Systematic Review

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Effectiveness of long-acting buprenorphine – A systematic review

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Abstract

Objective: To analyse the evidence of the effectiveness of long-acting injection buprenorphine (LAI-B) in the management of opioid use disorder (OUD).

Method: Databases were searched for studies reporting on the effectiveness of LAI-B for the treatment of OUD. Risk of bias was assessed, and a narrative synthesis of data was presented. The study adhered to PRISMA guidelines and was registered with PROSPERO (CRD42023396033).

Results: Eighteen studies were included in the final review: two double-blind randomised control trials, two open-label randomised control trials, two retrospective cohort studies, one non-controlled pilot study, and eleven observational studies. In comparative trials, LAI-B was superior to placebo and superior or non-inferior to treatment as usual. LAI-B was positively associated with improvements in abstinence rates and patient-centred outcomes. There was limited data on the long-term effects of continuous LAI-B prescription.

Conclusion: LAI-B is an effective treatment for OUD with advantages over existing forms of treatment. Patients reported high levels of medication satisfaction and there were no significant safety concerns. This review highlights the need for future research on long-term effectiveness outcomes, with participants of more varied demographics and psychiatric comorbidity, which is more reflective of the OUD population seen in community clinical settings.

Keywords: buprenorphine, opioid use disorder, long-acting injectable buprenorphine

Opioid Use Disorder (OUD) contributes to multiple adverse consequences including transmission of infectious diseases, criminal activity, incarceration, unintentional overdose, and death.[1] In 2021, opioids were the most common drug type involved in unintentional drug-induced deaths in Australia, contributing to 45.7% of total deaths in this category.[2]

Buprenorphine is a partial μ-opioid receptor agonist used in the treatment of OUD which has a safety profile superior to methadone.[3,4] Long-acting injection buprenorphine (LAI-B) is suggested to have multiple benefits for consumers, including greater convenience, less risk of drug diversion and greater medication adherence.[5] In Australia, two formulations of LAI-B were made available in April 2020: Buvidal is given as a weekly or monthly subcutaneous injection, and Sublocade is given as a monthly subcutaneous injection.[5]

A recently published systematic review by Martin et al. focussed their analysis on quantitative and qualitative studies assessing the impact of LAI-B on the social determinants of health, reporting a positive association.[6] Our review hopes to expand on their research, focussing on quantitative studies reporting on the effectiveness of LAI-B in treating OUD, including those not reporting on the social determinants of health, therefore adding further insight and analysis on the effectiveness of this novel medication.

Methods

The review was registered on PROSPERO (CRD: 42023396033) and adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for systematic reviews.[7]

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Search strategy

A database search was performed in January 2023 and repeated in August 2024 using Medline, Embase, PsycInfo and Cochrane CENTRAL. Limits applied included English language and year published 2010 to date of search (timeframe due to the recent development and approval of LAI-B). We accepted randomised control trials (RCT), interventional and observational studies measuring the effectiveness of LAI-B in OUD. The search strategy was sufficiently broad to capture all studies and included the terms: Buprenorphine, injections, sustained, controlled, timed, extended, slow, prolonged, delayed-action, opioid, opioid-related disorders, opioid use disorder, Buvidal, and Sublocade.

Eligibility criteria

Included studies required adults with a diagnosis of OUD who were prescribed LAI-B for at least 3 months' duration. Studies were excluded if patients were pregnant, prescribed LAI-B for an alternative diagnosis (e.g. chronic pain) or prescribed an additional form of opioid replacement therapy.

The primary outcome focus of effectiveness included abstinence from opioids, treatment retention, withdrawal, craving, patient centred outcomes and mortality. Secondary outcomes assessed included safety and the prevalence of reported side effects.

Data collection process

After database search, duplicates were removed. Titles and abstracts were then screened to identify studies meeting inclusion criteria. Studies which met the criteria had full-text articles assessed for eligibility by two independent researchers. For articles without consensus, there was a discussion between both reviewers to address eligibility. Data items collected included authorship, design, demographics, LAI-B prescription, comparison group, use of other medication, outcome measures, and funding sources.

Risk of bias

Randomised control trials were assessed for quality and bias using the Joanna Briggs checklist.[8] Observational studies were assessed using adapted versions of the Cochrane Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool[9] and the Joanna Briggs checklist for quasi-experimental studies.[10] Based on the ratings of each study, two independent researchers agreed on an overall rating of 'low risk of bias', 'some concerns', or 'high risk of bias'.

Data synthesis

Owing to the lack of available quality RCTs and differences in study methodology, data was synthesised using a narrative approach.

Results

Of 1388 studies identified, 1347 studies were excluded during the title and abstract screening. This left 41 studies for full-text assessment, of which, 18 studies were included in the final review. The study selection process is shown in the PRISMA flow diagram (Figure 1).

The studies were conducted across 3 continents including North America (n = 8), Australia (n = 7) and Europe (n = 3). Included studies comprised of two double-blind RCTs,[11,12] two open-label randomised control trials,[13,14] one open-label non-controlled pilot study,[15,] two retrospective cohort studies,[16,17] and eleven observational studies.[18–28] Most of the participants were white, middle-aged, and male. The included studies are summarised in Table 1.

Risk of bias assessment

None of the included studies were 'low risk of bias'. Fourteen included studies declared funding or support from a pharmaceutical company directly involved in the production and distribution of LAI-B.[11–14,18–27]

The RCTs by Lofwall (2018) and Haight (2019) were noted to have 'some concerns', due to potential bias introduced by unmasking of drug administrators, as well as potential bias related to funding source and self-reporting bias in certain outcome domains (mitigated by the use of urine drug screen for the primary outcome).[11,12] The RCT by Lofwall (2018) did not have an accurate measure of compliance in the sublingual suboxone group. The randomised clinical study by Lintzeris (2021) was assessed as having 'some concerns' related to potential bias through lack of blinding influencing the primary outcome of subjective treatment satisfaction.[13] The randomised trial by Marsden (2023) was assessed as having 'some concerns', due to lack of blinding.[14]

Most studies included were open-label, observational in design or utilised single-group pre-post designs. The absence of randomisation, blinding and comparative control group means that these studies were at greater risk of bias from confounding factors. Of the remaining studies, six were assessed as having 'some concerns',[16,18,20,24,25,27] and eight were assessed as being 'high risk of bias'.[15,17,19,21–23,26,28]

Abstinence from opioids

In the RCTs, Lofwall (2018) found LAI-B abstinence rates (17.4%) to be non-inferior to sublingual buprenorphine/naloxone (14.4%) and Haight (2019) found abstinence rates for both LAI-B concentrations (41.3%, 42.7%) were superior to volume matched placebo injection (5.0%, $p <$ 0.0001 for both) measured at multiple intervals over 24 weeks.[11,12]

Lintzeris (2021) found there was no significant difference in abstinence rates between the LAI-B group of 69.9%, and the sublingual buprenorphine group of 73.5% measured

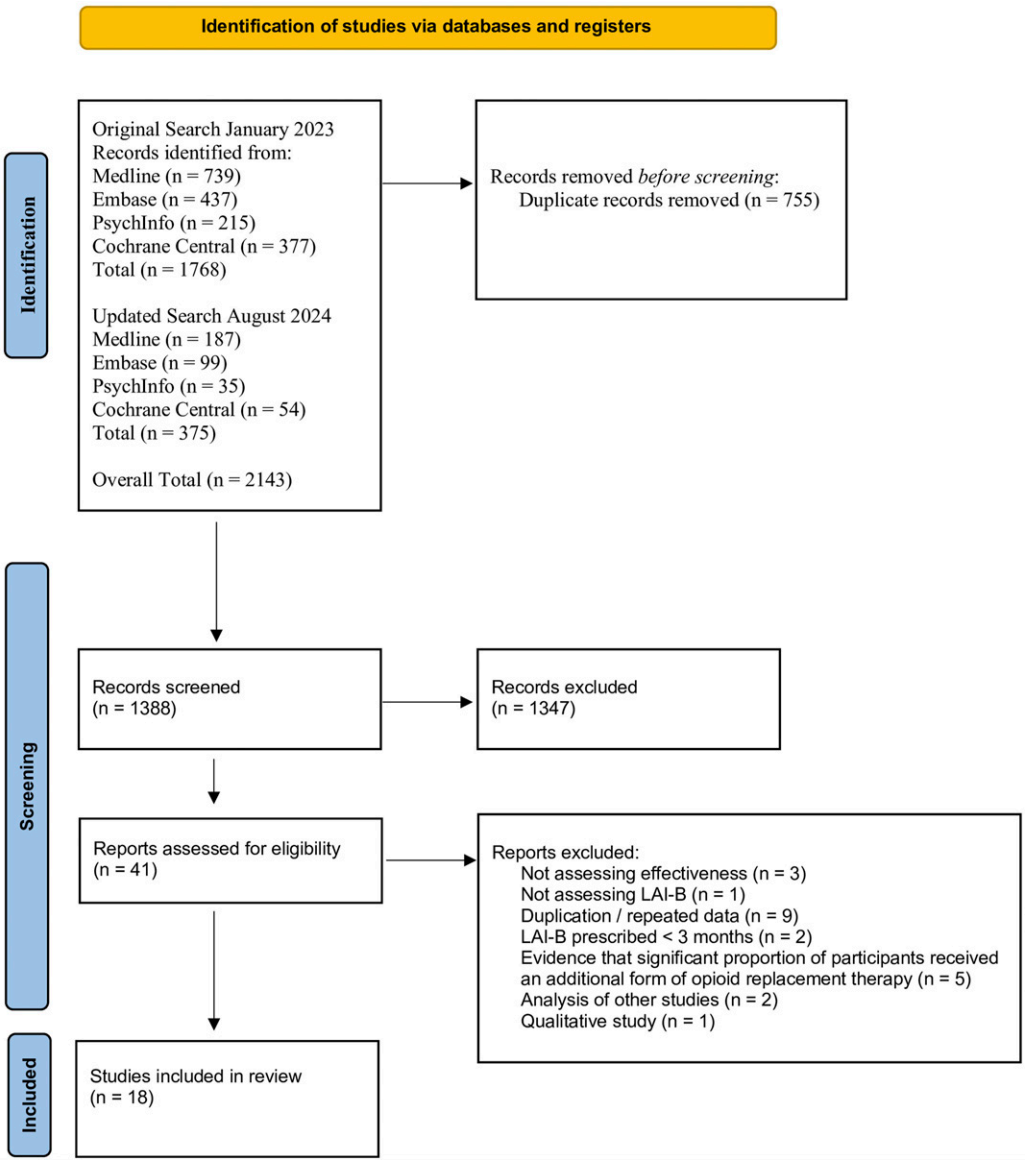

Figure 1. PRISMA flow diagram.

at week 24.[13] Marsden (2023) reported that participants receiving LAI-B had superior abstinence from opioids, with an adjusted mean of 123.43 days abstinent, compared to the group receiving methadone or sublingual/transmucosal buprenorphine who had an adjusted mean of 104.37 days abstinent ($p = 0.004$).[14]

Mlilo (2024) found adults with OUD released from custody on LAI-B had a lower incidence of positive opioid urine tests (10.7%), compared to the group on buprenorphine/naloxone (17.6%) over 6-month follow-up.[17] Hard (2023) reported all participants receiving LAI-B in group 1 remained abstinent from opioids and opioid use in group 2 reduced from baseline to study completion.[15]

As a summation of the remaining observational studies, longer-term abstinence rates ranged from 61.5% for rollover participants at 12 months[19] to 82.8% at 48 weeks for those converted from sublingual buprenorphine.[25] In the correctional setting, self-reported illicit opioid use decreased significantly between baseline (97%) and week 16 (12%) for participants prescribed LAI-B (OR = 0.0035, $p < 0.0001$).[26] Ling (2019) found that 50.8% of participants reported sustained 12-month abstinence and 68.0% reported past-week opioid abstinence at 12 months follow-up.[20] At 4 years follow-up, 55% self-reported abstinence from opioids since the previous study assessment (mean 2.26 years), 69% reported abstinence in the past 30 days and 61.1% of participants met DSM-5 criteria for remission from OUD, but only 43.5% of eligible individuals completed the study.[23] At 96-week follow-up of their single-arm observational trial, Farrell (2024) reported that fewer than one in twenty participants retained on

Table 1. Summary of included studies

Author	Design	Demographics	LAI-B	Comparator	Summary
Lofwall 2018 (USA)	RCT	Adults with moderate-to-severe OUD *n* = 428	Buvidal (16, 24, or 32 mg) weekly then (64, 96, 128, or 160 mg) monthly	Sublingual Buprenorphine/ Naloxone (SL-BUP/ NX) and placebo injection	LAI-B non-inferior to SL-BUP/NX on primary outcome measure for abstinence. Response rates* 14.4% for the SL-BUP/NX group and 17.4% for LAI-B group (95% CI, −4.0% to 9.9%; $p = 0.40$)**
Haight 2019 (USA)	RCT	Adults with moderate-to-severe OUD *n* = 504	Sublocade 300 mg/ 300 mg or 300 mg/ 100 mg monthly	Volume matched placebo injection at same intervals	LAI-B superior to placebo. Mean participants' response rates*** 41·3% for LAI-B 300 mg/300 mg and 42·7% for 300 mg/ 100 mg, compared with 5·0% for placebo ($p <$ 0·0001 for both LAI-B regimens).
Ling 2019 (USA)	Patient-centred outcomes collected during RCT by Haight (2019)	Adults with moderate-to-severe OUD *n* = 487	Sublocade 300 mg/ 300 mg or 300 mg/ 100 mg monthly	Volume matched placebo injection at same intervals	LAI-B (300/300 mg) superior to placebo in change from baseline EQ-5D-5 L Health Questionnaire score ($p = 0.003$). Both concentrations LAI-B superior to placebo in change from baseline EQ-5D-5 L Visual Analogue Scale (VAS) score ($p < 0.005$ for both). Statistically significant improvement in SF-36v2 change from baseline in 6 domains for LAI-B 300/300 mg and in 2 domains for LAI-B 300/100 mg versus placebo.

(Continued)

Table 1. (Continued)

Author	Design	Demographics	LAI-B	Comparator	Summary
Andorn 2020 (USA)	Open-label study with de novo and rollover participants from RCT by Haight et al. (2019)	Adults with moderate-to-severe OUD *n* = 669	Sublocade 300 mg monthly with flexible dosing	N/A	Abstinence**** at 12 months 61.5% for rollover participants and 75.8% for de novo participants. Retention at 12 months 50.6% for rollover participants and 50.5% for de novo participants. The most reported Treatment emergent adverse events (TEAE) leading to dose reduction were sedation (1.9%) and increased liver function value (1.5%).
Lintzeris 2021 (Australia)	Open-label randomised clinical trial	Adults with opioid dependence *n* = 119	Buvidal maximum dose 32 mg weekly or 160 mg monthly	Sublingual Buprenorphine (SL-BUP)	Mean Treatment Satisfaction Questionnaire for Medication (TSQM) global satisfaction score significantly higher in LAI-B group compared with SL-BP group at week 24 (mean score, 82.5 vs 74.3; difference, 8.2; 95% CI, 1.7 to 14.6; $p = 0.01$). Opioid Substitution Treatment Quality of Life scale (OSTQoL) scores were improved in the LAI-B versus SL-BUP group at week 12, but no significant difference between groups at week 24.

(Continued)

Table 1. (Continued)

Author	Design	Demographics	LAI-B	Comparator	Summary
Ling 2020, 1 (USA)	Follow-on study assessing long term outcomes from Haight (2019) and Andorn. (2020)	Adults with moderate-to-severe OUD *n* = 425	Non-interventional	N/A	At 12-month visit 50.8% self-reported sustained 12-month and 68.0% past-week opioid abstinence. Those receiving 12-month versus ≤ 2-month treatment duration had significantly higher likelihood of sustained abstinence (75.3% vs 24.1%; $p = 0.001$) Participants had fewer withdrawal symptoms, lower pain, positive health-related quality of life, minimal depression, and higher employment versus pre-trial visit.
Ling 2020, 2 (USA)	Patient-centred outcomes collected during study by Andorn (2020)	Adults with moderate-to-severe OUD *n* = 412	Sublocade 300 mg monthly with flexible dosing	N/A	EQ-5D-5 L index and VAS scores increased from screening to baseline visits (during the SL-BUP/NX run-in period) and remained stable to end of study period. No significant change in overall EQ-5D-5 L scores noted; however, mental component subset score did improve significantly (mean change 5.00, 96% CI 3.46–6.54) from baseline to end of study. Medication satisfaction questionnaire (MSQ) scores measured were >88% at end of study.

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Table 1. (Continued)

Author	Design	Demographics	LAI-B	Comparator	Summary
Craft 2022 (USA)	4-year follow-on study of participants from study by Ling et al. (2020, 1)	Adults with moderate-to-severe OUD *n* = 216	Non-interventional	N/A	Majority of participants reported abstinence from opioids since the last study assessment (mean 2.26 years; 55%) and in the past 30 days (69%). Participants reported low levels of depression and psychological distress. Employment rates at 4 years higher (33.2%) than pre-trial screening visit (20.3%)
Andrada 2022 (Australia)	Single-arm retrospective cohort study	Adults with opioid dependence *n* = 126	Sublocade 300 mg monthly with flexible dosing	N/A	Overall retention rate at 168 days was 62%. A total of 56 patients (44%) discontinued treatment. The most common reasons were loss to follow-up (38%) planned discontinuation (20%) and return to previous treatment (20%)
Frost 2019 (USA, Australia, Europe)	Open-label, observational trial	Adults with moderate-to-severe OUD *n* = 288	Buvidal maximum dose 32 mg weekly or 160 mg monthly	N/A	Retention in treatment was 73.6% at 48 weeks. Abstinence 63.0% in new-to-BUP participants and 82.8% for those converted from SL-BUP. Participants reported high levels of satisfaction with LAI-B. No serious adverse events were attributed to the study drug.

(Continued)

Table 1. (Continued)

Author	Design	Demographics	LAI-B	Comparator	Summary
Dunlop 2022 (Australia)	Open-label observational study in custodial setting	Adults with moderate-to-severe OUD serving custodial sentence ≥ 6 months *n* = 67	Buvidal maximum dose 32 mg weekly or 160 mg monthly	Daily oral methadone	Retention in LAI-B treatment was 92.3%. No diversion was identified. Prevalence of self-reported opioid use in LAI-B group decreased significantly between baseline (97%) and week 16 (12%, odds ratio = 0.0035, 95% CI 0.0007–0.018, $p <$ 0.0001).
Farrell 2022 (Australia)-	Single arm open-label observational study	Adults with opioid dependence *n* = 100	Sublocade 300 mg monthly with flexible dosing	N/A	Retention at 24 and 48 weeks was 86% and 75%, respectively. The odds of being employed increased 58% for every 4 weeks people were retained in LAI-B (OR 1.58, 95% CI 1.25–2.00). Statistically significant increases in Assessment of Quality of Life (AQoL4D) score by 3% (95% CI: 0.7%–4.8%) for every 4 weeks on LAI-B.
Cotton 2022 (USA)	Open-label observational study	Veterans with OUD *n* = 26	Sublocade 300 mg monthly with flexible dosing	N/A	High attrition rate (65%). Non-significant trend of reduction in healthcare resource utilisation compared to baseline. Homelessness halved from 34.6% at baseline to 15.4% after 6 months. Mortality rate was 23%; however, no deaths were attributed to LAI-B.

(Continued)

Table 1. (Continued)

Author	Design	Demographics	LAI-B	Comparator	Summary
Farrell 2024 (Australia)	Extended follow-up from Farrell (2022)	Adults with opioid dependence *n* = 100	Sublocade 300 mg monthly with flexible dosing	N/A	Retention was 47% at 96 weeks. Median retention time was 90 weeks. Quality of life and treatment satisfaction improved over time for those retained in treatment. Fewer than one in twenty participants retained on LAI-B at week 96 reported past four-week opioid use.
Daglish 2024 (Australia)	Retrospective observational cohort comparison	Adults with OUD *n* = 340	Buvidal (16, 24, or 32 mg) weekly or (64, 96, 128, or 160 mg) monthly Sublocade	N/A	Modal number of injections received was a single dose for 33 (9.7 %) participants. From Kaplan-Meier analysis, median expected duration of first episode LAI-B treatment was 13.1 months, which equated to 87 % of participants expected to remain in treatment at 31 days and 81 % at 62 days. The model predicted that at 1 year 50 % were expected to be still in their first episode of LAI-B treatment, which fell to 41 % at 2 years.
Mlilo 2024 (Australia)	Retrospective cohort study	Adults with OUD released from custody on Suboxone treatment in 2019, and on Buvidal in 2020 *n* = 62	Suboxone or Buvidal (doses not stated)	Sublingual Buprenorphine/ Naloxone (SL-BUP/ NX)	Participants on LAI-B had longer community treatment retention (mean 122.8 days), compared to those receiving SL-BUP/NX (mean 89.4 days). LAI-B group had reduced likelihood of reincarceration (21%) compared to SL-BUP/ NX group (38%).

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Table 1. (Continued)

Author	Design	Demographics	LAI-B	Comparator	Summary
Marsden 2023 (UK)	Pragmatic, parallel-group, open-label, multicenter, randomised, controlled, phase 3 trial	Adults with moderate-to-severe OUD *n* = 314	Sublocade 300 mg/ 300 mg or 300 mg/ 100 mg monthly	Oral methadone (dose range: 60–120 mg) or sublingual/ transmucosal buprenorphine (dose range: 8–24 mg)	LAI-B group had superior abstinence rates based on negative UDS screening (123.43 days) compared to standard treatment group (104.47 days, p = 0.004). LAI-B group had superior retention in treatment (144.6 adjusted total mean days) compared to the standard treatment group (128.5 days, p = 0.029). Safety profile was comparable in both treatment groups.
Hard 2023 (UK)	Open-label, prospective, non-controlled pilot study	Adults with OUD receiving opiate agonist therapy with good adherence (group 1) and poor adherence (group 2) *n* = 15	Buvidal, single weekly dose (16 mg or 24 mg) before transitioning to monthly doses or were given monthly doses from the outset. (64, 96 or 128 mg)	N/A	At 6-month follow-up all of group 1 and 70% of group 2 adhered to LAI-B therapy for the duration of the study. All participants opted to persist with LAI-B after study completion. All participants who remained on treatment demonstrated improvements in psychosocial and clinical severity assessment scores, with some returning to employment or education. Illicit opioid use remained absent in group 1 and was reduced in group 2.

Note. * Response rates defined as urine test result and self-report of drug use both negative for illicit opioids at pre-specified times during study period.

** Mistake noted in manuscript reporting difference in response rates. The correct value is $p = 0.40$, not $p < 0.001$.

*** Response rates defined as the % of each participant's negative urine samples and self-reports of illicit opioid use among 20 weekly opioid use assessments from week 5 to week 24.

**** Abstinence defined as the % of each participant's negative urine samples and self-reports of illicit opioid use at pre-set time periods.

LAI-B self-reported past four-week opioid use at study completion.[18] Longer duration of LAI-B treatment was associated with a significantly higher likelihood of sustained opioid abstinence across multiple studies.[18,20,27]

Treatment retention

In both RCTs, LAI-B treatment retention at 24 weeks was approximately 60%, which compared to 70.7% retention in the sublingual buprenorphine/naloxone group[11] and 34% in the volume matched placebo group.[12] Lintzeris (2021) reported 88.3% retention in the LAI-B group, compared to 93.3% retention in the sublingual buprenorphine group at week 24.[13] Marsden (2023) reported the group receiving LAI-B had superior retention of 144.6 adjusted total mean days in treatment compared to 128.5 days in the group receiving methadone or sublingual/transmucosal buprenorphine ($p = 0.029$).[14]

In the 30-month retrospective observational cohort comparison by Daglish (2024), based in standard clinical settings, the calculated median expected duration of first episode of LAI-B treatment was 13.1 months, which equated to 87 % of participants expected to remain in treatment at 31 days, and 81 % at 62 days. The model predicted that at 1 year 50% were expected to be still in their first episode of LAI-B treatment, which fell to 41% at 2 years. When re-engagement on LAI-B treatment was permitted in the model, the expected proportion in, or back in, treatment at 1 year increased to 61%.[16]

Mlilo (2024) found that former inmates treated with LAI-B stayed in treatment longer with an average of 122.8 days, compared to those treated with sublingual buprenorphine/naloxone, who stayed in treatment for an average of 89.4 days.[17] Hard (2023) reported that all of group 1, and 70% of participants in group 2 who had a history of poor treatment engagement, were retained in LAI-B therapy for the duration of the 6-month study.[15]

In community-based observational studies, retention in LAI-B ranged from 50% at 12 months[22] to 75% at 48 weeks.[27] In an extended follow-up from their open-label, observational trial, Farrell (2024) reported LAI-B treatment retention was 47% at 96 weeks, and median retention in treatment was 90 weeks.[18] Retention in LAI-B ranged from as low as 15% at 16 months in a Veterans Affairs OUD clinic[28] to as high as 92.3% at 113 days in the custodial setting.[26]

Control of craving and withdrawal symptoms

Opioid craving and withdrawal scores remained low in groups receiving LAI-B throughout studies. Marsden (2023) reported that LAI-B was more effective than methadone and sublingual/transmucosal buprenorphine in reducing craving scores.[14] In other studies, craving and withdrawal scores were equivalent to groups receiving other forms of buprenorphine and lower than placebo groups.[12,13,25] In one study, the odds of opioid craving were 38% lower (OR 0.62, 95% CI 0.5–0.76) for those retained in LAI-B across the study.[27]

Patient centred outcomes

Haight (2019) reported that employment rates increased from baseline in both LAI-B groups, in contrast to the placebo group which had a decrease in employment from baseline.[12] Ling (2020, 1) reported on the same study group and found participants receiving LAI-B had significantly fewer problems with anxiety/depression, fewer emergency department visits and fewer total days in hospital compared to those receiving placebo.[20] Both LAI-B groups had statistically significant improvements in quality-of-life questionnaire scores from baseline visits compared to placebo.[20]

Lintzeris (2021) reported that quality-of-life scores significantly improved with LAI-B versus sublingual buprenorphine at week 12. However, there was no difference between the groups at week 24.[13] Mlilo (2024) found that former inmates treated with LAI-B were less likely to be re-incarcerated (21%), compared to those treated with sublingual buprenorphine/naloxone (38%).[17]

As a summation of the observational studies, retention in LAI-B was associated with increased rates of employment,[21,23] lower levels of homelessness,[28] and reduced rates of depression over time.[18,21–23,26] Retention in LAI-B was associated with statistically significant improvement in quality-of-life questionnaire scores compared to placebo and baseline visits, some of which were retained at 12-month follow-up.[22,27] Farrell (2024) reported that improvement in quality-of-life survey responses increased over time for participants retained in treatment, and the odds of participants reporting moderate-to-severe depression declined by 99% from baseline to week 96.[18]

Satisfaction with medication

LAI-B scored favourably on treatment satisfaction surveys. Haight (2019) reported that 88% of participants in the LAI-B groups were satisfied with the medication, compared to 46% of the placebo group.[12] Lintzeris (2021) reported mean Treatment Satisfaction Questionnaire for Medication (TSQM) scores were significantly higher for the LAI-B group (82.5) compared with the sublingual group at week 24 (74.3, $p = 0.01$), and the number needed to treat to achieve a TSQM global satisfaction score of at least 80 was 5.1 for LAI-B versus sublingual buprenorphine.[13]

Farrell (2022) observed that participants receiving LAI-B had a statistically significant increase in treatment satisfaction of 5% for every 4 weeks on LAI-B up to 48 weeks,[27] and in their longitudinal follow-up study reported that participants' global satisfaction scores with LAI-B increased from week 12 to week 96 for those retained in treatment.[18] Hard (2023) reported that at 6-month follow-up, all participants remaining in their pilot study opted to remain on monthly LAI-B therapy rather than return to previous treatment.[15] Frost (2019) asked participants to rate their experience with LAI-B compared with previous

sublingual buprenorphine treatment, with 68.4% reporting that LAI-B was 'much better', while 3% responded that LAI-B was 'much worse' than sublingual buprenorphine.[25]

Safety

LAI-B was well tolerated across the studies and there were no mortality events attributed to the medication. The most common adverse events were injection-site pain, headache, constipation, nausea, vomiting, nasopharyngitis, withdrawal symptoms, injection-site pruritus, and erythema.[11–28] The most common reasons for discontinuation were being lost to follow-up, planned discontinuation, withdrawn consent, and changing OUD treatment.

Discussion

This is the first systematic review synthesising the quantitative evidence on the effectiveness of LAI-B for the treatment of OUD. In comparative clinical trials, LAI-B performed favourably to placebo and was equivalent or superior to other forms of opioid replacement therapy (ORT). Both LAI-B formulations were associated with improvements in abstinence rates and were effective in treating opioid craving and withdrawal. LAI-B was associated with improved quality-of-life outcomes and demonstrated a safety profile consistent with the known profile of buprenorphine.

LAI-B has many advantages over existing forms of opioid replacement therapy (ORT) such as oral methadone and sublingual buprenorphine. Weekly or monthly injections reduce the need for frequent attendance at dispensaries, giving consumers better lifestyle flexibility. This is especially advantageous for those living in rural communities, those with child-care obligations and those who are employed or seeking employment. The enhanced convenience of LAI-B compared to treatment as usual is reflected by high treatment satisfaction and improvement in quality-of-life scores seen across multiple studies included in this review. LAI-B reduces the need for negotiating 'take-away' or unsupervised buprenorphine doses, removing potential secondary gain of minimising intermittent opioid use, reducing the risk of consumers selling prescribed medication for financial gain, and creating a more transparent clinical consultation.[29] Further benefits of LAI-B include reduced risk of drug diversion, improved consumer choice and reduced stigma compared to daily dosing.[5] The protocol of some clinical trials included in this review, such as the double-dummy design by Lofwall (2018), likely negated some of the social benefits of LAI-B which would be more observable in real-world settings.

This review found retention in LAI-B was robust and largely comparable to other forms of ORT, which according to the systematic review by O'Connor (2020) is approximately 57% at 12 months,[30] Two studies in real-world conditions found retention in LAI-B was superior to other forms of ORT.[14,17] Our review included clinical trials which had strict eligibility criteria, controlled conditions and incentives designed to retain participants in treatment, which thus potentially may overestimate the retention seen in real-world settings. A recently published Canadian cohort study by Iacono (2023), which was excluded from our review due to the high proportion of participants receiving supplemental buprenorphine/naloxone, reported that one-year retention in initial LAI-B treatment was much lower at 29.5% in a population with high levels of psychiatric comorbidity and healthcare resource utilisation.[31] Reasons for early discontinuation were unclear, but the high proportion of participants receiving supplemental medication would suggest that some participants may require higher doses of LAI-B, or more frequent dosing, to achieve stability. The authors also reported that around 1/3 of participants who discontinued were subsequently re-initiated on LAI-B treatment, comparable to the Australian observational cohort comparison by Daglish (2024), who reported that the proportion in treatment at 12 months improved from 50% to 61% when re-engagement on LAI-B treatment was permitted in the model.[16] This would suggest that breaks in treatment may be common, but many patients appear willing to subsequently re-engage in LAI-B treatment.

Suggested disadvantages of LAI-B include adverse physical effects associated with injection-site reactions, reduced consumer contact with health professionals, and concerns that the effects of LAI-B can wear off before the next injection is due.[29,32] LAI-B appeared well tolerated throughout the studies and although injection-site reactions were common, most were of mild to moderate intensity.[25] Whilst reduced contact with health professionals may be advantageous for higher functioning individuals, those requiring more intense psychosocial input may benefit from a higher frequency of appointments whilst on LAI-B, and an individualised treatment approach is recommended. Concerns that the injection can wear off early appear to be more common in the initiation phase but should improve once steady-state equilibrium is achieved, which is approximately the fourth dose for Buvidal, the second dose for Sublocade (300/100 mg), and the sixth dose for Sublocade (300/300 mg).[5]

Whilst these are promising short-term results, there is limited data on long-term LAI-B use. In a 12-month follow-up of participants involved in previous clinical trials, only 35% of participants reported that they were still taking LAI-B.[20] At the four-year follow-up of the same participants, it was not clear how many participants continued to take LAI-B and the attrition rate was high.[23] Farrell (2024) reported 47% retention in LAI-B treatment at 96 weeks and had encouraging patient-centred outcomes, but 38% of the remaining participants were observed to have dropped out after 48 weeks.[27] LAI-B showed improvements in short-term quality-of-life measures across multiple studies, but it is unclear if these changes would continue over time.

Limitations

Only two double-blind RCTs were included in the review, and due to their differences in methodology and outcome

reporting, synthesising data in a meta-analysis was inappropriate. The small pilot study by Hard (2023) was included as it met inclusion criteria, whilst acknowledging that the study was underpowered and of higher risk of selection and publication bias.

Several of the studies had the same authors who followed up the same participants longitudinally, which limits the generalisability of overall results.[12,19–23] After consideration, these studies were included in the review because of the unique evidence provided, with care taken not to repeat data in the review. Most studies excluded patients with craving and withdrawal symptoms on entry, which is not reflective of typical patients with OUD who currently use illicit opioids or are chronically relapsing. Most participants were middle-aged, white males, which reflects the most common population contributing to opioid-overdose related fatalities in Australia.[1,2] However, Indigenous Australians are disproportionally affected by opioid-related fatality and had minimal representation in the studies included.[1,2] Other more clinically complex groups, such as patients with comorbid mental illness or chronic pain issues, were not represented in most studies included.

The eligibility requirement of a minimum of 3 months treatment for this systematic review duration does not necessarily reflect steady-state dosing, which is relevant for treatment effectiveness. This data was not easily extractable from included studies, but most used treatment retention as an outcome measure, with evidence that greater retention in treatment was associated with improved outcomes.

This review highlights the need for future focus of research on long-term effectiveness outcomes, with participants of more varied demographics and psychiatric comorbidity, which is more reflective of the OUD population seen in community clinical settings. Barriers to future research will include access to independent funding and longitudinal engagement of participants who tend to be of lower socioeconomic status, with high levels of itineracy and psychiatric comorbidity.[33]

Conclusion

LAI-B is an effective treatment for OUD with advantages over existing forms of treatment. This review highlights the need for future research on long-term effectiveness outcomes, with participants of more varied demographics and psychiatric comorbidity, which is more reflective of the OUD population seen in community clinical settings.

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