with placebo [74]. An open-label phase II trial was additionally performed within the same study in which participants were given the choice to administer between 5 mg daily to 20 mg 3 times per day of dronabinol and the option to reduce opioid usage for 4 weeks. In this study, overall pain scores significantly decreased from the initial baseline scores ($P < 0.001$), and biweekly perceptions of pain reductions were found (week 1 vs. week 3, $P < 0.05$; week 2 vs. week 4, $P < 0.05$) [74]. However, due to the open-label nature, there is difficulty in ascertaining whether the analgesic effects are due to placebo or

the pharmacological actions of dronabinol. Although dronabinol shows significant effects as an analgesic, key side effects including anxiety, tremors, dizziness and impaired concentration were found in two participants on the 20 mg dronabinol dose. In a double-blinded randomised placebo-controlled study, Dunn et al. investigated whether combinations of hydromorphone (4 mg) and dronabinol (either 2.5 mg, 5 mg, 10 mg) attenuated experimental pain in healthy individuals ($n = 29$) [75]. They found that 2.5 mg dronabinol combination treatment had additive analgesic effects compared to hydromorphone with placebo ($P < 0.02$) for acute pain, while higher doses of dronabinol had increased risk of abuse [75]. However, the literature on the opioid-sparing effects of dronabinol are conflicting. Babalonis et al. in a double-blinded randomised placebo-controlled study concluded that dronabinol did not increase the analgesic effects of oxycodone and simultaneously, many participants reported increased opioid-related sedation and drug liking from dronabinol use [76]. Additionally, Naef et al. showed dronabinol-morphine therapy had no significant additive analgesic effect [77]. Again, the experimental nature of these studies should be noted, as it limits generalisability to patients with chronic pain. At the present time, the consensus behind appropriate regimens of dosage and time frame is unclear. On the background of quite short follow-up periods, the true effect of these dronabinol regimens of opioid use outcomes in patients remains poorly characterised,

Cannabidiol Although medicinal cannabis is an established pain medication, only a limited number of studies have investigated the analgesic effects of pure CBD and pain-sparing effects have only been reported anecdotally [5, 63]. Furthermore, no pure CBD medications have yet to be approved for managing pain [63]. Despite this, many studies have reported the analgesic effect of CBD. Xu et al. in a randomised placebo-controlled trial evaluated the effect of 250 mg CBD on patients with peripheral neuropathy ($n = 15$) compared to placebo treatment ($n = 14$) [78]. They highlighted that after 4 weeks of CBD treatment, participants had significantly reduced intense sharp pain as assessed by a neuropathic pain scale [78]. Capano et al. in a prospective, single-arm cohort study investigated the effects of an 8-week treatment programme including CBD-rich hemp extract (containing primarily CBD; 15.7 mg CBD, 0.5 mg THC) in patients with chronic pain currently on opioid treatment for at least 1 year ($n = 131$) [79]. These authors showed that at the end of treatment, 53% of patients had reduced or eliminated prescription opioid use. In addition, using this CBD-rich gel had significant analgesic effects ($P = 0.006$) [79]. However, the results of this latter study would have been more rigorous with the addition of a randomised, placebo-controlled design.

To date, only one major clinical trial has investigated pure CBD as an opioid analgesic adjuvant. In a double-blinded randomised placebo-controlled trial, Bebee et al. investigated the analgesic effects of 400 mg CBD compared with placebo in patients with acute, non-traumatic lower back pain ($n = 100$) (80). Oxycodone was administered to these patients 4 h before and after CBD or placebo treatment and pain was measured using a verbal numerical pain scale. Overall, this study found no significant analgesic enhancement from CBD in comparison to placebo; however, it should be taken into account that pain was measured in a subjective manner. Similar to findings from other clinical and observational trials of cannabis analogues, it is clear that longer duration studies, encompassing a diverse demographic and with strong consideration into individual-level confounding factors are a necessary step towards the characterisation of the true effect of CBD on opioid use outcomes over time.

CHALLENGES AND LIMITATIONS IN THE IMPLEMENTATION OF MEDICAL CANNABIS

Despite cannabis-based interventions showing promise in certain areas such as pain management, anxiety and epilepsy treatment, limitations still remain surrounding their use in MOUD [34, 81, 82]. Evidence and preliminary research findings suggesting their role,

effectiveness and safety in MOUD use are very limited, with most studies conducted in small human populations, with a lack of contextual and cultural diversity and over time frames that are lacking in sufficient length [14, 56]. Cannabis use has been reported to be associated with an increased likelihood of relapse at the 6-month follow-up, with post-discharge cannabis use significantly increasing the risk of first use of any substance and reducing the likelihood of stable remission from use of any substance [83]. Among 117 patients who achieved sustained remission from substances such as cocaine and heroin, 44.4% subsequently relapsed, with the proportion of those who used cannabis during the follow-up period 5.58-fold higher among those who relapsed than among those who did not [83]. It is important to note that the study did not differentiate between the formulations of cannabis used by participants (i.e. THC or CBD). Current literature in this area unanimously agrees that larger, more rigorous and well-designed clinical trials are needed to establish cannabis' effectiveness in treatment of OUD in the general population [58, 84].

Response to cannabis can vary due to interactions with various medications, including those commonly used in MOUD, such as methadone or buprenorphine [85–87]. Effects also vary between individuals based on factors such as the formulation of cannabis, dosage, potency and metabolism and tolerance of the individual [16, 86]. Further, it is also clear from the literature that effects of cannabis-related interventions are heavily context- and time-dependent, with socioecological and individual-level factors such as culture, formed habits and individual reason for opioid use underrepresented or poorly considered in the current landscape of research [37]. Moreover, there is the potential for cannabis use to trigger relapse to other substances, the potential for interference with treatment engagement and adherence and the potential to exacerbate mental health conditions [65, 83, 85, 88, 89]. This response variability, lack of suitable longitudinal data and the potential of drug–drug or drug-condition interactions make it challenging to determine and standardise the ideal treatment regimen [86, 87]. Several studies have proposed the potential use of CBD specifically as an agent to inhibit the reinforcing and rewarding impacts of opioids, whereas the role of THC in this area may be limited due to its psychoactive effects [87]. Unlike CBD, THC is responsible for producing the 'high' associated with cannabis use [34, 56]. It is this psychoactive effect and reinforcement of rewarding properties that may play a role in the relapse into substance addiction and dependence [65, 83]. Furthermore, a study by Sholler et al. found that 83% of patients on a THC derivative reported at least one adverse drug reaction, with the study eventually discontinued due to increases in the rates of depression and suicidal ideation [90].

Preliminary evidence also suggests that some cannabis-based products may in fact, in synergism with opioids, increase euphoria [25, 42]. At the present time however, the evidence for this effect is limited and only based on a few small clinical trials; therefore, the true effect on populations that are opioid dependent remain poorly characterised [25, 42]. Critics of regular medicinal cannabis use have suggested that near daily use of medicinal and non-medicinal cannabis was less likely to lead to opioid discontinuation than abstinence from cannabis [91]. However, the mechanisms that explain this finding remain unclear, and it is difficult at this moment in time to attribute these findings to euphoria-seeking behaviour or the like. These non-committal results may be enough to sway policy-makers and stakeholders away from efforts at translating MCRPs into guidelines as MOUD, but they may also represent an opportunity for further robust research trials aimed at characterising whether these findings hold true in larger and more diverse populations. However, there are additional complexities associated with the integration of medicinal cannabis into treatment plans. MOUD use typically involves a comprehensive treatment approach that includes other evidence-based interventions such as support, counselling and other behavioural interventions. While medicinal cannabis might address some of the physical symptoms associated with opioid withdrawal, it may not address the underlying psychological factors that contribute to addiction [13, 88]. Additionally, these interventions alone

arguably only address the mechanistic aspect of opioid dependence. Policy-makers must also adopt a systems approach when it comes to the development and implementation of efficacious medicinal cannabis policy and guidelines [92]. Such an approach includes consideration across various domains, including cost, accessibility, marketing and advertisement, health promotion, destigmatisation and normalisation of product, tackling of drug diversion and illicit trade of opioids and cultural reliance on opioids at the individual and intrapersonal level.

The legal and regulatory landscape surrounding cannabis use in Australia is complex and can vary between states. The Therapeutic Goods Administration and Poisons Standards of Australia categorises medicinal cannabis products based on the CBD and THC content, with products having higher THC content subjected to stricter prescribing and storage requirements. The variations in regulations and inconsistency in quality control standards create challenges in the production, distribution for therapeutic use and integration into mainstream medical practice [14, 58, 83]. They hinder the integration of cannabis use into formalised treatment protocols and trials for MOUD and make it difficult for patients to access high-quality cannabis products [14, 58]. With prescribers currently requiring specific certifications and permit applications to prescribe evidence-based MOUD, the prescribing of CBD or THC can be expected to be just as difficult, if not more [93]. Formalised training and guidelines for the inclusion of cannabis products in treatment protocols will be required, with pharmacists also requiring additional training and education as those responsible for the safe and legal stocking, handling, ethical supply and counselling of medicinal cannabis [13, 14, 47, 52, 87, 94].

Notably, while cannabis may show promise as a potential MOUD, it should not be considered a standalone solution for opioid addiction [20]. The lack of robust evidence together with inconsistent and varying regulations create legal and ethical challenges for clinicians who are trying to balance patient autonomy with public safety concerns [93, 95]. More research is needed to understand the optimal dosage, treatment duration and long-term effects of medicinal cannabis as a MOUD before it can be recommended in evidence-based treatment plans [64, 85].

FUTURE DIRECTIONS

Regulatory limitations, including the classification of cannabis as a Schedule I drug in the USA, significantly impede research efforts and progress in this space [96]. Such regulatory limitations may in part explain the current lack of high-quality evidence in this area despite the increasing availability of and public interest in cannabis. In fact, even in the absence of reliable evidence, some US states have listed OUD as an indication for medicinal cannabis treatment, leading to misleading marketing from pharmacy dispensaries regarding therapeutic benefits [37]. Lucas argues that the severity of the current opioid crisis justifies the immediate implementation of cannabis-based interventions, which can subsequently be evaluated in terms of public health impact and safety [81]. Nevertheless, Lucas also highlights the importance of well-designed clinical trials in assessing dosages, formulations and outcomes [81]. Promisingly, in mid-2022, the "Medical Marijuana and Cannabidiol Research Expansion Act" was passed in the USA, which seeks to facilitate cannabis research by streamlining approvals of potential studies and improving access to cannabis for research, although cannabis' classification as a Schedule I substance remains unchanged. Such policy changes are an important first step in generating the substantial research base required for the approval of pharmaceuticals by the US Food and Drug Administration (FDA) (85). Governments could further support research in this area by directing funding to universities and research institutions given the significant resource requirements of large clinical trials.

Of note, the majority of existing research identified in this review was conducted in North America (acknowledging that the search excluded non-English language papers). As such, any findings may not be generalisable worldwide due to differences in the diversity of population

demographics and the cultural influences that drive opioid use in these respective jurisdictions. Cannabis formulations (both recreational and medicinal) are likely to differ across continents, as are regulations pertaining to their use. Future research should look to include a broader variety of populations in order to improve the applicability of results on a global scale. Generating epidemiological data from existing large-scale databases will likely be the most feasible method to achieve this in the short term, with a view to subsequently validate conclusions using large randomised controlled trials.

A final challenge in interpreting existing findings and designing future studies arises from the significant variability in cannabinoid products. Alongside the many components and derivatives of the cannabis plant (*Cannabis sativa*), an increasing number of synthetic cannabinoids (SCBs) have been formulated that have different effects and potency at cannabinoid receptors [69]. Similarly, drugs acting within the endocannabinoid system to mediate levels of endogenous cannabinoids have also been developed [90]. While this variability can make it difficult to interpret existing research findings (particularly when participants are taking recreational cannabis with unclear components), it also opens many avenues for future research, with the potential to develop cannabinoid formulations to target specific indications. In this case, cannabinoids with maximal impact on withdrawal suppression and minimal adverse effects would be most useful in targeting OUD outcomes. A number of these cannabinoid-based medications are already showing promising results in preclinical studies [31].

While time to market is likely years away for these newer SCBs, they highlight the exciting potential to design targeted formulations for a variety of indications, including substance use disorders. Evidently, our understanding of cannabinoids and their potential in clinical medicine is still in its infancy. With appropriate research effort and regulatory support in the coming decades we can look to optimise the benefits of cannabis-related compounds in improving outcomes in the current opioid epidemic and beyond.

CONCLUSION

The current literature landscape suggests that medicinal cannabis could be used as a therapy in OUD. However, the majority of existing research is preclinical, observational or epidemiological, hindering reliability due to the inability to generalise animal-findings to humans and the potential for extraneous factors to impact results in observational research. Looking forward, well-powered, randomised placebo-controlled clinical trials involving target populations are required to provide reliable evidence in this sphere. Studies should assess the impact of various MCRP formulations and dosages on different target populations, including those at risk of developing OUD, those requiring acute detoxification and those stabilised on treatment, and will need to assess safety profiles, especially when combined with known MOUD including buprenorphine, methadone and naltrexone. In our society where progressive laws look to further increase access to medicinal cannabis worldwide, there is an exciting potential to build upon the current evidence base for medicinal cannabis in OUD and leverage this potential to pave the way for new paradigm shifts in MOUD.

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Declarations

Conflict of Interest. Kelvin Le, Khang Duy Ricky Le, Johnny Nguyen, Jean Hua and Sarah Munday declare that they have nothing to disclose.

Ethical Approval. Ethical approval was not required for the generation of this manuscript given data and findings reported were derived from open-access and freely accessible literature from medical databases. Furthermore, this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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