Regulatory and other responses to the pharmaceutical opioid problem

How is Australia responding to the trends in pharmaceutical opioid utilisation and opioid harms?

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In the past 20 years, there have been substantial increases in the use of pharmaceutical opioids in many countries including Australia, which has one of the highest levels of opioid utilisation globally.[1] Almost 15 million opioid prescriptions were dispensed in 2015 and our use of high potency opioids has also increased.[2] One of the main drivers is the higher use of prescription opioids for chronic non-cancer pain (CNCP).[3] In parallel to escalating use, opioid-related harms have also increased. Since 2000, there has been a shift in hospitalisations due to opioid poisonings and opioid-related deaths from predominantly heroin to pharmaceutical opioids.[4] Extramedical use — defined as any use of a medication outside the formal medical system or inconsistent with a doctor's prescription[5] — is also relatively common; the most recent household survey indicates that "non-medical use" was reported by 4.8% of the Australian population.[4]

Possible strategies to minimise unnecessary opioid exposure and adverse events were highlighted in the National Pharmaceutical Drug Misuse Framework for Action (2012–2015),[6] including coordinated medication management systems, such as prescription drug monitoring programs (PDMPs); improvement of access to pain and addiction services; development of resources; and workforce development. To date, few of these strategies have been implemented. We summarise recent and emerging responses in Australia which aim to minimise harms from pharmaceutical opioids.

Regulatory responses aimed at reducing aberrant opioid prescribing and restricting opioid supply

Codeine rescheduling

In 2016, the most common analgesics Australians used for non-medical purposes were over-the-counter codeine products.[4] There have been several attempts to reduce extramedical use and harms from over-the-counter codeine. In May 2010, over-the-counter codeine products were up-scheduled from Schedule 2 (pharmacy medicine) to Schedule 3 (pharmacist-only medicine). This change, however, had no meaningful impact on codeine poisonings.[7] They were subsequently up-scheduled again in February 2018 to Schedule 4 (prescription-only medicines). The impacts of this decision remain to be seen.[8,9]

Prescription drug monitoring programs

PDMPs — designed to track prescribing and dispensing of prescription drugs of potential extramedical use — are being introduced in Australia, although their characteristics remain unclear and

there are likely to be jurisdictional differences, with potentially dissimilar outcomes. Differences may include whether the program is voluntary versus mandatory, whether it monitors Schedule 8 opioids only versus Schedule 8 opioids and benzodiazepines, whether it is fully automated or requires specific actions from the prescriber or pharmacist (eg, requesting a record), and whether it is real-time versus time-lagged.

International research on the impacts of PDMPs indicate mixed findings, with effectiveness varying according to program features.[10] For example, in the United States, some states with PDMPs report reductions in prescription opioid poisonings, with stronger protective effects where PDMPs monitored more schedules or required more regular reporting.[11] Less clear is how PDMPs will affect other aberrant behaviour (ie, patient practices that are divergent from those as directed by the prescriber,[5] such as use of opioid medicines for reasons other than pain, or use via unintended routes of administration), other substance use (prescribed or illicit), and opioid use disorders. Other unintended consequences have also been suggested, including stigmatisation of patients and a "chilling effect", in which prescribers underuse opioids due to fear of repercussions, rapidly reduce opioid doses, or cease opioids altogether, leading to inadequate pain relief or opioid withdrawal.[12] While PDMPs have intrinsic face validity, in practice there remain many unanswered questions.

An alternative approach to establishing stand-alone PDMPs is the impending expansion of My Health Record (MHR). Many aspects of PDMPs can be incorporated into MHR; however, the focus of MHR is to more broadly enhance coordination and quality of health care, efficiency and patient safety, rather than an emphasis on medications only, as is the case of PDMPs. The incorporation of prescription monitoring into MHR is likely to be less stigmatising, and may

offer better integration into routine health care than stand-alone PDMPs requiring their own infrastructure. There is concern among many groups about the manner in which these data could potentially be used, particularly in the criminal justice system. Medical and consumer groups will also need to consider how MHR will deal with Schedule 8 medications — the ability for a patient to opt out — or for a doctor to require access to MHR before opioid prescribing beyond emergency presentations.

Responses to minimise harmful patterns of use and harm

Misuse-deterrent opioid formulations are intended to minimise extramedical use by targeting use involving unintended routes of administration. Examples include making tablets tamper-resistant[13] or including naloxone to deter injection.[14] In Australia, available evidence from convenience samples suggests most individuals tampering with pharmaceutical opioids take these drugs via injection, on an infrequent basis, and use a variety of pharmaceutical opioids and heroin.[15] Australian post-marketing surveillance studies show reductions in use and tampering among people who inject drugs after the introduction of misuse-deterrent formulations, with no evidence of switching to other pharmaceutical opioids or heroin.[15] However, these formulations have not eradicated tampering and injection, and appear to have had limited impacts on overall opioid utilisation and population-level harm.[15] Unlike the Food and Drug Administration in the US, the Australian Therapeutic Goods Administration is yet to adopt a misuse-deterrent framework to enable the development and propagation of misuse-deterrent formulations over higher risk opioid formulations.

Other responses to reduce pharmaceutical opioid-related harms

Greater availability of multidisciplinary pain services for people with CNCP and addiction treatment services for opioid-dependent people are necessary to direct patients to more effective and safer treatment approaches than a reliance on opioid medications for CNCP. Screening for potential opioid problems is also important, with guidelines currently recommending that people with CNCP be assessed for such problems before initiating opioids.[16]

Access to multidisciplinary services

Contemporary guidelines regarding the management of CNCP emphasise the importance of multidisciplinary approaches that integrate medication and psychological and physical therapies. Many such services are most effectively and efficiently provided in multidisciplinary teams; however, few non-medical services are funded by Medicare in the community and are therefore out of reach for the majority of patients requiring their assistance. There continues to be an unmet capacity to deliver multidisciplinary team approaches within state-funded local health districts or private health services, and more needs to be done to enhance access. The inability to access effective non-medication-based treatments likely contributes to an over-reliance on opioid medications. There is a need to integrate more addiction services into pain management programs. In a review of 57 pain management services in Australia, only four offered a combined pain and addiction service.[17] National benchmarks for quality and access to multidisciplinary care for patients who have persistent pain are lacking. With the National Pain Strategy now back on the agenda, it is hoped that recommendations to collaborate more with addiction medicines will be become a priority area.

Access to opioid substitution therapy

Despite increasing concerns about pharmaceutical opioid dependence in Australia, the number of patients (per population) taking opioid substitution therapy (methadone or buprenorphine) has remained static for more than 15 years.[4] In a recent Australian study, few patients with concurrent chronic pain and opioid dependence[18] reported lifetime enrolment in opioid substitution therapy, with participants' indicating significant stigma associated with this therapy. The study highlighted the need to better integrate primary health, specialist pain and specialist addiction services.

Both methadone and buprenorphine are effective in the treatment of pharmaceutical opioid use disorders.[19,20] High dose buprenorphine or buprenorphine–naloxone is proving a useful approach for patients with chronic pain and opioid use disorder.[21] Yet, few Australian general practitioners — estimated at no more than 10% — prescribe methadone or buprenorphine–naloxone, despite the recent relaxation in training and credentialing requirements in most jurisdictions. Studies have identified a number of barriers to general practice participation, including feeling ill-equipped to deal with behavioural challenges,[22] workload concerns,[22,23] and a lack of accessible specialist support.[22,23] Many of these concerns can be lessened with improved workforce training and retention.[22,24,25] Concerted efforts are required to enhance the uptake of effective treatments by GPs and address many of the perceived barriers. Expansion of specialist addiction services will be required as PDMPs begin to identify patients with opioid use disorders.

Naloxone availability

Interest in the use of "take-home naloxone" (THN) as a strategy to reduce opioid overdose deaths, which is supported by the World Health Organization, has grown in recent years.[26] In Australia, THN programs are now incorporated in a range of services targeting people who inject drugs, including peer-based, needle and syringe programs, and alcohol and other drug treatment services.[26] However, THN programs have been less widely established outside of these settings.[26] Services targeting people with a history of injecting opioid use reach few patients with CNCP, and efforts are required to engage doctors who prescribe opioids to also consider THN interventions for their patients.

Since 1 February 2016, naloxone was rescheduled to Schedule 3 and is now available over-the-counter, but there has been limited uptake and strategies are urgently needed to improve pharmacists' knowledge and confidence in educating customers on opioid overdose and effective use of naloxone. Although previously only available as an injection, an intranasal formulation has recently been registered for use in Australia, which may improve its acceptability and attractiveness for use. However, while THN is important in reducing opioid-related overdoses, it is unlikely to have an impact on overall levels of opioid utilisation.

Education and advocacy for consumers and health care providers

In recent years, various government and non-government organisations have undertaken initiatives to promote education on the quality use of opioids, and also to increase awareness about opioid-related problems through various organisation-based websites and position statements. Examples include the NSW Agency for Clinical Innovation's Pain Management Network (www.aci.health.nsw.gov.au/chronic-pain), which provides information for consumers and health professionals on the management of chronic pain. ScriptWise (www.scriptwise.org.au) is a not-for-profit organisation that aims to prevent extramedical use of prescription medications and overdose fatalities in Australia. Within the pain management sector, there has also been growing emphasis on the need to deprescribe opioids and adopt multidisciplinary non-medication-based approaches to managing pain, as outlined in the Australian Pain Society's guiding principles for pain management (www.apsoc.org.au/position-papers).

Conclusion

It is important to reduce harms associated with pharmaceutical opioid use, but it is equally important that we do not prevent access for patients who may benefit from opioid treatment. Our emphasis should be on enhancing patient outcomes and safety and on recognising that regulatory responses such as rescheduling drugs, introducing PDMPs or misuse-deterrent medicines are merely a means to achieve that end, and are inadequate on their own. It is notable that these responses are required to occur in an environment with many competing interests (eg, industry *v* government), which can be challenging. Overall, we need better education of health care providers and consumers, better communication between providers through electronic clinical information systems, and increased availability of specialist pain and addiction services that work collaboratively with primary care providers. We must address the stigma of addiction that prevents patients and their doctors from effectively dealing with this problem — much in the same way we have made inroads in countering the stigma of mental health problems in the community over the past two decades. As a society, we need to reverse our over-reliance on medications as solutions for chronic health problems.

The vastness of the problem and the breadth of required approaches suggest that we need to revisit the role of a national policy with clear targets, implementation and evaluation strategies — absent from the last National Framework. Many of the solutions were identified a decade ago but have not been implemented. There are too many Australians experiencing opioid-related harms for us to neglect this problem for another decade.

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References are available online at www.mja.com.au.

1 Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet* 2016; 387: 1644–1656.

2 Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. *Br J Clin Pharmacol* 2016; 82: 255–267.

3 Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health* 2015; 36: 559–574.

4 Australian Institute of Health and Welfare. Non-medical use of pharmaceuticals: trends, harms and treatment, 2006–07 to 2015–16. (Drug treatment series no. 30. Cat. No. HSE 195) Canberra: AIHW; 2017. https://www.aihw.gov.au/reports/illicit-use-of-drugs/non-medical-use-pharmaceuticals/contents/table-of-contents (viewed Nov 2018).

5 Larance B, Degenhardt L, Lintzeris N, et al. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug Alcohol Rev* 2011; 30: 236–245.

6 National Drug Strategy. National Pharmaceutical Drug Misuse Framework for Action (2012–2015). Commonwealth of Australia; 2012. http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/drug-mu-frm-action (viewed Nov 2018).

7 Cairns R, Brown JA, Buckley NA. The impact of codeine re-scheduling on misuse: a retrospective review of calls to Australia's largest poisons centre. *Addiction* 2016; 111: 1848–1853.

8 Schug SA, Dobbin MD, Pilgrim JL. Caution with the forthcoming rescheduling of over-the-counter codeine-containing analgesics. *Med J Aust* 2018; 208: 51–52. https://www.mja.com.au/journal/2018/208/1/caution-forthcoming-rescheduling-over-counter-codeine-containing-analgesics

9 Therapeutic Goods Administration. Prescription strong (Schedule 8) opioid use and misuse in Australia — options for a regulatory response. Consultation paper. Canberra: Commonwealth of Australia; 2018. https://www.tga.gov.au/sites/default/files/consultation-prescription-strong-schedule-8-opiod-use-misuse-in-australia-options-for-regulatory-response.pdf (viewed Nov 2018).

10 Fink DS, Schleimer JP, Sarvet A, et al. Association between prescription drug monitoring programs and nonfatal and fatal drug overdoses. *Ann Intern Med* 2018; 168: 783–790.

11 Pauly NJ, Slavova S, Delcher C, et al. Features of prescription drug monitoring programs associated with reduced rates of prescription opioid-related poisonings. *Drug Alcohol Depend* 2018; 184: 26–32.

12 Islam MM, McRae IS. An inevitable wave of prescription drug monitoring programs in the context of prescription opioids: pros, cons and tensions. *BMC Pharmacol Toxicol* 2014; 15: 46.

13 Peacock A, Degenhardt L, Hordern A, et al. Methods and predictors of tampering with a tamper-resistant controlled-release oxycodone formulation. *Int J Drug Policy* 2015; 26: 1265–1272.

14 Larance B, Lintzeris N, Ali R, et al. The diversion and injection of a buprenorphine-naloxone soluble film formulation. *Drug Alcohol Depend* 2014; 136: 21–27.

15 Larance B, Dobbins T, Peacock A, et al. The effect of a potentially tamper-resistant oxycodone formulation on opioid use and harm: main findings of the National Opioid Medications Abuse Deterrence (NOMAD) study. *Lancet Psychiatry* 2018; 5: 155–166.

16 Therapeutic Guidelines. Analgesic: therapeutic guidelines. Melbourne: eTG Complete; 2018. https://tgldcdp.tg.org.au/etgcomplete (viewed Nov 2018).

17 Hogg MN, Gibson S, Helou A, et al. Waiting in pain: a systematic investigation into the provision of persistent pain services in Australia. *Med J Aust* 2012; 196: 386–390. https://www.mja.com.au/journal/2012/196/6/waiting-pain-systematic-investigation-provision-persistent-pain-services

18 Larance B, Campbell G, Moore T, et al. Concerns and help-seeking among patients using opioids for management of chronic noncancer pain. *Pain Med* 2018; https://doi.org/10.1093/pm/pny078 [Epub ahead of print].

19 Nielsen S, Larance B, Degenhardt L, et al. Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane Database Syst Rev* 2016; (5): CD011117.

20 Nielsen S, Larance B, Lintzeris N. Opioid agonist treatment for patients with dependence on prescription opioids. *JAMA* 2017; 317: 967–968.

21 Worley MJ, Heinzerling KG, Shoptaw S, Ling W. Pain volatility and prescription opioid addiction treatment outcomes in patients with chronic pain. *Exp Clin Psychopharmacol* 2015; 23: 428–435.

22 Holliday S, Magin P, Oldmeadow C, et al. An examination of the influences on New South Wales general practitioners regarding the provision of opioid substitution therapy. *Drug Alcohol Rev* 2013; 32: 495–503.

23 Scarborough J, Eliott J, Braunack-Mayer A. Opioid substitution therapy — a study of GP participation in prescribing. *Aust Fam Physician* 2011; 40: 241–245.

24 Hotham E, Roche A, Skinner N, Dollman B. The general practitioner pharmacotherapy prescribing workforce: examining sustainability from a systems perspective. *Drug Alcohol Rev* 2005; 24: 393–400.

25 Longman C, Lintzeris N, Temple-Smith M, Gilchrist G. Methadone and buprenorphine prescribing patterns of Victorian general practitioners: Their first 5 years after authorisation. *Drug Alcohol Rev* 2011; 30: 355–359.

26 Dwyer R, Olsen A, Fowlie C, et al. An overview of take-home naloxone programs in Australia. *Drug Alcohol Rev* 2018; 37: 440–449. ■