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# BMJ Open

## Is Extended-Release Buprenorphine associated with improved outcomes compared to oral Medication for Opioid Use Disorder?

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Is Extended-Release Buprenorphine associated with improved outcomes compared to oral Medication for Opioid Use Disorder?

Authors: <sup>1</sup>Catharine Montgomery, <sup>2</sup>Yasir Abbasi, <sup>1</sup>Andrew Jones, <sup>2</sup>Devon De Silva, <sup>3</sup>Rosalind Gittins & <sup>4</sup>Marie Claire Van Hout

Corresponding author: C Montgomery, [C.A.Montgomery@ljmu.ac.uk](mailto:C.A.Montgomery@ljmu.ac.uk)

Affiliations:

<sup>1</sup>School of Psychology, Liverpool John Moores University, UK.

<sup>2</sup>Via, 18 Dartmouth Street, London, UK.

<sup>3</sup>School of Pharmacy, Aston University, UK.

<sup>4</sup>School of Public and Allied Health, Liverpool John Moores University, UK.

Qualifications and Titles:

C Montgomery: PhD, PgCert LTHE, BSc (Hons), Reader in Psychopharmacology, Head of Institute for Health Research.

Y Abbasi: MB BS, FRCPsych, PG Cert, PG Dip, EDPM, Executive Medical Director & Consultant Addiction Psychiatrist

A Jones: PhD, Senior Lecturer in Psychology.

D De Silva: BA. IRU Manager.

R Gittins: MRPharmS (Hons) MSc CertPsychPharm MCMHP IP, Senior Lecturer.

MC Van Hout: PhD, LLM, M.Sc Health Professions Education, M.Sc Health Promotion, M.Sc International Addictions. PVC Research and Knowledge Exchange.

ORCID IDs:

Catharine Montgomery: 0000-0003-2805-5807

Yasir Abbasi: 0000-0002-4981-7914

Andrew Jones: 0000-0001-5951-889X

Rosalind Gittins: 0000-0002-0893-7936

Marie Claire Van Hout: 0000-0002-0018-4060

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**Abstract**

*Objectives:* Advances in the treatment of opioid use disorder (OUD) have seen the development of long-acting injectable opioid substitutes which could improve outcomes for people with OUD. However, comparative quantitative analysis of individual outcomes is lacking. The present study sought to investigate factors associated with prescribing of the extended-release Buprenorphine (XR-BUP) injectable Buvidal, and changes in outcome variables compared to oral Medication for Opioid Use Disorder (MOUD).

*Design:* Cross-sectional retrospective analysis of electronic health records.

*Setting:* Community substance use treatment service Via. Six sites shared their data between 15/08/2022 – 15/08/2023.

*Participants:* Anonymised data was extracted for 235 people receiving Buvidal and 266 people receiving oral MOUD.

*Primary and secondary outcomes:* Prescribing data, sociodemographic information (age, sex, IMD decile of individual’s residence, primary and secondary substance, number of previous treatment episodes, employment and ethnicity) and Treatment Outcome Profiles (substance use, physical and mental health, quality of life, employment) were extracted and analysed. To examine predictors of receiving Buvidal (vs MOUD) we conducted logistic regression including the demographic predictors. Psychological health, physical health and Quality of Life scores were analysed using Welch’s t-tests.

*Results:* Buvidal was associated with positive changes in quality of life between first and last assessments, and people prescribed Buvidal reported overall higher levels of psychological and physical health, and quality of life compared to people prescribed oral MOUD. Other

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demographic and situational factors were predictors of Buvidal initiation, indicating the intersectional nature of changes in health during recovery.

*Conclusions:* Buvidal is associated with improved outcomes over a 1-year period. Further research is needed to investigate the aetiology of improved wellbeing and outcomes over time.

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**MeSH Keywords**

Opiate dependence; buprenorphine; opiate substitution treatment; psychological wellbeing; quality of life; Long-acting injection; opioid related disorders.

**Article Summary**

Strengths and Limitations of this study

- Advances in the treatment of opioid use disorder (OUD) have seen the development of long-acting injectable opioid substitutes, which could improve outcomes, but there are no direct outcome comparisons to oral MOUD.
- This study found that people prescribed Buvidal were younger, more likely to be employed, and had more previous treatment episodes. Buvidal was associated with positive changes in quality of life between first and last assessments.
- People prescribed Buvidal reported overall higher levels of psychological and physical health, and quality of life.
- The data is limited in that it only gives us a snapshot of subjective wellbeing over a 10 year period.
- The data cannot tell us qualitatively how quality of life and perceived psychological wellbeing were better in the Buvidal VS. MOUD groups.

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## Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing disorder causing clinically significant distress or impairment and includes opioid dependence with addiction representing the most severe form of OUD [1,2]. Additional adverse health complications of OUD causing morbidity and mortality centre on blood-borne virus infection (HIV, hepatitis C), overdose, accidents, suicide, and poly use of other drugs [3-5]. OUD is treated with opioid substitutes as first line treatment (usually with methadone or buprenorphine) [6-9] though pharmacological treatment is advised to be integrated within a global therapeutic model focused on recovery and including psycho-social support [10]. However, low retention/high attrition rates limit the impact of these OUD treatment modalities with people reporting that daily mandatory consumption can impact upon wellbeing and opportunities for employment [11,12] and increase stigma and discrimination [13]. Effective engagement and retention is crucial for better treatment outcomes [14], and this can be a particular problem for OUD treatment with high rates of drop out observed in early phases of treatment [15,16]. Where there are issues with premature disengagement and sub-optimal care, mortality risks are also greater, particularly in the first month of treatment and post treatment cessation [17,3]. There is some evidence to suggest that management of OUD using buprenorphine is strongly protective against mortality, in relative risk terms when compared with methadone [18,19]. This is particularly the case when efficient mechanisms for shared decision-making regarding medicines optimisation, and individualised care in line with the UK National Institute for Health and Care Excellence [20] and Department of Health and Social Care [21] guidelines are followed.



In recent years extended-release subcutaneous injectable buprenorphine formulations (XR-BUP) have been proposed as offering improving rates of retention and adherence whilst reducing the risk of diversion [22-24]. XR-BUP have the potential to be highly effective due to their long-acting bioavailability and limited risk of diversion [25,26] and are ideal for individuals who do not wish to take daily oral doses, people living in rural areas and those in places where safe storage is problematic (e.g. experiencing street homelessness), or at increased risk of overdose, such as discharge from hospitals or following prison release [27]. Whilst oral buprenorphine is reported to be associated with reductions in fatal and non-fatal overdose [19,28] less is known about the potential for XR-BUP to reduce overdose risks. In one study, XR-BUP has been shown to be more effective at increasing abstinence than placebo plus counselling alone [29] which could be due to the reduction of risk of missed doses due to medication loss, lapses or diversion. Prior to initiation on XR-BUP, individuals should be offered an initial oral dose of buprenorphine to ensure tolerance and reduce the risk of adverse events. Optimal prescribed interventions incorporate shared decision-making [20,30] and clinicians are advised to offer flexible dosing schedules to support people to meet their personalised treatment goals [31].

While there is an evidence base for patient experiences of using methadone and SL-BUP, due to their relative novelty, there are fewer studies on lived experiences of XR-BUP, with studies in the United States (US), Australia and France reporting varied perspectives. Evidence suggests that XR-BUP has similar retention rates to buprenorphine and methadone [32]. Whilst perceived benefits of XR-BUP include improved choice, reduced travel, clinic and pharmacy attendance, and potential for reduced stigma and discrimination, individuals identified concerns regarding their loss of control of their medication, bodily autonomy and agency, isolation due to reduced therapeutic contact and potential adverse side effects [33-

36]. Real-world evaluation of XR-BUP with high risk populations in low-threshold settings in the US have reported on positive outcomes (choosing to continue, majority (65%) of individuals experienced no evidence of precipitated withdrawal or ongoing opioid use) with strong feasibility and tolerance [37]. In another US study, novel long acting buprenorphine formulations appealed to more than half of the individuals [38]. A study in France reported on the association between a person's interest in XR-BUP and perceived valued treatment outcomes. Individuals who showed interest in XR-BUP were more focused on treatment outcomes related to recovery and abstinence, and reported more frequent forgetting of their MOUD, or reported negative situations in which taking their MOUD wasn't practical or appropriate [39]. In Australia positive perceptions of XR-BUP were associated with being female, recent illicit drug use and various factors relating to perceived (in)convenience of current OUD treatment [40].

Our study concerns Buvidal an extended-release product - XR-BUP - which is a subcutaneous buprenorphine injection administered in weekly (8, 16, 24 or 32 mg) or monthly injections (64, 96, 128, 160 mg), and typically initiated on a weekly basis with subsequent transfer to monthly injections [41,42]. Efficacy has been demonstrated in a double-blind, double-dummy, randomised phase-III-study with 428 individuals, which found Buvidal to be non-inferior to sublingual buprenorphine with regard to primary (opioid use) and secondary (opioid free urine screening) outcomes [26]. With the exception of a systematic review and meta-analysis conducted in the UK examining efficacy, safety and tolerability data of Buvidal [43], two qualitative studies on individuals' views on long-acting opioid pharmacotherapy in England [35,36] and a service evaluation conducted in West Lothian, Scotland which yielded consistent demand and positive outcomes [9], very little is known about actual impacts of Buvidal prescribing on patient outcomes in the UK. Person-centred phase III trials of other XR-

BUP products in the US (e.g. SUBLOCADE) have demonstrated significant improvements in self-reported quality of life, increased employment and decreased healthcare utilisation relative to placebo and baseline, though there was no comparison with traditional oral MOUD [44,45]. These positive outcomes are supported elsewhere in the UK, where pilot studies have demonstrated that transition from oral MOUD to XR-BUP is feasible and acceptable for people with OUD accessing services in South Wales [46], with qualitative studies reporting positive subjective outcomes in four services in England and Wales [47]. While XR-BUP may result in improved outcomes for people with OUD, not all services in England offer XR-BUP to all eligible clients due to budget constraints; consequently, some people may be selected for XR-BUP treatment based on personal, social and individual characteristics, which could increase health inequalities in substance use treatment [48,49]. However, recent health economic studies in England suggest that initiation of XR-BUP results in overall reduction of direct (delivery, medication, psychosocial treatment) and indirect (e.g. criminal justice system, health care utilisation) treatment costs [50].

To date there has not been a large quantitative evaluation of outcome data for people accessing services in England for OUD and being prescribed XR-BUP compared to oral MOUD. The objective of this study is to compare outcomes and profiles for people prescribed Buprenorphine vs. oral MOUD. To do this we undertook a retrospective analysis of quantitative data from an English Substance Use treatment provider (Via), analysing sociodemographic characteristics to identify who is most likely to be prescribed Buprenorphine and comparing person-level outcomes for individuals who were prescribed Buprenorphine with a matched control of people on oral MOUD.

## Method

### *Design, Setting and Study Population*

We conducted a cross-sectional comparison of anonymised electronic records from substance use treatment provider Via. Data from six Via services were included in our analyses. The Data Controller provided us with routinely collected person-level sociodemographic data, prescribing data and physical and mental health assessment scores from the Treatment Outcome Profiles (TOPS) assessments. During the 12-month period, individuals completed TOPS at baseline and each review session, which allows comparison of changes in TOPS scores over the time period.

People were eligible to be included in the analysis if they were aged over 18 years, a Via service user in the last 12 months (15/08/2022 and 15/08/2023) and if they were either currently being prescribed Buprenorphine, or if they were a control on another MOUD. Data was extracted for 235 individuals who were currently receiving a Buprenorphine prescription and 266 matched individuals who were receiving another MOUD (total N = 501), stratified by gender, ethnicity and primary substance of abuse (from a larger sample of 2,049). This allowed us to detect small effect sizes between the groups ( $d \sim .25$ ) with 80% power and an alpha of .05 (independent samples t-test: one-tailed).

### *Patient and Public Involvement*

DDS is manager of the Via Innovation and Research Unit and was responsible for coordinating the PPI in this study. DDS engaged with people with opioid use disorder and clinicians in Via services to discuss the planned study. During analysis, DDS involved people with opioid use disorder and clinicians in discussions about the qualitative nature of changes in psychological

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wellbeing to allow us to accurately contextualise the results for people with lived experience of opioid use disorder.

*Procedure*

Outcome variables of interest:

Prescribing Data: Start date, end date, dose and medication name/strength for each prescribed medication over the time period.

Sociodemographic information: age, sex, Indices of Multiple Deprivation (IMD) decile of patient residence, primary and secondary substance, number of previous treatment episodes, employment status and ethnicity.

Substance Use, Mental and Physical health: We used the routinely collected TOPS data to assess substance use (number of days using opiates/opioids in the last month; number of days injecting in the last month), psychological health, physical health and quality of life (QoL) (visual analogue scale from 0 = poor to 20 = good), number of days in paid employment in the last month and number of days in education in the last month.

After gaining institutional ethical approval (LJMUREC 23/PSY/036), a Data Sharing Agreement was established between Liverpool John Moores University (LJMU) and Via. In Phase 1, pseudonymised demographic data for people receiving Buvidal and oral MOUD was downloaded from Via’s Case Management System (CMS) and uploaded to a secure shared folder on CM’s university file store. A stratified sample of individuals receiving oral MOUD were chosen for comparison to those prescribed Buvidal. To do this we used the ‘stratified’ function from the ‘splitstackshape’ package in R [51]. In Phase 2, full prescribing and outcome data for all individuals prescribed Buvidal, and the selected controls was

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downloaded from Via's CMS into a Microsoft Excel file and uploaded to a secure folder on CM's file store and shared with the research team for analysis (CM, AJ & MCVH).

### *Data Analysis*

To examine predictors of receiving Buvidal compared to oral MOUD we conducted a logistic regression. We included available demographic information. Despite stratifying based on sex, ethnicity and primary substance we included these in the regression to hold them constant.

Our TOPs analysis was limited to data collected between 15-08-2022 to 15-05-2023. It was possible to have multiple TOPs recordings in this period and as such we created two different outcome variables. First, we created a summary TOPs score for each outcome during the assessment period (the average if multiple reviews were taken). Second, if multiple reviews were taken, we also calculated a change score (the difference between the first and last review) to examine any change in TOPs scores during the time period.

Using this method, we analysed only psychological health, physical health and QoL TOPs scores. This is because the variables which measured number of days (opioid use, Intravenous (IV) drug use and paid work) were largely 0 counts, making them inappropriate for these analyses. In unadjusted models, we examined the effects of Buvidal (vs MOUD) on the indices. Psychological Health, Physical Health and QoL scores were analysed using Welch's t-tests. In adjusted models we conducted linear regressions including the demographic predictors (age, employment, ethnicity, age of first substance, number of episodes, sex and IMD). Data and analysis code for the study can be found here:

<https://opendata.ljmu.ac.uk/id/eprint/182>

### **Results**

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*Baseline Characteristics of participants:*

The baseline characteristics of individuals can be found in Table 1. Of the 235 individuals receiving Buvidal, 60 (25.5%) were female, 169 (71.9%) identified as White British, with the majority (186 clients – 79.1%) reporting illicit heroin as their primary substance. Of the 266 individuals receiving MOUD, 67 (25.2%) were female, 187 (70.3%) identified as White British, with the majority (220 clients – 82.7%) reporting illicit heroin as their primary substance. There were significant differences between the groups in current age ( $t(498.6) = 4.81, p < .001, d = .43$  [95% CI: .25 to .61], number of previous treatment episodes ( $t(463.6) = 3.40, p < .001, d = .31$  [95% CI: .13 to .48] and regular employment ( $X^2(1) = 6.27, p = .012$ ) with individuals who were receiving Buvidal being significantly younger, having more previous treatment episodes and having higher levels of regular employment.

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Table 1: Demographic breakdown of individuals prescribed Buvidal vs compared to oral MOUD. Total N = 501.

	Buvidal	Other
	Mean (SD)	Mean (SD)
<b>Current Age</b>	<b>43.17 (9.00)</b>	<b>47.23 (9.89)</b>
Age of first substance	22.44 (6.93)	23.36 (9.10)
<b>Number of episodes</b>	<b>1.86 (1.21)</b>	<b>1.52 (1.04)</b>
IMD	4.43 (2.53)	4.54 (2.35)
	N (%)	N (%)
<i>Ethnicity</i>		
White British	169 (71.9%)	187 (70.3%)
Other	66 (28.1%)	79 (29.7%)
<i>Employment</i>		
<b>Regular Employment</b>	<b>55 (23.4%)</b>	<b>38 (14.3%)</b>
<b>Other</b>	<b>180 (76.6%)</b>	<b>228 (85.7%)</b>
<i>Sex</i>		
Female	60 (25.5%)	67 (25.2%)
Male	175 (74.5%)	199 (74.8%)
<i>Primary Substance</i>		
Illicit Heroin	186 (79.1%)	220 (82.7%)
Other	49 (20.9%)	46 (17.3%)
<i>Secondary Substance</i>		
Cocaine (Crack)	122 (51.9%)	120 (45.1%)
No Second Substance	56 (23.8%)	78 (29.3%)
Other	57 (24.3%)	68 (25.6%)

Note – variables with categorical response are simplified due to large number of categories with small numbers of individuals within some categories. Reference categories were chosen based on the largest number (e.g. White British, illicit heroin). In the case of the employment variable, regular employment was not the most common category, but the 'other' comparison represents a lot of similar categories (e.g. 'retired', 'unemployed', 'homemaker'). IMD was also missing from 34 individuals due to having no fixed address or this not information being available. Variables in **bold** indicate a significant difference between the groups (Buvidal compared to oral MOUD).



Predictors of Buvidal prescribing

We included 8 variables in the logistic regression model to examine whether any predicted the increased/decreased odds of being prescribed Buvidal. These variables were; current age, employment (currently employed vs not), ethnicity (white vs other), age of first substance, number of episodes, client sex at registration of birth (sex - male vs female), IMD, and primary substance (illicit heroin pared to other substances). See Table 2, for model parameters. The overall model was able to predict around 7% of variance in the outcome. Individuals of a younger age, who were regularly employed, and had increased number of episodes, had increased odds of being prescribed Buvidal (compared to other MOUD).

Table 2: Logistic regression analysis examining predictors of being prescribed Buvidal (compared to oral MOUD).

Predictors	Buvidal (compared to oral MOUD)		
	Odds Ratios	CI	p
Current age	0.96	0.94 – 0.98	<0.001
Employment [Regular Employment]	1.89	1.13 – 3.20	0.016
Ethnicity [White British]	1.06	0.69 – 1.63	0.802
Age of first substance	1.00	0.98 – 1.03	0.825
Number of episodes	1.38	1.15 – 1.68	0.001
Sex [Male]	1.00	0.64 – 1.59	0.983
Primary substance [Other]	1.02	0.61 – 1.70	0.953
IMD	0.97	0.89 – 1.05	0.469
R <sup>2</sup> (Pseudo)			0.079

### *Difference in TOPS Scores*

For psychological health and physical health, there was no significant difference between individuals who were and were not prescribed Buvidal  $t(309.96) = 1.57, p = .12, d = -.16$ ;  $t(385.04) = 0.64, p = .52, d = .06$  respectively. For QoL there was a significant difference, in that individuals who were prescribed Buvidal reported positive change in QoL compared to other treatment  $t(381.57) = 2.21, p = .03, d = .22$ ; mean improvement Buvidal = 1.40, mean improvement other = 0.52.

In adjusted models there were no significant predictors of change in Psychological Health ( $R^2 = .00$ ), or Physical Health ( $R^2 = .00$ ). For QoL, individuals who were White British had a reduction in QoL ( $B = -1.08$  [95% CI:  $-2.03 - 0.13$ ],  $p = .026$ ), and Buvidal was no longer a significant predictor.

### *Summary TOPS Scores*

For psychological health (Figure 1a), physical health (Figure 1b) and QoL (Figure 1c) there were significantly greater health/QoL reports if people were prescribed Buvidal (vs other MOUD):  $t(382.77) = 3.00, p < .001, d = .30$ ,  $t(385) = 4.41, p < .001, d = .44$  and  $t(383) = 2.60, p < .001, d = .26$  respectively.

*Figure 1: Psychological health (1a), physical health (1b) and Quality of Life in Buvidal vs. compared to oral MOUD.*

<<Insert Figure 1 about here>>

In adjusted models the variables explained approximately 7% (Adjusted  $R^2 = 0.07$ ) of variance in psychological health. Buvidal was a significant positive predictor ( $B = .082$  [95% CI:  $0.16$  to  $1.47$ ],  $p = .014$ ), as was regular employment ( $B = 1.20$  [95% CI:  $0.40$  to  $2.00$ ],  $p = .003$ ), and being male ( $B = 1.28$  [95% CI:  $0.54$  to  $2.02$ ],  $p = .001$ ). Approximately 12% of variance was explained in physical Health (Adjusted  $R^2 = 0.12$ ). Buvidal was a significant

positive predictor ( $B = 0.85$  [95% CI: 0.21 to 1.49],  $p = .009$ ), as was regular employment ( $B = 1.32$  [95% CI: 0.53 to 2.10],  $p = .001$ ) and being male ( $B = 1.13$  [95% CI: 0.40 to 1.85],  $p = .002$ ). Age was a negative predictor of physical health ( $B = -.06$  [95% CI: -0.09 to -0.02],  $p = .001$ ). Approximately 11% of variance was explained in QoL (Adjusted  $R^2 = .11$ ). Buvidal was a significant positive predictor ( $B = 0.78$  [95% CI: 0.13 to 1.42],  $p = .018$ ), as was regular employment ( $B = 1.79$  [95% CI: 1.00 to 2.58],  $p < .001$ ), being male ( $B = 1.07$  [95% CI: 0.34 to 1.80],  $p = .004$ ) and age of first substance ( $B = 0.05$  [95% CI: 0.01 to 0.09],  $p = .021$ ). The number of episodes was a negative predictor of QoL ( $B = -0.35$  [95% CI: -0.04 to -0.66],  $p = .027$ ).

#### *TOPS substance use variables.*

To analyse TOPs opioid use and IV drug use reported in the last 28 days, we created a binary variable to identify whether any opioid or IV drug use was reported for the TOP scores. There were 151 instances in which no opioid use was reported and 252 in which any was. The odds of decreased opioid use was not statistically significantly associated with Buvidal (OR = 0.81 [95% CI: 0.54 to 1.23],  $p = .325$ ). In adjusted models the number of episodes was a significant positive predictor of increased opioid use OR = 1.40 [95% CI: 1.08 to 1.87],  $p = .016$ ).

There were 355 instances in which no IV drug use was reported and 38 instances in which it was. The odds of decreased IV use was not statistically significantly associated with Buvidal (OR = 1.27 [95% CI: 0.65 to 2.52],  $p = .485$ ). Due to the small number of instances, an adjusted model was not possible.

## Discussion

In this study we compared TOPs outcomes for individuals prescribed Buvidal vs. traditional oral MOUD; while previous research has examined retention and efficacy of Buvidal for treating OUD, there is comparatively little investigation of outcomes relating to individuals. This is one of the first large investigations of person-rated outcomes and demographic factors in Buvidal clients vs. traditional oral MOUD. In our analyses, individuals who were prescribed Buvidal were younger, more likely to be employed, and had more previous treatment episodes. Buvidal was associated with positive changes in QoL over the treatment period, and overall people prescribed Buvidal reported higher levels of psychological and physical health, and QoL compared to people receiving MOUD. Other demographic and situational factors were positive and negative predictors in these analyses indicating the intersectional nature of changes in health during recovery.

The findings in this study reflect those in previous research. For example, when considering factors associated with Buvidal prescribing, an evaluation of Buvidal in West Lothian found that Buvidal helped people consider employment, which is supported by higher employment in Buvidal clients in the present study [52], although we did not find associations with sex as reported in previous research [40]. Previous research investigating outcomes in people prescribed Buvidal has largely come from the US, France and Australia. In these studies, Buvidal has generally been associated with positive individual outcomes, and of particular relevance for the present study, Buvidal is associated with perceived valued treatment outcomes. For example, people who showed interest in XR-BUP were more focused on recovery and abstinence and reported more frequent forgetting of their MOUD [53]. In qualitative studies on acceptability of XR-BUP in people with OUD, one key

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theme that emerged was the perception that XR-BUP would allow individuals to get on with everyday life [36]. Analysis of person-level outcome measures in qualitative research in four treatment settings in England and Wales found that people reported overall satisfaction with XR-BUP, with qualitative data suggesting increased life satisfaction and improved self-care (specifically taking up sports and hobbies and improvements in mental health). Interestingly, 43% of individuals reported improved material resources such as employment while 86% (12 people) reported improved well-being [47] which are reflective of improvements in mental and physical health and QoL in the present study.

In our analyses, summary TOPs scores for psychological and physical health and QoL were positively predicted by Buvidal, employment and being male. For physical health, age was a negative predictor in the model indicating that older patients reported lower QoL, which could reflect the concomitant effects of age (or indeed longer-term substance use) on physical health and long-term conditions [see 54 for review]. For QoL, age of initiation of substance use was an additional positive predictor, indicating that people who started using substances later reported better QoL, presumably because their substance using history was shorter, which is in line with the age-related predictor on physical health noted above. Finally, number of treatment episodes was a negative predictor of QoL indicating that more treatment episodes was associated with lower QoL. These analyses highlight some important intersectional characteristics which could feed into health inequalities in treatment outcomes; for example, poorer self-reported outcomes for females compared to males is not in line with previous research [e.g. 40], and warrants further investigation. Previous studies in people using MOUD and SL-BUP [e.g., 54] have noted that initial improvements in QoL are not sustained over longer-term outcomes; thus further long-term

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analysis of the XR-BUP data is needed to assess if changes in QoL are sustained and if they are meaningful indicators of recovery.

This study had a number of limitations. Firstly, this was a time-limited study and we were only able to access data for a 1-year period within the scope of our funding. Thus, we were not able to fully investigate the associations between Buvidal and treatment outcomes in terms of QoL, physical/mental health and employment beyond the treatment journey, and conversely relapse. There was insufficient data available to investigate individuals who were discharged from the treatment service during this time. Future research should investigate outcomes and treatment trajectories over a longer-time period. We also believe that further studies should also look at societal impact outcomes, such as number of healthcare (e.g., GP, A&E) and police attendances, employment status, which we could not evaluate within the scope of the present study. Due to limited capacity to link all prescribing data within the Pharmacy team in Via, we statistically stratified our oral MOUD comparison group and selected 266 controls on oral MOUD. While we do not believe that these clients would have differed from the 1783 individuals on oral MOUD who were not selected, it remains a possibility that this sample differed in some way from the selected control group. While we found significant improvements in QoL, and significant differences between the people prescribed Buvidal in physical and mental health and QoL, the TOPs scales are visual analogue assessment scales, and there is no indication as to how or why individuals feel these indicators have changed on Buvidal. Follow-up qualitative analyses would allow for the characterisation of these indices during recovery.

To our knowledge, this is the first large study to compare outcomes for individuals prescribed Buvidal compared to oral MOUD. People initiated on Buvidal were younger,

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more likely to be employed, had more previous treatment episodes, and relative to the people on oral MOUD, had significant improvements in QoL over the 1-year period and significantly higher self-reported physical and mental health, and QoL. Future research should seek to investigate the aetiology of improved wellbeing using qualitative analysis and should perform a quantitative analysis of outcomes over a longer time period to investigate the impacts of Buvidal and intersectional characteristics on recovery outcomes.

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**Author Contributions**

Montgomery and Abbasi designed the study with input from Jones, Van Hout and De Silva. Montgomery, Abbasi and De Silva applied for funding to support the study. Gittins coordinated the curation of the raw prescribing data. Jones performed the statistical analysis including data curation, analysis, analytical strategy, reporting, and drafting the results section. Van Hout performed a critical review of the literature. De Silva liaised with people with opioid dependence and clinicians to discuss the study and contextualise results. Montgomery produced the first draft of the manuscript and all authors have provided critical revisions and approved the final manuscript.

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## Competing interests

This study was funded by Camurus AB. The funder had no role in the design, planning, execution or analyses in this study. CM and MCVH also receive funding from CSL Seqirus. YA has received honorarium from Camurus, Newbridge Pharma and Ethypharm. AJ, RG and DDS report no conflict of interest.

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## Data sharing statement

The data and analysis code for this study is available in the Liverpool John Moores University Data Repository: <https://opendata.ljmu.ac.uk/id/eprint/182>

## Ethics approval statement

This was a retrospective data analysis of anonymised health records and was approved as minimal risk by Liverpool John Moores University Research Ethics Committee (LJMUREC 23/PSY/036).



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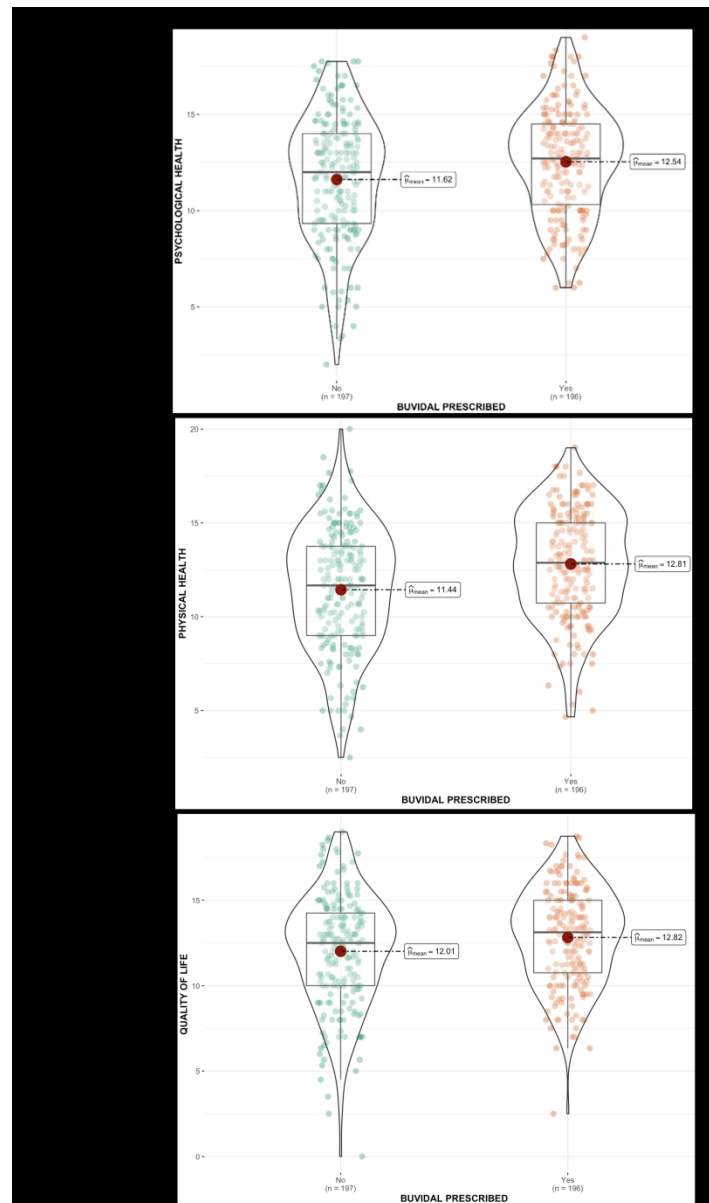


Figure 1: Psychological health (1a), physical health (1b) and Quality of Life in Buvidal vs. compared to oral MOUD.

274x465mm (236 x 236 DPI)

# BMJ Open

## Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

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Secondary Subject Heading:	Mental health, Patient-centred medicine, Public health
Keywords:	Substance misuse < PSYCHIATRY, Quality of Life, Health

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Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

Authors: <sup>1</sup>Catharine Montgomery, <sup>2</sup>Yasir Abbasi, <sup>1</sup>Andrew Jones, <sup>2</sup>Devon De Silva, <sup>3</sup>Rosalind Gittins & <sup>4</sup>Marie Claire Van Hout

Corresponding author: C Montgomery, [C.A.Montgomery@ljamu.ac.uk](mailto:C.A.Montgomery@ljamu.ac.uk)

Affiliations:

<sup>1</sup>School of Psychology, Liverpool John Moores University, UK.

<sup>2</sup>Via, 18 Dartmouth Street, London, UK.

<sup>3</sup>School of Pharmacy, Aston University, UK.

<sup>4</sup>School of Public and Allied Health, Liverpool John Moores University, UK.

Qualifications and Titles:

C Montgomery: PhD, PgCert LTHE, BSc (Hons), Reader in Psychopharmacology, Head of Institute for Health Research.

Y Abbasi: MB BS, FRCPsych, PG Cert, PG Dip, EDPM, Executive Medical Director & Consultant Addiction Psychiatrist

A Jones: PhD, Senior Lecturer in Psychology.

D De Silva: BA. IRU Manager.

R Gittins: MRPharmS (Hons) MSc CertPsychPharm MCMHP IP, Senior Lecturer.

MC Van Hout: PhD, LLM, M.Sc Health Professions Education, M.Sc Health Promotion, M.Sc International Addictions. PVC Research and Knowledge Exchange.

ORCID IDs:

Catharine Montgomery: 0000-0003-2805-5807

Yasir Abbasi: 0000-0002-4981-7914

Andrew Jones: 0000-0001-5951-889X

Rosalind Gittins: 0000-0002-0893-7936

Marie Claire Van Hout: 0000-0002-0018-4060



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**Abstract**

*Objectives:* Advances in the treatment of opioid use disorder have seen the development of long-acting injectable opioid substitutes which could improve outcomes for people with opioid use disorder. However, comparative quantitative analysis of individual outcomes is lacking. The present study sought to investigate factors associated with prescribing of the Long-Acting Injectable Buprenorphine preparation Buvidal®, and changes in outcome variables compared to oral medication for opioid use disorder.

*Design:* Cross-sectional retrospective analysis of electronic health records.

*Setting:* Community substance use treatment service Via. Six sites shared their data between 15/08/2022 – 15/08/2023.

*Participants:* Anonymised data was extracted for 235 people receiving Buvidal® and 266 people receiving oral medication for opioid use disorder.

*Primary and secondary outcomes:* Prescribing data, sociodemographic information (age, sex, IMD decile of individual’s residence, primary and secondary substance, number of previous treatment episodes, employment and ethnicity) and Treatment Outcome Profiles (substance use, physical and mental health, quality of life, employment) were extracted and analysed. To examine predictors of receiving Buvidal® (vs medication for opioid use disorder) we conducted logistic regression including the demographic predictors. Psychological health, physical health and quality of life scores were analysed using Welch’s t-tests.

*Results:* Buvidal® was associated with positive changes in quality of life between first and last assessments. Demographic and situational factors were predictors of Buvidal® initiation, indicating the potential for increasing health inequalities in substance use treatment.

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3 *Conclusions:* Buvidal® is associated with changes in quality of life over a 1-year period.  
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6 Further research is needed to investigate the aetiology of improved wellbeing and outcomes  
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**MeSH Keywords**

Opiate dependence; buprenorphine; opiate substitution treatment; psychological wellbeing; quality of life; Long-acting injection; opioid related disorders; Long-Acting Injectable Buprenorphine.

**Article Summary**

Strengths and Limitations of this study

- This analysis provides a characterisation of how standardised outcomes change in a one-year period of treatment for opioid use disorder.
- The analysis incorporates individual, demographic and situational factors to allow us to assess health inequalities in initiation of treatment.
- The data is limited in that it only gives us a snapshot of subjective wellbeing over a 1-year period.
- The data cannot tell us qualitatively *how* quality of life and perceived psychological wellbeing changed in the Buvidal® vs. medication for opioid use disorder groups.

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## Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing disorder causing clinically significant distress or impairment and includes opioid dependence, with addiction representing the most severe form of OUD [1,2]. Additional adverse health complications of OUD causing morbidity and mortality centre on blood-borne virus infection (HIV, hepatitis C), overdose, accidents, suicide, and poly use of other drugs [3-5]. OUD is treated with opioid substitutes as first line treatment (usually with methadone or buprenorphine) [6-9] though pharmacological treatment is advised to be integrated within a global therapeutic model focused on recovery and including psycho-social support [10]. Research has demonstrated that treatment with opioid agonist medications such as methadone or buprenorphine reduces mortality by around 50% in people with OUD [11-13] with reductions in overdose deaths and all-cause mortality for those retained in treatment [14]. While effective engagement and retention is crucial for better treatment outcomes including reduced opioid use [5] and reduced risk behaviours [15], high rates of drop out are observed in the early phases of treatment [16,17]. Premature disengagement, particularly in the first month of treatment and post treatment completion, is associated with significant increases in mortality risk [18,3]. Thus there is a need to understand if different Medications for Opioid Use Disorder (MOUD) are better at promoting treatment retention and improving outcomes.

Despite methadone and buprenorphine being associated with lower mortality, there are a number of individual factors which can limit the impact of these OUD treatment modalities. For example, people with OUD report that daily mandatory consumption can impact upon wellbeing and opportunities for employment [19,20] and increase stigma and discrimination [21]. In recent years extended-release subcutaneous injectable buprenorphine

formulations (Long-Acting Injectable Buprenorphine; LAIB) have been proposed as offering improved rates of retention and adherence [22-24]. LAIB preparations have the potential to be highly effective due to their long-acting bioavailability and limited risk of diversion [25,26]. Moreover, they are ideal for individuals who do not wish to take daily oral doses, people living in rural areas, people in places where safe storage is problematic (e.g. people experiencing street homelessness), or people who are at increased risk of overdose, after, for example, release from prison or hospital [27]. In one study, LAIB has been shown to be more effective at increasing abstinence than placebo plus counselling alone [28] which the authors suggest is due to the reduction of risk of missed doses due to medication loss, lapses or diversion.

While there is an evidence base for patient experiences of using methadone and sublingual buprenorphine, due to their relative novelty, there are fewer studies on lived experiences of LAIB, with studies in the United States (US), Australia and France reporting varied perspectives. In previous research, people have reported that perceived benefits of LAIB include improved choice, reduced travel, clinic and pharmacy attendance, and potential for reduced stigma and discrimination compared to supervised daily consumption. However, people also identified concerns regarding their loss of control over their medication, reduced bodily autonomy and agency, isolation due to reduced therapeutic contact and potential adverse side effects [29-32]. LAIB was also shown to be appealing as an alternative to sublingual buprenorphine, with another US study finding that LAIB preparations appealed to more than half of individuals with OUD entering opioid treatment [33]. Real-world evaluations of LAIB with high-risk populations in the US have also reported positive outcomes with people choosing to continue using LAIB, the majority of individuals (65%) tolerating LAIB well and experiencing no symptoms of precipitated withdrawal or ongoing opioid use [34]. In another study in people with OUD in France, interest in LAIB relative to other MOUD was related to

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perceived valued treatment outcomes. Individuals who showed interest in LAIB were more focused on outcomes related to recovery and abstinence, reported more frequent forgetting of their MOUD, or reported negative situations in which taking their MOUD wasn't practical or appropriate [35]. This was also reflected in a study in Australia where positive perceptions of LAIB were associated with being female, recent illicit drug use and perceived (in)convenience of current OUD treatment [36]. Moreover, a recent qualitative narrative synthesis of LAIB studies (N = 15) identified six themes from patient perspectives and patient reported outcomes. These included LAIB being associated with increased abstinence and reduced cravings, improved accessibility, increased productivity and participation in work, reduced acquisitive crime and improved social relationships. Within the review it was also identified that misinformation and mistrust were potential barriers to LAIB, and that LAIB could negatively affect some social relationships by, for example, removing the daily support of supervised consumption [37].

Our study concerns Buvidal®, which is an LAIB product typically initiated on a weekly basis with subsequent transfer to monthly injections [38,39]. Efficacy has been demonstrated in a double-blind, double-dummy, randomised phase-III-study with 428 individuals, which found Buvidal® to be non-inferior to sublingual buprenorphine with regard to primary (opioid use) and secondary (opioid free urine screening) outcomes [26]. Similar results were obtained in the UK in a phase III randomised control trial where LAIB (Sublocade®) was clinically superior compared to sublingual buprenorphine and methadone, resulting in increased abstinence from opioids, though it was not cost effective for the majority of participants. It was however identified as more effective and less costly in participants with longer treatment episodes (>28 days) and those with more severe OUD [40]. A systematic review and meta-analysis conducted in the UK examining efficacy, safety and tolerability data of Buvidal®

concluded that Buvidal® is safe, effective and improves retention compared to sublingual buprenorphine or placebo [41]. In terms of UK individual perspectives on Buvidal®, two qualitative studies [31,32] and a service evaluation [9] yielded consistent demand and perceived positive outcomes. While it is clear that people with OUD perceive initiation of LAIB positively, and if initiated on LAIB report positive experiences [42], little is known about actual impacts of Buvidal® prescribing on actual patient outcomes in the UK. Person-centred phase III trials of other LAIB products (Sublocade®) in the US have demonstrated significant improvements in self-reported Quality of Life (QoL), increased employment and decreased healthcare utilisation relative to placebo and baseline, though there was no comparison with traditional oral MOUD [43,44]. These positive outcomes are supported elsewhere in the UK, where pilot studies have demonstrated that transition from oral MOUD to LAIB is feasible and acceptable for people with OUD accessing services in South Wales [45], with qualitative studies reporting positive subjective outcomes in four services in England and Wales [46].

While there is qualitative evidence that LAIB results in improved outcomes for people with OUD, not all services in England offer LAIB to all eligible clients due to budget constraints. Between 2013-14 and 2023-24, there has been an average reduction of 50% in funding for UK substance use treatment [47]. As a result, some people may be selected for LAIB treatment based on personal, social and individual characteristics (i.e. those who are perceived to be a good investment based on whether they are stable), which could increase health inequalities in substance use treatment [48,49]. For example, Black people with substance use disorders in the UK may be disproportionately affected by this prioritisation because they are more likely to be living in poverty, unemployed or homeless and may therefore be deemed a less economically efficient option for initiation of LAIB [50]. This remains an issue for service providers despite recent health economic studies in England suggesting that initiation of LAIB

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3 results in overall reduction of direct (delivery, medication, psychosocial treatment) and  
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5 indirect (e.g. criminal justice system, health care utilisation) treatment costs [51]. Thus, in  
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7 addition to investigating if LAIB is associated with improved outcomes, one aim of the present  
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9 study was to investigate if there are any health inequalities in initiation of LAIB by  
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11 understanding individual and demographic predictors (e.g. social deprivation, ethnicity, age)  
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13 of being initiated on LAIB vs. other MOUD.  
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18 In summary, to date there has not been a large quantitative evaluation of outcome  
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20 data for people accessing services in England for OUD and being prescribed LAIB compared  
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22 to oral MOUD. The objective of this study is to compare outcomes and predictors for people  
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24 prescribed Buvidal® vs. oral MOUD. To do this we undertook a retrospective analysis of  
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26 quantitative data from an English substance use treatment provider (Via), analysing  
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28 sociodemographic characteristics to identify who is most likely to be prescribed Buvidal® and  
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30 comparing person-level outcomes for individuals who were prescribed Buvidal® with a  
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32 matched control of people on oral MOUD.  
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**Method**

*Design, Setting and Study Population*

We conducted a cross-sectional comparison of anonymised electronic records from substance use treatment provider Via. Data from six Via services were included in our analyses. The data controller provided us with routinely collected person-level sociodemographic data, prescribing data, substance use data and physical and mental health assessment scores from the Treatment Outcome Profile (TOP) assessments. During the 12-month period, individuals completed TOPs at every contact with Via which allows comparison of changes in TOPs scores over the time period.

People were eligible to be included in the analysis if they were aged over 18 years, a Via service user in the last 12 months (15/08/2022 and 15/08/2023) and if they were either currently being prescribed Buvidal®, or if they were a control on another MOUD. Data was extracted for 235 individuals who were currently receiving a Buvidal® prescription and 266 matched individuals who were receiving another MOUD (total N = 501). Matched controls were selected using the following procedure. We were provided with the patient identification and demographic information of 2,048 individuals who received oral MOUD. We used gender, ethnicity and primary substance of use as stratifiers to obtain a smaller sample (which reflected the balance of these stratifiers), using the 'stratified' function from the 'splitstackshape' package in R [52]. We aimed for a similar sample size to our Buvidal sample, which would still provide us with appropriate statistical power. We then provided the patient identifiers of the stratified sample to Via, who provided us with the TOPs and prescribing data for these individuals. We were unable to request data from all 2,048 individuals due to limited resources. Our overall sample size allowed us to detect small

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effect sizes between the groups on TOP scores ( $d \sim .25$ ) with 80% power and an alpha of .05 (independent samples t-test: one-tailed).

We reviewed the medicine scripts to allow us to summarise the most commonly prescribed Buvidal® and other MOUD dosages. For most individuals, dose changed over the 1-year period, and for some people in the oral MOUD group, type of MOUD changed. Based on information on the medicine scripts, the most common dose of Buvidal® was 64 mg prolonged release solution (27.8%), followed by 96 mg prolonged release solution (26.6%) and 128 mg prolonged release (17.5%). For other MOUD, the most common medication and dose was Methadone 1mg/ml oral solution (52.5%), followed by Buprenorphine 2mg sublingual tablets (19.7%).

#### *Patient and Public Involvement*

DDS is manager of the Via Innovation and Research Unit and was responsible for coordinating the PPI in this study. DDS engaged with people with opioid use disorder and clinicians in Via services to discuss the planned study. During analysis, DDS involved people with opioid use disorder and clinicians in discussions about the qualitative nature of changes in psychological wellbeing to allow us to accurately contextualise the results for people with lived experience of opioid use disorder.

#### *Measures*

Prescribing Data: Data was extracted from the pharmacy system (Nebula) for each individual over the 1-year period including the start date, end date, dose and name/strength for each prescribed medication.

Sociodemographic information: Routinely collected data including age, sex, Indices of Multiple Deprivation (IMD) decile of patient residence, primary and secondary substance,

number of previous treatment episodes, employment status and ethnicity were extracted from the Via Case Management System (CMS).

Outcome variables of interest:

TOP scores were used to assess changes in substance use, mental and physical health and QoL. The TOP is a standardised tool used in all UK substance use treatment settings to collect routine data at treatment entry and at set time points over the treatment journey (routinely at baseline, every 3 months until treatment exit; 3 & 6 months post treatment exit). The tool is comprised of a set of 20 psychometrically valid outcome measures [53] which have been shown to have good inter-rater reliability and test-retest reliability [54]. We used the routinely collected TOPs data to assess substance use (number of days using opiates/opioids in the last month; number of days injecting in the last month), psychological health, physical health and QoL (visual analogue scale from 0 = poor to 20 = good), number of days in paid employment in the last month and number of days in education in the last month.

Our TOPs analysis was limited to data collected between 15-08-2022 to 15-08-2023. As it was possible to have multiple TOP assessments in this period, we created two different outcome variables based on the TOP scores. If multiple assessments were taken during the one-year period (N = 383), we calculated a *TOPs change score* (the difference between the first and last assessment) to examine any change in TOPs scores during the time period. Secondly, we created a *summary TOPs score* for each outcome during the assessment period (the average for each TOP variable if multiple assessments were taken). Using this method, we analysed only psychological health, physical health and QoL TOPs scores.

Analyses for the *summary TOPs* score are reported in Supplementary file S1, containing supplementary Table 4 and Supplementary Figure 2.

We could not calculate change scores or summary scores for the TOP substance use and employment variables (opioid use, Intravenous (IV) drug use and paid work in the last 28 days) as they were largely 0 counts. For these variables we created a binary variable to identify whether any opioid use, IV drug use or paid employment was reported.

### *Procedure*

After gaining institutional ethical approval (LJMUREC 23/PSY/036), a Data Sharing Agreement was established between Liverpool John Moores University (LJMU) and Via. In Phase 1, pseudonymised demographic data for people receiving Buvidal® and oral MOUD was downloaded from Via's CMS and uploaded to a secure shared folder on CM's university file store. In Phase 2, full prescribing and outcome data for all individuals prescribed Buvidal®, and the selected controls was downloaded from Via's CMS into a Microsoft Excel file and uploaded to a secure folder on CM's file store and shared with the research team for analysis (CM & AJ).

### *Data Analysis*

To examine predictors of receiving Buvidal® compared to oral MOUD we conducted a logistic regression. We included available demographic information. Despite stratifying based on sex, ethnicity and primary substance we included these in the regression to hold them constant. For the logistic models we report Odds Ratios and 95% confidence intervals as parameter estimates.

Psychological health, physical health and QoL scores were analysed using Welch's t-tests. In adjusted models we conducted linear regressions including the demographic

predictors (age, employment, ethnicity, age of first substance, number of episodes, sex and IMD) to predict the TOPs change scores for psychological health, physical health and QoL (comparable analyses for summary scores can be found in supplementary file S1). There were some missing data for IMD (N = 34 / 6.7%) and age of first use (N = 20 / 4.0%). Missing data for IMD was likely reflective of people with no fixed abode (e.g. those experiencing street homelessness) and therefore was not missing at random. As such we did not conduct multiple imputation analyses as this may serve to increase possible bias [55]. However, we conduct all adjusted analyses with these variables removed as sensitivity analyses, and any deviation from adjusted analyses with these variables included is noted. For opioid use and IV drug use, we conducted logistic regressions in which any amount of opioid use or IV drug use recorded was coded as 1.

Data and analysis code for the study can be found here: [dataset]

<https://opendata.ljmu.ac.uk/id/eprint/182>

**Results**

*Baseline Characteristics of participants:*

The baseline characteristics of individuals can be found in Table 1. Of the 235 individuals receiving Buvidal®, 60 (25.5%) were female, 185 (78.7%) identified as White ethnicity, with the majority (186 clients – 79.1%) reporting illicit heroin as their primary substance. Of the 266 individuals receiving MOUD, 67 (25.2%) were female, 187 (70.3%) identified as White ethnicity, with the majority (220 clients – 82.7%) reporting illicit heroin as their primary substance. There were significant differences between the groups in current age ( $t(498.6) = 4.81, p < .001, d = .43$  [95% CI: .25 to .61], number of previous treatment episodes ( $t(463.6) = 3.40, p < .001, d = .31$  [95% CI: .13 to .48] and regular employment ( $X^2(1) = 6.27, p = .012$ )

with individuals who were receiving Buvidal® being significantly younger, having more previous treatment episodes and having higher levels of regular employment.

*Table 1: Demographic breakdown of individuals prescribed Buvidal® vs compared to oral MOUD. Total N = 501.*

	Buvidal®	Other
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
<b>Current Age</b>	<b>43.17 (9.00)</b>	<b>47.23 (9.89)</b>
Age of first substance	22.44 (6.93)	23.36 (9.10)
<b>Number of episodes</b>	<b>1.86 (1.21)</b>	<b>1.52 (1.04)</b>
IMD	4.43 (2.53)	4.54 (2.35)
	<i>N (%)</i>	<i>N (%)</i>
<i>Ethnicity</i>		
White	185 (78.7%)	213 (80.4%)
Asian / British Asian	27 (11.5%)	22 (8.3%)
Black /Black British / African	13 (5.5%)	7 (2.6%)
Mixed / Multiple	3 (1.3%)	9 (3.4%)
Unknown / Other	7 (3.0%)	14 (5.3%)
<i>Employment</i>		
<b>Regular Employment</b>	<b>55 (23.4%)</b>	<b>38 (14.3%)</b>
<b>Other</b>	<b>180 (76.6%)</b>	<b>228 (85.7%)</b>
<i>Sex</i>		
Female	60 (25.5%)	67 (25.2%)
Male	175 (74.5%)	199 (74.8%)
<i>Primary Substance</i>		
Illicit Heroin	186 (79.1%)	220 (82.7%)
Other	49 (20.9%)	46 (17.3%)
<i>Secondary Substance</i>		
Cocaine (Crack)	122 (51.9%)	120 (45.1%)
No Second Substance	56 (23.8%)	78 (29.3%)
Other	57 (24.3%)	68 (25.6%)

Note – variables with categorical response are simplified due to large number of categories with small numbers of individuals within some categories. Reference categories were chosen based on the largest number (e.g. White, illicit heroin). In the case of the employment variable, regular employment was not the most common category, but the ‘other’ comparison represents a lot of similar categories (e.g. ‘retired’, ‘unemployed’, ‘homemaker’). IMD was also missing from 34 individuals due to having no fixed address or this not information being available. Variables in **bold** indicate a significant difference between the groups (Buvidal® compared to oral MOUD).

*Predictors of Buvidal® prescribing*

We included 8 variables in the logistic regression model to examine whether any predicted the increased/decreased odds of being prescribed Buvidal®. These variables were; current age, employment (currently employed vs not), ethnicity (white vs other), age of first substance, number of episodes, client sex at registration of birth (sex - male vs female), IMD, and primary substance (illicit heroin pared to other substances). See Table 2, for model parameters. The overall model was able to predict around 7% of variance in the outcome. Individuals of a younger age, who were regularly employed, and had increased number of episodes, had increased odds of being prescribed Buvidal® (compared to other MOUD).

*Table 2: Logistic regression analysis examining predictors of being prescribed Buvidal® (compared to oral MOUD).*

<i>Predictors</i>	<b>Buvidal® (compared to oral MOUD)</b>		
	<i>Odds Ratios</i>	<i>CI</i>	<i>p</i>
<b>Current age</b>	<b>0.96</b>	<b>0.94 – 0.98</b>	<b>&lt;0.001</b>
<b>Employment [Regular Employment]</b>	<b>1.89</b>	<b>1.13 – 3.19</b>	<b>0.016</b>
Ethnicity [White British]	0.93	0.57 – 1.51	0.755
Age of first substance	1.00	0.98 – 1.03	0.880
<b>Number of episodes</b>	<b>1.38</b>	<b>1.15 – 1.68</b>	<b>0.001</b>
Sex [Male]	1.00	0.62 – 1.57	0.964

Primary substance [Other]	1.02	0.61 – 1.71	0.929
IMD	0.97	0.89 – 1.05	0.461
R <sup>2</sup> (Pseudo)			0.079

#### *Difference in TOPs Scores (Figure 1)*

For psychological health and physical health, there was no significant difference between individuals who were and were not prescribed Buvidal®  $t(390.96) = 1.57$ ,  $p = .12$ ,  $d = -.16$ ;  $t(385.04) = 0.64$ ,  $p = .52$ ,  $d = .06$  respectively. For QoL there was a significant difference, in that individuals who were prescribed Buvidal® reported positive change in QoL compared to other treatment  $t(381.57) = 2.21$ ,  $p = .03$ ,  $d = .22$ ; mean improvement Buvidal® = 1.40, mean improvement other = 0.52.

<<Insert Figure 1 here>>

In adjusted models there were no significant predictors of change in Psychological Health ( $R^2 = .00$ ), Physical Health ( $R^2 = .00$ ) or QoL ( $R^2 = .02$ ), though there was a trend for current age being negatively related to psychological health and IMD decile positively related to physical health. In adjusted models, Buvidal® was a marginally non-significant predictor of QoL ( $p = .051$ ) (see Table 3). In models with IMD and age of first use removed, Buvidal remained a non-significant predictor in all models; however, being of white ethnicity was associated with an improved QoL ( $B = -1.00$  [95% CI: -2.00 - -0.01],  $p = .048$ ) and physical health ( $B = -1.11$  [95% CI: -2.14 - -0.07],  $p = .036$ ). Age was a significant predictor of psychological health ( $B = -0.05$  [95% CI: -.010 - -0.01],  $p = .019$ ).



Table 3: Adjusted regression models for the effects of Buprenorphine vs other MOUD on TOP outcomes.

	Psychological Health		Physical Health		Quality of Life	
Predictors	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p
Medication [Other MOUD]	0.62 (-0.30 – 1.55)	0.185	0.31 (-0.60 – 1.23)	0.5	0.00 (-1.75 – 1.75)	0.051
Current age	-0.04 (-0.09 – 0.01)	0.092	-0.01 (-0.06 – 0.04)	0.642	-0.08 (-0.08 – 0.01)	0.168
Employment [Regular Employment]	0.15 (-0.99 – 1.28)	0.799	-0.25 (-1.38 – 0.87)	0.661	-1.63 (-1.63 – 0.52)	0.313
Ethnicity [Non White]	-0.02 (-1.14 – 1.10)	0.97	-0.83 (-1.94 – 0.28)	0.141	-1.97 (-1.97 – 0.15)	0.094
Age of first substance	0.01 (-0.05 – 0.07)	0.718	0.02 (-0.04 – 0.07)	0.515	0.03 (-0.03 – 0.08)	0.359
Number of episodes	-0.11 (-0.56 – 0.33)	0.608	-0.02 (-0.45 – 0.42)	0.946	0.01 (-0.41 – 0.43)	0.953
Sex [Female]	0.14 (-0.91 – 1.19)	0.79	-0.13 (-1.18 – 0.92)	0.806	0.06 (-0.94 – 1.06)	0.903
IMD	0 (-0.19 – 0.19)	0.997	0.17 (-0.02 – 0.35)	0.076	0.09 (-0.09 – 0.27)	0.314
Observations	354		354		354	
R <sup>2</sup> / R <sup>2</sup> adjusted	0.019 / 0.00		0.016 / 0.00		0.043 / 0.021	

IMD = Index of multiple deprivation; reference categories stated in []

### *TOPs substance use variables.*

There were 151 instances in which no opioid use was reported and 252 in which any was. The odds of decreased opioid use was not statistically significantly associated with Buvidal® (OR = 0.81 [95 CI: 0.54 to 1.23],  $p = .325$ ). In adjusted models the number of episodes was a significant positive predictor of increased opioid use OR = 1.40 [95% CI: 1.08 to 1.87],  $p = .016$ ).

There were 355 instances in which no IV drug use was reported and 38 instances in which it was. The odds of decreased IV use was not statistically significantly associated with Buvidal® (OR = 1.27 [95% CI: 0.65 to 2.52],  $p = .485$ ). Due to the small number of instances, an adjusted model was not possible.

### **Discussion**

In this study we compared TOPs outcomes for individuals prescribed Buvidal® vs. oral MOUD. While previous research has examined retention and efficacy of Buvidal® for treating OUD, there is comparatively little investigation of outcomes relating to individuals. This is one of the first large investigations of person-rated outcomes and demographic factors in people prescribed Buvidal® vs. oral MOUD. In our analyses, people who were prescribed Buvidal® were younger, more likely to be employed, and had more previous treatment episodes. Buvidal® was associated with positive changes in QoL over the treatment period. Supplementary analyses (see file S1) highlighted that overall people prescribed Buvidal® reported higher levels of psychological and physical health, and QoL compared to people receiving MOUD. Other demographic and situational factors were positive and negative predictors in these analyses indicating the intersectional nature of changes in health during recovery.

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The findings in this study reflect those in previous research. For example, when considering factors associated with Buvidal® prescribing, an evaluation of Buvidal® in West Lothian found that Buvidal® helped people consider employment, which is supported by higher employment in Buvidal® clients in the present study [56], although we did not find associations with sex as reported in previous research [36]. We were particularly interested in predictors of Buvidal® initiation in the present study as budget constraints in UK treatment services could increase health inequalities [48,49]. While we did not find evidence for inequalities in initiation of Buvidal® related to social deprivation (IMD), sex or ethnicity, we did find evidence that those who are younger, have more treatment episodes and are in regular employment are more likely to receive Buvidal®. This provides some tentative evidence that certain individual factors are associated with increased likelihood of receiving Buvidal® relative to oral MOUD. The finding for age is more concerning in terms of inequality as ageing populations of substance users are subject to greater levels of substance-related harms [58] but have been shown to achieve better treatment outcomes than their younger counterparts [59] and may also benefit from LAIB. In the present study we also identified that age was a significant negative predator of psychological health, indicating that older people may have unmet mental health needs and would benefit from LAIB initiation. However, one alternative explanation is that older people with OUD are reluctant to switch from methadone, a known entity, on to novel treatments. Substance treatment guidance in the UK suggests that people with longer OUD history (i.e. older individuals) or those with heightened withdrawal-related anxiety may prefer methadone to buprenorphine because of the sedative effect [60]. Thus we cannot say if older adults were not selected for, or declined, LAIB. Future research should seek to supplement the

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quantitative analyses with qualitative data to understand clinicians' and people with OUD's choice of treatment.

In our analyses of changes in self-reported outcomes over the 1-year period, Buvidal® was a significant predictor of changes in QoL, but not physical or mental health. In previous qualitative studies on acceptability of LAIB in people with OUD, one key theme that emerged was the perception that LAIB would allow individuals to get on with everyday life [32]. Indeed, analysis of person-level outcome measures in found that people on LAIB reported increased life satisfaction and improved self-care (specifically taking up sports and hobbies and improvements in mental health). Interestingly, 43% of individuals reported improved material resources such as employment while 86% (12 people) reported improved well-being [46] which are reflective of Buvidal®'s association with increased employment and QoL in the present study. However, previous studies in people using MOUD and sublingual buprenorphine [e.g., 59] have noted that initial improvements in QoL are not sustained over longer-term outcomes. Thus, further long-term analysis of the LAIB data is needed to assess if changes in QoL are sustained and if they are meaningful indicators of recovery. Inclusion of demographic predictors in the adjusted models reduced Buvidal® to just below statistical significance, indicating the intersectional nature of changes in QoL over the 1-year period. For example, in this analysis we identified that being of White ethnicity was associated with improved QoL and physical health, which indicates the role of ethnicity in treatment outcomes [48-50].

Supplementary analyses of summary TOPs scores indicated that psychological and physical health and QoL were positively predicted by Buvidal®, employment and being male. For physical health age was a negative predictor in the model (older people had worse

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physical health), while for QoL age of initiation was a positive predictor (people who started using later reported better QoL). Taken together, these results could reflect the concomitant effects of age (or indeed longer-term substance use) on wellbeing and long-term conditions [see 59 for review]. Finally, number of treatment episodes was a negative predictor of QoL indicating that more treatment episodes was associated with lower QoL. These analyses highlight some important individual characteristics related to treatment outcomes. For example, poorer self-reported outcomes for females compared to males is not in line with previous research [e.g. 36] and warrants further investigation.

This study had a number of limitations. Firstly, this was a time-limited study and we were only able to access data for a 1-year period within the scope of our funding. Thus, we were not able to fully investigate the associations between Buvidal® and treatment outcomes in terms of QoL, physical/mental health and employment beyond the treatment journey, and conversely relapse. There was insufficient data available to investigate individuals who were discharged from the treatment service during this time, and due to the cross-sectional nature, we could not include treatment duration in our analyses. Future research should investigate outcomes and treatment trajectories over a longer-time period taking in to account previous treatment episodes, durations and outcomes. We also believe that further studies should also look at societal impact outcomes, such as number of healthcare (e.g., GP, A&E) and police attendances, employment status, which we could not evaluate within the scope of the present study. Due to limited capacity to link all prescribing data within the Pharmacy team in Via, we statistically stratified our oral MOUD comparison group and selected 266 controls on oral MOUD. While we do not believe that these clients would have differed from the 1783 individuals on oral MOUD who were not selected, it remains a possibility that this sample differed in some way from the selected control group.

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While we found significant improvements in QoL, and significant differences between the people prescribed Buvidal® in physical and mental health and QoL, the TOPs scales are visual analogue assessment scales, and there is no indication as to how or why individuals feel these indicators have changed on Buvidal®. Follow-up qualitative analyses would allow for the characterisation of these indices during recovery.

To our knowledge, this is the first large study to compare self-reported outcomes for individuals prescribed Buvidal® compared to oral MOUD. People initiated on Buvidal® were younger, more likely to be employed, had more previous treatment episodes, and relative to the people on oral MOUD, had significant improvements in QoL over the 1-year period. Future research should seek to investigate the aetiology of improved wellbeing using qualitative analysis and should perform a quantitative analysis of outcomes over a longer period to investigate the impacts of Buvidal® and intersectional characteristics on recovery outcomes.

### Figure Legends

*Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.*

*Figure 2 (supplementary file S2): Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.*

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### Author Contributions

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Montgomery and Abbasi designed the study with input from Jones, Van Hout and De Silva. Montgomery, Abbasi and De Silva applied for funding to support the study. Gittins coordinated the curation of the raw prescribing data. Jones performed the statistical analysis including data curation, analysis, analytical strategy, reporting, and drafting the results section. Van Hout performed a critical review of the literature. De Silva liaised with people with opioid dependence and clinicians to discuss the study and contextualise results. Montgomery produced the first draft of the manuscript and all authors have provided critical revisions and approved the final manuscript. Montgomery is the guarantor.

**Competing interests**

This study was funded by Camurus AB. The funder had no role in the design, planning, execution or analyses in this study. CM and MCVH also receive funding from CSL Seqirus. YA has received honorarium from Camurus, Newbridge Pharma and Ethypharm. AJ, RG and DDS report no conflict of interest.

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**Data sharing statement**

[dataset] The data and analysis code for this study is available in the Liverpool John Moores University Data Repository: <https://opendata.ljmu.ac.uk/id/eprint/182>

**Ethics approval statement**

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This was a retrospective data analysis of anonymised health records and was approved as minimal risk by Liverpool John Moores University Research Ethics Committee (LJMUREC 23/PSY/036).

For peer review only

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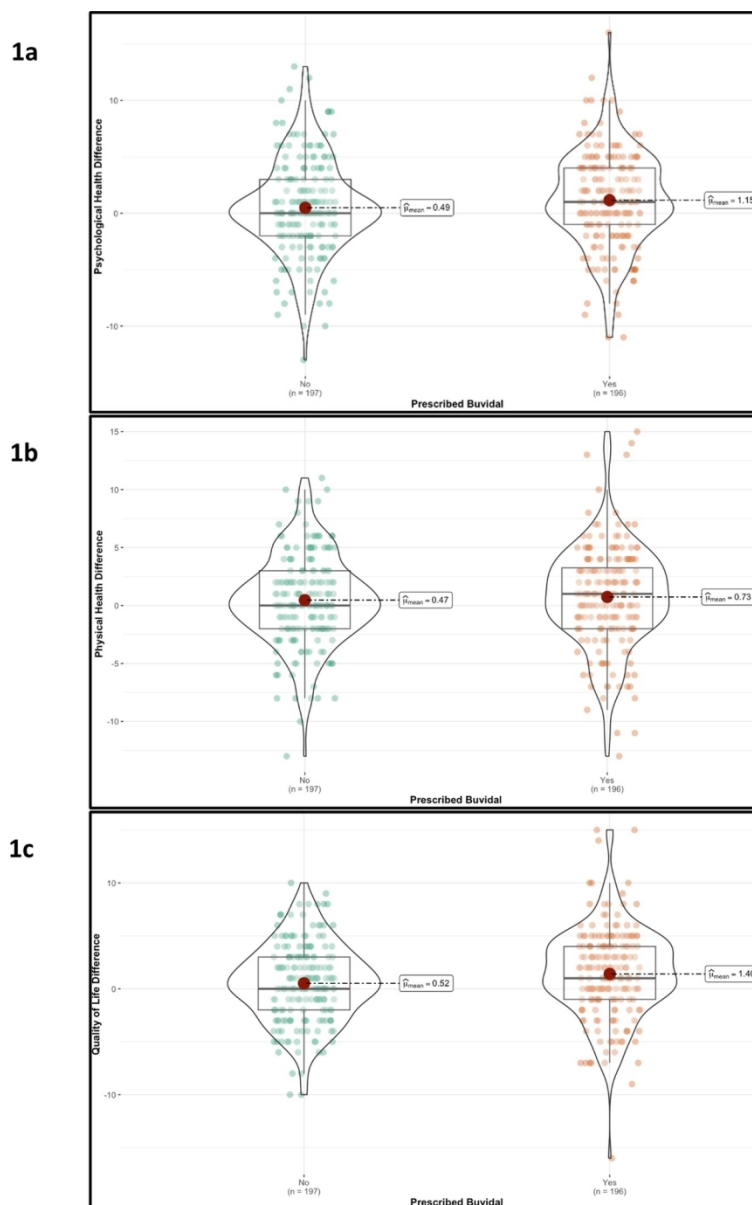


Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.

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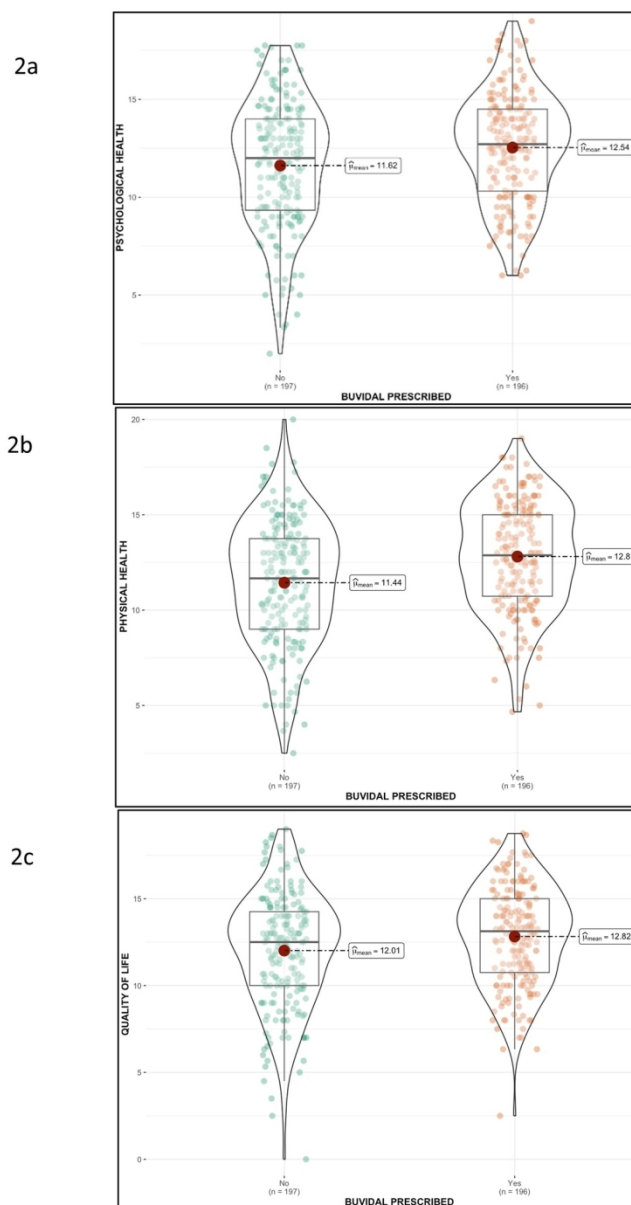


Figure 2: Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.

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### Analysis of summary TOPS Scores

For psychological health (Figure 1a), physical health (Figure 1b) and QoL (Figure 1c) there were significantly greater health/QoL reports if people were prescribed Buvidal<sup>®</sup> (vs other MOUD):  $t(382.77) = 3.00$   $p < .001$ ,  $d = .30$ ),  $t(385) = 4.41$ ,  $p < .001$ ,  $d = .44$ ) and  $t(383) = 2.60$ ,  $p < .001$ ,  $d = .26$ ) respectively.

*Figure 2: Psychological health (1a), physical health (1b) and Quality of Life in Buvidal<sup>®</sup> vs. compared to oral MOUD.*

In adjusted models the variables explained approximately 7% (Adjusted  $R^2 = 0.07$ ) of variance in psychological health. Buvidal<sup>®</sup> was a significant positive predictor ( $B = .081$  [95% CI: 0.16 to 1.46],  $p = .015$ ), as was regular employment ( $B = 1.21$  [95% CI: 0.42 to 2.01],  $p = .003$ ), and being male ( $B = 1.23$  [95% CI: 0.49 to 1.97],  $p = .001$ ). Approximately 12% of variance was explained in physical health (Adjusted  $R^2 = 0.12$ ). Buvidal<sup>®</sup> was a significant positive predictor ( $B = 0.85$  [95% CI: 0.21 to 1.49],  $p = .009$ ), as was regular employment ( $B = 1.33$  [95% CI: 0.54 to 2.12],  $p = .001$ ) and being male ( $B = 1.09$  [95% CI: 0.36 to 1.82],  $p = .004$ ). Age was a negative predictor of physical health ( $B = -0.06$  [95% CI: -0.09 to -0.02],  $p = .001$ ). Approximately 11% of variance was explained in QoL (Adjusted  $R^2 = .11$ ). Buvidal<sup>®</sup> was a significant positive predictor ( $B = 0.77$  [95% CI: 0.13 to 1.42],  $p = .019$ ), as was regular employment ( $B = 1.80$  [95% CI: 1.01 to 2.59],  $p < .001$ ), being male ( $B = 1.04$  [95% CI: 0.31 to 1.77],  $p = .006$ ) and age of first substance use ( $B = 0.05$  [95% CI: 0.01 to 0.08],  $p = .025$ ). The number of episodes was a negative predictor of QoL ( $B = -0.35$  [95% CI: -0.04 to -0.65],  $p = .027$ ).



Table 4

	Psychological Health			Physical Health			Quality of Life		
Predictors	Estimates	CI	p	Estimates	CI	p	Estimates	CI	p
Buvidal [Yes]	0.81	0.16 – 1.46	<b>0.015</b>	0.85	0.21 – 1.49	<b>0.009</b>	0.77	0.13 – 1.42	<b>0.019</b>
Age	0.00	-0.03 – 0.04	0.791	-0.06	-0.09 – -0.02	<b>0.001</b>	-0.00	-0.04 – 0.03	0.947
Employment [Regular Employment]	1.21	0.42 – 2.01	<b>0.003</b>	1.33	0.54 – 2.12	<b>0.001</b>	1.80	1.01 – 2.59	<b>&lt;0.001</b>
Ethnicity [white]	-0.58	-1.37 – 0.21	0.149	-0.53	-1.31 – 0.24	0.178	-0.38	-1.15 – 0.40	0.344
Age of first substance	0.03	-0.01 – 0.07	0.168	0.03	-0.01 – 0.07	0.136	0.05	0.01 – 0.08	<b>0.025</b>
Number of episodes	-0.23	-0.54 – 0.08	0.147	-0.23	-0.54 – 0.07	0.132	-0.35	-0.65 – -0.04	<b>0.027</b>
Gender [Male]	1.23	0.49 – 1.97	<b>0.001</b>	1.09	0.36 – 1.82	<b>0.004</b>	1.04	0.31 – 1.77	<b>0.006</b>
IMD	-0.03	-0.16 – 0.11	0.693	-0.05	-0.18 – 0.08	0.430	-0.08	-0.21 – 0.05	0.227
R <sup>2</sup> / R <sup>2</sup> adjusted	0.102 / 0.081			0.144 / 0.124			0.131 / 0.111		

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# BMJ Open

## Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

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Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

Authors: <sup>1</sup>Catharine Montgomery, <sup>2</sup>Yasir Abbasi, <sup>1</sup>Andrew Jones, <sup>2</sup>Devon De Silva, <sup>3</sup>Rosalind Gittins & <sup>4</sup>Marie Claire Van Hout

Corresponding author: C Montgomery, [C.A.Montgomery@ljamu.ac.uk](mailto:C.A.Montgomery@ljamu.ac.uk)

Affiliations:

<sup>1</sup>School of Psychology, Liverpool John Moores University, UK.

<sup>2</sup>Via, 18 Dartmouth Street, London, UK.

<sup>3</sup>School of Pharmacy, Aston University, UK.

<sup>4</sup>School of Public and Allied Health, Liverpool John Moores University, UK.

Qualifications and Titles:

C Montgomery: PhD, PgCert LTHE, BSc (Hons), Reader in Psychopharmacology, Head of Institute for Health Research.

Y Abbasi: MB BS, FRCPsych, PG Cert, PG Dip, EDPM, Executive Medical Director & Consultant Addiction Psychiatrist

A Jones: PhD, Senior Lecturer in Psychology.

D De Silva: BA. IRU Manager.

R Gittins: MRPharmS (Hons) MSc CertPsychPharm MCMHP IP, Senior Lecturer.

MC Van Hout: PhD, LLM, M.Sc Health Professions Education, M.Sc Health Promotion, M.Sc International Addictions. PVC Research and Knowledge Exchange.

ORCID IDs:

Catharine Montgomery: 0000-0003-2805-5807

Yasir Abbasi: 0000-0002-4981-7914

Andrew Jones: 0000-0001-5951-889X

Rosalind Gittins: 0000-0002-0893-7936

Marie Claire Van Hout: 0000-0002-0018-4060

**Abstract**

*Objectives:* Advances in the treatment of opioid use disorder have seen the development of long-acting injectable opioid substitutes which could improve outcomes for people with opioid use disorder. However, comparative quantitative analysis of individual outcomes is lacking. The present study sought to investigate factors associated with prescribing of the Long-Acting Injectable Buprenorphine preparation Buvidal®, and changes in outcome variables compared to oral medication for opioid use disorder.

*Design:* Cross-sectional retrospective analysis of electronic health records.

*Setting:* Community substance use treatment service Via. Six sites shared their data between 15/08/2022 – 15/08/2023.

*Participants:* Anonymised data was extracted for 235 people receiving Buvidal® and 266 people receiving oral medication for opioid use disorder.

*Primary and secondary outcomes:* Prescribing data, sociodemographic information (age, sex, IMD decile of individual’s residence, primary and secondary substance, number of previous treatment episodes, employment and ethnicity) and Treatment Outcome Profiles (substance use, physical and mental health, quality of life, employment) were extracted and analysed. To examine predictors of receiving Buvidal® (vs medication for opioid use disorder) we conducted logistic regression including the demographic predictors. Psychological health, physical health and quality of life scores were analysed using Welch’s t-tests.

*Results:* Buvidal® was associated with positive changes in quality of life between first and last assessments. Demographic and situational factors were predictors of Buvidal® initiation, indicating the potential for increasing health inequalities in substance use treatment.

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3 *Conclusions:* Buvidal® is associated with changes in quality of life over a 1-year period.  
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6 Further research is needed to investigate the aetiology of improved wellbeing and outcomes  
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**MeSH Keywords**

Opiate dependence; buprenorphine; opiate substitution treatment; psychological wellbeing; quality of life; Long-acting injection; opioid related disorders; Long-Acting Injectable Buprenorphine.

**Article Summary**

Strengths and Limitations of this study

- This analysis provides a characterisation of how standardised outcomes change in a one-year period of treatment for opioid use disorder.
- The analysis incorporates individual, demographic and situational factors to allow us to assess health inequalities in initiation of treatment.
- The data is limited in that it only gives us a snapshot of subjective wellbeing over a 1-year period.
- The data cannot tell us qualitatively *how* quality of life and perceived psychological wellbeing changed in the Buvidal® vs. medication for opioid use disorder groups.

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## Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing disorder causing clinically significant distress or impairment and includes opioid dependence, with addiction representing the most severe form of OUD [1,2]. Additional adverse health complications of OUD causing morbidity and mortality centre on blood-borne virus infection (HIV, hepatitis C), overdose, accidents, suicide, and poly use of other drugs [3-5]. OUD is treated with opioid substitutes as first line treatment (usually with methadone or buprenorphine) [6-9] though pharmacological treatment is advised to be integrated within a global therapeutic model focused on recovery and including psycho-social support [10]. Research has demonstrated that treatment with opioid agonist medications such as methadone or buprenorphine reduces mortality by around 50% in people with OUD [11-13] with reductions in overdose deaths and all-cause mortality for those retained in treatment [14]. While effective engagement and retention is crucial for better treatment outcomes including reduced opioid use [5] and reduced risk behaviours [15], high rates of drop out are observed in the early phases of treatment [16,17]. Premature disengagement, particularly in the first month of treatment and post treatment completion, is associated with significant increases in mortality risk [18,3]. Thus there is a need to understand if different Medications for Opioid Use Disorder (MOUD) are better at promoting treatment retention and improving outcomes.

Despite methadone and buprenorphine being associated with lower mortality, there are a number of individual factors which can limit the impact of these OUD treatment modalities. For example, people with OUD report that daily mandatory consumption can impact upon wellbeing and opportunities for employment [19,20] and increase stigma and discrimination [21]. In recent years extended-release subcutaneous injectable buprenorphine

formulations (Long-Acting Injectable Buprenorphine; LAIB) have been proposed as offering improved rates of retention and adherence [22-24]. LAIB preparations have the potential to be highly effective due to their long-acting bioavailability and limited risk of diversion [25,26]. Moreover, they are ideal for individuals who do not wish to take daily oral doses, people living in rural areas, people in places where safe storage is problematic (e.g. people experiencing street homelessness), or people who are at increased risk of overdose, after, for example, release from prison or hospital [27]. In one study, LAIB has been shown to be more effective at increasing abstinence than placebo plus counselling alone [28] which the authors suggest is due to the reduction of risk of missed doses due to medication loss, lapses or diversion.

While there is an evidence base for patient experiences of using methadone and sublingual buprenorphine, due to their relative novelty, there are fewer studies on lived experiences of LAIB, with studies in the United States (US), Australia and France reporting varied perspectives. In previous research, people have reported that perceived benefits of LAIB include improved choice, reduced travel, clinic and pharmacy attendance, and potential for reduced stigma and discrimination compared to supervised daily consumption. However, people also identified concerns regarding their loss of control over their medication, reduced bodily autonomy and agency, isolation due to reduced therapeutic contact and potential adverse side effects [29-32]. LAIB was also shown to be appealing as an alternative to sublingual buprenorphine, with another US study finding that LAIB preparations appealed to more than half of individuals with OUD entering opioid treatment [33]. Real-world evaluations of LAIB with high-risk populations in the US have also reported positive outcomes with people choosing to continue using LAIB, the majority of individuals (65%) tolerating LAIB well and experiencing no symptoms of precipitated withdrawal or ongoing opioid use [34].

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In another study in people with OUD in France, interest in LAIB relative to other MOUD was related to perceived valued treatment outcomes. Individuals who showed interest in LAIB were more focused on outcomes related to recovery and abstinence, reported more frequent forgetting of their MOUD, or reported negative situations in which taking their MOUD wasn't practical or appropriate [35]. This was also reflected in a study in Australia where positive perceptions of LAIB were associated with being female, recent illicit drug use and perceived (in)convenience of current OUD treatment [36]. Moreover, a recent qualitative narrative synthesis of LAIB studies (N = 15) identified six themes from patient perspectives and patient reported outcomes. These included LAIB being associated with increased abstinence and reduced cravings, improved accessibility, increased productivity and participation in work, reduced acquisitive crime and improved social relationships. Within the review it was also identified that misinformation and mistrust were potential barriers to LAIB, and that LAIB could negatively affect some social relationships by, for example, removing the daily support of supervised consumption [37].

Our study concerns Buvidal®, which is an LAIB product typically initiated on a weekly basis with subsequent transfer to monthly injections [38,39]. Efficacy has been demonstrated in a double-blind, double-dummy, randomised phase-III-study with 428 individuals, which found Buvidal® to be non-inferior to sublingual buprenorphine with regard to primary (opioid use) and secondary (opioid free urine screening) outcomes [26]. Similar results were obtained in the UK in a phase III randomised control trial where LAIB (Sublocade®) was clinically superior compared to sublingual buprenorphine and methadone, resulting in increased abstinence from opioids, though it was not cost effective for the majority of participants. It was however identified as more effective and less costly in participants with longer treatment episodes (>28 days) and those with more severe OUD [40]. A systematic review and meta-

analysis conducted in the UK examining efficacy, safety and tolerability data of Buvidal® concluded that Buvidal® is safe, effective and improves retention compared to sublingual buprenorphine or placebo [41]. In terms of UK individual perspectives on Buvidal®, two qualitative studies [31,32] and a service evaluation [9] yielded consistent demand and perceived positive outcomes.

While it is clear that people with OUD perceive initiation of LAIB positively, and if initiated on LAIB report positive experiences [42], little is known about actual impacts of Buvidal® prescribing on actual patient outcomes in the UK. Person-centred phase III trials of other LAIB products (Sublocade®) in the US have demonstrated significant improvements in self-reported Quality of Life (QoL), increased employment and decreased healthcare utilisation relative to placebo and baseline, though there was no comparison with traditional oral MOUD [43,44]. These positive outcomes are supported elsewhere in the UK, where pilot studies have demonstrated that transition from oral MOUD to LAIB is feasible and acceptable for people with OUD accessing services in South Wales [45], with qualitative studies reporting positive subjective outcomes in four services in England and Wales [46].

While there is qualitative evidence that LAIB results in improved outcomes for people with OUD, not all services in England offer LAIB to all eligible clients due to budget constraints. Between 2013-14 and 2023-24, there has been an average reduction of 50% in funding for UK substance use treatment [47]. As a result, some people may be selected for LAIB treatment based on personal, social and individual characteristics (i.e. those who are perceived to be a good investment based on whether they are stable), which could increase health inequalities in substance use treatment [48,49]. For example, Black people with substance use disorders in the UK may be disproportionately affected by this prioritisation because they are more

likely to be living in poverty, unemployed or homeless and may therefore be deemed a less economically efficient option for initiation of LAIB [50]. This remains an issue for service providers despite recent health economic studies in England suggesting that initiation of LAIB results in overall reduction of direct (delivery, medication, psychosocial treatment) and indirect (e.g. criminal justice system, health care utilisation) treatment costs [51]. Thus, in addition to investigating if LAIB is associated with improved outcomes, one aim of the present study was to investigate if there are any health inequalities in initiation of LAIB by understanding individual and demographic predictors (e.g. social deprivation, ethnicity, age) of being initiated on LAIB vs. other MOUD.

In summary, to date there has not been a large quantitative evaluation of outcome data for people accessing services in England for OUD and being prescribed LAIB compared to oral MOUD. The objective of this study is to compare outcomes and predictors for people prescribed Buvidal® vs. oral MOUD. To do this we undertook a retrospective analysis of quantitative data from an English substance use treatment provider (Via), analysing sociodemographic characteristics to identify who is most likely to be prescribed Buvidal® and comparing person-level outcomes for individuals who were prescribed Buvidal® with a matched control of people on oral MOUD.

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**Method**

*Design, Setting and Study Population*

We conducted a cross-sectional comparison of anonymised electronic records from substance use treatment provider Via. Data from six Via services were included in our analyses. The data controller provided us with routinely collected person-level sociodemographic data, prescribing data, substance use data and physical and mental health assessment scores from the Treatment Outcome Profile (TOP) assessments. During the 12-month period, individuals completed TOPs at every contact with Via which allows comparison of changes in TOPs scores over the time period.

People were eligible to be included in the analysis if they were aged over 18 years, a Via service user in the last 12 months (15/08/2022 and 15/08/2023) and if they were either currently being prescribed Buvidal®, or if they were a control on another MOUD. Data was extracted for 235 individuals who were currently receiving a Buvidal® prescription and 266 matched individuals who were receiving another MOUD (total N = 501). Matched controls were selected using the following procedure. We were provided with the patient identification and demographic information of 2,048 individuals who received oral MOUD. We used gender, ethnicity and primary substance of use as stratifiers to obtain a smaller sample (which reflected the balance of these stratifiers), using the 'stratified' function from the 'splitstackshape' package in R [52]. We aimed for a similar sample size to our Buvidal sample, which would still provide us with appropriate statistical power. We then provided the patient identifiers of the stratified sample to Via, who provided us with the TOPs and prescribing data for these individuals. We were unable to request data from all 2,048 individuals due to limited resources. Our overall sample size allowed us to detect small

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effect sizes between the groups on TOP scores ( $d \sim .25$ ) with 80% power and an alpha of .05 (independent samples t-test: one-tailed).

We reviewed the medicine scripts to allow us to summarise the most commonly prescribed Buvidal® and other MOUD dosages. For most individuals, dose changed over the 1-year period, and for some people in the oral MOUD group, type of MOUD changed. Based on information on the medicine scripts, the most common dose of Buvidal® was 64 mg prolonged release solution (27.8%), followed by 96 mg prolonged release solution (26.6%) and 128 mg prolonged release (17.5%). For other MOUD, the most common medication and dose was Methadone 1mg/ml oral solution (52.5%), followed by Buprenorphine 2mg sublingual tablets (19.7%).

#### *Patient and Public Involvement*

DDS is manager of the Via Innovation and Research Unit and was responsible for coordinating the PPI in this study. DDS engaged with people with opioid use disorder and clinicians in Via services to discuss the planned study. During analysis, DDS involved people with opioid use disorder and clinicians in discussions about the qualitative nature of changes in psychological wellbeing to allow us to accurately contextualise the results for people with lived experience of opioid use disorder.

#### *Measures*

Prescribing Data: Data was extracted from the pharmacy system (Nebula) for each individual over the 1-year period including the start date, end date, dose and name/strength for each prescribed medication.

Sociodemographic information: Routinely collected data including age, sex, Indices of Multiple Deprivation (IMD) decile of patient residence, primary and secondary substance,

number of previous treatment episodes, employment status and ethnicity were extracted from the Via Case Management System (CMS).

Outcome variables of interest:

TOP scores were used to assess changes in substance use, mental and physical health and QoL. The TOP is a standardised tool used in all UK substance use treatment settings to collect routine data at treatment entry and at set time points over the treatment journey (routinely at baseline, every 3 months until treatment exit; 3 & 6 months post treatment exit). The tool is comprised of a set of 20 psychometrically valid outcome measures [53] which have been shown to have good inter-rater reliability and test-retest reliability [54]. We used the routinely collected TOPs data to assess substance use (number of days using opiates/opioids in the last month; number of days injecting in the last month), psychological health, physical health and QoL (visual analogue scale from 0 = poor to 20 = good), number of days in paid employment in the last month and number of days in education in the last month.

Our TOPs analysis was limited to data collected between 15-08-2022 to 15-08-2023. As it was possible to have multiple TOP assessments in this period, we created two different outcome variables based on the TOP scores. If multiple assessments were taken during the one-year period (N = 383), we calculated a *TOPs change score* (the difference between the first and last assessment) to examine any change in TOPs scores during the time period. Secondly, we created a *summary TOPs score* for each outcome during the assessment period (the average for each TOP variable if multiple assessments were taken). Using this method, we analysed only psychological health, physical health and QoL TOPs scores.



Analyses for the *summary TOPs* score are reported in Supplementary file S1, containing supplementary Table 4 and Supplementary Figure 2.

We could not calculate change scores or summary scores for the TOP substance use and employment variables (opioid use, Intravenous (IV) drug use and paid work in the last 28 days) as they were largely 0 counts. For these variables we created a binary variable to identify whether any opioid use, IV drug use or paid employment was reported.

### *Procedure*

After gaining institutional ethical approval (LJMUREC 23/PSY/036), a Data Sharing Agreement was established between Liverpool John Moores University (LJMU) and Via. In Phase 1, pseudonymised demographic data for people receiving Buvidal® and oral MOUD was downloaded from Via's CMS and uploaded to a secure shared folder on CM's university file store. In Phase 2, full prescribing and outcome data for all individuals prescribed Buvidal®, and the selected controls was downloaded from Via's CMS into a Microsoft Excel file and uploaded to a secure folder on CM's file store and shared with the research team for analysis (CM & AJ).

### *Data Analysis*

To examine predictors of receiving Buvidal® compared to oral MOUD we conducted a logistic regression. We included available demographic information. Despite stratifying based on sex, ethnicity and primary substance we included these in the regression to hold them constant. For the logistic models we report Odds Ratios and 95% confidence intervals as parameter estimates.

Psychological health, physical health and QoL scores were analysed using Welch's t-tests. In adjusted models we conducted linear regressions including the demographic

predictors (age, employment, ethnicity, age of first substance, number of episodes, sex and IMD) to predict the TOPs change scores for psychological health, physical health and QoL (comparable analyses for summary scores can be found in supplementary file S1). There were some missing data for IMD (N = 34 / 6.7%) and age of first use (N = 20 / 4.0%). Missing data for IMD was likely reflective of people with no fixed abode (e.g. those experiencing street homelessness) and therefore was not missing at random. As such we did not conduct multiple imputation analyses as this may serve to increase possible bias [55]. However, we conduct all adjusted analyses with these variables removed as sensitivity analyses, and any deviation from adjusted analyses with these variables included is noted. For opioid use and IV drug use, we conducted logistic regressions in which any amount of opioid use or IV drug use recorded was coded as 1.

Data and analysis code for the study can be found here: [dataset]

<https://opendata.ljmu.ac.uk/id/eprint/182>

**Results**

*Baseline Characteristics of participants:*

The baseline characteristics of individuals can be found in Table 1. Of the 235 individuals receiving Buvidal®, 60 (25.5%) were female, 185 (78.7%) identified as White ethnicity, with the majority (186 clients – 79.1%) reporting illicit heroin as their primary substance. Of the 266 individuals receiving MOUD, 67 (25.2%) were female, 187 (70.3%) identified as White ethnicity, with the majority (220 clients – 82.7%) reporting illicit heroin as their primary substance. There were significant differences between the groups in current age ( $t(498.6) = 4.81, p < .001, d = .43$  [95% CI: .25 to .61], number of previous treatment episodes ( $t(463.6) = 3.40, p < .001, d = .31$  [95% CI: .13 to .48] and regular employment ( $X^2(1) = 6.27, p = .012$ )

with individuals who were receiving Buvidal® being significantly younger, having more previous treatment episodes and having higher levels of regular employment.

*Table 1: Demographic breakdown of individuals prescribed Buvidal® vs compared to oral MOUD. Total N = 501.*

	Buvidal®	Other
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
<b>Current Age</b>	<b>43.17 (9.00)</b>	<b>47.23 (9.89)</b>
Age of first substance	22.44 (6.93)	23.36 (9.10)
<b>Number of episodes</b>	<b>1.86 (1.21)</b>	<b>1.52 (1.04)</b>
IMD	4.43 (2.53)	4.54 (2.35)
	<i>N (%)</i>	<i>N (%)</i>
<i>Ethnicity</i>		
White	185 (78.7%)	213 (80.4%)
Asian / British Asian	27 (11.5%)	22 (8.3%)
Black /Black British / African	13 (5.5%)	7 (2.6%)
Mixed / Multiple	3 (1.3%)	9 (3.4%)
Unknown / Other	7 (3.0%)	14 (5.3%)
<i>Employment</i>		
<b>Regular Employment</b>	<b>55 (23.4%)</b>	<b>38 (14.3%)</b>
<b>Other</b>	<b>180 (76.6%)</b>	<b>228 (85.7%)</b>
<i>Sex</i>		
Female	60 (25.5%)	67 (25.2%)
Male	175 (74.5%)	199 (74.8%)
<i>Primary Substance</i>		
Illicit Heroin	186 (79.1%)	220 (82.7%)
Other	49 (20.9%)	46 (17.3%)
<i>Secondary Substance</i>		
Cocaine (Crack)	122 (51.9%)	120 (45.1%)
No Second Substance	56 (23.8%)	78 (29.3%)
Other	57 (24.3%)	68 (25.6%)

Note – variables with categorical response are simplified due to large number of categories with small numbers of individuals within some categories. Reference categories were chosen based on the largest number (e.g. White, illicit heroin). In the case of the employment variable, regular employment was not the most common category, but the ‘other’ comparison represents a lot of similar categories (e.g. ‘retired’, ‘unemployed’, ‘homemaker’). IMD was also missing from 34 individuals due to having no fixed address or this not information being available. Variables in **bold** indicate a significant difference between the groups (Buvidal® compared to oral MOUD).

*Predictors of Buvidal® prescribing*

We included 8 variables in the logistic regression model to examine whether any predicted the increased/decreased odds of being prescribed Buvidal®. These variables were; current age, employment (currently employed vs not), ethnicity (white vs other), age of first substance, number of episodes, client sex at registration of birth (sex - male vs female), IMD, and primary substance (illicit heroin pared to other substances). See Table 2, for model parameters. The overall model was able to predict around 7% of variance in the outcome. Individuals of a younger age, who were regularly employed, and had increased number of episodes, had increased odds of being prescribed Buvidal® (compared to other MOUD).

*Table 2: Logistic regression analysis examining predictors of being prescribed Buvidal® (compared to oral MOUD).*

<i>Predictors</i>	<b>Buvidal® (compared to oral MOUD)</b>		
	<i>Odds Ratios</i>	<i>CI</i>	<i>p</i>
<b>Current age</b>	<b>0.96</b>	<b>0.94 – 0.98</b>	<b>&lt;0.001</b>
<b>Employment [Regular Employment]</b>	<b>1.89</b>	<b>1.13 – 3.19</b>	<b>0.016</b>
Ethnicity [White British]	0.93	0.57 – 1.51	0.755
Age of first substance	1.00	0.98 – 1.03	0.880
<b>Number of episodes</b>	<b>1.38</b>	<b>1.15 – 1.68</b>	<b>0.001</b>
Sex [Male]	1.00	0.62 – 1.57	0.964

Primary substance [Other]	1.02	0.61 – 1.71	0.929
IMD	0.97	0.89 – 1.05	0.461
R <sup>2</sup> (Pseudo)			0.079

#### *Difference in TOPs Scores (Figure 1)*

For psychological health and physical health, there was no significant difference between individuals who were and were not prescribed Buvidal®  $t(390.96) = 1.57$ ,  $p = .12$ ,  $d = -.16$ ;  $t(385.04) = 0.64$ ,  $p = .52$ ,  $d = .06$  respectively. For QoL there was a significant difference, in that individuals who were prescribed Buvidal® reported positive change in QoL compared to other treatment  $t(381.57) = 2.21$ ,  $p = .03$ ,  $d = .22$ ; mean improvement Buvidal® = 1.40, mean improvement other = 0.52.

<<Insert Figure 1 here>>

In adjusted models there were no significant predictors of change in Psychological Health ( $R^2 = .00$ ), Physical Health ( $R^2 = .00$ ) or QoL ( $R^2 = .02$ ), though there was a trend for current age being negatively related to psychological health and IMD decile positively related to physical health. In adjusted models, Buvidal® was a marginally non-significant predictor of QoL ( $p = .051$ ) (see Table 3). In models with IMD and age of first use removed, Buvidal remained a non-significant predictor in all models; however, being of white ethnicity was associated with an improved QoL ( $B = -1.00$  [95% CI: -2.00 - -0.01],  $p = .048$ ) and physical health ( $B = -1.11$  [95% CI: -2.14 - -0.07],  $p = .036$ ). Age was a significant predictor of psychological health ( $B = -0.05$  [95% CI: -.010 - -0.01],  $p = .019$ ).

Table 3: Adjusted regression models for the effects of Buprenorphine vs other MOUD on TOP outcomes.

	Psychological Health		Physical Health		Quality of Life	
Predictors	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p
Medication [Other MOUD]	0.62 (-0.30 – 1.55)	0.185	0.31 (-0.60 – 1.23)	0.5	0.00 (-0.00 – 1.75)	0.051
Current age	-0.04 (-0.09 – 0.01)	0.092	-0.01 (-0.06 – 0.04)	0.642	-0.08 (-0.08 – 0.01)	0.168
Employment [Regular Employment]	0.15 (-0.99 – 1.28)	0.799	-0.25 (-1.38 – 0.87)	0.661	-1.63 (-1.63 – 0.52)	0.313
Ethnicity [Non White]	-0.02 (-1.14 – 1.10)	0.97	-0.83 (-1.94 – 0.28)	0.141	-1.97 (-1.97 – 0.15)	0.094
Age of first substance	0.01 (-0.05 – 0.07)	0.718	0.02 (-0.04 – 0.07)	0.515	0.03 (-0.03 – 0.08)	0.359
Number of episodes	-0.11 (-0.56 – 0.33)	0.608	-0.02 (-0.45 – 0.42)	0.946	0.01 (-0.41 – 0.43)	0.953
Sex [Female]	0.14 (-0.91 – 1.19)	0.79	-0.13 (-1.18 – 0.92)	0.806	0.06 (-0.94 – 1.06)	0.903
IMD	0 (-0.19 – 0.19)	0.997	0.17 (-0.02 – 0.35)	0.076	0.09 (-0.09 – 0.27)	0.314
Observations	354		354		354	
R <sup>2</sup> / R <sup>2</sup> adjusted	0.019 / 0.00		0.016 / 0.00		0.043 / 0.021	

IMD = Index of multiple deprivation; reference categories stated in []

### *TOPs substance use variables.*

There were 151 instances in which no opioid use was reported and 252 in which any was. The odds of decreased opioid use was not statistically significantly associated with Buvidal® (OR = 0.81 [95 CI: 0.54 to 1.23],  $p = .325$ ). In adjusted models the number of episodes was a significant positive predictor of increased opioid use OR = 1.40 [95% CI: 1.08 to 1.87],  $p = .016$ ).

There were 355 instances in which no IV drug use was reported and 38 instances in which it was. The odds of decreased IV use was not statistically significantly associated with Buvidal® (OR = 1.27 [95% CI: 0.65 to 2.52],  $p = .485$ ). Due to the small number of instances, an adjusted model was not possible.

### **Discussion**

In this study we compared TOPs outcomes for individuals prescribed Buvidal® vs. oral MOUD. While previous research has examined retention and efficacy of Buvidal® for treating OUD, there is comparatively little investigation of outcomes relating to individuals. This is one of the first large investigations of person-rated outcomes and demographic factors in people prescribed Buvidal® vs. oral MOUD. In our analyses, people who were prescribed Buvidal® were younger, more likely to be employed, and had more previous treatment episodes. Buvidal® was associated with positive changes in QoL over the treatment period. Supplementary analyses (see file S1) highlighted that overall people prescribed Buvidal® reported higher levels of psychological and physical health, and QoL compared to people receiving MOUD. Other demographic and situational factors were positive and negative predictors in these analyses indicating the intersectional nature of changes in health during recovery.

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The findings in this study reflect those in previous research. For example, when considering factors associated with Buvidal® prescribing, an evaluation of Buvidal® in West Lothian found that Buvidal® helped people consider employment, which is supported by higher employment in Buvidal® clients in the present study [57], although we did not find associations with sex as reported in previous research [36]. We were particularly interested in predictors of Buvidal® initiation in the present study as budget constraints in UK treatment services could increase health inequalities [48,49]. While we did not find evidence for inequalities in initiation of Buvidal® related to social deprivation (IMD), sex or ethnicity, we did find evidence that those who are younger, have more treatment episodes and are in regular employment are more likely to receive Buvidal®. This provides some tentative evidence that certain individual factors are associated with increased likelihood of receiving Buvidal® relative to oral MOUD. The finding for age is more concerning in terms of inequality as ageing populations of substance users are subject to greater levels of substance-related harms [59] but have been shown to achieve better treatment outcomes than their younger counterparts [60] and may also benefit from LAIB. In the present study we also identified that age was a significant negative predator of psychological health, indicating that older people may have unmet mental health needs and would benefit from LAIB initiation. However, one alternative explanation is that older people with OUD are reluctant to switch from methadone, a known entity, on to novel treatments. Substance treatment guidance in the UK suggests that people with longer OUD history (i.e. older individuals) or those with heightened withdrawal-related anxiety may prefer methadone to buprenorphine because of the sedative effect [61]. Thus we cannot say if older adults were not selected for, or declined, LAIB. Future research should seek to supplement the

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quantitative analyses with qualitative data to understand clinicians' and people with OUD's choice of treatment.

In our analyses of changes in self-reported outcomes over the 1-year period, Buvidal® was a significant predictor of changes in QoL, but not physical or mental health. In previous qualitative studies on acceptability of LAIB in people with OUD, one key theme that emerged was the perception that LAIB would allow individuals to get on with everyday life [32]. Indeed, analysis of person-level outcome measures in found that people on LAIB reported increased life satisfaction and improved self-care (specifically taking up sports and hobbies and improvements in mental health). Interestingly, 43% of individuals reported improved material resources such as employment while 86% (12 people) reported improved well-being [46] which are reflective of Buvidal®'s association with increased employment and QoL in the present study. However, previous studies in people using MOUD and sublingual buprenorphine [e.g., 60] have noted that initial improvements in QoL are not sustained over longer-term outcomes. Thus, further long-term analysis of the LAIB data is needed to assess if changes in QoL are sustained and if they are meaningful indicators of recovery. Inclusion of demographic predictors in the adjusted models reduced Buvidal® to just below statistical significance, indicating the intersectional nature of changes in QoL over the 1-year period. For example, in this analysis we identified that being of White ethnicity was associated with improved QoL and physical health, which indicates the role of ethnicity in treatment outcomes [48-50].

Supplementary analyses of summary TOPs scores indicated that psychological and physical health and QoL were positively predicted by Buvidal®, employment and being male. For physical health age was a negative predictor in the model (older people had worse

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physical health), while for QoL age of initiation was a positive predictor (people who started using later reported better QoL). Taken together, these results could reflect the concomitant effects of age (or indeed longer-term substance use) on wellbeing and long-term conditions [see 60 for review]. Finally, number of treatment episodes was a negative predictor of QoL indicating that more treatment episodes was associated with lower QoL. These analyses highlight some important individual characteristics related to treatment outcomes. For example, poorer self-reported outcomes for females compared to males is not in line with previous research [e.g. 36] and warrants further investigation.

This study had a number of limitations. Firstly, this was a time-limited study and we were only able to access data for a 1-year period within the scope of our funding. Thus, we were not able to fully investigate the associations between Buvidal® and treatment outcomes in terms of QoL, physical/mental health and employment beyond the treatment journey, and conversely relapse. There was insufficient data available to investigate individuals who were discharged from the treatment service during this time, and due to the cross-sectional nature, we could not include treatment duration in our analyses. Future research should investigate outcomes and treatment trajectories over a longer-time period taking in to account previous treatment episodes, durations and outcomes. We also believe that further studies should also look at societal impact outcomes, such as number of healthcare (e.g., GP, A&E) and police attendances, employment status, which we could not evaluate within the scope of the present study. Due to limited capacity to link all prescribing data within the Pharmacy team in Via, we statistically stratified our oral MOUD comparison group and selected 266 controls on oral MOUD. While we do not believe that these clients would have differed from the 1783 individuals on oral MOUD who were not selected, it remains a possibility that this sample differed in some way from the selected control group.

While we found significant improvements in QoL, and significant differences between the people prescribed Buvidal® in physical and mental health and QoL, the TOPs scales are visual analogue assessment scales, and there is no indication as to how or why individuals feel these indicators have changed on Buvidal®. Follow-up qualitative analyses would allow for the characterisation of these indices during recovery.

To our knowledge, this is the first large study to compare self-reported outcomes for individuals prescribed Buvidal® compared to oral MOUD. People initiated on Buvidal® were younger, more likely to be employed, had more previous treatment episodes, and relative to the people on oral MOUD, had significant improvements in QoL over the 1-year period. Future research should seek to investigate the aetiology of improved wellbeing using qualitative analysis and should perform a quantitative analysis of outcomes over a longer period to investigate the impacts of Buvidal® and intersectional characteristics on recovery outcomes.

### Figure Legends

*Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.*

*Figure 2 (supplementary file S2): Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.*

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### Author Contributions

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Montgomery and Abbasi designed the study with input from Jones, Van Hout and De Silva. Montgomery, Abbasi and De Silva applied for funding to support the study. Gittins coordinated the curation of the raw prescribing data. Jones performed the statistical analysis including data curation, analysis, analytical strategy, reporting, and drafting the results section. Van Hout performed a critical review of the literature. De Silva liaised with people with opioid dependence and clinicians to discuss the study and contextualise results. Montgomery produced the first draft of the manuscript and all authors have provided critical revisions and approved the final manuscript. Montgomery is the guarantor.

**Competing interests**

This study was funded by Camurus AB. The funder had no role in the design, planning, execution or analyses in this study. CM and MCVH also receive funding from CSL Seqirus. YA has received honorarium from Camurus, Newbridge Pharma and Ethypharm. AJ, RG and DDS report no conflict of interest.

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**Data sharing statement**

The data and analysis code for this study is available in the Liverpool John Moores University Data Repository: [dataset] <https://opendata.ljmu.ac.uk/id/eprint/182>

**Ethics approval statement**

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This was a retrospective data analysis of anonymised health records and was approved as minimal risk by Liverpool John Moores University Research Ethics Committee (LJMUREC 23/PSY/036).

For peer review only

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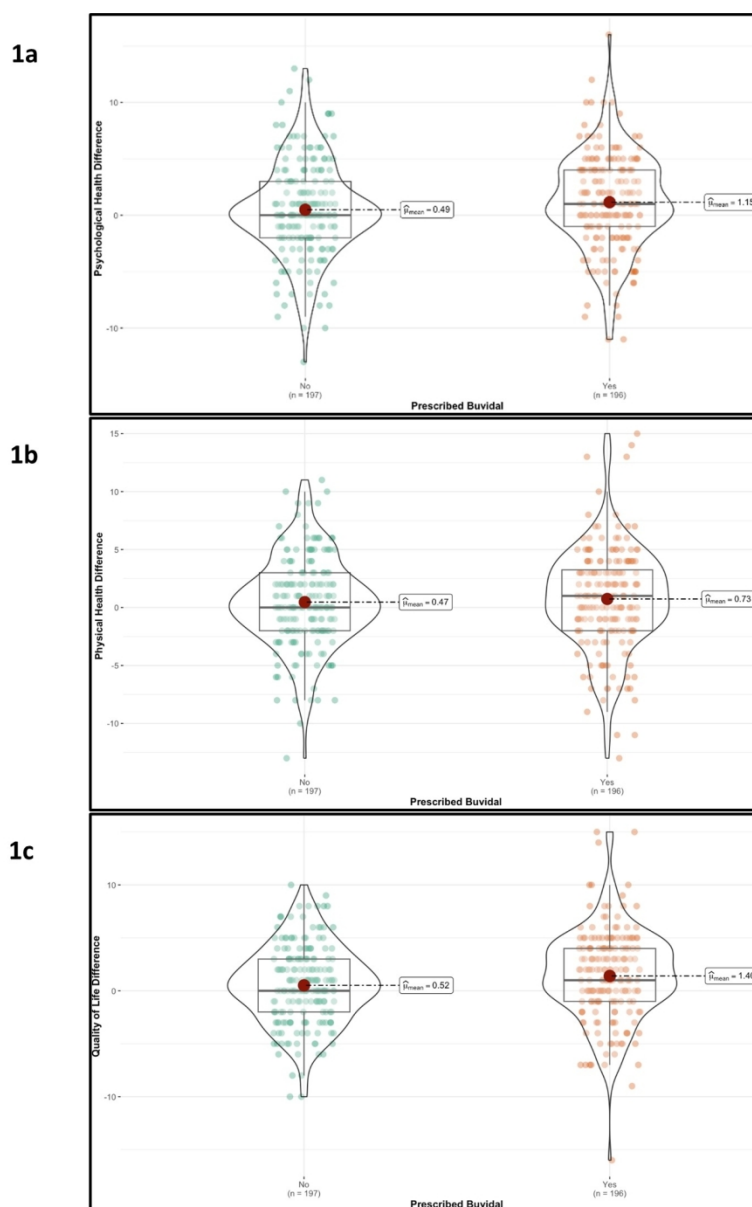


Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.

108x166mm (330 x 330 DPI)

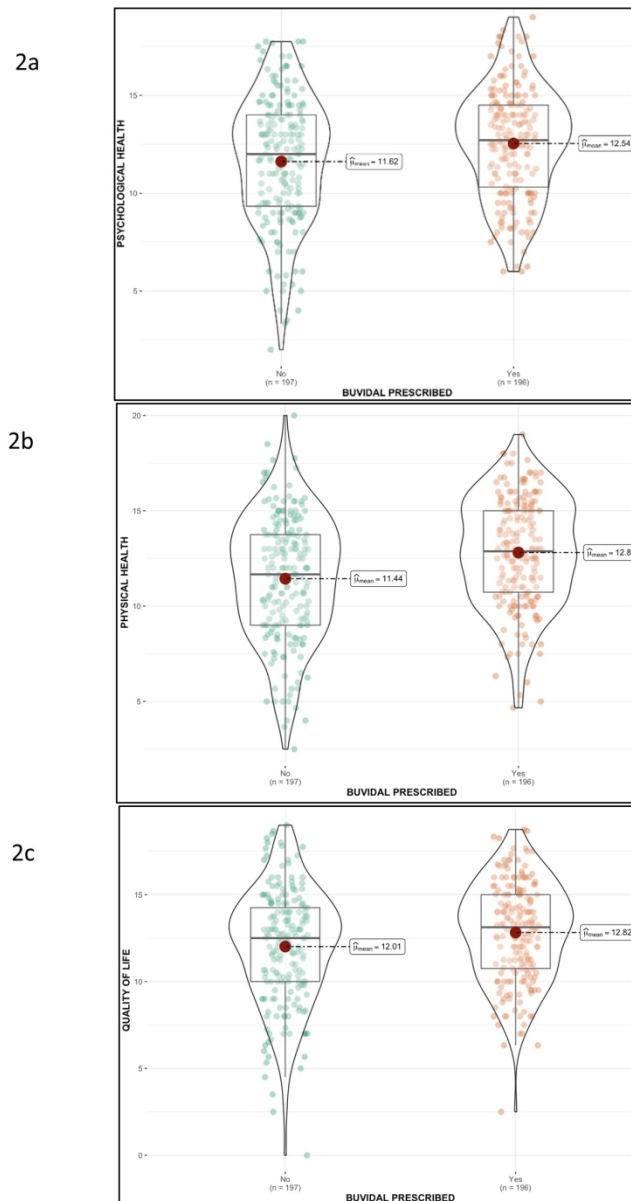


Figure 2: Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.

98x180mm (330 x 330 DPI)

Analysis of summary TOPS Scores

For psychological health (Figure 1a), physical health (Figure 1b) and QoL (Figure 1c) there were significantly greater health/QoL reports if people were prescribed Buvidal® (vs other MOUD):  $t(382.77) = 3.00$   $p < .001$ ,  $d = .30$ ),  $t(385) = 4.41$ ,  $p < .001$ ,  $d = .44$ ) and  $t(383) = 2.60$ ,  $p < .001$ ,  $d = .26$ ) respectively.

Figure 2: Psychological health (1a), physical health (1b) and Quality of Life in Buvidal® vs. compared to oral MOUD.

In adjusted models the variables explained approximately 7% (Adjusted  $R^2 = 0.07$ ) of variance in psychological health. Buvidal® was a significant positive predictor ( $B = .081$  [95% CI: 0.16 to 1.46],  $p = .015$ ), as was regular employment ( $B = 1.21$  [95% CI: 0.42 to 2.01],  $p = .003$ ), and being male ( $B = 1.23$  [95% CI: 0.49 to 1.97],  $p = .001$ ). Approximately 12% of variance was explained in physical health (Adjusted  $R^2 = 0.12$ ). Buvidal® was a significant positive predictor ( $B = 0.85$  [95% CI: 0.21 to 1.49],  $p = .009$ ), as was regular employment ( $B = 1.33$  [95% CI: 0.54 to 2.12],  $p = .001$ ) and being male ( $B = 1.09$  [95% CI: 0.36 to 1.82],  $p = .004$ ). Age was a negative predictor of physical health ( $B = -0.06$  [95% CI: -0.09 to -0.02],  $p = .001$ ). Approximately 11% of variance was explained in QoL (Adjusted  $R^2 = .11$ ). Buvidal® was a significant positive predictor ( $B = 0.77$  [95% CI: 0.13 to 1.42],  $p = .019$ ), as was regular employment ( $B = 1.80$  [95% CI: 1.01 to 2.59],  $p < .001$ ), being male ( $B = 1.04$  [95% CI: 0.31 to 1.77],  $p = .006$ ) and age of first substance use ( $B = 0.05$  [95% CI: 0.01 to 0.08],  $p = .025$ ). The number of episodes was a negative predictor of QoL ( $B = -0.35$  [95% CI: -0.04 to -0.65],  $p = .027$ ).

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Table 4

	Psychological Health			Physical Health			Quality of Life		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Buvidal [Yes]	0.81	0.16 – 1.46	<b>0.015</b>	0.85	0.21 – 1.49	<b>0.009</b>	0.77	0.13 – 1.42	<b>0.019</b>
Age	0.00	-0.03 – 0.04	0.791	-0.06	-0.09 – -0.02	<b>0.001</b>	-0.00	-0.04 – 0.03	0.947
Employment [Regular Employment]	1.21	0.42 – 2.01	<b>0.003</b>	1.33	0.54 – 2.12	<b>0.001</b>	1.80	1.01 – 2.59	<b>&lt;0.001</b>
Ethnicity [white]	-0.58	-1.37 – 0.21	0.149	-0.53	-1.31 – 0.24	0.178	-0.38	-1.15 – 0.40	0.344
Age of first substance	0.03	-0.01 – 0.07	0.168	0.03	-0.01 – 0.07	0.136	0.05	0.01 – 0.08	<b>0.025</b>
Number of episodes	-0.23	-0.54 – 0.08	0.147	-0.23	-0.54 – 0.07	0.132	-0.35	-0.65 – -0.04	<b>0.027</b>
Gender [Male]	1.23	0.49 – 1.97	<b>0.001</b>	1.09	0.36 – 1.82	<b>0.004</b>	1.04	0.31 – 1.77	<b>0.006</b>
IMD	-0.03	-0.16 – 0.11	0.693	-0.05	-0.18 – 0.08	0.430	-0.08	-0.21 – 0.05	0.227
R <sup>2</sup> / R <sup>2</sup> adjusted	0.102 / 0.081			0.144 / 0.124			0.131 / 0.111		

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# BMJ Open

## Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

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Date Submitted by the Author:	22-Dec-2024
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<b>Primary Subject Heading</b>:	Addiction
Secondary Subject Heading:	Mental health, Patient-centred medicine, Public health
Keywords:	Substance misuse < PSYCHIATRY, Quality of Life, Health

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Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

Authors: <sup>1</sup>Catharine Montgomery, <sup>2</sup>Yasir Abbasi, <sup>1</sup>Andrew Jones, <sup>2</sup>Devon De Silva, <sup>3</sup>Rosalind Gittins & <sup>4</sup>Marie Claire Van Hout

Corresponding author: C Montgomery, [C.A.Montgomery@ljmu.ac.uk](mailto:C.A.Montgomery@ljmu.ac.uk)

Affiliations:

<sup>1</sup>School of Psychology, Liverpool John Moores University, UK.

<sup>2</sup>Via, 18 Dartmouth Street, London, UK.

<sup>3</sup>School of Pharmacy, Aston University, UK.

<sup>4</sup>School of Public and Allied Health, Liverpool John Moores University, UK.

Qualifications and Titles:

C Montgomery: PhD, PgCert LTHE, BSc (Hons), Reader in Psychopharmacology, Head of Institute for Health Research.

Y Abbasi: MB BS, FRCPsych, PG Cert, PG Dip, EDPM, Executive Medical Director & Consultant Addiction Psychiatrist

A Jones: PhD, Senior Lecturer in Psychology.

D De Silva: BA. IRU Manager.

R Gittins: MRPharmS (Hons) MSc CertPsychPharm MCMHP IP, Senior Lecturer.

MC Van Hout: PhD, LLM, M.Sc Health Professions Education, M.Sc Health Promotion, M.Sc International Addictions. PVC Research and Knowledge Exchange.

ORCID IDs:

Catharine Montgomery: 0000-0003-2805-5807

Yasir Abbasi: 0000-0002-4981-7914

Andrew Jones: 0000-0001-5951-889X

Rosalind Gittins: 0000-0002-0893-7936

Marie Claire Van Hout: 0000-0002-0018-4060

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**Abstract**

*Objectives:* Advances in the treatment of opioid use disorder have seen the development of long-acting injectable opioid substitutes which could improve outcomes for people with opioid use disorder. However, comparative quantitative analysis of individual outcomes is lacking. The present study sought to investigate factors associated with prescribing of the Long-Acting Injectable Buprenorphine preparation Buvidal®, and changes in outcome variables compared to oral medication for opioid use disorder.

*Design:* Cross-sectional retrospective analysis of electronic health records.

*Setting:* Community substance use treatment service Via. Six sites shared their data between 15/08/2022 – 15/08/2023.

*Participants:* Anonymised data was extracted for 235 people receiving Buvidal® and 266 people receiving oral medication for opioid use disorder.

*Primary and secondary outcomes:* Prescribing data, sociodemographic information (age, sex, IMD decile of individual’s residence, primary and secondary substance, number of previous treatment episodes, employment and ethnicity) and Treatment Outcome Profiles (substance use, physical and mental health, quality of life, employment) were extracted and analysed. To examine predictors of receiving Buvidal® (vs medication for opioid use disorder) we conducted logistic regression including the demographic predictors. Psychological health, physical health and quality of life scores were analysed using Welch’s t-tests.

*Results:* Buvidal® was associated with positive changes in quality of life between first and last assessments. Demographic and situational factors were predictors of Buvidal® initiation, indicating the potential for increasing health inequalities in substance use treatment.

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3 *Conclusions:* Buvidal® is associated with changes in quality of life over a 1-year period.  
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6 Further research is needed to investigate the aetiology of improved wellbeing and outcomes  
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**MeSH Keywords**

Opiate dependence; buprenorphine; opiate substitution treatment; psychological wellbeing; quality of life; Long-acting injection; opioid related disorders; Long-Acting Injectable Buprenorphine.

**Article Summary**

Strengths and Limitations of this study

- This analysis provides a characterisation of how standardised outcomes change in a one-year period of treatment for opioid use disorder.
- The analysis incorporates individual, demographic and situational factors to allow us to assess health inequalities in initiation of treatment.
- The data is limited in that it only gives us a snapshot of subjective wellbeing over a 1-year period.
- The data cannot tell us qualitatively *how* quality of life and perceived psychological wellbeing changed in the Buvidal® vs. medication for opioid use disorder groups.

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## Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing disorder causing clinically significant distress or impairment and includes opioid dependence, with addiction representing the most severe form of OUD [1,2]. Additional adverse health complications of OUD causing morbidity and mortality centre on blood-borne virus infection (HIV, hepatitis C), overdose, accidents, suicide, and poly use of other drugs [3-5]. OUD is treated with opioid substitutes as first line treatment (usually with methadone or buprenorphine) [6-9] though pharmacological treatment is advised to be integrated within a global therapeutic model focused on recovery and including psycho-social support [10]. Research has demonstrated that treatment with opioid agonist medications such as methadone or buprenorphine reduces mortality by around 50% in people with OUD [11-13] with reductions in overdose deaths and all-cause mortality for those retained in treatment [14]. While effective engagement and retention is crucial for better treatment outcomes including reduced opioid use [5] and reduced risk behaviours [15], high rates of drop out are observed in the early phases of treatment [16,17]. Premature disengagement, particularly in the first month of treatment and post treatment completion, is associated with significant increases in mortality risk [18,3]. Thus there is a need to understand if different Medications for Opioid Use Disorder (MOUD) are better at promoting treatment retention and improving outcomes.

Despite methadone and buprenorphine being associated with lower mortality, there are a number of individual factors which can limit the impact of these OUD treatment modalities. For example, people with OUD report that daily mandatory consumption can impact upon wellbeing and opportunities for employment [19,20] and increase stigma and discrimination [21]. In recent years extended-release subcutaneous injectable buprenorphine

formulations (Long-Acting Injectable Buprenorphine; LAIB) have been proposed as offering improved rates of retention and adherence [22-24]. LAIB preparations have the potential to be highly effective due to their long-acting bioavailability and limited risk of diversion [25,26]. Moreover, they are ideal for individuals who do not wish to take daily oral doses, people living in rural areas, people in places where safe storage is problematic (e.g. people experiencing street homelessness), or people who are at increased risk of overdose, after, for example, release from prison or hospital [27]. In one study, LAIB has been shown to be more effective at increasing abstinence than placebo plus counselling alone [28] which the authors suggest is due to the reduction of risk of missed doses due to medication loss, lapses or diversion.

While there is an evidence base for patient experiences of using methadone and sublingual buprenorphine, due to their relative novelty, there are fewer studies on lived experiences of LAIB, with studies in the United States (US), Australia and France reporting varied perspectives. In previous research, people have reported that perceived benefits of LAIB include improved choice, reduced travel, clinic and pharmacy attendance, and potential for reduced stigma and discrimination compared to supervised daily consumption. However, people also identified concerns regarding their loss of control over their medication, reduced bodily autonomy and agency, isolation due to reduced therapeutic contact and potential adverse side effects [29-32]. LAIB was also shown to be appealing as an alternative to sublingual buprenorphine, with another US study finding that LAIB preparations appealed to more than half of individuals with OUD entering opioid treatment [33]. Real-world evaluations of LAIB with high-risk populations in the US have also reported positive outcomes with people choosing to continue using LAIB, the majority of individuals (65%) tolerating LAIB well and experiencing no symptoms of precipitated withdrawal or ongoing opioid use [34].

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In another study in people with OUD in France, interest in LAIB relative to other MOUD was related to perceived valued treatment outcomes. Individuals who showed interest in LAIB were more focused on outcomes related to recovery and abstinence, reported more frequent forgetting of their MOUD, or reported negative situations in which taking their MOUD wasn't practical or appropriate [35]. This was also reflected in a study in Australia where positive perceptions of LAIB were associated with being female, recent illicit drug use and perceived (in)convenience of current OUD treatment [36]. Moreover, a recent qualitative narrative synthesis of LAIB studies (N = 15) identified six themes from patient perspectives and patient reported outcomes. These included LAIB being associated with increased abstinence and reduced cravings, improved accessibility, increased productivity and participation in work, reduced acquisitive crime and improved social relationships. Within the review it was also identified that misinformation and mistrust were potential barriers to LAIB, and that LAIB could negatively affect some social relationships by, for example, removing the daily support of supervised consumption [37].

Our study concerns Buvidal®, which is an LAIB product typically initiated on a weekly basis with subsequent transfer to monthly injections [38,39]. Efficacy has been demonstrated in a double-blind, double-dummy, randomised phase-III-study with 428 individuals, which found Buvidal® to be non-inferior to sublingual buprenorphine with regard to primary (opioid use) and secondary (opioid free urine screening) outcomes [26]. Similar results were obtained in the UK in a phase III randomised control trial where LAIB (Sublocade®) was clinically superior compared to sublingual buprenorphine and methadone, resulting in increased abstinence from opioids, though it was not cost effective for the majority of participants. It was however identified as more effective and less costly in participants with longer treatment episodes (>28 days) and those with more severe OUD [40]. A systematic review and meta-

analysis conducted in the UK examining efficacy, safety and tolerability data of Buvidal® concluded that Buvidal® is safe, effective and improves retention compared to sublingual buprenorphine or placebo [41]. In terms of UK individual perspectives on Buvidal®, two qualitative studies [31,32] and a service evaluation [9] yielded consistent demand and perceived positive outcomes.

While it is clear that people with OUD perceive initiation of LAIB positively, and if initiated on LAIB report positive experiences [42], little is known about actual impacts of Buvidal® prescribing on actual patient outcomes in the UK. Person-centred phase III trials of other LAIB products (Sublocade®) in the US have demonstrated significant improvements in self-reported Quality of Life (QoL), increased employment and decreased healthcare utilisation relative to placebo and baseline, though there was no comparison with traditional oral MOUD [43,44]. These positive outcomes are supported elsewhere in the UK, where pilot studies have demonstrated that transition from oral MOUD to LAIB is feasible and acceptable for people with OUD accessing services in South Wales [45], with qualitative studies reporting positive subjective outcomes in four services in England and Wales [46].

While there is qualitative evidence that LAIB results in improved outcomes for people with OUD, not all services in England offer LAIB to all eligible clients due to budget constraints. Between 2013-14 and 2023-24, there has been an average reduction of 50% in funding for UK substance use treatment [47]. As a result, some people may be selected for LAIB treatment based on personal, social and individual characteristics (i.e. those who are perceived to be a good investment based on whether they are stable), which could increase health inequalities in substance use treatment [48,49]. For example, Black people with substance use disorders in the UK may be disproportionately affected by this prioritisation because they are more

likely to be living in poverty, unemployed or homeless and may therefore be deemed a less economically efficient option for initiation of LAIB [50]. This remains an issue for service providers despite recent health economic studies in England suggesting that initiation of LAIB results in overall reduction of direct (delivery, medication, psychosocial treatment) and indirect (e.g. criminal justice system, health care utilisation) treatment costs [51]. Thus, in addition to investigating if LAIB is associated with improved outcomes, one aim of the present study was to investigate if there are any health inequalities in initiation of LAIB by understanding individual and demographic predictors (e.g. social deprivation, ethnicity, age) of being initiated on LAIB vs. other MOUD.

In summary, to date there has not been a large quantitative evaluation of outcome data for people accessing services in England for OUD and being prescribed LAIB compared to oral MOUD. The objective of this study is to compare outcomes and predictors for people prescribed Buvidal® vs. oral MOUD. To do this we undertook a retrospective analysis of quantitative data from an English substance use treatment provider (Via), analysing sociodemographic characteristics to identify who is most likely to be prescribed Buvidal® and comparing person-level outcomes for individuals who were prescribed Buvidal® with a matched control of people on oral MOUD.

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**Method**

*Design, Setting and Study Population*

We conducted a cross-sectional comparison of anonymised electronic records from substance use treatment provider Via. Data from six Via services were included in our analyses. The data controller provided us with routinely collected person-level sociodemographic data, prescribing data, substance use data and physical and mental health assessment scores from the Treatment Outcome Profile (TOP) assessments. During the 12-month period, individuals completed TOPs at every contact with Via which allows comparison of changes in TOPs scores over the time period.

People were eligible to be included in the analysis if they were aged over 18 years, a Via service user in the last 12 months (15/08/2022 and 15/08/2023) and if they were either currently being prescribed Buvidal®, or if they were a control on another MOUD. Data was extracted for 235 individuals who were currently receiving a Buvidal® prescription and 266 matched individuals who were receiving another MOUD (total N = 501). Matched controls were selected using the following procedure. We were provided with the patient identification and demographic information of 2,048 individuals who received oral MOUD. We used gender, ethnicity and primary substance of use as stratifiers to obtain a smaller sample (which reflected the balance of these stratifiers), using the 'stratified' function from the 'splitstackshape' package in R [52]. We aimed for a similar sample size to our Buvidal sample, which would still provide us with appropriate statistical power. We then provided the patient identifiers of the stratified sample to Via, who provided us with the TOPs and prescribing data for these individuals. We were unable to request data from all 2,048 individuals due to limited resources. Our overall sample size allowed us to detect small

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effect sizes between the groups on TOP scores ( $d \sim .25$ ) with 80% power and an alpha of .05 (independent samples t-test: one-tailed).

We reviewed the medicine scripts to allow us to summarise the most commonly prescribed Buvidal® and other MOUD dosages. For most individuals, dose changed over the 1-year period, and for some people in the oral MOUD group, type of MOUD changed. Based on information on the medicine scripts, the most common dose of Buvidal® was 64 mg prolonged release solution (27.8%), followed by 96 mg prolonged release solution (26.6%) and 128 mg prolonged release (17.5%). For other MOUD, the most common medication and dose was Methadone 1mg/ml oral solution (52.5%), followed by Buprenorphine 2mg sublingual tablets (19.7%).

#### *Patient and Public Involvement*

DDS is manager of the Via Innovation and Research Unit and was responsible for coordinating the PPI in this study. DDS engaged with people with opioid use disorder and clinicians in Via services to discuss the planned study. During analysis, DDS involved people with opioid use disorder and clinicians in discussions about the qualitative nature of changes in psychological wellbeing to allow us to accurately contextualise the results for people with lived experience of opioid use disorder.

#### *Measures*

Prescribing Data: Data was extracted from the pharmacy system (Nebula) for each individual over the 1-year period including the start date, end date, dose and name/strength for each prescribed medication.

Sociodemographic information: Routinely collected data including age, sex, Indices of Multiple Deprivation (IMD) decile of patient residence, primary and secondary substance,

number of previous treatment episodes, employment status and ethnicity were extracted from the Via Case Management System (CMS).

Outcome variables of interest:

TOP scores were used to assess changes in substance use, mental and physical health and QoL. The TOP is a standardised tool used in all UK substance use treatment settings to collect routine data at treatment entry and at set time points over the treatment journey (routinely at baseline, every 3 months until treatment exit; 3 & 6 months post treatment exit). The tool is comprised of a set of 20 psychometrically valid outcome measures [53] which have been shown to have good inter-rater reliability and test-retest reliability [54]. We used the routinely collected TOPs data to assess substance use (number of days using opiates/opioids in the last month; number of days injecting in the last month), psychological health, physical health and QoL (visual analogue scale from 0 = poor to 20 = good), number of days in paid employment in the last month and number of days in education in the last month.

Our TOPs analysis was limited to data collected between 15-08-2022 to 15-08-2023. As it was possible to have multiple TOP assessments in this period, we created two different outcome variables based on the TOP scores. If multiple assessments were taken during the one-year period (N = 383), we calculated a *TOPs change score* (the difference between the first and last assessment) to examine any change in TOPs scores during the time period. Secondly, we created a *summary TOPs score* for each outcome during the assessment period (the average for each TOP variable if multiple assessments were taken). Using this method, we analysed only psychological health, physical health and QoL TOPs scores.

Analyses for the *summary TOPs* score are reported in Supplementary file S1, containing supplementary Table 4 and Supplementary Figure 2.

We could not calculate change scores or summary scores for the TOP substance use and employment variables (opioid use, Intravenous (IV) drug use and paid work in the last 28 days) as they were largely 0 counts. For these variables we created a binary variable to identify whether any opioid use, IV drug use or paid employment was reported.

### *Procedure*

After gaining institutional ethical approval (LJMUREC 23/PSY/036), a Data Sharing Agreement was established between Liverpool John Moores University (LJMU) and Via. In Phase 1, pseudonymised demographic data for people receiving Buvidal® and oral MOUD was downloaded from Via's CMS and uploaded to a secure shared folder on CM's university file store. In Phase 2, full prescribing and outcome data for all individuals prescribed Buvidal®, and the selected controls was downloaded from Via's CMS into a Microsoft Excel file and uploaded to a secure folder on CM's file store and shared with the research team for analysis (CM & AJ).

### *Data Analysis*

To examine predictors of receiving Buvidal® compared to oral MOUD we conducted a logistic regression. We included available demographic information. Despite stratifying based on sex, ethnicity and primary substance we included these in the regression to hold them constant. For the logistic models we report Odds Ratios and 95% confidence intervals as parameter estimates.

Psychological health, physical health and QoL scores were analysed using Welch's t-tests. In adjusted models we conducted linear regressions including the demographic

predictors (age, employment, ethnicity, age of first substance, number of episodes, sex and IMD) to predict the TOPs change scores for psychological health, physical health and QoL (comparable analyses for summary scores can be found in supplementary file S1). There were some missing data for IMD (N = 34 / 6.7%) and age of first use (N = 20 / 4.0%). Missing data for IMD was likely reflective of people with no fixed abode (e.g. those experiencing street homelessness) and therefore was not missing at random. As such we did not conduct multiple imputation analyses as this may serve to increase possible bias [55]. However, we conduct all adjusted analyses with these variables removed as sensitivity analyses, and any deviation from adjusted analyses with these variables included is noted. For opioid use and IV drug use, we conducted logistic regressions in which any amount of opioid use or IV drug use recorded was coded as 1.

Data and analysis code for the study can be found here: [dataset]

<https://opendata.ljmu.ac.uk/id/eprint/182>

**Results**

*Baseline Characteristics of participants:*

The baseline characteristics of individuals can be found in Table 1. Of the 235 individuals receiving Buvidal®, 60 (25.5%) were female, 185 (78.7%) identified as White ethnicity, with the majority (186 clients – 79.1%) reporting illicit heroin as their primary substance. Of the 266 individuals receiving MOUD, 67 (25.2%) were female, 187 (70.3%) identified as White ethnicity, with the majority (220 clients – 82.7%) reporting illicit heroin as their primary substance. There were significant differences between the groups in current age ( $t(498.6) = 4.81, p < .001, d = .43$  [95% CI: .25 to .61], number of previous treatment episodes ( $t(463.6) = 3.40, p < .001, d = .31$  [95% CI: .13 to .48] and regular employment ( $X^2(1) = 6.27, p = .012$ )



with individuals who were receiving Buvidal® being significantly younger, having more previous treatment episodes and having higher levels of regular employment.

*Table 1: Demographic breakdown of individuals prescribed Buvidal® vs compared to oral MOUD. Total N = 501.*

	Buvidal®	Other
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
<b>Current Age</b>	<b>43.17 (9.00)</b>	<b>47.23 (9.89)</b>
Age of first substance	22.44 (6.93)	23.36 (9.10)
<b>Number of episodes</b>	<b>1.86 (1.21)</b>	<b>1.52 (1.04)</b>
IMD	4.43 (2.53)	4.54 (2.35)
	<i>N (%)</i>	<i>N (%)</i>
<i>Ethnicity</i>		
White	185 (78.7%)	213 (80.4%)
Asian / British Asian	27 (11.5%)	22 (8.3%)
Black /Black British / African	13 (5.5%)	7 (2.6%)
Mixed / Multiple	3 (1.3%)	9 (3.4%)
Unknown / Other	7 (3.0%)	14 (5.3%)
<i>Employment</i>		
<b>Regular Employment</b>	<b>55 (23.4%)</b>	<b>38 (14.3%)</b>
<b>Other</b>	<b>180 (76.6%)</b>	<b>228 (85.7%)</b>
<i>Sex</i>		
Female	60 (25.5%)	67 (25.2%)
Male	175 (74.5%)	199 (74.8%)
<i>Primary Substance</i>		
Illicit Heroin	186 (79.1%)	220 (82.7%)
Other	49 (20.9%)	46 (17.3%)
<i>Secondary Substance</i>		
Cocaine (Crack)	122 (51.9%)	120 (45.1%)
No Second Substance	56 (23.8%)	78 (29.3%)
Other	57 (24.3%)	68 (25.6%)

Note – variables with categorical response are simplified due to large number of categories with small numbers of individuals within some categories. Reference categories were chosen based on the largest number (e.g. White, illicit heroin). In the case of the employment variable, regular employment was not the most common category, but the ‘other’ comparison represents a lot of similar categories (e.g. ‘retired’, ‘unemployed’, ‘homemaker’). IMD was also missing from 34 individuals due to having no fixed address or this not information being available. Variables in **bold** indicate a significant difference between the groups (Buvidal® compared to oral MOUD).

Predictors of Buvidal® prescribing

We included 8 variables in the logistic regression model to examine whether any predicted the increased/decreased odds of being prescribed Buvidal®. These variables were; current age, employment (currently employed vs not), ethnicity (white vs other), age of first substance, number of episodes, client sex at registration of birth (sex - male vs female), IMD, and primary substance (illicit heroin pared to other substances). See Table 2, for model parameters. The overall model was able to predict around 7% of variance in the outcome. Individuals of a younger age, who were regularly employed, and had increased number of episodes, had increased odds of being prescribed Buvidal® (compared to other MOUD).

Table 2: Logistic regression analysis examining predictors of being prescribed Buvidal® (compared to oral MOUD).

Predictors	Buvidal® (compared to oral MOUD)		
	Odds Ratios	CI	p
Current age	0.96	0.94 – 0.98	<0.001
Employment [Regular Employment]	1.89	1.13 – 3.19	0.016
Ethnicity [White British]	0.93	0.57 – 1.51	0.755
Age of first substance	1.00	0.98 – 1.03	0.880
Number of episodes	1.38	1.15 – 1.68	0.001
Sex [Male]	1.00	0.62 – 1.57	0.964

Primary substance [Other]	1.02	0.61 – 1.71	0.929
IMD	0.97	0.89 – 1.05	0.461
R <sup>2</sup> (Pseudo)			0.079

#### *Difference in TOPs Scores (Figure 1)*

For psychological health and physical health, there was no significant difference between individuals who were and were not prescribed Buvidal®  $t(390.96) = 1.57$ ,  $p = .12$ ,  $d = -.16$ ;  $t(385.04) = 0.64$ ,  $p = .52$ ,  $d = .06$  respectively. For QoL there was a significant difference, in that individuals who were prescribed Buvidal® reported positive change in QoL compared to other treatment  $t(381.57) = 2.21$ ,  $p = .03$ ,  $d = .22$ ; mean improvement Buvidal® = 1.40, mean improvement other = 0.52.

<<Insert Figure 1 here>>

In adjusted models there were no significant predictors of change in Psychological Health ( $R^2 = .00$ ), Physical Health ( $R^2 = .00$ ) or QoL ( $R^2 = .02$ ), though there was a trend for current age being negatively related to psychological health and IMD decile positively related to physical health. In adjusted models, Buvidal® was a marginally non-significant predictor of QoL ( $p = .051$ ) (see Table 3). In models with IMD and age of first use removed, Buvidal remained a non-significant predictor in all models; however, being of white ethnicity was associated with an improved QoL ( $B = -1.00$  [95% CI: -2.00 - -0.01],  $p = .048$ ) and physical health ( $B = -1.11$  [95% CI: -2.14 - -0.07],  $p = .036$ ). Age was a significant predictor of psychological health ( $B = -0.05$  [95% CI: -.010 - -0.01],  $p = .019$ ).

Table 3: Adjusted regression models for the effects of Buprenorphine vs other MOUD on TOP outcomes.

	Psychological Health		Physical Health		Quality of Life	
Predictors	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p
Medication [Other MOUD]	0.62 (-0.30 – 1.55)	0.185	0.31 (-0.60 – 1.23)	0.5	0.00 (-0.00 – 1.75)	0.051
Current age	-0.04 (-0.09 – 0.01)	0.092	-0.01 (-0.06 – 0.04)	0.642	-0.08 (-0.08 – 0.01)	0.168
Employment [Regular Employment]	0.15 (-0.99 – 1.28)	0.799	-0.25 (-1.38 – 0.87)	0.661	-1.63 (-1.63 – 0.52)	0.313
Ethnicity [Non White]	-0.02 (-1.14 – 1.10)	0.97	-0.83 (-1.94 – 0.28)	0.141	-1.97 (-1.97 – 0.15)	0.094
Age of first substance	0.01 (-0.05 – 0.07)	0.718	0.02 (-0.04 – 0.07)	0.515	0.03 (-0.03 – 0.08)	0.359
Number of episodes	-0.11 (-0.56 – 0.33)	0.608	-0.02 (-0.45 – 0.42)	0.946	0.01 (-0.41 – 0.43)	0.953
Sex [Female]	0.14 (-0.91 – 1.19)	0.79	-0.13 (-1.18 – 0.92)	0.806	0.06 (-0.94 – 1.06)	0.903
IMD	0 (-0.19 – 0.19)	0.997	0.17 (-0.02 – 0.35)	0.076	0.09 (-0.09 – 0.27)	0.314
Observations	354		354		354	
R <sup>2</sup> / R <sup>2</sup> adjusted	0.019 / 0.00		0.016 / 0.00		0.043 / 0.021	

IMD = Index of multiple deprivation; reference categories stated in []

### *TOPs substance use variables.*

There were 151 instances in which no opioid use was reported and 252 in which any was. The odds of decreased opioid use was not statistically significantly associated with Buvidal® (OR = 0.81 [95 CI: 0.54 to 1.23],  $p = .325$ ). In adjusted models the number of episodes was a significant positive predictor of increased opioid use OR = 1.40 [95% CI: 1.08 to 1.87],  $p = .016$ ).

There were 355 instances in which no IV drug use was reported and 38 instances in which it was. The odds of decreased IV use was not statistically significantly associated with Buvidal® (OR = 1.27 [95% CI: 0.65 to 2.52],  $p = .485$ ). Due to the small number of instances, an adjusted model was not possible.

### **Discussion**

In this study we compared TOPs outcomes for individuals prescribed Buvidal® vs. oral MOUD. While previous research has examined retention and efficacy of Buvidal® for treating OUD, there is comparatively little investigation of outcomes relating to individuals. This is one of the first large investigations of person-rated outcomes and demographic factors in people prescribed Buvidal® vs. oral MOUD. In our analyses, people who were prescribed Buvidal® were younger, more likely to be employed, and had more previous treatment episodes. Buvidal® was associated with positive changes in QoL over the treatment period. Supplementary analyses (see file S1) highlighted that overall people prescribed Buvidal® reported higher levels of psychological and physical health, and QoL compared to people receiving MOUD. Other demographic and situational factors were positive and negative predictors in these analyses indicating the intersectional nature of changes in health during recovery.

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The findings in this study reflect those in previous research. For example, when considering factors associated with Buvidal® prescribing, an evaluation of Buvidal® in West Lothian found that Buvidal® helped people consider employment, which is supported by higher employment in Buvidal® clients in the present study [57], although we did not find associations with sex as reported in previous research [36]. We were particularly interested in predictors of Buvidal® initiation in the present study as budget constraints in UK treatment services could increase health inequalities [48,49]. While we did not find evidence for inequalities in initiation of Buvidal® related to social deprivation (IMD), sex or ethnicity, we did find evidence that those who are younger, have more treatment episodes and are in regular employment are more likely to receive Buvidal®. This provides some tentative evidence that certain individual factors are associated with increased likelihood of receiving Buvidal® relative to oral MOUD. The finding for age is more concerning in terms of inequality as ageing populations of substance users are subject to greater levels of substance-related harms [59] but have been shown to achieve better treatment outcomes than their younger counterparts [60] and may also benefit from LAIB. In the present study we also identified that age was a significant negative predator of psychological health, indicating that older people may have unmet mental health needs and would benefit from LAIB initiation. However, one alternative explanation is that older people with OUD are reluctant to switch from methadone, a known entity, on to novel treatments. Substance treatment guidance in the UK suggests that people with longer OUD history (i.e. older individuals) or those with heightened withdrawal-related anxiety may prefer methadone to buprenorphine because of the sedative effect [61]. Thus we cannot say if older adults were not selected for, or declined, LAIB. Future research should seek to supplement the

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quantitative analyses with qualitative data to understand clinicians' and people with OUD's choice of treatment.

In our analyses of changes in self-reported outcomes over the 1-year period, Buvidal® was a significant predictor of changes in QoL, but not physical or mental health. In previous qualitative studies on acceptability of LAIB in people with OUD, one key theme that emerged was the perception that LAIB would allow individuals to get on with everyday life [32]. Indeed, analysis of person-level outcome measures in found that people on LAIB reported increased life satisfaction and improved self-care (specifically taking up sports and hobbies and improvements in mental health). Interestingly, 43% of individuals reported improved material resources such as employment while 86% (12 people) reported improved well-being [46] which are reflective of Buvidal®'s association with increased employment and QoL in the present study. However, previous studies in people using MOUD and sublingual buprenorphine [e.g., 60] have noted that initial improvements in QoL are not sustained over longer-term outcomes. Thus, further long-term analysis of the LAIB data is needed to assess if changes in QoL are sustained and if they are meaningful indicators of recovery. Inclusion of demographic predictors in the adjusted models reduced Buvidal® to just below statistical significance, indicating the intersectional nature of changes in QoL over the 1-year period. For example, in this analysis we identified that being of White ethnicity was associated with improved QoL and physical health, which indicates the role of ethnicity in treatment outcomes [48-50].

Supplementary analyses of summary TOPs scores indicated that psychological and physical health and QoL were positively predicted by Buvidal®, employment and being male. For physical health age was a negative predictor in the model (older people had worse

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physical health), while for QoL age of initiation was a positive predictor (people who started using later reported better QoL). Taken together, these results could reflect the concomitant effects of age (or indeed longer-term substance use) on wellbeing and long-term conditions [see 60 for review]. Finally, number of treatment episodes was a negative predictor of QoL indicating that more treatment episodes was associated with lower QoL. These analyses highlight some important individual characteristics related to treatment outcomes. For example, poorer self-reported outcomes for females compared to males is not in line with previous research [e.g. 36] and warrants further investigation.

This study had a number of limitations. Firstly, this was a time-limited study and we were only able to access data for a 1-year period within the scope of our funding. Thus, we were not able to fully investigate the associations between Buvidal® and treatment outcomes in terms of QoL, physical/mental health and employment beyond the treatment journey, and conversely relapse. There was insufficient data available to investigate individuals who were discharged from the treatment service during this time, and due to the cross-sectional nature, we could not include treatment duration in our analyses. Future research should investigate outcomes and treatment trajectories over a longer-time period taking in to account previous treatment episodes, durations and outcomes. We also believe that further studies should also look at societal impact outcomes, such as number of healthcare (e.g., GP, A&E) and police attendances, employment status, which we could not evaluate within the scope of the present study. Due to limited capacity to link all prescribing data within the Pharmacy team in Via, we statistically stratified our oral MOUD comparison group and selected 266 controls on oral MOUD. While we do not believe that these clients would have differed from the 1783 individuals on oral MOUD who were not selected, it remains a possibility that this sample differed in some way from the selected control group.



While we found significant improvements in QoL, and significant differences between the people prescribed Buvidal® in physical and mental health and QoL, the TOPs scales are visual analogue assessment scales, and there is no indication as to how or why individuals feel these indicators have changed on Buvidal®. Follow-up qualitative analyses would allow for the characterisation of these indices during recovery.

To our knowledge, this is the first large study to compare self-reported outcomes for individuals prescribed Buvidal® compared to oral MOUD. People initiated on Buvidal® were younger, more likely to be employed, had more previous treatment episodes, and relative to the people on oral MOUD, had significant improvements in QoL over the 1-year period. Future research should seek to investigate the aetiology of improved wellbeing using qualitative analysis and should perform a quantitative analysis of outcomes over a longer period to investigate the impacts of Buvidal® and intersectional characteristics on recovery outcomes.

### Figure Legends

*Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.*

*Figure 2 (supplementary file S2): Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.*

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### Author Contributions

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Montgomery and Abbasi designed the study with input from Jones, Van Hout and De Silva. Montgomery, Abbasi and De Silva applied for funding to support the study. Gittins coordinated the curation of the raw prescribing data. Jones performed the statistical analysis including data curation, analysis, analytical strategy, reporting, and drafting the results section. Van Hout performed a critical review of the literature. De Silva liaised with people with opioid dependence and clinicians to discuss the study and contextualise results. Montgomery produced the first draft of the manuscript and all authors have provided critical revisions and approved the final manuscript. Montgomery is the guarantor.

**Competing interests**

This study was funded by Camurus AB. The funder had no role in the design, planning, execution or analyses in this study. CM and MCVH also receive funding from CSL Seqirus. YA has received honorarium from Camurus, Newbridge Pharma and Ethypharm. AJ, RG and DDS report no conflict of interest.

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**Data sharing statement**

The data and analysis code for this study is available in the Liverpool John Moores University Data Repository: [dataset] <https://opendata.ljmu.ac.uk/id/eprint/182>

**Ethics approval statement**

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This was a retrospective data analysis of anonymised health records and was approved as minimal risk by Liverpool John Moores University Research Ethics Committee (LJMUREC 23/PSY/036).

For peer review only

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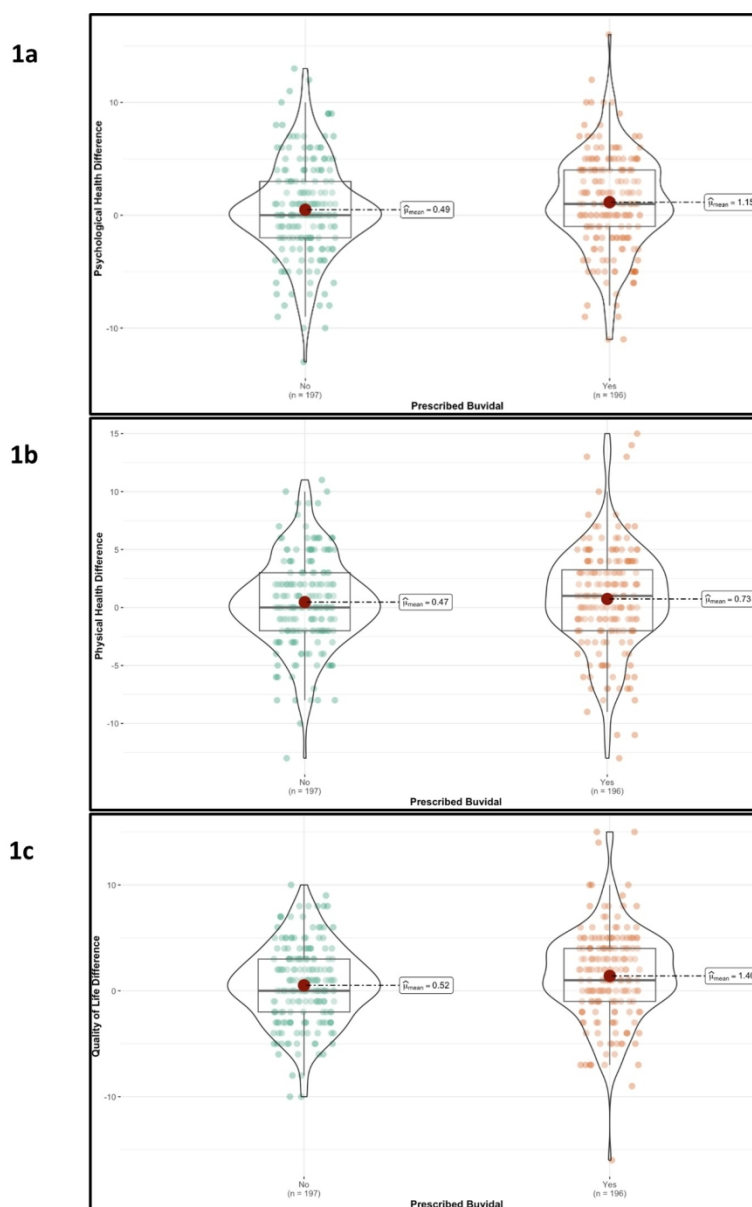


Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.

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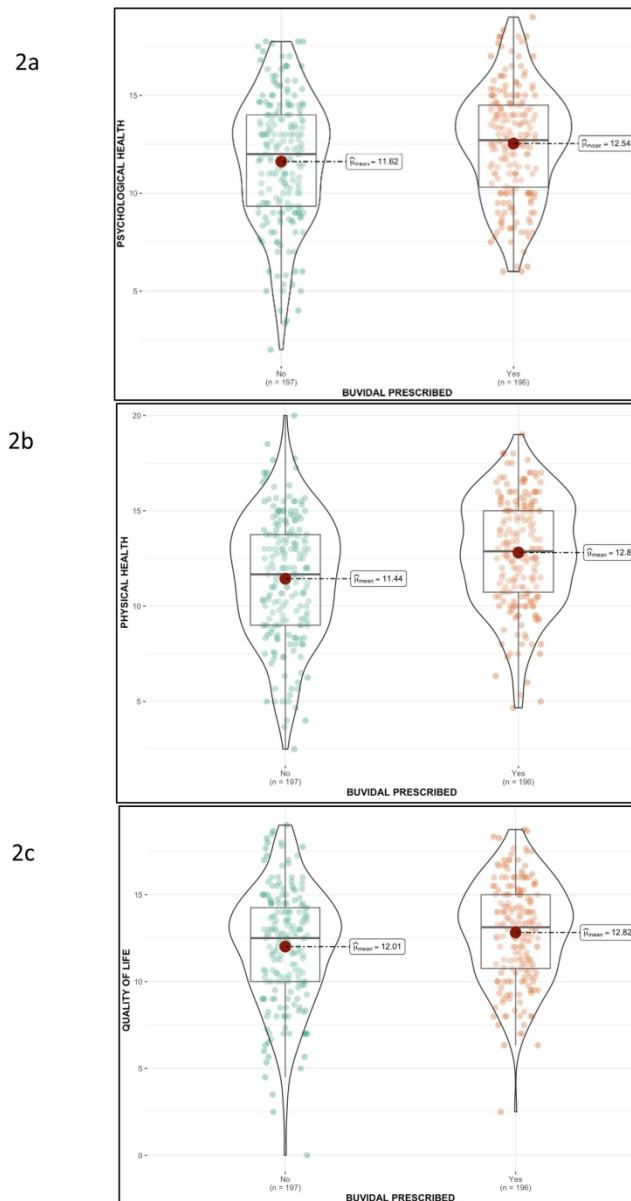


Figure 2: Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.

98x180mm (330 x 330 DPI)

Analysis of summary TOPS Scores

For psychological health (Figure 1a), physical health (Figure 1b) and QoL (Figure 1c) there were significantly greater health/QoL reports if people were prescribed Buvidal® (vs other MOUD):  $t(382.77) = 3.00$   $p < .001$ ,  $d = .30$ ),  $t(385) = 4.41$ ,  $p < .001$ ,  $d = .44$ ) and  $t(383) = 2.60$ ,  $p < .001$ ,  $d = .26$ ) respectively.

Figure 2: Psychological health (1a), physical health (1b) and Quality of Life in Buvidal® vs. compared to oral MOUD.

In adjusted models the variables explained approximately 7% (Adjusted  $R^2 = 0.07$ ) of variance in psychological health. Buvidal® was a significant positive predictor ( $B = .081$  [95% CI: 0.16 to 1.46],  $p = .015$ ), as was regular employment ( $B = 1.21$  [95% CI: 0.42 to 2.01],  $p = .003$ ), and being male ( $B = 1.23$  [95% CI: 0.49 to 1.97],  $p = .001$ ). Approximately 12% of variance was explained in physical health (Adjusted  $R^2 = 0.12$ ). Buvidal® was a significant positive predictor ( $B = 0.85$  [95% CI: 0.21 to 1.49],  $p = .009$ ), as was regular employment ( $B = 1.33$  [95% CI: 0.54 to 2.12],  $p = .001$ ) and being male ( $B = 1.09$  [95% CI: 0.36 to 1.82],  $p = .004$ ). Age was a negative predictor of physical health ( $B = -0.06$  [95% CI: -0.09 to -0.02],  $p = .001$ ). Approximately 11% of variance was explained in QoL (Adjusted  $R^2 = .11$ ). Buvidal® was a significant positive predictor ( $B = 0.77$  [95% CI: 0.13 to 1.42],  $p = .019$ ), as was regular employment ( $B = 1.80$  [95% CI: 1.01 to 2.59],  $p < .001$ ), being male ( $B = 1.04$  [95% CI: 0.31 to 1.77],  $p = .006$ ) and age of first substance use ( $B = 0.05$  [95% CI: 0.01 to 0.08],  $p = .025$ ). The number of episodes was a negative predictor of QoL ( $B = -0.35$  [95% CI: -0.04 to -0.65],  $p = .027$ ).

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Table 4

	Psychological Health			Physical Health			Quality of Life		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Buvidal [Yes]	0.81	0.16 – 1.46	<b>0.015</b>	0.85	0.21 – 1.49	<b>0.009</b>	0.77	0.13 – 1.42	<b>0.019</b>
Age	0.00	-0.03 – 0.04	0.791	-0.06	-0.09 – -0.02	<b>0.001</b>	-0.00	-0.04 – 0.03	0.947
Employment [Regular Employment]	1.21	0.42 – 2.01	<b>0.003</b>	1.33	0.54 – 2.12	<b>0.001</b>	1.80	1.01 – 2.59	<b>&lt;0.001</b>
Ethnicity [white]	-0.58	-1.37 – 0.21	0.149	-0.53	-1.31 – 0.24	0.178	-0.38	-1.15 – 0.40	0.344
Age of first substance	0.03	-0.01 – 0.07	0.168	0.03	-0.01 – 0.07	0.136	0.05	0.01 – 0.08	<b>0.025</b>
Number of episodes	-0.23	-0.54 – 0.08	0.147	-0.23	-0.54 – 0.07	0.132	-0.35	-0.65 – -0.04	<b>0.027</b>
Gender [Male]	1.23	0.49 – 1.97	<b>0.001</b>	1.09	0.36 – 1.82	<b>0.004</b>	1.04	0.31 – 1.77	<b>0.006</b>
IMD	-0.03	-0.16 – 0.11	0.693	-0.05	-0.18 – 0.08	0.430	-0.08	-0.21 – 0.05	0.227
R <sup>2</sup> / R <sup>2</sup> adjusted	0.102 / 0.081			0.144 / 0.124			0.131 / 0.111		

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# BMJ Open

## Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-090736.R4
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Date Submitted by the Author:	24-Jan-2025
Complete List of Authors:	Montgomery, Catharine; Liverpool John Moores University Abbasi, Yasir; Via Community Ltd De Silva, Devon; Via Community Ltd Gittins, Rosalind; Aston University Jones, Andrew; Liverpool John Moores University Van Hout, Marie-Claire; Liverpool John Moores University, Public Health Institute
<b>Primary Subject Heading</b>:	Addiction
Secondary Subject Heading:	Mental health, Patient-centred medicine, Public health
Keywords:	Substance misuse < PSYCHIATRY, Quality of Life, Health

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Investigating outcomes in a substance use treatment provider: A cross-sectional comparison of Long-Acting Injectable Buprenorphine and oral Medication for Opioid Use Disorder.

Authors: <sup>1</sup>Catharine Montgomery, <sup>2</sup>Yasir Abbasi, <sup>1</sup>Andrew Jones, <sup>2</sup>Devon De Silva, <sup>3</sup>Rosalind Gittins & <sup>4</sup>Marie Claire Van Hout

Corresponding author: C Montgomery, [C.A.Montgomery@ljamu.ac.uk](mailto:C.A.Montgomery@ljamu.ac.uk)

Affiliations:

<sup>1</sup>School of Psychology, Liverpool John Moores University, UK.

<sup>2</sup>Via, 18 Dartmouth Street, London, UK.

<sup>3</sup>School of Pharmacy, Aston University, UK.

<sup>4</sup>School of Public and Allied Health, Liverpool John Moores University, UK.

Qualifications and Titles:

C Montgomery: PhD, PgCert LTHE, BSc (Hons), Reader in Psychopharmacology, Head of Institute for Health Research.

Y Abbasi: MB BS, FRCPsych, PG Cert, PG Dip, EDPM, Executive Medical Director & Consultant Addiction Psychiatrist

A Jones: PhD, Senior Lecturer in Psychology.

D De Silva: BA. IRU Manager.

R Gittins: MRPharmS (Hons) MSc CertPsychPharm MCMHP IP, Senior Lecturer.

MC Van Hout: PhD, LLM, M.Sc Health Professions Education, M.Sc Health Promotion, M.Sc International Addictions. PVC Research and Knowledge Exchange.

ORCID IDs:

Catharine Montgomery: 0000-0003-2805-5807

Yasir Abbasi: 0000-0002-4981-7914

Andrew Jones: 0000-0001-5951-889X

Rosalind Gittins: 0000-0002-0893-7936

Marie Claire Van Hout: 0000-0002-0018-4060

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**Abstract**

*Objectives:* Advances in the treatment of opioid use disorder have seen the development of long-acting injectable opioid substitutes which could improve outcomes for people with opioid use disorder. However, comparative quantitative analysis of individual outcomes is lacking. The present study sought to investigate factors associated with prescribing of Long-Acting Injectable Buprenorphine (LAIB), and changes in outcome variables compared to oral medication for opioid use disorder.

*Design:* Cross-sectional retrospective analysis of electronic health records.

*Setting:* Community substance use treatment service Via. Six sites shared their data between 15/08/2022 – 15/08/2023.

*Participants:* Anonymised data was extracted for 235 people receiving LAIB and 266 people receiving oral medication for opioid use disorder.

*Primary and secondary outcomes:* Prescribing data, sociodemographic information (age, sex, IMD decile of individual’s residence, primary and secondary substance, number of previous treatment episodes, employment and ethnicity) and Treatment Outcome Profiles (substance use, physical and mental health, quality of life, employment) were extracted and analysed. To examine predictors of receiving LAIB (vs medication for opioid use disorder) we conducted logistic regression including the demographic predictors. Psychological health, physical health and quality of life scores were analysed using Welch’s t-tests.

*Results:* LAIB was associated with positive changes in quality of life between first and last assessments. Demographic and situational factors were predictors of LAIB initiation, indicating the potential for increasing health inequalities in substance use treatment.

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3 *Conclusions:* LAIB is associated with changes in quality of life over a 1-year period. Further  
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**MeSH Keywords**

Opiate dependence; buprenorphine; opiate substitution treatment; psychological wellbeing; quality of life; Long-acting injection; opioid related disorders; Long-Acting Injectable Buprenorphine.

**Article Summary**

Strengths and Limitations of this study

- This analysis provides a characterisation of how standardised outcomes change in a one-year period of treatment for opioid use disorder.
- The analysis incorporates individual, demographic and situational factors to allow us to assess health inequalities in initiation of treatment.
- The data is limited in that it only gives us a snapshot of subjective wellbeing over a 1-year period.
- The data cannot tell us qualitatively *how* quality of life and perceived psychological wellbeing changed in the LAIB vs. medication for opioid use disorder groups.

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## Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing disorder causing clinically significant distress or impairment and includes opioid dependence, with addiction representing the most severe form of OUD [1,2]. Additional adverse health complications of OUD causing morbidity and mortality centre on blood-borne virus infection (HIV, hepatitis C), overdose, accidents, suicide, and poly use of other drugs [3-5]. OUD is treated with opioid substitutes as first line treatment (usually with methadone or buprenorphine) [6-9] though pharmacological treatment is advised to be integrated within a global therapeutic model focused on recovery and including psycho-social support [10]. Research has demonstrated that treatment with opioid agonist medications such as methadone or buprenorphine reduces mortality by around 50% in people with OUD [11-13] with reductions in overdose deaths and all-cause mortality for those retained in treatment [14]. While effective engagement and retention is crucial for better treatment outcomes including reduced opioid use [5] and reduced risk behaviours [15], high rates of drop out are observed in the early phases of treatment [16,17]. Premature disengagement, particularly in the first month of treatment and post treatment completion, is associated with significant increases in mortality risk [18,3]. Thus there is a need to understand if different Medications for Opioid Use Disorder (MOUD) are better at promoting treatment retention and improving outcomes.

Despite methadone and buprenorphine being associated with lower mortality, there are a number of individual factors which can limit the impact of these OUD treatment modalities. For example, people with OUD report that daily mandatory consumption can impact upon wellbeing and opportunities for employment [19,20] and increase stigma and discrimination [21]. In recent years extended-release subcutaneous injectable buprenorphine

formulations (Long-Acting Injectable Buprenorphine; LAIB) have been proposed as offering improved rates of retention and adherence [22-24]. LAIB preparations have the potential to be highly effective due to their long-acting bioavailability and limited risk of diversion [25,26]. Moreover, they are ideal for individuals who do not wish to take daily oral doses, people living in rural areas, people in places where safe storage is problematic (e.g. people experiencing street homelessness), or people who are at increased risk of overdose, after, for example, release from prison or hospital [27]. In one study, LAIB has been shown to be more effective at increasing abstinence than placebo plus counselling alone [28] which the authors suggest is due to the reduction of risk of missed doses due to medication loss, lapses or diversion.

While there is an evidence base for patient experiences of using methadone and sublingual buprenorphine, due to their relative novelty, there are fewer studies on lived experiences of LAIB, with studies in the United States (US), Australia and France reporting varied perspectives. In previous research, people have reported that perceived benefits of LAIB include improved choice, reduced travel, clinic and pharmacy attendance, and potential for reduced stigma and discrimination compared to supervised daily consumption. However, people also identified concerns regarding their loss of control over their medication, reduced bodily autonomy and agency, isolation due to reduced therapeutic contact and potential adverse side effects [29-32]. LAIB was also shown to be appealing as an alternative to sublingual buprenorphine, with another US study finding that LAIB preparations appealed to more than half of individuals with OUD entering opioid treatment [33]. Real-world evaluations of LAIB with high-risk populations in the US have also reported positive outcomes with people choosing to continue using LAIB, the majority of individuals (65%) tolerating LAIB well and experiencing no symptoms of precipitated withdrawal or ongoing opioid use [34].

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In another study in people with OUD in France, interest in LAIB relative to other MOUD was related to perceived valued treatment outcomes. Individuals who showed interest in LAIB were more focused on outcomes related to recovery and abstinence, reported more frequent forgetting of their MOUD, or reported negative situations in which taking their MOUD wasn't practical or appropriate [35]. This was also reflected in a study in Australia where positive perceptions of LAIB were associated with being female, recent illicit drug use and perceived (in)convenience of current OUD treatment [36]. Moreover, a recent qualitative narrative synthesis of LAIB studies (N = 15) identified six themes from patient perspectives and patient reported outcomes. These included LAIB being associated with increased abstinence and reduced cravings, improved accessibility, increased productivity and participation in work, reduced acquisitive crime and improved social relationships. Within the review it was also identified that misinformation and mistrust were potential barriers to LAIB, and that LAIB could negatively affect some social relationships by, for example, removing the daily support of supervised consumption [37].

Our study concerns Buvidal®, which is an LAIB product typically initiated on a weekly basis with subsequent transfer to monthly injections [38,39]. Efficacy has been demonstrated in a double-blind, double-dummy, randomised phase-III-study with 428 individuals, which found Buvidal® to be non-inferior to sublingual buprenorphine with regard to primary (opioid use) and secondary (opioid free urine screening) outcomes [26]. Similar results were obtained in the UK in a phase III randomised control trial where LAIB (Sublocade®) was clinically superior compared to sublingual buprenorphine and methadone, resulting in increased abstinence from opioids, though it was not cost effective for the majority of participants. It was however identified as more effective and less costly in participants with longer treatment episodes (>28 days) and those with more severe OUD [40]. A systematic review and meta-

analysis conducted in the UK examining efficacy, safety and tolerability data of Buvidal® concluded that Buvidal® is safe, effective and improves retention compared to sublingual buprenorphine or placebo [41]. In terms of UK individual perspectives on Buvidal®, two qualitative studies [31,32] and a service evaluation [9] yielded consistent demand and perceived positive outcomes.

While it is clear that people with OUD perceive initiation of LAIB positively, and if initiated on LAIB report positive experiences [42], little is known about actual impacts of Buvidal® prescribing on actual patient outcomes in the UK. Person-centred phase III trials of other LAIB products (Sublocade®) in the US have demonstrated significant improvements in self-reported Quality of Life (QoL), increased employment and decreased healthcare utilisation relative to placebo and baseline, though there was no comparison with traditional oral MOUD [43,44]. These positive outcomes are supported elsewhere in the UK, where pilot studies have demonstrated that transition from oral MOUD to LAIB is feasible and acceptable for people with OUD accessing services in South Wales [45], with qualitative studies reporting positive subjective outcomes in four services in England and Wales [46].

While there is qualitative evidence that LAIB results in improved outcomes for people with OUD, not all services in England offer LAIB to all eligible clients due to budget constraints. Between 2013-14 and 2023-24, there has been an average reduction of 50% in funding for UK substance use treatment [47]. As a result, some people may be selected for LAIB treatment based on personal, social and individual characteristics (i.e. those who are perceived to be a good investment based on whether they are stable), which could increase health inequalities in substance use treatment [48,49]. For example, Black people with substance use disorders in the UK may be disproportionately affected by this prioritisation because they are more



likely to be living in poverty, unemployed or homeless and may therefore be deemed a less economically efficient option for initiation of LAIB [50]. This remains an issue for service providers despite recent health economic studies in England suggesting that initiation of LAIB results in overall reduction of direct (delivery, medication, psychosocial treatment) and indirect (e.g. criminal justice system, health care utilisation) treatment costs [51]. Thus, in addition to investigating if LAIB is associated with improved outcomes, one aim of the present study was to investigate if there are any health inequalities in initiation of LAIB by understanding individual and demographic predictors (e.g. social deprivation, ethnicity, age) of being initiated on LAIB vs. other MOUD.

In summary, to date there has not been a large quantitative evaluation of outcome data for people accessing services in England for OUD and being prescribed LAIB compared to oral MOUD. The objective of this study is to compare outcomes and predictors for people prescribed LAIB vs. oral MOUD. To do this we undertook a retrospective analysis of quantitative data from an English substance use treatment provider (Via), analysing sociodemographic characteristics to identify who is most likely to be prescribed LAIB and comparing person-level outcomes for individuals who were prescribed LAIB with a matched control of people on oral MOUD.

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**Method**

*Design, Setting and Study Population*

We conducted a cross-sectional comparison of anonymised electronic records from substance use treatment provider Via. Data from six Via services were included in our analyses. The data controller provided us with routinely collected person-level sociodemographic data, prescribing data, substance use data and physical and mental health assessment scores from the Treatment Outcome Profile (TOP) assessments. During the 12-month period, individuals completed TOPs at every contact with Via which allows comparison of changes in TOPs scores over the time period.

People were eligible to be included in the analysis if they were aged over 18 years, a Via service user in the last 12 months (15/08/2022 and 15/08/2023) and if they were either currently being prescribed LAIB, or if they were a control on another MOUD. Data was extracted for 235 individuals who were currently receiving a LAIB prescription and 266 matched individuals who were receiving another MOUD (total N = 501). Matched controls were selected using the following procedure. We were provided with the patient identification and demographic information of 2,048 individuals who received oral MOUD. We used gender, ethnicity and primary substance of use as stratifiers to obtain a smaller sample (which reflected the balance of these stratifiers), using the 'stratified' function from the 'splitstackshape' package in R [52]. We aimed for a similar sample size to our LAIB sample, which would still provide us with appropriate statistical power. We then provided the patient identifiers of the stratified sample to Via, who provided us with the TOPs and prescribing data for these individuals. We were unable to request data from all 2,048 individuals due to limited resources. Our overall sample size allowed us to detect small

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effect sizes between the groups on TOP scores ( $d \sim .25$ ) with 80% power and an alpha of .05 (independent samples t-test: one-tailed).

We reviewed the medicine scripts to allow us to summarise the most commonly prescribed LAIB and other MOUD dosages. For most individuals, dose changed over the 1-year period, and for some people in the oral MOUD group, type of MOUD changed. Based on information on the medicine scripts, the most common dose of LAIB was 64 mg prolonged release solution (27.8%), followed by 96 mg prolonged release solution (26.6%) and 128 mg prolonged release (17.5%). For other MOUD, the most common medication and dose was Methadone 1mg/ml oral solution (52.5%), followed by Buprenorphine 2mg sublingual tablets (19.7%).

### *Patient and Public Involvement*

DDS is manager of the Via Innovation and Research Unit and was responsible for coordinating the PPI in this study. DDS engaged with people with opioid use disorder and clinicians in Via services to discuss the planned study. During analysis, DDS involved people with opioid use disorder and clinicians in discussions about the qualitative nature of changes in psychological wellbeing to allow us to accurately contextualise the results for people with lived experience of opioid use disorder.

### *Measures*

Prescribing Data: Data was extracted from the pharmacy system (Nebula) for each individual over the 1-year period including the start date, end date, dose and name/strength for each prescribed medication.

Sociodemographic information: Routinely collected data including age, sex, Indices of Multiple Deprivation (IMD) decile of patient residence, primary and secondary substance,

number of previous treatment episodes, employment status and ethnicity were extracted from the Via Case Management System (CMS).

Outcome variables of interest:

TOP scores were used to assess changes in substance use, mental and physical health and QoL. The TOP is a standardised tool used in all UK substance use treatment settings to collect routine data at treatment entry and at set time points over the treatment journey (routinely at baseline, every 3 months until treatment exit; 3 & 6 months post treatment exit). The tool is comprised of a set of 20 psychometrically valid outcome measures [53] which have been shown to have good inter-rater reliability and test-retest reliability [54]. We used the routinely collected TOPs data to assess substance use (number of days using opiates/opioids in the last month; number of days injecting in the last month), psychological health, physical health and QoL (visual analogue scale from 0 = poor to 20 = good), number of days in paid employment in the last month and number of days in education in the last month.

Our TOPs analysis was limited to data collected between 15-08-2022 to 15-08-2023. As it was possible to have multiple TOP assessments in this period, we created two different outcome variables based on the TOP scores. If multiple assessments were taken during the one-year period (N = 383), we calculated a *TOPs change score* (the difference between the first and last assessment) to examine any change in TOPs scores during the time period. Secondly, we created a *summary TOPs score* for each outcome during the assessment period (the average for each TOP variable if multiple assessments were taken). Using this method, we analysed only psychological health, physical health and QoL TOPs scores.

Analyses for the *summary TOPs* score are reported in Supplementary file S1, containing supplementary Table 4 and Supplementary Figure 2.

We could not calculate change scores or summary scores for the TOP substance use and employment variables (opioid use, Intravenous (IV) drug use and paid work in the last 28 days) as they were largely 0 counts. For these variables we created a binary variable to identify whether any opioid use, IV drug use or paid employment was reported.

### *Procedure*

After gaining institutional ethical approval (LJMUREC 23/PSY/036), a Data Sharing Agreement was established between Liverpool John Moores University (LJMU) and Via. In Phase 1, pseudonymised demographic data for people receiving LAIB and oral MOUD was downloaded from Via's CMS and uploaded to a secure shared folder on CM's university file store. In Phase 2, full prescribing and outcome data for all individuals prescribed LAIB, and the selected controls was downloaded from Via's CMS into a Microsoft Excel file and uploaded to a secure folder on CM's file store and shared with the research team for analysis (CM & AJ).

### *Data Analysis*

To examine predictors of receiving LAIB compared to oral MOUD we conducted a logistic regression. We included available demographic information. Despite stratifying based on sex, ethnicity and primary substance we included these in the regression to hold them constant. For the logistic models we report Odds Ratios and 95% confidence intervals as parameter estimates.

Psychological health, physical health and QoL scores were analysed using Welch's t-tests. In adjusted models we conducted linear regressions including the demographic

predictors (age, employment, ethnicity, age of first substance, number of episodes, sex and IMD) to predict the TOPs change scores for psychological health, physical health and QoL (comparable analyses for summary scores can be found in supplementary file S1). There were some missing data for IMD (N = 34 / 6.7%) and age of first use (N = 20 / 4.0%). Missing data for IMD was likely reflective of people with no fixed abode (e.g. those experiencing street homelessness) and therefore was not missing at random. As such we did not conduct multiple imputation analyses as this may serve to increase possible bias [55]. However, we conduct all adjusted analyses with these variables removed as sensitivity analyses, and any deviation from adjusted analyses with these variables included is noted. For opioid use and IV drug use, we conducted logistic regressions in which any amount of opioid use or IV drug use recorded was coded as 1.

Data and analysis code for the study can be found here: [dataset]

<https://opendata.ljmu.ac.uk/id/eprint/182>

**Results**

*Baseline Characteristics of participants:*

The baseline characteristics of individuals can be found in Table 1. Of the 235 individuals receiving LAIB, 60 (25.5%) were female, 185 (78.7%) identified as White ethnicity, with the majority (186 clients – 79.1%) reporting illicit heroin as their primary substance. Of the 266 individuals receiving MOUD, 67 (25.2%) were female, 187 (70.3%) identified as White ethnicity, with the majority (220 clients – 82.7%) reporting illicit heroin as their primary substance. There were significant differences between the groups in current age ( $t(498.6) = 4.81, p < .001, d = .43$  [95% CI: .25 to .61], number of previous treatment episodes ( $t(463.6) = 3.40, p < .001, d = .31$  [95% CI: .13 to .48] and regular employment ( $X^2(1) = 6.27, p = .012$ )

with individuals who were receiving LAIB being significantly younger, having more previous treatment episodes and having higher levels of regular employment.

*Table 1: Demographic breakdown of individuals prescribed LAIB vs compared to oral MOUD.*

*Total N = 501.*

	LAIB	Other
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
<b>Current Age</b>	<b>43.17 (9.00)</b>	<b>47.23 (9.89)</b>
Age of first substance	22.44 (6.93)	23.36 (9.10)
<b>Number of episodes</b>	<b>1.86 (1.21)</b>	<b>1.52 (1.04)</b>
IMD	4.43 (2.53)	4.54 (2.35)
	<i>N (%)</i>	<i>N (%)</i>
<i>Ethnicity</i>		
White	185 (78.7%)	213 (80.4%)
Asian / British Asian	27 (11.5%)	22 (8.3%)
Black /Black British / African	13 (5.5%)	7 (2.6%)
Mixed / Multiple	3 (1.3%)	9 (3.4%)
Unknown / Other	7 (3.0%)	14 (5.3%)
<i>Employment</i>		
<b>Regular Employment</b>	<b>55 (23.4%)</b>	<b>38 (14.3%)</b>
<b>Other</b>	<b>180 (76.6%)</b>	<b>228 (85.7%)</b>
<i>Sex</i>		
Female	60 (25.5%)	67 (25.2%)
Male	175 (74.5%)	199 (74.8%)
<i>Primary Substance</i>		
Illicit Heroin	186 (79.1%)	220 (82.7%)
Other	49 (20.9%)	46 (17.3%)
<i>Secondary Substance</i>		
Cocaine (Crack)	122 (51.9%)	120 (45.1%)
No Second Substance	56 (23.8%)	78 (29.3%)
Other	57 (24.3%)	68 (25.6%)

Note – variables with categorical response are simplified due to large number of categories with small numbers of individuals within some categories. Reference categories were chosen based on the largest number (e.g. White, illicit heroin). In the case of the employment variable, regular employment was not the most common category, but the 'other' comparison represents a lot of similar categories (e.g. 'retired', 'unemployed', 'homemaker'). IMD was also missing from 34 individuals due to having no fixed address or this not information being available. Variables in **bold** indicate a significant difference between the groups (LAIB compared to oral MOUD).

Predictors of LAIB prescribing

We included 8 variables in the logistic regression model to examine whether any predicted the increased/decreased odds of being prescribed LAIB. These variables were; current age, employment (currently employed vs not), ethnicity (white vs other), age of first substance, number of episodes, client sex at registration of birth (sex - male vs female), IMD, and primary substance (illicit heroin pared to other substances). See Table 2, for model parameters. The overall model was able to predict around 7% of variance in the outcome. Individuals of a younger age, who were regularly employed, and had increased number of episodes, had increased odds of being prescribed LAIB (compared to other MOUD).

Table 2: Logistic regression analysis examining predictors of being prescribed LAIB (compared to oral MOUD).

Predictors	LAIB (compared to oral MOUD)		
	Odds Ratios	CI	p
Current age	0.96	0.94 – 0.98	<0.001
Employment [Regular Employment]	1.89	1.13 – 3.19	0.016
Ethnicity [White British]	0.93	0.57 – 1.51	0.755
Age of first substance	1.00	0.98 – 1.03	0.880
Number of episodes	1.38	1.15 – 1.68	0.001
Sex [Male]	1.00	0.62 – 1.57	0.964



Primary substance [Other]	1.02	0.61 – 1.71	0.929
IMD	0.97	0.89 – 1.05	0.461
R <sup>2</sup> (Pseudo)			0.079

#### *Difference in TOPs Scores (Figure 1)*

For psychological health and physical health, there was no significant difference between individuals who were and were not prescribed LAIB  $t(390.96) = 1.57$ ,  $p = .12$ ,  $d = -.16$ ;  $t(385.04) = 0.64$ ,  $p = .52$ ,  $d = .06$  respectively. For QoL there was a significant difference, in that individuals who were prescribed LAIB reported positive change in QoL compared to other treatment  $t(381.57) = 2.21$ ,  $p = .03$ ,  $d = .22$ ; mean improvement LAIB = 1.40, mean improvement other = 0.52.

<<Insert Figure 1 here>>

In adjusted models there were no significant predictors of change in Psychological Health ( $R^2 = .00$ ), Physical Health ( $R^2 = .00$ ) or QoL ( $R^2 = .02$ ), though there was a trend for current age being negatively related to psychological health and IMD decile positively related to physical health. In adjusted models, LAIB was a marginally non-significant predictor of QoL ( $p = .051$ ) (see Table 3). In models with IMD and age of first use removed, LAIB remained a non-significant predictor in all models; however, being of white ethnicity was associated with an improved QoL ( $B = -1.00$  [95% CI:  $-2.00 - -0.01$ ],  $p = .048$ ) and physical health ( $B = -1.11$  [95% CI:  $-2.14 - -0.07$ ],  $p = .036$ ). Age was a significant predictor of psychological health ( $B = -0.05$  [95% CI:  $-.010 - -0.01$ ],  $p = .019$ ).

Table 3: Adjusted regression models for the effects of LAIB vs other MOUD on TOP outcomes.

	Psychological Health		Physical Health		Quality of Life	
Predictors	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p	Estimates (Confidence Interval)	p
Medication [Other MOUD]	0.62 (-0.30 – 1.55)	0.185	0.31 (-0.60 – 1.23)	0.5	0.00 (-1.75 – 1.75)	0.051
Current age	-0.04 (-0.09 – 0.01)	0.092	-0.01 (-0.06 – 0.04)	0.642	-0.08 (-0.08 – 0.01)	0.168
Employment [Regular Employment]	0.15 (-0.99 – 1.28)	0.799	-0.25 (-1.38 – 0.87)	0.661	-1.63 (-1.63 – 0.52)	0.313
Ethnicity [Non White]	-0.02 (-1.14 – 1.10)	0.97	-0.83 (-1.94 – 0.28)	0.141	-1.97 (-1.97 – 0.15)	0.094
Age of first substance	0.01 (-0.05 – 0.07)	0.718	0.02 (-0.04 – 0.07)	0.515	0.03 (-0.03 – 0.08)	0.359
Number of episodes	-0.11 (-0.56 – 0.33)	0.608	-0.02 (-0.45 – 0.42)	0.946	0.01 (-0.41 – 0.43)	0.953
Sex [Female]	0.14 (-0.91 – 1.19)	0.79	-0.13 (-1.18 – 0.92)	0.806	0.06 (-0.94 – 1.06)	0.903
IMD	0 (-0.19 – 0.19)	0.997	0.17 (-0.02 – 0.35)	0.076	0.09 (-0.09 – 0.27)	0.314
Observations	354		354		354	
R <sup>2</sup> / R <sup>2</sup> adjusted	0.019 / 0.00		0.016 / 0.00		0.043 / 0.021	

IMD = Index of multiple deprivation; reference categories stated in []

### *TOPs substance use variables.*

There were 151 instances in which no opioid use was reported and 252 in which any was. The odds of decreased opioid use was not statistically significantly associated with LAIB (OR = 0.81 [95 CI: 0.54 to 1.23],  $p = .325$ ). In adjusted models the number of episodes was a significant positive predictor of increased opioid use OR = 1.40 [95% CI: 1.08 to 1.87],  $p = .016$ ).

There were 355 instances in which no IV drug use was reported and 38 instances in which it was. The odds of decreased IV use was not statistically significantly associated with LAIB (OR = 1.27 [95% CI: 0.65 to 2.52],  $p = .485$ ). Due to the small number of instances, an adjusted model was not possible.

### **Discussion**

In this study we compared TOPs outcomes for individuals prescribed LAIB vs. oral MOUD. While previous research has examined retention and efficacy of LAIB for treating OUD, there is comparatively little investigation of outcomes relating to individuals. This is one of the first large investigations of person-rated outcomes and demographic factors in people prescribed LAIB vs. oral MOUD. In our analyses, people who were prescribed LAIB were younger, more likely to be employed, and had more previous treatment episodes. LAIB was associated with positive changes in QoL over the treatment period. Supplementary analyses (see file S1) highlighted that overall people prescribed LAIB reported higher levels of psychological and physical health, and QoL compared to people receiving MOUD. Other demographic and situational factors were positive and negative predictors in these analyses indicating the intersectional nature of changes in health during recovery.

The findings in this study reflect those in previous research. For example, when considering factors associated with LAIB prescribing, an evaluation of LAIB in West Lothian found that LAIB helped people consider employment, which is supported by higher employment in LAIB clients in the present study [57], although we did not find associations with sex as reported in previous research [36]. We were particularly interested in predictors of LAIB initiation in the present study as budget constraints in UK treatment services could increase health inequalities [48,49]. While we did not find evidence for inequalities in initiation of LAIB related to social deprivation (IMD), sex or ethnicity, we did find evidence that those who are younger, have more treatment episodes and are in regular employment are more likely to receive LAIB. This provides some tentative evidence that certain individual factors are associated with increased likelihood of receiving LAIB relative to oral MOUD. The finding for age is more concerning in terms of inequality as ageing populations of substance users are subject to greater levels of substance-related harms [59] but have been shown to achieve better treatment outcomes than their younger counterparts [60] and may also benefit from LAIB. In the present study we also identified that age was a significant negative predictor of psychological health, indicating that older people may have unmet mental health needs and would benefit from LAIB initiation. However, one alternative explanation is that older people with OUD are reluctant to switch from methadone, a known entity, on to novel treatments. Substance treatment guidance in the UK suggests that people with longer OUD history (i.e. older individuals) or those with heightened withdrawal-related anxiety may prefer methadone to buprenorphine because of the sedative effect [61]. Thus we cannot say if older adults were not selected for, or declined, LAIB. Future research should seek to supplement the quantitative analyses with qualitative data to understand clinicians' and people with OUD's choice of treatment.

In our analyses of changes in self-reported outcomes over the 1-year period, LAIB was a significant predictor of changes in QoL, but not physical or mental health. In previous qualitative studies on acceptability of LAIB in people with OUD, one key theme that emerged was the perception that LAIB would allow individuals to get on with everyday life [32]. Indeed, analysis of person-level outcome measures in found that people on LAIB reported increased life satisfaction and improved self-care (specifically taking up sports and hobbies and improvements in mental health). Interestingly, 43% of individuals reported improved material resources such as employment while 86% (12 people) reported improved well-being [46] which are reflective of LAIB's association with increased employment and QoL in the present study. However, previous studies in people using MOUD and sublingual buprenorphine [e.g., 60] have noted that initial improvements in QoL are not sustained over longer-term outcomes. Thus, further long-term analysis of the LAIB data is needed to assess if changes in QoL are sustained and if they are meaningful indicators of recovery. Inclusion of demographic predictors in the adjusted models reduced LAIB to just below statistical significance, indicating the intersectional nature of changes in QoL over the 1-year period. For example, in this analysis we identified that being of White ethnicity was associated with improved QoL and physical health, which indicates the role of ethnicity in treatment outcomes [48-50].

Supplementary analyses of summary TOPs scores indicated that psychological and physical health and QoL were positively predicted by LAIB, employment and being male. For physical health age was a negative predictor in the model (older people had worse physical health), while for QoL age of initiation was a positive predictor (people who started using later reported better QoL). Taken together, these results could reflect the concomitant effects of age (or indeed longer-term substance use) on wellbeing and long-term conditions

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[see 60 for review]. Finally, number of treatment episodes was a negative predictor of QoL indicating that more treatment episodes was associated with lower QoL. These analyses highlight some important individual characteristics related to treatment outcomes. For example, poorer self-reported outcomes for females compared to males is not in line with previous research [e.g. 36] and warrants further investigation.

This study had a number of limitations. Firstly, this was a time-limited study and we were only able to access data for a 1-year period within the scope of our funding. Thus, we were not able to fully investigate the associations between LAIB and treatment outcomes in terms of QoL, physical/mental health and employment beyond the treatment journey, and conversely relapse. There was insufficient data available to investigate individuals who were discharged from the treatment service during this time, and due to the cross-sectional nature, we could not include treatment duration in our analyses. Future research should investigate outcomes and treatment trajectories over a longer-time period taking in to account previous treatment episodes, durations and outcomes. We also believe that further studies should also look at societal impact outcomes, such as number of healthcare (e.g., GP, A&E) and police attendances, employment status, which we could not evaluate within the scope of the present study. Due to limited capacity to link all prescribing data within the Pharmacy team in Via, we statistically stratified our oral MOUD comparison group and selected 266 controls on oral MOUD. While we do not believe that these clients would have differed from the 1783 individuals on oral MOUD who were not selected, it remains a possibility that this sample differed in some way from the selected control group. While we found significant improvements in QoL, and significant differences between the people prescribed LAIB in physical and mental health and QoL, the TOPs scales are visual analogue assessment scales, and there is no indication as to how or why individuals feel these

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indicators have changed on LAIB. Follow-up qualitative analyses would allow for the characterisation of these indices during recovery.

To our knowledge, this is the first large study to compare self-reported outcomes for individuals prescribed LAIB compared to oral MOUD. People initiated on LAIB were younger, more likely to be employed, had more previous treatment episodes, and relative to the people on oral MOUD, had significant improvements in QoL over the 1-year period. Future research should seek to investigate the aetiology of improved wellbeing using qualitative analysis and should perform a quantitative analysis of outcomes over a longer period to investigate the impacts of LAIB and intersectional characteristics on recovery outcomes.

### Figure Legends

*Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in LAIB compared to oral MOUD.*

*Figure 2 (supplementary file S2): Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in LAIB compared to oral MOUD.*

### Acknowledgements

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### Author Contributions

Montgomery and Abbasi designed the study with input from Jones, Van Hout and De Silva.

Montgomery, Abbasi and De Silva applied for funding to support the study. Gittins coordinated the curation of the raw prescribing data. Jones performed the statistical analysis including data curation, analysis, analytical strategy, reporting, and drafting the results section. Van Hout performed a critical review of the literature. De Silva liaised with

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people with opioid dependence and clinicians to discuss the study and contextualise results. Montgomery produced the first draft of the manuscript and all authors have provided critical revisions and approved the final manuscript. Montgomery is the guarantor.

**Competing interests**

This study was funded by Camurus AB. The funder had no role in the design, planning, execution or analyses in this study. CM and MCVH also receive funding from CSL Seqirus. YA has received honorarium from Camurus, Newbridge Pharma and Ethypharm. AJ, RG and DDS report no conflict of interest.

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**Data sharing statement**

The data and analysis code for this study is available in the Liverpool John Moores University Data Repository: [dataset] <https://opendata.ljmu.ac.uk/id/eprint/182>

**Ethics approval statement**

This was a retrospective data analysis of anonymised health records and was approved as minimal risk by Liverpool John Moores University Research Ethics Committee (LJMUREC 23/PSY/036).

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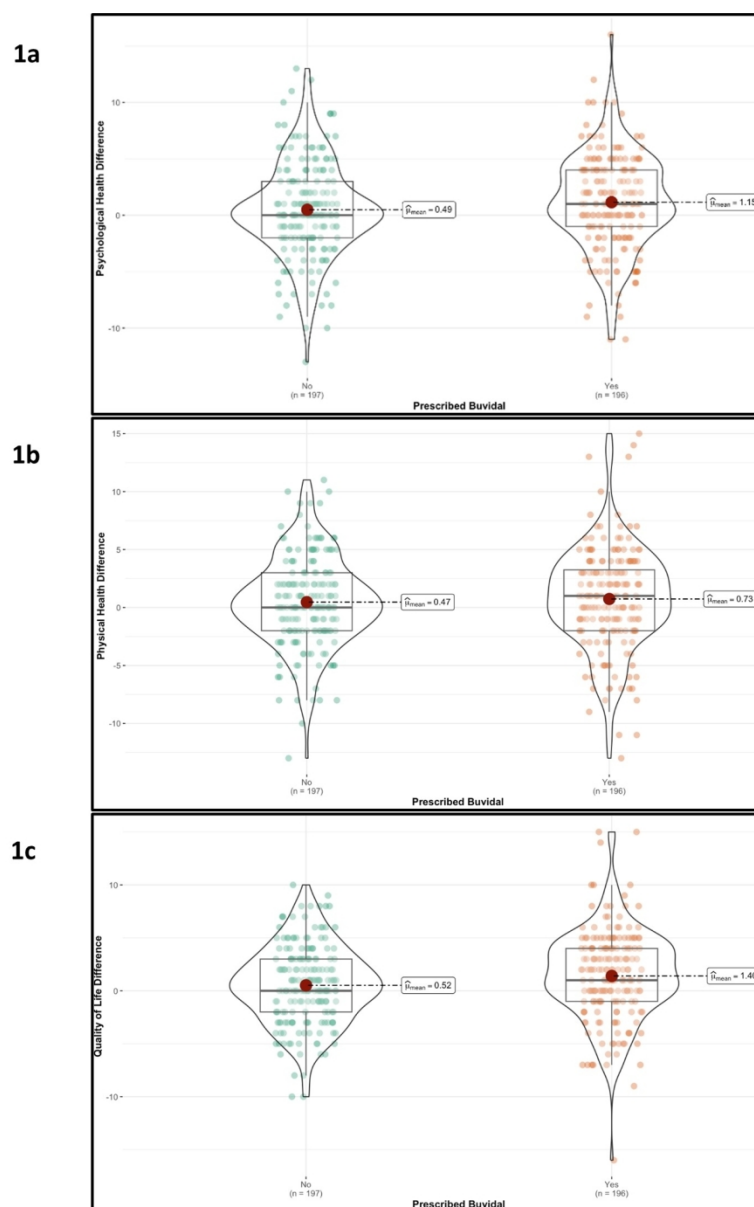


Figure 1: Changes in psychological health (1a), physical health (1b) and Quality of Life (1c) in Buvidal compared to oral MOUD.

108x166mm (330 x 330 DPI)

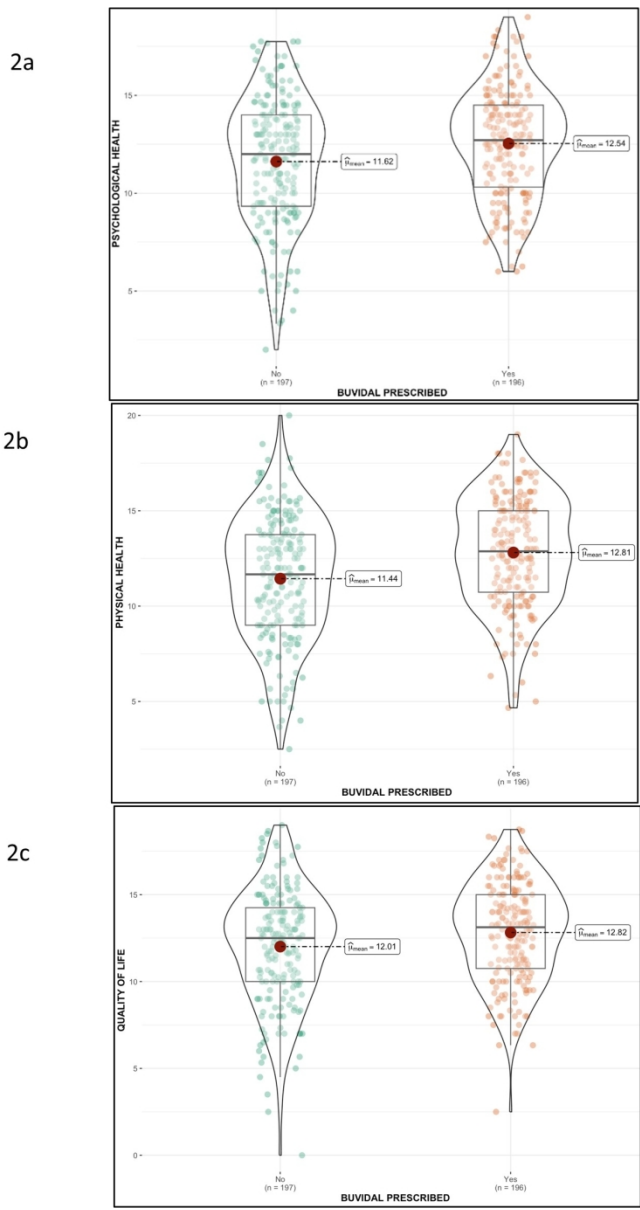


Figure 2: Average (summary) psychological health (2a), physical health (2b) and Quality of Life (2c) in Buvidal compared to oral MOUD.

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Analysis of summary TOPS Scores

For psychological health (Figure 1a), physical health (Figure 1b) and QoL (Figure 1c) there were significantly greater health/QoL reports if people were prescribed LAIB (vs other MOUD):  $t(382.77) = 3.00$   $p < .001$ ,  $d = .30$ ,  $t(385) = 4.41$ ,  $p < .001$ ,  $d = .44$ ) and  $t(383) = 2.60$ ,  $p < .001$ ,  $d = .26$ ) respectively.

Figure 2: Psychological health (1a), physical health (1b) and Quality of Life in LAIB vs. compared to oral MOUD.

In adjusted models the variables explained approximately 7% (Adjusted  $R^2 = 0.07$ ) of variance in psychological health. LAIB was a significant positive predictor ( $B = .081$  [95% CI: 0.16 to 1.46],  $p = .015$ ), as was regular employment ( $B = 1.21$  [95% CI: 0.42 to 2.01],  $p = .003$ ), and being male ( $B = 1.23$  [95% CI: 0.49 to 1.97],  $p = .001$ ). Approximately 12% of variance was explained in physical health (Adjusted  $R^2 = 0.12$ ). LAIB was a significant positive predictor ( $B = 0.85$  [95% CI: 0.21 to 1.49],  $p = .009$ ), as was regular employment ( $B = 1.33$  [95% CI: 0.54 to 2.12],  $p = .001$ ) and being male ( $B = 1.09$  [95% CI: 0.36 to 1.82],  $p = .004$ ). Age was a negative predictor of physical health ( $B = -0.06$  [95% CI: -0.09 to -0.02],  $p = .001$ ). Approximately 11% of variance was explained in QoL (Adjusted  $R^2 = .11$ ). LAIB was a significant positive predictor ( $B = 0.77$  [95% CI: 0.13 to 1.42],  $p = .019$ ), as was regular employment ( $B = 1.80$  [95% CI: 1.01 to 2.59],  $p < .001$ ), being male ( $B = 1.04$  [95% CI: 0.31 to 1.77],  $p = .006$ ) and age of first substance use ( $B = 0.05$  [95% CI: 0.01 to 0.08],  $p = .025$ ). The number of episodes was a negative predictor of QoL ( $B = -0.35$  [95% CI: -0.04 to -0.65],  $p = .027$ ).

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Table 4

	Psychological Health			Physical Health			Quality of Life		
<i>Predictors</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>	<i>Estimates</i>	<i>CI</i>	<i>p</i>
LAIB [Yes]	0.81	0.16 – 1.46	<b>0.015</b>	0.85	0.21 – 1.49	<b>0.009</b>	0.77	0.13 – 1.42	<b>0.019</b>
Age	0.00	-0.03 – 0.04	0.791	-0.06	-0.09 – -0.02	<b>0.001</b>	-0.00	-0.04 – 0.03	0.947
Employment [Regular Employment]	1.21	0.42 – 2.01	<b>0.003</b>	1.33	0.54 – 2.12	<b>0.001</b>	1.80	1.01 – 2.59	<b>&lt;0.001</b>
Ethnicity [white]	-0.58	-1.37 – 0.21	0.149	-0.53	-1.31 – 0.24	0.178	-0.38	-1.15 – 0.40	0.344
Age of first substance	0.03	-0.01 – 0.07	0.168	0.03	-0.01 – 0.07	0.136	0.05	0.01 – 0.08	<b>0.025</b>
Number of episodes	-0.23	-0.54 – 0.08	0.147	-0.23	-0.54 – 0.07	0.132	-0.35	-0.65 – -0.04	<b>0.027</b>
Gender [Male]	1.23	0.49 – 1.97	<b>0.001</b>	1.09	0.36 – 1.82	<b>0.004</b>	1.04	0.31 – 1.77	<b>0.006</b>
IMD	-0.03	-0.16 – 0.11	0.693	-0.05	-0.18 – 0.08	0.430	-0.08	-0.21 – 0.05	0.227
R <sup>2</sup> / R <sup>2</sup> adjusted	0.102 / 0.081			0.144 / 0.124			0.131 / 0.111		

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