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The effectiveness of changes to drug policy, regulation and legislation for reducing harms associated with opioids and supporting their medicinal use in Australia, Canada and the UK: A systematic review

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Abstract

Governments and health agencies in Australia, Canada and the United Kingdom (UK) have implemented changes to drug policy, regulation and/or legislation for reducing increasing rates of dependency, overdose and other harms associated with prescription and over-the-counter opioid drugs, and supporting their medicinal use. However, there has been no systematic evaluation of empirical evidence on the effectiveness of the drug policy changes. A systematic review of studies was conducted to assess the evidence. Studies included peer-reviewed and grey literature. The findings of studies were synthesised to identify common features and outcomes of changes to drug policy, including reductions in overdose, death and other indicators of effectiveness. There were 21 studies that met review criteria, and were of changes that generally aimed to: increase access to treatment for issues with opioid drugs; or, restrict access to opioids and other drugs. The evidence base was limited, and overall showed no major impacts in reducing harms and supporting medicinal use. However, studies of changes focused on increasing access to naloxone suggested the most promising evidence of effectiveness. More research and evaluation is required. With the risk of increased harms associated with opioid drug use in Australian, Canadian and United Kingdom settings, policymakers and other stakeholders need to prioritize measures that support: more research and evaluation; national campaigns publicising awareness of risks associated with opioid drug use and their appropriate medicinal use; and investment in health care services offering more appropriate clinical management of pain and opioid drugs.

Keywords
Policy Effectiveness, Opioids, Australia, Canada, UK.

To address the increasing risk of dependency, overdose and other problems associated with prescription and over-the-counter (OTC) opioids, and to continue to support their medicinal use, such as morphine for acute pain management (Schug et al., 2015), Australian, Canadian and United Kingdom (UK) governments and health organisations have implemented a number of changes to drug policy, legislation and/or regulation. Changes include increasing the availability of opioid agonist treatment in the UK (Weisberg et al., 2014), introducing naloxone formulations to Canadian community-based prevention programs (Fairbairn et al., 2017) and the up-scheduling of codeine in Australia (Therapeutic Goods Administration (TGA), 2018).

Little is known, however, about whether these drug policy changes have been effective or whether

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they create unintended consequences. For example, real-time prescription monitoring can lead to a 'chilling' effect on doctors, who become reluctant to prescribe opioids, even when medically appropriate, for fear of legal consequences (Wang and Christo, 2009). Time and effort may be better spent on other preventative work, such as more investment in access to pain management clinics and services (Larance et al., 2018). Generally, there is a major gap in knowledge about which drug policy changes in Australia, Canada and the UK may or may not work best, and researchers have called for greater understanding of their impact (National Centre for Education and Training on Addiction National Centre for Education and Training on Addiction (NCETA) and Flinders University, 2011; Shand et al., 2013; Larance et al., 2018).

This evidence review seeks to identify which drug policy changes are effective at reducing problems associated with opioids and supporting their medicinal use. We argue that more effective approaches to drug policy can help to reduce the risk of side effects, dependency, overdose, death and other harms associated with opioids, and potentially improve their medicinal application. Our research suggests that an approach to reducing problems with opioids and supporting their medicinal use requires actions beyond drug policy changes, including more research and evaluation, awareness-raising and investment in appropriate treatment and health care.

For the purposes of this review, the term 'drug policy' is generally used to describe legislation, regulation and policy systems and mechanisms and frameworks that make available and monitor the use of opioid drugs. In some cases, such as the discussion of dosage requirements or the scheduling of drugs, specific terms are used instead.

Background

Prescription and OTC opioid drugs are drugs that are derived from or resemble substances in the opium poppy plant, *Papaver somniferum* (Rassool, 2018). Common opioid drugs are medications like codeine, morphine, fentanyl and methadone that are only available with a prescription from a doctor or suitably qualified health professional (Larance et al., 2018). While Australia recently up-scheduled medicines containing codeine to make them prescription-only (Therapeutic Goods Administration (TGA), 2018), at the time of writing, in Canada and the UK, medicines containing codeine remain available over the counter, without a prescription (Nielsen and Van Hout, 2017).

Opioid drugs act on receptors in the central nervous system and peripheral tissues of the human body (Rassool, 2018). Opioids help to relieve pain, produce sedation and create feelings of euphoria and wellbeing (Feng et al., 2012; Rassool, 2018). Opioids can also have adverse affects like constipation, dependency and respiratory problems (Khansari et al., 2013). Opioids are short or long acting and are usually taken in tablet form and swallowed (Rassool, 2018). Other forms of administration include patches and intravenous injection (Alcohol and Drug Foundation, 2020).

Opioids are often used for pain relief after surgery, such as in hospital and dental settings (National Centre for Education and Training on Addiction (NCETA) and Flinders University, 2011), or as part of treatment for cancer-related pain and palliative care (Zeppetella and Davies, 2013; Heneka et al., 2018). In the past, opioids were used for managing chronic pain from arthritis, migraines, nerve damage and other conditions (National Centre for Education and Training on Addiction (NCETA) and Flinders University, 2011). However, evidence suggests that when opioids are used for the long-term management of chronic non–cancer-related pain, the risk of serious harms increases (Chou et al., 2014). There is increasing recognition of the need for different ways to manage chronic pain and the use of opioids, such as trying other non–drug-based pain management approaches, including physical and psychological therapies (Gatchel et al., 2014; Knoerl et al., 2016; Kamper et al., 2014). Opioids are also used as part of opioid substitution therapy (OST) for issues with opioid dependency (Kimber et al., 2015).

In Australia, evidence suggests that the use of prescription opioid drugs is widespread and associated with considerable risk of dependency and overdose. While opioids have clear medicinal benefits and are often used to relieve and manage pain (Schug and Ting, 2017), the rates of dependency and death associated with codeine, oxycodone and fentanyl have all increased (Pilgrim et al., 2015; Roxburgh et al., 2015, 2017). Other countries with healthcare systems similar to Australia's (i.e., liberal welfare states) have experienced problems with opioids. Like the government in Australia, the Canadian and UK governments provide healthcare funding for their populations and similar regulatory and healthcare systems. The regulatory similarities between these countries, and studies that have looked at changes to some of these regulations and their associated outcomes, make them important for comparison, and for generating insights that can inform future work in each country.

In Canada, prescription opioids have contributed to overdose-related hospitalisations (Gomes et al., 2018), they have been associated with increasing

rates of death and, more generally, issues with their use have been associated with major negative impacts on the lives of many people across the country, leading to it being described as an opioid crisis (Belzak and Halverson, 2018). Codeine dependence is a problem in the UK (Kimergard et al., 2017), and the consumption of prescription opioids more generally has increased, although there has not been an increase in reported misuse or drug-related deaths (Weisberg et al., 2014).

A range of factors are likely to be driving increasing harms associated with opioid drugs. The subsidisation of opioid drugs for the treatment of chronic pain is linked to increases in their use (Karanges et al., 2016). A lack of public access to appropriate pain management due to health system barriers—including limited health professional understanding and training in pain management and long travel times to healthcare services in rural and remote areas—is an issue, too, in Australia (Berends et al., 2015; Nicola et al., 2019). Canadian research reports that the country has seen rises in the availability of extremely potent synthetic opioids such as fentanyl on the illegal drug market and that they are increasingly being combined with other substances, which increases the risk of overdose (Belzak and Halverson, 2018). Barriers to accessing support and services associated with poverty and other structural inequalities and stigma are major issues, too (Leece et al., 2019). Problems with fentanyl have also been seen in the UK (Mounteney et al., 2015), as well as issues with appropriate responses to overdoses from opioids, such as sufficient training and knowledge in administering correct medical procedures (Holloway et al., 2018).

Australia, Canada and the UK all have major drug policy frameworks and measures in place to help reduce problems associated with opioids and ensure they can be used as part of treatment for pain management and other medicinal purposes. Frameworks and measures include: drug scheduling (how drugs are categorised according to their level of safety risk—drugs with a low safety risk are generally less tightly controlled than those with a high safety risk); prescribing requirements (e.g., pharmacies reporting monthly on dispensing and applications for authority to prescribe); emergency assistance legislation such as 'good Samaritan' laws to protect members of the public who administer naloxone for preventing overdoses from opioids; drug dosages; pack sizes; advertising; funding for program implementation and/or resources; evaluation and monitoring, including real-time prescription monitoring technology; and national drug strategies (HealthDirect, 2018; Bird et al., 2016; Tobin et al., 2013; Fernandes et al., 2016).

There is a need to assess which drug policy reforms are most effective, however, to reduce harms associated with opioids and support their medicinal use in Australia, Canada and the UK. This review aims to improve understanding of what could be more effective approaches to drug policy for opioids, and help improve the lives of people managing issues with the drugs and their experiences of pain and related problems.

Method

A systematic review can help to identify which policy approaches are effective in the field of drug policy (Burton et al., 2017; El-Jardali et al., 2015) as well as trends, interventions and issues in the management of opioid drugs (Voon et al., 2017). This systematic review synthesises the available evidence to assist policymakers, researchers, practitioners and other stakeholders in Australia, Canada and the UK to make decisions about developing and implementing policy approaches that address problems with opioid drugs and support their medicinal use.

A range of databases were searched and the PRISMA criteria were used to identify, screen and include studies. Databases included: MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Asia Proquest, EBSCO, Social Care Online, Social Sciences Citation Index, Sociological Abstracts EMBASE and ISI Citation Index. Academic databases were searched for studies published up to the end of January 2019. Search strings used were:

- 'opioid' AND 'effective' AND 'intervention' AND ('Australia' OR 'Canada' OR 'United Kingdom').
- 'opioid' AND 'harm' AND 'effective' AND 'intervention' AND ('Australia' OR 'Canada' OR 'United Kingdom').
- ('opioid' OR 'opiate' OR 'oxycodone' OR 'codeine' OR 'buprenorphine' OR 'morphine' OR 'fentanyl' OR 'hydrocodone' OR 'methadone' OR 'meperidine' OR 'tapentadol' OR 'tramadol' OR 'hydromorphone' OR 'dextropropoxyphene') AND 'harm' AND 'effective' AND 'intervention' AND ('Australia' OR 'Canada' OR 'United Kingdom').
- 'opioid' AND ('harm' OR 'hospitalisation' OR 'infection' OR 'overdose' OR 'mortality' OR 'crime' OR 'emergency' OR 'death' OR 'asphyxia' OR 'fall' OR 'fracture' OR 'motor vehicle accident') AND ('misuse' OR 'opioid use' OR 'abuse' OR 'nonmedical use' OR 'extramedical use' OR 'non-prescribed use' OR 'doctor shopping') AND

'effective' AND 'intervention' AND ('Australia' OR 'Canada' OR 'United Kingdom').
- 'opioid' AND 'harm' AND 'effective' AND ('prevention' OR 'regulation' OR 'legislation' OR 'intervention' OR 'policy' OR 'response' OR 'communication' OR 'treatment' OR 'initiative' OR 'harm reduction' OR 'supply' OR 'scheduling' OR 'demand') AND ('Australia' OR 'Canada' OR 'United Kingdom').
- 'opioid' AND 'effective' AND ('use' OR 'medicinal' OR 'therapeutic' OR 'management' OR 'pain' OR 'overdose response' OR 'take-home naloxone' OR 'treatment' OR 'guidelines' OR 'drug therapy' OR 'administration' OR 'post-operative' OR 'chronic pain' OR 'chronic non-cancer pain') AND ('Australia' OR 'Canada' OR 'United Kingdom').

The studies included were empirical in approach (mostly quantitative and literature review studies), conducted in English, focused on Australia, Canada and/or the UK and assessed the effectiveness of drug policy in reducing problems associated with opioids and supporting their medicinal use. Studies had to consider how effective were changes to drug policy frameworks and measures such as the rescheduling of opioids and/or treatment drugs, funding for program implementation, emergency assistance laws, prescribing requirements and similar activities. A hierarchy of evidence was also used to preferentially select higher-quality studies (Burton et al., 2017). Higher-quality studies were defined as those which sat higher up the evidence hierarchy, such as randomised control trials (RCTs) and natural experiments. The hierarchy was in the following order of highest to lowest: meta-analyses, systematic reviews and expert reviews; RCTs and natural experiments; modelling; observational studies; surveys/fieldwork; and background information (Burton et al., 2017). Studies were excluded if they did not assess the effectiveness of drug policy, legislation and/or regulation in reducing problems associated with opioids and supporting their medicinal use, were not in English, did not focus on Australia, the UK or Canada and/or were not empirical in approach.

The grey literature search included documents published on the websites of Australian, Canadian and UK federal and state government departments and non-profit agencies and peak bodies that have performed policy development and related work. The criteria for studies included and excluded were the same as those used for academic work.

Results of the review are provided in the PRISMA diagram (see Figure 1). The results were analysed to identify characteristics of effective changes to drug policy for reducing problems with opioids and supporting their medicinal use. See Table 1 for the results of studies included in the review.

This review used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method to rate the quality of the evidence identified by the search of academic and grey literature (Guyatt et al., 2008). The GRADE method is a recognised approach to assessing evidence associated with the effectiveness of drug policy (Burton et al., 2017). Using GRADE, studies may begin as high quality or low quality, but confidence in the evidence can lessen or increase based on specific reasons, such as the methodological limitations or strengths of a study (Burton et al., 2017). Each study reviewed in this paper was given a quality rating according to the GRADE criteria (see Figure 2) and the following factors: the nature of the evidence and study design used; the impact of the change to policy, legislation and/or regulation on study outcome measures; the coverage/reach of change evaluated; and barriers to implementation.

The review also analysed a small number of studies using both quantitative and qualitative research methods. Including qualitative research that explores the experiences of people and communities from hard to reach settings, such as those experiencing homelessness and who inject drugs, can help provide another option for engaging people who may not participate in other forms of research, and help to develop greater nuance and complexity in understanding healthcare experiences (Brener et al., 2013). Researchers in health have also established that qualitative and quantitative studies can be used in a systematic review to synthesise evidence that helps guide more effective implementation of policy and practice (Thomas et al., 2004).

Results

The review identified a total of 9,970 records from the peer-reviewed (2,098) and grey literature (7,872). Of the records identified, there were 16 peer-reviewed and five grey literature studies that met the review's inclusion criteria (Table 1).

The 21 studies focused on Australia (8), Canada (8), Scotland (1), as well as England, Wales and Northern Ireland (1). Two studies assessed work in multiple countries: the United States (US), Australia and the UK; and Australia, New Zealand and the UK. The studies all assessed the effectiveness of policy approaches used to reduce problems associated with opioids and support their medicinal

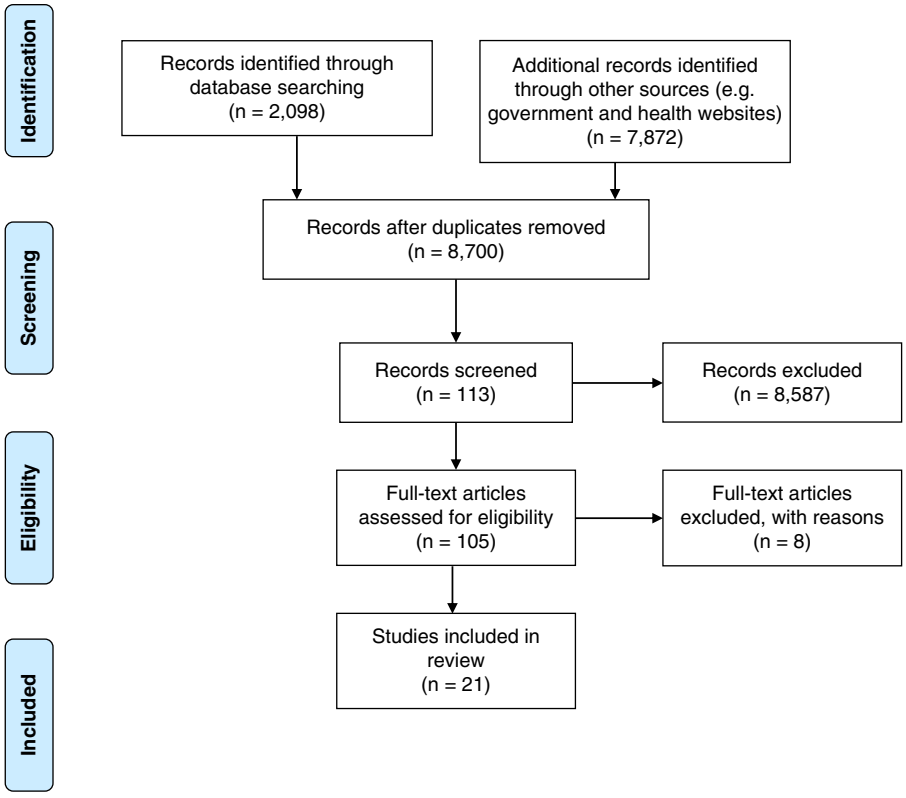

Figure 1: PRISMA flow diagram (Moher et al., 2009).

use in Australia, the UK or Canada. Quantitative and qualitative techniques were used in the studies.

All the studies explored approaches to policy changes for the legal access of opioid drugs and/or naloxone or cannabis. The studies were of approaches to policy changes that generally aimed to either increase access to treatment for issues with opioid drugs or restrict access to opioids and other drugs. The major features of these approaches were policy changes that addressed: drug scheduling/classification, funding for access to treatment drugs, prescribing practices, administration of a drug, advertising, dosage, pack sizes and/or related legislative activities. The major features are summarised in Table 2.

Access to treatment

Overall, 11 quantitative studies found increased access to treatment and/or support for issues with opioid drugs and/or related issues (Bird et al., 2016; Chronister et al., 2018; Health Canada, 2018; Information Services Division, 2018; Lucas and Walsh, 2017; Mahoney, 2018; Ministry of Mental Health and Addictions, 2019; Office of the Provincial Health Officer, 2019; O'Halloran et al., 2017; Olsen et al., 2015; Pricolo and Nielsen, 2018). The 11 studies were mostly focused on naloxone for the treatment of issues with opioids. Research was conducted in the following settings: legislative, prisons and hospitals and drug treatment facilities, including those that were part of community centres and pharmacies.

Broadly, the 11 studies found that government, health, pharmaceutical, community and/or other related services, and/or members of the public, had a greater ability to provide treatment and/or support. Five of the 11 studies identified reductions in deaths and other harms, and four of these studies also found increased understanding and capacity to increase access to treatment. Four studies found increased understanding and capacity to increase access to treatment, and two of these also identified investments in training and research. Of the remaining two studies, one found that baseline data had been established, and the second identified a change in perception regarding the potential of replacing opioids with cannabis for pain management.

In accordance with the GRADE criteria, six of the 11 studies were strong in quality due to their use of

Table 1. Summary: Studies of changes to drug policy, legislation and regulation to reduce problems associated with prescription and OTC opioids and support their medicinal use in Australia, Canada and the United Kingdom (see Attachment 1 for detailed table of studies).

Author and year	Country	Policy change	Outcome	Quality
Chronister et al., 2018	Australia	Increasing access to naloxone by modelling a health service program on 'established international overdose education programs and the Expanded Naloxone Availability in the Australian Capital Territory program'	Significant improvements in knowledge and attitudes after training. A lot was retained at follow-up, 'particularly regarding feeling informed enough (97%) and confident to inject naloxone (100%)'	High
Deacon et al., 2016	Australia	Rescheduling alprazolam from Schedule 4 to Schedule 8, making its access more restricted	Reductions in alprazolam use; no change in other substance use; and an increase in the cost of street alprazolam	High
Bird et al., 2016	Scotland (UK)	Introduction of the 'centrally funded, coordinated and evaluated National Naloxone Policy (NNP)' in Scotland, including take-home naloxone (THN) as a 'funded public health policy', with evaluation	The study found an associated 36 percent reduction in the 'proportion of opioid-related deaths that occurred in the 4 weeks following release from prison'	Moderate
Cairns et al., 2016	Australia	The rescheduling of codeine combination analgesics in May 2010. The analgesics were 'up-scheduled to Schedule 3 ("Pharmacist Only Medicine"—pharmacist required in sale, cannot be self-selected) and Schedule 4 ("Prescription Only Medicine"), depending on tablet strength and pack size'	No significant change. Misuse of codeine combination products 'appeared to be increasing in Australia', and the rescheduling in 2010 'failed to curb this increase'	Moderate
Fernandes et al., 2016	Canada	Publication of Canadian clinical practice guidelines for use of opioids in chronic non-cancer pain (May 2010) and implementation of Ontario's *Narcotics Safety and Awareness Act* (*NSAA*; November 2011)	A decline in opioid prescribing rates among Ontario Drug Benefit beneficiaries, however, there was no significant change in rates of opioid-related hospitalisations	Moderate
Fischer et al., 2013	Canada	Major policy and related interventions implemented ad hoc, including the *Narcotics Safety and Awareness Act* (*NSAA*) and a 'prescription monitoring program (PMP) centrally collecting information on POs [prescription opioids] dispensed by prescribers and patients', and the delisting of Oxycontin	Potentially, a major decrease in non-medical use of prescription opioids in Ontario adults, but other factors may have been involved, such as 'extensive media reporting'	Moderate

Hooper et al., 2009	Australia	Regulation placing additional requirements on prescription and dispensing, including: 1) monthly reporting; 2) application for authority to prescribe being required where alprazolam is prescribed in excess of four weeks to patients who are also prescribed opioid medication; 3) patients enrolled in methadone or buprenorphine maintenance programs being required to have explicit approval to receive prescriptions of alprazolam; and 4) medical practitioners required to be notified not to prescribe alprazolam to patients receiving benzodiazepines and/or opioids from another medical practitioner	Reductions in alprazolam prescribing in Tasmania associated with GP education, coupled with changes to prescribing regulations that made them more stringent	Moderate
Larance et al., 2015	Australia	Differing approaches to introducing policies for BNX film across Australian states. In South Australia, the change from tablets to film was mandated, while in Victoria and New South Wales it was less stringent	Perception of 'restricted choice in medication may have undermined initial acceptance in' South Australia	Moderate
Lucas and Walsh, 2017	Canada	Introduction of regulation allowing multiple licensed producers of cannabis	Self-reports that cannabis was: 1) perceived to be an effective medicinal treatment for diverse conditions, with pain and mental health the most prominent; 2) used a lot as a substitute for prescription drugs, particularly pharmaceutical opioids, benzodiazepines and antidepressants; 3) substituted for alcohol, cigarettes/tobacco and illicit drugs; 4) accessed from illegal/unregulated sources in addition to access via licensed producers (LPs); and 5) associated with a charge for participants when they received a medical recommendation to use the drug, with some paying $300 or more	Moderate
National Drug and Alcohol Research Centre NDARC, 2012	Australia	In Tasmania: regulatory change and GP education to reduce prescribing of alprazolam with opioids (more restrictions on prescribing through greater authorisation of and reporting on prescribing). International literature: use of prescription monitoring programs	Reduction in the number of individuals receiving alprazolam with opioids following the interventions. Evidence also suggests that there is a need for effective regulatory interfaces to 'take on more than a punitive approach, and to engender a shared sense of sound clinical governance from the industry partners, prescribers, pharmacists, and educators'	Moderate

Author and year	Country	Policy change	Outcome	Quality
O'Halloran et al., 2017	England, Wales, Northern Ireland (UK)	A change to UK regulations that allowed naloxone to be 'supplied by drug treatment services (including prison and pharmacy-based services) without a prescription. Previously, it could only be prescribed either directly to a named patient or through a PGD'	Baseline data have been established for 'monitoring the impact of the 2015 UK policy change to improve take-home naloxone access'	Moderate
Olsen et al., 2015	Australia	ACT Health, through the provision of financial resources and creating an 'enabling policy environment' for a naloxone program, reinforced a broader movement whereby 'governments in many of the nations with naloxone programs have enacted laws (such as specific Good Samaritan legislation) to support access to naloxone outside the medical setting and protect members of the public who administer it in an overdose emergency'	Training of program participants to administer THN in 'appropriate circumstances'. There were also 57 separate episodes of program-issued naloxone being used without adverse events. Participants reported 'a sense of empowerment, and positive emotional impacts associated with program participation'. The program contributed another model to the field	Moderate
Pricolo and Nielsen, 2018	Australia	Naloxone was made more accessible through 'down-scheduling'	Three main results: 1) 'a submission to reschedule naloxone was successfully instigated by a member of the public'; 2) the 'change may help remove access barriers to naloxone by allowing pharmacist supply'; and 3) 'cost, pharmacist training, existing naloxone formulation, presentation and packaging remain challenges to address'	Moderate
Schleihauf et al., 2018	Canada	The introduction of a prescription monitoring program and, much later, of changes to prescribing guidelines	The establishment of monitoring approaches to identify trends in population-level effects (whether intended or unintended) of interventions related to opioid prescribing	Moderate

Socias et al., 2017	Canada	There were several regulatory changes introduced to the 'MMT program in the province of British Columbia': methadone replacement with a 'pre-mixed cherry flavoured and 10-times more concentrated methadone solution'; persons on methadone were 'transitioned to prescriptions of an equivalent dose of the new formulation'; and the restriction of 'methadone home deliveries to only "extraordinary circumstances" (e.g., clients with severe mobility restrictions) and with a written authorization by the prescribing physician'	After the regulatory changes, there were 'immediate increases in illicit heroin injection and decreases in antiretroviral therapy (ART) adherence'	Moderate
Tobin et al., 2013	Australia, New Zealand, UK	Changes to: scheduling (became pharmacy-only); dosage (increased); pack size; advertising (not permitted)	Comparison with recommendations from New Zealand and the UK suggests that 'actions in response to OTC codeine misuse were appropriate given the available evidence of misuse and harm, but highlights opportunities to utilise additional regulatory levers	Moderate
Health Canada, 2018	Canada	Regulatory changes allowing importation and sale of drugs not approved in Canada, but approved in the US, the European Union or Switzerland for 'urgent public health needs', including some drugs used for treating opioid-use disorder and other urgent public health needs. Actions supporting proposed regulatory changes, including mandatory warning stickers, medication label updates and restrictions on advertising and marketing	Establishment of work to support reductions in harm, increased access to treatment and dedicated monitoring	Low

Author and year	Country	Policy change	Outcome	Quality
Information Services Division, 2018	Scotland, UK	Introduction of the National Naloxone Programme in Scotland from November 2010, which allowed provision of naloxone to those at risk of opioid overdose once they had undergone training. The training was also available to family, friends and service workers. In late 2015, supply 'via a third route (dispensing in a community pharmacy via prescription) increased in some NHS [National Health Service] Boards following two key changes in the regulatory and policy frameworks': 1) changes aimed to make THN (take-home naloxone) more widely available by allowing direct THN supply to family members or carers for administration in the event of opioid overdose; and 2) stopping the central reimbursement of the cost of THN kits and NHS Boards assuming 'responsibility for the funding of THN supplies to opioid users at risk of accidental overdose'	An increase in distribution of naloxone kits and a reduction in deaths associated with opioids after the implementation of the program	Low
Mahoney, 2018	US, Australia, UK	Proactive changes to legislation allowing easier access to naloxone	Reductions in deaths and other harms associated with the introduction of proactive legislation in Australia and the UK, and easier access to naloxone, to prevent harms associated with opioids	Low
Ministry of Mental Health and Addictions, 2019	Canada	Changes to prescription drug legislation in 2016 allowing the non-prescription emergency use of take-home naloxone; opioid agonist treatment clinic fee reimbursements; new legislation to prevent the illegal production of illicit opioids; training and treatment pilots	Increases in naloxone kit distribution, awareness-raising and investment in services, programs, research, training and other initiatives	Low
Office of the Provincial Health Officer, 2019	Canada	Changing prescribing legislation to allow the wide distribution of publicly funded naloxone and supporting activities, including 'establishing overdose prevention services and new supervised consumption services, and offering drug checking for people who use drugs'. Also, increasing access to evidence-based treatment	Since actions were taken to address the 'overdose crisis': 'The combined impact of these interventions has been shown to have averted 60 per cent of all possible overdose deaths since the declaration of the public health emergency.' Evidence suggests that 'for every 10 naloxone kits that are used, one death has been averted'	Low

GRADE (Guyatt et al. 2008)

Quality rating	Reason
Very low	Any estimate of effect is very uncertain
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
High	Further research is very unlikely to change our confidence in the estimate of effect

Figure 2: GRADE (Guyatt et al., 2008).

relatively rigorous and consistent methodologies (Guyatt et al., 2008). The studies used statistical analysis of government mortality records, blood samples, health and community services data and analyses of survey data to assess associated policy outcomes. One of the studies was of a high quality due to a consistently strong methodological approach, with further research unlikely to change the

Table 2. Main features associated with drug policy, legislation and regulation changes to reduce problems associated with prescription and OTC opioids and to support their medicinal use in Australia, Canada and the United Kingdom.

Approach	Main feature(s)	Supporting studies
Legislative and/or regulatory	Changes to one and/or a number of the following: • dosage • pack size • advertising • scheduling and/or prescribing regulations for opioids and/or treatment-related drugs • legislation beyond medical settings—for example, emergency (good Samaritan laws)	Bird et al., 2016; Cairns et al., 2016; Chronister et al., 2018; Deacon et al., 2016; Fernandes et al., 2016; Fischer et al., 2013; Hooper et al., 2009; Larance et al., 2015; Lucas and Walsh, 2017; Mahoney, 2018; O'Halloran et al., 2017; Olsen et al., 2015; Pricolo and Nielsen, 2018; Socias et al., 2017; Tobin et al., 2013
Policy supporting the change	National and/or state and/or territory policy supporting the change	Bird et al., 2016; Chronister et al., 2018; Fernandes et al., 2016; Fischer et al., 2013; Larance et al., 2015; Olsen et al., 2015
Funding	Government-funded reimbursements for naloxone kits, workforce education and training and/or information resources	Bird et al., 2016; Chronister et al., 2018; Olsen et al., 2015
Evaluation and monitoring	Scientific and appropriately designed evaluation of policy implementation, training and/or related activities; prescription monitoring programs	Bird et al., 2016; Chronister et al., 2018; Fischer et al., 2013; Hooper et al., 2009; Olsen et al., 2015
Workforce education and training	Use of internationally established overdose education programs for the training of health professionals (e.g., drug treatment facilities, community pharmacies) and members of the community who administer naloxone in emergency situations	Bird et al., 2016; Chronister et al., 2018; O'Halloran et al., 2017; Olsen et al., 2015
Clinical guidelines	Development of clinical guidelines for use of opioids in the management of non–cancer-related pain	Fernandes et al., 2016

confidence of its conclusions, and it used statistical analysis of service data.

The remaining five studies were of a low quality due to their lack of information demonstrating their methodological approaches. Further research is likely to have a major change on findings and conclusions. The studies were mostly grey literature, and they analysed policy and legislative documents, service data and trends in drug usage.

Restrictions on opioids and other drugs

Ten of the quantitative studies identified increased restrictions on opioid and/or benzodiazepine drugs (Cairns et al., 2016; Deacon et al., 2016; Fernandes et al., 2016; Fischer et al., 2013; Hooper et al., 2009; Larance et al., 2015; Schleihauf et al., 2018; Socias et al., 2017; Tobin et al., 2013; National Drug and Alcohol Research Centre NDARC, 2012). The studies were mostly focused on opioids, including prescription opioids and OTC codeine, buprenorphine-naloxone (opioid agonist) and alprazolam (benzodiazepine). Restrictions were mostly achieved as part of drug scheduling changes (up-scheduling) and increased requirements and reporting for prescribing, including the use of prescription monitoring programs. Research was conducted in drug treatment facilities, using prescription data, prescribing regulation and drug scheduling, legislation and policy development settings.

The studies identified various outcomes: reductions in prescribing, potential major reductions in non-medical use, the establishment of prescription monitoring and no major changes in opioid use, with one study examining the 'up-scheduling' of codeine combination analgesics to Schedules 3 and 4 (depending on strength and tablet size), suggesting a potential increase in codeine use. One study found that restrictions made to the availability of OTC codeine were appropriate (Tobin et al., 2013).

Two studies found that policy changes were able to replace certain opioid drugs in opioid substitution therapy (OST) (Larance et al., 2015; Socias et al., 2017). The changes were associated with varied levels of treatment acceptance, some potential undermining of acceptance and decreases in treatment adherence and increases in illicit heroin injection.

All 10 studies (Cairns et al., 2016; Deacon et al., 2016; Fernandes et al., 2016; Fischer et al., 2013; Hooper et al., 2009; Larance et al., 2015; Schleihauf et al., 2018; Socias et al., 2017; Tobin et al., 2013; National Drug and Alcohol Research Centre NDARC, 2012) were strong in quality due to their use of relatively rigorous and consistent methodologies (Guyatt et al., 2008). However, nine of the studies (Cairns et al., 2016; Fernandes et al., 2016; Fischer et al., 2013; Hooper et al., 2009; Larance et al., 2015; Schleihauf et al., 2018; Socias et al., 2017; Tobin et al., 2013; National Drug and Alcohol Research Centre NDARC, 2012) were likely to benefit from further research that may change confidence in their estimates of effect and conclusions. Methodological approaches included: statistical analysis of health service and program data, prescribing data and coronial data; and analysis of literature on prescribing practices and public documents related to regulatory and legislative approaches. One study (Deacon et al., 2016) was of a high quality due to a consistently strong methodological approach, with further research unlikely to change the confidence of its conclusions, and it used statistical analysis of service data.

Studies by country

Of the 21 the studies, eight were focused on Australia (Cairns et al., 2016; Chronister et al., 2018; Deacon et al., 2016; Hooper et al., 2009; Larance et al., 2015; National Drug and Alcohol Research Centre NDARC, 2012; Olsen et al., 2015; Pricolo and Nielsen, 2018). The Australian studies focused on naloxone (Chronister et al., 2018; Olsen et al., 2015; Pricolo and Nielsen, 2018), alprazolam (Deacon et al., 2016; Hooper et al., 2009), opioids and alprazolam (National Drug and Alcohol Research Centre NDARC, 2012), codeine (Cairns et al., 2016) and buprenorphine-naloxone (Larance et al., 2015). Five of the studies explored greater restrictions on access to opioids, benzodiazepine drugs and a formulation of buprenorphine-naloxone (Deacon et al., 2016; Hooper et al., 2009), opioids and alprazolam (National Drug and Alcohol Research Centre NDARC, 2012), codeine (Cairns et al., 2016) and buprenorphine-naloxone (Larance et al., 2015), although in the last study a replacement formulation of buprenorphine-naloxone was introduced. The restrictions were achieved mostly through changes to drug scheduling (up-scheduling) and prescribing practices (greater reporting and authority to prescribe).

The studies resulted in varied outcomes: no major changes in codeine misuse observed, and a potential increase in misuse of the drug (Cairns et al., 2016); reductions in alprazolam use, but no change in other substance use and an increase in the cost of street alprazolam (Deacon et al., 2016); reductions in alprazolam prescribing (Hooper et al., 2009) and the number of individuals receiving alprazolam with opioids in Tasmania (National Drug and Alcohol Research Centre NDARC, 2012); and perceived

restriction of choice of medication that may have undermined OST treatment acceptance in South Australia (Larance et al., 2015).

Three Australian studies examined increased access to treatment for issues with opioids (Chronister et al., 2018; Olsen et al., 2015; Pricolo and Nielsen, 2018). Increased access to treatment was achieved through changes to drug scheduling for easier access to naloxone (Olsen et al., 2015; Pricolo and Nielsen, 2018) and provision of financial resources, program development based on international evidence and an 'enabling policy environment' for a naloxone program in the Australian Capital Territory, including greater engagement with 'good Samaritan' legislation (Chronister et al., 2018). The studies found improvements in the ability to administer naloxone, prevention of adverse events with the use of naloxone and that a submission can be made by the public to reschedule naloxone and potentially make it more accessible.

Two studies also considered Australia in relation to the US and the UK (Mahoney, 2018), and New Zealand and the UK (Tobin et al., 2013). The studies were of improving access to naloxone through legislative change (e.g., down-scheduling and use of laws permitting use of naloxone in emergency situations) (Mahoney, 2018) and restricting access to OTC codeine through up-scheduling, dosage changes and restrictions on advertising (Tobin et al., 2013). The impacts identified by the studies were reductions in deaths and other harms from increased access to naloxone, and that Australian responses to issues with OTC codeine were appropriate.

Eight studies were conducted in Canada (Fernandes et al., 2016; Fischer et al., 2013; Health Canada, 2018; Lucas and Walsh, 2017; Ministry of Mental Health and Addictions, 2019; Office of the Provincial Health Officer, 2019; Schleihauf et al., 2018; Socias et al., 2017). Canadian studies were of drug policy reforms to increase access to treatment drugs including naloxone, methadone and potentially cannabis (Lucas and Walsh, 2017; Health Canada, 2018; Ministry of Mental Health and Addictions, 2019; Office of the Provincial Health Officer, 2019), and restrictions on access to opioids (Fernandes et al., 2016; Fischer et al., 2013; Schleihauf et al., 2018; Socias et al., 2017). Restrictions on opioids included reduced availability of methadone in the home, the introduction of prescription monitoring and greater reporting on opioids and delisting of oxycontin. The studies of restrictions found reductions in opioid prescribing but no change in opioid hospitalisations (Fernandes et al., 2016), potential reductions in non-medical use of opioids (Fischer et al., 2013), the establishment of monitoring to identify opioid-related trends (Schleihauf et al., 2018) and increases in illicit heroin use and treatment adherence (Socias et al., 2017).

Greater access to treatment drugs was created by laws permitting the use of naloxone by laypersons in emergency situations (Ministry of Mental Health and Addictions, 2019), changes to prescribing legislation to allow wide distribution of publicly funded naloxone and associated funding and service investments (Office of the Provincial Health Officer, 2019), and changes to legislation to allow multiple producers of cannabis (Lucas and Walsh, 2017) and the availability of other treatment drugs from overseas (Health Canada, 2018). The studies of increasing access to treatment found: greater capacity to reduce harms, increased access to treatment and trend monitoring (Health Canada, 2018); changed perceptions of the potential for cannabis to be used medicinally as an alternative to opioids (Lucas and Walsh, 2017); greater distribution of naloxone, more awareness-raising activities and investments in services, programs, research and related work (Ministry of Mental Health and Addictions, 2019); and reductions in overdoses and deaths (Office of the Provincial Health Officer, 2019).

The three studies based in the UK were of changes to legislation to allow naloxone to be supplied by drug treatment services without a prescription in England, Wales and Northern Ireland (O'Halloran et al., 2017), and funded implementation and evaluation of the National Naloxone Programme in Scotland (Bird et al., 2016; Information Services Division, 2018), including distribution of take-home naloxone. The studies found reductions in opioid-related deaths (Bird et al., 2016; Information Services Division, 2018) and the establishment of baseline data for monitoring (O'Halloran et al., 2017).

Discussion

This review has found that the evidence base about the effectiveness of changes to drug policy in reducing problems associated with opioid drugs and supporting their medicinal use in Australia, Canada and the UK shows there are promising areas for future work. The evidence base is, however, very limited in its applicability.

The evidence base is relatively small and, while of a strong quality, it suggests that the major outcomes associated with changes to drug policy were: an increased ability to provide treatment for issues with opioid drugs in services and the community; and greater restrictions on prescribing practices. Overall, there is no conclusive evidence that any changes

were associated with major reductions in overdoses, harms and other problems resulting from prescription and OTC opioid drugs, or with supporting their medicinal use.

A major strength of the evidence base is that most studies were of a strong methodological quality, particularly those exploring restrictions on opioids and other drugs. The strong methodological quality is due to consistent and rigorous approaches in the use of statistical and other analysis of prescribing data, coronial mortality records, blood samples, health and community services data and government and academic literature. Another strength is that the evidence base includes some studies conducted at a national level—mostly in Australia and Canada—as well as studies of recently implemented policy changes, and specifically those relating to naloxone access in Canada. Generally, the studies focused on the specific regions of: Scotland; the Australian Capital Territory, Tasmania and New South Wales; and British Columbia, Ontario and Nova Scotia. The studies provided important information about the effectiveness of changes and their impacts in particular areas of each country. Some studies also included findings from qualitative research involving people who may not participate in broader drug-related surveys and research due to issues such as stigma and homelessness, helping to broaden understanding of the complexity of issues associated with prescription and OTC opioids. Additionally, the inclusion of grey literature helps balance potential gaps in academic knowledge.

However, there are major limitations in current evidence, the first of which is a lack of coverage in the studies reviewed. Most of the studies in Australia, Canada and the UK were not conducted at the national level, and most were in Australia and Canada. Without national-level knowledge in each country, it is harder to determine which reforms to drug policy, or other actions, are more likely to help improve the management of prescription and OTC opioid drugs with a broad range of people and communities that access similar health systems. Also, the evidence base does not contain comprehensive information about changes impacting on the full range of opioid drugs across all countries. Codeine remains available over the counter in Canada and the UK. No study was identified in the UK that focused primarily on morphine, oxycodone, fentanyl or other relatively more powerful opioids. Australian research also explored restrictions on access to benzodiazepines and their associated impacts on opioid use, but this review did not identify similar work in Canada and the UK. Limited study of the full range of opioid drugs reduces the ability to generate insights for improving their management with a greater range of people.

Furthermore, a lack of evidence from the UK suggests that the strongest conclusions, based on the evidence from the three countries, relate to impacts, issues and opportunities associated with increasing access to naloxone to address overdoses from opioids, and in particular community settings.

The second major limitation is that, while most studies of access to treatment were of a strong methodological quality, overall, they were relatively weaker in quality when compared with the studies of restricting access to opioids. The difference in quality suggests that further research is required on access to treatment to improve the reliability of findings.

Another limitation relating to the quality of evidence is that grey literature, while able to balance academic literature, can be problematic. A lack of peer reviews, limited methodological quality and possible errors in the grey literature reduce the reliability of its conclusions (Adams et al., 2017). Issues with the grey literature were reflected in the studies reviewed.

Given the limitations of the evidence base, the findings of this review are most relevant to Australia and Canada, and to actions focused on naloxone and prescription opioid drugs in a broad sense.

Despite the relatively small evidence base and its limitations, it suggests useful and important options for future work. Options from a review of evidence are a recognised approach in relevant studies of drug policy (Burton et al., 2017). Based on the findings of this review, it is reasonable to assume that there are three broad options relevant to policy work seeking to reduce problems with opioid drugs and support their medicinal use in Australia, Canada and the UK: 1) increasing access to treatment for issues associated with opioid drugs, such as the use of naloxone, opioid substitution therapy and more effective pain management; 2) restricting access to opioid drugs through more prescribing requirements and up-scheduling while still ensuring their availability for medicinal use; and 3) actions beyond drug policy, including more research and evaluation, and supporting greater investment in more effective pain management and drug-dependency services.

Most evidence suggests that the first option—increasing access to treatment for issues with the full range of opioid drugs—has been found ineffective. Option one is, however, the most promising option (see Table 3, 4) because most studies of access to treatment focused on naloxone, and many of these studies showed reductions in overdoses, deaths and other harms. The use of option one is advisable if, at this stage, work focuses on naloxone in overdose

Table 3. Options for drug policy, legislation and regulation to help reduce problems associated with prescription and OTC opioids and support their medicinal use in Australia, Canada and the United Kingdom.

Option	Approach	Potential features
1	Increasing access to treatment for dependency, overdose, pain management and other issues associated with opioid drugs	National-level investment in programs for: take-home naloxone (including legislative changes for access without a prescription in emergency situations), evaluation, training and related activities; and GP training for more prescribing of OST to treat dependency on codeine, oxycodone and other prescription opioids
2	Restricting access to opioid drugs through prescribing practices and drug scheduling, while still making them available for medicinal use	Placing greater requirements on prescribers (e.g., applications for authority to prescribe); up-scheduling opioid drugs (changing opioid drug categorisation to a higher level of safety risk for tighter control)
3	Taking actions beyond changes to drug policy, legislation and regulation	National-level research and evaluation into opioid drug use and effective chronic pain management; greater investment in more effective pain management and drug-dependency services; reducing barriers to health services; national-level education and awareness campaigns

situations, as it is not likely to reduce overall levels of opioid use—an issue noted previously by researchers (Campbell et al., 2019). Once more evidence of effectiveness has been established through work focused on option one, it may be beneficial to expand and evaluate the treatment options for a broad range of opioid drugs at a population level across Australia, Canada and the UK. Such work could include increasing the ability of GPs to make greater use of opioid substitution therapy with patients, including the use of methadone and buprenorphine, as currently there is a major gap in the evidence base relating to the impacts of this kind of approach.

The second option is restricting access to opioid drugs in Australia, Canada and the UK (see Table 3) while ensuring medicinal access for those who need them. At this stage, the evidence base finds that changes to restrict access to opioid drugs have been ineffective, and there have been varied outcomes, with a small number of studies suggesting potential harms. Therefore, the second option is less promising, and is not advised. However, given the relatively higher-quality research methods used in studies of restricting access to opioids, learning from their methods may have applicability for work on naloxone and other related activities.

The third option is reducing harms associated with opioid drugs and supporting their medicinal use by taking action beyond changes to drug policy, due to the lack of effectiveness associated with this work, as established by the evidence base (see Table 3). Potential reforms in drug policy could focus on developing medical approaches that are closely linked to opioid drug management—specifically: supporting more research and evaluation at a national level, greater investment in healthcare services, including those for pain management and drug dependency, and enhanced use of education and awareness-raising initiatives. It may be best to explore the third option after assessing the viability of implementing actions from the first option identified in this review.

More research and evaluation activities into the use of opioid drugs need to be conducted at a national level across Australia, Canada and the UK to improve the evidence base. Research will benefit from a focus on a better understanding of opioid drug use; the clinical, social and economic aspects of pain, including chronic pain management and mental health (National Pain Summit Initiative, 2011; Department of Health, 2019); and more reliable information on the full extent and related experiences of chronic pain and its effective management, including its relationship to ageing populations (Fayaz et al., 2016; Wilson et al., 2015). Through evaluation and data-gathering, it is also necessary to more clearly establish the impacts from real-time prescription monitoring (Larance et al., 2018). Much remains unknown about how real-time prescription monitoring

Table 4. Detailed information about studies of changes to drug policy, legislation and regulation to reduce problems associated with prescription and OTC opioids and to support their medicinal use in Australia, Canada and the United Kingdom.

Author and year	Title	Source	Country	Population (s)	Sampling method	Policy approach	Outcome	Quality
Bird et al., 2016	Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: A before (2006–10) versus after (2011–13) comparison	*Addiction*	Scotland (United Kingdom)	People at risk of overdose from opioids	The study used data on opioid-related deaths (ORDs) from the National Records of Scotland and: 1) ran '$\chi 2$ tests on one degree of freedom to compare the proportion of prison release opioid related deaths between 2006 and 2010, as baseline, and 2011–13, the first 3 years of Scotland's NNP'; 2) looked at prison release or hospital discharge ORDs; and 3) computed '95% confidence intervals (CI) for the reduction in primary and secondary outcomes'	Introduction of the 'centrally funded, coordinated and evaluated National Naloxone Policy (NNP)' in Scotland. The policy introduced take-home naloxone (THN) as a funded public health policy, with formal evaluation	The study found that the program was associated with a '36% reduction in the proportion of opioid-related deaths that occurred in the 4 weeks following release from prison'	Moderate
Cairns et al., 2016	The impact of codeine re-scheduling on misuse: A retrospective review of calls to Australia's largest poisons centre	*Addiction*	Australia	People experiencing issues associated with codeine	A 'retrospective review of calls regarding codeine misuse made to the New South Wales Poisons Information Centre (NSWPIC, Australia's largest poisons centre), 2004–15'. The study used software to 'quantify the average annual change in calls, and whether there was a significant change in trend at any time, including following rescheduling'	The rescheduling of codeine combination analgesics in May 2010. The analgesics were 'up-scheduled to Schedule 3 ("Pharmacist Only Medicine"—pharmacist required in sale, cannot be self-selected) and Schedule 4 ("Prescription Only Medicine"), depending on tablet strength and pack size'	No significant change in trend was observed. The study suggested that misuse of codeine combination products 'appeared to be increasing in Australia' and that the rescheduling in 2010 'failed to curb this increase'	Moderate

Chronister et al., 2018	Findings and lessons learnt from implementing Australia's first health service based take-home naloxone program	*Drug and Alcohol Review*	Australia	People experiencing issues associated with opioids and receiving education and take-home naloxone	Participants were recruited from two facilities in Sydney between July 2012 and March 2014, and among the 83 individuals who used opioids and participated in the project, (67) (81%) were recruited at KRC and 16 (19%) at TLC	Increasing access to naloxone by modelling a health service program on 'established international overdose education programs and the Expanded Naloxone Availability in the Australian Capital Territory program'	Significant improvements in knowledge and attitudes after training. A lot was retained at follow-up, 'particularly regarding feeling informed enough (97%) and confident to inject naloxone (100%)'	High
Deacon et al., 2016	Alprazolam use and related harm among opioid substitution treatment clients: 12 months follow up after regulatory rescheduling	*International Journal of Drug Policy*	Australia	People experiencing issues associated with benzodiazepines (alprazolam) and opioids and in treatment	Participants were recruited from three public specialist opioid substitution therapy (OST) clinics in Sydney. A linear mixed-models approach was used to analyse changes in alprazolam and other benzodiazepine use from 57 OST treatment clients' self-reported patterns of drug use, drug availability and mental and physical health	Rescheduling alprazolam from Schedule 4 to Schedule 8, making its access more restricted	Reductions in alprazolam use; no change in other substance use; and an increase in the cost of street alprazolam	High
Fernandes et al., 2016	High-dose opioid prescribing and opioid-related hospitalization: A population-based study	*PLOS ONE*	Canada	People accessing the Ontario Drug Benefit (ODB) who were aged 15 to 64 years from 2003 to 2014	A time-series intervention (interrupted) analysis was conducted of 'a cohort of individuals aged 15 to 64 eligible for drug coverage through the Ontario Public Drug Program (OPDP) between January 1st, 2003 and December 31st, 2014'	Publication of Canadian clinical practice guidelines for use of opioids in chronic non-cancer pain (May 2010) and implementation of Ontario's *Narcotics Safety and Awareness Act* (*NSAA*; November 2011)	The clinical practice guidelines led to a decline in opioid prescribing rates among ODB beneficiaries, however, the 'guidelines and subsequent Ontario legislation did not result in a significant change in rates of opioid-related hospitalizations'	Moderate

Fischer et al., 2013	Reductions in non-medical prescription opioid use among adults in Ontario, Canada: Are recent policy interventions working?	*Substance Abuse, Treatment and Policy*	Canada	People experiencing issues with opioids	Indicators of use of and issues with opioids were identified through annual cycles from 'telephone interviews with randomly selected annual samples of n = 2024 (2010) and n = 1999 (2011; response rate 51% for both years) adults ages 18 and older', and 'representative of the Ontario general adult population'	Major policy and related interventions, implemented on an ad hoc basis, including 'the "Narcotics Safety and Awareness Act" (NSAA) as the legal foundation of its new provincial "Narcotics Strategy"'; the 'implementation of a prescription monitoring program (PMP) centrally collecting information on POs dispensed by prescribers and patients'; and the delisting of Oxycontin	The study observed a substantial decrease in non-medical use of prescription opioids in the Ontario adult population, which 'could be related to recent policy interventions, alongside extensive media reporting, focusing on NMPOU and PO-related harms, and may mean that these interventions have shown initial effects. Other factors may have been involved, however'	Moderate
Health Canada 2018	*2017–18 Departmental Results Report*	Health Canada	Canada	People experiencing issues with opioids	Data were selected from government documents such as strategies, plans, financial statements and research publications and literature	Regulatory amendments to 'allow the importation and sale of drugs not approved in Canada, but approved in the United States, the European Union, or Switzerland for urgent public health needs', including some drugs used for treating opioid-use disorder and other urgent public health needs. Actions supporting proposed regulatory changes, including publication of information about mandatory warning stickers, medication label updates and restriction of advertising and marketing	Establishment of work to support reductions in harm, increased access to treatment and dedicated monitoring	Low

Hooper et al., 2009	Alprazolam prescribing in Tasmania: A two-fold intervention designed to reduce inappropriate prescribing and concomitant opiate prescription	*Australasian Psychiatry*	Australia	People experiencing issues associated with benzodiazepines (alprazolam) and opioids	Prescription data drawn from: 1) alprazolam prescriptions subsidised through the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) for the period 1 January 2000 to 31 August 2008, from Tasmania and the rest of Australia (Australian Bureau of Statistics annual population data); and 2) Tasmanian data for the numbers of individual patients receiving alprazolam prescriptions via private or subsidised prescriptions from the Tasmanian Pharmaceutical Services Branch, period 1 September 2007 to 30 September 2008	Regulation placing additional requirements on prescription and dispensing, including: 1) monthly reporting; 2) application for authority to prescribe being required where alprazolam is prescribed in excess of four weeks to patients who are also prescribed opioid medication; 3) patients enrolled in methadone or buprenorphine maintenance programs being required to have explicit approval to receive prescriptions of alprazolam; and 4) medical practitioners required to be notified not to prescribe alprazolam to patients receiving benzodiazepines and/or opioids from another medical practitioner	Reductions in alprazolam prescribing in Tasmania associated with GP education, coupled with changes to prescribing regulations that made them more stringent	Moderate

Information Services Division, 2018	*National Naloxone Programme Scotland: Monitoring report 2017/18*	NHS National Services Scotland	Scotland, United Kingdom	People experiencing overdoses associated with opioids and people able to administer naloxone	The report had two major sources of data: 1) take-home naloxone kits supplied in Scotland between 2011–12 and 2017–18 (community outlets, prisons, community prescription); and 2) an extraction of data from National Records of Scotland (NRS) containing information about drug-related death records for each relevant year with 'opioid' deaths (prisons, hospitals)	The introduction and rollout of the National Naloxone Programme in Scotland from November 2010, which allowed provision of naloxone to those at risk of opioid overdose once they had undergone training. The training was also available to family, friends and service workers. In late 2015, supply 'via a third route (dispensing in a community pharmacy via prescription) increased in some NHS Boards following two key changes in the regulatory and policy frameworks': 1) changes aimed to make take-home naloxone (THN) more widely available by allowing direct THN supply to family members or carers for administration in the event of opioid overdose; and 2) the stopping of central reimbursement of the cost of THN kits, and 'NHS Boards assumed responsibility for the funding of THN supplies to opioid users at risk of accidental overdose'	An increase in distribution of naloxone kits and a reduction in deaths associated with opioids after the implementation of the program	Low

Larance et al., 2015	The introduction of buprenorphine-naloxone film in opioid substitution therapy in Australia: Uptake and issues arising from changing buprenorphine formulations	*Drug and Alcohol Review*	Australia	People experiencing issues with opioid dependency and accessing OST	The study used data 'collected for the wider post-marketing surveillance studies of BNX film conducted in 2012'. This included a survey of '334 buprenorphine (BPN), BNX tablet and BNX film clients and semi-structured interviews with 39 key experts (KEs) in 2012'. Comparisons were made between NSW, Victoria and South Australia	There was a key difference in the way the policies of different Australian states introduced BNX film. In South Australia, the change from tablets to film was mandated, while in Victoria and NSW it was less stringent	The 'introduction of BNX film in Australia varied across States', and perception of 'restricted choice in medication may have undermined initial acceptance in' South Australia	Moderate
Lucas and Walsh, 2017	Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients	*International Journal of Drug Policy*	Canada	People accessing and using cannabis as a substitute for opioids and other substances	Patients registered to purchase cannabis from a federally authorised producer and who were invited to complete an online survey consisting of 107 questions on demographics, patterns of use and the cannabis substitution effect. The survey was completed by 271 patients	Regulation allowing multiple licensed producers of cannabis	With the introduction of Canadian regulation that moved from a single licensed producer (LP) of cannabis to multiple licensed producers, self-reports that: 1) overall, cannabis was perceived to be an effective medicinal treatment for diverse conditions, with pain and mental health the most prominent; 2) high use of cannabis as a substitute for prescription drugs, particularly pharmaceutical opioids, benzodiazepines and antidepressants; 3) cannabis being substituted for alcohol, cigarettes/ tobacco and illicit drugs; 4) cannabis being accessed from illegal/unregulated sources in addition to access via LPs; and 5) participants were charged to receive a medical recommendation to use cannabis, some paying $300 or more	Moderate

Mahoney, 2018	The global opioid crisis: Effective laws to fight rising overdose fatalities through access to naloxone	*Arizona Journal of International and Comparative Law*	United States, Australia and the United Kingdom	People experiencing issues associated with opioids	A selection of evidence showing: trends in opioid-related harms in the US, UK and Australia; legal background and legal access to naloxone; and how improved access to and use of naloxone through legislative change can help prevent further harms	Proactive changes to legislation allowing easier access to naloxone	Reductions in deaths and other harms associated with the introduction of proactive legislation in Australia and the UK, and easier access to naloxone, for preventing harms associated with opioids	Low
Ministry of Mental Health and Addictions, 2019	*Responding to B.C.'s Overdose Emergency: Progress update November 2018 – February 2019*	Government of British Columbia	Canada	People experiencing issues associated with opioids	Data from services, health agencies and other relevant stakeholders in British Columbia demonstrating: distribution of take-home naloxone kits, public awareness campaigns and the launching of projects including training, piloting of treatment, research and other actions to reduce issues with opioids	Changes to prescription drug legislation in 2016 allowing the non-prescription emergency use of take-home naloxone; opioid agonist treatment clinic fee reimbursements; new legislation to prevent the illegal production of illicit opioids; training and treatment pilots	Increases in naloxone kit distribution, awareness-raising and investment in services, programs, research, training and other initiatives	Low
National Drug and Alcohol Research Centre NDARC, 2012	*A Review of Opioid Prescribing in Tasmania: A blueprint for the future*	University of New South Wales	Australia	People experiencing overdose and other harms associated with opioids	The study used evidence from three sources: 1) international and national literature identifying consistent and substantial increases in opioid analgesic prescribing across a range of developed nations since the early 1990s; 2) data on Tasmanian prescribing practices since the late 1990s; and 3) consultations with health professionals	In Tasmania, regulatory change and GP education to reduce prescribing of alprazolam with opioids (more restrictions on prescribing through greater authorisation of and reporting on prescribing). International literature: prescription monitoring programs	Reduction in the number of individuals receiving alprazolam with opioids following the interventions. Evidence also suggests that there is a need for effective regulatory interfaces to 'take on more than a punitive approach, and to engender a shared sense of sound clinical governance from the industry partners, prescribers, pharmacists, and educators'	Moderate

Office of the Provincial Health Officer, 2019	*Stopping the Harm: Decriminalization of people who use drugs in BC*	British Columbia Health	Canada	People experiencing issues with drugs, including opioids	A selection of evidence from: drug use and trend data in Canada; policies, law and legislation; and practice approaches in health and criminal justice	Changing prescribing legislation to allow the wide distribution of publicly funded naloxone, and supporting activities including: 'establishing overdose-prevention services and new supervised consumption services, and offering drug checking for people who use drugs'. Also increasing access to evidence-based treatment	Since actions were taken to address the 'overdose crisis': 'The combined impact of these interventions has been shown to have averted 60 per cent of all possible overdose deaths since the declaration of the public health emergency.' Evidence suggests that 'for every 10 naloxone kits that are used, one death has been averted'	Low
O'Halloran et al., 2017	The extent of and factors associated with self-reported overdose and self-reported receipt of naloxone among people who inject drugs (PWID) in England, Wales and Northern Ireland	*International Journal of Drug Policy*	England, Wales and Northern Ireland (United Kingdom)	People experiencing issues with opioids and who inject drugs	Agencies throughout the UK, except Scotland, who provide services to people who inject drugs (PWID) invite clients who have ever injected a psychoactive drug to participate in an annual survey. Those who consent to participate provide a biological sample (currently a dried blood spot: DBS) and self-complete a short questionnaire. The DBS samples are tested for antibodies to HIV (anti-HIV), hepatitis C (anti-HCV) and the hepatitis B core antigen (anti-HBc) using published methods. In 2013 a question relating to naloxone was added to the survey. The survey was completed by 3,850 participants	A change to UK regulations that allowed naloxone to be 'supplied by drug treatment services (including prison and pharmacy-based services) without a prescription. Previously, it could only be prescribed either directly to a named patient or through a PGD'	Baseline data have been established for 'monitoring the impact of the 2015 UK policy change to improve take-home naloxone access'	Moderate

Olsen et al., 2015	Independent Evaluation of the 'Implementing Expanded Naloxone Availability in the ACT (I-ENAACT)' Program, 2011-2014	Centre for Research Into Injecting Drug Use	Australia	People experiencing issues with opioids and at risk of overdose	Data were collected at three main points: 1 and 2) questionnaires administered both before and after the THN training; and 3) at follow-up interviews primarily held between three and six months after the THN training or after the report of an overdose reversal. Data were analysed using quantitative and qualitative techniques. Over 200 participants were trained	ACT Health, through the provision of financial resources and creating an enabling policy environment for the program. It reinforced a broader movement whereby 'governments in many of the nations with naloxone programs have enacted laws (such as specific Good Samaritan legislation) to support access to naloxone outside the medical setting and protect members of the public who administer it in an overdose emergency'	'Participants can be trained to administer THN in appropriate circumstances'. Additionally, 57 separate episodes of program-issued naloxone being used without adverse events were documented. Participants reported 'a sense of empowerment', and positive emotional impacts associated with program participation. The program contributed another model to the field	Moderate
Pricolo and Nielsen, 2018	Naloxone rescheduling in Australia: Processes, implementation and challenges with supply of naloxone as a 'pharmacist only' over-the-counter medicine	*Drug and Alcohol Review*	Australia	People experiencing overdose and mortality associated with opioids	The authors describe 'the process of rescheduling from initial proposal development to gaining support and submissions from a range of individuals and professional bodies to support this change. The implications of the change, particularly for pharmacy supply of naloxone, are discussed, including next steps to facilitate implementation of this change in the Australian context'	Naloxone was made more accessible through 'down' scheduling	The study had three main results related to rescheduling, its potential impact and next steps for action: 1) 'a submission to reschedule naloxone was successfully instigated by a member of the public'; 2) the 'change may help remove access barriers to naloxone by allowing pharmacist supply'; and 3) 'cost, pharmacist training, existing naloxone formulation, presentation and packaging remain challenges to address'	Moderate

Schleihauf et al., 2018	At-a-glance: Concurrent monitoring of opioid prescribing practices and opioid-related deaths—The context in Nova Scotia, Canada	*Health Promotion and Chronic Disease Prevention in Canada*	Canada	People experiencing issues with opioids	Data were drawn from two sources: 1) cases investigated by NSMES for deaths occurring between 1 January 2011 and 31 December 2017; and 2) the NSPMP database, including 'counts of unique health card numbers for which monitored opioids were dispensed and sums of MME, by drug type and quarter from 2011 to 2017'	The introduction of a prescription monitoring program and, much later, the introduction of changes to prescribing guidelines	The establishment of monitoring approaches to identify trends in population-level effects (whether intended or unintended) of interventions related to opioid prescribing	Moderate
Socias et al., 2017	Unintended impacts of regulatory changes to British Columbia Methadone Maintenance Program on addiction and HIV-related outcomes: An interrupted time series analysis	*International Journal of Drug Policy*	Canada	People who are HIV-positive and who use illicit drugs	Data were drawn from the 'AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective cohort of HIV-positive adults who use illicit drugs'. There were 331 opioid users included in the study. 'Interrupted Time Series Analyses were used to evaluate impacts of the policy change on monthly rates of MMT enrolment, illicit heroin injection, antiretroviral therapy (ART) adherence, and HIV viral suppression among HIV-positive opioid users between November 2012 and May 2015'	There were several regulatory changes introduced to the 'MMT program in the province of British Columbia': methadone replacement with a 'pre-mixed cherry flavoured and 10-times more concentrated methadone solution'; persons on methadone were 'transitioned to prescriptions of an equivalent dose of the new formulation'; and the restricting of 'methadone home deliveries to only "extraordinary circumstances" (e.g., clients with severe mobility restrictions) and with a written authorization by the prescribing physician'	After the regulatory changes, there were 'immediate increases in illicit heroin injection and decreases in ART adherence'	Moderate

Tobin et al., 2013	Regulatory responses to over-the-counter codeine analgesic misuse in Australia, New Zealand and the United Kingdom	*Australian and New Zealand Journal of Public Health*	Australia, New Zealand and the United Kingdom	People experiencing issues with OTC codeine containing analgesics	An analysis of public documents of medicine regulators and their expert advisory committees in Australia, New Zealand and the UK 'to identify regulatory responses to OTC codeine analgesic misuse'. Search restrictions were the 'period when controls on these analgesics were under consideration by regulatory authorities: February 2008 to June 2009 in Australia; December 2007 to November 2009 in New Zealand; and July to September' in the UK	Changes to: scheduling (became pharmacy-only); dosage (increased); pack size; advertising (not permitted)	Comparison with recommendations from New Zealand and the UK suggests that 'actions in response to OTC codeine misuse were appropriate given the available evidence of misuse and harm, but highlights opportunities to utilise additional regulatory levers'	Moderate

affects people using opioids and prescribers, as well as any unintended consequences that may hamper appropriate medicinal use (Campbell et al., 2019). It is also reasonable to assume, based on the lack of conclusive evidence, that more rigorous evaluation needs to be performed on all forms of drug policy change for opioids to better assess their effectiveness, and to design future interventions.

Similarly, more research into codeine use, including its extent and related issues in the UK and Canada, given it remains available over the counter there (Kimergard et al., 2017; Sproule et al., 2009), and impacts from the Australian rescheduling in 2018 (Middleton and Nielsen, 2019), could shed light on how to best manage issues with its use and medicinal application. Recent research in Australia offers useful insight and suggests that, so far, there has not been substitution of OTC codeine with stronger prescribed codeine at a population level, nor has a shift to other prescribed opioids occurred since the rescheduling (Middleton and Nielsen, 2019). Australian research could examine other potential impacts, such as the use of other pain management medications or treatment approaches, and help inform Canadian and UK work.

A better understanding of the impact of naloxone availability, at a national level across Australia, Canada and the UK, may help to determine how to best leverage promising findings from its rescheduling and/or help to increase its accessibility. A focus on the role of naloxone funding, training and dispensing is likely to help generate a better understanding of the degree to which increased naloxone availability reduces harms across the three countries (Choremis et al., 2019; Southwell et al., 2019; Pricolo and Nielsen, 2018). More investigation of the different formulations of naloxone, such as the recently developed intranasal formulation in Australia, could increase understanding of how to best apply the drug given the intranasal formulation has been found to be more timely in responding to overdoses (Dietze and Cantwell, 2016).

Improving the evidence base is also critical for helping to find drug policy changes that are more likely to be effective, as research suggests that prescription and OTC opioid overdoses and other harms are growing. The rate of overdoses associated with prescription and OTC opioids in Australia, Canada and the UK has increased over time, and during the period of focus of this review. From 2005 to 2015, Australia experienced a small but significant increase in harms associated with prescription and OTC opioids, including overdoses and deaths, mostly from codeine, oxycodone and fentanyl (O'Mara and Sherker, 2017). At the end of 2019, the Therapeutic Goods Administration reported that prescription

and OTC opioids exceeded heroin deaths by 2 to 2.5 times—the 'reverse' of what was recorded in the 1990s (The Royal College of Anaesthetists, 2019; Therapeutic Goods Administration (TGA), 2019).

In Canada, more research is required to better understand the harms associated with prescription and OTC opioids at the national level, but studies do find that they have been increasing since 1999 (Belzak and Halverson, 2018). Hospitalisations due to prescription and illicit opioid overdoses increased by more than 50 percent between 2007 and 2017 (Belzak and Halverson, 2018). The situation is similar in the UK. Evidence suggests that deaths associated with drug poisonings, including prescription opioids, have increased over time, and particularly in recent years (Office for National Statistics ONS, 2019).

The growing number of overdoses, deaths and other harms associated with prescription and OTC opioids in Australia, Canada and the UK has occurred despite various previous drug policy changes made to address harms and support the medicinal use of opioids. The growing harms reinforce an urgent need to improve understanding of which drug policy changes may be more effective or what other actions must be taken.

Beyond research, it is important to help increase access to more effective pain management (Rayner et al., 2016; Wilson et al., 2015; Mishriky et al., 2019) and drug-dependency support through health care (Valentine et al., 2018; Dube et al., 2018; Kelly et al., 2018) and increase awareness of and education about prescription and OTC opioids in Canada and the UK, and prescription opioids in Australia. Healthcare services are likely to benefit from workforce training and retention and increasing the ability of GPs and other health professionals to use effective treatments, such as prescribing methadone or buprenorphine/naloxone for prescription or OTC opioid dependency (Campbell et al., 2019). An increase in drug-dependency services will also help to address the increasing need for people to access help with opioid dependency. Similarly, greater availability of multidisciplinary pain services for people with chronic non–cancer-related pain is required to help improve pain management. Multidisciplinary pain services can offer more effective pain management approaches, such as the integration of medications with psychological and physical therapies (Campbell et al., 2019).

Barriers to accessing health services are an ongoing issue that need to be addressed. Access to pain management services is often difficult due to a lack of appropriately trained health professionals (Hadi et al., 2017), long waiting times (Rod, 2016), a lack of understanding in the healthcare system of chronic pain (Toye et al., 2017), stigma (Nicola et al., 2019) and major financial barriers experienced by patients, such as a lack of coverage in health insurance or ability to access treatments at a subsidised cost (Rod, 2016; Nielsen et al., 2016). There is also a need for greater integration of combined pain and dependency services (Campbell et al., 2019). Work addressing the barriers to health service access is a necessary part of developing an improved ability to manage pain and reduce problems with opioids and to support their medicinal use among people from a range of backgrounds, including those experiencing poverty and exclusion and others more likely to suffer a disproportionate level of harm associated with opioid issues.

Finally, there is an opportunity for education and awareness-raising initiatives to build on and enhance past efforts at increasing understanding in the general public of the potential side effects and other problems associated with the use of prescription and OTC opioids, and of how the medicines can be best used. Australian, Canadian and UK health agencies have all developed online campaigns and resources about prescription and OTC opioids, including: *Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain*, a resource from the UK's Royal College of Anaesthetists (2019); Canada's national campaign about the country's opioid crisis, which includes videos with information about stigma, the Good Samaritan Law, fentanyl and the use of naloxone (Government of Canada, 2019); and, in Australia, the NSW Agency for Clinical Innovation's Pain Management Network provides information for consumers and health professionals on the management of chronic pain, including 'Painbytes', which has videos and other information about chronic pain and how it can be managed (Agency for Clinical Innovation (ACI), 2019).

Given the importance of pain management, it may be useful for future campaigns to advocate for the integration of pain management strategies and advice and the need to reduce barriers to pain management services, at all levels, with efforts to reduce problems with opioids. Greater advocacy for national pain management strategies in Canada and the UK is of particular importance given both countries currently lack such national strategies. There may also be an opportunity for future work to be more inclusive in campaign development, and to perform tailoring based on language and cultural backgrounds, particularly given the diversity of populations in Australia, Canada and the UK.

Conclusion

The evidence base, while limited, suggests that changes to drug policy in Australia, Canada and the UK have not been associated with major reductions in overdoses and other harms from prescription and OTC opioid drugs, while also supporting their medicinal use. The lack of evidence demonstrating effectiveness suggests a need to consider specific options for future work.

Increasing access to naloxone is a promising option for opioid policy reform; however, a better understanding of naloxone implementation and its effectiveness at a national level in all three countries is required. Future research and evaluation will also help establish the full extent of issues associated with opioid drugs, including OTC codeine use in Canada and the UK, as well as the potential benefits from more effective approaches to the management of chronic pain and opioid dependency, at a population level.

It is necessary to also consider actions beyond changes to drug policy. Supporting greater investment in healthcare services, including workforce training and greater use of integrated, multidisciplinary approaches in drug-dependency and pain management services, has the potential to reduce the risk of opioid dependency, overdoses and other harms. More awareness-raising and education initiatives among people from a range of backgrounds, at the national level across all three countries, could help increase understanding of what helps in pain management and the appropriate use of opioids. Importantly, there are opportunities to address the stigma associated with dependency on opioids and help more people access help for pain management and other issues.

By further exploring ways of increasing access to naloxone and supporting targeted research and investment in health care, education and awareness-raising, future work in drug policy can play an important role in reducing the rates of dependency and overdose in Australia, Canada and the UK. With better understanding and the medicinal use of opioids, more unnecessary and tragic overdoses and deaths can be avoided, and more people can have an opportunity to access improved care for pain and drug-dependency issues.

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