REVIEW ARTICLE

The Efficacy and Safety of Injectable Prolonged-Release Buprenorphine (Buvidal) in Adults with Opioid Dependence: A Systematic Review and Meta-Analysis

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Abstract

Background: The development of a long-acting buprenorphine injection may resolve issues of non-compliance, diversion, accidental overdose, and misuse in opiate dependency treatment. Our systematic review and meta-analysis examined safety and efficacy data for prolonged-release Buprenorphine injections.

Methods: Data sources: We searched Ovid, PubMed, Cochrane Library and Google Scholar from inception until 01/10/2022. Intervention was long-acting injectable buprenorphine compared to control including sublingual buprenorphine or placebo. We included RCTs that reported on efficacy and safety outcomes in inpatients and outpatients over 18 years with opiate dependency. Primary outcome measure was treatment efficacy, using the markers negative urine drug screen results and treatment retention. Secondary outcomes focused on side effects.

Results: Regarding treatment retention, Buvidal demonstrated a statistically significant increase compared to the control group (OR = 1.46, 95% CI = 1.12 to 1.89, P=0.005). Regarding negative urine samples, Buvidal again demonstrated a statistically significant increase in negative urine samples compared to the control group (OR = 1.38, 95% CI = 1.26 to 1.52, P < 0.00001). There were no statistically significant differences between the two groups in relation to the secondary outcome measures.

Conclusions: In our experience, this is the only systematic review and meta-analysis regarding efficacy and safety of Buvidal, and our results support its use as a treatment option for recovery of opiate users.

Keywords
Buvidal, Substance Use Disorder, Efficacy, Prevention.

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Introduction

Opiate use and related overdose deaths contribute to a significant worldwide mortality burden and can also lead to an array of physical health issues, psychological distress, and social difficulties for the affected individual[1]. Opioid Use Disorder (OUD) is characterized as a vicious circle of substance misuse and dependence, followed by symptoms of withdrawal and craving, leading to relapse and failure to detoxification[2]. The burden of OUD is well studied and includes physical health issues, financial problems, and reduced life expectancy[3]. People with OUD have worse hospital outcomes, are more likely to die of non-communicable diseases, and have significantly reduced life expectancies compared to the general population[4]. Treatment for opioid maintenance and psychosocial interventions are key elements in the treatment of OUD[5,6,7]. When treating OUD, major aims include reduction of opioid use or abstinence[8,9].
Current medications that are widely available for the treatment of OUD include methadone and sublingual buprenorphine. These medications have limitations to their use, particularly their potential for non-compliance and decreased clinical efficacy and the opportunities for service users to misuse, divert and accidentally overdose on them often despite prescribers' best efforts[10]. Additionally, many service users find the frequency of attendance at the pharmacy for supervised dispensing to be restrictive and inconvenient[1], particularly when they are looking to free themselves of a life revolving around substances and wishing to focus on other areas such as education or occupation.

Buprenorphine, as an injectable extended-release formulation, has been introduced as an option for the treatment of opiate use[11]. Currently, both weekly and monthly preparations are available, and a significantly higher percentage of abstinence for both preparations has been reported in early trials compared to placebo[12]. The benefit of an injectable form includes easy administration by healthcare staff, which reduces the risks of misuse, non-compliance and diversion1. This has the potential to improve the quality of the service user's life. Our systematic review and meta-analysis examined the available efficacy and safety data, with a particular focus on medication-related side effects.

Methodology

Search Strategy and Selection Criteria

The study included randomized controlled trials only, reporting raw data examining efficacy and safety outcomes associated with injectable prolonged-release buprenorphine. All other types of studies were excluded. We included studies with an adult population between 18 and 65 years. We excluded studies that contained data on the buprenorphine implantable device.

Our primary outcome was efficacy, using the surrogate outcomes of retention in treatment and negative urine drug screens. Our secondary outcomes were severe adverse events, drug-related adverse events, mortality, non-fatal serious adverse events, discontinuation, and drug overdose. Four independent reviewers systematically searched the published literature in Google Scholar, PubMed, Cochrane Library and Ovid (EMBASE and Medline) databases. Articles were limited to English text only, and articles published in the last 20 years up until the search date (01/10/2022) were included. Reviewers utilized the snowball method, exploring the reference lists of included articles to identify any additional studies that might fulfil the eligibility criteria and the reference lists of any systematic reviews on the topic. Using the search strategy, two independent authors reviewed the titles of articles produced by each database. The authors then selected the articles for inclusion based on reviewing the abstracts and comparing the full texts against the eligibility criteria (Supplementary-II). Articles for inclusion were discussed among the authors. No automation tools were used in the process of study selection.

A total of 10,202 articles (PubMed 830, Ovid 79, Google Scholar 8920, and Cochrane 373) were returned from the literature searches of the four databases. On reviewing the articles against the inclusion and exclusion criteria, six articles[10,12,13,14,15,16] were shortlisted for data extraction (Figure-1).

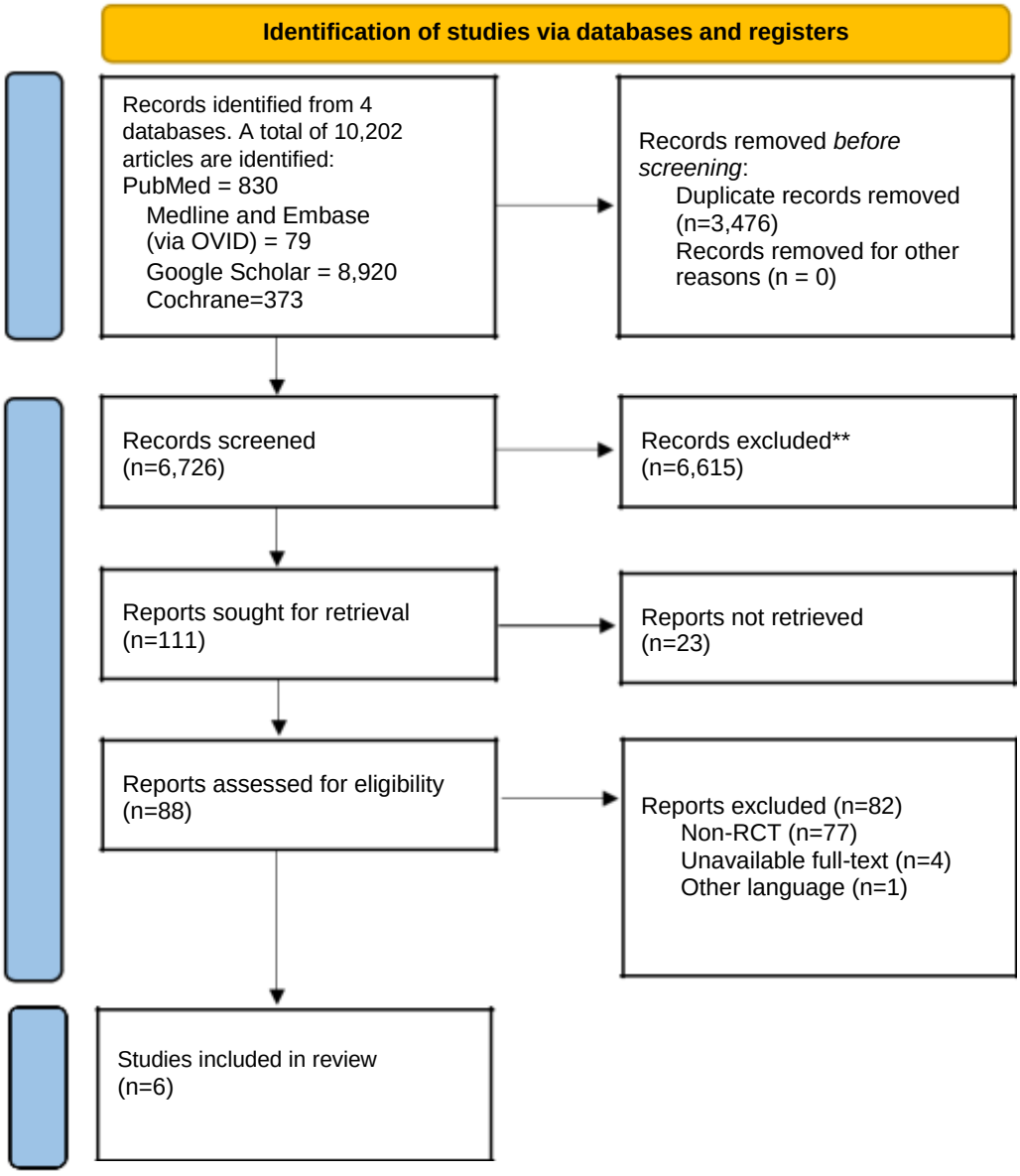

Figure-1 PRISM flow diagram of study selection

The following study characteristics were extracted: publication year, country, journal, study design, study size, study participants and control used. The following study population demographics were extracted: age, sex, and educational attainment (completion of high school) (Table-1).

Table-1 Study characteristics

First author	Publication year	Country	Journal	Study size	Control used	Age (Buvidal vs. control)	Female (Buvidal vs. control)	Did not complete high school (Buvidal vs. control)
Lofwall	2018	USA	JAMA Internal Medicine	428	SL-BPN/NX	38.7 +/- 11.2 vs 38.0 +/- 10.9	92/213 vs. 73/215	36/213 vs. 37/215
Haight	2019	USA	The Lancet	504	Placebo	39.3 +/- 11.0 vs. 40.4 +/- 11.2 vs. 39.2 +/- 11.0	130/390 vs. 35/99	N/A
Lintzeris	2021	Australia	JAMA Network Open	119	SLB	43.6 +/- 10.4 vs. 45.3 +/- 10.6	26/60 vs. 23/59	N/A
Lee	2021	USA	JAMA Network Open	52	SLB	43.1 +/- 9.2 vs. 42.3 +/- 10.8	3/26 vs. 4/26	11/26 vs. 10/26
Andorn	2020	USA	Journal of Clinical Psychopharmacology	669	Placebo	38.4 +/- 12.1 vs. 40.4 +/- 11.1 vs. 42.2 +/- 11.1 vs 43.8 +/- 10.7	227/637 vs. 10/32	N/A
Sigmon	2004	USA	Addiction	13	Placebo	36.2 +/- 1.9 vs. 34.6 +/- 1.9	0/6 vs. 1/7	N/A

Finally, the following outcomes were extracted: the primary outcome measure was efficacy, using the surrogate endpoints of treatment retention and negative urine drug screens; and the secondary outcome measures of discontinuation, drug overdose, mortality, drug-related adverse events, severe adverse events, and nonfatal serious adverse events (Table 2).

Table-2 Primary and secondary outcome data

First author	Negative urine sample	Retention in treatment	Adverse effects (any drug related)	Adverse effects (severe)	Nonfatal serious effects	Mortality	Discontinuation	Drug overdose
Lofwall	1347/3834 vs. 1099/3870	156/215 vs. 147/213	70/213 vs. 64/215	6/213 vs. 15/213	5/213 vs. 13/215	1/213 vs. 0/215	7/213 vs. 3/215	0/213 vs. 5/215
Haight	N/A	254/404 vs. 34/100	289/404 vs. 56/100	28/404 vs. 4/100	11/404 vs. 5/100	1/404 vs. 0/100	17/404 vs. 2/100	0/404 vs. 1/100
Lintzeris	N/A	53/60 vs. 56/60	39/60 vs. 12/59	9/60 vs. 9/59	1/60 vs. 0/59	0/60 vs. 0/59	0/60 vs. 0/59	0/60 vs. 4/59
Lee	72/130 vs. 50/130	18/26 vs. 9/26	N/A	N/A	2/26 vs. 0/26	0/26 vs. 0/26	N/A	0/26 vs.0/26
Andorn	N/A	113/225 vs. 26/32	225/637 vs. 9/32	43/637 vs. 1/32	25/637 vs. 1/32	0/637 vs. 0/32	17/637 vs. 1/32	N/A
Sigmon	N/A	N/A	N/A	N/A	N/A	N/A	0/15 vs. 2/15	N/A

Data and Statistical Analysis

For each article, we completed the CASP (Clinical Appraisal Skills Programme),Randomised Controlled Trial checklist and the Cochrane Risk of Bias scale. The authors completed these assessments independently and compared their results. Any discrepancies were resolved by discussion amongst the authors.

For data synthesis, Review Manager 5.4.1 was used. The odds ratio (OR) was calculated as the summary measure with corresponding 95% Confidence Interval (CI) due to our outcome variables being dichotomous. No summary statistics or requirements for data conversions were missing in our data synthesis.

Given the expected clinical heterogeneity between the included studies, we used a Random Effect (RE) model for the statistical analysis. The robustness of the synthesized results was determined using a sensitivity analysis. Forest plots were produced to demonstrate our results.

Results

A total of 10,202 articles were returned from the literature search of the four databases (PubMed 830, Ovid 79, Google Scholar 8920, and Cochrane 373). All articles were screened by title, with 10,091 being excluded. The remaining 111 articles were included for full-text reviews. Reference list searches of these articles did not reveal any new articles for inclusion. Of the 111 articles, six studies were deemed suitable for the final meta-analysis. All were randomised control trials. There were a total of 1785 participants within the six studies.

Three of the included articles[10,12,13]compared injectable buprenorphine with placebo, two of the articles[14,15] compared with sublingual buprenorphine, and the final article8 compared with 'Suboxone' (an oral preparation of buprenorphine combined with naloxone).

We utilised the RoB2 tool and CASP assessment for certainty and confidence in the quality of data used in our meta-analysis. Authors independently completed the CASP (Clinical Appraisal Skills Programme) Randomised Controlled Trial checklist for each included study. Three of the six studies were double-masked [10,13,16] and one[16] also incorporated a double-dummy design. We found that results from all bar one study[15] could easily be generalised to our target population; Lee[15] specifically examined prison populations. Some[13,14,15] had relatively small sample sizes, whereas others had relatively large sample sizes[10,12,16]. We were unable to identify any other significant methodological concerns with any of the included articles. Two authors independently scored the included articles using the Cochrane Risk of Bias 2 scale. Five of the articles[10,12,14,15,16] were deemed low risk for bias, with the sixth article[13] deemed some concerns (unblinded and 'per protocol' analysis). Due to the small number of available articles, all were included regardless of their RoB2 score. No automation tools were used in the risk of bias assessment (Table-3).

Table-3 RoB2 tool and CASP assessment

Design	Study	Experimental	Comparator	D1 Randomisation process	D2 Deviations from the intended interventions	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall
ITT	Lofwall	Buvidal	Suboxone	+	+	+	+	+	+
ITT	Haight	Buvidal	Placebo	+	+	+	+	+	+
ITT	Lintzeria	Buvidal	SL Bup	+	+	+	+	+	+
ITT	Lee	Buvidal	SL Bup	+	+	+	+	+	+

ITT	Andorn	Buvidal	Placebo	+	+	+	+	+	+
PP	Sigmon	Buvidal	Placebo	!	+	+	+	!	!

Low risk	+
Some concerns	!
High risk	-

To examine our primary outcome of efficacy, we utilised the surrogate endpoints of retention in treatment and negative urine samples. Treatment retention was reported in 5 studies[10,12,14, 15,16]. The Buvidal group was found to be statistically significant for increased treatment retention compared to the control group (OR = 1.46, 95% CI = 1.12 to 1.89, P=0.005). Negative urine samples were reported in 2 studies [15, 16], and again the 'Buvidal' group was found to be statistically significant in its increase in negative urine samples as compared to the control group (OR = 1.38, 95% CI = 1.26 to 1.52, P < 0.00001) (Figure-2).

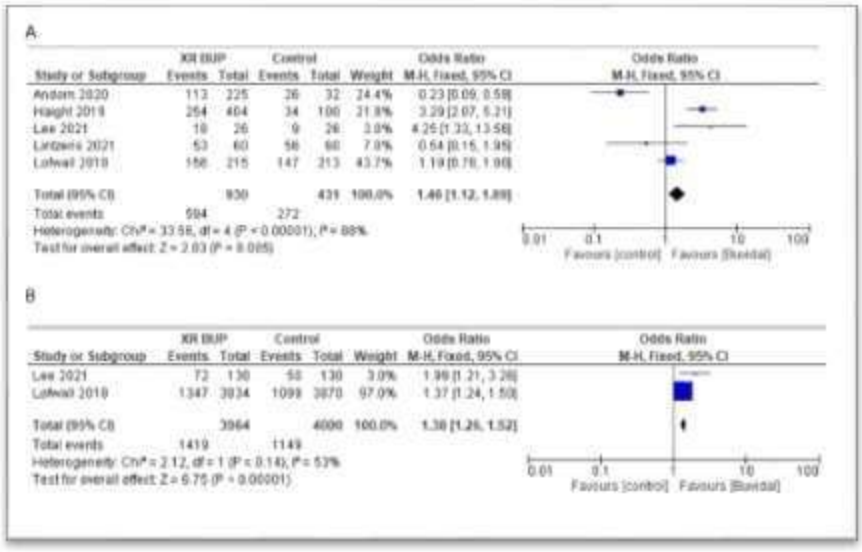

Figure-2 Primary outcomes: Treatment retention (A) and Negative urine samples (B)

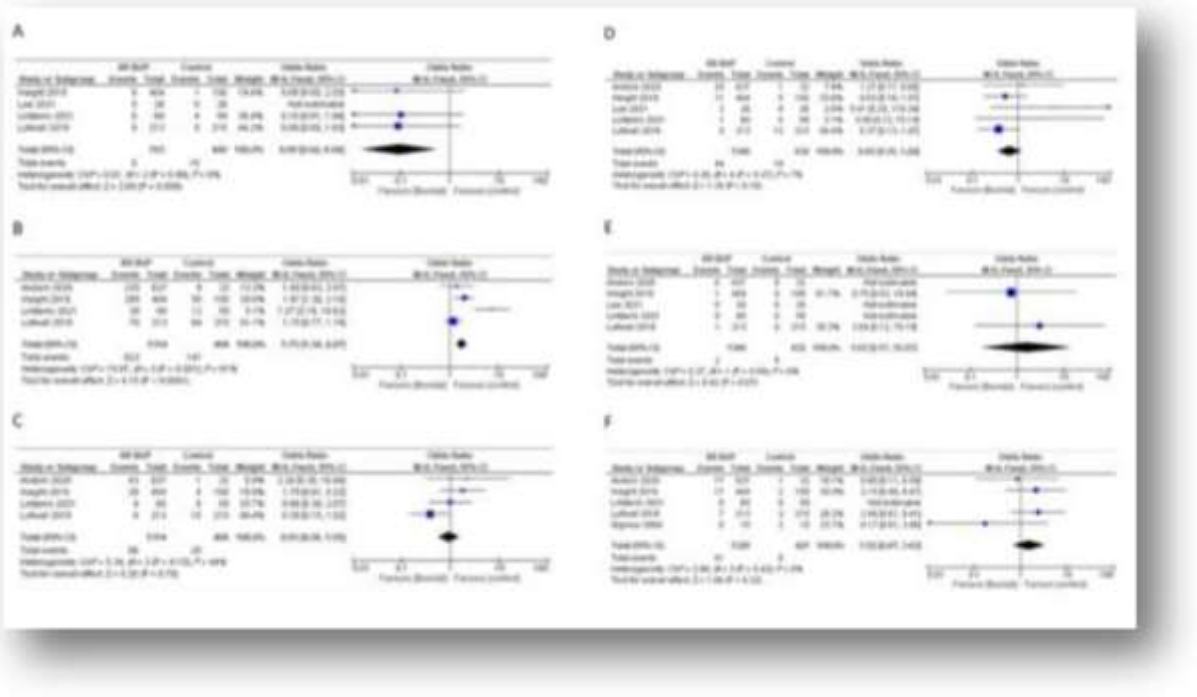

Figure-3 Secondary outcomes: Drug overdoses (A), Drug related adverse events (B), Severe adverse events (C), Nonfatal serious effects (D), Mortality (E) and Discontinuation (F

Drug overdoses were reported in 4 studies[12, 14, 15, 16]. There were no drug overdoses reported in the Buvidal participants in any of the included studies, and hence, there was a statistically significant result (OR = 0.09, 95% CI = 0.02 to 0.56, P = 0.009) in favour of the Buvidal group. Drug-related adverse events were reported in 4 studies[12, 10, 14, 16]. Statistical significance was found to be present in favour of the control group rather than the Buvidal group (OR = 1.75, 95% CI = 1.34 to 2.27, P < 0.0001).

Severe adverse events were reported in 4 studies[10,12,14,16]. There was no statistical difference between the Buvidal and the control group (OR = 0.93, 95% CI = 0.56 to 1.55, P = 0.78). Nonfatal serious effects were reported in 5 studies [10,12,14,15,16]. There were no statistical differences between the Buvidal and the control group (OR = 0.65, 95% CI = 0.35 to 1.22, P = 0.18).

Mortality was reported in 5 studies[10,12,14,15,16]. There were no statistical differences between the Buvidal and the control group (OR = 1.63, 95% CI = 0.17 to 15.57, P = 0.67).

Discontinuation was reported in 5 studies[10,12,13, 14,16]. There were no statistical differences between the Buvidal and the control group (OR = 1.52, 95% CI = 0.67 to 3.43, P = 0.32).

The sensitivity analysis allowed us to understand the effect of individual studies on the overall effect size using the 'leave one out' technique. Removal of any of the individual studies had no effect on the overall outcome or the statistical significance of the results for nonfatal serious effects, mortality, severe adverse events, drug-related adverse events, discontinuation, drug overdose and negative urine samples. However, when we began removing the individual studies, the removal of Haight et al. changed the retention in treatment results from being statistically significant in favour of the Buvidal group to the loss of its statistical significance. This study contains the highest number of participants, which may explain this finding.

We undertook a subgroup analysis on the primary outcome variables, examining if gender or level of education affected the statistical significance of our results. The studies containing the highest proportion of females were Haight and Lofwall, and the studies which collected data on participants who did not complete high school were Lee and Lofwall. Regarding treatment retention, the removal of Haight and Lofwall16] caused a shift from the results being statistically significant in favour of the Buvidal group to losing its statistical significance, which implies that females have better treatment retention.

Regarding negative urine samples, there was no change in the statistical significance in favour of Buvidal on the removal of Lofwall, a study which contained a high proportion of female participants. This implies that gender has no bearing on the results.

The removal of Leeand Lofwall to explore the relationship between the level of education (completion of high school) and treatment retention does not have any effect on the results. Lee and Lofwall were the only two studies that commented on both negative urine samples and completion of high school; therefore, we cannot comment on the effect. Lintzeris (an Australian study) was the only study undertaken outside of the USA. We undertook a subgroup analysis to examine whether this would affect the results of the various outcomes. We found that removal of Lintzeris resulted in no change in treatment retention, nonfatal serious effects, discontinuation, drug overdose, mortality, drug-related adverse events, or severe adverse events. This implies that the location of the study does not have any effect on the results. Due to having fewer than ten articles, we were unable to construct funnel plots to assess for publication bias.

Discussion

The long-acting buprenorphine formulations have significantly widened the therapeutic arena in OUD treatment[17,18]. It provides an opportunity to reduce the risk of diversion, and treatment

retention will be more significant[19, 20]. The data reviewed provides evidence that the long-acting buprenorphine formulations are as efficient as sublingual buprenorphine as a substitute treatment with a comparable side effect profile except for some side effects related to injection [21]. Other observational studies on these medications are ongoing to provide further safety data[19, 20].

We noted similar findings in our study. Our primary outcome was efficacy, using the surrogate endpoints of retention in treatment and negative urine samples. Retention in treatment and negative urine samples were statistically significant in favour of Buvidal as opposed to the control group. Our secondary outcomes focussed on the safety and tolerability of Buvidal. Results from the Buvidal group showed no statistically significant differences compared to control groups for severe adverse events, nonfatal serious effects, mortality, and discontinuation. This difference demonstrates the similarity of crucial safety outcomes between Buvidal and the controls. Of note, drug overdoses were found to be statistically significant in favour of the Buvidal group, which would be advantageous. Conversely, we found that drug-related adverse events were statistically significant in favour of the control group.

The strength of our systematic review and meta-analysis is that it is the first to examine the efficacy and safety of long-acting buprenorphine injections. We assessed randomized and controlled trials only as they provide the highest quality of evidence. The study supports the hypothesis that Buvidal is more effective in keeping service users in treatment and maintaining negative urine samples, meaning they stay in treatment and maintain abstinence longer than those on other forms of opiate substitution. It is also considered to be as safe as other treatments for opiate dependence. Of note, there were fewer drug overdoses in the Buvidal group than control, and this was a statistically significant result.

There were a few limitations in our study. Buvidal is a relatively new medication; therefore, few Randomised Controlled Trials were available at the time of writing. Although the included studies were deemed acceptable regarding their methodology, some were open-label in their design[10, 14, 15], and some involved only a small number of participants[13,15].

We could not complete a publication bias assessment due to the availability of less than ten articles.Future research in this area would look to incorporate any new Randomised Controlled Trials, particularly comparing Buvidal to other forms of opiate substitution therapy such as Methadone or the Buprenorphine implant.

Conclusion

This systematic review has confirmed existing evidence that service users tolerate Buvidal well, that serious adverse effects are no more likely than with using other Buprenorphine preparations, and that they can abstain from illicit opiate use for longer. It supports the continued use and funding of this relatively new treatment, enabling its expansion to reach as many service users as possible.

Acknowledgment
Nona.

Conflict of Interest
None.

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None.

REFERENCES

1. Frost M, Bailey GL, Lintzeris N, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. Addiction (Abingdon, England). 2019;114(8):1416-1426. doi: https://doi.org/10.1111/add.14636.
2. Svenaeus F. Diagnosing mental disorders and saving the normal: American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, American Psychiatric Publishing: Washington, DC. 991 pp., ISBN: 978-0890425558. Price: $122.70. Medicine, Health Care and Philosophy. 2014 May; 17:241-4.
3. Chang KC, Lee KY, Lu TH, Hwang JS, Lin CN, Ting SY, Chang CC, Wang JD. Opioid agonist treatment reduces losses in quality of life and quality-adjusted life expectancy in heroin users: Evidence from real world data. Drug and alcohol dependence. 2019 Aug 1; 201:197-204.
4. Nordeck CD, Welsh C, Schwartz RP, Mitchell SG, Cohen A, O'Grady KE, Gryczynski J. Rehospitalization and substance use disorder (SUD) treatment entry among patients seen by a hospital SUD consultation-liaison service. Drug and alcohol dependence. 2018 May 1; 186:23-8.
5. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, Bruneau J, Altice FL, Henderson G, Rahimi-Movaghar A, Larney S. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet 2019; 394: 1560-1579.
6. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. Lancet 2019; 393: 1760-1772.
7. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies--tackling the opioid overdose epidemic. N Engl J Med 2014; 370: 2063-2066.
8. Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. Drug Alcohol Depend 2001; 62: 255-264.
9. Bell J. Pharmacological maintenance treatments of opiate addiction. Br J Clin Pharmacol 2014; 77: 253-263.

10. Andorn AC, Haight BR, Shinde S, et al. Treating Opioid Use Disorder With a Monthly Subcutaneous Buprenorphine Depot Injection: 12-Month Safety, Tolerability, and Efficacy Analysis. Journal of Clinical Psychopharmacology. 2020;40(3):231-239.
11. NICE National Institute for Health and Care Excellence. Opioid dependence: buprenorphine prolonged-release injection (Buvidal) [Internet]. 2019 [cited 23 October 2023]. Available from: Opioid dependence: buprenorphine prolonged-release injection (Buvidal) (nice.org.uk).
12. Haight BR, Learned SM, Laffont CM, et al. Efficacy and Safety of a Monthly Buprenorphine Depot Injection for Opioid Use Disorder: A Multicentre, Randomised, Double-Blind, Placebo-Controlled Trial. SSRN Electronic Journal. Published online 2018.
13. Sigmon SC, Wong CJ, Chausmer AL, Liebson IA, Bigelow GE. Evaluation of an injection depot formulation of buprenorphine: placebo comparison. Addiction. 2004;99(11):1439-1449.
14. Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-Reported Outcomes of Treatment of Opioid Dependence with Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine. JAMA Network Open. 2021;4(5): e219041.
15. Lee JD, Malone M, McDonald R, et al. Comparison of Treatment Retention of Adults with Opioid Addiction Managed with Extended-Release Buprenorphine vs Daily Sublingual Buprenorphine-Naloxone at Time of Release from Jail. JAMA Network Open. 2021;4(9): e2123032.
16. Lofwall MR, Walsh SL, Nunes EV, et al. Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder. JAMA Internal Medicine. 2018;178(6):764.
17. Soyka M. Novel Long-Acting Buprenorphine Medications for Opioid Dependence: Current Update. Pharmacopsychiatry 2021; 54: 18-22.
18. Allikmets S, Vink JP. Clinical applications of buprenorphine depot injection for opioid use disorder. Addiction 2020; 115: 190.
19. Schulte B, Lehmann K, Schmidt CS, Rühling E, Weber B, Schäfer I, Reimer J, Verthein U. Addiction Recovery Among Opioid-Dependent Patients Treated With Injectable Subcutaneous Depot Buprenorphine: Study Protocol of a Non-randomized Prospective Observational Study (ARIDE). Front Psychiatry 2020; 11: 580863.
20. Larance B, Byrne M, Lintzeris N, Nielsen S, Grebely J, Degenhardt L, Shahbazi J, Shanahan M, Lancaster K, Dore G, Ali R, Farrell M; CoLAB study team. Open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: protocol for the CoLAB study. BMJ Open 2020; 10: e034389.

21. Coe MA, Lofwall MR, Walsh SL. Buprenorphine pharmacology review: update on transmucosal and long-acting formulations. Journal of addiction medicine. 2019 Mar;13(2):93.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design: William L

Acquisition, Analysis or Interpretation of Data: Saima, Dhandapani, A

Manuscript Writing & Approval: Ikuewumi O

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.