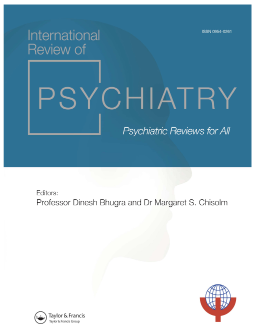

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What does the ecological and epidemiological evidence indicate about the potential for cannabinoids to reduce opioid use and harms? A comprehensive review

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REVIEW

What does the ecological and epidemiological evidence indicate about the potential for cannabinoids to reduce opioid use and harms? A comprehensive review

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ABSTRACT

Pre-clinical research supports that cannabinoids reduce opioid dose requirements, but few studies have tested this in humans. This review evaluates ecological and epidemiological studies that have been cited as evidence that medical cannabis use may reduce opioid use and opioid-related harms. Medline and Embase were searched for relevant articles. Data were extracted on study setting, analyses approach, covariates, and outcomes. Eleven ecological and 14 epidemiological studies were found. In ecological studies, states that allow medical cannabis laws have reported a slower rate of increase in opioid overdose deaths compared with states without such laws. These differences have increased over time and persisted after controlling for state socio-demographic characteristics and use of prescription monitoring programmes. Few studies have controlled for other potential confounders such as opioid dependence treatment and imprisonment rates. Some epidemiological studies provide evidence that cannabis availability may reduce opioid use, but are limited by selection bias, cross-sectional designs, and self-reported assessments of the opioid-sparing effects of cannabis. Some epidemiological and ecological studies suggest that cannabis may reduce opioid use and harms, although important methodological weaknesses were identified. Well-designed clinical studies may provide more conclusive evidence on whether cannabinoids can reduce opioid use and related harm.

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Opioid; cannabinoid; mortality; overdose; opioid-sparing; review

Introduction

In the US, opioid overdose deaths have reached epidemic levels, bringing into sharp focus the need for strategies to reduce use and harms (Seth, Scholl, Rudd, & Bacon, 2018). The US has some of the highest rates of opioid prescribing per capita in the world (Berterame et al., 2016), which has contributed to the dramatic increases in opioid-related overdose deaths observed (Compton, Boyle, & Wargo, 2015; Kolodny et al., 2015; Madras, 2017).

Deaths were initially attributed to the liberal prescribing of high-dose sustained-release opioids, such as oxycodone for chronic non-cancer pain (Kolodny et al., 2015). Recently, some shifts have been observed from use of pharmaceutical opioids to heroin, including heroin laced with fentanyl (Compton, Jones, & Baldwin, 2016; Kolodny et al., 2015). In the US, since the introduction of more restrictive opioid prescribing guidelines and prescription monitoring programmes, heroin is reported to be cheaper and more readily available than pharmaceutical opioids (Kolodny et al., 2015).

Overdose deaths from prescription opioids and heroin have reduced life expectancy among middle-aged white Americans, one population group badly affected by the opioid epidemic (Case & Deaton, 2015). These trends have increased community and political interest in finding ways to reduce the huge toll of opioid overdose deaths and opioid addiction in the US (National Academies of Sciences & Medicine, 2017).

One policy proposal to reduce opioid overdose deaths has been expanding access to medical cannabis programmes for chronic pain and opioid dependence (New York State Department of Health, 2018). This policy was prompted by a paper of Bachhuber, Saloner, Cunningham, and Barry (2014) which attracted considerable media attention because it

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reported that rates of opioid overdose deaths had increased at a slower rate in US states that allowed medical use of cannabis than in states that did not. Media stories suggested that this was because patients with chronic pain substituted medical cannabis for opioid use, or used medical cannabis to reduce their opioid doses, thereby reducing their risks of fatal opioid overdoses (Lake, 2017).

The hypothesis is *prima facie* plausible. Pain relief is a common reason given for medical cannabis use in the US states that allow it (National Academies of Sciences & Medicine, 2017). Numerous reviews of the analgesic effects of cannabinoids in humans have found that cannabinoids produce statistically significant but clinically modest reductions in pain (Mucke, Phillips, Radbruch, Petzke, & Hauser, 2018; Nugent et al., 2017; Stockings et al., 2018; Whiting et al., 2015).

There is also robust evidence from pre-clinical studies that co-administration of cannabinoids and opioids reduces opioid dose requirements (Nielsen et al., 2017). Meta-analysis of these pre-clinical studies indicated clear opioid-sparing effects; the median effective dose of morphine when administered with tetrahydrocannabinol (THC) is 3.6-times lower (95% CI = 1.95–6.76) than when morphine is administered alone, enabling opioids to produce the same analgesic effects at much lower doses (Nielsen et al., 2017).

A small number of low quality clinical studies have tested the opioid-sparing effects of cannabinoids (Nielsen et al., 2017). Most clinical trials that have examined concurrent opioid and cannabinoids administration have required that participants maintained stable opioid doses while trialling cannabinoids (Nielsen et al., 2017) or have not measured or reported changes in opioid dose. There remains a lack of high-quality clinical trials that clearly demonstrate whether cannabinoids may reduce opioid dose requirements.

A major gap in our understanding remains as to whether the correlation reported by Bachhuber et al. (2014) can be explained by large enough numbers of patients using medical cannabis instead of opioids, thereby reducing opioid-related deaths at the population level. The aim of this paper is to review the extant literature to assess how convincing the evidence from ecological and epidemiological studies in the US and elsewhere is that the use of cannabis and cannabinoids for medical purposes can reduce opioid-related mortality.

Methods

Inclusion criteria

The review considered any:

1. Ecological studies that described the effects of changing availability of medical cannabis or laws regulating medical cannabis use on indicators of opioid use and opioid-related harms (e.g. fatal overdoses) at a population-level; and
2. Epidemiological studies that assessed the effects of cannabis use on opioid use and harms at the individual level in the general population or clinical samples.

Data extracted included: study author, location, study population, period of observation, study design, outcomes examined, covariates included in analyses, main findings, and any other considerations in relation to the findings.

Outcomes of interest

Data were extracted on the following outcome measures:

1. Non-fatal and fatal opioid overdose associated with change in cannabis laws;
2. Changes in the frequency of opioid use associated with cannabis use; and
3. Changes in opioid *dose* associated with cannabis use.

Other outcomes relating to opioid use, opioid dependence, or pain were also documented.

Exclusion criteria

Clinical trials and pre-clinical studies of concurrent opioid and cannabinoid administration, and articles without empirical data (e.g. letters, commentaries, and reviews) were excluded. Studies in which outcomes only related to substance use treatment (e.g. treatment retention) were also excluded.

Search strategy

We searched Medline and Embase using the following search terms: Cannabis; cannabis/therapeutic use; medical cannabis; medical marijuana; analgesics, opioid [pharmacological action]; opioid dose; drug overdose; opioid overdose; opioid-related disorders/

Table 1. Excluded studies.

#	Study	Reason for exclusion
1	Feingold, D., Brill, S., Goor-Aryeh, I., Delayahu, Y., Lev-Ran, S. (2017). Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana. *Journal of Affective Disorders*, 218, 1–7. (Feingold, Brill, Goor-Aryeh, Delayahu, & Lev-Ran, 2017)	Not relevant to topic
2	Chandra, S. & Chandra, M. (2015). Do consumers substitute opium for hashish? An economic analysis of simultaneous cannabinoid and opiate consumption in a legal regime. *Drug and Alcohol Dependence*, 156, 170–175. (Chandra & Chandra, 2015)	Not relevant to topic
3	Portenoy, R., Doina Ganae-Motan, E., Allende, S., Yanagihara, R., Shaiova, L., Weinstein, S., McQuade, R., Wright, S., Fallonz, M. (2012). Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *The Journal of Pain*, *13* (5), 438–449. (Portenoy et al., 2012)	Opioid sparing could not be fairly assessed
4	Raby, W., Carpenter, K., Rothernberg, J., Brooks, A., Jiang, H., Sullivan, M., Bisaga, A., Comer, S., Nunes, E. (2009). Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. *The American Journal on Addictions*, 18, 301–308. (Raby et al., 2009)	Not relevant to topic
5	Reisfield, G., Wasan, A., Jamison, R. (2009). The prevalence and significance of cannabis use in patients prescribed chronic opioid therapy: a review of the extant literature. *Pain Medicine*, 10 (8), 1434–1441. (Reisfield et al., 2009)	Review
6	Wilson, M., Gogulski, H., Cuttler, C., Bigand, T., Oluwoye, O., Barbosa-Leiker, C., Roberts, M. (2018). Cannabis use moderates the relationship between pain and negative affect in adults with opioid use disorder. *Addictive Behaviours*, 77, 225–231. (Wilson et al., 2018)	Not relevant
7	Bagra, I., Krishnan, V., Rao, R., Agrawal, A. (2018). Does cannabis use influence opioid outcomes and quality of life among buprenorphine maintained patients? A cross-sectional, comparative study. Journal of Addictive Behaviours, epublish 16.03.18. (Bagra, Krishnan, Rao, & Agrawal, 2018)	Not relevant
8	Hiill, K., Saxon, A (2018) The Role of Cannabis Legalization in the Opioid Crisis, *JAMA Internal Medicine*, Epub 04/04/18. (Hill & Saxon, 2018)	Commentary
9	Sohler, N. L., Starrels, J. L., Khalid, L., Bachhuber, M. A., Arnsten, J. H., Nahvi, S., … Cunningham, C. O. (2018). Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. *Substance Use and Misuse*, 1–6. doi: 10.1080/10826084.2017.1416408. (Sohler et al., 2018)	Sub-population not generalizable

mortality; epidemiology; cohort; opioid sparing; opioid cessation; opioid taper.

Searches were run in April 2018, covering the years 2000–2018, limited to human studies and English.

One reviewer (SN or GC) independently examined titles and abstracts using Endnote Software. The full text of relevant articles were assessed for inclusion independently by two authors (SN + GC), with reasons for exclusion documented (see Table 1). Inter-reviewer disagreement on inclusion was discussed among the authors, and consensus reached on all occasions.

Data extraction

Data were extracted using a standardized data extraction tool in an Excel spreadsheet. The tool was piloted and reviewed by the study authors before being finalized.

Data synthesis

Findings were qualitatively synthesized; outcomes were not reported in a way that enabled quantitative synthesis.

Ecological studies provide the weakest type of evidence for causal inferences, and so are rarely included in evidence hierarchies. Each ecological study was assessed for the strength of the evidence it provided by evaluating (1) whether the study provided credible evidence for a correlation between medical cannabis laws (MCL) and opioid overdose mortality rates; (2) to what extent the study had evaluated other competing explanations of the association by controlling for relevant variables; and (3) whether the study was able to test alternative explanations of the correlation.

Epidemiological studies were similarly assessed for the strengths and limitations of each study. To evaluate quality while accounting for variations in methodological approaches in the ecological studies we assessed the quality of epidemiological studies using a modified Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. (Joanna Briggs Institute, 2016). To enable the use of a single tool across all study designs, the JBI tool was reduced from eight to five items, and an additional item from the EBL Critical Appraisal Tool was used to assess sample bias (Glynn, 2006). A total score out of 6 was possible for quality, with higher scores reflecting greater study quality.

Results

We identified 11 eligible ecological studies and 14 eligible epidemiological studies (see Tables 2 and 3). All but one study assessed the effects of cannabis used for medical reasons on opioid use or opioid-related harm.

Ecological studies of opioid overdose mortality and medical cannabis laws (MCL)

Bachhuber et al. (2014) used mortality data compiled by the US Centers for Disease Control and

Table 2. Findings from ecological studies.

Authors	Location	Outcome	Period	Comparison?	Analysis	Covariates	Findings	Other notes
Bachhuber et al. (2014)	US	Opioid overdose deaths	1999–2010	MCL: 0, 1 Years post-MCL	Regression. Sensitivity analyses for deaths included	Population Age, education, unemployment PDMPs, ID for pharmacies, regulation of pain clinics	Rate of increase in opioid overdose deaths slower in states with MCL Difference between MCL and non-MCL states increased with years since passage of MCL Robust in sensitivity analyses	
Bradford et al. (2018)	US	Total number of daily doses of opioids filled	2010–2015	MCL	Longitudinal regression analysis	States with and without MCL, Dispensary vs home cultivation, State aggregate for prescribing of different opioids	States with active dispensaries saw 3.742 million fewer daily doses filled (95% CI = −6.289 to −1.194); states with home cultivation only MCLs saw 1.792 million fewer filled daily doses (95% CI = −3.532 to −0.052)	
Heaghney (2017)		Opioid overdose deaths	2003–2014	MCL: 0,1 Years post-MCL	Regression Sensitivity analyses	Poverty, education, health insurance coverage, poverty × education	Rate of opioid OD deaths higher in states with MCL The longer MCL in place the larger the decrease in opioid OD deaths Robust in sensitivity analyses	
Kim et al. (2016)	US	Positive opioid test in road fatalities	1999–2013	MCL states 0,1 and pre–-post-MCL		MCL, age, gender, blood alcohol content, PDMP characteristics	Comparing states with and without MCL, no difference in testing positive for opioids. Age-stratified analyses indicated a significant reduction in opioid positivity for drivers aged 21–40 years (OR =0.50; 95% CI =0.37–0.67; interaction $p < 0.001$). Pre- and post-MCL analysis not significant	Mixed, decline in certain age group in MCL states vs not, but no difference in comparisons of states pre-/post-MCL laws and non-age stratified analysis
Livingston et al. (2017)	US	Opioid-related deaths	2000–2015	Recreational cannabis legalization	Interrupted time series	Controlled for comparison state trends (2 states one with medicinal cannabis laws only and one without any cannabis legalization) and PDMP	Opioid-related deaths decreased by ~0.7 deaths per month relative to the baseline period (b = −0.68; 95% CI = −1.34, −0.03) 6.5% reduction in opioid-related deaths after legalization of cannabis	Short-term reduction in opioid related-deaths
Pardo (2017)	US	Opioid overdose deaths	1999–2014	Dispensaries: 0,1	Regression	Household income, education, proportion white, PDMPs, naloxone provided	Rate of increase in opioid overdose deaths slower in states with MCL Rates slower in states with stronger PDMPs	
Phillips and Gazmararian (2017)	US	Age-adjusted opioid overdose deaths for 50 states and District of Columbia	2011–2014	MCL, Mandatory PDMP vs none	Multivariate repeated measures analysis	MCL's PDMP's State level aggregate rates for population on disability, population living in urban area, educational attainment and unemployment	Mean age-adjusted opioid-related mortality rate higher in mandatory PDMP states (11.4% increase in mean annual age adjusted opioid related mortality rate ($p = 0.005$)) Mean age-adjusted opioid-related mortality rate higher in MCL states Non-MCL states saw a greater mean increase in mortality rate (0.8 additional deaths per 100,000 in MCL states vs 2.5 additional deaths per 100,000 in states without). MCL was associated with an increase of 21.7% in mean annual age adjusted opioid related mortality ($p < 0.0001$)	Data extracted from Master's thesis due to the inability to access full text of published article

(*continued*)

Table 2. Continued.

Authors	Location	Outcome	Period	Comparison?	Analysis	Covariates	Findings	Other notes
Powell et al. (2018)	US	Opioid overdose deaths	1999–2013	MCL: 0,1 Years post-MCL Dispensaries: 0,1	Difference in difference & synthetic cohort	Population size Sex, proportion white Unemployment Alcohol tax rate PDMP	Rate of increase in opioid overdose deaths slower in states with MCL Association stronger in synthetic cohort analysis Association stronger for states with dispensaries	
Shi (2017)	US	Opioid-related hospitalizations	1997–2014	MCL	Linear time-series regressions	Other cannabis- and opioid-related policies, socioeconomic factors, and state and year fixed effects	Medical cannabis legalization was associated with 23% ($p = 0.008$) and 13% ($p = 0.025$) reductions in hospitalizations related to opioid dependence or abuse and OPR overdose, respectively	
Smart (2016)	US	Opioid overdose deaths	1990–2013	Number of registered cannabis patients	Poisson Regression	State population, age Unemployment, per capita income Cannabis decriminalisation Beer and tobacco taxes	Rate of increase in opioid overdose deaths inversely related to number of medical cannabis patients in adults aged 45–64 years in states with MCL	
Wen and Hockenberry (2018)	US	Opioid prescriptions	2011–2016	MCL and adult-use cannabis laws	Quasi-experimental difference-in-differences design	National levelling off and gradual reduction in annual opioid prescribing rate, rising public awareness of the role of opioids in pain management, role of buprenorphine in OUD treatment	State implementation of MCL was associated with a 5.88% lower rate of opioid prescribing (95% CI = −11.55% to ∼ −0.21%) Adult-use cannabis laws, which all occurred in states with existing MCL, were associated with a 6.38% lower rate of opioid prescribing (95% CI = −12.20% to ∼ −0.56%)	

PDMP: Prescription Drug Monitoring Programs; MCL: Medical Cannabis Laws; OD: overdose; CI: confidence interval.

Prevention over the period 1999–2010 to compare trends in opioid overdose mortality rates in US states that did and did not allow medical cannabis use.

The study controlled for state differences in population age, education, and unemployment. The authors also coded for the presence or absence of prescription drug monitoring programmes (PDMP) and patient ID checks in pharmacies. They modelled medical cannabis policy by: (a) present or absent by year; and (b) by year since implementation, in order to take account of the fact that it may take time to implement medical cannabis policies after the passage of laws that allow it.

Opioid overdose deaths increased over the study period at a slower rate in states with MCL than in states without them. This difference persisted after controlling for demographic and policy differences between states. The association was reduced and no longer statistically significant when they included a state-specific term in their model to take account of unmeasured differences between states in opioid overdose mortality trends. They found the same results if they excluded opioid-related suicides and heroin-related deaths.

Similar findings emerged when they analysed the association between MCL and opioid overdose deaths by the number of years since the laws were enacted. They found that the difference in rate of increase in opioid overdose deaths increased with each year since the passage of the MCL. The rates of overdose deaths were higher in states that passed MCL, and the slowing in the rate of opioid overdose deaths in these states was most apparent in the last 2 years of the study period, i.e. in 2009 and 2010.

According to Bachhuber et al. (2014), these associations suggested that increased access to medical cannabis use for pain relief may have reduced opioid overdose deaths. They acknowledged that their data were ecological, so they were not able to control for all relevant differences between states that may affect opioid overdose deaths; and they could not control for changing attitudes and behaviour towards opioid use that may have varied over time between different states. They called for 'further more rigorous evaluation' before 'recommending medical cannabis as a strategy to reduce opioid overdose deaths' (p. 1672).

Bradford, Bradford, Abraham, and Bagwell Adams (2018) conducted a longitudinal analysis to examine the effects of state MCL on daily doses of opioids filled in Medicare Part D for all opioids as a group and category of opioids by state. Additionally, the authors examined if daily opioid doses varied by

Table 3. Findings from epidemiological studies.

Authors	Location	Population	Period	Study design	Outcomes examined	Covariates	Main findings	Overall	Considerations
Abuhasira et al. (2018)	Israel	2736 patients over 65 years of age receiving medicinal cannabis	2015–2017	Prospective cohort	Self-report change in analgesic medication use at 6 months	None	143 patients (18.1%) of 791 patients who completed the 6-month assessment and answered questions on medication changes reported they stopped or reduced their analgesic medications	Reduction in analgesic use, though high-rates of attrition	Based on a sample of patients from a medical cannabis clinic
Boehnke et al. (2016)	US	244 medical cannabis patients	2013–2015	Cross-sectional	Self-report PO use	None	The mean change in self-reported opioid use among all respondents answering this question was 64%	Self-reported reduction in PO use	Recruited through medicinal cannabis program
Cerda et al. (2018)	US	Nationally representative sample of adolescents in 48 contiguous US states. 1,179,372 US 8th, 10th, and 12th graders	1991–2015	Nationally representative, annual cross-sectional survey of students	Participant reports of any cannabis use or non-medical prescription opioid use within past 30 days Exposure variable was state-level MCL	Individual-level covariates -grade, age, sex, race/ethnicity, and socioeconomic status, education State-level covariates: % male, white, age, education	No difference in non-medical PO use between MCL states and not. MCL states had significant decline in non-medical PO use in 8th graders (2.1% vs 0.9%, OR $=0.43$ (95% CI $=0.36$–0.52, $p<0.0001$). Significant increase in non-medical PO use among 12th graders after MCL (2.2 vs 3.1, OR $=1.42$, 95% CI $=1.21$–1.66, $p<0.0001$)	Mixed findings	Non-medical use of opioids and cannabis use, not medicinal cannabis
Corroon et al. (2017)	US	Self-selected convenience sample of 2774 who reported recent cannabis use	2013–2016	Cross-sectional	Used cannabis as a substitute for prescription drugs, yes/no	None	36% cannabis use as a substitute for opioids	Cannabis used a substitute for opioids	Convenience sample
Degenhardt et al. (2015) and Campbell et al. (2018)	Australia	Convenience sample of chronic pain patients prescribed opioids	2012–2017	Cohort (cross-sectional and longitudinal analyses)	Opioid-dose, self-reported pain relief, pain interference	Age, sex, pain characteristics mental health and SUD history, opioid dose and pain self-efficacy	Those that had used cannabis had greater pain, lower pain coping, and higher opioids doses compared with those that had not used cannabis. Those that used cannabis reported greater pain relief from cannabis than from other medications	Those that had used cannabis represent a more complex group, non-medical cannabis use not associated with lower opioid doses	Those that did and did not use cannabis had important baseline differences. Medical cannabis unavailable at time of study
Hamilton et al. (2017)	Canada	401 participants reporting cannabis use in annual CAMH monitor survey	2013 and 2014	Cross-sectional survey	Binary measure of past 12-month medical use of PO	Age, sex, marital status overall health problematic cannabis use	In adjusted models people who used cannabis for therapeutic purposes were more likely to report past year medical use of PO, OR $=2.66$, 95% CI $=1.11$–6.36)	PO use more likely with therapeutic cannabis use	
Haroutounian et al. (2016)	Israel	274 participants recruited through a pain clinic	2010–2013	Prospective, open-label	Discontinuation of opioids Decreased opioid use	None	32/73 participants on opioids at baseline discontinued at follow-up ($p<0.001$)	Statistically significant in opioid discontinuance, but not median OME	
Kral et al. (2015)	US	653 people who inject drugs who had used heroin or non-medical use of opioids	2011–2013	Cross-sectional survey	Number of times opioids (heroin or non-medical PO) used in past 30 days	Age, ethnicity, age of first injection, health insurance, past 30 days SUD treatment	Cannabis use associated with a decline in past 30 day use of opioids b $=-0.346$, 95% CI $=-0.575$, -0.116)	Decline in opioid use	Illicit use of cannabis and mainly heroin use
Lucas and Walsh (2017)	Canada	271 patients registered for medicinal cannabis access	2015	Cross-sectional survey	Substitute cannabis for opioids (yes/no)	None	32% reported they substitute cannabis for PO. Those who used cannabis for pain-related conditions were more likely to substitute cannabis for opioids (42% ($n=57$) vs 20% for non-pain ($n=23$)	Opioids were the prescription medication that cannabis most frequently substituted for	Participants were compensated $10 credit for Tilray cannabis
Maida et al. (2008)	Canada	112 patients in a palliative medicine programme; 47 treated with nabilone, 65 not treated with nabilone	2005–2006	Prospective observational	Prescription opioid use	Propensity score for gender, age, site of contact, number of comorbidities, pain score, and baseline symptom level	Log morphine sulphate equivalent lower at 30 days for nabilone treated patients. Mean at follow-up 3.7 vs 4.3, $p<0.001$	Nabilone reduced morphine sulphate equivalent dose	

(*continued*)

Table 3. Continued.

Authors	Location	Population	Period	Study design	Outcomes examined	Covariates	Main findings	Overall	Considerations
Novak et al. (2016)	US	National Survey on Drug Use and Health aged 12 and over, ~55,000/year	2003 and 2013	Cross-sectional nationally representative survey	Past-year non-medical pain reliever use	Weighted to control for demographic compositions across the US	Higher levels of cannabis use were consistently associated with more frequent consumption of prescription pain relievers	Greater non-medical PO use among people who use cannabis	Illicit use of PO and cannabis
Reiman et al. (2017)	US	2897 medical cannabis patients	Not stated	Cross-sectional	Self-report 'strongly agreed/agreed' able to reduce opioids when using cannabis	None	97% of the sample 'strongly agreed/agreed' that they are able to decrease the amount of opioids they consume when they also use cannabis	Cannabis associated with decline in opioid use	Sampling approach may contribute to bias
Shah et al. (2017)	US	Patients from a chronic pain clinic. 48 patients with + urine screen for THC and 24 matched patients with THC – urine screen	2015	Prospective	PO use and dose (OME)	Non-cannabis group matched on age, gender, education, ethnicity, and PO use on admission Gender, age	Doses of PO were not statistically different among the cannabis and non-cannabis groups	No difference in PO use between people who use cannabis and people who don't	Preliminary data. Small sample using opioids at admission, $n = 14$
Vigil et al. (2017)	US	37 habitual opioid using chronic pain patients enrolled in Medical Cannabis Programme and 29 comparisons	2010–2015	Cohort study	Reduction in opioid consumption Percentage change in opioid consumption Ceased opioid consumption	Age, gender	Increased PO cessation (41% vs 3%, $p < 0.001$) Reduced opioid dose (84% vs 45%, p 0.001) Percentage point change in daily opioid (−47% ± 63 vs 10% ± 115 $p = 0.013$) Reduced daily PO dosage (−12.0 ± 23.4 vs 3.9 ± 13.2, $p = 0.101$)	Reduction in PO use in patients using legal medicinal cannabis	Small sample and people enrolled in medical cannabis programme

MCL: medical cannabis laws; PO: Prescription opioid; SUD: Substance Use Disorder; THC: tetrahydrocannabinol.

whether a state had implemented a medicinal cannabis law that allowed either dispensary-based or home cultivation only. The study utilized data from Medicare Part D, an optional prescription drug benefit plan available to 70% of Medicare enrollees subscribed. The authors examined data from 2010–2015, in which there were 132.6 million physician drug–year observations. They used the total number of daily doses prescribed by each physician, and the key dependent variable was the total number of daily doses (in millions) for any opioid medication prescribed in Medicare Part D in each state in each year. The independent variable was whether states had MCL in place or not. Within the study period, nine states implemented some form of MCL, 14 states had some form of active MCL for the entire study period, and 27 states had not implemented a MCL by the end of the study period. Home cultivation and dispensary programmes were also examined. In longitudinal regression analysis, states with MCL had a decrease of 2.211 million daily doses in filled prescriptions, compared with states without active MCL, although this was not statistically significant (beta = −2.211, 95% CI = −4.574 − 0.152, % change =8.5%, p-value =0.06). States with cannabis dispensaries had a statistically significant annual daily dose reduction (14.4% change =3.742 million, 95% CI = −6.289 to −1.194, $p < 0.005$) compared with states with no MCLs. States with access via home cultivation were associated with a 1.792 million annual daily dose reduction (6.9% change, 95% CI = −3.532 to −0.052, $p = 0.4$), compared with states with no MCLs. In secondary analysis examining specific opioids, there was a statistically significant reduction in hydrocodone and morphine prescriptions in states with dispensary-based MCLs.

Heaghney (2017) analysed rates of unintentional overdose deaths involving opioids, heroin, and alcohol in 50 states and the District of Columbia over the period 2003–2014. A binary code was also used to indicate whether states allowed medical cannabis use or not, and he conducted a secondary analysis using years since implementation of MCL. He controlled for state opioid policies and sociodemographic differences between states that may have affected opioid overdose deaths. He conducted sensitivity analyses which used the whole state population and only the white population, and re-ran analyses after removing deaths involving alcohol to control for state differences in polydrug use.

Heaghney (2017) found that the rate of overdose deaths was *higher* in states with medical cannabis than those without, but the rate of increase in opioid overdose deaths was slower in states with MCL. This finding persisted after adjustment for differences between states in education, unemployment, and poverty. There was an interaction between level of education and poverty in the state, which indicated that rates of opioid overdose death were much higher in US states whose populations had low levels of education and high rates of poverty. These results were supported by sensitivity analyses which showed that the findings did not depend on: whether the whole population or only the white population was included in the analysis; whether the medical cannabis policy was modelled as a binary variable or as years since medical cannabis was allowed; or whether opioid overdose deaths involving alcohol were included or excluded from the data.

Kim et al. (2016) analysed toxicology reports collected 1 h after road fatalities from 1999–2013 in 18 states that conducted drug and alcohol testing on at least 80% of fatally injured drivers. They collected information on opioid use from toxicology reports and compared states with and without MCLs (either dispensary or home-based laws). They included information on whether states had prescription monitoring programmes in their analyses. They found a non-significant reduction in opioid-positivity in road fatalities for most states over the study period, but no difference between states with and without MCLs. The authors did, however, find interaction with age. They found significantly lower rates of opioid positivity among drivers aged between 21–40 years in states that implemented MCL compared with states that had not.

Livingston, Barnett, Delcher, and Wagenaar (2017) examined monthly opioid-related deaths before and after the introduction of Colorado's recreational cannabis legalization from 2000–2015. They used an interrupted time-series design covering 168 baseline months before legalization and 24 months after legalization. The long baseline time allowed them to account for slow changing confounders, such as changes to Colorado's prescription drug monitoring programme (PDMP), which was introduced 5 months after recreational cannabis legalization. Comparisons were also made with other states, namely Nevada, which permits the sale of medicinal cannabis only, and Utah, a state where any cannabis use still remains illegal.

After controlling for comparison state trends and Colorado's PDMP, Livingston et al. (2017) found that opioid-related deaths decreased by ∼0.7 death per month compared to the baseline period. Comparison of modelled-smoothed opioid-related deaths per month just prior and at the end of follow-up found a 6.5% reduction in opioid-related deaths, a much smaller reduction than Bachhuber et al. (2014) found. This finding held, after controlling for comparison states and adjusting for the tightening of Colorado's PDMP programme. These findings provide only an assessment of the short-term effects of Colorado's recreational cannabis legalization on opioid-related deaths.

Phillips and Gazmararian (2017) assessed the effect of MCL on overdose mortality in 50 states and the district of Columbia from 2011–2014. States with and without MCL's and PDMP were compared. They found states with MCL's had an increase of 21.7% in mean-adjusted opioid-related mortality ($p < 0.001$). However, they found that the longer MCL were implemented the smaller the rate of decrease in opioid-related overdose from 21.7% to 1.7%. States with PDMP's were associated with a 11.4% increase in mean-adjusted opioid-related mortality. In states with both MCL and PDMP, there was a 10.1% decrease in opioid-related mortality, although this was not significant ($p = 0.055$).

Powell, Pacula, and Jacobson (2018) examined the relationship between opioid overdose deaths and MCL using two different analyses to test the robustness of their finding. They modelled the association using difference in the log of age-adjusted opioid overdose deaths between states over the study period. They also conducted a synthetic cohort analysis that compared the age-adjusted opioid overdose mortality rates in the average of all states that did or did not allow medical cannabis use in each year of observation. They used two measures of each state's medical cannabis status: a binary coding of whether or not a state's laws allowed medical cannabis use, and a measure of whether the states allowed legal medical cannabis dispensaries. They controlled for differences between states in population size, the proportions which were male and white, the unemployment rate, alcohol tax rate, and whether the state had a PDMP, and, if so, what type.

Powell et al. (2018) also examined trends in each state in the numbers of persons treated for opioid dependence and household survey data on the prevalence of self-reported non-medical opioid use. Their data covered 1999–2013 for overdose deaths, 1999–2012 for opioid treatment, and 1999–2013 for prevalence of self-reported non-medical opioid use.

The difference in differences analysis replicated the reduction in rate of opioid overdose deaths found by Bachhuber et al. (2014), i.e. states with MCLs had a slower rate of increase in opioid overdose mortality than states without these laws, and the rate of increase declined more in states that had implemented these laws earlier in the study period. They found a larger difference in the increase in opioid overdose mortality rates between medical cannabis and non-medical cannabis states using the synthetic cohort method of analysis. They found similar results in rates of treatment for opiate dependence and their analysis of household survey data suggested that both PDMPs and medical cannabis dispensaries reduced non-medical opioid use.

Powell et al. (2018) cautioned that the mechanisms for any effect of MCLs on opioid overdose deaths were unclear. Specifically, they were uncertain whether the decline in opioid overdose deaths could be explained by a reduction in medical or non-medical opioid use or both. It was also unclear whether the effects they observed were only short-term or likely to produce greater declines in opioid overdose death rates in the future.

Pardo (2017) analysed overdose mortality rates in the 50 states of the US between 1999 and 2014. His primary aim was to assess the effects of state prescription monitoring programmes on opioid overdose mortality rates. He coded each state on whether it had introduced a PDMP and the strength of the state's PDMP. He also included two measures of state policies towards medical cannabis use: (a) whether or not a state allowed medical use, and (b) if so, whether the state allowed legally protected medical cannabis dispensaries. In these analyses he controlled for state differences in median household income, the proportion of adults over the age of 25 years with a high school education, and the proportion of the population that was white.

Pardo (2017) found that states with PDMPs had lower rates of increase in opioid overdose mortality compared to those without, and that this difference was larger in states that more effectively implemented PDMPs. He also found that states with MCL, and states that allowed medical cannabis dispensaries, had a slower rate of increase in opioid overdose deaths than states without these laws or dispensaries. The reduction in the rate of increase for medical cannabis states was of a similar magnitude to that reported by Bachhuber et al. (2014) and Powell et al. (2018).

Smart's (2016) analysis of the association between state MCL and overdose deaths improved on earlier studies by collecting data on the number of registered medical cannabis patients in those states that kept a register. Her analysis excluded Washington State, which had no patient registration, and California, where registration was voluntary. She also examined differences in associations between medical cannabis use and opioid use in different age groups. Her analyses controlled for state population, average age, unemployment rate, per capita income, cannabis decriminalization, and beer and tobacco taxes. Smart found that the number of registered medical cannabis patients in each state was associated with a slower rate of increase in opioid overdose deaths only among adults aged 45–64 years.

Shi (2017) utilized state-level annual administration records of hospital discharges from 1997–2014 to examine rates of hospitalizations involving cannabis abuse or dependence and opioid abuse or dependence and opioid-related overdose. The analyses were based on 27 states; nine states had implemented MCL between 1997–2014. Shi found that states with MCL had a 23% reduction in hospitalizations related to opioid dependence or abuse ($p = 0.008$) and a 13% reduction in hospitalizations related to opioid-related overdose ($p = 0.025$). MM dispensaries were associated with a 13% reduction in opioid dependence or abuse ($p = 0.010$), and a 11% reduction in opioid-related overdose ($p = 0.006$) compared with states with MCL's that did not allow dispensaries. Dispensaries were not independently associated, however, with a reduction in opioid abuse or dependence in adjusted models.

Wen and Hockenberry (2018) examined data collected through Medicaid, which had expanded to include more high-risk, low income adult enrollees with a higher risk of chronic pain, opioid use disorder, and overdose. They examined data from 2011–2016 to minimize influences of nationwide policies and guidelines introduced before 2011 and prior to their implementation in 2016. The latter included reformulation of oxycodone, national guidelines for opioid prescribing in chronic pain, the Surgeon General's warning of the opioid crisis, and the Centre for Disease Control and Prevention Guidelines for use of prescription opioids in chronic pain. The authors examined state level opioid prescribing rates, defined as the number of opioid prescriptions primarily for pain management covered by Medicaid, on a quarterly basis per-1000 Medicaid enrollees, in each state. They compared opioid prescribing in states with MCL's and adult-use cannabis laws (i.e. recreational and medicinal use). The implementation of MCL's was associated with a 5.88%

lower rate of Medicaid-covered prescriptions for all opioids (95% CI = −11.55% to −0.21%). They estimated that this was equivalent to 39.41 fewer opioid prescriptions per 1000 enrollees per year. In additional analyses, the authors found that, when MCL states implemented adult-use cannabis laws there was an additional 6.38% decline in opioid prescription rate (95% CI = −12.20 to ∼ −0.56%).

Epidemiological studies

Epidemiological studies of persons who use opioids and medical cannabis can test the plausibility of one of the most popular explanations of the association reported in ecological studies; namely, that opioid users who use medical cannabis, use lower doses of opioids than those who do not, or are more likely to stop using opioids. Fourteen studies provided epidemiological evidence of this sort. Ten were cross-sectional studies and four were prospective clinical cohort or observational studies. The epidemiological studies were of mixed quality with a mean score of 4 out of 6 (range =0–6).

Cross-sectional studies

Abuhasira, Schleider, Mechoulam, and Novack (2018) examined the safety and efficacy of medicinal cannabis in a prospective cohort of 2736 patients over the age of 65 years who were receiving medical cannabis from 2015–2017. Patients completed questionnaires at baseline, 1-month, and 6-months. Forty-three per cent completed the 1-month follow-up and 33% completed the 6-month follow-up. Of the 791 patients who answered questions on changes in medication at 6-months, 14.4% ($n = 114$) reported they stopped using their opioid analgesic, 3.7% ($n = 29$) reported they reduced their opioid analgesic medication, and 0.8% ($n = 6$) reported they increased their opioid analgesic medication.

Boehnke, Litinas, and Clauw (2016) reported a cross-sectional survey of 244 patients (185 of whom had complete questionnaires), with chronic pain enrolled in a medical cannabis programme. Study participants self-reported a 64% decrease in opioid use and improved quality-of-life (45%). These findings suggest that patients with pain in medical cannabis programmes reduce their opioid dose, but the population was small, self-selected, the outcomes were based on patient self-report that was obtained retrospectively, and we do not know what proportion of patients they represented, or whether those that provided data differed from those that did not.

Cerda et al. (2018) used data from the annual Monitoring the Future (MTF) survey, a nationally representative, cross-sectional survey of 1,179,372 US school students from 1991–2015. They reported on self-reported past-30-day use of cannabis, non-medical use of opioids, and other substance use. Findings from this study were mixed. There was a significant decrease in non-medical opioid use among 8th grade students, but a significant increase among 12th grade students after the introduction of MCL. The study did not measure the direct effect of cannabis consumption on opioid use. Instead it used state MCL as a proxy measure of exposure. Other factors may explain the increase in non-medical prescribed opioid use.

Corroon, Mischley, and Sexton (2017) studied an online anonymous convenience sample of 2774 people who reported having used cannabis at least once in the previous 90 days. Recruitment occurred through social media and cannabis dispensaries, introducing a probable selection bias in favour of people pre-disposed to be positive about the effects of cannabis. The study found that those using medical cannabis were more likely to self-report that they substituted pharmaceutical drugs (most commonly narcotics/opioids) than those who reported using non-medical cannabis. They did not find any effect of state MCL on prescription drug substitution.

Degenhardt et al. (2015) reported a cross-sectional analysis of data from 1200 chronic pain patients who had used opioids for at least 6 weeks, and a later longitudinal analyses of the same cohort (Campbell et al., 2018; Degenhardt et al., 2015). They compared opioid doses and self-reported pain in patients who did and did not report using illicit cannabis for pain. Patients who used illicit cannabis did not use lower opioid doses, and reported poorer pain control and poorer psychosocial outcomes than patients who did not use cannabis (Campbell et al., 2018; Degenhardt et al., 2015).

Hamilton, Brands, Ialomiteanu, and Mann (2017) conducted a repeated cross-sectional survey (2013 and 2014) of adults from Ontario, Canada (the CAMH Monitor Survey). This included 401 people who reported using cannabis for medical reasons. Medical cannabis use was associated with more frequent cannabis use, a moderate-to-high risk of problematic cannabis use, and a *greater* likelihood of using prescription opioids for medical purposes. There was little difference in rates of medical cannabis use by sex, age, and marital status after adjusting for opioid use and problematic cannabis use.

Kral et al. (2015) reported a study of a purposefully recruited sample of people who injected drugs to assess if recent self-reported cannabis use was associated with recent self-reported opioid use. Those who reported cannabis use reported a lower mean and median frequency of opioid use in the past 30 days. This was significant after controlling for age, age at first injection, being Latino, recruitment site, health insurance, and methadone treatment. In this study the cannabis and opioids were not used in the context of medical treatment.

Lucas and Walsh (2017) conducted an online survey of medical cannabis patients in Canada ($n = 271$, 21% response rate). One in three (32% of) patients reported that they substituted cannabis for opioids. This was higher (42%, 57 of 137) among those who reported using cannabis for pain. This finding needs to be interpreted in light of the fact that the survey was conducted and published by a commercial cannabis supplier.

Novak, Peiper, and Zarkin (2016) examined concurrent use of cannabis with non-medical prescription opioid and alcohol use in the US National Survey on Drug Use and Health. They found that higher levels of cannabis use were associated with more frequent consumption of prescription pain relievers. The study population was a large nationally representative sample, and findings were replicated in two different time periods, but this study focused on the illicit use of both cannabis and prescribed opioids, rather than the therapeutic use of either drug.

Reiman, Welty, and Solomon (2017) examined the self-reported effects of cannabis from 2897 medical cannabis patients recruited through a digital cannabis health and wellness platform that provided Telehealth evaluations of potential patients for medical cannabis recommendations in California. Three in 10 ($n = 841$) reported using an opioid analgesic in the past 6 months. Of these, most (97%) agreed that cannabis reduced the opioid dose and 71% agreed cannabis was as effective as opioids for their pain. The questions asked participants for their opinion in a leading way that may have reduced the reliability of the data. It is also difficult to assess the extent to which patients' responses may have been affected by a belief that their responses may have affected their eligibility for access to medical cannabis.

Prospective clinical studies

Haroutounian et al. (2016) described an open label trial reporting a reduction in opioid use in chronic pain patients who used medical cannabis. Participants ($n = 206$) attended a pain clinic in Israel and were prospectively followed-up and assessed for pain, opioid use, and discontinuation at baseline and follow-up. Analyses did not control for any co-variates. Of the 73 participants using opioids at baseline, 44% reported ceasing them during the study. They did not find a significant reduction in opioid dose among those who continued to take opioids between baseline and follow-up.

Maida, Ennis, Irani, Corbo, and Dolzhykov (2008) conducted a prospective open-label observational study of 112 patients to assess the effects of the synthetic pharmaceutical cannabinoid nabilone on pain and other symptoms experienced by patients with advanced cancer. Propensity score matching with 47 treated and 65 untreated patients found that patients treated with nabilone had lower pain scores and used lower opioids doses than untreated patients, after adjusting for baseline differences between the two groups.

Shah, Craner, and Cunningham (2017) reported on a matched cohort ($n = 48$, 24 in each group) of patients entering a pain programme with a positive urine drug screen for cannabis. Seven patients in each group were using opioids at cohort entry, and there was no difference in their mean opioid doses at cohort entry. There were no differences in clinical outcomes between those using and not using cannabis at cohort entry. The study reported that patients were asked to cease both cannabis and opioids as part of the pain management programme. The very small sample size (with only 14 people using opioids) severely limited their ability to detect any effects of cannabis use on opioid-related outcomes.

Vigil, Stith, Adams, and Reeve (2017) conducted a matched cohort study, with 37 patients entering a medical cannabis programme, who were compared with 29 patients who declined to enrol in a medical cannabis programme and were not using cannabis (confirmed by a urine drug screen). Data from a prescription monitoring programme showed that enrolment in the medical cannabis programme was associated with greater odds (aOR = 17.27, 95% CI = 1.89–157.36) of ceasing opioids, which persisted after controlling for age and gender. Similarly, there were higher odds of reducing the opioid dose (aOR = 5.12, 95% CI = 1.56–16.88) after adjusting for age and gender. The wide confidence intervals around these estimates indicate considerable uncertainty arising from the small sample size. The data indicated improvements in pain reduction, quality-of-life, social life, activity levels, and concentration.

Discussion

Ecological and epidemiological studies have provided mixed support for pre-clinical evidence that the use of cannabis for medical purposes may reduce opioid use. Ecological studies have found a slower rate of increase in opioid overdose deaths in US states that allow the medical use of cannabinoids than states that do not (Bachhuber et al., 2014). Epidemiological studies, however, provide more mixed evidence on whether people who use cannabinoids use lower opioid doses.

Limitations of ecological studies

The major weakness of the ecological studies is that data on opioid overdose deaths in each US state may not reflect the behaviour of individuals who use medical cannabis or opioids (Finney, Humphreys, & Harris, 2015).

Second, the simple presence or absence of MCL in each state (Hayes & Brown, 2014) does not necessarily reflect the number of patients in each state who use cannabis for medical purposes or the proportion of patients who do so for pain relief. The most careful studies have differentiated between states with MCL that allow protected medical dispensaries (e.g. Pardo, 2017), and some studies have used the number of registered medical cannabis patients to estimate the extent of medical cannabis use in states that have registries (Powell et al., 2018; Smart, 2016). Nonetheless, none of these studies has been able to directly assess the extent to which pain patients have used medical cannabis for pain relief instead of opioids in states that allow medical cannabis use.

Third, it is difficult to control for the effects of other confounding variables when the data apply to a whole state rather than to individual citizens. Citizens in these states vary widely in their characteristics and in their access to and use of cannabis for medical purposes (Finney et al., 2015)

Fourth, a major weakness of the ecological studies is that they have not been able to control for state differences that are likely to reduce or increase opioid overdose mortality over the study period. The most critical missing variable is access to methadone and buprenorphine maintenance treatment for opioid dependence in each state over time. These treatments substantially reduce opioid overdose deaths while opioid dependent persons remain in treatment (Sordo et al., 2017). If access to these treatments is correlated with medical cannabis policies, then this could explain the slower rate of increase of opioid overdose mortality in medical cannabis states. This correlation may be expected as expanding treatment and increasing cannabis access both represent more progressive approaches to drug policy.

The converse may also be true of states where more conservative approaches to drug policy are applied. For example, the ecological trends could also be explained if US states differed in the extent to which they rely on abstinence-oriented detoxification, rather than opioid maintenance treatment, as a treatment for opioid dependence. Detoxification in the absence of follow-up treatment increases opioid overdose deaths when patients who complete detoxification return to using opioids (Darke & Hall, 2003). If detoxification were the primary treatment approach in US states without MCL (which may also reflect more conservative drug policy), then this could also explain the slower rate of increase of opioid overdose mortality in medical cannabis states.

None of these studies has measured state differences in rates of imprisonment for opioid use. The risk of an opioid overdose death increases dramatically in the 2 weeks immediately after release from prison when opioid-dependent persons resume opioid use with a reduced opioid tolerance (Darke & Hall, 2003; Merrall et al., 2010). If states differ in the proportion of opioid users that they imprisoned, or the frequency with which they are imprisoned, this could explain differences in rates of increase in opioid overdose deaths between states.

There are other possible explanations of the correlation that cannot be evaluated. One is that cannabis intended for medical use has been diverted to the illicit market and used as an intoxicant by non-medical opioid users, or substituted for CNS depressants, such as alcohol and benzodiazepines, that play a role in opioid overdose deaths. These possibilities would reduce the number of overdose deaths among *non-medical* opioid users rather among medical users with chronic pain. The Powell et al. (2018) analysis provided some support for this hypothesis, in that it found a greater decline in non-medical opioid use in household surveys in states with liberal MCL than in those without.

Epidemiological studies

In order to address the limitations of ecological studies we need epidemiological studies that collect data on individuals' medical cannabis use, opioid use, pain, and risk of opioid overdose. Unfortunately, there is limited evidence of this type and it is conflicting. In some studies, people with chronic pain who use medical cannabis may be *more* likely to misuse opioid medications than patients who do not use cannabis (Reisfield, Wasan, & Jamison, 2009). In contrast, other observational studies have found 44–64% reductions in opioid consumption in cohorts of patients with chronic pain using cannabis, significant reductions in pain severity and interference, and improved quality-of-life (Boehnke et al., 2016; Haroutounian et al., 2016). Patients in some studies report that cannabinoids reduce their need for opioids, e.g. 30% of Canadian medical cannabis users reported cannabis use enabled a reduction of their prescription opioids use (Lucas & Walsh, 2017). In other studies, pain patients who reported using cannabis report using lower opioid doses, but in a 4-year follow-up of a large cohort of Australian pain patients, cannabis use was not associated with lower opioid dose (Campbell et al., 2018). This study was conducted when medical cannabis was not widely available, meaning most cannabis use would have been outside a medical context.

Limitations of epidemiological studies

Among the major limitations of the epidemiological studies were: the fact that most were cross-sectional; they often did not distinguish between illicit and medical cannabis use; they frequently sampled patients in ways that may introduce selection bias (e.g. by recruiting from cannabis dispensaries or online advocacy websites); and they often relied on patient judgements about the effects of cannabis use on opioids rather than on comparisons of opioid doses between patients who do and do not use medical cannabis, or between the same people when they were or were not using cannabis. There was little data from outside North America, limiting generalizability to other settings given the scale of the opioid overdose problem in North America.

Questions and future research

Unintended outcomes from using cannabis also need to be considered. Cannabinoid use may have an adverse effect on patient safety or stability in treatment. Observational studies of persons being treated for opioid dependence, for example, suggest that those using cannabis (especially those reporting daily use) are more likely to cease opioid treatment (Franklyn, Eibl, Gauthier, & Marsh, 2017). Additionally, studies examining the effect of cannabinoids on opioid withdrawal symptoms have been mixed, and a recent study found that dronabinol increased the heart rate, which may limit its clinical use (Bisaga et al., 2015; Epstein & Preston, 2015; Jicha et al., 2015).

Systematic reviews of clinical trials of the effects of cannabinoids on pain have also found that cannabinoids have modest analgesic effects. These cannabinoids produce clinically significant reductions in pain in a minority of patients with chronic pain and only a marginally larger proportion among patients receiving cannabinoids than placebo. For example, a recent Cochrane review concluded that there was low-to-moderate quality evidence that cannabinoids reduced chronic neuropathic pain. It found that analgesic effects of cannabinoids were modest: 21% of patients who received cannabinoids reported a 50% reduction in pain compared with 17% of those who received a placebo (Mucke et al., 2018). Twenty patients needed to be treated with a cannabinoid for one to benefit (Mucke et al., 2018).

What type of data are needed?

We need epidemiological studies that collect data prospectively on individuals who use opioids to assess whether medical cannabis (or cannabinoid) use reduces opioid use and consequently reduces opioid overdose. This could include prospective studies of: (1) chronic pain patients who use opioids to assess the extent to which cannabis use affects opioid dose requirements, and other substance (e.g. alcohol) use, and their risks of a fatal opioid overdose; (2) people who use opioids non-medically, to see if those who use cannabis use lower doses of opioids and, hence, have a lower opioid overdose risk; and (3) patients with chronic pain who use medical cannabis for pain control. If cannabis use reduced overdose deaths in pain patients or people who use opioids non-medically, this would represent a public health gain, albeit by different mechanisms with very different policy implications.

An important policy question for other countries will be more difficult to answer: will any opioid sparing benefits of medical cannabis use be specific to the US? The US has the world's highest rate of opioid prescribing (Humphreys, 2017), and the rate of opioid overdose mortality in the US is higher than that in most other developed countries. It is unclear, therefore, to what extent any benefits of increased medical cannabis use in the US in reducing opioid overdose deaths would also be found in other developed countries with much lower rates of opioid prescribing and lower rates of population cannabis use.

In conclusion, both ecological and epidemiological evidence suggest that the availability and use of cannabis for medical purposes may be associated with reduced opioid use and related harms. At this point the findings are not conclusive, and clear evidence of causality is lacking. The direction of effects in ecological studies is consistent with pre-clinical research, but these results are difficult to interpret because these studies have been unable to control for important variables that may explain state differences in rates of opioid overdose (e.g. access to treatment for opioid overdose, rates of poly drug use, and rates of imprisonment among people who use opioids). Well-conducted clinical studies are needed to measure any opioid-sparing effects of cannabis, and to assess the prevalence of any adverse or unintended effects of using cannabinoids.

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