International Journal of Drug Policy 100 (2022) 103492

Contents lists available at ScienceDirect

International Journal of Drug Policy

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

Research paper

Outcomes of a single-arm implementation trial of extended-release subcutaneous buprenorphine depot injections in people with opioid dependence

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ARTICLE INFO

Keywords:
Opioid dependence
Opioid agonist treatment
Buprenorphine

ABSTRACT

Background: Opioid agonist treatment (OAT) is an effective intervention for opioid dependence. Extended-release buprenorphine injections (BUP-XR) may have additional potential benefits over sublingual buprenorphine. This single-arm trial evaluated outcomes among people receiving 48 weeks of BUP-XR in diverse community health-care settings in Australia, permitting examination of outcomes when BUP-XR is delivered in standard practice.

Methods: Participants were recruited from a network of specialist public drug treatment services, primary care and some private practices in three states. Following a minimum 7 days on 8–32 mg of sublingual buprenorphine (±naloxone), participants received monthly subcutaneous BUP-XR injections administered by a healthcare practitioner and completed monthly research interviews. The primary endpoint was retention in treatment at 48 weeks.

Findings: Participants (n = 100) were 28% women, mean age 44 years with a long history of OAT (median 5.8 years); heroin was the most common opioid of concern (58%). Treatment retention at 24 and 48 weeks was 86% and 75%, respectively. Participants with past-month injecting drug use (OR 0.23; 95%CI: 0.09–0.61) or heroin use (OR 0.23; 95%CI: 0.08–0.65) at baseline had lower odds of being retained in treatment to 48 weeks. Reductions in multiple forms of extra-medical drug use were observed. Improvements in quality of life, participation in employment, and treatment satisfaction measures were also observed.

Interpretation: This real-world implementation study of BUP-XR demonstrated high retention and treatment satisfaction. This study provides important additional data on the uptake and experience of clients, with relevance for policy makers, health service planners, administrators, and practitioners.

Funding: Indivior.

Trial registration: ClinicalTrials.gov Identifier: NCT03809143

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https://doi.org/10.1016/j.drugpo.2021.103492

Introduction

Systematic reviews demonstrate that opioid agonist treatment (OAT) for opioid dependence is highly effective in reducing illicit opioid use (Amato et al., 2005; Mattick, Breen, Kimber, & Davoli, 2009; Mattick, Breen, Kimber, & Davoli, 2014) as well as multiple other health and social outcomes (Degenhardt et al., 2019) including reducing HIV and HCV incidence (MacArthur et al., 2012; Platt et al., 2017), criminal activity (Gisev et al., 2019), overdose (Sordo et al., 2017), and mortality (Santo et al., 2021; Sordo et al., 2017).

Despite these clear benefits, OAT carries some risks, including adverse events, injection of medication intended for oral/sublingual administration, diversion and overdose (e.g., Albayaty et al., 2017; Haasen, Linden, & Tiberg, 2017; Rowe, 2007). In response to these risks, supervised daily dosing at a specialist clinic or pharmacy is a feature of OAT in many countries at least during the early stages of treatment (e.g. Clinical Guidelines on Drug Misuse & Dependence Update, 2017, 2017; Gowing, Ali, Dunlop, Farrell, & Lintzeris, 2014; Rhodes, 2018; Vuong et al., 2016). Attendance for daily dosing is burdensome for both clients and service providers. Attendance for supervised dosing is restrictive on many aspects of daily life (Madden, Lea, Bath, & Winstock, 2008) especially if significant travel time, cost and inconvenience is involved in attending during limited clinic dosing hours. Additionally, in Australia, people receiving OAT frequently pay the costs of pharmacy dispensing fees (Zahra et al., under review), which is a significant burden for many clients, and also a barrier to treatment access for many who are on income support payments or disability support pensions. In some Australian jurisdictions, publicly-funded specialist treatment services cover the costs of supervised dosing so there is no cost to the client, but this requires substantial staffing resources that may be alternatively utilised for case management or providing health-related and/or psychosocial interventions.

Recently developed extended-release buprenorphine (BUP-XR) formulations present a potentially significant development in the treatment of opioid dependence. BUP-XR is a weekly (Camurus Pty Ltd, 2018) or monthly (Camurus Pty Ltd, 2018; Indivior Inc, 2019) injectable formulation administered subcutaneously and provides sustained release of buprenorphine over the dosing interval. Benefits include potentially improved retention; greater choice and flexibility for clients; and reduced burden of regular clinic or pharmacy attendance. An additional benefit of BUP-XR formulations is the reduced need for face to face contact on a regular basis, which during the COVID pandemic is an additional benefit to both clients and the health professionals with whom they interact in reducing the requirement for regular personal contact. Nonetheless, many people who are opioid dependent would not choose XR-BUP (Larance et al., 2020); concerns include reduced control of medication doses and treatment cessation, potential side effects, and perhaps perversely, reduced choice of medications.

Randomised controlled trials of extended-release buprenorphine include a double-blind placebo-controlled trial of a monthly injection (Sublocade®, manufactured by Indivior) (Haight et al., 2019), a double-blind trial comparing weekly or monthly injection (Buvidal®, manufactured by Camurus) to daily sublingual buprenorphine (Lofwall et al., 2018), and an open-label (unblinded) trial comparing weekly or monthly injection to daily sublingual buprenorphine (Lintzeris et al., 2021). In double-blinded trials, XR-BUP was superior to placebo and non-inferior to sublingual buprenorphine in reducing illicit opioid use and XR-BUP retention ranged from 67% (Haight et al., 2019) to 73% (Lofwall et al., 2018) at 24 weeks. An observational study of extended-release buprenorphine also demonstrated high retention at 24 weeks (67%) (Ling et al., 2020). Retention in BUP-XR treatment at 48 weeks ranged from 49% (Ling et al., 2020) to 74% (Andorn et al., 2020; Frost et al., 2019). Retention with BUP-XR was higher than that observed with sublingual buprenorphine treatment (Haasen et al., 2017). In an open-label RCT (Frost et al., 2019), people receiving BUP-XR reported significantly higher medication satisfaction compared to those randomised to sublingual buprenorphine (Lintzeris et al., 2021). However, there are few studies that have evaluated the implementation of extended-release buprenorphine in community settings.

The Community Long-Acting Buprenorphine (CoLAB) study was designed to evaluate outcomes following initiation of monthly BUP-XR injections for the treatment of opioid dependence in community settings (Larance et al., 2020). The primary aim was to examine retention in BUP-XR at 48 weeks. This study also sought to evaluate the potential impacts of BUP-XR treatment on substance use, mental and physical health, social functioning, and patient-reported perceptions of treatment quality (Larance et al., 2020).

Method

Study design

The CoLAB study is a prospective single-arm, multicentre, open-label trial to evaluate the outcomes and implementation of extended-release buprenorphine (BUP-XR) among people with opioid dependence across a diverse range of healthcare settings (Larance et al., 2020); CONSORT checklist is provided in Supplementary Material Table A1. Participants were enrolled from seven sites in New South Wales (three sites), Victoria (three sites), and South Australia (one site), including five specialist drug treatment clinics, one private general practice, and one community clinic. Most services provided publicly-funded treatment with a multidisciplinary team delivering both methadone and buprenorphine treatment.

Participants were aged 18–65 and had opioid dependence (assessed by a clinician). Participants had to be receiving sublingual buprenorphine treatment (8–32 mg) for seven days prior to BUP-XR treatment initiation. Participants who were pregnant or breast-feeding, had severe hepatic disease, severe renal or respiratory disease, severe cognitive impairment or psychiatric condition that impaired the ability to provide informed consent, or prior allergic or adverse response to the ATRIGEL Delivery System gel polymer component of BUP-XR were to be excluded. Participants had to be adherent to the seven-day lead-in with buprenorphine (minimum 8 mg) prior to the first BUP-XR injection. However, protocol exemptions were possible in people stable on buprenorphine with a missed dose during the seven-day period. For full eligibility criteria, see the CoLAB protocol paper (Larance et al., 2020); details are also provided in the Supplementary Material.

All participants gave written informed consent before study procedures started. The study was approved by St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221) and conducted in compliance with Good Clinical Practice regulations and the ethical principles originated from the Declaration of Helsinki, the International Council for Harmonisation guidance, and all applicable local regulations. An independent data and safety monitoring board reviewed the progress of the study. This study is registered with ClinicalTrials.gov, number NCT03809143.

Medication dosing

This trial used a subcutaneously injected, extended-release monthly buprenorphine formulation, delivered via an ATRIGEL system (Sublocade© – "BUP-XR"). BUP-XR was designed to provide sustained exposure of buprenorphine over the entire monthly dosing interval. The dosing standard schedule involved two doses of 300 mg BUP-XR at baseline and month one. Thereafter, doses were flexible with 100 mg or 300 mg every 28 days (−2/+14 days), based on clinical decisions between participants and treating doctors. BUP-XR was provided in prefilled syringes with seven-day room temperature expiry window. Following screening and confirmation of eligibility, participants were administered BUP-XR injections in the abdomen between the transpyloric and transtubercular planes, with sites rotated for each administration.

Table 1
Detailed description of primary and secondary endpoints.

Primary objective	Primary endpoint	Details of measure
To examine BUP-XR treatment retention at 48 weeks	Proportion of participants retained in treatment at 48 weeks following initiation of monthly BUP-XR injections. Treatment retention is defined as remaining on active BUP-XR medication at 48 weeks.	Clinical records
Secondary objective	**Secondary endpoint**	
To examine BUP-XR treatment retention and engagement in ongoing clinical care at 48 weeks	Percentage of participants retained in treatment at 48 weeks following initiation of monthly BUP-XR injections and engaged in ongoing clinical care. Treatment retention is defined as remaining on active BUP-XR medication AND completing a clinical assessment at 48 weeks.	Clinical records
To examine BUP-XR treatment retention at 24 weeks	Percentage of participants retained in treatment at 24 weeks following initiation of monthly BUP-XR injections. Treatment retention is defined as remaining on active BUP-XR medication at 24 weeks.	Clinical records
To evaluate opioid craving, withdrawal, opioid and other drug use	Change in clinically assessed (urinary drug screen) and client-reported use of opioids and other drugs and clinically assessed opioid craving and withdrawal	• Australian Treatment Outcome Profile (every 4 weeks) • Clinical Opiate Withdrawal Scale (COWS) (First three visits, and then only if withdrawal was reported) • Subjective Opiate Withdrawal Scale (SOWS) (every 12 weeks) • Opioid Craving Visual Analogue Scale (every 4 weeks)
To evaluate client utilisation of buprenorphine medication during the study, including BUP-XR dose variation, adherence with dosing schedule, and dose supplementation	• Percentage of participants requiring dose adjustments with sublingual buprenorphine / buprenorphine-naloxone (and dose) during treatment • Percentage of participants maintained on 300 mg per month and 100 mg per month after the initial 2×300mg injections • Mean duration (days) between administered injections Mean duration of continuous treatment (weeks) • Percentage of participants presenting to receive treatment within 7 and 14 days of the next scheduled injection • Reasons for drop-out among non-completers;	Clinical records
To evaluate treatment safety and tolerability by monitoring adverse events, and events of clinical interest such as drug-drug interactions and pain management in clients treated with BUP-XR	• Percentage of participants with different types of events of special interest (AESI)[1] • Percentage of participants with common adverse events (greater than 5%) • Percentage of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event • Percentage of participants withdrawn from treatment due to unacceptable adverse events	Clinical records
To describe client-reported changes to health and social well-being	Changes in depression, pain, quality of life and hours of employment	• Australian Quality of Life four-dimension (AQol-4D) • Patient Health Quality 9 (PHQ-9) • Pain, Enjoyment, General Activity scale (PEG)
To evaluate client-reported experience of treatment	Client-reported treatment satisfaction and experience	• Treatment Satisfaction Questionnaire for Medication (TSQM) • Treatment Perceptions Questionnaire (TPQ)
To evaluate factors associated with treatment outcomes	Demographic, drug use and treatment characteristics associated with treatment outcomes, e.g. retention	Study specific Demographics questionnaire

1. AESI include: pregnancy, buprenorphine overdose, severe hepatic impairment, BUP-XR removal and severe precipitated withdrawal.

Procedures

The study consisted of a screening phase (up to 4 weeks); treatment intervention phase (48 weeks), and follow-up at 4 weeks after the last dose of study medication. Scheduled assessments included pregnancy testing in women of child-bearing potential, urine drug screening (conducted at three selected sites for validation of self-reported substance use), clinical assessment of dose adequacy and withdrawal (using the Clinical Opiate Withdrawal Scale completed at the first three dosing visits, and thereafter only if participants reported withdrawal or dose inadequacy) and adverse events.

Several other assessments were completed in research interviews by trained researchers. These included: The Subjective Opiate Withdrawal Scale (SOWS), Assessment of Quality of Life (AQoL-4D), Pain intensity, Enjoyment, General activity scale (PEG), Opioid Craving Visual Analogues Scale (0–100), dose adequacy (5 point Likert scale), self-reported substance use in the past four weeks using the Australian Treatment Outcome Profile (ATOP), Patient Health Questionnaire-9 (PHQ-9), Treatment Satisfaction Questionnaire for Medication (TSQM) and the Treatment Perception Questionnaire (TPQ). These assessments were conducted at intervals of every 28 days or quarterly (±4 days) following the administration of first dose and were independent of dosing schedule and treatment status. If treatment was discontinued, participants were still followed up for research interviews.

Outcomes

The primary and secondary endpoints are listed in detail in Table 1 (additional data on operationalisation is presented in Supplementary Material Table A3). The primary endpoint was treatment retention at 48 weeks following initiation of BUP-XR injections. Secondary endpoints included opioid craving, opioid withdrawal, opioid and other drug use, treatment adherence, health and social well-being, and participant reported experiences of treatment.

Statistical analysis

100 participants were planned for enrolment and evaluation as the intention-to-treat population. This study population was chosen to provide a precise measure of retention and evaluate how feasible it was to recruit people who were opioid dependent into a trial of extended-release buprenorphine across a range of community-based settings. Based on the assumption of an overall retention of 69%, the 95% CI around this estimate was expected to be 60–78%.

The overall population included all participants who received at least one dose of BUP-XR. Data on BUP-XR dosage received by each participant over the treatment period was visualised using a heatmap (Fig. 2). The effects of demographic variables and substance use at baseline on retention to treatment at 48 weeks were examined using binomial generalised linear models. The dichotomous response variable was retention/non-retention in BUP-XR treatment to 48 weeks. Covariates of clinical importance were determined a priori and included age; gender; length of time in OAT treatment; primary opioid of concern; injecting drug use, heroin use and amphetamine use at baseline. Initially, unadjusted odds ratios were estimated for each covariate in single-variable logistic regression models. Two multivariable logistic regression models were also fitted to provide adjusted, marginal estimates of the same effect. Both multivariable models included linear covariates for age and length of time in OAT and a gender factor (an indicator variable for female). In addition to these, model 1 included injecting drug use in the month prior to baseline, and model 2 included heroin use and amphetamine use in the month prior to the baseline interview. Sensitivity to the assumption of a linear effect on logit-scale retention was tested using equivalent models with discretised age factors.

The effects of the treatment on outcomes of interest were assessed by modelling the response variable on a linear function of time in treatment. Participants' use of a range of substances were modelled using binomial Generalised Linear Mixed Models (GLMMs). Self-reported use of each modelled substance was coded as a dichotomous response variable corresponding to zero versus non-zero use of the drug over the four weeks prior to each monthly interview. Non-response for questions on substance use was taken as positive for heroin and illicit drug use and treated as missing for other substances. For each participant, the logit transformed probability of using each substance was assumed to be a linear function of the number of months retained in treatment. Up to 13 observations per participant were available to be fitted to each of the substance use models while they were retained on BUP-XR. Differences among participants in these probabilities were modelled using participant-specific random intercepts accounting for intra-participant dependence in use of each substance. Binary outcomes not pertaining to substance use were modelled similarly, but most were measured quarterly rather than monthly.

Model adequacy was checked using residual diagnostics. Where the assumption of normally distributed residuals was violated, such as with employment, semi-continuous responses were transformed to dichotomous variables and positive responses modelled as Bernoulli random variables. Models with treatment duration treated as a continuous variable were compared with equivalent models with a discrete treatment-number factor using the Akaike Information Criterion (Bozdogan, 1987). For all analyses, we used two-sided p values of 0.05 as the cut-off for statistically significant differences. Additional details on statistical methods can be found in the Supplementary Material. All models were fitted using Stata Version 16 (Stata Corporation, 2019) and R Version 4.0.3 (R Core Team, 2021).

Role of the funding source

This study (including study drugs) was funded by a research grant from Indivior PLC. The funder had no role in the analysis and interpretation of the study results. LD and MC had access to the raw data. The sponsor (National Drug & Alcohol Research Centre, UNSW Sydney) designed the study, collected data, monitored study conduct, had access to all data, and did the statistical analysis. MF and LD were responsible for the decision to submit for publication.

Fig. 1. Study profile.
Note: Treatment completion is defined as retained in treatment at 48 weeks following initiation of monthly BUP-XR injection.
*screened is anyone who signed the consent and did not pursue after screening. More participants were pre-screened by site staff for eligibility, before approaching them for consent.

Results

Of 102 screened, 100 people were enrolled between May 2019 to November 2019 (Fig. 1). Participants were predominantly male (72%) and had a mean age of 44 years (Table 2). For 55% of participants, heroin was the primary opioid of concern in the three months prior to the baseline while 44% reported pharmaceutical opioids as their primary drug of concern at treatment entry.

Overall, the group had a long OAT history, with a median of 5.8 years of total lifetime duration considering both methadone and buprenorphine treatments. The median current OAT episode length at recruitment to the study was 2.2 years. In the seven days prior to enrolment, 60% had received >16 mg sublingual buprenorphine. At baseline, most reported no opioid withdrawal (90%). Additional details about the sample are presented in Table 2.

Treatment utilisation and adherence

All participants received a 300 mg dose of BUP-XR at baseline. Adherence and retention to treatment are shown in Fig. 2 and Table 3 (see also Supplementary Material Table A4 for additional data on XR-BUP use). The average number of days between administered injections across the study was 29 days. Three participants were automatically

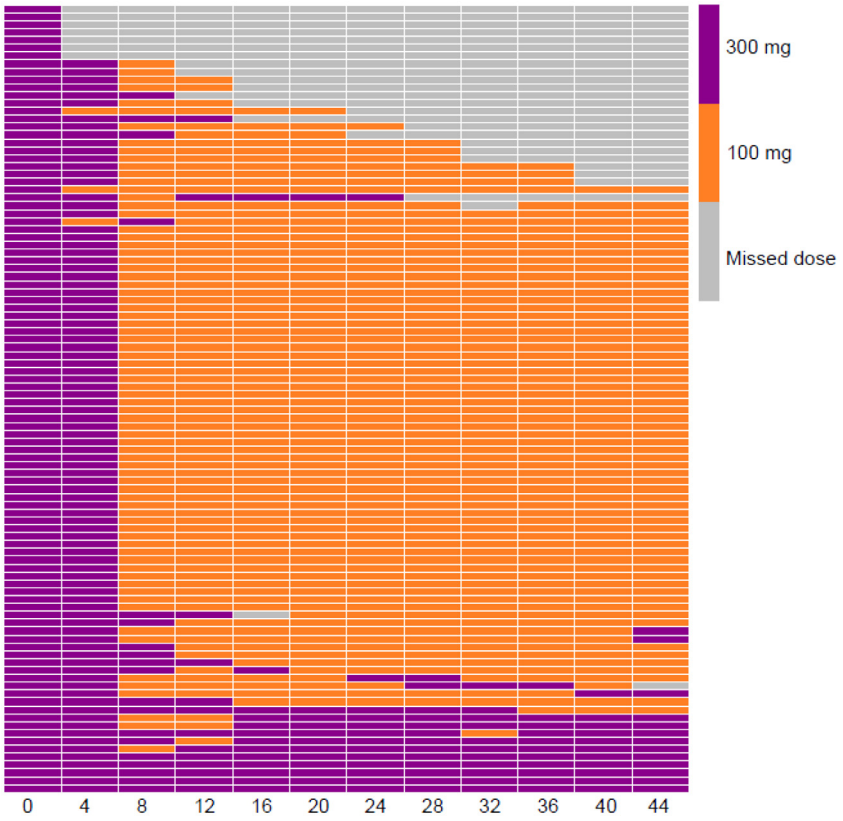

Fig. 2. BUP-XR utilisation for each participant across the study period.
Monthly adherence to treatment and dosing schedule at an individual level over the entire 48 weeks of treatment. Each row represents an individual participant and the column represents the treatment timepoint (in weeks). Grey boxes represent missed doses, orange (100 mg BUP-XR) and purple (300 mg BUP-XR). Failure to recive a BUP-XR for more than 56 days between injections would mean non-adherence to protocol defined dosing regimen and would result in automatic discontinuation from treatment. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

discontinued due to failure to receive a BUP-XR for more than 56 days between injections, meaning non-adherence to the protocol-defined dosing regimen. Ten participants who discontinued treatment maintained contact with the research study and participated in the follow up research interviews after ceasing treatment. In total, 85 participants were followed up for 48 weeks; 75 were on active treatment at week 48.

The majority of patients transferred as per protocol from 300 mg to 100 mg monthly by the third injection and did not require supplementary medication. Most commonly, this reflected client anxiety about the experience of withdrawal rather than actual withdrawal. The vast majority of patients were successfully treated with 100 mg monthly doses from the third month of treatment, and only a small minority (5%) were treated with the higher dose of 300 mg for the duration of the study (Table 3, Fig. 2). Supplemental doses of up to 8 mg sublingual buprenorphine daily for up to 14 days were permitted if withdrawal symptoms were reported, on patient request, investigator decision or other reason. During the early period of follow-up (weeks 4–12), 17% of the retained participants received sublingual buprenorphine top-up doses (irrespective of COWS score), for an average of 5 days and a median dose of 8 mg per day during the entire study period; the primary reason reported was for withdrawal symptoms. Prescription of sublingual top-up buprenorphine declined significantly in the second half of the study period, with three participants receiving top up during weeks 16–24, and 1 in each of weeks 28–36 and 40–48 (Table 3, Supplementary Material Table A5). Seven participants dropped out of treatment prior to their second BUP-XR injection, of whom three had requested (and had received) supplementary sublingual buprenorphine due to withdrawal symptoms.

Primary endpoint

Retention at 48 weeks was 75% (Table 3; see also Supplementary Material Figure A1); 73 participants received 12 injections. A secondary endpoint was the percentage of participants who were maintained on active BUP-XR as well as receiving ongoing clinical care at week 48 (defined as attending for a clinical visit at week 48), which occurred for 73% of people. Retention at 24 weeks was 86%.

Heroin use in the month prior to baseline (unadjusted OR 0.23, 95%CI 0.08–0.65) and injecting drug use in the month prior to baseline (unadjusted OR 0.23, 95%CI 0.09–0.61) were associated with reduced retention at 48 weeks. The effects of these and other baseline covariates adjusted for other factors estimated in the multivariable logistic regression models were similar. None of gender, age, nor length of time in OAT were significantly associated in any of the retention models fitted. Likewise, the fitted models suggested no evidence of an effect of amphetamine use or non-prescription opioids other than heroin in the month prior to baseline on the odds of being retained to 48 weeks. Lastly, there was no evidence that participants whose primary opioid of concern was a pharmaceutical opioid were more or less likely to be retained to the study until week 48 (Table 4). As the number of participants that were not retained to week 48 was low, statistical power to estimate most effects was limited.

Secondary endpoints

Table A7 displays the prevalence of secondary endpoints for those retained in BUP-XR across the study (data on these endpoints for all people retained in research interviews, including those who left BUP-XR, are reported in Supplementary Material Table A8). Fig. 3 presents data on the association between retention in BUP-XR and the secondary endpoints (Table A6 presents these data in tabular form).

The odds of use of all illicit substances except for cannabis use decreased significantly with time retained in BUP-XR. The odds of heroin use in the past month decreased by 20% on average for every four weeks retained in BUP-XR (OR 0.80, 95%CI 0.71–0.89). The marked decline in the proportion of participants using heroin early in the trial is readily apparent in the quarterly summaries (Table A7). A small minority of participants continued to use heroin throughout the trial.

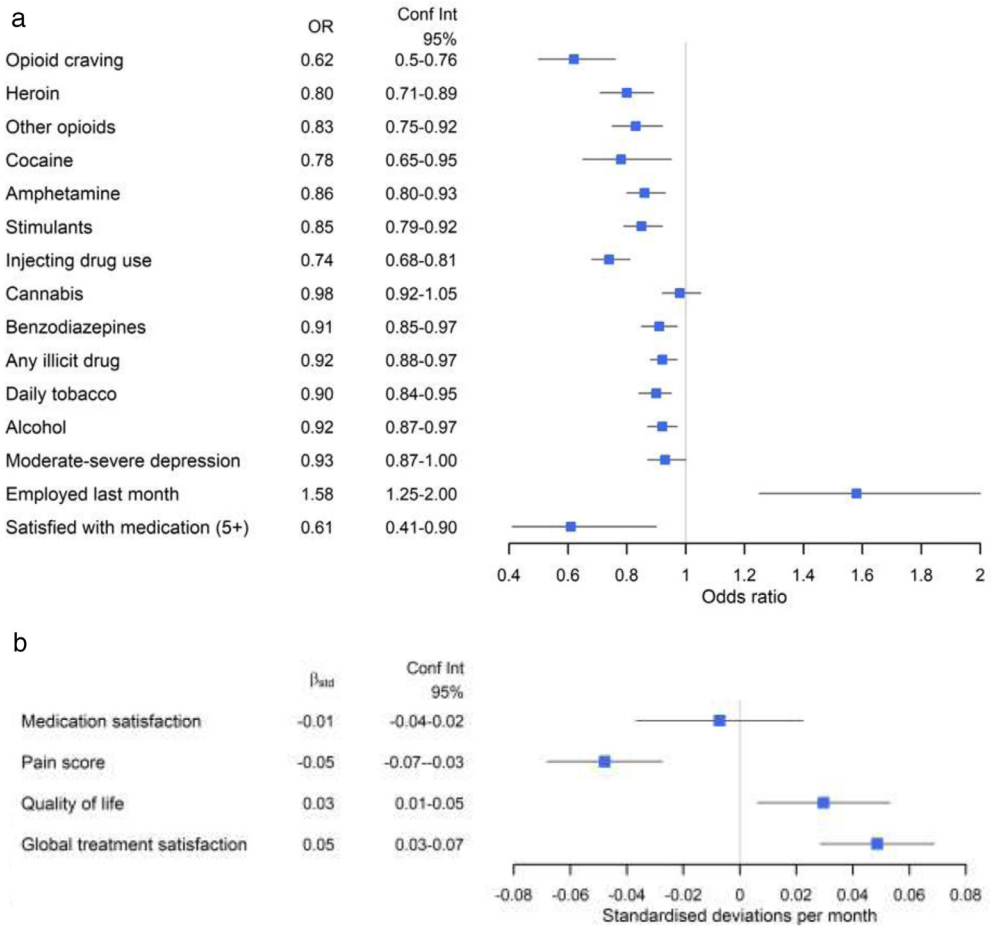

Fig. 3. Associations between retention in BUP-XR and secondary endpoints; 3a: Estimated multiplicative change in odds of outcome of an additional 28 days in treatment. Fig. 3b Estimated standardised coefficient of additive effect of time retained in treatment on outcome score scaled as a monthly proportion of standard deviation after accounting for heterogeneity between participants.
Notes: These data are reported in full in Supplementary Material Table A6. For the estimates of these outcomes at baseline, 12, 24 and 48 weeks among those retained in BUP-XR, please see Supplementary Material Table A7. For the estimates of these outcomes among all people retained in research interviews (i.e. including those who had ceased BUP-XR), please see Supplementary Material Table A8.
Fig. 3a: Generalised linear mixed models examining effect of time, with people who leave treatment censored.
Fig. 3b: Linear mixed models examining effect of time, with people who leave treatment censored.
1, Any illicit drug use defined as any heroin, opioid, cocaine, amphetamine or cannabis use. 2, Measured via the Patient Health Questionnaire; a cutoff score of >=10 was used to indicate moderate-severe depression. 3, Measured via the Pain, Enjoyment, General Activity scale. A higher score indicates worse pain., 4. Measured via the Australian Quality of Life four-dimension scale. Higher scores indicate better functioning. 5. Measured via the Treatment Satisfaction Questionnaire for Medication scale. Higher scores indicate greater satisfaction.6, Measured via the Treatment Perceptions Questionnaire (Marsden et al., 2000) (maximum score = 40).

The odds of non-prescribed opioid use reduced by 17% (OR 0.83, 95%CI 0.75–0.92), and the odds of past month injecting drug use decreased 26% for every four weeks retained in BUP-XR (OR 0.74, 95%CI 0.68–0.81). Concordance of self-reported substance use and urine test results were 94%, 92%, 93%, 88% and 100% for cannabis, amphetamines, opioids, benzodiazepines and cocaine respectively.

The odds of being employed increased 58% for every 4 weeks people were retained in BUP-XR, (Fig. 3). There was a statistically significant seven percent reduction in the odds of moderate-severe depression for every 4 weeks retained in BUP-XR.

Significant increases in quality of life [measured by the AQoL4D, 3% (95%CI: 0.7% - 4.8%) for every four weeks on treatment], and treatment satisfaction [measured by the TPQ, 5% (95%CI: 2.9% - 6.9%) for every four weeks on treatment] were observed. There was a significant decline in pain [measured by the PEG measure, 5% (95% CI: 2.8% - 6.8%) for every four weeks on treatment] (Fig. 3; see Supplementary Material Table A6, Table A7 for summaries of the mean scores across the study period among those retained, and Supplementary Material Table A8 for all people who completed the research interviews). Evidence was not found of a change in medication satisfaction after its measurement at the week 12 interview; however, mean treatment satisfaction (measured by the TSQM) at week 12, after 3 months of depot was 15% higher than baseline following sublingual treatment ($p<0.001$). Importantly, satisfaction with both the medication and with treatment were very high across the study period.

Adverse events and events of special interest

Of the 100 participants enrolled, 91% of participants had at least one adverse event; 45 were probably related to treatment. Sixteen participants had at least one serious adverse event (twenty events in total); none were treatment-related (Table 5). The most common adverse events (top 3) were withdrawal symptoms, injection site pain, and injection site itching. None of the injection site pain, itchiness, and redness were serious. Other reported adverse events such as headache, constipation, lethargy and nausea were expected and consistent with product label information and previous safety studies. There were no deaths during the study period.

Events of special interest included pregnancy, buprenorphine overdose, severe hepatic impairment, BUP-XR removal and severe precipitated withdrawal. There were two cases of pregnancy. There were no cases of buprenorphine-related overdose, severe hepatic impairment, BUP-XR removal, or severe precipitated withdrawal reported.

Discussion

This study evaluated treatment retention, drug use, and other key outcomes following treatment with extended-release buprenorphine among people who are opioid dependent with previous treatment experience. Retention following treatment with extended-release buprenorphine was 75% at 48 weeks, comparable to a similar open-label study of an alternate formulation of BUP-XR (74% at 12 months) (Frost et al.,

Table 2
Baseline demographics and characteristics.

	(*N* = 100)
Age, mean (SD)	44 (9)
Female, n (%)	28 (28)
Born in Australia, n (%)	88 (88)
Main source of income pension or benefit, n (%)	70 (70)
Completed year 10 education or more, n (%)	69 (69)
Present living condition, n (%)	
Boarding house	6 (6)
Other	21 (21)
Privately owned house or flat	22 (22)
Rented house or flat	51 (51)
Age of first opioid use, mean (SD)	24 (8)
First opioid used, n (%)	
Heroin	58 (58)
Pharmaceutical opioid	40 (40)
Other	2 (2)
Age of first treatment episode, mean (SD)	34 (10)
First OAT medication prescribed was methadone, n (%)	41 (41)
OAT treatment in the past 3 months*, n (%)	
Methadone	7 (6)
Buprenorphine-naloxone	99 (90)
Buprenorphine	4 (4)
Primary opioid of concern at treatment entry, n (%)	
Heroin	55 (55)
Pharmaceutical opioids	45(45)
Other illicit (opium)	1 (1)
Length on current treatment in years, median (IQR)	2.2 (3.9)
Total lifetime OAT duration in years, median (IQR)	
Methadone	0.5 [5.4]
Buprenorphine	3 [4]
Combined	5.8 (8.5)
Past month substance use, n (%)	
Any illicit drug use	54 (54)
Injected any drug	28 (28)
Any opioid	28 (28)
Heroin	20 (20)
Other Opioids	11 (11)
Amphetamine Type Substances	25 (25)
Cocaine	4 (4)
Benzodiazepines	33 (33)
Alcohol	50 (50)
Cannabis	35 (35)
Daily tobacco smoking	73 (73)
Non-fatal overdose in the past year	14 (14)
Opioid Craving VAS, median (IQR)	0 (18)
Subjective Opiate Withdrawal Scale, median (IQR)	2 (5.5)
Clinical Opiate Withdrawal Scale, n (%)	
No opioid withdrawal reported (below 5)	90 (90)
Mild withdrawal reported(5–12)	10 (10)
Significant withdrawal reported (13 and above)	0 (0)
Moderately-severely depressed (PHQ-9), n (%)	42 (42)
Pain Score (PEG), mean (SD)	10.1 (9.0)
Quality of Life (AQoL-4D), mean (SD)	0.53 (0.27)

*Some participants reported multiple treatments in the past three months, particularly few transitioned to sublingual buprenorphine from methadone in order to receive BUP-XR injections.

Table 3
Buprenorphine utilisation and adherence.

	n	%
Primary outcome		
Treatment retention at 48 weeks,%	75	75
Secondary outcomes		
Treatment retention at 24 weeks,%	86	86
Treatment retention at 48 weeks and engaged in ongoing clinical care,%	73	73
Other measures of utilisation		
Percentage of participants who completed 12 injections	73	73
Percentage of participants who had dose adjustments	23	23
…had second injection of 100 mg dose instead of 300 mg	3	3
…had 100% of 3rd to 12th injections using 300 mg dose[1]	5	5
Percentage of participants maintained on 300 mg throughout the study[1]	5	5
Number of participants who received sublingual top up at each interval		
Week 4 - 12	17	
Week 16 –24	3	
Week 28–36	1	
Week 40 - 48	1	
…duration of sublingual buprenorphine top-up (days), Mean (SD)	5 (5)	
…dose of sublingual buprenorphine top-up (mg), Mean (SD)	7 (3)	
Main reasons for sublingual prescription (number of people)	N	%
Patient request	1	3
Patient reporting withdrawal symptoms	16	52
Investigator decision	4	13
Other	10	32

Notes: For additional detail on utilisation and adherence, please see Supplementary Material Table A5.
1. "Maintained on 300 mg dose" in study protocol endpoint description i.e. received 300 mg BUP-XR throughout the entire duration of the treatment period.

2019). A major strength of this study is that study sites reflected "real-world" community-based services, primarily consisting of publicly funded drug treatment services.

This study also overcame limitations of previous studies by following multiple outcomes to 48 weeks, which only one study has previously done (Frost et al., 2019). We found that during treatment, declines in heroin use, non-prescribed opioid use, and injecting drug use were observed. Improvements in employment, depression, quality of life, and treatment satisfaction were also observed. Although modest, these improvements are consistent with ongoing retention and stabilisation within a treatment programme among a cohort of people already very treatment-experienced.

This study provides critical data that can provide guidance on clinical management of opioid dependence and will have an impact on guidelines and health policy in Australia and internationally. It provided important information on retention and a range of other secondary outcomes during treatment with long-acting injectable buprenorphine which guides clinical management for opioid dependence treatment. This study also identified important factors associated with retention in treatment with long-acting injectable buprenorphine, identifying participants in whom this therapy may not be ideally suited, again informing clinical management for opioid dependence treatment.

The retention following treatment with BUP-XR (86% at 24 weeks and 75% at 48 weeks) is at the higher end of findings from clini-

Table 4
Estimated odds ratios of covariates for retention to 48 weeks estimated using binomial GLMs.

	Unadjusted Models			Adjusted Model 1			Adjusted Model 2		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95%CI	P-value
Age (baseline)	1.05	1.00 - 1.11	0.070	1.05	1.00 – 1.11	0.068	1.05	0.99 – 1.11	0.098
Gender - female	0.60	0.23 – 1.59	0.306	0.40	0.13 – 1.25	0.114	0.50	0.16 – 1.59	0.243
Injecting drug use (baseline)	0.23	0.09 – 0.61	0.003	0.15	0.05 – 0.52	0.003	..	..	
Heroin use (baseline)	0.23	0.08 - 0.65	0.006	..	..	..	0.16	0.04 – 0.68	0.013
Other non-prescribed opioids (baseline)	3.69	0.44 - 30.39	0.225	..	..	..	4.48	0.46 – 44.0	0.198
Amphetamine use (baseline)	0.48	0.18 – 1.29	0.147	..	..	..	0.63	0.18 – 2.13	0.454
Length of time in OAT prior to study (years)	1.21	0.93 – 1.58	0.158	1.10	0.93 – 1.30	0.249	1.09	0.93 – 1.30	0.290
Primary opioid of concern pharmaceutical opioids	1.24	0.50 – 3.12	0.642	0.63	0.20 – 2.00	0.434	0.62	0.18 – 2.20	0.461

Table 5
Adverse events and events of special interest.

	n
Total number of serious adverse events	26
Total number of incidents where serious adverse events occurred	20
Number of deaths	0
Number of people with a serious adverse event over the treatment period	16
Number of people with a treatment-related adverse event	45
Top 3 treatment-related adverse events	
Withdrawal symptom	17
Injection site pain	11
Injection site itching	14
Number with a serious treatment-related adverse event	0
Top 10 Adverse Events (number of events)	
Withdrawal symptom	44
Injection site pain	16
Injection site itching	14
Headache	11
Injection site lump	9
Constipation	8
Lethargy	7
Nausea	7
Injection site redness	6
Product leakage due to faulty syringe	4
Events of special interest	
Pregnancy	2
Buprenorphine overdose	0
Severe hepatic impairment	0
Depot removal	0
Severe precipitated withdrawal	0

cal trials evaluating retention at 24 weeks (66–85%) (Andorn et al., 2020; Frost et al., 2019; Haight et al., 2019; Ling et al., 2020; Lintzeris et al., 2021; Lofwall et al., 2018) and 48 weeks (49–74%) (Andorn et al., 2020; Frost et al., 2019; Ling et al., 2020). Further, retention was substantially higher than population-based data on retention in sublingual buprenorphine in New South Wales, Australia (of people entering in 2015, 46% retained at 12 months) (Bharat et al., 2021). The high retention BUP-XR in this study could reflect the fact that the cohort recruited were already well-engaged in OAT.

The majority of patients transferred as per protocol from 300 mg to 100 mg monthly by the third injection and did not require supplementary medication. Most commonly, this reflected client anxiety about the experience of withdrawal rather than actual withdrawal; it is likely that the rates of provision of additional sublingual doses will reduce as clinicians become more familiar with these products. Treatment was well-tolerated and there were no study deaths; under half (45%) reported at least one adverse event, which is lower than the levels reported in the RCT of this medication (56–76% across study groups) (Haight et al., 2019). The vast majority of patients were successfully treated with 100 mg monthly doses from the third month of treatment, and only a small minority (5%) were treated with the higher dose of 300 mg for the duration of the study. Future studies will be required to determine the optimum interval for administration for different individuals.

Overall, this study indicates that BUP-XR has a significant contribution to make to the further development and quality improvement of OAT. The positive results found across varied sites suggest that the challenge of further expansion of this treatment option can be incorporated well within the existing service system. The flexibility afforded by extended-release formulations may mean it is more easily delivered in varied settings, although it remains to be seen how they are integrated into smaller scale general practice settings (as opposed to larger scale public clinics and large GP practices). This importantly includes issues around where (in terms of which settings, as well as requiring availability of appropriate, dedicated space to provide the injection in settings such as pharmacies) and by whom the injections can be and are administered.

Extended-release formulations of buprenorphine represent an additional potential option for people considering treatment for opioid dependence, and there is evidence that many might be interested in this treatment form (Mezaache et al., 2021). For example, we have previously found that around two thirds of a sample of Australian people who were opioid dependent thought that extended-release formulations of buprenorphine might be a treatment option for them (Larance et al., 2020). Those with less flexibility in their current OAT (e.g. who have to travel considerable distances to attend for supervised dosing, and those who have few if any takeaway doses, instead being forced to attend daily or near daily for dosing), are more interested in extended release formulations as an option for them (Larance et al., 2020). Other benefits of these formulations have been identified as reducing experience of stigma and reducing negative rituals and habits around dosing (Neale, Tompkins, McDonald, & Strang, 2018; Tompkins, Neale, & Strang, 2019). Nonetheless it is crucial that OAT choice remains. For some, particularly those who already have flexibility in their OAT (e.g. already receiving unsupervised doses), this formulation may be less attractive (Larance et al., 2020). It is important to ensure that patient choice around which medications they receive in OAT are retained, to ensure that the impact of choice on treatment outcomes is given full consideration in future planning and service change.

Limitations

This real-world implementation study found positive results and outcomes consistent with the shorter term RCTs that have been reported. However, both the impact of a new medication and reduced travel and attendance demands may have had a disproportionately positive effect for those with longer term experience of opioid dependence treatment. Future work is required to determine if such treatment gains are maintained.

Participants were recruited from community-based services with experience in drug treatment and were a group already engaged in care; the findings for both retention and other outcomes in this cohort might not be generalisable to all people who are opioid dependent. Although we did not find a relationship between length of previous treatment retention, the cohort had long OAT histories, and results may not be the same for those new to treatment for opioid dependence. Further studies will be required to elucidate whether the impacts differ for newly-enrolled or first-time treatment entrants, and to determine the impact of a broader roll out and implementation of this mode of treatment.

Given the small number of sites involved in this trial, caution should be adopted when interpreting how the experience of early BUP-XR adopters will apply within a larger roll out of this type of treatment. Additionally, the study was powered to provide a reasonably precise estimate of retention at 48 weeks, and to evaluate how feasible it was to provide BUP-XR in real-world settings. It was not specifically powered to examine factors associated with retention to the end of the study period. Finally, participants were incentivised to participate in research follow up interviews, and had monthly contacts with the research study team, which may have increased engagement with the study; this may have had some role in improving retention in treatment.

Conclusions

This 12-month study of a new BUP-XR medication found high retention rates. Additionally, modest improvements in other areas of health and well-being indicate optimism for this medication.

Funding

This study was supported by an Externally Sponsored Collaborative Research grant from Indivior PLC. Indivior contributed to the study design and analysis plan; Indivior had no role in collection, analysis and interpretation of data; in the writing of the manuscript; or

in the decision to submit the manuscript for publication. NDARC and The Kirby Institute are funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. JG is supported by a\ National Health and Medical Research Council Investigator Grant (1176131). L.D. is supported by an NHMRC Senior Principal Research Fellowship (1135991) and a US National Institute of Health (NIH) National Institute on Drug Abuse (NIDA) grant (R01DA1104470).

Declarations of Interest

This study was supported by an Externally Sponsored Collaborative Research grant from Indivior PLC (MF, BL, LD, NL, AD, RA, SN, GD, JG). In the past three years, MF and LD have received funding from Indivior, Seqirus for studies of new opioid medications in Australia. JG reports grants and personal fees from Abbvie, Camurus, Cepheid, Hologic, Indivior, Gilead Sciences, and Merck. NL has received reimbursement for participation in Advisory Boards for Mundipharma, Indivior and Chiesi Pharmaceuticals; he received funding from Camurus for a company-sponsored trial of BUP-XR. RA has received untied educational grants from Reckitt Benckiser and an untied educational grant from Mundipharma. AJD reports grants from Braeburn/Camurus AB, to conduct clinical studies with buprenorphine products and travel support to Hunter New England Local Health District, which employs AJD. He has served as an honorary on advisory boards for Mundipharma and Seqiris. GJD has received research grant funding from Gilead and Abbvie. MM has served as an honorary on advisory boards for Pfizer and AbbVieMC. JS and MB have no conflicts to declare. SN has received untied research funding from Seqirus to conduct research on prescription opioid related harms.

Acknowledgements

The authors thank the study participants for their contribution to research, as well as current and past researchers and staff. We acknowledge the following people: Jude Byrne (Australian Injecting & Illicit Drug Users League, Canberra, Australia), Mahshid Tamaddoni (Data manager, Kirby Institute, UNSW Sydney, Australia); Madeline News, Zoe Griffin, Zein Ali (research assistants, NDARC, UNSW Sydney, Australia); Jason Gascoigne (study coordinator, DASSA, South Australia, Australia), Mariana Nasr, Adelaine Nyau, Rebecca Lewis, Linda Broadbent, Xiu Qin Lim, Raphela Van Der Laan, Natasha Kuller, Jessica Leonard, Tammy Dix, James Buchanan, Duncan Tyson (Clinic staff, DASSA, Adelaide, Australia); Teodora Zanesheva-Karamanlieva (study coordinator, St Vincent's Hospital, Sydney, Australia), Tom Kural, Linda Hotong (Clinic Staff, St Vincent's Hospital, Sydney, Australia); Bonny Puszka (study coordinator, Royal North Shore Hospital, Sydney, Australia), Alison Blazey, Esther Han, Helena Cheung, Bernard Chiuarah, Jenny Trinh Lee, Ariana McCauley, Leanne Walsh, Jan Armstrong, Nouvelle Thwaites, Ivy Kwon (clinic staff, Royal North Shore Hospital, Sydney, Australia); Rachael Skews (study coordinator, Frankston Healthcare, Melbourne, Australia), Lionel Kok, Belinda Smith, Naren Morris (clinic staff, Frankston Healthcare, Melbourne, Australia); Danielle Cassar, Teresa Fitzmaurice (study coordinator, Western Health hospital, Melbourne, Australia), Anthony Hew, Shani Pavia, Dimce Kotevski, Fiona Goodwin, Marcus Forsythe, David Silkoff, Tracy Wrigley (Clinic staff, Western Health hospital, Melbourne, Australia); Susan Hazelwood, Louise Go (study coordinator, Newcastle Pharmacotherapy Service, Newcastle, Australia), Michelle Hall, Callen Farmer, Cathy Cochrane, Anthony Winmill, Sally McKenna, Stacey Weedon, Tarun Yadav (Newcastle Pharmacotherapy Service, Newcastle, Australia).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2021.103492.

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