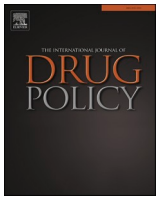
International Journal of Drug Policy 123 (2024) 104255

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo



Research Paper

Trends in use of medicines for opioid agonist treatment in Australia, 2013–2022

Chrianna Bharat [a,*], Kendal Chidwick [a], Natasa Gisev [a], Michael Farrell [a], Robert Ali [a,b], Louisa Degenhardt [a]

[a] National Drug and Alcohol Research Centre, UNSW Sydney, Randwick, NSW, Australia
[b] Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

ARTICLE INFO

Keywords:
Opioid agonist treatment
Methadone
Buprenorphine
Post-marketing surveillance
Drug utilisation

ABSTRACT

Background: There are limited longitudinal data on national patterns of opioid agonist treatment (OAT). This study describes 10-year trends in the sales of OAT medicines in Australia.
Methods: A descriptive and time-series analysis of methadone, sublingual (SL) buprenorphine (+/−naloxone), and long-acting injectable (LAI) buprenorphine sold in Australia between 2013 and 2022 was performed. Total units sold were converted into an estimate of the number of clients that could be treated over a 28-day period with that amount of medicine ('client-months').
Results: Between January 2013 and December 2022, the estimated number of client-months on: any OAT increased by 50 % to 53,501, methadone decreased (−8.5%), SL buprenorphine increased (+78%), and LAI buprenorphine increased substantially after September 2019. In January 2013, 78 % of OAT client-months received methadone. By December 2022, 48 % received methadone, 26 % SL buprenorphine, and 26 % LAI buprenorphine. Between 2013 to 2022, OAT client-months per capita were highest in the state of New South Wales. Over the study period, greater increases in OAT were observed in very remote areas (88%) compared to major cities (53%). The number of client-months in non-community pharmacy settings remained stable from 2013 to 2019/20, before increasing markedly. The introduction of LAI buprenorphine was associated with an immediate, sustained increase of 1,636 OAT client-months, and further increases of 190 OAT client-months each month.
Conclusion: Patterns of OAT have shifted over the last 10-years with buprenorphine (SL/LAI) now the most common OAT used in Australia. The introduction of LAI buprenorphine has expanded OAT access, particularly in non-community pharmacy settings, and in remote areas.

Introduction

Opioid agonist treatment (OAT) is well established as a first-line treatment for opioid dependence (World Health Organization & Department of Mental Health & Substance Abuse, 2009). Involving the regular and long-term provision of a prescribed opioid of known concentration and purity, OAT has the broad goal of reducing harm due to non-medical use of opioids (Degenhardt et al., 2019). In addition, there is strong evidence to support the effectiveness of OAT in reducing injecting and injecting-related injuries, criminal activity, and mortality (Colledge-Frisby et al., 2022; Degenhardt et al., 2019; Gisev et al., 2019; Santo et al., 2021). The most commonly used pharmacotherapies for OAT globally are methadone and buprenorphine (Colledge-Frisby et al., 2023; World Health Organization, 2012), with both listed as essential medicines for this indication by the World Health Organization (World Health Organization, 2017).

Methadone and buprenorphine (with or without naloxone) may be prescribed for opioid dependence in Australia by authorised medical practitioners and specialist nurse practitioners (Gowing et al., 2014). OAT is dispensed in a variety of settings including community pharmacies, private and public clinics, and correctional facilities, as well as in local hospitals in more rural areas. OAT medicines are listed on the national Pharmaceutical Benefit Scheme (PBS) which subsidises their cost for the treatment of opioid dependence. However, before July 2023 (The Pharmaceutical Benefits Scheme, 2023), OAT clients who had their medication dispensed at private clinics or community pharmacies were

* Corresponding author.
E-mail address: c.bharat@unsw.edu.au (C. Bharat).

https://doi.org/10.1016/j.drugpo.2023.104255

Available online 28 November 2023

charged daily dispensing fees (in the range of AUD$5-8 per day) (Ritter & Chalmers, 2009).

A recent development in the treatment of opioid dependence relates to the registration and introduction of long-acting injectable (LAI) formulations of buprenorphine (Lintzeris et al., 2019). In Australia, LAI buprenorphine was first listed on the PBS in September 2019. Administered via weekly or monthly subcutaneous injections, the suspension formulation slowly releases buprenorphine over an estimated time interval. In this way, LAI buprenorphine reduces the burden of regular clinic or pharmacy attendance, potentially offering enhanced client outcomes through improved treatment retention (Frost et al., 2019; Haight et al., 2019). Early evidence suggests LAI buprenorphine is associated with a range of benefits including increased quality of life, employment, and treatment satisfaction (Farrell et al., 2022), and varying, unintended social impacts as well (Barnett et al., 2021; Clay et al., 2023; Lancaster et al., 2023).

In Australia, the scale-up of LAI buprenorphine was accelerated during the COVID-19 pandemic as a strategy to maintain treatment continuity, while at the same time reducing interactions and attendance of OAT clients at health services. National guidance developed by professional and consumer groups also recommended increases in the provision of take-away doses, greater use of telehealth services for client appointments, reductions in activity monitoring (e.g., urine drug screens), and strategies for ensuring continuity of treatment for persons while in quarantine (Lintzeris et al., 2020). These changes to OAT delivery addressed long-standing logistical barriers to treatment accessibility and engagement, including the significant time and distance involved in attending services (Hall et al., 2021). Although their implementation was not mandated, understanding the extent to which these changes were reflected in the level and type of OAT access is important to demonstrate the adaptability of the service model to support client needs.

Despite being subsidised on the PBS, methadone and buprenorphine for the treatment of opioid dependence are not recorded in the national PBS data set - the data source used for the majority of medicines research in Australia (Mellish et al., 2015). Each year, data collected on snapshot day/s by state and territory health departments are compiled to provide a national overview of OAT pharmacotherapies used in Australia (Australian Institute of Health Welfare, 2023). Although jurisdictions strive to report data consistent with agreed standards, there exist inconsistencies in the methods of data collection and elements reported across jurisdictions (Australian Government Australian Institute of Health & Welfare, 2022). For example, driven by each jurisdiction's particular legislation, information technology systems, and resources: the number of clients receiving OAT in Western Australia is reported throughout the month of June rather than on a snapshot day; New South Wales is unable to differentiate between clients prescribed sublingual (SL) or LAI buprenorphine; and data were not available in 2021 for Queensland. These (and other) inconsistencies (Australian Government Australian Institute of Health & Welfare, 2022) combined with the intermittent (annual) monitoring mean that these data are not suitable to provide a nuanced understanding of how the profile of individual medicines in OAT in Australia has changed over time and how overall utilisation has changed in different settings (e.g., regional v. remote, community vs. prison). In particular, it is not known to what extent the population-level profile of OAT use changed in the months following the September 2019 introduction of LAI buprenorphine and April 2020 amendments to OAT guidance and policies in response to the COVID-19 pandemic (Lintzeris et al., 2020). Therefore, this study aims to provide a detailed examination of OAT medicines in Australia and to consider periodic factors that may have affected patterns of utilisation. Specifically, our aims are to:

1 Examine trends in the estimated number of clients on all OAT medicines in Australia between 2013 and 2022.
2 Examine variation in the number of OAT clients by jurisdiction, remoteness, socio-economic status and setting, and
3 Evaluate the impact of (a) the introduction of LAI buprenorphine, and (b) published prescribing guidelines in response to COVID-19, on the estimated number of OAT client-months per month in Australia.

Methods

Design and setting

This study was a descriptive post-marketing evaluation of population-level sales of OAT medicines used in Australia. Data on all formulations of OAT medicines (methadone, buprenorphine, buprenorphine-naloxone, and LAI buprenorphine) sold in Australia between January 2013 and December 2022 (inclusive) were included. Data was provided by IQVIA Inc. (https://www.iqvia.com/) who collect information on sales of medicines to community pharmacies, hospitals, and other providers, including prisons, by pharmaceutical wholesalers and manufacturers. IQVIA declares around 97 % coverage of the Australian pharmacy and hospital market (Brown et al., 2020). Due to the legal requirements for secure storage and monitoring of OAT medicines in pharmacies, the number of packs sold over a 12-month period should very closely approximate the number of medicines used by OAT clients nationally.

Measures

Exposures

All available OAT medicines, by formulation and strength, are provided in Table 1. Formulations of methadone and buprenorphine listed on the PBS solely for the treatment of opioid dependence in Australia were included, as well as methadone liquid 200 mL. Other formulations, including methadone tablets and buprenorphine patches, are not included under the PBS opioid dependence treatment program and were therefore not included in the analysis. Methadone liquid 200 mL, which is indicated in Australia for both pain and opioid dependence, was included in these analyses since (1) methadone is not recommended for acute pain in Australia (The Royal Australian College of General Practitioners, 2017), (2) guidelines indicate tablets are preferred in practice over liquid for managing persistent pain (The Royal Australian College of General Practitioners, 2017), and (3) data on almost all costs (AUD) of these medicines to the purchasing pharmacy were recorded as zero, indicating they were funded by the Australian Government's PBS opioid dependence treatment program (Expert Review Panel, 2023) (data not shown). Sales of LAI buprenorphine were disaggregated into five groups by strength and injection frequency - weekly low and high strengths, and monthly low, medium and high strengths (see 'LAIB Group' in Table 1).

Outcomes

The amounts of OAT medicines sold do not directly equate to the amounts dispensed or used. For this reason, it was not possible to estimate patterns of use at the client level nor determine the exact number of clients receiving OAT in each month. Oral morphine equivalents (OME), which are based on the idea that different doses of different opioids may give a similar analgesic effect, could not be reliably estimated for LAI buprenorphine (Nielsen et al., 2014). Therefore, OAT utilisation was estimated by totalling the number of packs sold each month and converting this result into an estimate of the number of clients that could be treated over a 28-day period with that amount of medicine (herein referred to as 'client-months').

For methadone and SL buprenorphine formulations, OAT utilisation was estimated by summing the total milligrams (mg) contained in the packs sold that month and dividing by the average dose (mg) to treat a single person for 28 days e.g.,

Table 1
Medicines available* in the Australian opioid agonist treatment program.

Active ingredient	Form	Brand name	Strength (mg)	LAIB† group	Entry to market
Methadone	Oral (liquid)	Biodone Forte, Methadone Syrup	5 mg/mL	N/A	June 1994
Buprenorphine	Sublingual tablet	Subutex	0.4, 2, 8	N/A	August 2001
Buprenorphine / naloxone	Sublingual tablet	Suboxone	2/0.5, 8/2	N/A	November 2000
Buprenorphine	Long acting injection	Buvidal weekly	8, 16	Weekly LAIB – low	September 2019
Buprenorphine	Long acting injection	Buvidal weekly	24, 32	Weekly LAIB – high	September 2019
Buprenorphine	Long acting injection	Buvidal monthly	64	Monthly LAIB – low	September 2019
Buprenorphine	Long acting injection	Buvidal monthly	96, 128	Monthly LAIB – med	September 2019
Buprenorphine	Long-acting injection	Buvidal monthly	160	Monthly LAIB – high	May 2022
Buprenorphine	Long-acting injection	Sublocade	100	Monthly LAIB – low	March 2020
Buprenorphine	Long-acting injection	Sublocade	300	Monthly LAIB – high	February 2020

*, listed on the Pharmaceutical Benefit Scheme; †LAIB: Long-acting injectable buprenorphine.

$$\text{OAT client-months} = \frac{[\text{mg per pack} \times \text{Total no. of packs sold that month}]}{[\text{Average daily dose (mg) for a single person} \times 28\ \text{days}]}$$

Average dose estimates were evaluated from previously published studies. Specifically, a systematic search of MEDLINE, Embase, and PsycINFO databases were conducted to identify studies with information on OAT received in Australia. Searches were limited to studies published in the past five years (2016–2021) to identify the most current data available. Quantitative data on methadone and buprenorphine doses were extracted from the included studies and meta-analysed. The pooled mean dose (mg/day; 95 % confidence interval [CI]) was 74.06 (95 % CI: 69.44, 78.69) for methadone and 16.00 (95 % CI: 14.39, 17.61) for SL buprenorphine (see Table S1). Further methodological details of this review are summarised elsewhere (Expert Review Panel, 2023).

For LAI buprenorphine formulations, estimates of client-months were based on the number of packs (injections) sold. Specifically, one pack of weekly and one pack of monthly LAI buprenorphine were evaluated to treat 0.25 and 1 client, respectively, over a 28-day period, aligning with the recommended dosing schedules (Lintzeris et al., 2019). Given that it is possible for recommended and administered doses to vary (Lintzeris et al., 2019), a retrospective chart review of three Australian OAT providers was conducted to evaluate real world dosing intervals for these medicines in the Australian context (Chidwick, et al., 2023a, 2023b). These analyses confirmed that an estimated interval of 28-days between LAI doses aligned with real-world LAI buprenorphine dosing intervals (Chidwick, et al., 2023a, 2023b).

To account for small fluctuations in sales data that reflect the ordering behaviour of pharmacies and other providers (such as stockpiling), three-month moving averages are provided.

Variables

Monthly OAT utilisation was summarised overall and disaggregated by jurisdiction, setting, remoteness, and socioeconomic status. The Australian jurisdictions includes six states (New South Wales (NSW), Queensland (QLD), South Australia (SA), Tasmania (TAS), Victoria (VIC), Western Australia (WA), and two territories (Australian Capital Territory (ACT) and the Northern Territories (NT)). Setting refers to the outlet type which purchased the medicines, and includes 'community pharmacy', 'hospital', 'aged and community healthcare', 'clinics and medical centres', and 'other (including prisons)'.

Measures of remoteness and socioeconomic status represent the location of the outlet purchasing the OAT medicines and are used as a proxy for where OAT was received by clients. The Australian Bureau of Statistics (ABS) mapping of Postcode 2017 was used to map sales data to the Australian Statistical Geography Standard (ASGS) Remoteness Areas 2016 data (Australia Bureau of Statistics, 2018a) and to the Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) 2016 data (Australia Bureau of Statistics, 2018b) (see Appendix Methods S2). Australian remoteness categories include 'Major Cities', 'Inner Regional', 'Outer Regional', 'Remote' and 'Very Remote'. IRSAD summarises information about the economic and social conditions of people and households within an area, with lower quintiles indicating relatively greater disadvantage and higher quintiles indicating relatively greater advantage.

Statistical Analysis

Descriptive statistics and data visualisations were used to describe trends over time, and by OAT medicine, jurisdiction, remoteness, socioeconomic status and setting. The estimated number of client-months, overall and by individual medicines, were evaluated as a count standardised against population size and/or as a proportion (%) of the total number of OAT client-months. Per capita estimates were based on the estimated residential population at June 30 each year, provided by the Australia Bureau of Statistics (Australian Bureau of Statistics, 2022), overall and by jurisdiction, remoteness and IRSAD. Population estimates were not available by setting.

Interrupted time-series analysis was used to assess the population-level effect of the introduction of LAI buprenorphine (1 September 2019) using Autoregressive Integrated Moving Average (ARIMA) models to account for autocorrelation and seasonality (Box et al., 2015). The intervention (i.e., introduction of the LAI formulation of buprenorphine) was assessed by modelling both a permanent level-shift using an indicator variable and a change in slope (ramp). This modelling allowed for the time-series to permanently increase or decrease after the intervention (level-shift) and for the trend line to also change, with these estimates and their statistical significance used to summarise the effect of the intervention. The form of the ARIMA model was determined using the auto.arima function of the forecast (Hyndman et al., 2016) software package in R for all OAT medicines combined and for methadone and SL buprenorphine individually. The assumptions of the selected ARIMA models were assessed graphically by examining histograms and quantile–quantile plots of residuals to assess normality, time-series plot of residuals to assess the assumption of white noise, and autocorrelation function plots of residuals to confirm that residuals were uncorrelated.

Sensitivity analysis

To assess the robustness of the client-month estimates, the main analyses were replicated using the lower and upper bounds of the 95 % CI of pooled mean daily doses for methadone and SL buprenorphine (see Table S1) and the 25th (Q1) and 75th (Q3) centiles of the dosing intervals from the LAI buprenorphine chart audit (Chidwick, et al., 2023a, 2023b).

Analyses were conducted using SAS Enterprise Guide 9.4 (SAS Institute Inc., Cary, NC, USA), RStudio 2023.03.0 (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA) and Microsoft Excel for Microsoft 365 (Microsoft, Seattle, WA, USA).

Ethics approval

Ethics approval was not required as data from IQVIA were received in deidentified aggregated form.

Results

Trends in the sales of all OAT medicines

Over the study period, the estimated number of OAT client-months in Australia increased steadily, from 35,733 client-months in January 2013 to 53,501 client-months in December 2022 (50 % increase; Fig. 1A, Table S3). Accounting for population size, this equated to a 33 % increase in the rate of use from 15 to 21 per 10,000 capita (2013–2022; Fig. 1B, Table S3). In the OAT program, the estimated number of client-months was unusually high in March 2020, coinciding with the introduction of two new LAI buprenorphine formulations to market (see Table 1) and the COVID-19 restrictions nationally; this was followed by a decrease in April 2020 (Fig. 1A).

The distribution of OAT medicines in Australia changed over time. In January 2013, an estimated four-fifths (78.0 %) of OAT client-months were for methadone, with the remainder for SL buprenorphine (22.0 %). In December 2022, fewer than half (47.8 %) of all client-months were estimated to be for methadone, with the remainder (52.5 %) receiving one of the two buprenorphine formulations (26.4 % SL buprenorphine and 25.9 % LAI buprenorphine; Fig. 1C, Table S3). This change in the distribution of OAT medicines was the result of a large increase in SL buprenorphine (+78 % from 2013 to 2022) and a substantial uptake (from 597 client-months in September 2019 to 13,959 client-months in December 2022) of LAI buprenorphine following its introduction to the program. In contrast, rates of methadone use decreased (−8.5 %) from 27,862 client-months in January 2013 to 25,495 in December 2022 (Fig. 1A, Table S3).

Trends by jurisdiction

Across the decade, OAT client-months per capita were highest in NSW, ACT and VIC and lowest in the NT and WA. In December 2022, the number of OAT client-months per capita in NSW was more than three-fold the number in the NT (28 vs 9 per 10,000 capita; Fig. 2, Table S4). Rates of OAT use increased across almost all jurisdictions over the decade, except for WA which remained steady and Tasmania which

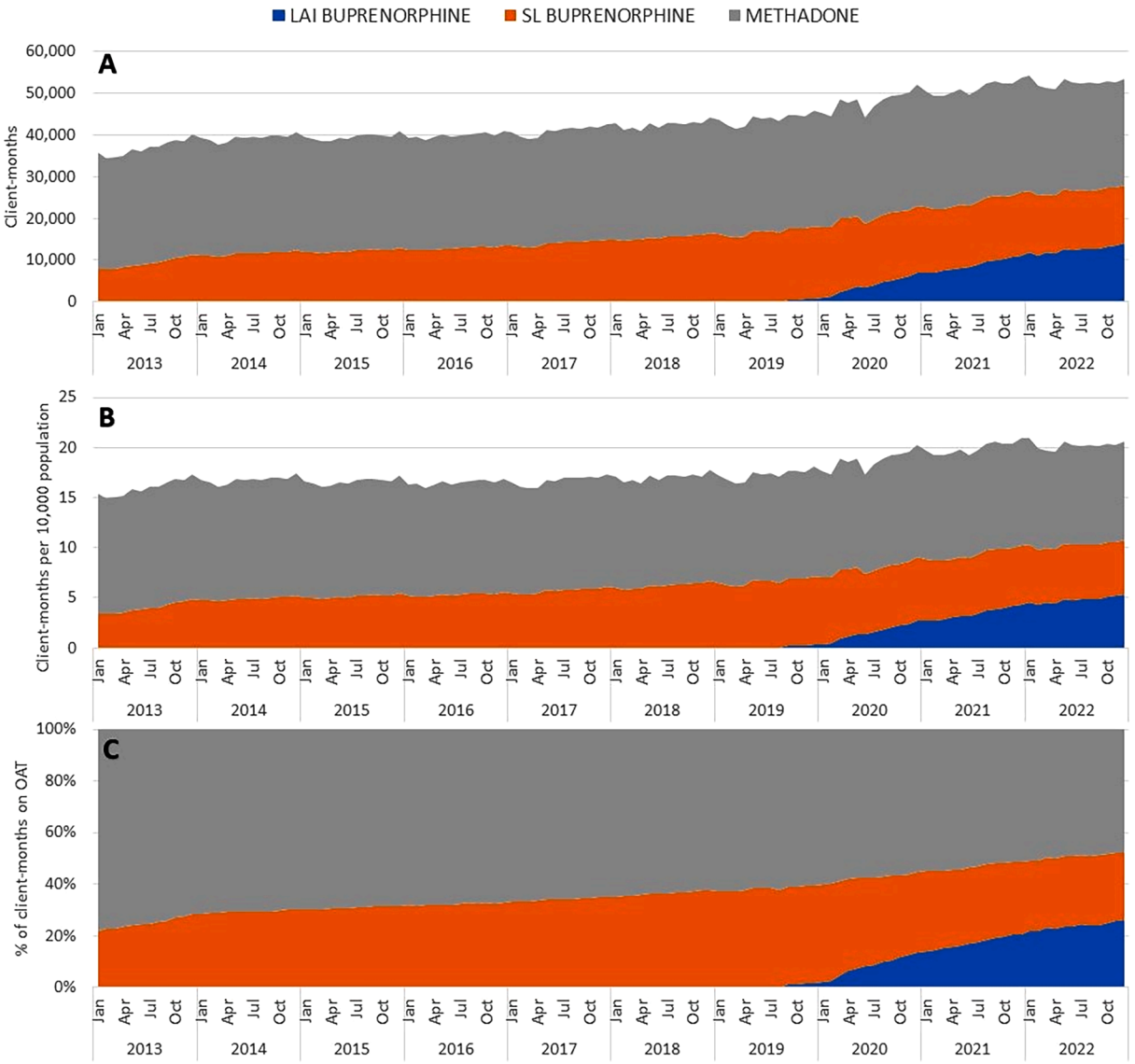
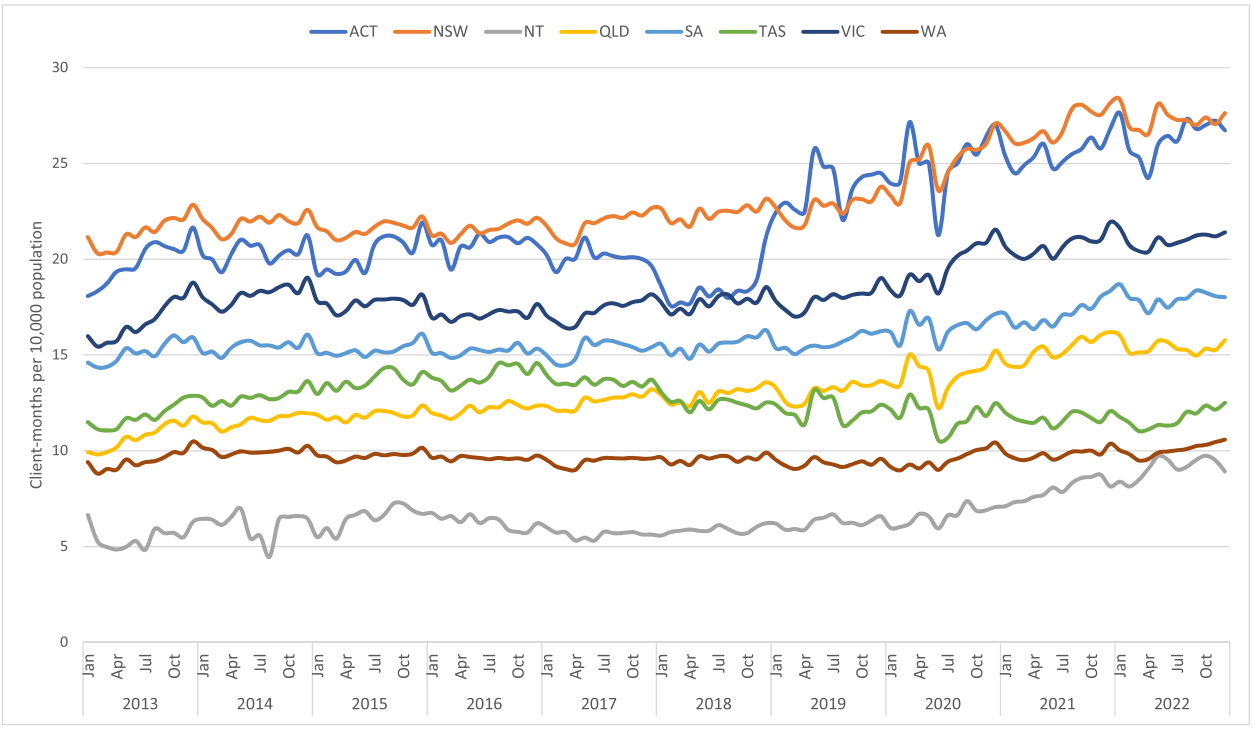


Fig. 1. Estimated number of OAT client-months (A), OAT client-months per 10,000 population (B), and proportion of total OAT client-months (C), per month by medicine in Australia (2013–2022).



ACT: Australian Capital Territory, NSW: New South Wales, NT: Northern Territories, QLD: Queensland, SA: South Australia, TAS: Tasmania, VIC: Victoria, WA: Western Australia

Fig. 2. Number of OAT client-months per 10,000 population per month by Australian jurisdiction (2013–2022).

increased from 2013 to 2016 before declining (Fig. 2).

Trends by setting

The majority (70–86 %) of OAT was accessed at community pharmacies (Table S5). The estimated number of client-months accessing OAT in community pharmacy increased by 32 % from January 2013 to December 2020, remaining relatively stable to the end of 2022. In contrast, the number of client-months accessing OAT in non-community pharmacy settings remained relatively stable from 2013 to 2019/2020, before increasing markedly (Fig. 3, Table S5). At the beginning of the study period, fewer than 1 % of client-months accessed OAT in 'other (including prisons)' settings; between 2019 and 2022, this figure rose to 5 % (Table S5).

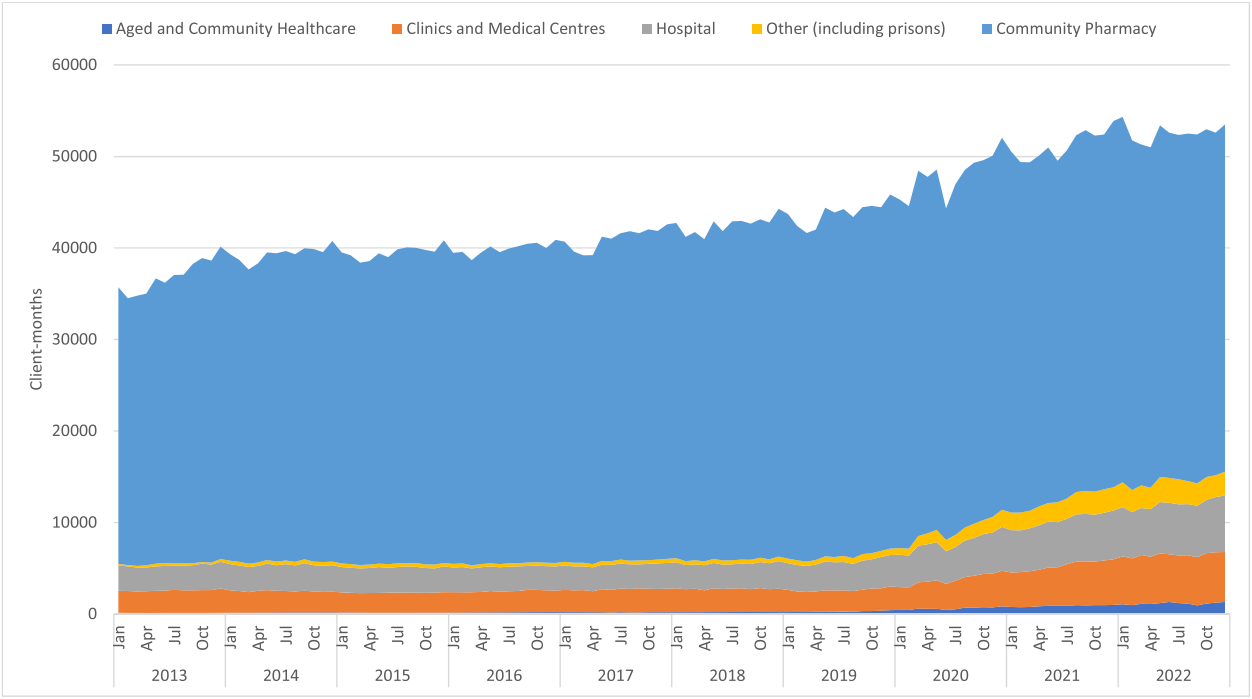


Fig. 3. Number of OAT client-months per month by Australian sales setting (2013–2022).

The distribution of medicines varied by setting (Fig. 4, Table S6). By December 2022, more than half (57.9 %) of the 37,932 OAT client-months in community pharmacy were estimated to be on methadone, with the remainder receiving one of the two buprenorphine formulations (33.3 % SL buprenorphine and 8.8 % LAI buprenorphine). In comparison, in December 2022, an estimated 2,607 client-months were utilised in other settings (including prisons) of which 93 % received LAI buprenorphine and the remainder methadone (6.5 %) or SL buprenorphine (0.5 %) (Fig. 4, Table S6).

Trends by remoteness

Consistently over the study period, approximately 70 % of OAT was provided in major cities and 20 % in inner regional areas (Table S7). Less than 2 % of OAT was provided in remote and very remote areas. Rates of OAT use increased across all remoteness categories over the decade (Fig. 5). From 2013 to 2022, the greatest increase in OAT was observed in very remote areas, from 9 client-months per 10,000 capita in January 2013 to 16 per 10,000 capita in December 2022 (+78 %). In comparison, major cities increased from a rate of 16 to 21 client-months per 10,000 capita (+31 %) over the same timeframe. The gap between major cities and very remote areas reduced from a difference of 7 OAT client-months per 10,000 capita in January 2013 to a difference of 5 OAT client-months per 10,000 in December 2022 (Fig. 5, Table S7).

Trends by socioeconomic status

Across the decade, approximately 26 % of OAT was delivered in the most advantaged quintile areas and 18–20 % in the most disadvantaged areas (Table S8). Levels of OAT were highest in the most advantaged areas (quintile 5) and lowest in the second most disadvantaged areas (quintile 2) (Fig. 6). From 2013 to 2022, rates of OAT use increased across all IRSAD quintiles. The greatest increases in OAT client-months were observed in the third IRSAD quintile, from 14 client-months per 10,000 capita in January 2013 to 20 per 10,000 capita in December 2022 (+43 %). The smallest increase in OAT was observed in the most disadvantaged quintile, from 16 client-months per 10,000 capita in January 2013 to 20 per 10,000 capita in December 2022 (+25 %). The gap between the most advantaged quintile and the second most disadvantaged quintile increased from a difference of 6 OAT client-months per 10,000 capita in January 2013 to a difference of 8 OAT client-months per 10,000 in December 2022 (Fig. 6, Table S8).

Impact of the introduction of LAI buprenorphine

Fig. 7 shows the estimated number of client-months predicted by our ARIMA model in absence of LAI buprenorphine being introduced into OAT programs in Australia (counterfactual, red line) compared with the observed values (blue line). The estimated step change was +1.636 client-months (95 % CI 710 to 2,562) while the estimated change in

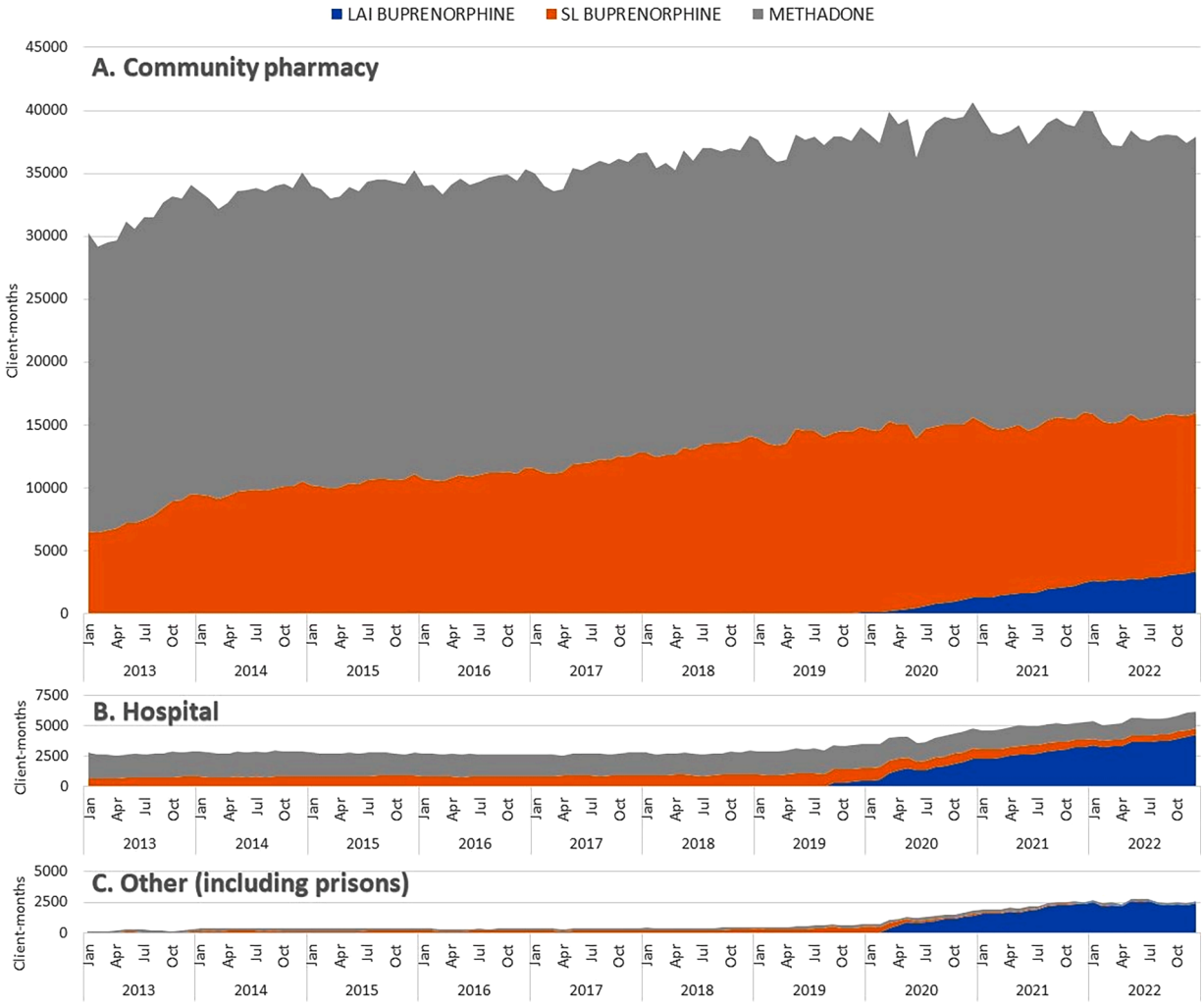


Fig. 4. Cumulative number of OAT client-months per month by medicine in: community pharmacy (A), hospital (B), and other (including prisons) (C) settings (2013–2022).

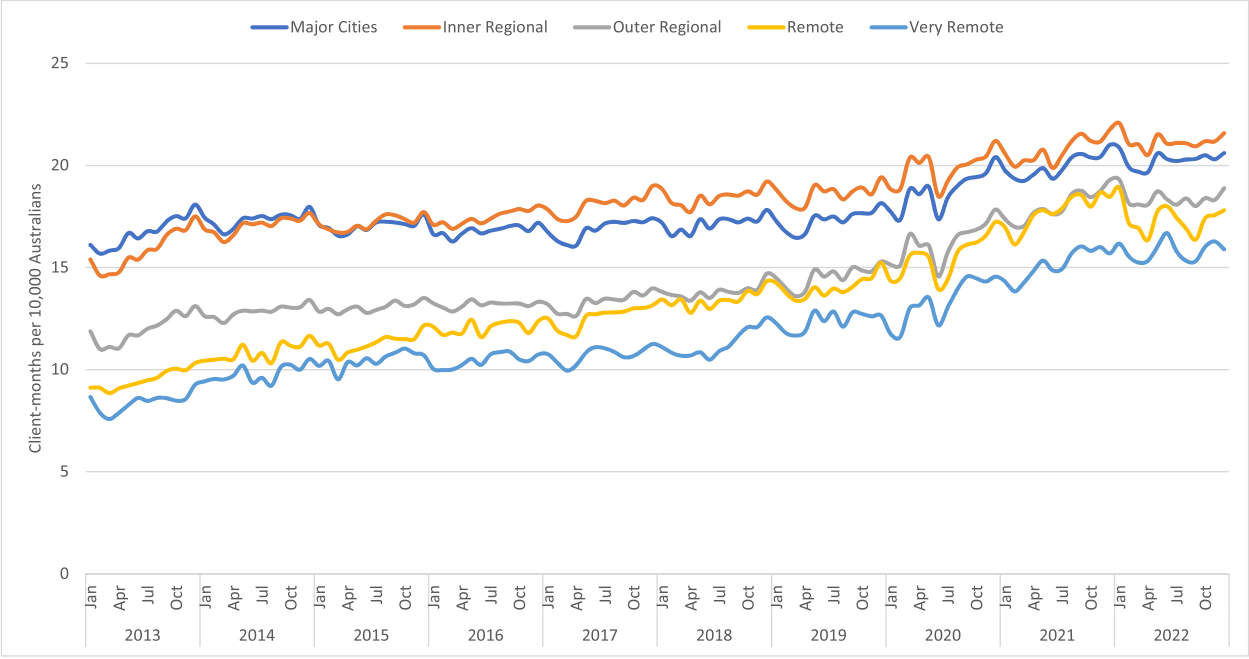


Fig. 5. Number of OAT client-months per 10,000 population per month by remoteness category (2013–2022).

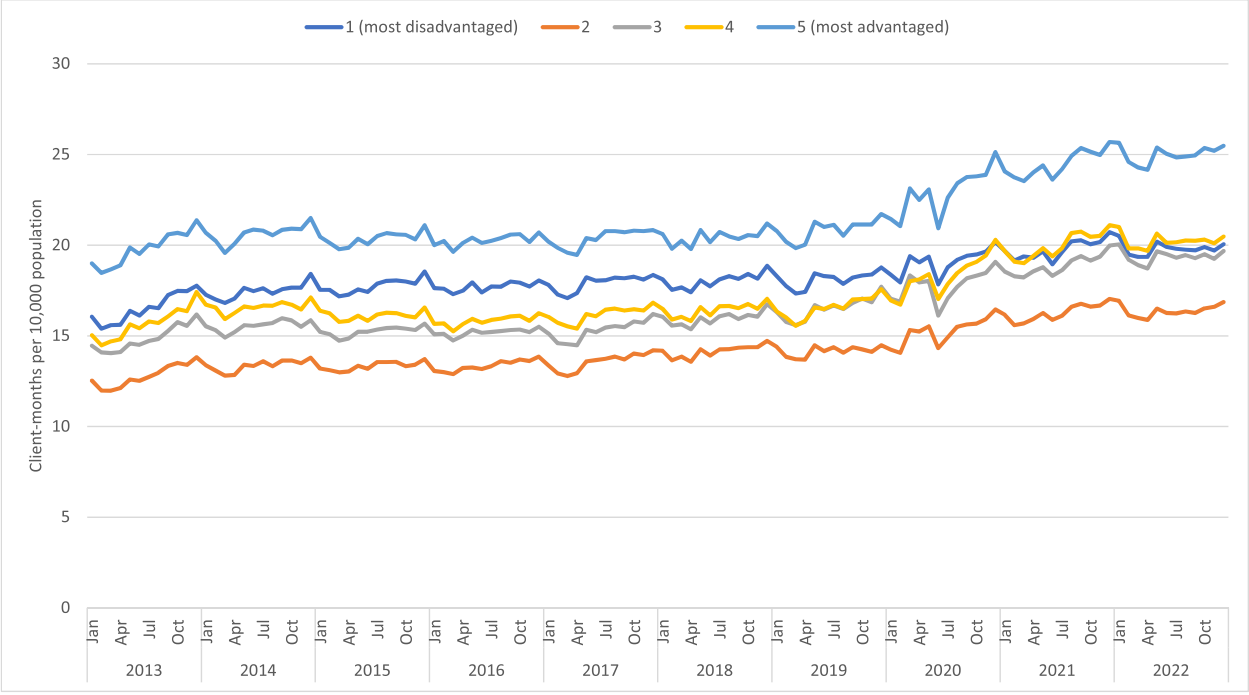


Fig. 6. Number of OAT client-months per 10,000 population per month by Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) quintile (2013–2022).

slope was +190 client-months per month (95 % CI 28 to 351) (Table S9). This means that the introduction of LAI buprenorphine in September 2019 was associated with an immediate, sustained increase of 1636 OAT client-months, with a further increase of 190 OAT client-months every month.

After adjusting for population size, there was no evidence of a statistically significant step change, however, the estimated change in slope was weakly significant at +0.8 client-months per 100,000 Australians per month (95 % CI −0.00 to 0.17) (Table S9). When SL buprenorphine and methadone were modelled individually, there was an immediate increase of 768 SL buprenorphine client-months in September 2019 (95 % CI 390 to 1148), followed by a decrease of 205 SL buprenorphine client-months per month (95 % CI −299 to −111) until December 2022 and a change in slope of −59 methadone client-months per month (95 % CI −95 to −24) (Table S9).

Trends in the sales of LAI buprenorphine

Since the introduction of LAI buprenorphine, the majority of use was for monthly rather than weekly formulations (Fig. 8, Table S10). The

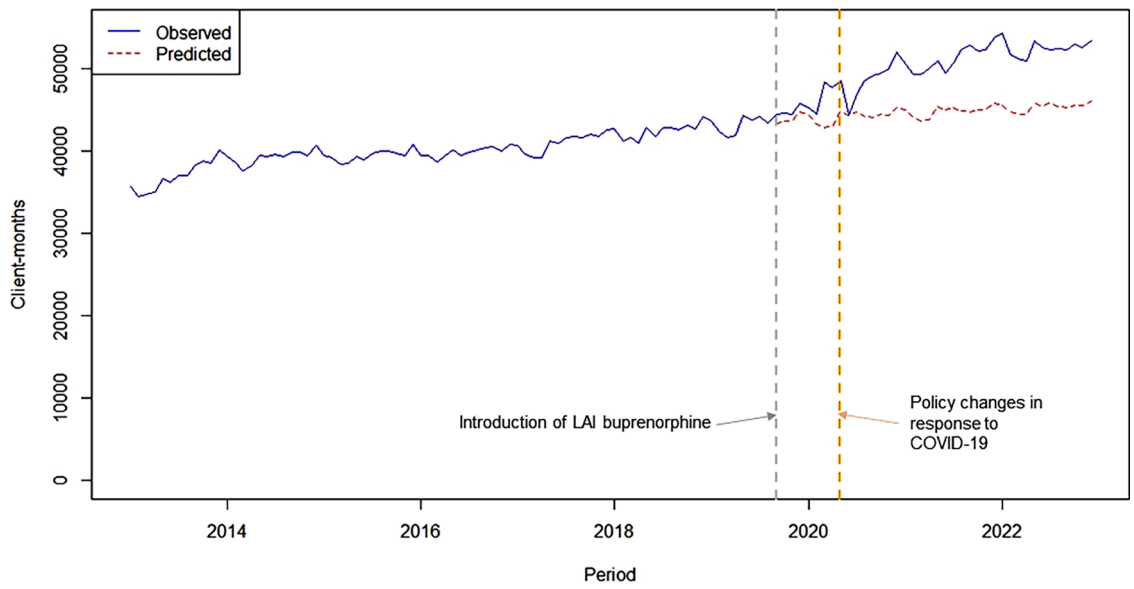
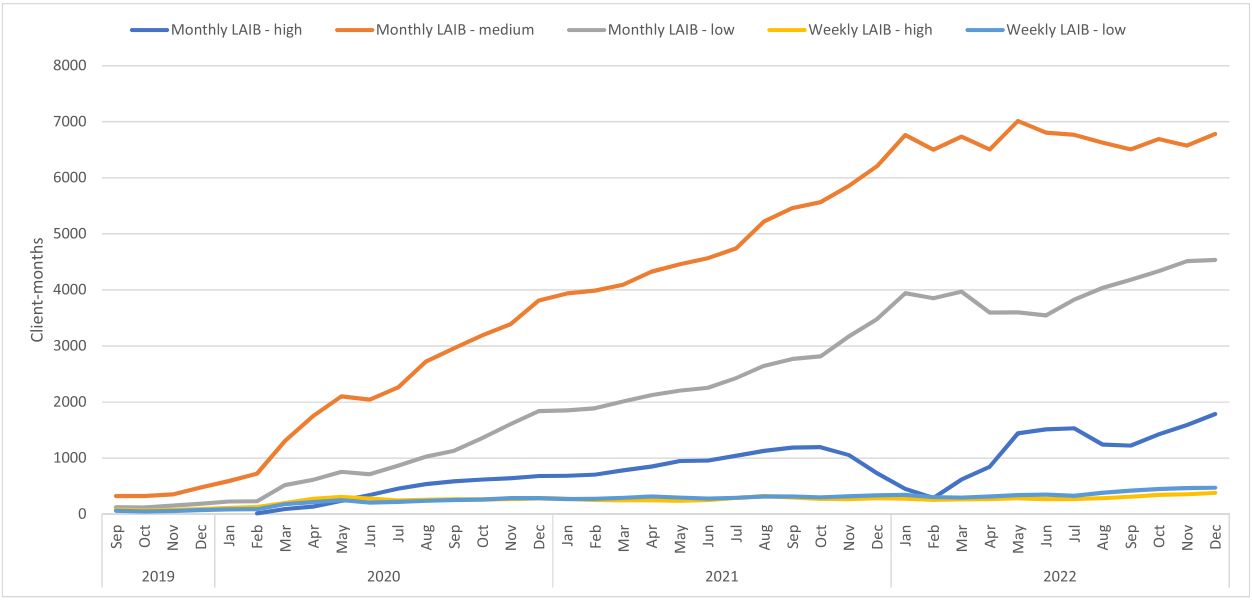


Fig. 7. Number of OAT client-months per month: observed values (blue) and predicted values (red) in absence of the introduction of LAI buprenorphine in September 2019 based on ARIMA model.



† LAIB groups are defined in Table S1

Fig. 8. Number of OAT client-months per month by strength of long-acting injectable buprenorphine (LAIB; monthly high, medium, and low strengths; weekly high and low strengths) †, Australia 2013–2022.
† LAIB groups are defined in Table 1.

medium strength monthly formulations were used most commonly followed by low strength, with high strengths used less frequently. From September 2019 to December 2022, the uptake of medium strength monthly formulations increased from 325 to 6,782 client-months (+1986 %), low strengths from 71 to 4,536 client-months (+6288 %) and high strengths from 90 client-months in February 2020 to 1,787 client-months in December 2022 (+1508 %; Fig. 8, Table S10).

Sensitivity analysis

Using the lower and upper bounds of the 95 % CI of pooled mean daily doses for methadone (69.4 mg to 78.7 mg per day) and SL buprenorphine (14.4 mg to 17.6 mg per day), and the 25th and 75th centiles (26 to 31 days) of the dosing intervals for LAI buprenorphine from the chart review (Chidwick, et al., 2023a, 2023b), a range is provided for the estimated number of total OAT, methadone, and SL buprenorphine client-months (Fig. S1) and estimated number of LAI buprenorphine client-months only (Fig. S2). The estimated number of client-months from sensitivity analyses ranges from 33,464 to 38,585 at the beginning of the study (January 2013) and from 49,891 to 58,827 OAT client-months at the end of the study period (December 2022) (Fig. S1). The estimated number of LAI buprenorphine client-months at the end of the study period (December 2022) ranged from 13,041 to 15,400 (Fig. S2).

Discussion

This longitudinal post-marketing study used national sales data to evaluate trends in the number of OAT client-months and the types of OAT medicines used in Australia between 2013 and 2022. Over the study period, the overall level of OAT access increased steadily, with a + 33 % estimated increase in the population-standardised number of OAT client-months. The pattern of use of OAT medicines changed over time, with the most common OAT medicine being methadone in 2013 and buprenorphine in 2022. An increase in OAT utilisation was observed in non-dominant settings and remote and very remote geographic areas from early 2020 – coinciding with the introduction of LAI buprenorphine, the COVID-19 pandemic, and related interim OAT guidance and policies. The introduction of LAI buprenorphine in September 2019 was associated with an immediate, sustained increase in client-months in Australia. These findings have significant implications for our understanding of service features which engage and support people seeking treatment for their opioid dependence, guiding the focus of ongoing evaluations, and supporting the strategic planning of associated policy directions and priorities.

In Australia, there has been a significant increase in the use of LAI buprenorphine for OAT, such that between September 2019 (the first month LAI buprenorphine was listed on the Australian PBS) and December 2022, the estimated number of client-months on LAI buprenorphine increased 23-fold, ultimately accounting for a quarter of all Australian OAT client-months. The monthly depot injections are more commonly used than weekly injections and account for the vast majority of the LAI buprenorphine market. As described earlier, scale-up of LAI buprenorphine was accelerated as a strategy to protect clients from COVID exposure, and help adhere with density limits and social distancing rules during the COVID-19 pandemic (Lintzeris et al., 2020). Such models included the rapid upscale of LAI buprenorphine in correctional centres in NSW for all new OAT clients and those already receiving buprenorphine-naloxone, helping to relieve staffing resources for other clinical activities (Roberts et al., 2021). In metropolitan Melbourne, Victoria, a rapid-access clinic dedicated to LAI buprenorphine was established that accepted a wide range of referral pathways at no cost to attendees (Roberts et al., 2021; Straub et al., 2021). Despite being approved by the Food and Drug Administration in 2017, a similar level of uptake of LAI buprenorphine in the United States has not yet been observed (Morgan et al., 2021), with reports that program implementation is hampered by significant logistical, administrative, and regulatory barriers (Shah et al., 2023). Our findings highlight the advantage that LAI buprenorphine represents as an additional option for people seeking treatment for their opioid dependence, with promising initial findings relating to retention (Farrell et al., 2022). Further research is needed to understand whether LAI buprenorphine offers similar benefits to SL buprenorphine and methadone with respect to health and social outcomes. Given OAT coverage remains low to moderate in many countries (Larney et al., 2017), LAI buprenorphine represents a potential strategy for increasing intervention coverage – especially in prisons and other human resource-constrained settings (Harm Reduction International, 2022).

In line with the increasing uptake of LAI buprenorphine has been the shift towards buprenorphine (incl. SL and LAI buprenorphine formulations) as the most common OAT used in Australia, with the estimated proportion of all OAT client-months on buprenorphine increasing from a fifth (22.0 %) in January 2013, to a third (36.9 %) in January 2019, to more than half (52.3 %) of all estimated OAT client-months in December 2022. Given the estimated number of client-months on methadone over the study period remained relatively stable, this finding aligns with previous reports that buprenorphine is increasingly the medicine most OAT clients initiate on in Australia (Bharat et al., 2021). This contrasts with the global trend, whereby buprenorphine is not offered as a form of OAT in a third of countries where OAT programs are available (Larney et al., 2017). Cost may be an important driving factor, with methadone cheaper and more cost-effective than SL buprenorphine (World Health Organization & Department of Mental Health & Substance Abuse, 2009). In comparison, preliminary economic modelling from seven Australian correctional centres suggests that, despite higher medication costs, LAI buprenorphine may be a less costly option to administer compared to methadone (Ling et al., 2022). It is important to note that methadone and buprenorphine have different pharmacological profiles (Strang et al., 2020), and differ on select treatment outcomes (Degenhardt et al., 2019), including longer retention for methadone compared with SL buprenorphine, and increased all-cause mortality risk in the first 4 weeks for methadone but not buprenorphine (Santo et al., 2021). Even so, both medicines are safe, effective, and (in Australia) first-line treatment options for opioid dependence (Gowing et al., 2014). This highlights the importance of offering different medicines within OAT programs to cater for different client treatment needs and preferences (Yarborough et al., 2016).

There is potentially a multitude of factors influencing the increasing level of OAT utilisation over the study period. This finding may reflect the increasing number of people with opioid dependence who benefited from OAT and other harm reduction initiatives in the 1970s and 80s who have survived to date and into older age (Australian Injecting and Illicit Drug Users League (AIVL), 2011), resulting in a larger cohort of older people engaging in OAT; this is reflected in the median age of OAT clients in Australia increasing from 40 years in 2013 to 44 years in 2022 (Australian Institute of Health Welfare, 2023). It may be that the number and types of opioid drugs for which people are seeking treatment for may have expanded over time, with increased prescribing of opioids for chronic non-cancer pain producing a new sub-group of clients with iatrogenic opioid dependence (Ballantyne & LaForge, 2007; Nielsen et al., 2016; van Rijswijk et al., 2019). Indeed, recent population estimates indicate that, in NSW between 2014 and 2016, the prevalence of opioid dependence had increased (Downing et al., 2023).

As a result of the COVID-19 pandemic, both nationally and internationally, there were significant changes to the dosing frequency for both methadone and buprenorphine, including a move to support increased take-home doses (Kitchen et al., 2022; Lintzeris et al., 2020; Panwala et al., 2023). In Australia, publication of these program changes in late April 2020 preceded the largest estimate of OAT use in a given month up to that point of the study (May 2020: 48,560 client-months). Despite these observations, estimates of the impact of the LAI buprenorphine introduction (September 2019) on population-level OAT trends showed that, to the end of the study period, the number of client-months on methadone remained stable while the number of SL buprenorphine client-months declined slightly. Considering the latter in the context of the newly available buprenorphine formulation (LAI buprenorphine), these analyses suggest that, at the population-level, the rapid adjustment to a more flexible and less frequent attendance model may have succeeded in mitigating anticipated COVID-19 related barriers to individual clients receiving ongoing OAT. Future work is needed to understand how the COVID-19 pandemic-related guidance and policy amendments for OAT delivery impacted patterns of treatment accessibility and engagement, as well as related outcomes. This, along with an economic evaluation of delivering OAT including different medicines in different settings, and accounting for the recent (July 2023) reduction in client-borne costs to access OAT in Australia (Australian Government Department of Health & Aged Care, 2023), could be used to inform and ensure the economic viability of existing and future dosing sites, and the program more broadly.

This study builds on the National Opioid Pharmacotherapy Statistics Annual Data, which provide a national overview of the number of OAT clients in Australia on snapshot day/s by state and territory health departments (Australian Institute of Health Welfare, 2023). The trends seen in this study largely align with the annual summaries from the NOPSAD, however some differences were observed. The client estimates are somewhat lower than those reported in NOPSAD. At the beginning of the study, the estimated number of OAT client-months was 24 % lower

than the number of clients quoted by NOPSAD [June 2013: 36,215 client-months (sensitivity analysis range: 33,887 to 39,142) vs 47,442 clients in NOPSAD] and by the end of the study period this difference had reduced, to only 6 % lower [June 2022: 52,606 client-months (sensitivity analysis range: 49,045 to 57,343) vs 55,741 clients in NOPSAD]. While both data sources show increasing per-capita OAT use between 2013 and 2022, the magnitude of the increase was higher in this study than NOPSAD. From June 2013 to June 2022, data indicate per capita OAT use increased by +25 % in this study (from 16 to 20 OAT clients per 10,000 population) and by +5 % (from 20 to 21 OAT clients per 10,000 population) according to the NOPSAD collection. These differences may be explained by differences in the ways clients are identified in the two data sources and incomplete capture of sales in some jurisdictions in the IQVIA data, particularly from settings other than community pharmacy and hospital in earlier years of the study. NOPSAD collects data on clients receiving OAT on specific day/s per year, whereas the client estimates in this report are based on a conversion of packs sold into clients treated over a month, with the assumption that clients are retained in OAT over the full 28-day interval. As some attrition from OAT is expected, this study may underestimate the total number of clients accessing OAT over the month, however, if OAT retention rates have improved over time (Bharat et al., 2021), the potential for this source of underestimation would have diminished over the study time period.

Strengths and limitations

Strengths of this study include the use of national sales data, which provided longitudinal information on OAT not otherwise available in any other national dataset, and capture of the vast majority of all OAT medicine sales at monthly intervals in Australia over the study period. Utilisation of interrupted time series analyses, a robust quasi-experimental design method, also provided an estimate of the impact of LAI buprenorphine on population-level OAT use. However, the findings should be considered alongside several limitations.

First, the approach used in estimating the number of client-months on OAT assumes that real-world OAT doses – and the factors known to influence dose, including disorder severity - have remained stable over time and across different settings. The parameters used to derive these estimates were informed by the literature; even so, there are no population-based data on individual-level OAT doses from Australia on which those parameters can be verified. Further, the estimates assume clients receive OAT over the full 28-day interval; where this is not the case, the number of clients accessing OAT at least once a month would be higher. Second, as the weekly low dose LAI buprenorphine formulation can be used for top-up or supplemental dosing (Lintzeris et al., 2019), inclusion of these formulations may have resulted in an overestimate of the number of client-months. However, this product constituted a very small fraction (<3 %) of all LAI buprenorphine (Fig. 7, Table S10), so it is unlikely that this has a large influence on the findings. Third, it is not possible to eliminate the potential that these findings were influenced by unmeasured (and/or unknown) co-occurring interventions. Therefore, residual confounding in the reported estimates is possible. Fourth, IQVIA coverage may have improved over time, which could lead to an underestimate of OAT client-months in earlier years of the study and an overestimate of the percentage change between 2013 and 2022. Furthermore, in some jurisdictions (Chidwick, et al., 2023a, 2023b), there is incomplete capture of sales from OAT settings other than community pharmacy and hospitals (e.g., prisons, clinics and medical centres) in the IQVIA data, which could lead to a slight underestimate of national OAT client-months. Finally, the geographic information provided by IQVIA for non-community pharmacy/hospital settings was less granular so there may be some misclassification of remoteness and socioeconomic categories in these settings.

In conclusion, there has been an increase in OAT utilisation in Australia over the past decade, with variation in patterns for individual medicines, such that buprenorphine has replaced methadone as the most common OAT used. Importantly, there has been an increase in OAT utilisation in non-community settings, and in remote and very remote geographic areas since early 2020 - coinciding with the introduction of LAI buprenorphine, the COVID-19 pandemic, and related interim OAT guidance and policies. Collectively, these results suggest that – at the population-level - the benefits afforded by these changes in service organisation and delivery improved the accessibility of OAT for people with opioid dependence, especially minority groups. It is yet to be determined if the increased utilisation is associated with net benefits or harms for people with opioid dependence, so determining the clinical outcomes of these changes is now critical. Future work on the overall costs and cost effectiveness of OAT would assist in future service planning.

Ethics approval

The authors declare that the work reported herein did not require ethics approval because it did not involve animal or human participation.

CRediT authorship contribution statement

Chrianna Bharat: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Kendal Chidwick:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Natasa Gisev:** Writing – review & editing, Investigation, Funding acquisition, Data curation. **Michael Farrell:** Writing – review & editing, Resources, Funding acquisition, Data curation. **Robert Ali:** Writing – review & editing, Validation. **Louisa Degenhardt:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L. D. has received untied educational funding from Reckitt Benckiser, Indivior, Mundipharma Pty Ltd, and Seqirus. M.F. has received untied funding from Indivior and Seqirus. These untied grants are all unrelated to the current study. All other authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2023.104255.

References

Australia Bureau of Statistics. (2018a). Australian statistical geography standard (ASGS): Volume 5 - remoteness structure, July 2016 Canberra. https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1270.0.55.005July%202016?OpenDocument.

Australia Bureau of Statistics. (2018b). Census of population and housing: Socio-economic indexes for areas (SEIFA), Australia, 2016 (2033.0.55.001). Canberra. https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.0012016?OpenDocument.

Australian Bureau of Statistics. (September 2022). *National, state and territory population*. ABS. https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/sep-2022.

Australian Government Australian Institute of Health and Welfare. (2022). *National opioid pharmacotherapy statistics annual data collection, 2022;* Quality Statement. https://meteor.aihw.gov.au/content/774516.

Australian Government Department of Health and Aged Care. (2023, Last Updated: 28 June 2023). The pharmaceutical benefits scheme: Opioid dependence treatment program. https://www.pbs.gov.au/browse/section100-md.

Australian Injecting and Illicit Drug Users League (AIVL). (2011). *'Double jeopardy': Older injecting opioid users in Australia - AIVL Discussion paper*. Canberra, Australia: AIVL. https://nceta.flinders.edu.au/application/files/5915/0646/7770/AVIL_2011.pdf.

Australian Institute of Health Welfare. (2023). *National opioid pharmacotherapy statistics annual data collection*. Canberra: AIHW. https://www.aihw.gov.au/reports/alcohol-other-drug-treatment-services/national-opioid-pharmacotherapy-statistics.

Ballantyne, J. C., & LaForge, K. S (2007). Opioid dependence and addiction during opioid treatment of chronic pain. *Pain, 129*(3), 235–255.

Barnett, A., Savic, M., Lintzeris, N., Bathish, R., Arunogiri, S., Dunlop, A. J., Haber, P., Graham, R., Hayes, V., & Lubman, D. I. (2021). Tracing the affordances of long-acting injectable depot buprenorphine: A qualitative study of patients' experiences in Australia. *Drug and Alcohol Dependence, 227*, Article 108959. https://doi.org/10.1016/j.drugalcdep.2021.108959

Bharat, C., Larney, S., Barbieri, S., Dobbins, T., Jones, N. R., Hickman, M., Gisev, N., Ali, R., & Degenhardt, L. (2021). The effect of person, treatment and prescriber characteristics on retention in opioid agonist treatment: A 15-year retrospective cohort study. *Addiction (Abingdon, England), 116*(11), 3139–3152. https://doi.org/10.1111/add.15514

Box, G.E., Jenkins, G.M., Reinsel, G.C., & Ljung, G.M. (2015). *Time series analysis: Forecasting and control*. John Wiley & Sons.

Brown, C., Dagley, M., Amantham, S., Brockway, A., & Bryant, T. (2020). *Navigating COVID-19 impact: An initial assessment of the pandemic's effect on Australian healthcare*. https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-anz-covid-19_white-paper.pdf.

Chidwick, K., Bharat, C., Gisev, N., Farrell, M., & Degenhardt, L. (2023a). *Real-world dosing intervals of long-acting buprenorphine for opioid agonist treatment*. Sydney: National Drug and Alcohol Research Centre, University of New South Wales. NDARC Technical Report, Issue No. 345 http://doi.org/10.26190/ayet-f348.

Chidwick, K., Gisev, N., Degenhardt, L., Farrell, M., & Bharat, C (2023b). *Trends in the use of opioid agonist treatment in victoria, 2013–2022*. Sydney: National Drug and Alcohol Research Centre, University of New South Wales. NDARC Technical Report, Issue No. 352 http://doi.org/10.26190/gjpp-py45.

Clay, S., Treloar, C., Degenhardt, L., Grebely, J., Christmass, M., Gough, C., Hayllar, J., McDonough, M., Henderson, C., Crawford, S., Farrell, M., & Marshall, A. (2023). 'I just thought that was the best thing for me to do at this point': Exploring patient experiences with depot buprenorphine and their motivations to discontinue. *International Journal of Drug Policy, 115*, Article 104002. https://doi.org/10.1016/j.drugpo.2023.104002

Colledge-Frisby, S., Jones, N., Larney, S., Peacock, A., Lewer, D., Brothers, T. D., Hickman, M., Farrell, M., & Degenhardt, L. (2022). The impact of opioid agonist treatment on hospitalisations for injecting-related diseases among an opioid dependent population: A retrospective data linkage study. *Drug and Alcohol Dependence, 236*, Article 109494. https://doi.org/10.1016/j.drugalcdep.2022.109494

Colledge-Frisby, S., Ottaviano, S., Webb, P., Grebely, J., Wheeler, A., Cunningham, E. B., Hajarizadeh, B., Leung, J., Peacock, A., Vickerman, P., Farrell, M., Dore, G. J., Hickman, M., & Degenhardt, L. (2023). Global coverage of interventions to prevent and manage drug-related harms among people who inject drugs: A systematic review. *The Lancet Global Health, 11*(5), e673–e683. https://doi.org/10.1016/S2214-109X(23)00058-X

Degenhardt, L., Grebely, J., Stone, J., Hickman, M., Vickerman, P., Marshall, B. D., Bruneau, J., Altice, F. L., Henderson, G., & Rahimi-Movaghar, A. (2019). Global patterns of opioid use and dependence: Harms to populations, interventions, and future action. *The Lancet, 394*(10208), 1560–1579.

Downing, B. C., Hickman, M., Jones, N. R., Larney, S., Sweeting, M. J., Xu, Y., … Jones, H. E. (2023). Prevalence of opioid dependence in New South Wales, Australia, 2014-16: Indirect estimation from multiple data sources using a Bayesian approach. *Addiction (Abingdon, England), 118*(10), 1994–2006. https://doi.org/10.1111/add.16268

Expert Review Panel. (2023). *Interim report for the post-market review of opioid dependence treatment program medicines – report to the PBAC*. The Pharmaceutical Benefits Scheme: Australian Government Department of Health and Aged Care. https://www.pbs.gov.au/reviews/post-market-review-of-opiate-dependence-treatment-program/Interim-Report-for-the-PMR-of-ODTP-medicines.pdf.

Farrell, M., Shahbazi, J., Byrne, M., Grebely, J., Lintzeris, N., Chambers, M., Larance, B., Ali, R., Nielsen, S., Dunlop, A., Dore, G. J., McDonough, M., Montebello, M., Nicholas, T., Weiss, R., Rodgers, C., Cook, J., & Degenhardt, L. (2022). Outcomes of a single-arm implementation trial of extended-release subcutaneous buprenorphine depot injections in people with opioid dependence. *International Journal of Drug Policy, 100*, Article 103492. https://doi.org/10.1016/j.drugpo.2021.103492

Frost, M., Bailey, G. L., Lintzeris, N., Strang, J., Dunlop, A., Nunes, E. V., Jansen, J. B., Frey, L. C., Weber, B., Haber, P., Oosman, S., Kim, S., & Tiberg, F. (2019). Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. *Addiction (Abingdon, England), 114*(8), 1416–1426. https://doi.org/10.1111/add.14636

Gisev, N., Bharat, C., Larney, S., Dobbins, T., Weatherburn, D., Hickman, M., Farrell, M., & Degenhardt, L. (2019). The effect of entry and retention in opioid agonist treatment on contact with the criminal justice system among opioid-dependent people: A retrospective cohort study. *The Lancet Public Health, 4*(7), e334–e342. https://doi.org/10.1016/S2468-2667(19)30060-X

Gowing, L., Ali, R., Dunlop, A., Farrell, M., & Lintzeris, N. (2014). *National guidelines for medication-assisted treatment of opioid dependence* (pp. 38–39). Canberra Commonwealth of Australia.

Haight, B. R., Learned, S. M., Laffont, C. M., Fudala, P. J., Zhao, Y., Garofalo, A. S., Greenwald, M. K., Nadipelli, V. R., Ling, W., & Heidbreder, C. (2019). Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet, 393*(10173), 778–790. https://doi.org/10.1016/s0140-6736(18)32259-1

Hall, N. Y., Le, L., Majmudar, I., & Mihalopoulos, C. (2021). Barriers to accessing opioid substitution treatment for opioid use disorder: A systematic review from the client perspective. *Drug and Alcohol Dependence, 221*, Article 108651. https://doi.org/10.1016/j.drugalcdep.2021.108651

Harm Reduction International. (2022). Global state of harm reduction 2022. London.

Hyndman, R., Athanasopoulos, G., Bergmeir, C., Caceres, G., Chhay, L., O'Hara-Wild, M., Petropoulos, F., Razbash, S., Wang, E., & Yasmeen, F. (2016). *Forecast: Forecasting functions for time series and linear models*. in: R package version 7.3. In https://pkg.robjhyndman.com/forecast/.

Kitchen, S. A., Campbell, T. J., Men, S., Bozinoff, N., Tadrous, M., Antoniou, T., Wyman, J., Werb, D., Munro, C., & Gomes, T. (2022). Impact of the COVID-19 pandemic on the provision of take-home doses of opioid agonist therapy in Ontario, Canada: A population-based time-series analysis. *International Journal of Drug Policy, 103*, Article 103644. https://doi.org/10.1016/j.drugpo.2022.103644

Lancaster, K., Gendera, S., Treloar, C., Rhodes, T., Shahbazi, J., Byrne, M., Degenhardt, L., & Farrell, M. (2023). The social, material, and temporal effects of monthly extended-release buprenorphine depot treatment for opioid dependence: An Australian qualitative study. *Contemporary Drug Problems, 50*(1), 105–120. https://doi.org/10.1177/00914509221140959

Larney, S., Peacock, A., Leung, J., Colledge, S., Hickman, M., Vickerman, P., Grebely, J., Dumchev, K. V., Griffiths, P., Hines, L., Cunningham, E. B., Mattick, R. P., Lynskey, M., Marsden, J., Strang, J., & Degenhardt, L. (2017). Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: A systematic review. *The Lancet Global Health, 5*(12), e1208–e1220. https://doi.org/10.1016/S2214-109X(17)30373-X

Ling, R., White, B., Roberts, J., Cretikos, M., Howard, M. V., Haber, P. S., Lintzeris, N., Reeves, P., Dunlop, A. J., & Searles, A. (2022). Depot buprenorphine as an opioid agonist therapy in New South Wales correctional centres: A costing model. *BMC Health Services Research, 22*(1), 1326. https://doi.org/10.1186/s12913-022-08687-8

Lintzeris, N., Dunlop, A., & Masters, D. (2019). *Clinical guidelines for use of depot buprenorphine (Buvidal and sublocade) in the treatment of opioid dependence*. NSW Ministry of Health.

Lintzeris, N., Hayes, V., & Arunogiri, S. (2020). *Interim guidance for the delivery of medication assisted treatment of opioid dependence in response to COVID-19: A national response*. Royal Australasian College of Physicians. https://www.racp.edu.au/docs/default-source/news-and-events/covid-19/interim-guidance-delivery-of-medication-assisted-treatment-of-opiod-dependence-covid-19.pdf?sfvrsn=e36eeb1a_4.

Mellish, L., Karanges, E. A., Litchfield, M. J., Schaffer, A. L., Blanch, B., Daniels, B. J., Segrave, A., & Pearson, S.-A. (2015). The Australian pharmaceutical benefits scheme data collection: A practical guide for researchers. *BMC Research Notes, 8*(1), 634. https://doi.org/10.1186/s13104-015-1616-8

Morgan, J. R., Walley, A. Y., Murphy, S. M., Chatterjee, A., Hadland, S. E., Barocas, J., Linas, B. P., & Assoumou, S. A. (2021). Characterizing initiation, use, and discontinuation of extended-release buprenorphine in a nationally representative United States commercially insured cohort. *Drug and Alcohol Dependence, 225*, Article 108764. https://doi.org/10.1016/j.drugalcdep.2021.108764

Nielsen, S., Degenhardt, L., Hoban, B., & Gisev, N. (2014). *Comparing opioids: A guide to estimating oral morphine equivalents (OME) in research no. 329)*. Sydney: National Drug and Alcohol Research Centre, University of New South Wales.

Nielsen, S., Tse, W. C., & Larance, B. (2022). Opioid agonist treatment for people who are dependent on pharmaceutical opioids. *The Cochrane database of systematic reviews, 9*(9), CD011117. https://doi.org/10.1002/14651858.CD011117.pub3.

Panwala, V., Joudrey, P., Kowalski, M., Bach, P., & Amram, O. (2023). Changes to methadone maintenance therapy in the United States, Canada, and Australia during the COVID-19 pandemic: A narrative review. *Journal of Substance Use and Addiction Treatment, 152*, Article 209086. https://doi.org/10.1016/j.josat.2023.209086

Ritter, A., & Chalmers, J. (2009). *Polygon: The many sides to the Australian opioid pharmacotherapy maintenance system*. Australian National Council on Drugs.

Roberts, J., White, B., Attalla, D., Ward, S., & Dunlop, A. J. (2021). Rapid upscale of depot buprenorphine (CAM2038) in custodial settings during the early COVID-19 pandemic in New South Wales, Australia. *Addiction, 116*(2), 426–427.

Santo, T., Clark, B., Hickman, M., Grebely, J., Campbell, G., Sordo, L., … Padmanathan, P. (2021). Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: A systematic review and meta-analysis. *JAMA Psychiatry, 78*(9), 979–993.

Shah, R., Hendrickson, S., Fanucchi, L., Lofwall, M., Platt, T., & Rhudy, C. (2023). Utility of an integrated health system specialty pharmacy in provision of extended-release buprenorphine for patients with opioid use disorder. *American Journal of Health-System Pharmacy, 80*(1), e59–e66. https://doi.org/10.1093/ajhp/zxac269

Strang, J., Volkow, N. D., Degenhardt, L., Hickman, M., Johnson, K., Koob, G. F., Marshall, B. D. L., Tyndall, M., & Walsh, S. L. (2020). Opioid use disorder. *Nature Reviews Disease Primers, 6*(1), 3. https://doi.org/10.1038/s41572-019-0137-5

Straub, A., Pastor, A., Lloyd-Jones, M., O'Neill, H., & Bonomo, Y. (2021). The development and implementation of a rapid-access long-acting injectable buprenorphine clinic in metropolitan Melbourne during the COVID-19 pandemic. *Drug and Alcohol Review, 40*(4), 681–682. https://doi.org/10.1111/dar.13161

The Pharmaceutical Benefits Scheme. (2023). *Reforming Opioid Dependence Treatment Access*. Australian Government Department of Health and Aged Care. https://www.pbs.gov.au/info/news/2023/05/reforming-opioid-dependence-treatment-access.

The Royal Australian College of General Practitioners. (2017). *Prescribing drugs of dependence in general practice, part C2: The role of opioids in pain management*. East Melbourne, VIC: RACGP.

van Rijswijk, S. M., van Beek, M. H. C. T., Schoof, G. M., Schene, A. H., Steegers, M., & Schellekens, A. F. (2019). Iatrogenic opioid use disorder, chronic pain and psychiatric comorbidity: A systematic review. *General Hospital Psychiatry, 59*, 37–50. https://doi.org/10.1016/j.genhosppsych.2019.04.008

World Health Organization. (2012). WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users–2012 revision.
World Health Organization. (2017). WHO model list of essential medicines http://www.who.int/medicines/publications/essentialmedicines/en/.
World Health Organization, & Department of Mental Health and Substance Abuse. (2009). *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. World Health Organization.
Yarborough, B. J., Stumbo, S. P., McCarty, D., Mertens, J., Weisner, C., & Green, C. A. (2016). Methadone, buprenorphine and preferences for opioid agonist treatment: A qualitative analysis. *Drug and Alcohol Dependence, 160*, 112–118. https://doi.org/10.1016/j.drugalcdep.2015.12.031