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Medication-Assisted Treatment of Opioid Dependence

A White Paper

16 May 2018

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Evaluate

Evaluate was formed in September 2016, to bring fresh thinking to policy and economic questions, particularly those in the social sphere.

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Funding

This White Paper was funded by a grant from Indivior Pty Ltd.

Acknowledgements

The authors wish to thank and acknowledge the many individuals who participated in consultations as part of the preparation of this White Paper. Any misinterpretations or errors are entirely those of the authors.

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Introduction

Purpose of work

In 2017, the concept of this White Paper was discussed together with the value of creating a document that provided some context and information regarding the provision of Medication-Assisted Treatment of Opioid Dependence (MATOD) in Australia, including an overview of the role and evolution of policy and products.

It is intended that this paper will be utilised to highlight the opportunities that exist to both review and enhance MATOD in the light of the challenges facing the system at present and the evolving nature of products currently in development. Clarifying these future treatment options and how they may interact with current treatment frameworks is critical to ensure that the outcomes available from these therapies are optimised. To do this, regulatory and policy settings will need to change and identifying appropriate pathways is necessary.

Critical to achieving that change is the recognition of the value these therapies deliver and the broader value of MATOD in our communities. This is considered in both economic and social terms.

Further, it is intended that this paper will support an ongoing focus on the area of opioid dependence. Whilst other drugs of addiction appear to receive significant attention in terms of policy documentation, media coverage and even public focus, opioid dependence needs to remain a major priority area due to its disproportionate harms compared to its usage prevalence.

Scope of work

This work does not purport to provide a full history of the policy work, ministerial and other organisations involved in medication-assisted treatment of opioid dependence (MATOD) or treatment options. As highlighted above, its purpose is to provide context and information that informs how Australia reached its current treatment paradigms in relation to opioid dependence; the emerging trends and products in that area; and identify some of the challenges and opportunities that exist going forward to enhance the treatment framework that governs this area.

Terminology

The authors acknowledge the ongoing discussions regarding the terminology describing people receiving MATOD and the use of the term itself.

Given the medical nature of opioid dependence, we have deliberately chosen to utilise the term *patients* in this work as opposed to clients and/or customers or any alternate phrase. Similarly, to both continue this emphasis on the medical nature of the dependency and the broader treatment framework and the usage in the National Guidelines, the term medication-assisted treatment of opioid dependence (MATOD) has been adopted throughout. This is done whilst acknowledging the fact that this paper primarily focuses on the medication-related aspects of treatment rather than the full suite of treatment encompassing medication and psychosocial support.

Executive Summary

History of Medication-Assisted Treatment for Opioid Dependence in Australia

Methadone was first used to treat heroin dependence in Australia in 1969. A National Methadone Policy was adopted in 1993 to reflect a national position on the role of methadone and the principles that should inform service delivery. By 1995, methadone was available in every State and Territory, except the Northern Territory, and provided in a variety of both public and private sector settings.

After many years of having a single treatment option, buprenorphine (Subutex™) was listed on the Pharmaceutical Benefits Schedule (PBS) in August 2001. This represented a significant change and opportunity for patients with opioid dependency.

Medication-Assisted Treatment for Opioid Dependence (MATOD) is guided by the principle of national direction coupled with jurisdictional implementation. This is central to a number of issues raised in this paper and to the experience of patients in MATOD programs.

Australia's *National Drug Strategy, 2017-26*, notes that implementation at jurisdictional level allows specific state and territory governments to act within the national harm minimisation approach whilst adopting strategies and actions that reflect their local circumstances. The national approach acts to assist all jurisdictions share best practice and encourage better policy and other responses. The Australian Health Ministers' Advisory Council noted that this task remains complex.

The *Strategy* also notes the decrease in heroin usage in recent years but highlights the increase in prescription and use of licit opioids, particularly in relation to the supply of oxycodone and fentanyl which increased 22 fold and 46 fold between 1997 and 2012. The number of opioid prescriptions filled under the Pharmaceutical Benefits Scheme (PBS) increased to 7 million in the fifteen years to 2007.

The *National Guidelines for Medication-Assisted Treatment of Opioid Dependence* aim 'to reduce the health, social and economic harms to individual and the community arising from unsanctioned opioid use'. Whilst recognising that community expectations of treatment for drug dependence might also anticipate that it will result in drug-free lifestyles, the *Guidelines* are clear that this view does not sufficiently recognise the complexities of dependence nor the extended treatment needed in some cases. This treatment should involve addressing patients' broader medical, social and psychological issues in concert with their opioid dependence.

The National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) Collection shows that, on snapshot days in May and June 2017, nearly 50,000 patients in Australia received pharmacotherapy for opioid dependence. 3,074 prescribers were authorised to prescribe MATOD and doses were distributed from 2,732 dosing sites.

The heterogeneity of the treatment population should not be underestimated. Some patients are extremely high functioning whilst others come from a background of polydrug use and may continue this in treatment. Physical and mental health problems are common and many experience significant psychosocial issues, such as unemployment, complex family problems and financial stress.

Medications available for use in MATOD fall into two broad categories: opioid agonists and antagonists. They include methadone; buprenorphine; and naltrexone and naloxone, which are used to treat overdose. Between 2008 and 2017, buprenorphine-naloxone use increased from 16% to 25% of total treatment while mono-buprenorphine remained stable with 15% of patients receiving it. For the first time, buprenorphine-naloxone is now prescribed more than mono-buprenorphine. This aligns with the *National Guidelines* that recommend its use due to a lower anticipated risk of illicit diversion. In addition, four states and territories – Victoria, Queensland, Tasmania and the Northern Territory – also now use buprenorphine-containing medications more commonly than methadone.

Buprenorphine in Australia

Use of buprenorphine for the treatment of opioid dependence started in the 1980s and buprenorphine, tradenamed Subutex®, was added to the Australian Register of Therapeutic Goods in October 2000. In July 2005, the Therapeutic Goods Administration (TGA) approved a second sublingual tablet formulation, Suboxone®, containing buprenorphine and naloxone. A third formulation, the Suboxone® film, was added in 2011 with the TGA Clinical Evaluation Report noting the potential for improved compliance from the film compared to the tablets and that both the diversion and intravenous use of the film should be reduced compared to the tablets.

Buprenorphine was listed on the PBS in August 2001 and Suboxone® (buprenorphine-naloxone) in April 2006. The *National Pharmacotherapy Policy for People Dependent on Opioids 2007* noted the 'properties of the combination product are intended to limit the abuse potential of buprenorphine'.

In March 2011, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended that a sublingual film version of buprenorphine-naloxone be made available on the PBS, noting the 'likely advantages of the film over the tablet formation in terms of reduced diversion and reduced dose supervision time in pharmacies and clinics'.

Differences in bioavailability between the film and tablet formulations were also noted and the PBAC considered that this might have quality use of medicines (QUM) implications when patients switched formulations. Given these concerns, the PBAC requested that the sponsor consider withdrawal of the sublingual buprenorphine-naloxone tablet formulation from the market.

The sponsor indicated their willingness to withdraw the tablet formulation whilst the film was available on the PBS, noting the necessity for an overlap period. This was agreed and the buprenorphine-naloxone sublingual film was introduced in Australia in 2011 'as an alternative to tablets'. The 'Suboxone sublingual tablet was delisted from the PBS on 1 September 2013 following the sponsor's agreement to PBAC's request for withdrawal due to quality use of medicines issues'.

This background is important given that consultations indicated that few clinicians appeared to be aware of the PBAC's request in this regard and also due to 'growing noise' currently regarding the possible entry to Australia of a branded generic version of a sublingual buprenorphine-naloxone tablet. This is of concern given the PBAC's earlier desire for withdrawal of the original tablet due to the QUM advantage of the buprenorphine-naloxone film.

The sponsor's agreement to this request is entirely in line with their commitment to harm minimisation and safe product use, particularly their work in educating and partnering with various stakeholders, including policy makers, funders, healthcare professionals and governments over time.

The value and benefits of buprenorphine, both in tablet and film formulations, offered a variety of benefits, including in its potential to attract more people into treatment. The *National Pharmacotherapy Policy 2007* noted other advantages 'in terms of safety, the relative ease of withdrawal, the need for less frequent administration, ease of transition into other treatments and flexibility of treatment'.

Various trials and research, many in Australian settings, demonstrated the following benefits: effectiveness and cost-effectiveness; ease of supervision; lower levels of diversion and injecting; lower risk of overdose; ease of transfer from one formulation to another; significant reduction in heroin use; improvements in relation to crime; safety; and other patient outcomes, such as mental health symptoms, psychosocial functioning and quality of life.

40% of Australian MATOD patients now receive a buprenorphine-containing medicine. NSW data do not differentiate between mono-buprenorphine and buprenorphine-naloxone and, if this is excluded from NOPSAD, 43% of Australians receive buprenorphine-naloxone; 5% buprenorphine; and the remaining 52% methadone. This is a reduction of 5% of patients receiving methadone from the previous year, the largest drop recorded in any one-year period.

Ongoing Evolution of MATOD

The introduction of any new medication or formulation to MATOD programs 'can be associated with anxiety for patients, and can be resisted by some patients and service providers'. At the same time, new products offer the opportunity to potentially attract new cohorts of patients into treatment and offer current or returning patients an alternative and possibly more effective form of medication.

On 30 November 2017, the US Food and Drug Administration (FDA) approved Sublocade™, the first once-monthly injectable buprenorphine formulation, for medication-assisted treatment of opioid disorder. Sublocade™ (buprenorphine extended-release) offers an alternative for those patients who may appreciate the benefits of a once-monthly injection compared to daily dosing. This is particularly attractive in a setting such as Australia, where barriers to treatment include supervision and stigma-inducing activities, including queuing.

In clinical trials, Sublocade™ was shown to have an overall safety profile consistent with the known safety profile of transmucosal buprenorphine, with the exception of some reactions at the site of injection.

Consistent with Indivior's commitment to safe use of buprenorphine, the company has committed to a restricted distribution system in the USA and would intend the same approach in Australia when Sublocade™ become available locally. This is intended to stop Sublocade™ being directly distributed to patients given the risks that could occur as a result of intravenous self-administration.

Contrary to some rumours heard during consultations for this paper, Sublocade™ can be stored at room temperature for up to seven days. Whilst facilitating early entry into regular usage, it must be noted that,

while Sublocade™ provides a significant opportunity, it also creates a requirement to review the Australian treatment framework to both attract more patients into MATOD and to enhance the experience of those already receiving therapy.

Another long acting injection medication (LAI), CAM2038, has also been assessed by the FDA which has requested additional information before further considering the application. A new drug application refilling is underway.

A number of assumptions exist in relation to the anticipated introduction of the LAIs to Australia's MATOD framework. Being injectable, the LAIs will need to be administered by a healthcare professional – either a doctor or a nurse – so consideration needs to be given to administration locations and their associated security and other regulatory requirements. This needs to be worked through prior to the LAIs' introduction.

Working through issues related to LAIs prior to their introduction is important. This is highlighted by comments made during consultations for this paper that noted some of the mistakes made during the introduction of buprenorphine to Australia, including the opportunity that new products present to review overall treatment frameworks when they offer a new paradigm. Meaningful improvements in terms of access and other benefits to patients and the broader community could be generated if this approach is taken.

There are other issues of relevance to the ongoing evolution of MATOD at present. These include real-time prescription drug monitoring programs; the rescheduling of codeine; and the ageing of the patient population in MATOD programs. All of these require careful consideration and management.

Treatment Framework for MATOD

Whilst MATOD programs operate within a national framework, individual jurisdictions are responsible for administering programs in their state or territory together with the development of local policies and the training and authorisation requirements for medical practitioners and other professionals. This results in significant disparities between the settings in which patients are treated and between prescribing patterns more generally.

These differences relate to whether patients are predominantly treated in public or private settings with consequences for patients' financial outlays. Amongst other issues, they also include the authorisation and training systems in place for prescribers and pharmacists; the numbers of patients to whom doctors can prescribe and to whom pharmacies can dose; and the number of take-away doses which may be prescribed and dispensed to a patient.

Whilst there is significant unmet need for treatment in Australia, a number of challenges and barriers exist in the treatment framework. These range from the capacity for patients to effectively access treatment through to cost considerations and the patient experience.

Key challenges include access to prescribers, both in terms of their number and location; access to dispensing sites; travel time and costs; limits to patient numbers; and opening hours. In addition, there are

challenges and barriers to treatment in regards to cost which include dispensing fees, particularly considering that patients are required to pay their own dispensing fees unlike in other treatment areas; and the costs of actually receiving treatment.

There are also a number of social and mental challenges patients experience in relation to MATOD. The experience of queuing to be dosed is regularly raised as a significant issue as is the availability and flexibility of dosing, including arrangements necessary if a patient needs to travel for work or other reasons. Stigma is also a common part of the patient experience and features prominently in reports by patients and their families and carers. This is experienced directly and indirectly, overtly and subtly and even from healthcare professionals in treatment settings.

Economic and social benefits and challenges

In creating an economic model for opioid dependence and treatment, four key components have been considered, including: losses of economic opportunity due to addiction; direct welfare costs; the cost of medical support, both acute and for MATOD; and a series of discount factors relating to the ease with which patients with opioid dependencies are able to access individually appropriate treatment.

Within these components, issues considered include impairment to earning potential as well as welfare payments to individuals, such as unemployment benefits; welfare payments to dependents, such as partners and children; and the direct costs to the public purse of criminal activity. Whilst allocating values to the various discount factors has been undertaken, it is intended that these proposed values are initially for discussion purposes as to their absolute and relative magnitudes.

A literature review is also reported, considering the cost-effectiveness of MATOD per quality-adjusted life year (QALY), the costs of prescription opioid dependency and costs associated with healthcare, criminal justice and lost productivity. The use of relative impacts allows us to compare different national regimes more effectively, as noted in the case studies below.

The overall conclusion from the review of evidence is that the effectiveness of MATOD programs is highly subject to the regulatory regimes within which they operate and consideration is given to competing guidelines.

Essentially, this is about maximum return on treatment models, focusing on compliance and the freedom for clinicians to discern suitable treatment programs. The model is not a full cost-benefit analysis but may provide the basis for a new look at relative benefits and will hopefully lead to further economic discussion about the priorities and models for MATOD in Australia.

International Case Studies

Case studies are detailed for Ontario, France and the United States as opportunities to reflect on different national approaches and frameworks for MATOD.

MATOD in Ontario is based in specialist clinics. A 2016 inquiry into opioid maintenance recommended that buprenorphine-naloxone should be moved from limited use approval to the same status as methadone, thus making the guidelines clinically indifferent and allowing patient and clinician choice. Further recommendations included some nurse practitioner prescribing to improve access to treatment; the need for medication-assisted treatment to be delivered in concert with psychosocial and mental health support services; and that consideration be given to alternative remuneration models for physicians with the goal of removing cost as a barrier to treatment. All these address the factors considered in the proposed economic model.

France's approach to opioid dependence was founded in the 1990s as part of the Government's response to having the European Union's highest rate of HIV/AIDS. France was the first country in the world to launch buprenorphine (Subutex) to treat opioid dependence in February 1996. Seven years on from this, France experienced a halving of the prevalence of new HIV infections amongst intravenous opioid users; an 81% reduction in mortality; and a 77% reduction in the rate of heroin-related arrests.

In relation to guideline design, a multi-ministry approach is taken to maximise treatment outcomes. This leads to coordinated programs across the French Government, with cooperative strategies between key stakeholders and KPIs for patient outcomes. It further delivers high levels of patient satisfaction, recently recorded at 88% for a random sample of patients in MATOD programs across France.

The rapid improvement in key metrics around the French opioid problem – particularly those regarding reduction in long-term health costs – are a compelling argument for this more integrated approach.

Approaches in the United States of America are highly variable due to State powers and the overriding context of the long-running 'war on drugs'. This often tends to stigmatise rather than encourage innovative treatments. Further, the complexity of the US health system, with its extensive reliance on private payment and with health insurance predominantly linked to employment, further complicates strategies to deliver MATOD.

There is however good evidence on compliance which allows comparison of self-reported illicit opioid use with quantitative detection from urine testing. Analysis of this data allows the primary conclusion that compliance is the key to lower rates of illicit opioid use which emphasises the importance of making compliance easier. Proposals from the American Society of Addiction Medicines and the American Psychiatric Association also describe a broad set of both treatment modalities and the patient characteristics to be taken into account when selecting a treatment program. They illustrate the complexity and requirement for flexibility in MATOD.

Taking the case studies together, there is a convergence of insights. If we take the willingness to reform shown in Ontario, combined with the complex coordination and harm reduction focus of the French model, and introduce both the data management tools and flexible criteria of the American system, interlinked benefits of focus on patients can be observed. From a health economics perspective, this makes good sense, as there appears limited benefit in pursuing a homogeneous enforcement problem compared to substantial potential reward from opening the MATOD system to flexibility, patient choice and individual program design by clinicians.

Issues for further consideration

A number of issues are recommended for further consideration including a national definition for opioid dependency and national consistency of guidelines for treatment. Whilst it may be suggested that definitions are not themselves priorities, the absence of consistent definitions inevitably leads to misunderstanding and/or differences as to targets, processes and clinical outcomes. These are already challenges in the Australian context. National consistency of guidelines would enable greater flexibility and certainty for patients who are required or choose to move as well as potentially enabling greater integration of MATOD across the country.

Strong evidence exists that providing dispensing fee relief to patients would improve program continuity, with an observed association between higher costs and significantly poorer treatment compliance. Significant benefits to patients could therefore be achieved with the introduction of national funding to meet dispensing fees, in whole or in part. Given that the out-of-pocket costs on a per-patient basis will be dwarfed by the per-person costs of illicit opioid use, this makes sense not only in relation to compliance but also economically. It also addresses an issue of inequity in the health system.

Other issues for further consideration include increasing the number of prescribers; addressing pharmacy issues; describing successful treatment; and decreasing stigma.

Given the challenges raised by the coming availability of LAIs, a treatment framework that encompasses these is required. Likewise, in light of the challenges these pose for the collection of future NOPSAD, a means of effectively tracking MATOD following the introduction of LAIs needs to be agreed.

Proposed timetable for addressing key issues

The most pressing issue that needs to be addressed in relation to MATOD is the challenge posed by the coming advent of the LAIs. A National Agreement is needed on how these treatments can be best introduced in a way that maximises patient safety whilst capturing the benefits available from them. Having appropriate mechanisms in place to manage the LAIs is critical and involves the identification and implementation of new models. This will involve reviewing the current treatment framework.

Given that the Ministerial Drug and Alcohol Forum has the necessary representation from Commonwealth, State and Territory Governments and membership from both the health/community services and justice/law enforcement portfolios, this would appear the appropriate body to address this issue. In light of the fact that the LAIs could be available in Australia in 2019, action is needed now to ensure that Australia's MATOD framework is appropriately prepared.

New national guidelines will also be required to facilitate the entry of the LAIs into the treatment framework and help educate healthcare practitioners about their use. Work should be initiated now given the information available from the FDA and the fact that clinical trials are underway in Australia.

A coordinated approach to all these activities is vital and *resolution is needed by mid 2019 on both implementation pathways for the LAIs and guidelines that support their use*. A means to address the NOPSAD Collection is linked to this and should be resolved simultaneously. It may well involve the real-time prescription drug monitoring systems under development.

Whilst these issues are the most critical in terms of timing, the other areas identified for consideration should not be ignored. Working groups could be established under the auspices of the National Drug Strategy Committee to consider a national definition of opioid dependency; national consistent guidelines for treatment; and the description of what successful treatment means. Whilst these may appear critical, their absence clearly affects targets, processes and clinical outcomes.

National funding of dispensing fees is a barrier to treatment, a clear issue of equity and one that should be able to be resolved, particularly given the health economic arguments involved. Discussions with the Commonwealth Minister for Health and Ageing, the Department of Health and Ageing and the Pharmacy Guild should be initiated immediately and clinicians should support and encourage these.

The matters relating to prescribers and pharmacists are clearly less easy to resolve and link strongly to the issue of stigma regarding MATOD. Being able to clearly communicate what successful treatment is should assist in addressing stigma and education is needed to support this. The significant body of work that exists regarding the barriers for doctors and pharmacists in delivering MATOD should be used to develop clear strategies and activities to help healthcare professionals engage in this work with confidence and the knowledge that their peers and communities understand its value and goals.

Given the extensive body of work that exists in relation to MATOD and the fact that much of it has been generated from Australian experience, the current and future challenges can be addressed. What is needed is a consistent focus, a clear workplan and the ongoing recognition that this work has as its goal the wellbeing of patients and the broader Australian community.

History of Medication-Assisted Treatment for Opioid Dependence in Australia

History and context

Methadone was first used to treat heroin dependence in Australia in 1969.[1]

The National Campaign Against Drug Abuse endorsed methadone in 1985 as an appropriate treatment for heroin dependence[2] and methadone has been prescribed with public subsidy since the 1970s.[3]

A National Methadone Policy was adopted in 1993 that reflected a national position on the role of methadone and the principles that should inform service delivery. Whilst there was agreement in regards to the principles adopted, significant divergence emerged between the range of service settings adopted and other control mechanisms. Different roles for private and public sectors also existed between state jurisdictions, a situation that continues to this day.

In 1995, the Commonwealth Government ascertained that methadone was available in every State and Territory except for the Northern Territory, and provided in a variety of settings including both the public and private sectors.

At the time, it was suggested the number of regular heroin users in Australia was around 60,000 people with potentially twice that many being occasional or irregular users.[4]

Australia's most recent *National Drug Strategy, 2017-2026* aims to 'build safe, healthy and resilient Australian communities through preventing and minimising alcohol, tobacco and other drug-related health, social, cultural and economic harms among individuals, families and communities'.[5] Its focus continues – as with past strategies – to be on harm minimisation and this is supported by three pillars – demand reduction, supply reduction and harm reduction.

Critically, in working to achieve its goals, the Strategy has within it a number of key strategic principles including: partnerships; coordination & collaboration; evidence-informed responses; and national direction with jurisdictional implementation.

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[1] Commonwealth Department of Human Services and Health, *A Review of Methadone Treatment in Australia: final report,* 1995. http://www.health.gov.au/internet/main/publishing.nsf/Content/phd-illicit-review-of-methadone-treatment/%24File/ndsp7.11.pdf Accessed 13 April 2018.

[2] Blewett, N., 'National Campaign Against Drug Abuse: Assumptions, arguments and aspirations: The 1987 Leonard Ball Oration', *Australian Drug and Alcohol Review,* (7) 1988. https://onlinelibrary.wiley.com/doi/abs/10.1080/09595238880000391 Accessed 13 April 2018.

[3] Larance, B., et al., 'The Diversion and Injection of a buprenorphine-naloxone soluble film formulation', *Drug and Alcohol Dependence*, 2013. http://dx.doi.org./10.1016/j.drugalcdep.2013.12.005 Accessed 27 February 2018.

[4] Commonwealth Department of Human Services and Health, *A Review of Methadone Treatment in Australia: final report*, 1995.

[5] Commonwealth of Australia, *National Drug Strategy 2017-2026,* 2017. http://www.health.gov.au/internet/main/publishing.nsf/Content/55E4796388E9EDE5CA25808F00035035/$File/National-Drug-Strategy-2017-2026.pdf Accessed 25 February 2018.

Whilst all of these are important to the delivery of Medication Assisted Treatment for Opioid Dependence (MATOD) in Australia, the principle of national direction coupled with jurisdictional implementation is central to a number of issues raised in this paper and to the experiences of patients in MATOD programs.

Funding and implementation does occur at all levels of government in Australia. The *Strategy* notes however that implementation at jurisdictional level allows specific governments to act within the national harm minimisation approach whilst adopting strategies and actions that reflect their local circumstances, differences and any emerging issues. At the same time, a national approach should assist all jurisdictions by sharing best practice and encouraging better policy and other responses.

The *Strategy* notes the decrease in heroin usage 'in the last twelve years' over the period 1998 to 2016 but highlights the increase in the prescription and use of licit opioids, particularly in relation to the supply of oxycodone and fentanyl which increased 22 fold and 46 fold respectively between 1997 and 2012. The *Strategy* further highlights that the rise in the number of opioid prescriptions filled under the Pharmaceutical Benefits Scheme which, in the fifteen years to 2007, increased to 7 million.

The *Strategy* continues to list opioids including heroin as priority substances but, in keeping with the perception that heroin particularly is receiving less attention than previously, this is towards the end of priority list. At the same time, the document notes the availability of opioid treatment programs and the importance of reducing stigma as evidence of good practice. Both of these will be discussed in more detail later in this paper.

Overall, however, the *Strategy* and other relevant documents continue to place an important focus on opioid dependence and this context is important to how we approach MATOD throughout this paper.

Goals of MATOD

The broad goal of treatment for opioid dependence, according to the *National Guidelines for Medication-Assisted Treatment of Opioid Dependence* is 'to reduce the health, social and economic harms to individuals and the community arising from unsanctioned opioid use'.[6]

The Guidelines also note that community expectations of treatment for drug dependence is that it will result in drug-free lifestyle being achieved by drug users. Whilst acknowledging the importance of abstinence as a goal, the Guidelines are clear that this viewpoint does not sufficiently recognise the complexities of dependence nor of the extended treatment needed in some cases.

Other aims and achievements are also critical and need to be acknowledged, particularly in light of their contribution to the broader goal identified above. The World Health Organisation notes a range of goals in addition to abstinence including:

- Reducing dependence on illicit drugs;
- Reducing the morbidity and mortality caused by using illicit opioids;

[6] Commonwealth of Australia, *National Guidelines for Medication-Assisted Treatment for Opioid Dependence'*, 2014. http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/ng-mat-op-dep Accessed 28 March 2018.

- Reducing the risk of infectious diseases;
- Improving physical and psychological health;
- Reducing criminal behaviour;
- Reintegration into the workforce and educational system; and
- Improving social functioning.[7]

The goals of the program are particularly worth highlighting given the changing perspective about heroin in our society. The *National Drug Strategy Household Survey 2016* highlighted these changes with only 14.0% of people surveyed first nominating heroin when asked to identify a specific drug problem compared to 30.3% in 2007.[8] Whilst this may be explained in part due to the shifting of media attention to drugs such as ice and others, this lowering of focus on heroin by the community would be troubling if it were reflected in policy and implementation. The significant costs to society and the economy from heroin (see below), the frequency of heroin injecting by those who use and the value inherent in the goals above mean that an ongoing focus on this treatment area is critical.

One of the key aims of opioid-dependence programs is to bring patients into a comprehensive treatment environment where their broader, and potentially causal, medical, social and psychological issues are addressed in concert with their dependence on opioids. Encouraging people to stop injecting drugs is also important due to the role of shared needle use and hygiene in the transmission of HIV, hepatitis and other blood-borne diseases.

Population using illicit drugs[9]

Understanding the population numbers who inject drugs is critical for planning service provision in terms of both treatment and harm reduction.

Lifetime use of drugs in Australia has changed since 2001. In 2001, 63% of people in their 20s were most likely to report that they had used illicit drugs in their lifetime whilst, in 2016, the dominant group was more likely to be people in aged 30–39 and 40–49 with 55% of both groups reporting lifetime usage. Younger age groups were less likely in 2016 to have experimented with illicit drugs than in 2001 with close to 40% of the age group reporting usage in 2001 compared to slightly over 20% in 2016.

In 2016, around 3.1 million, or 15.6% of, people aged 14 or older reported using an illicit drug in the previous 12 months, a usage level that has been relatively consistent since 2004. 8.6% of the population had used an illicit drug in the previous month while 5.6% had in the last week.

[7] World Health Organisation, Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, 2009. http://apps.who.int/iris/bitstream/handle/10665/43948/9789241547543_eng.pdf;jsessionid=505D2F289F7F90DE096CF921B3046EA3?sequence=1 Accessed 28 March 2018.
[8] Australian Institute of Health and Wellbeing, *National Drug Strategy Household Survey (NDSHS) 2016: detailed findings.* https://www.aihw.gov.au/getmedia/15db8c15-7062-4cde-bfa4-3c2079f30af3/21028a.pdf.aspx?inline=true Accessed 9 April 2018.
[9] Except where otherwise noted, data in this section was drawn from Australian Institute of Health and Wellbeing, *National Drug Strategy Household Survey (NDSHS) 2016.*

The proportion of the population aged 14 or older who had used heroin or injected illicit drugs in the 12 months prior to the survey was low for the entire period 2001 to 2016. Injecting drug use moved from a high of 0.6% in 2001 to lows of 0.3% in 2013 and 2016.

The *National Household Drug Survey 2016* reported that, of a population aged 14 and over of slightly over 19 million, 0.2% had used heroin in the previous twelve months equating to 38,000 people. In contrast, 3.6% of over 14 year olds had misused painkillers, analgesics or opioids (excluding non-codeine products) – 685,000 people or nearly twenty times the number of heroin users. 0.1% of over 14 year olds had used methadone or buprenorphine or slightly over 19,000 individuals.

Interestingly these percentages have remained largely stable since 2001 although other related statistics have changed. Since 2007, the percentage of deaths considered by the community to be caused by heroin has changed with figures quoted at 9.8% in 2007, 15.9% in 2010, 14.1% in 2013 and a significant reduction to 10.6% in 2016. Deaths attributed to non-medical use of painkillers, analgesics and opioids were not recorded prior to 2007 but rose from 0.9% in 2007 to 1.9% in 2016.

Recent use of heroin was – as highlighted above – stable at about 0.2% of the population and, whilst this was largely stable from 2001 to 2016, it is worth noting a peak of 0.8% of population identified by the Survey as having tried heroin in 1998. Interesting, frequency of use with heroin is much higher than with other drugs. 49% of users report using heroin as often as weekly with 41% of injecting drugs users overall reporting injecting at least twice a week.

Injecting drug users are overwhelming sourcing needles and syringes from appropriate sources with 44% sourced from pharmacies and 41% from needle and syringe programs. There was a significant decrease in the number of injecting drug users who had shared needles in their lifetime with this dropping from 47% in 2001 to 29% in 2016. Nonetheless, this remains a disturbing figure.

52% of people misusing pharmaceutical analgesics and opioids bought them from a pharmacy and about 1 in 5 obtained them with a prescription or by "doctor shopping".

Treatment Population for MATOD[10]

In 1997, there were an estimated 74,000 dependent heroin users in Australia.[11] The National Methadone Statistics in June 2000 indicated that slightly more than 30,000 patients were registered and collecting methadone. Of those, approximately 65% collected their methadone from a pharmacy, 16% from a public clinic, 8% through a private clinic and the remainder from a correctional facility or other source.

[10] Statistics in this section are drawn from NOPSAD 2017 data unless otherwise noted. Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017. https://www.aihw.gov.au/reports/alcohol-other-drug-treatment-services/nopsad-2017/contents/summary* and associated tables. Accessed 12 April 2018.

[11] Hall, W., Ross, J., Lynskey, M., Law, M. & Degenhardt, L., 'How many dependent opioid users are there in Australia?', NDARC Monograph No. 44, National Drug and Alcohol Research Centre, University of New South Wales, Sydney: 2000. http://www.abs.gov.au/AUSSTATS/abs@.nsf/66f306f503e529a5ca25697e0017661f/eddb1bf8e48095a5ca256b11001dbbd9!OpenDocument Accessed 13 April 2018.

More recently, the National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) Collection has provided benchmark data on the number of people receiving opioid pharmacotherapy treatment as well as information regarding the provision of treatment, prescribing practitioners and dosing sites dispensing pharmacotherapy. This annual collection data enables the identification of both short and longer-term trends and information about opioid treatment across jurisdictions.

Traditionally, opioid dependence has been associated with illicit heroin use. In the last fifteen years, however, both prescribed and over-the-counter (OTC) pharmaceuticals have been used in greater numbers, including in regards to the management of chronic pain. Linked to this, there has been an increase in the number of people who have become opioid dependent. These people require management of other underlying medical conditions together with their opioid dependency.[12]

The heterogeneity of the treatment population should not be underestimated, an issue highlighted by many of those with whom the authors consulted. As noted elsewhere, some patients are extremely high functioning whilst others come from a background of polydrug use and may continue this during treatment. Physical and mental health problems are common amongst patients and many experience significant psychosocial issues, such as unemployment, complex family problems and financial stress.[13] One clinician commented on the experience of a highly functioning patient who had held senior and responsible employment throughout their treatment whilst others reflected on the significant patient population in Australia's prisons.

On snapshot days in May and June 2017, nearly 50,000 patients in Australia received pharmacotherapy for opioid dependence. 3,074 prescribers were authorised to prescribe pharmacotherapy medicines, representing a prescriber increase of 3% from the previous year. On average, this means that each prescriber treats 16 patients but the variance of patient-prescriber distribution shows significant modal departures from the average. Doses were distributed from 2,732 dosing sites with 89% of those being pharmacies.

NOPSAD data demonstrate that both the total number of people and the national rate of people receiving pharmacotherapy treatment have remained reasonably stable since 2010. There are variations in individual state growth however.

New South Wales continues to be the state with the highest rate of people receiving treatment at 26 patients per 10,000 people while Victoria is the only state that indicated an increase in the rate of people receiving treatment, moving from 22 to 23 patients per 10,000 people since the previous year. State and territory variations are shown in Figure 1.[14]

[12] Lintzeris, Nick, 'Treatment of patients with opioid dependence', *Medicines Today,* June 2015. https://medicinetoday.com.au/sites/default/files/cpd/3-MT2015-06SUPPL-PRESCRIPTION_OPIOID_MISUSE-LINTZERIS.pdf Accessed 19 April 2018.

[13] Ritter, A., and Chalmers, J, *Polygon: the many sides to the Australian opioid pharmacotherapy maintenance system*. Canberra: Australian National Council on Drugs, 2009.

[14] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017*.

FIGURE 1: Population rates for clients receiving pharmacotherapy treatment on a snapshot day, states and territories, 2017

People receiving treatment last year were aged from late teens to 87 years old. The median age was 42 years – as it was in 2016 – but this has gradually been rising from 38 years since the data began being collected in 2011.

The bulk of patients, or 66%, were aged between 30 and 49 with the number and percentage of patients over 60 years steading increasing from 1%, or 223 patients in 2008 to 6% or 3,192 last year. Those under 30 years continues to decline markedly, with 28% of patients being younger than 30 in 2006 compared to only 7% last year.

The Report specifically notes the ageing of the patient cohort received treatment, noting that it is consistent across other services for drug treatment. Reasons for this are identified as:

- The duration of the programme with methadone treatment, now having been available for over 40 years;
- Treatment contributing to longevity with some patients now having received treatment for decades; and
- An older age at which patients first seek treatment.

Variations exist across jurisdictions in terms of the age of patients receiving treatment. The lowest median age is seen in the Australian Capital Territory, Tasmania and Victoria at 41 years whilst the highest median age of 44 is experienced in South Australia and New South Wales.

Around 66% of patients receiving treatment in 2017 were male and, where reported, around 1 in 10 identified as Aboriginal or Torres Strait Islander. In the ACT, the Northern Territory, Tasmania, Victoria and Western Australia, 58% of patients were classed as ongoing patients; similar status data was not available for New South Wales or Queensland.

It is also the case that more people in MATOD programs are now living their lives fully integrated within their communities and holding regular employment.[15]

Current Treatments in MATOD

Medications available for use in MATOD fall into two broad categories: opioid agonists and antagonists.

The medications can be utilised in Australia to treat opioid dependence include:

- Methadone, which is a full opioid agonist and, as such, binds to the brain's mu opioid receptors, and activates them;
- Buprenorphine, which is a partial mu opioid agonist and acts in a similar way as methadone, although with a different profile; and
- Naltrexone and naloxone, which are opioid antagonists and also bind to the mu receptors in the brain. Rather than activating them however, these treatments prevent the activation of the receptors by agonists thereby blocking their effect. Except in combination, naloxone is used to treat overdose in opioid dependent patients.

A key difference between full and partial mu opioid agonists is the ceiling, or "topping out" effect found with partial agonists. As partial agonists occupy receptors, this means that the impact of buprenorphine at some point reaches a maximum level in patients with no further impact on respiration or the subjective experience of the drug.

Of the above, three medications are currently registered for long-term maintenance treatment of opioid dependence – methadone, buprenorphine and buprenorphine-naloxone. These medications are utilised to 'eliminate withdrawal, control or eliminate cravings or block the euphoric effect of further opioid use'.[16]

As highlighted above, methadone has been prescribed with public subsidy in Australia since the 1970s whilst buprenorphine tablets became available in 2001, buprenorphine-naloxone tablets in 2006 and buprenorphine-naloxone film in 2011.

Naltrexone has been registered in Australia as a tablet since 2007[17] and can also be administered as an implant.[18] The implants are not registered on the Australian Register of Therapeutic Goods and are therefore available only under the TGA's Special Access Scheme. They have not been approved by the US FDA although the FDA approved monthly injections of naltrexone for opioid dependency in October 2010.[19]

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[15] Puplick, Chris, 'Towards Reintegration: Review of the New South Wales Opioid Treatment Program', Stakeholder Consultation Component, Report, November 2014. http://www.health.nsw.gov.au/aod/resources/Documents/otp-review-report-2014.pdf Accessed 1 March 2018.
[16] Commonwealth of Australia, *National Guidelines for Medication-Assisted Treatment for Opioid Dependence'*, 2014.
[17] Australian Register of Therapeutic Goods, 'ARTG ID 128710', https://www.tga.gov.au/artg/artg-id-128710 Accessed 29 April 2018.
[18] Alcohol and Drug Foundation, 'Naltrexone', https://adf.org.au/drug-facts/naltrexone/ Accessed 29 April 2018.
[19] American Addiction Centres, 'Using Naltrexone to treat opiate and alcohol addiction', https://americanaddictioncenters.org/addiction-medications/naltrexone/ Accessed 29 April 2018.

There are also other medications to treat opioid dependency that do not form part of Australia's MATOD program. These include prescription heroin, which has been available in the UK since 1926 although never commonly used; intravenous methadone, which has also been utilised in the UK; and sustained release oral morphine.[20]

Levomethadyl acetate (LAAM) is a synthetic opioid analgesic that is a methadone derivative and has been investigated as a pharmacological alternative to methadone. Similar in its effect to methadone, it has a longer half-life meaning that it could reduce administration costs due to administration on alternate days. Whilst reported in 2001 as potentially being available in Australia 'within the next few years',[21] LAAM is not registered on the ARTG and was in fact removed from the market in the EU in 2001.[22] With the USA discontinuing use shortly thereafter, LAAM has effectively been withdrawn globally.

Treatment Received

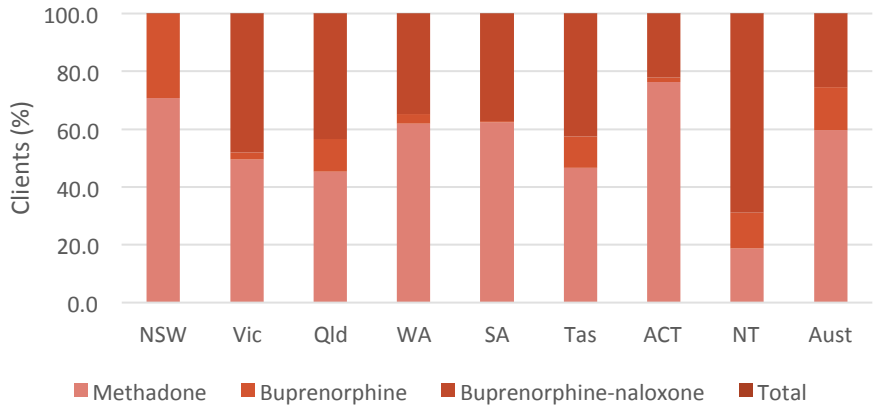
Over time, the balance of treatments received by patients receiving MATOD has varied. Between 2008 and 2017, buprenorphine-naloxone use increased from 16% to 25% of total treatment while mono-buprenorphine remained stable with 15% of patients receiving it.[23]

This means that, for the first time since the introduction of buprenorphine-naloxone, it has been prescribed more often than buprenorphine. This aligns with the *National Guidelines* that recommend its use due to a lower anticipated risk of diversion.

In addition, four states now use buprenorphine-containing medications more commonly than methadone in MATOD. A majority of patients have long received buprenorphine-containing medications in the Northern Territory, with this being mirrored in Queensland in 2014, Tasmania in 2016 and Victoria in 2017. In 2017, 81.1% of patients in the Northern Territory received buprenorphine or buprenorphine-naloxone, 54.8% of patients in Queensland, 53.3% in Tasmania and 50.4% in Victoria. Methadone was most used in the ACT, where 76% of people received it. Treating patterns between states and territories can be seen in Figure 2.[24]

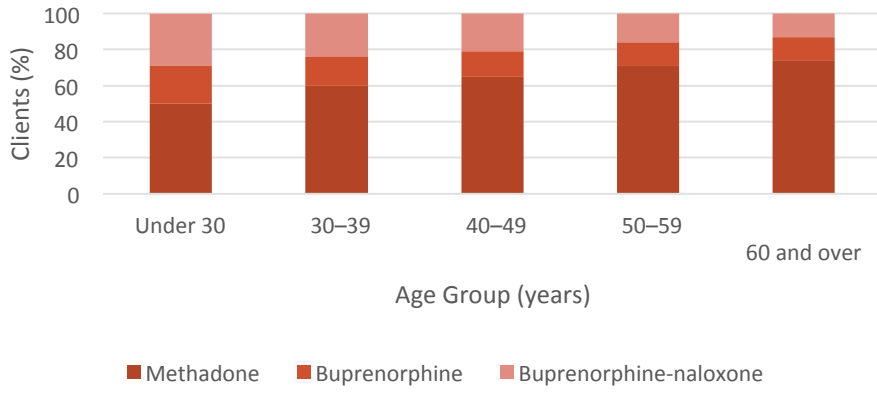
[20] Wodak, Alex, 'Drug Treatment for Opioid Dependence', *Australian Prescriber*, 24 (1) 2001. https://www.nps.org.au/australian-prescriber/articles/drug-treatment-for-opioid-dependence Accessed 29 April 2018.
[21] Wodak, Alex, 'Drug Treatment for Opioid Dependence', 2001.
[22] The European Agency for the Evaluation of Medicinal Products, 'Public Statement on the Recommendation to Suspend the Marketing Authorisation of Orlaam (levacetylmethadol) in the European Union', 19 April 2001. http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/12/WC500018335.pdf Accessed 29 April 2018.
[23] As noted elsewhere in this paper, NSW does not distinguish buprenorphine usage from buprenorphine-naloxone usage. This has a distorting impact on reporting various data.
[24] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017*.

FIGURE 2: Clients receiving pharmacotherapy treatment on a snapshot day, by pharmacotherapy type, states and territories, 2017



In addition, buprenorphine and buprenorphine-naloxone are more likely to be prescribed in younger cohorts whilst older patients are more likely to be treated with methadone as demonstrated in Figure 3.[25]

FIGURE 3: Clients receiving pharmacotherapy treatment on a snapshot day, by age group and pharmacotherapy type, 2017



Whilst the use of buprenorphine and its combinations have increased significantly, methadone continues to be the most commonly prescribed pharmacotherapy across all age groups. It is worth noting that the increase in buprenorphine-naloxone usage reflected a corresponding drop in the use of methadone, with 60% of patients receiving methadone in 2017 compared to 70% in 2008.

Whilst – where reported[26] – around 1 in 10 patients recorded by NOPSAD identify as being Aboriginal or Torres Strait Islander, indigenous Australians are significantly more likely to receive pharmacotherapy than non-indigenous people at 70 people per 10,000 indigenous Australians compared to 26 people per 10,000.

[25] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017*.
[26] WA does not report the indigenous status of patients whilst Victoria does not breakdown the pharmacotherapy type for indigenous patients.

Indigenous patients are also more likely to be treated with methadone, at 54% compared to 41% of non-indigenous patients.

Treatment was provided for a variety of opioid drugs, including illicit drugs, such as heroin, and pharmaceutical opioids, including those prescribed; OTC medications, such as codeine combination medicines; and those accessed illicitly. It should be noted, however, that 38% of people are recorded as not identifying the source of their opioid dependence.

The most common drug of dependence was heroin with 38% of people identifying it. Further, it was the most common drug in all States and Territories, except Northern Territory and Tasmania where morphine was the most common. Methadone, codeine and morphine were reported by 4% of patients each with 5% identifying oxycodone as their opioid of dependence.

Current Guidelines and Policy Settings

The federated nature of Australian health system is clearly demonstrated within the settings for MATOD and for illicit drugs more generally.

At the legislative level, the Commonwealth Government is responsible for those laws governing the import and export of certain drugs, including narcotics, cannabis and most pharmaceutical products. In contrast, State and Territory laws regulate the possession, use and supply of illicit drugs.

The Commonwealth Government also leads the national approach towards early intervention and prevention of illicit drug use, agreeing this with States and Territories along with other policy settings and frameworks, including treatment guidelines and the like.

The Australian Health Ministers' Advisory Council, in signing off the *National Guidelines for Medication-Assisted Treatment of Opioid Dependence*, noted that the task of 'providing a broad policy context and framework with a view to promoting a national standard whilst recognising jurisdictional responsibilities and the need for flexibility to accommodate different jurisdictional approaches' is a complex one.[27]

That this is the case is clearly identified within the same section of the *Guidelines* which notes that, whilst the Tasmanian Government endorsed the overall direction of the *Guidelines* and recognised them as a much needed national guide for treating opioid dependence, it did not endorse either 'the framework or criteria for takeaways and unsupervised dosing'.

The complexity of the task and of the policy and jurisdictional structure is also underscored by the fact that the 2014 Guidelines replace four previously separate documents, updating and combining them into one source. These included the:

- National Pharmacotherapy Policy for People Dependent on Opioids;

[27] Commonwealth of Australia, *National Guidelines for Medication-Assisted Treatment for Opioid Dependence'*, 2014, Acknowledgements.

- Clinical Guidelines and Procedures for the Use of Methadone in the Maintenance Treatment of Opioid Dependence;
- National Clinical Guidelines and procedures for the Use of Buprenorphine in the Maintenance Treatment of Opioid Dependence; and
- Clinical Guidelines and Procedures for the Use of Naltrexone in the Management of Opioid Dependence.

Further, the *Guidelines* note that they are simply a 'general guide to appropriate practice, to be followed subject to the clinician's judgment and patient's preference in each individual case'. They are intended principally to provide information to help with decision-making.

In addition to the national treatment guidelines, additional layers of state-based and established guidelines, accreditation and other policy mechanisms and settings exist in relation to MATOD. This means there are considerable variations between Australian jurisdictions in relation to the mechanisms by which their MATOD programs are provided. Some of these stem from the history of program development but differences can include to the extent of centralised versus decentralised control; the roles of the public and private sectors; and treatment settings, such as specialist clinics or private practitioners.

What is common is the large number of agencies and policies that govern the provision of MATOD programs. States and Territories have a plethora of guidelines, programs and documentation that guide practice that may include, but are certainly not limited to:

- Training programs for prescribers wanting to prescribe medicines under a MATOD program;
- Authorities for the prescribing or supplying a drug of dependence or a drug-dependent person;
- Requirements for prescribers wanting to prescribe medicines to treat opioid dependence;
- Authority forms for each patient to be supplied with medications under a MATOD program;
- Termination and renewal forms for MATOD programs;
- Guidelines for pharmacists involved in the supply of medicines under MATOD programs;
- Unsupervised dosing policies;
- Guidelines for serious breaches of MATOD;
- Incident reporting protocols and forms; and
- Clinical guidelines covering induction, regular use, takeaway doses and other related matters.

Some of these, together with their impact, will be considered in more detail in sections below.

Buprenorphine in Australia

History

Registration and Inclusion on the Pharmaceutical Benefits Scheme

Since the 1980s, buprenorphine had been used in many countries, including Australia, as a medication for pain relief. Use of buprenorphine for the treatment of opioid dependence started in the 1980s and, in 1996, France became the first country to use buprenorphine as an opioid substitution product.[28]

Buprenorphine, tradenamed Subutex®, was added to the Australian Register of Therapeutic Goods in October 2000. In July 2005, the Therapeutic Goods Administration (TGA) approved a second sublingual tablet formulation, Suboxone®, containing buprenorphine and naloxone. A third formulation, the Suboxone® film, was added in 2011 with the TGA Clinical Evaluation report noting the potential for improved compliance from the film compared to the tablets and that both diversion and intravenous use of the film should be reduced compared to the tablets.

All three products are listed under Schedule 8 of the *Standard for the Uniform Scheduling of Drugs and Poisons* for the management of opioid dependence within a framework of medical, social and psychological treatment. Buprenorphine is indicated for use in the maintenance and detoxification treatment of opioid dependence.

Inclusion on the Pharmaceutical Benefits Scheme

Buprenorphine (Subutex®) was listed on the Australian Pharmaceutical Benefits Scheme (PBS) in August 2001 on a cost-effectiveness basis with methadone as its primary comparator. Announcing the listing, then Federal Health Minister, Dr Michael Wooldridge, noted that the decision would 'increase access and affordability of this effective new treatment option for opioid dependent people'. He further noted that The National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD), funded under the National Illicit Drug Strategy, together with clinical trials conducted both in Australia and overseas, clearly identified buprenorphine as an effective treatment.[29]

Whilst not noted in the Minister's announcement, it was also recognised that buprenorphine is associated with a lesser risk of overdose than methadone, particularly in the first four weeks of treatment.[30] It is intrinsically safer for this reason.

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[28] Commonwealth of Australia, *National Pharmacotherapy Policy for People Dependent on Opioids,* January 2007. http://www.emcdda.europa.eu/attachements.cfm/att_231080_EN_INT02_Australia,%20pharmacotherapy%20policy%202007.pdf Accessed 28 February 2018.

[29] Wooldridge, Hon Dr Michael, 'Access to Buprenorphine on the PBS', Press Release, 31 July 2001. http://parlinfo.aph.gov.au/parlInfo/search/display/display.w3p;query=Id%3A%22media/pressrel/DOIH6%22 Accessed 13 April 2018.

[30] Dunlop, A., et al., 'Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone for the treatment of heroin dependence in a randomized waitlist controlled trial', *Drug and Alcohol Dependence,* March 2017. https://www.ncbi.nlm.nih.gov/pubmed/28371689 Accessed 28 February 2018.

Suboxone® (buprenorphine-naloxone) was listed in April 2006 on a cost-minimisation basis as an alternative to buprenorphine. It was estimated that there would be 29,402 patients treated in the first four years of listing at an additional cost to the PBS of $7.2 million.[31]

The *National Pharmacotherapy Policy for People Dependent on Opioids 2007* identified that a key rationale for treating individuals with buprenorphine-naloxone is that the combination is such that, when taken sublingually, it will act as though it is buprenorphine alone. However, should the combination be injected, the naloxone's effect is such that it is likely to attenuate the effects of the buprenorphine in the short term as well as being likely to precipitate withdrawal symptoms in opioid-dependent people using heroin or methadone. The policy states that the 'properties of the combination product are intended to limit the abuse potential of buprenorphine'. [32]

This is important in terms of both diversion to third-party users and illicit use. Both buprenorphine and buprenorphine-naloxone were at this time only available in sublingual tablet form.

Introduction of buprenorphine-naloxone film and withdrawal of the buprenorphine-naloxone tablet

In consultations for this White Paper, it became apparent that clinicians were not universally aware of the reasons behind the market withdrawal of the buprenorphine-naloxone tablet. This lack of awareness reinforced the relevance of incorporating within this White Paper the history of buprenorphine and decisions made in relation to it.

In March 2011, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended to the Minister of Health that a sublingual film version of buprenorphine-naloxone be made available on the PBS, noting the 'likely advantages of the film over the tablet formulation in terms of reduced diversion and reduced dose supervision time in pharmacies and clinics'.[33]

In addition, the PBAC noted the differences in bioavailability between the sublingual film and sublingual tablet formulations and considered this might have quality use of medicines (QUM) implications when patients switched formulations.

Given these concerns, the PBAC requested that the sponsor of the product, Reckitt Benckiser (Australia) Pty Ltd, consider withdrawal of the sublingual buprenorphine-naloxone tablet formulation from the market.[34]

Correspondence in May 2011 confirmed the sponsor's willingness to withdraw the buprenorphine-naloxone tablet once the film was available on the PBS, noting that a period of overlap would be necessary.[35] Ongoing correspondence identified this transition timeframe as anticipated to be a 24-month period unless a smooth switch occurred prior to those timelines in which case the sponsor agreed that

[31] Abbott, Hon Tony, 'New listings on the Pharmaceutical Benefits Schedule', Media Release, 31 March 2006. http://parlinfo.aph.gov.au/parlInfo/download/media/pressrel/UF8J6/upload_binary/uf8j62.pdf;fileType=application%2Fpdf#search=%22buprenorphine%22 Accessed 13 April 2018.
[32] Commonwealth of Australia, *National Pharmacotherapy Policy for People Dependent on Opioids,* January 2007.
[33] Pharmaceutical Benefits Advisory Council, 'March 2011 Short Minutes - ratified', Commercial-in-Confidence. Supplied to authors by sponsor.
[34] Pharmaceutical Benefits Advisory Council, 'March 2011 Short Minutes - ratified'.
[35] Indivior, 'Correspondence to Department of Health', 11 May 2011, Commercial-in-Confidence. Supplied to authors.

delisting would occur sooner. It was agreed that this would depend on the clinical environment given the serious patient issues involved.[36]

The buprenorphine-naloxone sublingual film was introduced in Australia in 2011 'as an alternative to tablets'.[37]

In May 2012, a further meeting occurred between the Department and the sponsor at which the Department expressed their satisfaction with the progress toward intended timing of the buprenorphine-naloxone tablet withdrawal.

Further, the sponsor was informed that the concerns expressed by the PBAC regarding the concurrent availability of buprenorphine-naloxone tablets and film – given the fact that the two formulations are not bioequivalent – would hold true for *all* tablet formulations of buprenorphine and naloxone.[38]

These meetings and correspondence affirm the sponsor's ongoing commitment to the safest and most effective use of their product, including the evolution of its formulation from buprenorphine to buprenorphine with naloxone, and from sublingual tablet to sublingual film. These documents also confirm the sponsor's willingness to work with the Department to deliver upon the PBAC's desire for the tablet's withdrawal, the achievement of which was further noted in the PBAC's March 2016 minutes which note the 'Suboxone sublingual tablet was delisted from the PBS on 1 September 2013 following the sponsor's agreement to PBAC's request for withdrawal due to quality use of medicines issues'.[39]

Growing 'noise' currently exists regarding the possible entry to Australia of a branded generic version of a sublingual buprenorphine-naloxone tablet. This is of concern for both commercial reasons for the sponsor but also in relation to the PBAC's previously stated desire that the original buprenorphine-naloxone tablet be removed from the market due to the QUM advantages delivered by the buprenorphine-naloxone film.

Indivior's commitment to harm minimisation and safe product use

Indivior's company vision is that 'all patients around the world will have access to evidence-based treatment for the chronic conditions and co-occurring disorders of addiction' with their website outlining the aspiration that, one day, addiction will no longer be viewed through the social lens of scorn and shame.[40] The website goes on to talk about enabling the medicalization of addiction so that it is recognised and treated as a chronic relapsing condition and the suffering of patients can be humanised. This commitment is certainly demonstrated in the company's ongoing work on products for these conditions and the pipeline outlined in the Annual Report.

[36] Indivior, 'Correspondence to Department of Health', 2011.
[37] Lintzeris, N., et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence'. *Drug and Alcohol Dependence*, 2013. http://dx.doi.org/10.1016/j.drugalcdep.2012.12.009 Accessed 28 February 2018.
[38] Indivior, 'Meeting with Department of Health – notes', 8 May 2012, Commercial-in-Confidence. Supplied to authors.
[39] Pharmaceutical Benefits Advisory Council, 'March 2016 Minutes - ratified', Commercial-in-Confidence. Supplied to authors by sponsor.
[40] Indivior, 'Focus on You', http://www.indivior.com Accessed 1 May 2018.

Indivior's website also speaks of their work in educating and partnering with various stakeholders, including policy makers, funders, healthcare professionals and governments through grassroots efforts. Identifying and addressing the unmet treatment needs of patients is also highlighted.[41]

This focus and work is borne out in the Australian context.

Even prior to the National Evaluation of Pharmacotherapies for Opioid Dependence, the company had been engaged with Australian policy makers and clinicians. This led to their commitment to the NEPOD process and their contribution of buprenorphine to that research.

The Federal, State and ACT Governments all contributed to funding of the NEPOD as did the National Health and Medical Research Council (NHMRC). Each Government funded research within their own jurisdiction and a number of the trials conducted in the NEPOD were also funded by the NHMRC whilst the Commonwealth Department of Health and Aged Care Project was funded by that organisation.[42] The NEPOD saw trials established in key centres to consider the effectiveness, safety, cost and cost-effectiveness of medications for opioid dependency. Indivior legacy company, Reckitt Benckiser, contributed around $50,000 to the trials as well as providing the buprenorphine used in trials in NSW, South Australia and Victoria.[43]

The company also worked with Turning Point around this time to establish the Buprenorphine Training Programme. This program was rolled out in South Australia and Victoria before subsequently being used globally. Likewise, the National Treatment Guidelines established following the Victorian trials were granted a copyright waiver to enable their use elsewhere. These guidelines, termed the "best in the world" by a former staff member, were subsequently utilised in various Scandinavian and Asian countries or used as a basis for locally developed guidelines.[44]

Importantly, patients were actively involved in the development of various materials used to communicate about buprenorphine. Individuals at Turning Point involved user groups to ensure that booklets and other materials were appropriate and patient insights, via key patient advocacy group Australian Injecting & Illicit Drug Users League, were also embedded. Somewhat controversially at the time, the company also included a patient advocate in the initial Advisory Board for buprenorphine in Australia. They also funded other research, such as a PhD in this area, in addition to the usual regulatory and health economics work. This activity has been mirrored elsewhere in the world.

In Australia, Indivior has continued the early focus on research with many of the sources used in this paper noting their contribution, particularly of buprenorphine products. The company has also been active in more recent challenges in relation to opioid dependency, particularly in relation to the growing contribution of prescription and OTC medicines to opioid dependency.

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[41] Indivior, 'Our History', http://www.indivior.com/about/our-history/ Accessed 1 May 2018.
[42] Commonwealth of Australia, *National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD): Report of Results and Recommendations*, Monograph Series No. 52, 2004. http://webarchive.nla.gov.au/gov/20140211195842/http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/mono52 Accessed 1 May 2018.
[43] Information provided to authors by Indivior.
[44] Information sourced from consultations.

The company created the *Turn to Help* (www.turntohelp.com.au) website to help patients find out more about codeine and opioid painkiller dependence. This website also provides valuable tools such as a screening test for people to test their signs of dependence as well as a search engine that helps identify local doctors who can help identify and treat dependence.

Materials have also been produced for general practitioners to help in diagnosis as well as publications, such as *Medicine Today,* running a special edition to provide 'a balanced discussion of the issues surrounding opiates, addition and pain'.[45] Like this work, many of these materials have been supported by an unrestricted grant from Indivior as part of their education work.

As also noted further in this paper, work is underway with the Faculty of Pain Medicine on a workshop scheduled for June 2018 to begin the process of creating new guidelines for the management of emergency operations in the treatment of opioid dependent patients

This work appears to reflect the company's ongoing focus on ensuring appropriate patient access to and safe use of their products. The removal of the buprenorphine-naloxone tablet from the Australian market is part of this commitment and focus and, in consultations for this paper, the authors have been struck by positive comments about the company's history of working with and in the sector.

Value and benefits of buprenorphine

The introduction of buprenorphine, both in tablet and film formulations, offered a variety of benefits, both to individuals and the broader community. The *National Pharmacotherapy Policy for People Dependent on Opioids 2007* noted that buprenorphine is 'an important alternative to methadone for the treatment of opioid dependence, and may attract more people into treatment'. The *Policy* further noted the potential advantages from buprenorphine 'in terms of safety, the relative ease of withdrawal, the need for less frequent administration, ease of transition into other treatments and flexibility of treatment'.[46]

Various trials, including many in Australian-specific settings, demonstrated the following:

Effectiveness and cost-effectiveness

Fundamentally, buprenorphine was proven as both effective and cost-effective for the treatment of opioid dependence and it was these attributes that underpinned its inclusion in its various formulations on the Pharmaceutical Benefits Scheme.

Unsupervised dosing of buprenorphine-naloxone has also been shown to be more cost-effective than supervised administration.[47]

Further evidence is discussed in the economic section of this white paper. But it is important to note that the question of 'cost-effectiveness' is different from the question of simple effectiveness. The latter is how

[45] *Medicine Today – Supplement,* 'Prescription opioid misuse: Contemporary challenges', June 2015.
[46] Commonwealth of Australia, *National Pharmacotherapy Policy for People Dependent on Opioids,* 2007.
[47] Bell, J., et al., 'A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence', Addiction, 102, 2007. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1360-0443.2007.01979.x Accessed 28 February 2018.

well the treatment compares regardless of price, whereas cost-effectiveness discounts outcomes to a per-dollar welfare gain or similar parity measure.

Ease of supervision

Buprenorphine sublingual tablets, whilst a cost-effective treatment, faced practical difficulties in terms of supervision of dosing. Tablets routinely required between 3 and 8 minutes to dissolve with the result that supervision is 'inconvenient, labour intensive and often stigmatizing for patients', particularly in community pharmacy treatment settings. In addition, this 'substantially increases the cost of treatment'.[48]

Various approaches were utilised to address this with papers reporting off-label crushing of tablets with the aim of reducing time to dissolve and supervise dosing.

Similar challenges existed in relation to buprenorphine-naloxone tablets which, whilst delivering other benefits, did not address the time taken for staff to supervise patient dosing.[49]

The introduction of the sublingual buprenorphine-naloxone film in 2011 anticipated that it would be less easy to remove given its adherence to sublingual mucosa and thus require less supervision time.[50]

Randomised trials indicated that the dosing time for the sublingual film should be reduced to around 30 seconds. Compared to the several minutes required for effective dosing of the tablet formulation, the trial outcomes expected that the film's introduction would result in supervised dosing becoming more convenient and less costly.[51] These findings aligned with the manufacturer's information.

Diversion and injecting

Post-marketing surveillance studies regarding the diversion and injection of buprenorphine-naloxone tablets were carried out from 2006 to 2008 with the introduction of the tablets being expected to help address the issues relating to diversion or misuse. This was demonstrated with levels of buprenorphine-naloxone tablet injection amongst both people injecting drugs found to be lower relative to those injecting buprenorphine from buprenorphine tablets and fewer patients receiving buprenorphine-naloxone tablets from MATOD programs also injecting their medication compared to buprenorphine or methadone.[52] This is consistent with expectations.

With the introduction of buprenorphine-naloxone film, further clinical trials were undertaken. The randomised trial that demonstrated shorter dosing time for the sublingual film also indicated that the sublingual film should deliver reduced intentional removal of doses by patients and less subsequent diversion or injection by others. This study also found that the capacity to partially or completely remove the film once dosed was related to the number of films administered and, given this, initial placement of

[48] Bell et al., 'A randomized trial of effectiveness and cost-effectiveness of observed versus unobserved administration of buprenorphine-naloxone for heroin dependence', 2007.
[49] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets', 2013.
[50] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets', 2013.
[51] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets', 2013.
[52] Larance, B., et al., 'Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised dosing', *Drug and Alcohol Dependence*, 2011. http://www.drugandalcoholdependence.com/article/S0376-8716(11)00158-X/fulltext Accessed 28 February 2018.

the films should be carefully observed to ensure that films do not overlap. Given these findings, the trial's authors concluded it was an 'example of an abuse deterrent opioid formulation'. [53]

This finding was subsequently tested and the prevalence of regular (weekly or more frequent) injection amongst patients receiving buprenorphine-naloxone film as their medication was found to be 3%. This was substantially lower than those patients receiving buprenorphine (11%) or buprenorphine-naloxone tablets (9%).[54] When adjusted for the total number of doses dispensed to patients overall, more buprenorphine and buprenorphine-naloxone tablet doses were subsequently injected compared to either buprenorphine-naloxone film or methadone doses.

The study also found that fewer people who inject drugs and who were not in treatment reported recent injection of diverted buprenorphine-naloxone film compared to methadone, and buprenorphine and buprenorphine-naloxone tablets.[55]

The decision by the Department of Health to request the sponsor to remove the buprenorphine-naloxone tablet from the market following the introduction of the buprenorphine-naloxone film reflected similar recognition of these benefits. In addition, it reflected the reality that minimising diversion and injection of the products utilised to deliver MATOD both 'reduces the harm to the individual (such as injection-related injuries and diseases, and overdose) and protects the reputation and integrity' of MATOD programs.[56]

Overdose

Buprenorphine is also associated with a lower risk of overdose than methadone, particularly in the first four weeks of treatment,[57] due to its ceiling effective on respiratory depression. There is also less risk of opioid toxicity.

Ease of transfer from one formulation to another

Randomised trials indicate that most patients can readily transfer from the tablets to the film with little requirement to adjust dosages. [58]

Heroin Use

An Australian trial showed that, when compared with remaining on a waiting list, take-home self-administered buprenorphine-naloxone was associated with significant reductions in heroin use for people with heroin dependence.[59] This was reported at all three of the trial's time points as well as an effect over the twelve-week period of the trial compared to the waitlist control group. Self-reported use of other opioids, such as illicit methadone, buprenorphine, buprenorphine-naloxone, morphine and oxycodone, was also significantly lower in the cohort receiving treatment.

[53] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets', 2013.
[54] Larance et al., 'The Diversion and Injection of a buprenorphine-naloxone soluble film formulation', 2013.
[55] The study did not find evidence of superiority of the Suboxone film formulation to the Suboxone tablet, however, in terms of reducing non-adherence or diversion.
[56] Larance et al., 'The Diversion and Injection of a buprenorphine-naloxone soluble film formulation', 2013.
[57] Dunlop et al., 'Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone', 2017.
[58] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets, 2013.
[59] Dunlop et al., 'Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone', 2017.

Crime

The trial comparing between patients receiving take-home, self-administered buprenorphine-naloxone to those on a waiting list also demonstrated significant and sustained improvements for the treatment groups at all time points in the trial and also as an effect over time in relation to crime. This is consistent with other studies of buprenorphine treatment and also represents a significant driver of the cost savings identified by the trial.[60]

Safety

In addition to the safety aspects outlined previous in regards to patients, the buprenorphine-naloxone film is packaged in a more tamper-proof unit and this is considered to decrease the likelihood of children accidentally accessing or consuming it.[61] This is important, particularly in relation to take-away doses where concerns regarding child safety and exposure to opioid treatments exist.

Other Patient Outcomes

Mental health symptoms, psychosocial functioning and quality of life outcomes were all positively impacted by the use of buprenorphine-naloxone as self-administered, take-away doses compared to being on a waiting list. These impacts were statistically significant.

Given these findings, it would be reasonable to anticipate that the advantages available from introducing greater flexibility of use together with unsupervised dosing would be captured from the introduction of buprenorphine, particularly in the film formulation with naloxone. This will be examined in greater detail below.

The *National Guidelines* and buprenorphine

The initial guidelines for buprenorphine in Australia were developed as a specific component of an implementation trial undertaken in Victoria between 1999 and 2001. The trial demonstrated that buprenorphine maintenance treatment could effectively and safely be delivered in community settings and that the outcomes achieved by patients were comparable to those delivered with methadone treatment in regards to both frequency of heroin use and treatment retention.

The guidelines developed were not intended to be research-related but rather 'relevant to the existing treatment system… [that] could be immediately adopted in clinical practice'.[62] After the completion of the trial, the guidelines developed were reviewed by a multidisciplinary panel and, with minor changes,

[60] Dunlop et al., 'Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone', 2017.
[61] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets' 2013.
[62] Bammer, G., et al., 'Fast-tracking implementation through trial design: the case of buprenorphine treatment in Victoria', *Australian and New Zealand Journal of Public Health,* 33.no.1 (2009). https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1753-6405.2009.00335.x Accessed 28 February 2018.

became the national guidelines following buprenorphine's registration.[63] Not only this but the work done in the implementation trial almost certainly led to the rapid uptake of buprenorphine in Victoria given specialist and other involvement in the trial and development of the guidelines.

Those guidelines have been updated various times since and are now, as highlighted above, incorporated into the broader *National Guidelines.*

Treatment Selection

The decision about whether or not to commence treatment with buprenorphine or methadone when substituting for another opioid should be made informed by patients' preferences and goals and made in consultation with them.

The *National Guidelines* identify some elements that should be taken into account, including:

- It is easier to 'transition in and out of treatment with buprenorphine compared to methadone' which offers benefits in terms of flexibility;
- 'Safer and easier' induction with buprenorphine usually;
- More common association of overdose together with the sedating effects of methadone;
- Different impact on cognitive function with some patients indicating that methadone has a greater effect than buprenorphine; and
- Drug interactions, particularly for patients with HIV or TB, are more likely to be clinically relevant with methadone.

Induction

In the first month of treatment, the goal is to achieve an adequate dose of medication, stabilise the patient's opioid use and to address co-existing conditions, according to the *National Guidelines.*

In inducting patients onto buprenorphine, key principles include that:

- Patients should start taking buprenorphine-naloxone unless they are pregnant, breastfeeding or are known to be allergic to naloxone. This is noted as 'an abuse deterrent strategy'; and
- Most patients will be able to achieve their target dose within a few days of commencing buprenorphine due to it being 'a safer opioid than methadone with regards to the potential for over-sedation, respiratory depression and overdose'.

Daily review is recommended for patients during the early days of treatment when commencing buprenorphine and it is recommended that the first dose of buprenorphine occur when a patient is experiencing withdrawal. Dosing is then recommended at different levels depending on the severity of

[63] The guidelines were published as *National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Heroin Dependence 2001* and authored by Lintzeris N., et al.

withdrawal experience. The guidelines note that, for patients transferring from methadone, a minority will find buprenorphine 'unsatisfactory' and request a return.

Maintenance

The *Guidelines* note that 'the characteristics of buprenorphine allow a wide range of dosing regimens, from several times a day to once every two or three days', commenting that key reasons for considering less regular dosing include patient convenience and less staffing requirements for supervised dosing.

Stabilising patients on daily dosing is recommended prior to allowing patients to try alternate-day dosing should patients wish to trial less frequent dosing. If successful, after two weeks, it is recommended that patients then try a thrice weekly dosing schedule. If not successful at any point, patients should return to a more frequent dosing schedule.

Guidelines are given as to review times, recommended doses and comfort levels for patients trialing less than daily dosing.

Takeaways and unsupervised dosing

The *Guidelines* define takeaways as 'involving the provision of medication to be taken from the dispensing point for later consumption' and unsupervised dosing as 'the consumption of medication that is not witnessed by a responsible adult'.[64]

Decisions about takeaway doses are made by the prescriber and should balance patient autonomy with the management of risk, particularly to others and the broader community.

Takeaways and unsupervised doses are noted as offering the opportunity to:

- Improve treatment outcomes for patients where increased access to takeaway doses engender positive behaviours such as regular dosing or avoidance of other substance use;
- Enhance patients' reintegration into normal daily activities and routines by reducing the need for regular pharmacy visits, particularly for those in employment or residing in rural or regional locations;
- Decrease the stigma associated with visiting dosing locations;
- Reduce patients' cost of treatment through lower dispensing and travel costs; and
- Deliver greater patient autonomy which is aligned with chronic disease management principles.

Uptake and use

[64] A person not misusing alcohol or other drugs and able to adequately assess the appropriateness of administering methadone or buprenorphine.

As highlighted above, methadone continues to retain the largest market share in MATOD programs across Australia. The introduction of buprenorphine in 2005 saw its market share grow from 25% in 2005 to 32% in 2012.[65] Following the introduction of buprenorphine-naloxone tablets, mono-buprenorphine sales steadily fell with buprenorphine-naloxone tablets accounting for the largest market share of overall buprenorphine sales from March 2007 to March 2012. The introduction of buprenorphine-naloxone film overtook sales of both tablet formulations with film being the predominant formulation from April 2012 onwards.[66]

40% of Australian MATOD patients now receive a buprenorphine-containing medicine. NSW does not differentiate between reporting of buprenorphine use compared to that of buprenorphine-naloxone. When NSW data is excluded from NOPSAD, 43% of Australian patients receive buprenorphine-naloxone, 5% buprenorphine and the remaining 52% methadone.[67] This represents a reduction of 5% of patients receiving methadone, a significant change in one year and the largest drop in methadone usage recorded in any one-year period.

Further, three states now record the majority of patients as receiving a buprenorphine-based product – Queensland, Tasmania and Victoria – in addition to the Northern Territory. This represents a significant change in recent years.

These statistics do not capture the entire picture however with substantial differences experienced depending on the treatment setting. It is worth noting that private prescribers are most likely to prescribe buprenorphine-naloxone compared with public providers and those in correctional facilities with the percentages being 23%, 21% and 3% of patients respectively. Equally, given that patients receiving buprenorphine-naloxone in NSW are recorded as receiving buprenorphine, it is worth noting that the buprenorphine-naloxone figures are significantly underestimated.[68]

Pharmacist Reported Benefits from buprenorphine-naloxone film[69]

In 2018, Indivior undertook a qualitative survey of pharmacists as part of the ongoing evolution of its product offerings for MATOD. As part of this study, and recognising the quality use of medicines issues highlighted by the PBAC when requesting that buprenorphine-naloxone tablets be removed from the market, the question of buprenorphine-naloxone tablets returning to the treatment framework was tested.

Pharmacists were clear in their overwhelming preference for the film formulation of buprenorphine-naloxone, noting that it required less monitoring, was subject (in their experience) to less diversion and, critically, there is strong patient preference for film over tablets.

The film formulation was reported as requiring patients to spend less time in the pharmacy, which is perceived as a benefit both to the pharmacist and other staff and to the patients themselves. This was

[65] Larance et al., 'The Diversion and Injection of a buprenorphine-naloxone soluble film formulation', 2013.
[66] Larance et al., 'The Diversion and Injection of a buprenorphine-naloxone soluble film formulation', 2013.
[67] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017.*
[68] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017.*
[69] So What Research, Qualitative survey of pharmacists undertaken on behalf of Indivior, 2017, Commercial-in-Confidence. Supplied to authors.

largely due to the requirement for less patient supervision whilst the observations regarding diversion of film related to it being identified as harder to spit out or remove once the patient has taken it.

These issues variously result in patients preferring the film formulation. Patients anecdotally find it less degrading not having to show their mouths to the pharmacist to confirm dissolution of their dose and they are able to leave the pharmacy more quickly.

In addition to the benefits to both the pharmacist and patient, a significant number of pharmacists, or 58%, considered that there would confusion if the buprenorphine-naloxone tablet had been kept available at the same time as the film. This was identified as a potential source of confusion without any corresponding benefit.

A further 32% of pharmacists thought there may not have been much confusion had the buprenorphine-naloxone tablet remained available but did not see any reason to maintain the tablet's availability. One pharmacist commented 'I don't think there would have been confusion we'd have all handled it but the film was just a better one for them [the patients], and we only needed one or the other'.

Only 5% of pharmacists surveyed thought maintaining both formulations on the market would have been a good thing. This was identified as due to their view of patient preference which does not correspond with the views of the majority of pharmacists and also does not reflect the benefits from minimising potential diversion.

Ongoing Evolution of MATOD

Overview of emerging Long Acting Injectable Medications

The introduction of any new medication or formulation to the MATOD 'can be associated with anxiety for patients, and can be resisted by some patients and service providers'. Questions raised typically include how new formulations compare in regard to dose effects and equivalence; adverse effects; patient satisfaction; time required for supervised dosing; and impact on treatment outcomes. [70]

At the same time, new products offer the opportunity to potentially attract new cohorts of patients into treatment and offer current or returning patients an alternative and possibly more effective form of medication.

The most recent development in relation to MATOD is long acting injectable products that aim to provide patients with alternatives to daily dosing. These extended-release formulations offer to remove many of the burdens associated with the current daily treatment framework whilst still providing the benefits available from stable ongoing therapy.

Sublocade™, the First Approved Once-Monthly Injectable Buprenorphine Formulation

On 30 November 2017, the US Food and Drug Administration approved Sublocade™, the first once-monthly injectable buprenorphine formulation, for medication-assisted treatment of opioid use disorder.[71] Indicated for patients who have been on a stable dose of transmucosal buprenorphine treatment for a minimum of seven days, Sublocade™ (buprenorphine extended-release) offers an alternative for those who may appreciate the benefits of a once-monthly injection compared to, for example, the burden of taking medication daily. This is particularly attractive in a setting such as Australia, where barriers to treatment include supervision and stigma-inducing activities (discussed further in the following chapter).

Sublocade™ injection for subcutaneous use will deliver buprenorphine to patients at a sustained rate of at least 2 ng/mL over a one-month period. Sublocade™ will be administered only by healthcare professionals and is intended to be used as part of a broader program involving counseling and psychosocial support.[72]

Sublocade™'s ability to block the subjective effects of illicit opioids, including 'drug-liking' was investigated via an Opioid Blockade Study. In the twelve-week study, Sublocade™ was demonstrated to fully block the drug-liking effect of hydromorphone that is commonly used to evaluate opioid drug-liking.[73]

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[70] Lintzeris et al., 'A randomised controlled trail of sublingual buprenorphine-naloxone film versus tablets', 2013.
[71] US Food and Drug Administration, 'FDA approves first once-monthly buprenorphine injection, a medication-assisted treatment option for opioid use disorder', News Release, 30 November 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587312.htm Accessed 16 April 2018.
[72] Indivior, 'FDA approves SUBLOCADE™ (Buprenorphine Extended-Release), the First and Only Once-Monthly Injectable Buprenorphine Formulation to Treat Moderate to Severe Opioid Use Disorder', Press Release, 30 November 2017. http://indivior.com/investor-news/fda-approves-sublocade-buprenorphine-extended-release-first-monthly-injectable-buprenorphine-formulation-treat-moderate-severe-opioid-use-disorder/ Accessed 16 April 2018.
[73] Indivior, 'FDA approves SUBLOCADE™', 2017.

In clinical trials, Sublocade™ was shown to have an overall safety profile consistent with the known safety profile of transmucosal buprenorphine, with the exception of some reactions at the site of injection. Injection site reactions were reported in under 20% of patients and none of these were serious with only one leading to discontinuation in the study.

Indivior has committed to a restricted distribution system in the USA and aims for a similar system in Australia when Sublocade™ becomes available locally. This is intended to prevent Sublocade™ being directly distributed to patients given the risks of harm or death that could occur as a result of intravenous self-administration.

Consistent with Indivior's commitment to patient access and the safe use of buprenorphine, the company has worked closely with the FDA to include appropriate warnings and precautions, including a boxed warning as part of the product's label. In addition, the company has implemented a Risk Evaluation and Mitigation Strategy (REMS) Program and pharmacies and others that order and/or dispense Sublocade are required to be enrolled in this program. Indivior has also committed to enhancing its compliance program given the anticipated increase in patient numbers.

In its briefing materials to the FDA Advisory Committee, and in addition to the benefits available due to being able to avoid the burden of daily medication adherence, the company also noted the opportunity that Sublocade™ offers to encourage compliance with the goals of MATOD 'by removing the ability to periodically discontinue medication (i.e., taking a "drug holiday") to overcome the opioid blocking effects and therefore experience the positive subjective effects of an illicit opioid'.[74]

This is supported by experience in the clinical program which recorded only two surgical removals of the product. One of these related to a patient who withdrew from the opioid blockade study and requested removal and the other was in a Phase I study where the long acting injectable was removed due to abnormal liver chemistry. No long acting injectables were surgically removed in Phase 3 studies and nor were any reports made of patients attempting removal in any Phase 3 study.[75]

Contrary to some rumours heard by the authors in consultation for this paper, Sublocade™ can be stored at room temperature for up to seven days, facilitating its entry into regular usage.

Indivior's 2017 Annual Report states that Sublocade™ 'represents an evidence-based, paradigm shift from how we approach treatment of moderate to severe opioid use disorder'.[76] In practice, the product provides a significant opportunity, as well as a requirement, to review the Australian treatment framework to further attract more patients into MATOD and to enhance the experience of those already receiving therapy.

[74] Indivior, 'RBP-6000 Briefing Document', 31 October 2017. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM582449.pdf Accessed 16 April 2018.
[75] Indivior, 'RBP-6000 Briefing Document', 2017.
[76] Indivior, *2017 Annual Report.* http://www.indivior.com/2017-annual-report/ Accessed 16 April 2018.

Other Long Acting Injectable Medication

On 1 November 2017, Braeburn Pharmaceutical announced that it received a complete response letter from the FDA regarding their new drug application for CAM2038, an investigational buprenorphine weekly and monthly depot injection for the treatment of adults with opioid use disorder in conjunction with a comprehensive treatment plan that would include counseling and psychosocial support.[77] Rather than the desired approval, the FDA had requested additional information before further considering the application.

According to Braeburn, CAM2038 is designed for 'flexible and individualized treatment from initiation and stabilisation to longer-term maintenance therapy, providing sustained buprenorphine release in once weekly and once monthly formulations'. Administration would be undertaken by healthcare professionals and the safety profile of CAM2038 has been reported to be generally consistent with the known safety profile of buprenorphine, with the exception of mild-to-moderate injection-site adverse events.[78]

In their presentation to the FDA Advisory Committee, Braeburn notes CAM2038's characteristics as including weekly and monthly dosing; pre-filled syringe; range of fixed doses; no reconstitution or mixing; delivered in any subcutaneous tissue; ease of administration; needle stick safety device; and no refrigeration.[79]

The company's website notes that a new drug application refiling is underway.[80]

Adding LAIs to the treatment framework[81]

Several assumptions and conditions exist in relation to the anticipated introduction of the LAIs to Australia's MATOD framework.

Being an injectable treatment, LAIs must be administered by a healthcare professional, either a nurse or a doctor. Both products will be administered subcutaneously and it is anticipated that patients need to be monitored for a period of time – in Sublocade™'s case, five minutes – following administration.

The LAIs will be, as with all other Schedule 8 medicines, required to be kept in locked secure storage and, although the usual wholesale delivery and other channels will be utilised to distribute LAI medication – as it is anticipated that patients will not handle the product directly – additional channels will be required to establish administration sites in Australia.

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[77] Braeburn Pharmaceuticals, Braeburn Receives Complete Response Letter for CAM2038 Injectable Buprenorphine Depot, Press Release, 21 January 2018. https://www.braeburnpharmaceuticals.com/braeburn-receives-complete-response-letter-cam2038-injectable-buprenorphine-depot/ Accessed 16 April 2018.

[78] Braeburn Pharmaceuticals, Braeburn Receives Complete Response Letter for CAM2038', 2018.

[79] Braeburn Pharmaceuticals, CAM2038 for Treatment of Opioid Use Disorder, Presentation for Joint Meeting of the Psychopharmacologic Drugs and Drug Safety and Risk Management Advisory Committees of the Food and Drug Administration, 1 November 2017. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM586734.pdf Accessed 16 April 2018.

[80] Braeburn Pharmaceuticals, 'In the Pipeline'. https://www.braeburnpharmaceuticals.com/products-and-pipeline/ Accessed 16 April 2018.

[81] Given the scheduling of the LAIs will be the same, it is assumed that similar issues will be need to be managed in their introduction. It should be noted that, in identifying these issues, the authors have utilised the Sublocade™ Product Profile provided to the authors by Indivior.

This is because, currently, pharmacists are not permitted to physically inject an LAI. Administration sites may therefore include pharmacies willing to employ nurses to administer LAIs or, given that market research indicated that this option is unlikely to be taken up by many,[82] alternative mechanisms will need to be introduced. This could involve pharmacists delivering direct to medical practices or medical practices ordering directly from wholesalers. The involvement of medical practices in administering an LAI of this nature will require these sites to meet security and other regulatory requirements. Whilst this has not been tested, given other evidence in this paper, it is reasonable to assume that this is likely to deter some practices from being involved.

Finally, it is expected that the LAIs will be subsidised by the Federal Government in line with the current approach to other buprenorphine and methadone products. Research indicates that costs for patients should be lower than current dispensing fees.[83]

Alignment with current policies

In terms of aligning with the current policy aims and goals of MATOD, the long acting injectable medications offer benefits to patients in relation to burden of treatment and the opportunity to readily achieve medication adherence.

In addition, both the products and the systems established to administer them offer the capacity to reduce the risks of diversion, misuse and accidental exposure, particularly for example to children.

As such, the long acting injectable medications closely align with current policy goals and offer new opportunities for more convenient patient treatment. They also may have a particular application in prison settings.

Potential Impact of LAIs on the treatment framework

In introducing the long acting injectable products into the market, lessons should be learnt from previous product introductions.

During the course of consultations for this paper, numerous comments were made to the authors regarding the initial introduction of buprenorphine to Australia and some of the mistakes made during that process. Comments reflected that, rather than treating buprenorphine as 'methadone II', in retrospect, buprenorphine offered the opportunity to review the model around the provision of MATOD, opportunities supported by the clinical and other studies and trials outlined above.

Whilst commenting that this was not done largely because Australia was one of the first countries in the world to pursue buprenorphine usage in its MATOD programs and clinical practice suggested that new products should be compared with and aligned with the practice relating to previously available products.

[82] Indivior, 'Market Research', Commercial-in-Confidence, supplied to authors.
[83] Indivior, 'Market Research'.

This was in order to collect effective and usable data, but some degree of missed opportunity was expressed.

In reflecting on this and the significant change that the availability of long acting injectable products represents compared to the current daily dosing framework, a significant and valuable opportunity exists to review the current treatment framework. This could lead to meaningful improvements in terms of access and other benefits to patients and, through this, to the broader community.

It should also be recognised, however, that this is not only an opportunity: the introduction of long acting products into the MATOD framework actually requires changes to the current model. This is not simply about changing the patient's experience due to these products but operational requirements of the products themselves.

As highlighted above, LAIs needs to be administered by a healthcare professional. Consequently, the current model by which pharmacists dispense MATOD products directly to patients will change as the intent is that no patient will handle the new medications. This in itself represents a significant shift and one which requires the treatment framework to change.

Other issues in the environment that will impact the treatment framework

Real-time prescription drug monitoring programs

The Australian Government is supporting the creation of a national system and has provided funding for the development of the Electronic Reporting and Recording of Controlled Drugs system to help State and Territory governments improve their monitoring and regulation of controlled medicines in 2013. In 2017, the Government announced a further investment of over $16 million to deliver the national roll-out of a Real Time Prescription Monitoring system to provide an instant alert to pharmacists and doctors if patients received multiple supplies of prescription-only medicines.

Real-time prescription drug monitoring programs are intended to identify drug diversion and inappropriate prescribing or dispensing. A real-time prescription monitoring system involves computer software to allow pharmacy dispensing records for chosen medicines to be sent to a centralised database which can be accessed by doctors and pharmacists during a consultation or dispensing process.

Moves to introduce these systems recognise the recent increases in prescription of pharmaceutical opioids and their associated harms with Federal Health Minister, Greg Hunt, noting the need to assist doctors and pharmacists to identify patients who are at risk of harm due to dependency, misuse or abuse of controlled medicines and patient who are diverting these medicines[84].

[84] Hunt, Hon Greg, 'National Approach to Prescription Drug Misuse', Press Release, 28 July 2017. http://www.greghunt.com.au/Home/LatestNews/tabid/133/ID/4309/National-approach-to-prescription-drug-misuse.aspx Accessed 10 April 2018.

Currently Tasmania has the only real-time prescription drug monitoring program with Victoria's currently in development for implementation this year and the ACT announcing their intent to create one in 2017.[85] New South Wales also has a system under development as does Western Australia whilst a real-time prescription drug monitoring program was the subject of an election promise by the current South Australian Government.[86]

The Victorian Government website, in explaining the need for real-time prescription monitoring, cites the 330 Victorian drug overdose deaths in 2015 that involved pharmaceutical medicines. It noted that this was higher than the 217 overdose deaths involving illicit drugs or the state's 252 person road toll.

Meeghan Fitzharris, the ACT's Health and Wellbeing Minister, noted the 1400 ACT patients identified between August 2016 and May 2017, who appeared to be accessing controlled medicine without authority or gaining access to quantities larger than appropriate.

Coverage of real-time prescription drug monitoring is critical in ensuring that all appropriate medications are tracked. Currently, the proposed Australian model seeks to only monitor S8 medications with the result that some opioids will be excluded, despite the growth in prescription numbers and their capacity to cause harm.

The impact of real-time reporting systems has not been significantly researched, partly because many of those in operation are only relatively recent. However, a study of an emergency department in Ohio in the United States reported that prescribers changed their opioid prescription in 41% of cases following review of the patient's history in real time. Consequently, no or fewer opioids were prescribed to 61% of those patients than originally intended. The remainder of patients, or 39%, received higher doses than originally planned. However, there is also evidence that prescribers' confidence in prescribing opioids may, in fact, be increased as a result of real-time prescription monitoring.[87]

Codeine rescheduling

Australia's Advisory Committee on Medicine Scheduling made the unanimous recommendation in August 2015 and again in March 2016 that products containing codeine should be moved from being available over the counter in a pharmacy to being prescription-only. The Advisory Committee on the Safety of Medicines agreed with this proposal and support for the change was also provided by the Australian Medical Association, the Royal Australian College of General Practitioners, the Royal Australian College of

[85] Turning Point, 'Submission: Inquiry into Drug Law Reform', March 2017. https://www.turningpoint.org.au/sites/default/files/inline-files/TP%20Submission_IDLR-3.pdf Accessed 11 April 2018; Victorian Government, 'Safescript', https://www2.health.vic.gov.au/public-health/drugs-and-poisons/safescript, Accessed 11 April 2018; Fitzharris, Meeghan, 'Losing Paul: ACT government has learned from Paul Fennessy's death', opinion piece, *The Age,* 10 February, 2018. https://www.theage.com.au/politics/act/losing-paul-act-government-has-learned-from-paul-fennessys-death-20180209-h0vudd.html Accessed 10 April 2018.

[86] Liberal Party of Australia – South Australia, 'Prescribing a Safer System for Pharmaceuticals', Media Release, 19 January 2018. https://www.saliberal.org.au/prescribing_a_safer_system_for_pharmaceuticals Accessed 16 April 2018.

[87] Shand, Fiona L. et al, 'Real-time monitoring of Schedule 8 medicines in Australia: evaluation is essential', *Medical Journal of Australia,* 198 (2), 4 February 2013.

Physicians, Pain Australia and the Rural Doctors Association amongst other health-related bodies and organisations.[88]

Research informing this decision showed that around half a million Australians misuse OTC products containing codeine and many people become dependent on them with resulting health complications.

The decision to change the scheduling of codeine medicines from Schedule 2 (pharmacy only) to Schedule 4 such that they require a prescription to be dispensed is consistent with the practice in many countries, including the USA, Japan, Russian, the United Arab Emirates and most of Europe.[89]

This decision came into effect on 1 February 2018 and was preceded by a significant advertising campaign to ensure consumers were aware of the upcoming changes. Whilst some pharmacies reported selling out of codeine amongst media reports of consumer stockpiling, interviews for this paper suggest that this has not translated into large numbers of Australians seeking medical treatment for codeine-related issues nor into people seeking help for addictive behaviour associated with codeine.

There were some suggestions that this may yet occur however as doctors and general practitioners slowly encounter individuals experiencing problems and, after initially trying to manage them, filter them into addiction and dependence services. Whether this in fact eventuates remains to be seen.

An ageing treatment population

Given the ageing population of people receiving treatment for opioid dependence demonstrated in the NOPSAD data, this is likely to create new challenges in coming years as these individuals begin to experience comorbidities and other health challenges associated, not with their dependency, but with their ageing.

Whilst the mean age in all jurisdictions is in the 41-44 year old segment, the percentage of people over 60 years old has increased significantly from 223 or 1% of total patients in 2008 to 3,192 or 6% in 2017.[90]

Assuming the ageing pattern of this population continues, which is likely given trends to date, additional challenges in other healthcare settings will emerge as MATOD patients require surgery; emergency treatment; and other health care associated with age. This will require other health care professionals, many of whom will not necessarily have exposure to opioid dependent patients in their usual scope of practice, to effectively manage and treat a cohort of patients with presentations which with they have little familiarity.

Recognising this challenge, the sponsor of Sublocade has indicated that they have initiated conversations with the Faculty of Pain Medicine to hold a workshop (scheduled by end of 2018) to draw up new guidelines for the management of acute nociceptive pain in opioid dependent patients in the MAT program.

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[88] Hunt, Hon Greg, 'Transcript of doorstep, Queanbeyan', 2018.
[89] Hunt, Hon Greg, and Murphy, Professor Brendan, 'Codeine change will save lives', Joint Press Release, 1 February 2018. http://www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarel-yr2018-hunt014.htm?OpenDocument&yr=2018&mth=02 Accessed 9 April 2018.
[90] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017.*

Treatment Framework for MATOD

Current treatment settings and arrangements

Whilst MATOD programs operate within a national framework, individual jurisdictions are responsible for administration of the program in their state or territory together with the development of local policies and determining the training and authorisation requirements for medical practitioners and other professionals involved. This results in significant disparities between the settings in which patients are treated and between prescribing patterns more generally.

The differences in treatment settings are clearly illustrated by the NOPSAD. Whilst across the country, the majority of dosing points are located in pharmacies (88.7%), there is a stark difference in relation to public and private clinic dosing locations. Nationwide, 2% of dosing points are in public clinics and 0.7% in private clinics yet, in Victoria, there are no dosing points in public clinics. In addition, in the Australian Capital Territory, Northern Territory South Australia, Tasmania, Western Australia and Victoria have no dosing points in private clinics. The public clinic model is dominant in New South Wales and Queensland however.

Victoria has many more dosing points in correctional facilities compared to other states with 13 of the 33 nationwide, although nationally these account for only 1.2% of all sites. New South Wales, Victoria and Queensland all have significant numbers of 'other' sites including hospitals, mobile sites, community health clinics, NGOs, doctors' surgeries and sites 'not stated'.[91]

The following provides a brief outline of the different arrangements in each state and territory in relation to prescriber and pharmacist authorisation and approvals, patient limits and agreements and the like.

New South Wales

MATOD is delivered in NSW through specialist clinics; community pharmacies; general practitioners; nurse practitioners; public hospitals; and in prisons and juvenile detention centres with outpatient clinics, community pharmacies and local hospitals being the most common.[92] The role of specialist clinics in NSW is of particular importance, especially compared with other states. These clinics, both public and private, are usually multidisciplinary with staff including nurses, medical practitioners and allied health professionals. Some general practitioners who are also authorised prescribers may also share case management with staff from drug and alcohol services or, in some cases, perform this role themselves.

Since 2006, nurse practitioners in NSW may also be authorised prescribers with this role performed principally in the public sector.

The Director-General of the Department of Health is responsible for approving prescribers for MATOD. To be approved, prescribers must complete the Pharmacotherapy Accreditation Course, either in person or

[91] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017.*

[92] Department of Health (NSW), 'Opioid Treatment Program: Clinical Guidelines for methadone and buprenorphine treatment', 2006. http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2006_019.pdf Accessed 3 May 2018.

on-line; successfully sit an exam; and undertake a clinical placement or have a written clinical case successfully assessed.

Prescribers are initially limited to treating no more than 25 patients although, after six months, an application can be lodged to increase this number. Any locum arrangements need to be notified to the Pharmaceutical Services Branch (PSB) of the Department of Health and no locum is supposed to accept responsibility for more than 50% above their own authorised patient number or for a total of more than 250.

An authority to prescribe is required for each patient and approval is required from the PSB before treatment can be initiated. The authority to prescribe is valid for a maximum of one year.

Services that dispense MATOD are also required to attain and maintain accreditation. Those dispensing MATOD are required to determine whether each dose is appropriate and can withhold dosing if they deem this appropriate or necessary. Patients must be positively identified before dosing occurs.

In order to receive take-away doses, patients must be assessed as reliable and stable. They must not be hazardously using opioids or other drugs, including alcohol; comply with the Opioid Treatment Program; be able to appropriately store their take-away doses; understand the potential risks of accidental dosing by children; and show improved social functioning.

The nature of NSW's geography is acknowledged within the Guidelines with seven-day-a-week on-site dosing recognised as impractical in remote areas. In this instance, services are empowered to develop an alternative policy whilst also being required to document reasons for going beyond or outside guidelines. It is not permitted to ignore the 'absolute contraindications' for take-away doses however. These include chaotic and unpredictable behaviour; being at risk of self-harm; current hazardous use of drugs; repeated intoxication on presentation for dosing; and the patient having a child(ren) living in their household and concerns existing for their wellbeing.[93]

Where take-away doses are permitted, guidelines exist as to how many doses are allowed per week which depends on the patient's length of time in treatment. These vary from zero to four for methadone and zero to 28 days scripts for buprenorphine-naloxone. Prescriptions for take-away doses are required to be in the prescriber's own handwriting and signed with the dates when a patient is to receive take-away doses identified.

Victoria

Victoria's MATOD system is largely community-based except for patients in prison or hospital. Victoria has long relied on fee-for-service treatment which is not characteristic of other Australian states and territories. In Victoria, treatment is largely delivered by GPs and the state currently has no public prescribers of MATOD.[94]

This approach differs significantly from other states and is the result of a decision by the Victorian Government during the 1990s to move to a community-based model for MATOD. Benefits anticipated

[93] Department of Health (NSW), 'Opioid Treatment Program', 2006.
[94] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017.*

from this decision included leveraging the ongoing relationship between a patient and their general practitioner; better integration of MATOD with general mental and physical healthcare of individual patients; limiting the congregating of patients around clinics and dosing points to help patients avoid their traditional drug-using community; and decreasing stigma.[95]

The approach taken in Victoria has, according to some of the consultations undertaken for this paper, resulted in stasis within the Victorian system and some other, potentially unanticipated, outcomes. The number of trainees and specialist positions in addiction in Victoria, for example, lags far behind NSW with NSW having nearly ten times the numbers of addiction doctors in training as Victoria as well as numerous funded specialist positions within each health service.[96] In addition, Victoria's focus on community care has resulted in many addiction specialists moving interstate over recent years whilst many of those remaining are apparently close to retirement.[97]

In other ways, the Victorian approach mirrors that of other states with pharmacotherapy training provided for medical and nurse practitioners. All medical practitioners, as well as nurse practitioners with a notation for a category in which buprenorphine-naloxone prescription is authorised, may prescribe buprenorphine-naloxone up to five patients without the need for pharmacotherapy training although this is encouraged. Training is mandatory in order to prescribe methadone or buprenorphine, or buprenorphine-naloxone to more than five patients.

Initially, all prescribers are limited to prescribing to no more than five patients unless under the supervision of an established prescriber. Permission is then required to manage a larger number of patients and maintaining authorisation to prescribe requires adherence to the policy for maintenance pharmacotherapy.

Separate permits are required for each patient: these need to be applied for and received from the Department of Health and Human Services being treatment begins. This is not required however when a patient is an inpatient being treated in hospital; a prisoner treated in prison; or a resident treated in an aged care facility.

Pharmacies need to apply for permission to supply MATOD and will have their systems inspected and an induction process prior to being given approval. Initially permission will be limited to treating a maximum of five patients and additional clearance is required before that number can be increased. The maximum number of patients per pharmacy is 85 unless particular authorisation is granted due to special circumstances. Pharmacists must also be certified to provide a dosing service and prescriptions are valid for a maximum of six months.

Take-away doses are permitted for patients assessed as stable by their prescriber and whose pharmacist has confirmed that dose collection and behaviour has been stable and regular. Up to four take-away doses a week may be issued to patients taking methadone if they have been in treatment for at least six continuous months. Up to six take-away doses a week may be given to patients receiving buprenorphine-naloxone after the same period whilst buprenorphine without naloxone is not recommended for take-away

[95] Department of Health and Human Services (Vic), *Policy for maintenance pharmacotherapy for opioid dependence*, effective 1 September 2016. https://www2.health.vic.gov.au/public-health/drugs-and-poisons/pharmacotherapy/pharmacotherapy-policy-in-victoria Accessed 2 May 2018.
[96] Turning Point, 'Submission: Inquiry into Drug Law Reform', March 2017.
[97] Anecdotal advice from consultations.

doses unless certain circumstances exist, such as pregnancy, breastfeeding or a documented allergy to naloxone.

Queensland

All prescribers for MATOD need to be approved by the Chief Executive of Queensland Health prior to initiating treatment. To gain approval, prescribers need to complete the Prescriber's Accreditation Course; this includes a formal training program, a knowledge test and a supervised clinical attachment within two months of the training program. This is facilitated by the Drugs of Dependence Unit within Queensland Health and authorisation to prescribe will be granted following successful completion.[98]

Prescribers are then required to get approval to prescribe to each individual they treat.

In Queensland, dosing sites may include opioid treatment clinics or community or hospital pharmacies with community pharmacies being the most common. More than a third of pharmacies in Queensland are approved as a dispensing pharmacy for MATOD.[99] To begin dispensing, the pharmacy must be provided with a letter of introduction from a patient's prescriber or clinic. This letter requires a photograph to be attached to ensure that the person presenting the letter is the person for whom MATOD has been prescribed.

As with other states, patients need to be assessed as stable before being provided with take-away doses. Criteria for stability include, but are not limited to, regular presentation for dosing; compliance with any care plan; secure and stable accommodation; regular contact with their prescriber or care manager; and no evidence of hazardous substance use.[100]

Limits for take-away doses range from zero to four a week for patients being treated with methadone and between zero a week and 31 for patients taking buprenorphine-naloxone. A stepped approach is recommended for take-away doses. Patients taking buprenorphine only should be given their take-away doses in the combination formulation.

Western Australia

MATOD is provided in Western Australia through the Community Program for Opioid Pharmacotherapy (CPOP). To become a prescriber under this program, a medical practitioner must apply; undertake a training program; do the relevant assessment; and agree to comply with the relevant policies and procedures for MATOD.[101] The Department of Health will then provide the prescriber with authorisation to participate in the program.

To maintain authorisation, prescribers need to treat a minimum of two patients in a twelve-month period. In the event that a prescriber fails to do this, refresher training may be required or an extension granted.

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[98] Queensland Health, 'Queensland Opioid Treatment Program: Clinical Guidelines 2012'. https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence?a=167342 Accessed 2 May 2018.
[99] Queensland Health, 'Queensland Opioid Treatment Program', 2018. https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/medicines/drugs-of-dependence/qld-opioid-treatment Accessed 2 May 2018.
[100] Queensland Health, 'Queensland Opioid Treatment Program: Clinical Guidelines 2012'.
[101] Western Australian Drug and Alcohol Authority, 'Clinical Policies and Procedures for the Use of Methadone and Buprenorphine in the Treatment of Opioid Dependence', 2014. https://www.mhc.wa.gov.au/media/1614/wa-clinical-policies-and-procedures-for-the-use-of-methadone.pdf Accessed 2 May 2018.

Further, a prescriber needs to provide evidence of undertaking continuing professional development activity each three years.

Once authorised, prescribers require a client authority for each patient. These are issued by the Chief Executive Officer of the Department of Health and are usually issued for two years. Sole medical practitioners are generally allowed to treat a maximum of 50 patients with MATOD with sole regional prescribers being limited to 25. These numbers may be exceeded where specific approvals are granted.

Pharmacies must likewise be authorised by the CEO of the Department of Health and must also comply with the relevant policies and procedures. All pharmacists participating in the program must complete an online training program and the individual holding the pharmacy licence must ensure that all associated pharmacists have done so. In addition, participating pharmacists must undertake continuing professional development and engage with the online training updates provided.

Participating pharmacies can dispense to a maximum of 50 patients per day or seek an authorisation for additional patients.

As in other states, take-away doses may be prescribed for patients deemed stable in treatment with similar criteria in terms of definitions and requirements. An application and agreement must be completed for all patients requesting take-away doses and the patient must sign the agreement. No take-away doses will be provided to patients who have been in treatment for less than six months, no more than three take-away doses of methadone will be permitted in a week and no more than four doses of Suboxone where the patient is receiving dosing daily. Prescribers can apply to prescribe more than these amounts on a regular basis where there are exceptional circumstances. These are usually work- or health-related and are approved on a case-by-case basis.

South Australia

The MATOD program in South Australia is delivered by medical or nurse practitioners and there are also four public clinics that are operated by Drug and Alcohol Services South Australia that are involved. It is estimated, however, that community prescribers, the majority of whom are general practitioners, manage two-thirds of patients.[102]

The Drugs of Dependence Unit within SA Health is responsible for overseeing MATOD authorisation and approvals in South Australia. In 2011, the Suboxone® Opioid Substitution Program (SOSP) was introduced which allows up to five patients to be treated for opioid dependence with buprenorphine-naloxone film by any medical practitioner before the practitioner needs to undertake accreditation training. The practitioner is still required to be authorised however.

[102] SA Health, 'GP Program - Medication assisted treatment for opioid dependence'. http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs/drug+and+alcohol+programs/gp+program+medication+assisted+treatment+for+opioid+dependence Accessed 2 May 2018.

Accreditation is required by a medical practitioner before they can treat more than this number of patients with buprenorphine-naloxone, with buprenorphine alone or methadone. Accreditation involves training, an exam and clinical placement and authorisation is needed before treatment can begin.[103]

Training is offered to South Australian pharmacists and interns and guidelines exist to assist them in delivering MATOD. Patient/pharmacist template contracts are provided as part of the guidelines and the pharmacy is required to keep a signed copy.

In terms of take-away doses, these are not permitted in the first two months of treatment and, for the first nine months of treatment, take-away doses must not exceed six doses per month at pharmacies open seven days a week or two doses a month, plus public holidays and Sundays, at pharmacies open six days a week. This doubles to twelve doses a month at a pharmacy open seven days and to eight doses a week at a pharmacy open six days a week from nine to eighteen months of treatment whilst, after eighteen months, take-away doses can be increased further. A patient must receive at least three supervised doses weekly of methadone however and at least two of buprenorphine even after this time.[104]

Tasmania

Tasmania delivers MATOD through both specialist public clinics and community-based medical practitioners with both hospital and community pharmacies involved in dispensing. Tasmania acknowledges the challenges facing its population, nearly half of whom live in rural and remote areas, noting that multipurpose health centres or community hospital pharmacies are critical in dispensing.[105]

Alcohol and Drug Services (ADS) are responsible for accrediting doctors and pharmacists to prescribe and dispense MATOD. ADS are also responsible for the initial assessment and induction of patients; managing the care of complex, non-compliant or moderate to high risk patients; supporting primary care and dosing pharmacies; and providing access to other services. It is ADS that transfers patients to community-based medical practitioners where appropriate and/or possible.

Primary care physicians can assess, induct and stabilise patients if they are approved by the ADS; have an appropriate prescribing authority for each patient; and they are experienced in MATOD. A twelve-month probationary authorisation is issued initially which also involves peer support, review and advice sessions. Ongoing authorisation involves annual renewal through completion of a competency-based e-learning package.

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[103] SA Health, 'Guidelines for South Australian pharmacists dispensing Medication Assisted Treatment of Opioid Dependence', 2016. http://www.sahealth.sa.gov.au/wps/wcm/connect/8875c9804008e393b7ffbf4826472d56/Pharmacist+Guidelines+for+SA+Pharmacists+Dispensing+MATOD+FINAL+Jan+2016.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-8875c9804008e393b7ffbf4826472d56-lztg2QA Accessed 2 May 2018.

[104] SA Health, 'Policy for non-supervised dosing of methadone and buprenorphine in drug treatment programs'. http://www.sahealth.sa.gov.au/wps/wcm/connect/a04170004ddd0c8e9d5dff6d722e1562/MATOD+unsupervised+dosing+policy.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-a04170004ddd0c8e9d5dff6d722e1562-m8aZ5q2 Accessed 2 May 2018.

[105] Department of Health and Human Services (Tasmania), *Tasmanian Opioid Pharmacotherapy Program, Policy and Clinical Practice Standards*, 2012. http://www.dhhs.tas.gov.au/mentalhealth/alcohol_and_drug/publications/statewide_strategy_and_plans/tasmanian_opioid_pharmacotherapy_policy_and_clinical_practice_standards Accessed 3 May 2018.

Authorities are issued for each patient commencing MATOD and limits exist to each medical practitioner's caseload. A full time general practitioner can prescribe MATOD to a maximum of 20 patients but applications can be made to the Clinical Director of the ADS to increase this number.

In terms of pharmacies, to become a dosing site for MATOD, the ADS must approve the pharmacy and then each pharmacist involved in dosing requires accreditation. This accreditation requires the pharmacist to participate in a professional development program and examination. It is recommended that each patient is interviewed by a pharmacy before accepting them as a new patient. Detailed instructions are provided regarding dosing procedures for all MATOD medications and take-away doses can be issued to patients considered stable in treatment.[106]

Australian Capital Territory

In the ACT, prescribers of MATOD must follow the *National Guidelines* and, further, endeavour to comply with local policies and procedures wherever possible.[107] Prescribers need to be approved by the Chief Health Officer before prescribing MATOD as well as holding an endorsement if they wish to prescribe for more than five patients or initiate patients onto treatment although this is waived if they work in specific ACT institutions, such as prisons or hospitals. To gain endorsement, prescribers need to undergo training, be examined and also undertake a practical placement.[108]

Before pharmacists begin dosing patients, they are also required to undertake training. Their training, 'Risk Management of the Process of Dosing Drug Dependent Customers' is run by Canberra Hospital Pharmacy Services.

Community pharmacies also require licenses in order for dispensing to take place. They are licensed as Opioid Dependency Treatment Centres for up to three years and the holders of these licenses need to ensure that all pharmacists and pharmacy staff involved in MATOD have completed the required training course and examination for dispensers in the ACT. Refresher training for both prescribers and pharmacists is required every five years.

To be eligible for take-away doses, patients need to be clinically assessed as stable in treatment. Prescribers then need to detail the authorisation of take-away doses and these must also be maintained on the patient's record. Limits exist depending on how long a patient has been in treatment. These vary from 0 to 4 doses per week for patients taking methadone and from 0 to 27 out of 28 days for patients on buprenorphine-naloxone.[109]

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[106] Department of Health and Human Services (Tasmania), *Tasmanian Opioid Pharmacotherapy Program, Policy and Clinical Practice Standards*, 2012.

[107] ACT Government, 'Opioid Maintenance Treatment', http://www.health.act.gov.au/our-services/alcohol-and-other-drugs/opioid-maintenance-treatment Accessed 4 May 2018.

[108] ACT Health, 'Opioid Maintenance Treatment in the ACT: Local Policies and Procedures', http://www.health.act.gov.au/sites/default/files//Opioid%20Maintenance%20Treatment%20in%20the%20ACT%20-%20Local%20Policies%20and%20Procedures%202018.pdf Accessed 4 May 2018.

[109] ACT Health, 'Medicines, Poisons and Therapeutic Goods (Category Approval) Determination 2018 (No 1), Notifiable instrument NI2018-77', 2018. http://www.legislation.act.gov.au/ni/2018-77/current/pdf/2018-77.pdf Accessed 4 May 2018.

Significant processes exist for patients transferring in or out of the ACT, with four weeks notice recommended for patients seeking a permanent transfer either to or from the Territory.[110]

Northern Territory

A separate 'Application for authorisation to prescribe a restricted Schedule 8 substance for the treatment of addiction' must be filled out by an accredited prescriber for each individual patient in the Northern Territory and provided, together with a photograph of the patient, to the Department of Health, Medicines and Poisons Control. The authorisation must be signed and returned to the prescriber before treatment can be initiated.[111]

Prescribers also need to complete approved training prior to providing MATOD and, further to this, show ongoing clinical involvement and undertake refresher training in order to continue doing so.

A contract is also drawn up between the prescriber, the patient and the supplying pharmacy for all maintenance treatment and this information is stored in the Drug Monitoring System database.

Prescriptions must include the name of the dispensing pharmacy; the dosage regime including specific dosing days; and any takeaways allowed. The prescription is valid for three days from the prescribing date or the start date if they are different. In the event that a prescription is not presented within three days of prescribing, it becomes invalid. Prescriptions can only cover a supply period of three months.[112]

In terms of unsupervised or take-away doses, these may be prescribed to patients who are defined as stable; have reduced or stopped using illicit substances; and have provided urine samples clear of illicit substances. The maximum doses is one per week for people on alternate day dosing or three per week for people on daily dosing unless otherwise authorised by the Chief Health Officer. There are requirements for the labeling and storage of these doses.

Challenges and barriers with treatment framework

Whilst there is significant unmet demand for treatment in Australia,[113] a number of challenges and barriers exist in relation to the current treatment framework. These range from the capacity for patients to effectively access treatment through to cost considerations and the patient experience.

Challenges and barriers with treatment framework: Access

Prescribers – numbers and location

The shortage of prescribers for MATOD programs in Australia has long been identified as a significant challenge in terms of meeting current and projected demand with a study in the early 2000s reporting

[110] ACT Health, 'Opioid Maintenance Treatment in the ACT: Local Policies and Procedures'.
[111] Australian Institute of Health and Wellbeing, *National Opioid Pharmacotherapy Statistics 2017.*
[112] Northern Territory Department of Health, 'Summary of Requirements for Prescriptions for Schedule 8 Substances (S8s)', https://health.nt.gov.au/professionals/environmental-health/pharmacists-and-schedule-8-medicines Accessed 3 May 2018.
[113] Ritter and Chalmers, *Polygon*, 2009.

shortfalls in all four of the states examined – New South Wales, South Australia, Queensland and Victoria.[114]

A later study published in 2011 showed that, of the 168 Victorian GPs first authorised to prescribe MATOD, 46% of them *never* held a patient permit whilst, at any given time, around two-thirds of them did not hold a permit. Those GPs who were treating patients usually had fewer than ten patients whilst only 12.5% ever prescribed to more than 50 patients.[115] This is also particularly problematic in Victoria given the traditional concentration of patients with a small cohort of prescribers. This was noted in the same study, with two GPs at one point prescribing to almost half of the state's 2,400 MATOD patients and one GP holding nearly 900 patient permits. Victoria continues to be reliant on a relatively small cohort of prescribing GPs.

A number of reasons are reported for the shortage of prescribers providing MATOD. The majority of GPs invited to undertake training for MATOD decline and, of those who do undertake training, the majority prescribe to either few or no patients.[116]

A study undertaken with Victorian GPs explored this situation and identified a number of issues. Those GPs who chose not to undertake training for MATOD were principally influenced by unpleasant experiences previously with patients seeking drugs who were not regular attendees at their practices. Other factors also influenced their decisions, including the opinion that the work 'is not enjoyable and quite stressful', current heavy workload, poor remuneration from the work and the pejoratively assessed value of the program compared to treating patients with 'real illnesses'.[117]

Of those GPs who chose not to prescribe following their training, numerous reasons were given. These included: disapproval of colleagues or practice staff; current patient workload, although this was a significant deterrent only for solo GPs and those in rural locations; part-time work, especially in relation to female GPs; lack of confidence in prescribing MATOD; lack of patients; remuneration; and, over time, deskilling.

Other GPs who did undertake training and prescribed clearly had different experiences and motivations, including recognition of local need, an interest in MATOD more generally and a belief in the practice as 'an important treatment that should be offered in general practice'.[118]

The challenges of geographic access to GPs who prescribe MATOD are well-documented in the literature, particularly relating to regional and rural areas in Australia. Demonstrating it extremely effectively however is the *Turn to Help* website where you can enter any Australian postcode and the website will identify those GPs nearby who 'understands how to treat opioid painkiller dependence'.

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[114] Hotham, E., Roche, A., Skinner, N. and Dollman, B., 'The general practitioner pharmacotherapy prescribing workforce: examining sustainability from a systems perspectives', *Drug and Alcohol Review,* 24, September 2005. http://www.academia.edu/17892224/The_general_practitioner_pharmacotherapy_prescribing_workforce_examining_sustainability_from_a_systems_perspective Accessed 28 February 2018.

[115] Longman, C., Lintzeris, N., Temple-Smith, M. and Gilchrist, G., 'Methadone and buprenorphine prescribing patters of general practitioners: their first 5 years after authorisation', *Drug and Alcohol Review*, (30) July 2011. https://www.ncbi.nlm.nih.gov/pubmed/21355929 Accessed 28 February 2018.

[116] Longman, C., Temple-Smith, M., Gilchrist, G. and Lintzeris, N, 'Reluctant to train, reluctant to prescribe: barriers to general practitioner prescribing of opioid substitution treatment', *Australian Journal of Primary Health,* 18 (4) November 2012.

[117] Longman et al, 'Reluctant to train, reluctant to prescribe', 2012.

[118] Longman et al, 'Reluctant to train, reluctant to prescribe', 2012.

Entering inner Melbourne postcodes, such as Richmond (3121), yields significant results with 25 clinics or individual doctors listed in that instance. Compared to that, the towns of Warrnambool (3280), Portland (3305) and Stawell (3380) in Victoria's west – towns of 35,000, 11,000 and 6,000 people each – delivers no listings beyond the phone number for DirectLine, a confidential alcohol and drug counselling and referral line.

Similar results are returned in New South Wales with Cremorne (2090) and Penrith (2750) both returning 25 listings whilst Tamworth (2340) and Griffith (2680), cities of around 63,000 and 30,000 people each returning none. Wagga Wagga (2650), which has a population of 65,000, and Dubbo (2830), with nearly 40,000 people, return 4 and 2 listings respectively.

Whilst naturally this does not represent either a comprehensive or scientific study, and the website notes that it may not include all doctors and clinics in an area, the above is a good indication of the challenges faced by those living outside metropolitan centres without even exploring the equivalent figures in the less populous states and territories.

Access to dispensing sites

A number of issues impact the number and location of dispensing sites including jurisdictional arrangements; metropolitan, regional and rural geographic location; and the decision of the local pharmacists in providing services. As with prescribers, the literature reports limitations to both numbers and locations of dispensing sites with corresponding impacts for patients on access to treatment.

Stigma is also a reason why pharmacists may not provide MATOD. Key reasons identified as influencing pharmacists' participation are mainly stigma and fear although lack of financial support for patients is also noted.[119]

Whilst there are subsidy schemes in Tasmania and the ACT and an incentive payment in New South Wales, most pharmacists receive no payment for their participation in MATOD beyond the payment of dispensing fees by patients.[120] Evidence indicates that these dispensing fees do not meet the costs of the program to pharmacists.[121] This is likely to undermine pharmacists' satisfaction and involvement in the program as well as the capacity to attract new pharmacists.[122]

Travel

Stories abound in the literature regarding both the travel requirements facing patients and the effect opening hours can have on travel. This has impacts for patients in relation to their capacity to work and maintain treatment. Danny, a 46 year old male, is reported in one article as travelling a significant distance

[119] Charr, B et al, 'Factors influencing pharmacy services in opioid substitution treatment', *Drug and Alcohol Review*, 32, July 2013. https://www.researchgate.net/publication/235739194_Factors_Influencing_Pharmacy_Services_in_Opioid_Substitution_Treatment Accessed 19 April 2018.
[120] Penington Institute, *Chronic unfairness: Equal treatment for addiction medicines?* Carlton, Vic: April 2015.
[121] Feyer, A., et al., *A National Funding Model for Pharmacotherappy Dependence in Community Pharmacy.* Sydney, NSW: Department of Health and Ageing, The Pharmacy Guild of Australia, National Drug and Research Centre, Price Waterhouse Coopers, 2008. http://6cpa.com.au/wp-content/uploads/A-National-Funding-Model-for-Pharmacotherapy-Treatment-for-Opioid-Dependence-in-Community-Pharmacy-Final-Report.pdf Accessed 28 March 2018.
[122] Penington Institute, *Chronic unfairness,* 2015.

to be dosed at a clinic that opened at 6.15am, earlier than a dosing point local to him, to gain a favourable position in the queue and receive his treatment before work.[123]

The comments above regarding the geographic location of treating doctors and dispensing pharmacists again reinforces some of the challenges likely to be experienced in relation to travel for those participating in MATOD programs.

Limits to patient numbers

Various limits exist to patient numbers across the country in regard to treatment and/or dispensing.

There are also treatment caps in some jurisdictions for prescribers. All medical practitioners and nurse practitioners in Victoria must obtain a permit before prescribing buprenorphine-naloxone. However, to facilitate better access for patients, these individuals are allowed to prescribe buprenorphine-naloxone to up to five patients without completing the relevant training program.[124]

New South Wales has, for example, a cap on pharmacies that limits their MATOD base to 50 patients,[125] although patients receiving their medication weekly are not included in this cap. This is not the case in other states, however, and Victorian pharmacies are, in some instances, reported as providing services for hundreds of patients. No evidence exists to suggest that this service is of a lesser quality than that provided in New South Wales. [126]

Opening hours

Whilst opening hours of dosing points has long been reported as an issue for patients,[127] with more patients receiving treatment being in stable or regular employment, the capacity of these individuals to attend pharmacies for dosing during work hours is limited.[128] These constraints have the capacity to discourage people from receiving treatment or from pursuing work opportunities that help to re-integrate them into their communities, thus also affecting their economic circumstances.

Challenges and barriers with treatment framework: Cost

Dispensing fees

Financing for MATOD is generated from three key sources: the Commonwealth Government which pays for medication and GP services provided via Medicare; State and Territory Government which, where applicable, support public clinics and hospitals which prescribe and dispense; and patients who pay fees for

[123] Fraser, Suzanne, 'The chronotype of the queue: Methadone maintenance treatment and the production of time, space and subjects', *International Journal of Drug Policy,* 17: 2006. http://www.ijdp.org/article/S0955-3959(06)00081-8/pdf Accessed 28 February 2018.
[124] Department of Heath and Human Services (Vic), *Policy for maintenance pharmacotherapy for opioid dependence*, 2016.
[125] Government of New South Wales, *Poisons and Therapeutic Goods Regulation 2008,* S92(1). https://www.legislation.nsw.gov.au/#/view/regulation/2008/392/part4/div4/subdiv1/sec92 Accessed 19 April 2018.
[126] Puplick, 'Towards Reintegration', 2014.
[127] Fraser, 'The chronotype of the queue', 2006.
[128] Puplick, 'Towards Reintegration', 2014.

GP consultations and dispensing of medication. In NSW, where public clinics operate and exist, 37% of total program costs are identified as being paid by patients.[129]

Dispensing fees are an ongoing issue for both MATOD patients and their pharmacists. Whilst Medicare rebates are paid for GP consultations, dispensing fees charged by the pharmacists vary from $1 to $10 a day. This payment may also be per dose with the result that the patient pays the fees regardless of whether they are dispensed with takeaway doses, and thus make fewer visits to the pharmacy, or are dispensed with their doses daily.

The cost of dispensing fees on patients is 'profound, potentially jeopardizing treatment continuity and their therapeutic relationship with their pharmacists'[130] with one Australian study recently finding that the main reason that patients stopped opioid dependency treatment was the financial impact of dispensing fees.[131] These fees add to the financial stress already experienced by patients and this stress is not helpful to achieving the goals of MATOD, including being an active member of the community given the additional marginalisation associated with poverty.

This situation is not experienced by other patients receiving medication for lifestyle-related or chronic diseases, with the Penington Institute noting that people with smoking-related illnesses or diabetes do not pay dispensing fees for their medication. The authors agree with the Penington Institute that this is clearly discriminatory and inequitable and makes little economic or other sense.[132]

Costs of receiving treatment

Treatment is free in public clinics and this has long been recognised as a major incentive to attend these dosing points compared to private clinics or pharmacies.[133] Whilst the cost-shifting that may be involved in this may not be substantive, certainly reports exist of patients choosing to remain at public clinics when they might well otherwise shift to treatment in a private setting.

Of greater importance is the fact that, where this occurs, a person remaining in treatment in a public setting may prevent another person accessing treatment from that clinic with its attendant opportunity cost.

Challenges and barriers with treatment framework: Patient Experience

Patient experiences with MATOD are often unfavourable in terms of travel, opening hours and the like as mentioned above. The impact of these issues on maintaining patients in treatment needs consideration.

[129] Puplick, 'Towards Reintegration', 2014.
[130] Penington Institute, *Chronic unfairness',* 2015.
[131] Shepherd, A., et al., 'The impact of dispensing fees on compliance with opioid substitution therapy: a mixed model study', *Substance Abuse Treatment, Prevention, and Policy,* 9 (32) 2014. https://substanceabusepolicy.biomedcentral.com/articles/10.1186/1747-597X-9-32 Accessed 28 February 2018.
[132] Penington Institute, *Chronic unfairness',* 2015.
[133] Fraser, 'The chronotype of the queue', 2006.

Queues

Whilst anecdotal concerns are raised by pharmacists and other practitioners in regards to offering MATOD, the experience of patients is also not always positive. Queues, both in clinical and pharmacy settings, are mentioned regularly as are the behaviours in those queues.

Alison, a 44 year old woman, reported long, slow queues as a 'permanent feature of treatment' with all sorts of negative interactions as people aimed to gain a more positive position. In winter, she spoke of fires being lit so that those receiving treatment could keep warm and noted that behaviour like this 'gives everyone a bad name'.[134]

Lisa, a 34 year old woman in the same study, spoke about how discussions in the queue about jail experiences, violence and criminal activity resulted in her being wary of various individuals receiving treatment and how they seemed 'dangerous type people'. Yet, many patients spend significant amounts in each other's' company due to the process and organisation of daily dosing routines and set-ups.[135]

Lisa also highlighted the fact that often being around the other patients in treatment in the queue was problematic due to the capacity for the environment to bring others together who are engaged in illicit behaviour: 'there are people there who want to do things like, sell methadone, buy methadone or um sell drugs, buy drugs, whatever'. For those seeking to undertake treatment and avoid illicit drug use, these environments are clearly not ideal.

Availability and flexibility of dosing

Whilst accessing a prescriber or dispenser may be a barrier to treatment, so too can be the availability of a patient's dosing. Whilst some of the challenges to relation to accessing take-away doses have been identified above, it is important to also reflect how this impact patients' experiences.

When talking to clinicians and others in preparing this paper, issues of availability of dosing came up in relation to work situations, holidays and other situations. Patients were reported as being limited in their movements outside their own environments due to their dosing regime, particularly in relation to the availability of take-away doses. The paperwork and 'bureaucracy' involved in getting doses dispensed in different states was mentioned and the time needed to organise this is clearly challenging. Dosing flexibility was raised as an issue by many, even, ironically, in relation to individuals wishing to attend the National MATOD Summit in Canberra in May 2018.

Whilst this impact may not be dominant in people's minds, the impact on patients trying to organise attendance at work functions, go on family holidays or potentially attend events, such as weddings or birthdays, this matter should not be ignored as impacting on patients' experience of MATOD and possibly also on their retention or continuity in treatment.

[134] Fraser, 'The chronotype of the queue', 2006.
[135] Fraser, 'The chronotype of the queue', 2006.

Stigma

Stigma is also a common part of the patient experience and is experienced from both health professionals and the general public. According to the NSW *Towards Reintegration* report, 'no issue figured more prominently in the responses of patients, families, carers and their organisations than the enormous extent of stigma and discrimination experienced, directly and indirectly, overtly and subtly against patients' in MATOD programs.[136]

Examples were provided of discrimination and stigma in numerous settings and instances including:

- Patients in pharmacies being required to wait until everyone else in the pharmacy was either served or had left before receiving treatment;
- Particular times of the day being specified for MATOD patients;
- Service providers making negative or disparaging comments about patients receiving MATOD, including about their status or moral value;
- Lack of respect for the privacy of MATOD patients;
- Specific entrances and exits by which patients had to access pharmacies and health centres; and
- Inappropriate or prejudicial language.

This list of examples mirrors like instances identified throughout the literature.

Queuing is also associated with stigma. Renee, aged 37 years, reflected this when speaking about her experience when seen by people who knew her in a queue for treatment: 'I've got to stand out the front [of the pharmacy]…and nobody will leave because their place will be lost…and it's obvious who they are, and I was standing there one day and three of the mothers from the school walked past, looked and then did a double take…now I stand up the other end'.[137]

[136] Puplick, 'Towards Reintegration', 2014.
[137] Fraser, 'The chronotype of the queue', 2006.

Economic and social benefits and challenges

General Model

In order to create an economic model for opioid dependence and treatment, we have considered four components, viz.:

1. Losses of economic opportunity, due to addiction. This may be considered either as an aggregate of lost earning power to individuals, or a broader loss of productivity and tax revenues. This may include potentially productive activity lost due to impairment, premature death or imprisonment;

2. Direct welfare costs. These will include both support costs due to incapacity to participate in the productive economy, as well as the costs related to criminal activity, such as investigation and enforcement;[138]

3. The cost of medical support, both acute support (e.g. for overdoses, comorbidities) as well as for MATOD. Some of these are public costs (e.g. the MBS and PBS, as well as State health services) and some are out-of-pocket costs; and,

4. A series of discount factors, which represents the ease with which patients with opioid dependencies are able to access individually appropriate treatment. The definition of individually appropriate treatment for our purposes is: 'the treatment with which the patient will most likely comply for an extended period'. This may not be a complete lifetime as given the nature of dependency, there is always risk of relapse.

This gives us an economic approach which has three units of cost, discounted by the factor represented by improvement in access. Expressed as a simple equation, it would be:

$$c = -\{\Sigma f_{(1,2,\dots,n)} d_f + \Sigma w_{(1,2,\dots,n)} d_w + \Sigma m_{(1,2,\dots,n)} d_m\}$$

Where:

c is the aggregate *cost* or loss associated with opiate addiction in Australia

$\Sigma f_{(1,2,\dots,n)}$ is the sum of all *foregone* economic opportunity

$\Sigma w_{(1,2,\dots,n)}$ is the sum of all direct *welfare* costs

$\Sigma m_{(1,2,\dots,n)}$ is the sum of all *medical* costs

$d_{(f,w,m)}$ are the respective discount factors representing ease of access to and effectiveness of treatments to mitigate these costs.

Before looking at potential valuations of each factor, some further assumptions are noted.

[138] The latter are opportunity costs to welfare due to diversion of monies that might be spent on other public goods.

First, *c* will always be a negative number. We are dealing in the field of opioid dependence where a chronic relapsing condition is generally only ameliorated, not resolved. Positive outcomes from this are therefore lower costs, such as costs of management, and societal and individual gains, not nil costs or an overall positive outcome.

Second, to simplify the model, we have not considered tax effects. These are to some extent represented in *f*, as lost economic opportunity is also nominally an opportunity cost to the Treasury. There are also tax revenues associated with private sector provision of services, from medicine to prisons, but inclusion of these would seem to trivialise the problem: it would simply lead to a nett cost of these items to the public purse, which is different from the other discount factors we consider. There will also be some revenues from income tax of people employed in MATOD provision, but this is equally not included.

Third, we have not considered the cost of criminal activity impacting on the broader community, whether this is crime against person and property. These are certainly significant costs but, within our model, the costs of investigation and enforcement (including incarceration) offer a proxy, as discussed below.

As a corollary to this, we have not considered costs and risks associated with the broader black economy, part of which is financed through illegal sales of opioids (both street and prescription medicines). A subset of this is that we have not focused on the issue of diversion of prescribed opioid substitution medicines. We view this simply as a fact of the illicit drug market, not as a separable cost (although it should be taken into account in program design and guidelines).

Nonetheless, we might speculate that programs that have their greatest effect on crime reduction (using the investigation/prison proxy) have a greater value than those that improve productivity or reduce government costs. This is a matter of political limits: crime reduction is commonly a stronger impetus to policy change than fiscal savings or increased productivity.

This issue of political constraints is important. We presume that if this type of model were to be followed, Governments would identify preferred cost and loss metrics against which to measure predicted v. actual outcomes. These would provide actual dollar amounts against which to apply our proposed discount factors.

And finally, although this is a model equally applicable at the individual patient level, we are interested in this as a national policy question, so are looking at aggregate costs. The issue of disparity or distribution of patient type is addressed below in the discussion on discount factors. Essentially, it is a matter of distribution and we are predominantly interested in the means.

Cost Components

It is not within the scope of this paper to undertake a new analysis of the economic burden of opioid dependency and/or its treatment in Australia. Instead, we have undertaken a desktop survey of observed cost sources, which is discussed below.

However, to understand how we might undertake a relative valuation of different regulatory settings for MATOD, we need to understand the componentry of what we are seeking to avoid (or in our model, discount).

Without becoming excessively granular, we would offer the following bases for valuation. First, for income foregone:

> $\Sigma f_{(1,2,\ldots,n)}$ is the least complicated figure. Given we are dealing with a national question, we would treat it as the reduction in per capita GDP (currently $63,788[139]) from average opioid impairment multiplied by the number of prospective patients for treatment:
>
> So, $\Sigma f_{(1,2,\ldots,n)} = \$63{,}788 * d_i * p_o$ where,
>
> d_i is the average impairment (discount) applicable to earning potential across all patients in MATOD programs. This is a non-zero figure, as many individuals with an opioid dependency do some work, though some do not. This appears to be roughly bimodal, between those people taking illicit opioids compared to those using prescription or over-the-counter opioids, and,
>
> p_o is the population of prospective candidates for treatment.

A note here: it is commonly assumed that opioid dependency is a issue experienced by lower socio-economic groups, and consequently, we might expect *potential* GDP contribution (earning potential) to be lower than the average. This is inconsistent with much of what we know about opioid dependency in Australia. And further, it is a pejorative assumption, as we cannot make any credible propositions about what this cohort may have earned in the absence of their shared condition. So, the average is appropriate.

Looking at direct welfare costs:

> $\Sigma w_{(1,2,\ldots,n)}$ is a sum of broadly three categories of potential welfare costs, variously:
>
> Welfare payments to individuals, such as unemployment benefits, which would not be required but for the dependency described above;
>
> Welfare payments to dependents, including partners and children, from economic impairment and family breakdown; and,
>
> The direct costs to the public purse of criminal activity, which may include policing costs, incarceration, community case management (e.g. parole) and any compensation paid to victims of drug-related crime from public sources.

As noted above, the last point is used as a proxy for the costs borne by the victims of crime. Our reasoning here is that – as we are principally interested in relative effects – any effect (discount) to the rate of crime will be equally felt in terms of demand on public services, as it will by the community. This is to say that we are interested in what will reduce the rate of crime, and investigation and enforcement is an effective proxy for this.

[139] https://data.worldbank.org/indicator/NY.GDP.PCAP.CD accessed 16 April 2018. Data provided as US$49,755, converted at a rate of 0.78.

Third, on the cost of medical services:

> Looking at $\Sigma m_{(1,2,\ldots,n)}$ we hold that it is self-evident that the cost of unplanned medical services (i.e., ambulance, emergency admission, treatment of communicable diseases) exceeds the cost of programmed treatment.
>
> The import of this is that the aggregate burden of medical costs should go down at a predictable rate where we introduce treatments for opioid dependence in place of unmanaged addiction. The addition of treatment programs will not increase overall costs.
>
> Importantly, there may also be some cost-shifting here. At least part of the cost of opioid treatment – particularly dispensing – will be borne by the patient, whereas we would expect no capacity to recoup unplanned medical interventions.

This understanding of the various cost components further informs our treatment of proposed discount factors.

Valuing Discount Factors

Each of the discount factors $d_{(f,w,m)}$ should be valued between 0 and 1. 0 would represent complete mitigation of the cost-base, whereas 1 would suggest no impact. We do not anticipate values greater than 1, as this would imply that MATOD is likely to exacerbate costs and losses. In theory, this is possible in the case that – for example – we preferred radical reduction in crime even if it led to greater work impairment through sedation, but this is not consistent with the programs considered by this paper or any approaches suggested during our consultations.

Rather than using a single overall discount factor designed to represent access and compliance, we have allowed that different regulatory settings, and different treatment programs/products will affect the independent cost-bases at different rates.

We discuss the features of various settings and options further below, but our capital assumptions are:

> d_f will increase as programs and products are made 'work-friendly'. This means that they minimise the time taken to receive treatment, as this is an opportunity cost to time available for work. This is particularly sensitive to frequency of presentation for dosing, as this is likely to constrain participation in normal work hours. Further, the clinical effects of the product will be relevant.
>
> d_w is a hybrid of behaviour modification, combined with access to work, relating it in part to d_f: people in work require less welfare support. They are also less likely to commit crime, because they have income and more predictable costs, though this is also an effect of fundamental behaviour modification associated with appropriate treatment and dose management. In terms of economic theories of rational criminal activity, these people should also have a lower expected return (which may be negative).

d_m is in a way the most generic measure of access and compliance: unpredictable health interventions should be radically reduced by programmatic management with modern medicines.

There is clearly some overlap and intersection between these factors, but they require individual values. For the purposes of this paper, we have allocated some nominal values, effectively providing a discount score against the criteria described above. However, these are not absolute or objective, but are most useful for comparing one option against another.

We intend that these proposed values are initially for discussion purposes as to their absolute and relative magnitudes.

What is interesting from a policy perspective is the relative size of the discount, in two ways: first to provide a potential order of preference between options; and secondarily, to look at the size of incremental difference, which may be useful for a future cost-benefit analysis.

Measuring the Cost of Opioid Dependency: Some Challenges

The most recent WHO Guidelines (2009) on MATOD cite various studies which estimate the primary economic burden (loss) from opioid dependency ranging from 0.2-2% of GDP for industrialised countries.[140] This will vary depending on the narcotics markets of individual countries. For example, Australia – compared to the US – has an anecdotally much higher heroin to methamphetamine price ratio.

The hypothecation of cost to opioid dependency is also subject to some judgements about how much of the problem is opioid-specific, and how much is really undifferentiated narcotic-seeking behaviour. As an illustration of this, our consultation with clinicians in preparation for this paper identifies some radically different views of 'product loyalty', from:

- Views that people with opioid dependency are highly loyal, only substituting within their preferred species of analgesia;
- Contrasting views that where there is a drought of a particular product, prospective MATOD patients will gravitate to a radically different form of narcotic, such as cocaine or methamphetamine; to,
- Evidence that access is a dominant part of the opioid-seeker's equation: in particular anecdotal information that where a methadone prescriber ceases practice, up to 30% of patients will cease both MATOD and other opioid-seeking activity.

This makes it difficult to isolate the true cost of opioid dependency in Australia, or elsewhere.

[140] World Health Organisation, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence,* 2009.

Some direct costs can be identified. For example, a recent study of the cost of opioid use in the USA found that 70% of prescription medicine overdoses were from opioids.[141] This is consistent with the observed high level of hydrocodone dependency in the United States.

This same study quantified the US costs, including healthcare, criminal justice and lost productivity costs – similar categories to our model – at US$78 Billion for the 2013 financial year.[142] Given a GDP for that year of some US$16.69 Trillion, this implies an observed cost of around 0.5% of GDP. Notably this is all from dependency on prescription opioids.

If we look to a European comparison, a 2017 study of five countries – France, Germany, Italy, Spain and the United Kingdom – finds substantial disparity between the cost of prescription opioid dependency across national borders.[143] This seems unusual, given some shared economic characteristics, and also the supervening role of the EU (though healthcare is substantially a subsidiary power).

Addressing healthcare costs in particular, the study found a dramatic range of costs between €6,264 per 100,000 population for Spain and €10.901 for Italy, through to €238,691 for France and €279,927 for Germany, with a high median of €160,835 for the United Kingdom.[144] Much of the variation appears to be attributable to different prescription regulations, which has a critical effect on the rate of substitution between street and prescription opioids. We would not expect fundamentally different demand characteristics otherwise.

Further, a gateway to some study data is the point of entry to MATOD, which may reflect a skewed population[145] and may amplify national differences.

What these studies show is the immense complexity of calculating actual cost of dependency. This conclusion supports our argument for using a relative scale for valuing the impact of MATOD programs, rather than seeking an absolute dollar value, though this may be refined in future work.

The use of relative impacts also allows us to compare different national regimes more effectively, as noted in the case studies below.

Review of Literature on Economic Evaluation of MATOD

A 2007 study from Professor Chris Doran, then of the University of Queensland, benchmarked economic evaluation of all interventions for illicit opioid dependence, comparing information from 259 published articles.[146] This was used as a foundation document for the current WHO guidelines for MATOD.

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[141] Florence, Curtis S et al, 'The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013', *Medical Care*, 54 (10) October 2016, p.1 . https://www.researchgate.net/profile/Chao_Zhou36/publication/308339245_The_Economic_Burden_of_Prescription_Opioid_Overdose_Abuse_and_Dependence_in_the_United_States_2013/links/59f8aa56a6fdcc075ec991dd/The-Economic-Burden-of-Prescription-Opioid-Overdose-Abuse-and-Dependence-in-the-United-States-2013.pdf Accessed 17 April 2018.

[142] Florence et al, 'The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States', 2016.

[143] Shei, Amie et al, 'Estimating the health care burden of prescription opioid abuse in five European countries', *ClinicoEconomics and Outcomes Research*, 7 (2015), pp.477-488.

[144] Shei et al, 'Estimating the health care burden of prescription opioid abuse in five European countries', 2015.

[145] Shei et al, 'Estimating the health care burden of prescription opioid abuse in five European countries', 2015.

Looking to the comparison between buprenorphine and methadone, the study found mixed evidence. From both third-party papers, and controlled studies undertaken by teams involving the author, possible conclusions included:[147]

- A vast range for the cost-effectiveness of buprenorphine, from US$10,800 to US$84,700 per quality-adjusted life year (QALY) at 1998 prices. We note here that use of a QALY basis for consideration of MATOD is useful from a medicine-price point of view, but does not take into account all the costs of opioid dependence in which we are interested;

- Some evidence that methadone may be more cost-effective, but an open question as to whether a buprenorphine-naloxone combination could assist with high-cost lapses, where there are substantial cost-savings to be made, i.e. some opioid users dominate the total societal cost of dependency, and are not assisted by existing MATOD; and,

- An Australian study that showed that in randomised assignment of different forms of MATOD, methadone may dominate buprenorphine cost-effectively, but that this is not statistically significant.

On the last example, we note a key feature of our question of effectiveness, which it relies on a regime where appropriate treatment is: "the treatment with which the patient will most likely comply for an extended period". While generalised assessments of cost-effectiveness from random allocation are important tools, they do not address this question.

A more recent review from researchers at the Universities of Wollongong and New South Wales looked at economic modelling of health interventions around opioid dependence, and found limitations in typical approaches, including both decision-tree and Markov models, mainly due to the heterogeneity of the opioid-dependent population.[148]

This issue of heterogeneity is critical. It includes variables such as: circumstances and causes of first opioid use; current circumstances, including housing, work and support; and, prior experiences with MATOD. As noted elsewhere in this paper, it will also include in which state or territory the potential patient lives.

Further, this study notes that an individually-based model is useful in that it simulates actual trajectories of dependence and medical engagement over a lifetime, though it is extremely data-heavy.[149] In a sense, this defines the middle ground which we seek to address with our model: we are interested in relative values representing regulatory guidelines which maximise aggregate reductions in cost burden, by permitting patient-specific clinical interventions.

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[146] Doran, Chris, 'Economic Evaluation of Interventions for Illicit Opioid Dependence: a review of evidence', Background Document Prepared for Third Meeting of Technical Development Group (TDG) For The WHO *Guidelines for Psychosocially Assisted Pharmacotherapy of Opioid Dependence*, Geneva, Switzerland: 17-21 September, 2007. http://www.who.int/substance_abuse/activities/economic_evaluation_interventions.pdf Accessed 17 April 2018.

[147] Doran, 'Economic Evaluation of Interventions for Illicit Opioid Dependence', 2007

[148] Hoang, Van Phuong et al, 'A systematic review of modelling approaches in economic evaluations of health interventions for drug and alcohol problems', *BMC Health Services Research*, 16:127 (2016), pp.11-12 http://ro.uow.edu.au/cgi/viewcontent.cgi?article=6448&context=eispapers Accessed 16 April 2018.

[149] Hoang et al, 'A systematic review of modelling approaches in economic evaluations of health interventions', 2016.

Other European research looks at the direct cost of MATOD, and finds convergent pricing between industrialised economies. We see a *per diem* prescription cost of opioid substitution medicines in the UK of around €10, compared to €9 for Luxembourg, and a German estimate of oral methadone maintenance at €10. Outliers are €2 per day for some English methadone programs, compared to €37 for Norway.[150] Some of this may simply be a matter of differential labour costs and general purchasing-power parity.

Cost of treatment programs is important, because it is the only incrementally negative component of on our *c* datum (which is always itself negative). As noted above, we are confident that any such costs will outweigh alternative acute health intervention costs, though the rate at which they do this is relevant to different medicines' cost-effectiveness.

Notably, this may be substantially reduced by changed guidelines. For example, longer prescriptions or long-acting injections may reduce the labour cost of MATOD, which is consistently more than 50% of treatment cost across all surveyed countries.[151]

If we consider an example such as the US data above, the US$87 Billion annual cost of opioid dependence is for an estimated 1.9 million dependent individuals.[152] At an individual cost of over US$45,000 per prospective patient, we do not need to undertake currency conversion to see that a modal expenditure of €3,650 represents good value.

This may seem consistent with observed patient charging in Australia at $1 to $10 per day. However, the evidence here is that by relying on out-of-pocket costs, compliance is made more difficult with patients needing to prioritise dispensing fees over necessities.[153] This is a hurdle to participation as well as a partial incentive to depart from MATOD, and should be addressed. Again, the out-of-pocket costs on a per-patient basis will be dwarfed by the per-person costs of illicit opiate use.

Looking to direct comparison between buprenorphine and methadone, recent UK evidence further supports our view that clinical freedom and patient customisation is the key to value in setting MATOD guidelines.

In particular, we note a conclusion that: '… the [methadone] programme is slightly more cost effective in terms of retaining patients in a drug treatment programme, but the [buprenorphine] programme is superior in terms of helping patients to stop illicit drug use.'[154]

This may initially appear confusing or counter-intuitive: it seems that there should be a strong correlation between reduction in illicit opioid dependence and compliance with MATOD programs. However, this observation concurs with feedback received in consultation, which differentiates between the two measures. In particular, it recognises the heterogeneous life paths taken by opioid dependent patients, who may move in and out of programs, depending on various personal and circumstantial factors.

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[150] European Monitoring Centre for Drugs and Drug Addiction, *Cost and Financing of Drug Treatment Services in Europe: An Exploratory Study* (Lisbon: 2011), p.17. http://www.emcdda.europa.eu/attachements.cfm/att_143682_EN_TDSI11001ENC.pdf Accessed 17 April 2018

[151] European Monitoring Centre for Drugs and Drug Addiction, *Cost and Financing of Drug Treatment Services in Europe,* 2011.

[152] Florence et al, 'The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States', 2016.

[153] Penington Institute, *Chronic unfairness,* 2015.

[154] Maas, Jim et al, 'Economic evaluation: A comparison of methadone versus buprenorphine for opiate substitution treatment, *Drug and Alcohol Dependence*, 133 (2013).

This leads in turn to judgements by clinicians about what is most appropriate given an individual's circumstances. Choices between medicines may involve judgements between the prospect of medium-term maintenance versus the likelihood of permanent compliance and the capacity of various MATOD options is different for these prospects.

Separate research on street opioid users, focused on the metric of 'additional day free of heroin use' found a statistically insignificant benefit for buprenorphine in overall terms, but a dominant cost-effectiveness if criminal costs are included.[155] Again, there is ambiguity here, and this further supports the arguments of choice and clinical appropriateness.

There is also evidence of different outcomes from different delivery modes, particularly in buprenorphine. Here, there is evidence that, while there is no major clinical difference between film and tablet formulations, the rapid adhesion of film delivers less prospect of diversion of this medication to illicit markets.[156] Consequently, there is a likely saving in crime costs. It will be interesting to see further data around emerging long-acting injectables from various proponents.

The overall conclusion from this review of evidence is that the effectiveness of MATOD programs is highly subject to the regulatory regimes within which they operate (as for that matter is access to prescription opioids). From here, and in light of the Australian guidelines and those considered in the case studies in the following chapter, we consider some competing guidelines, and then build on our proposed model to suggest a framework for comparing different regulatory settings.

Setting Values for Different Clinical Guideline Options

As noted, our proposed model uses relative values for its various discount factors $d_{(f,w,m)}$ on a scale ranging from 0 to 1. Again, the lower the number, the greater the effect on individual sources of cost or economic loss.

There is an element of subjectivity to this, but we are guided by what clinicians tell us is a priority. Critically, we do not prefer one medicine over another and again note that there is a range of competing evidence on this. Our view is that this is effectively sifted by clinicians, to optimise outcomes in particular settings, and for the pathways of individual patients.

Nonetheless, we do take the view that there may be substantial benefits from different modes of delivery, including longer prescriptions for patients with demonstrable and persistent compliance and from long-acting injectables.

This is not simply a matter of permitting normal work attendance or other reduction in time required to comply with MATOD. It also intersects with two essentially unquantifiable aspects of managing patients with opioid dependence, viz.: trust; and stigma. Some element of the latter is unavoidable, though some is

[155] Harris, Anthony H., Gospodarevskaya, Elena and Ritter, Alison J., 'A Randomised Trial of the Cost Effectiveness of Buprenorphine as an Alternative to Methadone Maintenance Treatment for Heroin Dependence in a Primary Care Setting', *Pharmacoeconomics*, 23:1 (2005), pp.85,87.
[156] Lintzeris et al, 'A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets', 2013.

avoidable, such as the fact that clinicians report significant variability in the attitude and personal behaviour of dispensing pharmacists.

There is also stigma associated with regular participation in queues outside identified treatment centres. It is clear how this undermines the psychosocial goals of MATOD: treatment is designed not only to treat the opioid dependency but also to 'normalise' and reintegrate patients, which improves both individual utility and aggregate economic effects. Stigma is a high-sensitivity problem, which will also inevitably reduce compliance.

The obverse of this is trust. The prospect of re-emergence as a trusted member of society and the productive economy should increase the value of the program to individual patients and, consequently, improve compliance and retention.

In regards to compliance, we again note this paper is indifferent to selection of specific medicines, which is a clinical issue. Capital value is placed on continuing in any MATOD program, though we note that there may be some differential savings sources per the literature discussion above.

The following table proposes a series of relative values for the purposes of further discussion. Our baseline measure of 1 for each discount factor is a range of current restrictions governed at State level under the current Australian national guidelines for MATOD.[157] We have based these on feedback from clinicians and the literature.

We consider a selection of potential variations to these guidelines, based on our assumptions, and the evidence from international case studies and literature. We note here a bias toward capacity to participate in normal economic activity as this is likely to be the most critical breakthrough for most patients.

[157] Commonwealth of Australia, *National Guidelines for Medication-Assisted Treatment for Opioid Dependence'*, 2014.

Table One: Proposed Discount Factors for Economic Model

Guideline	Principal Effects	Δd_f	Δd_w	Δd_m
Choice of medicine	In a methadone-dominant regime, some patients may have adverse reactions. Further, choice of medicine is associated with positive treatment outcomes, which may have both medical and psychological bases[158]	0.9	0.9	0.8
Reducing daily dosing	Reduction in stigma and freedom for normal work routine	0.7	0.7	0.6
Moving from clinics to GPs	Ease of access, particularly in lower-density areas	0.9	0.9	0.9
Increased prescriber base (e.g. nurse practitioners)	Offers increased access options, particularly in poorly-served regional areas, and may also provide a higher level of comfort for some patients	0.9	0.5	0.9
Long-acting injectables	Further freedom for normal work routine, although presumably there is no self-injectable available	0.5	0.9	0.6
Ensuring all MATOD includes mental health services	While this is common in Australia, it seems optimal that it should be included in all circumstances, to address the psychological causes of opioid demand and dependence. It is also important to help reduce stigma and build trust	0.8	0.8	0.8
Further funding for current out-of-pocket costs	Removes a potential key hurdle to enrolment and continuation in MATOD programs: particularly where there is low income, this should not be an alternative to expected normal quality-of-life expenditure	0.5	0.5	0.6
Establishment of implementation plans to complement guidelines	Active promotion and development of plans for MATOD growth. There are savings from every person who moves from illicit use to medication-assisted treatment. While this does not address the cost-benefit of program design, there is an overall nett benefit from opioid treatment. This is a system-level initiative but we have hypothecated values to individual patients	0.8	0.8	0.8
Reclassification as a chronic relapsing condition	Removal of stigma, which has potential flow-on effects to health providers, such as emergency rooms and pharmaceutical dispensers. Priority around medical stabilisation, ahead of enforcement. Allows more effective marketing of MATOD	0.8	0.8	0.7

[158] Ritter, Alison et al, *Expanding treatment options for heroin dependence in Victoria: buprenorphine, LAAM, naltrexone and slow-release oral morphine* (Turning Point Alcohol and Drug Centre Inc: December 1997), p.xii.

These initial values are offered as estimates for discussion. They reflect some informed assessment of available literature plus consultation feedback around the priority of the impact of various settings on the costs of non-participation and non-compliance in MATOD. Nonetheless, they will be refined through further debate.

There are six observations we would make with respect to the proposed discount factors in Table 1:

1. First, they need to be read in columns, not rows. Because the size of the losses and costs we are addressing is not specified, it may be that a high aggregate discount in one row is dominated by a single higher discount to one component of the cost of illicit opioid use. In practical terms, this is a political filter: Governments will set their own priorities as to what aspect of costs or losses are their highest priorities, and may select accordingly. Per our discussion above, the different cost bases of opioid addiction should be value separately, so this is appropriate;

2. Second, we propose that multiple discounts can be aggregated. In applying this, we would suggest that there are overlapping effects. For example, providing the option of a long-acting injection may address some of the same available foregone economic opportunity as does general reduction in presentation for case management. Accordingly, we cannot add the implied savings, but suggest multiplying relevant factors within a column. This should reflect a principle of diminishing returns;

3. Our estimates are deliberately conservative. This is a highly complex series of problems, and one that will not be radically addressed by any one measure. This is the same argument as to why there is no zero discount rate for any activity. As an example, a long-term opioid user with complex comorbidities, low education levels and a history of incarceration may have difficult work prospects, and may continue to participate in a criminal milieu, even while otherwise complying with treatment;

4. The estimates are averages associated with individual patients within continuing MATOD treatment. There are three sub-points for consideration here:

    a. The potential for captured benefit goes up with the number of participating patients: this may be more than linear, as higher levels of participation may for example interrupt illicit markets or reduce stigma, with compounding benefits;

    b. Benefits gained are time-sensitive, given the tendency for patients to require more than one MATOD program enrolment over a lifetime;

    c. As an average, these benefits may not be realised for all individual patients (but for some are likely higher); and,

5. We expect that this is iterative. Some combinations of treatment may emerge which dominate others, and the matrix will require adjustment over time; and

6. Broadly speaking, these are only discounts to first-round effects. We do not consider, for example, that the model can be sufficiently refined to consider onflow consumption from increased employment.

We would hope from this model and the discount matrix, further economic discussion will take place as to priorities and models for MATOD in Australia.

This is essentially about maximum return on treatment options, focusing on compliance and the freedom for clinicians to discern suitable treatment programs. It is not a full cost-benefit analysis, though it may provide the basis for a new look at relative benefits.

International Case Studies

Ontario: Responding to a Crisis

As with all the case studies we consider here, Canada's Ontario has some different population characteristics, and different opioid dependency experience from Australia. A recent summary of key issues for MATOD in Ontario includes:[159]

- Using the measure of emergency visits related to opioids (avoidable acute health intervention), there was an increase for the entire Province from 2008-09 to 2010-11 from 2.6 to 3.7 per 10,000 population. This rises to 22.9 for regional Northern Ontario and to 55 for First Nations people. This shows an escalating crisis, and particular regional dependence, with an assessment that in some indigenous communities, 70-80% of people may suffer from opioid dependence;
- 12.4% of students in years 7-12 in 2014 used prescription opioids for non-medical purposes, which suggests a troubling 'cultural normalisation' of illicit opioid use;
- Over the previous 10 years, patient enrolment in methadone programs rose from 6,000 to 42,000, serviced by 350 doctors;
- Within Ontario, historically, methadone maintenance has been seen as the most cost-effective strategy for management of opioid dependence, and this is the standard of care in current guidelines; and,
- There is a gap between Ontario MATOD and broader mental health services, which means incomplete psychosocial care.

MATOD in Ontario is based in specialist clinics.

Past review of treatment guidelines in Ontario provided the basis on which methadone maintenance was set as the standard. Specifically, this was due to a weight of studies that preferred methadone maintenance therapy as the standard approach, though buprenorphine and buprenorphine-naloxone options are also included, determined by patient preference and clinical settings.[160]

A more recent Canadian National review has found similar outcomes to those reported above, wherein methadone is more likely to keep patients in a program whereas buprenorphine is more likely to keep them from using illicit opioids, with the latter evidence based on urine testing. This study also noted the emphasis on clinical circumstances and patient preference, and noted that the buprenorphine-naloxone

[159] All Morin, Kristen, PhD Candidate, *Coordination of Opioid Dependence Treatment: Northern Ontario Context,* Laurentian University School of Rural and Northern Health. http://www.addictionsandmentalhealthontario.ca/uploads/1/8/6/3/18638346/mc3a_-_medication_assisted_therapy_for_opioid_dependence_in_northern_ontario.ppsx Accessed 17 April 2018.

[160] Canadian Agency for Drugs and Technologies in Health, *Treatment for Opioid Dependence: A Review of Guidelines*, 14 September, 2012, p.4.

combination is cost-effective compared to methadone and had no statistical difference from methadone when looking at harm or mortality.[161]

A 2016 inquiry into opioid maintenance made several recommendations for reform that are germane to our consideration, and from which we would highlight:[162]

- First, on access, it is recommended that buprenorphine-naloxone be moved from limited use approval to the same status as methadone, thus making the guidelines clinically indifferent, permitting clinician and patient choice;
- To improve access, some nurse practitioner prescribing of these medicines is recommended;
- Opioid agonist therapies should be delivered in concert with psychosocial and mental health support services; and
- Regarding patient-specific care: 'The Ministry of Health and Long-Term Care and Local Health Integration Networks should ensure that models, pathways, and funding support Health Service Providers to develop appropriate transition plans tailored to the specialized needs of the patient to support continuity of care';
- MATOD patients should be prioritised for primary care, particularly interdisciplinary primary care; and,
- Consideration should be given to alternative physician remuneration structures to remove cost as a barrier to treatment.

All of these address the factors we consider in our proposed economic model.

We understand that these and other changes will be substantially implemented in forthcoming guidelines. While we might view Ontario as an example of change driven by an escalating opioid crisis, it illustrates the key pathways to improvement of treatment options, particularly where there is rapidly increasing demand.

These recommendations complement recent proposals by the Canadian Research Initiative in Substance Misuse (CRISM: a research group representing four Provinces, including Ontario), which has proposed a national guideline including as its strongest recommendations:[163]

- Initiate opioid agonist treatment with buprenorphine–naloxone whenever feasible to reduce the risk of toxicity, morbidity and death, and to facilitate safer take-home dosing (with methadone treatment as a first and second line where there is poor response); and,

[161] Canadian Agency for Drugs and Technologies in Health, *Buprenorphine/Naloxone Versus Methadone for the Treatment of Opioid Dependence: A Review of Comparative Clinical Effectiveness, Cost-Effectiveness and Guidelines,* 2 September 2016, p.3.
[162] Methadone Treatment and Services Advisory Committee, *Final Report,* Ontario Minister for Health and Long-Term Care: June 9, 2016, pp.5-7.
[163] Bruneau, Julie et al, 'Management of opioid use disorders: a national clinical practice guideline', *Canadian Medical Association Journal,* March 5, 2018, p.E250.

- For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to buprenorphine–naloxone because its superior safety profile allows for more routine take-home dosing and less frequent medical appointments.

This is a strong recommendation for the buprenorphine-naloxone combination on safety and flexibility grounds, but does not formally conflict with more general recommendations for clinical discretion.

One important difference to note here between Ontario and Australian States is that Canadian Provinces have substantially greater autonomy on social services together with independent revenue-raising powers to support these. This may permit more rapid reform of services.

France: Outcome-focused Program Design

Part of the history of French responses to opioid dependence is found in the 1990s, as a subset of the Government's response to having the European Union's highest rate of HIV/AIDS.[164]

In 1994, as part of its exploration of alternatives to reduce the injectable opioid/HIV transmission crisis, the French Government was instrumental in accelerating trials of buprenorphine, alongside the prescription codeine product, Neocodein®. This in turn led to early approval of commercial buprenorphine (Subutex) to treat opioid dependence in France in 1995, with a launch in February 1996.

In seven years from this expansion of treatment access, France experienced:[165]

- Halved prevalence of new HIV infections amongst intravenous opioid users;
- 81% reduction in mortality; and,
- A 77% reduction in the rate of heroin-related arrests.

The French experience differs from that of Canada in that it is dominated by buprenorphine. At 2008, it was estimated that there were 90-100,000 patients enrolled in buprenorphine-based MATOD, compared to 10-15,000 on methadone.[166] This has narrowed in recent years to 63% buprenorphine and 37% methadone.[167]

France has also seen further investigation of treatment options, including injections of buprenorphine, which are much safer with respect to overdose than full-agonists. These are appropriate for those who do not respond to oral buprenorphine and are already acculturated to injectable drugs[168] although they are not as yet available for general treatment.

[164] Much of this narrative is from clinician consultation.
[165] Emmanuelli, J & Desenclos, JC, 'Harm reduction interventions, behaviours and associated health outcomes in France, 1996-2003', *Addiction*, 100:11 (2005), pp.1690-1700.
[166] Data supplied from clinicians during consultations for this paper.
[167] European Monitoring Centre for Drugs and Drug Addiction, *France Country Drug Report 2017*, p.13.
[168] Roux, Perrine et al, 'Willingness to receive intravenous buprenorphine treatment in opioid-dependent people refractory to oral opioid maintenance treatment: results from a community-based survey in France', *Substance Abuse Treatment, Prevention and*

With respect to guideline design, the French Government takes a multi-ministry approach to maximise treatment outcomes, under the umbrella of the Inter-Ministerial Mission for Combating Drugs and Addictive Behaviours (MILDECA).[169] This, along with the history of prioritising treatment options rather than worrying about signalling tolerance for illicit use, has driven an open and patient-centred regime.

MILDECA specifies five priorities for its programs, viz.:[170]

1. Promoting prevention, care and risk reduction;
2. Stepping up the fight against trafficking;
3. Improving the application of the law;
4. Basing policies for combating drugs and addictive behaviours on research and evaluation studies; and,
5. Reinforcing coordination at the national and international levels.

This in turn leads to coordinated programs across the French Government, with cooperative strategies with key stakeholders and KPIs for patient outcomes.

Notably, this leads to high levels of patient satisfaction, recently recorded at 88% for a random sample of participants in MATOD programs across France.[171]

This is an enlightened approach, which – while not shying away from criminal enforcement – focuses on managing opioid dependency as a multi-faceted problem, the centre of which is the opioid dependent or potential patient. It should also be noted that the majority of patients in France are treated by GPs and that GPs can prescribe buprenorphine without accreditation.

The rapid improvement in key metrics around the French opioid problem – particularly those of reduction in long-term health costs – are a compelling argument for this more integrated approach.

United States of America: Insights in Spite of Diversity

There is a vast amount of data on opioid use, impact and treatment in the United States. Approaches are highly variable because of State powers, and the overriding context of the long-running 'war on drugs' often tends to stigmatise rather than encourage innovative treatments.

The complexity of the US health system, with its extensive reliance on private payment and with health insurance predominantly linked to employment, further complicates strategies to deliver MATOD. However, there is some national information worth considering.

Policy, 12:46 (2017) https://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-017-0131-4 Accessed 18 April 2018.

[169] European Monitoring Centre for Drugs and Drug Addiction, *France Country Drug Report 2017*, p.2.

[170] European Monitoring Centre for Drugs and Drug Addiction, *France Country Drug Report 2017* (list quoted directly).

[171] Benyamina, Amine, 'The current status of opioid maintenance treatment in France: a survey of physicians, patients, and out-of-treatment opioid users', *International Journal of General Medicine,* 9 September 2014, p.452.

The first is that there is good data on compliance (and the circumstances that support compliance, through the implementation of the Comprehensive Analysis of Reported Drugs (CARD™) which allows comparison of self-reported illicit opioid use with quantitative detection from urine testing.[172]

These data, properly analysed, permit consideration of guidelines that lead to smaller gaps between reported and actual behaviour, which is a metric of success for a MATOD program.

The primary conclusion from this study is that compliance is the key to lower rates of illicit opioid use, i.e. patients were not also complementing their prescription with illegal purchases or improper OTC opioid use.[173] This is in itself unsurprising, but it emphasises the importance of making compliance easier.

The CARD study found statistically significant differences between the five States examined (which may be at least partly explained by different regulatory regimes), and identified better outcomes for outpatients than for inpatients, particularly those in residential facilities.[174] It is likely that there are intervening demand characteristics here: patients placed in residential facilities are likely to have more complex problems, though (speculatively) there may also be some evidence here for the benefits of trust. In any case, there is no evidence that delivery in intensive in-patient settings dominates outpatient care.

The second useful evidence from the United States is on proposed guidelines on opioid treatment. This is a combination of proposals from the American Society of Addiction Medicine, and the American Psychiatric Association. In summary, the criteria proposed for treatment are:[175]

- Treatment design and delivery to address:
    - Acute intoxication and or/withdrawal potential;
    - Biomedical conditions and complications;
    - Emotional, behavioural, or cognitive conditions and complications;
    - Readiness to change;
    - Relapse, continued use, or continued problem potential;
    - Recovery/living environment; and
- Three modalities for management of dependence:
    - Opioid substitution with methadone or buprenorphine, followed by a gradual taper;
    - Abrupt opioid discontinuation with the use of clonidine to suppress withdrawal symptoms; or,

[172] Blum, Kenneth et al, 'A Systematic, Intensive Statistical Investigation of Data from the Comprehensive Analysis of reported Drugs (CARD) for Compliance and Illicit Opioid Abstinence in Substance Addiction Treatment with Buprenorphine/naloxone', *Substance Use & Misuse*, 53:2 (2018).
[173] Blum et al, 'A Systematic, Intensive Statistical Investigation of Data from the Comprehensive Analysis of reported Drugs', 2018.
[174] Blum et al, 'A Systematic, Intensive Statistical Investigation of Data from the Comprehensive Analysis of reported Drugs', 2018.
[175] Quoted in Nicholls, Lance, Bragaw, Lisa and Ruetsch, Charles, 'Opioid Dependence Treatment and Guidelines', *Supplement to Journal of Managed Care Pharmacy*, 16:1 (2010), p.S14.

- Clonidine-naltrexone detoxification.

These proposals describe a broad set of both treatment modalities, and the patient characteristics to be taken into account when selecting a treatment program. They illustrate the complexity and requirement for flexibility in MATOD.

Key insights from the case studies

Looking at the three jurisdictions discussed above, we can see a convergence of insights. If we take the willingness to reform shown in Ontario, combined with the complex coordination and harm reduction focus of the French model, and introduce both the data management tools and flexible criteria of the American system, we can see interlinked benefits of focus on patients. From a health economics perspective, this makes good sense, as there appears limited benefit in pursuing a homogeneous enforcement problem compared to substantial potential reward from opening the MATOD system to flexibility, patient choice and individual program design by clinicians.

The challenge here, as always, will be to maximise flexibility while limiting individual costs and ensuring safety.

Areas for further consideration

National definition

At present, whilst various official and treatment-related documents refer to opioid drug dependence, Australia has no specific or uniform national definition of this. Dependence on opioid drugs or medication – and both terms are used in various different documents – is acknowledged as being associated with multiple health and social problems impacting individuals, families, friends and the broader community or public. Health and other problems associated with opioid dependence are also recognised, such as medical and psychological problems; overdose; social and family disruption; impacts on child welfare; contribution to violence and crime; and a contribution to blood-borne diseases. Opioid dependence's role as a serious public health issue is not questioned in the literature.

There is not a nationally agreed definition of opioid dependence however. The *National Guidelines* refer, in Appendix One, to the criteria for opioid dependence outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) whilst also noting the definition provided in the *International Classification of Diseases, 10th edition (ICD-10)*.

NOPSAD also utilises the ICD-10 definition, stating that it defines 'dependence system' due to the use of opioids as:

> 'A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state'.

While preparing this paper, a number of people with whom the authors consulted suggested that a national definition of opioid dependence would be useful. Whilst acknowledging this might prove challenging, given even issues around preferred terminology usage, the authors agree that an agree definition might assist in clarifying some of these matters as well as forming a strong basis on which to engage the public. This is particularly important given the evolving nature of opioid dependence and populations experiencing it.

It may be suggested that definitions are not of themselves priorities. However, the absence of such definitions inevitably leads to misunderstandings and/or differences as to targets, processes and clinical outcomes, which is in part the source of so many of the disparities in MATOD around Australia.

National consistency of guidelines for treatment

Whilst recognising the realities of the federated nature of Australia's health system and the role of state and territory governments in setting various elements of the MATOD framework, it would be ideal to work towards a national consistency in guidelines for treatment, such as take away doses, as well as issues such as accreditation for professionals engaged in treatment and so forth. Equally, it would be useful for the mobility, including GPs, as well as access to interstate locums.

National consistency would enable greater flexibility and certainty for patients who are required or choose to move as well as reflecting the situation striven towards in many other areas of health care.

Importantly, agreement about guidelines for treatment should also enable greater integration of MATOD across the country and might work to assist broader recognition of this problem as a key public health issue.

National funding for dispensing fees

Strong evidence exists that providing dispensing fee relief to patients would improve program continuity and patient-pharmacist relationships with an observed association between higher costs and significantly poorer treatment compliance.[176]

The Penington Institute recommended a model by which methadone and buprenorphine, when dispensed for opioid dependence treatment, would attract a monthly payment to the pharmacist each month for each patient to cover costs of dispensing, handling, counseling and pharmaceutical care. In addition, and in line with current PBS arrangements, a regular patient contribution would be payable at either full or concessional rate.

Whilst indifferent to the funding model introduced, significant benefits to patients could be achieved with the introduction of national funding to meet dispensing fees, in whole or in part. This is because these costs represent a significant hurdle to patient participation as well as a partial incentive to depart from MATOD, and should be addressed. It is not simply a matter of cost of the medicines but also that this presents an opportunity cost (substitute expenditure) to normal cost-of-living requirements. This contributes to non-compliance and other undesirable outcomes.

Given that the out-of-pocket costs on a per patient basis will be dwarfed by the per person costs of illicit opiate use, this makes not only makes sense in relation to compliance sense but economic sense also. It also addresses an issue of inequity in the health system.

An unsupervised treatment system

MATOD programs globally need to deal with a variety of trade-offs, especially in relation to the questions of supervised versus unsupervised dosing regimes.

Supervised dosing may decrease levels of diversion of medications to people who are not currently in treatment and other negative effects, such as patient cohorts that might otherwise inject their doses.

At the same time, considering the burden on patients outlined above and the capacity to attract larger numbers and more diverse groups of people into treatment as a result of increased treatment flexibility,

[176] Penington Institute, *Chronic unfairness*, 2015.

reduced regulation and higher levels of unsupervised dosing,[177] there is little doubt that the policy settings regarding this require revisiting.

The revisiting of these policy settings is further supported given the potential benefits in relation to better treatment retention and less crime. A trial in Australia under similar conditions to US office-based treatment provides support for the adoption of that model here.[178]

It is also worth noting that the regular supervision of all dispensed doses under MATOD is 'an approach developed for methadone maintenance treatment, due to concern regarding the diversion, the risk of hazardous use by injection and particularly the risk of overdose if used by non-tolerant individuals'.[179]

There is also little doubt that the new treatment options soon to be available to patients are likely to only exacerbate the current tensions existing for patients in terms of supervised dosing regimes and appropriate consideration of all these factors needs effective consideration and preparation prior to the long-acting injectable medications becoming available.

Increasing the number of prescribers

In 2011, it was identified that 'strategies must be explored that enhance the capacity and willingness of active OST prescribers to increase the number of patients in treatment, and of inactive prescribers to commence or resume OST prescribing'.[180] This continues to be a key need for the sustainable delivery of MATOD in Australia. Geographic delivery of MATOD also needs to be addressed and identifying strategies to assist in this should be a key activity of policy and decision makers.

Given that, in the Victorian study discussed earlier, GPs who attended a training workshop on MATOD prescribing were universally enthused by their training and motivated to begin prescribing,[181] focus should be given to increasing training participation.

Individual work circumstances were cited in the study, particularly those around the capacity to provide continuity of care, a pre-requisite for effective and safe treatment. Lack of patients, GP understanding of the medications involved and lack of patients were also mentioned but were, by the study's authors, considered less difficult to resolve.

In resolving the issues of continuity of care and the broader lack of access to care, the role of nurse practitioners should be given serious consideration, particularly in light of evidence from the USA in relation to drug and alcohol programs and also some of the work in New South Wales.[182]

Reports currently indicate that there are only 10-12 drug and alcohol focused nurse practitioners exist across Australia.[183] Considering the capacity that effective utilisation of nurse practitioners could add to

[177] Larance et al., 'The Diversion and Injection of a buprenorphine-naloxone soluble film formulation', 2018.
[178] Dunlop et al., 'Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone' 2017.
[179] Dunlop et al., 'Effectiveness and cost-effectiveness of unsupervised buprenorphine-naloxone', 2017.
[180] Longman et al, 'Methadone and buprenorphine prescribing patters of general practitioners', 2011.
[181] Longman et al, 'Reluctant to train, reluctant to prescribe', 2012.
[182] Ling, Stephen, 'Nurse practitioners in drug and alcohol: where are they?', *Australian Journal of Advanced Nursing*, 26 (4) 2007. http://www.ajan.com.au/Vol26/26-4_Ling.pdf Accessed 28 February 2018.

the MATOD system, particularly in regional, rural and remote areas, this should be recognised and encouraged. We would also recommend a specific review into any regulatory barriers existing to their ability to prescribe MATOD.

In addition, support available from allied health workers to should be considered by GPs undertaking this work, particularly in relation to counseling and other ancillary programs.

Whilst not mentioned in the Victorian study, the onerous nature of the paperwork involved in MATOD was commented upon to this paper's authors by multiple stakeholders. Seeking ways to ameliorate or share this burden should also be considered, something that could be facilitated again by the support of nurse practitioners and other practice staff.

Other support, such as access to addiction specialists (especially in Victoria) and other follow up to training could be appropriate to help overcome barriers both to prescribing and to the number of prescribers. A source of ready advice together with a sense of collegial support should prove invaluable in this environment.

Finally, given the comments by female GPs about the potential impact of part-time work on their capacity to provide appropriate continuity of care and the growing number of part-time female GPs in the workforce, opportunities to better coordinate care within a medical practice and between GPs should also be given consideration. This is particularly true given the future profile of this cohort.

Whilst further work may be required in this area to determine the most effective means of boosting workforce numbers, a number of options exist, many of which could be trialed at the same time they are evaluated with the goal of more effectively supporting GPs and others involved in MATOD.

Addressing pharmacy issues

Earlier education and training in issues relating opioid misuse and treatment has been recommended as a means of beginning to address the number of pharmacists participating in MATOD. Any such training should address, not simply the issues relating to pharmacology, but matters such as stigmatisation which limit the success of MATOD.

In NSW, other issues were also identified that might assist recruiting pharmacists into MATOD as well as encouraging a more holistic approach to alcohol and drug management. These included:

- Greater ease in completing registration requirements;
- Greater education about the aims of MATOD and advice about the potential client population;
- Support via peer groups and advice networks as well as mentoring;
- Advice regarding start-up costs, debt management and other financial issues;

[183] Puplick, 'Towards Reintegration', 2014.

- Advice regarding amenity issues and other matters such as loitering, police support and physical arrangements including relationships with other local businesses; and
- Training for pharmacy staff.

In addition, clear statements of support from the public health authorities including on the re-absorption of difficult patients into the public system was also identified as helpful.[184]

Description of successful treatment

Part of the challenge in identifying a definition for "successful" treatment in MATOD relates to the different goals that may be experienced by those participating in it. For clinicians, the focus is traditionally on the cessation of drug use and improved health outcomes for patients. In contrast, for patients, the goals may be relief from injecting drug use,[185] drug free life or even effective management of day-to-day life.

Accepting this, there is still room for a description to be agreed in relation to successful treatment. Identifying this might enable the goals of the program to be better explained to the general public, treating clinicians and other healthcare professionals and current and potential patients. This may help broaden the understanding of MATOD and its role in society, including the nature of opioid dependence as a chronic-relapsing condition.

Decreasing stigma

Being able to communicate clearly what successful treatment means, and that this may not necessarily involve an entirely opioid-free existence all of the time, might help decrease the stigma associated with opioid dependence by enhancing people's understanding of the program, its goals and its successes.

Certainly identifying means by which to decrease the stigma associated with opioid dependence, whether that by better education and communication or other means, should be a key goal. Traditionally, those dependent on opioids may have been viewed as rule-breakers and takers of illicit drugs. However, it may prove that, with the increasing numbers of dependents having a more commonly used drug, and a medicine at that, as their source of dependence, community views may shift. Regardless of whether this occurs or not, however, means need to be identified that reduce the stigma experienced by those seeking MATOD.

Again, we would stress the importance of firmly establishing opioid dependence as being a chronic-relapsing condition, in both medical and political environments.

[184] Puplick, 'Towards Reintegration', 2014.
[185] Ritter and Chalmers, *Polygon*, 2009.

A treatment framework that encompasses LAIs

Whilst the introduction of LAIs offers a significant opportunity to patients accessing MATOD, it needs to be recognised that the new products require changes to the current model.

As highlighted above, LAIs needs to be administered by a healthcare professional. Consequently, the current model by which pharmacists dispense MATOD products direct to patients needs to change. This is both because patients will not be directly in contact with the new medications and because pharmacists are not able to administer these products.

New models are required to manage this and the treatment framework will be required to flex, or change, in order to enable the appropriate level of access for patients to the new medications. This is particularly important given the opportunity these products do offer in relation to flexibility of treatment and decreasing the associated stigma.

Future collection of NOPSAD data

NOPSAD provides critical information to both policy makers and other stakeholders about MATOD in Australia. Maintaining the currency and effectiveness of this data source is important yet it is, and will continue to be, challenged by issues both in and developing in the program.

At the present time, data within NOPSAD are not readily comparable due to the difference in reporting by states about buprenorphine compared to buprenorphine-naloxone. These data should be reported in a consistent manner such that they are readily comparable.

Given this, consideration should be given to ensuring that data are uniformly collected in a way that either distinguishes buprenorphine use from that of buprenorphine-naloxone or combined such that buprenorphine and buprenorphine-naloxone use are reported together.

Given that NOPSAD data are collected on what are termed 'snapshot' day(s), they traditionally capture information purely on those individuals who receive dosing or are dispensed with MATOD on that or those particular days. The introduction of LAIs challenges the capacity of the current data collection method to adequately capture information that truly reflects the number and type of people receiving MATOD given that people treated with LAIs may very well not receive their treatment on the snapshot day. This may result in underestimation of the number of people receiving MATOD across Australia as well as likely skewing the representation, based on current data, towards custodial settings, those receiving methadone and so forth.

The importance of NOPSAD suggests that this would not be an appropriate or acceptable outcome and, given that, a means of effectively capturing a true data reflection of MATOD – including those individuals being treated with LAIs – needs to be agreed. This may be possible from supply or funding data.

Proposed timetable for addressing key issues

The most pressing issue that needs to be addressed in relation to MATOD is the challenge posed by the coming advent of the LAIs. A National Agreement is needed on how these treatments can best be introduced in a way that maximises patient safety whilst capturing the benefits available from them. Ensuring that appropriate mechanisms are in place to manage the LAIs is critical so that, for example, patients cannot directly handle them. Having these ready and in place in advance of the LAIs' availability involves the identification and implementation of new models. This will involve reviewing the current treatment framework.

Given that the Ministerial Drug and Alcohol Forum has the necessary representation from Commonwealth, State and Territory Governments and membership from both the health/community services and justice/law enforcement portfolios, this would appear the appropriate body to address this issue. In light of the fact that the LAIs could be available in Australia in 2019, action is needed now to ensure that Australia's MATOD framework is appropriately prepared.

New national guidelines will also be required to facilitate the entry of the LAIs into the treatment framework and help educate healthcare practitioners about their use. Given the long timeframes involved in these, work should be initiated now given the information available from the FDA and the fact that clinical trials are underway in Australia.

A coordinated approach to all these activities is vital and *resolution is needed by mid 2019 on both implementation pathways for the LAIs and guidelines that support their use*. A means to address the NOPSAD Collection is linked to this and should be resolved simultaneously. It may well involve the real-time prescription drug monitoring systems under development.

Whilst these issues are the most critical in terms of timing, the other areas identified for consideration should not be ignored. Working groups could be established under the auspices of the National Drug Strategy Committee to consider a national definition of opioid dependency; national consistent guidelines for treatment; and the description of what successful treatment means. Whilst these may appear critical, their absence clearly affects targets, processes and clinical outcomes.

National funding of dispensing fees is a barrier to treatment, a clear issue of equity and one that should be able to be resolved, particularly given the health economic arguments involved. Further modelling of this should not be required but, if it would be helpful, it should be undertaken. Discussions with the Commonwealth Minister for Health and Ageing, the Department of Health and Ageing and the Pharmacy Guild should be initiated immediately and clinicians should support and encourage these.

The matters relating to prescribers and pharmacists are clearly less easy to resolve and link strongly to the issue of stigma regarding MATOD. Being able to clearly communicate what successful treatment is should assist in addressing stigma and education is needed to support this. The significant body of work that exists regarding the barriers for doctors and pharmacists in delivering MATOD should be used to develop clear strategies and activities to help healthcare professionals engage in this work with confidence and the knowledge that their peers and communities understand its value and goals.

Given the extensive in relation to MATOD and the fact that much of it has been generated from Australian experience, the current and future challenges can be addressed. What is needed is a consistent focus, a clear workplan and the ongoing recognition that this work has as its goal the wellbeing of patients and the broader Australian community.

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