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Long-acting injectable buprenorphine for opioid use disorder: A systematic review of impact of use on social determinants of health

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ABSTRACT

Objectives: This systematic review synthesizes evidence on both the effects and perspectives of the use of novel long-acting injectable buprenorphine (LAIB) as part of medication-assisted treatment (MAT) and its impact on social determinants of health (SDH), specifically abstinence, accessibility, employment, forensic matters, and gender and social relationships via a framework approach.

Methods: The study team searched three databases between January 2010 and June 2020 to identify English-language original research published in peer reviewed journals. This search yielded 9253 papers. A comprehensive search followed by 67 full text publication screenings by two independent reviewers yielded 15 papers meeting inclusion criteria. The study included three randomized control trials, one open label safety study, two case series, and six qualitative papers examining patient perspectives toward the LAIB prior to use. The team assessed the quality of studies via standardized quality assessment tools.

Results: The LAIB was positively associated with improvements in abstinence, accessibility, employment, social relationships, and forensic matters. Limited evidence exists on gender equity within the current literature. The qualitative papers highlighted the importance of patients' preferences and individualization of treatment planning to ensure the success of MAT.

Conclusion: The quality of evidence was rated as medium or high risk of bias, which does limit interpretation of the results. Overall, the LAIB was positively associated with SDH and should be offered as part of MAT in alignment with the recovery model. Future research should evaluate the implementation and longitudinal impacts of LAI buprenorphine compared to treatment as usual (TAU).

1. Introduction

Opioid use disorder (OUD) is characterized as a problematic cycle of substance intoxication and binging, followed by associated withdrawal and craving, which contributes to compulsive relapses (American Psychiatric Association, 2013). The well-recognized global burden of OUD includes significant physical, economic, and social consequences, amounting to 16.6 million disability-adjusted life-years (DALYs) (Degenhardt et al., 2019). People with OUD have worse hospital outcomes, are more likely to die of noncommunicable diseases, and have significantly reduced life expectancies compared to the general population (Lewer, Jones, Hickman, Nielsen, & Degenhardt, 2020; Nordeck et al., 2018).

Causation and course of OUD are complex, with research increasingly recognizing the interplay between individual and social factors in the development and perpetuation of OUD (Gowing et al., 2014). While genetic and physiological characteristics can predispose individuals to OUD, social determinants of health (SDH)—defined by the World Health Organization (WHO) as the conditions in which "people are born, grow, live, work and age" (World Health Organization, 2021)—play critical

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roles. Understanding the diverse influences underlying the onset and maintenance of OUD is necessary for effective prevention and intervention strategies. The SDH framework is aimed at identifying and addressing factors that impact health outcomes (Marmot & Wilkinson, 2005; Wilkinson & Marmot, 2003). SDH include the domains of employment, social exclusion, public health programs, gender equity, early child development, globalization, health systems, urbanization, and measurement and evidence (see Table 1) (Wilkinson & Marmot, 2003).

Screening and measuring for SDH has gained recognition recently within the health literature, although no widely used validated tool exists (Andermann, 2018; Garg, Toy, Tripodis, Silverstein, & Freeman, 2015; Shokoohi et al., 2019). Shokoohi et al. (2019) explored the association of opioid and stimulant use in women living with human immunodeficiency virus (HIV) and found that vulnerabilities within SDH were associated with higher substance use rates. Furthermore, in a large longitudinal prospective cohort study of 615 heroin users, greater time spent in treatment for OUD was associated with improvements in aspects of SDH, such as criminality, psychopathology, and mental health (Teesson et al., 2008). This evidence suggests that optimization of SDH as part of effective treatment may positively impact the lives and health outcomes of those with OUD.

The current gold standard treatment of OUD is medication for addiction treatment (MAT) (Kourounis et al., 2016). MAT is often provided in combination with harm minimization strategies using a biopsychosocial approach that has been found to improve retention rates, mental and physical health, as well as reduce illicit opioid use, criminal behaviors, and risky injecting habits (American Society of Addiction Medicine, 2015; World Health Organization, 2009; Gowing et al., 2014; National Institute for Health and Care Excellence, 2007; Degenhardt et al., 2019; Teesson et al., 2008). Pharmacological interventions of MAT encompass a range of opioid agonists and antagonists, including buprenorphine, methadone, hydromorphone, and naltrexone (National Institute for Health and Care Excellence, 2007; World Health Organization, 2009; American Society of Addiction Medicine, 2015). Research has found MAT to be economically effective (Connock et al., 2007; Kenworthy et al., 2017), and to improve health outcomes with reduced quality-adjusted life-years lost compared to no treatment or non-pharmacological interventions (Bray et al., 2017; Chang et al., 2019; Mitchell et al., 2015; Ponizovsky & Grinshpoon, 2007).

Table 1
The social determinants of health.

The social determinants of health	Description
Employment	The ability for people to access and sustain fair employment opportunities and working conditions with regards to the influence of both illness and treatment.
Social exclusion	Social exclusion is driven by unequal power relationships interacting across economic, political, cultural, racial and social aspects at all levels of health, and the use of the health care systems to correct potential inequalities.
Public health programmes	Utilizing public health programmes effectively to address health inequity, via the design, implementation and access.
Women and gender equity	Striving to improve gender equity in all aspects of health.
Early child development	The implementation of child health programmes that are inclusive of physical, social, emotional and cognitive development.
Globalization	The ability for increasing global connectedness, global marketplaces and global governance to bolster or erode health care systems impacting on healthcare markets and economic security.
Health systems	Ensuring health systems are designed to support the health needs of all populations, including those who are disadvantaged and marginalised.
Measurement and evidence	Ensuring the impact health programmes have on social determinants of health and health inequality is measured and that health programmes are implemented in an evidence-based manner.
Urbanization	Healthy urbanization through town planning and development is paramount to ensure healthy living, working and social environments.

(Marmot & Wilkinson, 2005).

Despite these benefits, opioid-based MAT in its current form has several limitations. The need for medication collection, often daily, has attracted the nickname "liquid handcuffs" (Wood, Opie, Tucci, Franklin, & Anderson, 2019). Sublingual buprenorphine (SLB) preparations have provided dosing flexibility, due to its reduced risk of overdose and long half-life (American Society of Addiction Medicine, 2015; Gowing et al., 2014; World Health Organization, 2018; National Institute for Health and Care Excellence, 2007). Despite these improvements, retention in MAT remains low (Gryczynski et al., 2014; O'Connor, Cousins, Durand, Barry, & Boland, 2020). A recent systematic review analyzing almost 300,000 participants from 21 countries reported that more than half (57%) of people in MAT were not retained at 12 months, and participation rates continued to decline over time, with 38.4% retained at three years (O'Connor et al., 2020). Several psychosocial factors were positively associated with retention, including stable relationships, accommodation, and employment (O'Connor et al., 2020). Risk factors for treatment disengagement included criminal activity, homelessness, and unemployment (O'Connor et al., 2020). MAT, with its frequent dispensing, may negatively impact SDH, and treatment should monitor and address psychosocial factors (Gryczynski et al., 2014; O'Connor et al., 2020). Long-acting injectable and implantable naltrexone are alternatives to that of its oral preparation and opioid-based preparations and research has shown them to improve retention rates, and reduce relapse rates and mortality rates (Ma et al., 2019; Reimer et al., 2011). The introduction of novel pharmacological formulations of opioid-based treatments could overcome some of these limitations and may have implications for SDH of people with OUD.

In 2017, the Food and Drug Administration (2017) approved use of long-acting injectable buprenorphine (LAIB) in a monthly preparation, which offered an alternative to daily dosing. Treatment options were further expanded in 2018 with the approval of a weekly LAIB (Camarus, 2018). LAIB allows for sustained plasma levels and is considered a safe and effective treatment option for OUD in clinical trials; however, we know little about associated psychosocial impacts for those with OUD (Haight et al., 2019; Ling et al., 2020). Given the benefits of long-acting naltrexone, LAIB may be uniquely placed to improve retention, lessen the burdens of daily medication collection, and lessen the risk of diversion with MAT. LAIB may improve SDH via better treatment accessibility; and promote abstinence, employment, education, childcare, and social equity by providing sustained therapeutic levels and reducing the burden of frequent dosing. The primary objective of this review was to characterize the psychosocial impact of the novel LAIB as a treatment for those with OUD, utilizing the SDH framework. In the context of a novel treatment and the anticipated small, emerging body of relevant literature, our secondary aim was to examine studies that evaluated the perception of those with OUD who had not received LAIB (LAIB-naïve), utilizing the SDH framework.

2. Materials and methods

2.1. Protocol and search strategy

The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). This review was not prospectively registered. The study team searched three databases, PubMed, Embase and Scopus, for original articles published in peer-reviewed journals between January 2010 and June 2020. The team applied to these databases MeSH terms, keywords, Scopus field codes, and explosion of terms: "buprenorphine" and "opioid use disorder" or

"opiate addiction" and "dependence" (Scopus only field code) (see Appendix 1). This search string was intentionally broad to ensure it captured all relevant data, as there is no universally accepted term for LAIB, and SDH is emerging area in the literature. The team did not apply any language restrictions, and potentially relevant non-English language articles were translated. The team limited the search to publications after and including 2010 due to the recent development and release of LAIB. The study team imported all references into an Endnote X9 database, where we removed duplicates. Two authors (EM and HM) independently screened titles, abstracts, and assessed the articles at full text. The research supervisor (KYC) resolved disagreements. At full text review, the team hand searched reference lists to identify any other relevant articles.

2.2. Eligibility criteria

The following study designs were eligible for inclusion: case series, observational cohort, qualitative, and interventional studies. The study excluded grey literature. Inclusion criteria included: (1) described LAIB treatment outcomes, or LAIB-naïve participant perspectives regarding potential treatment with this agent; (2) reported, directly, or indirectly, on the SDH in relation to the provision of LAIB; and (3) published in a peer-reviewed journal. Studies were excluded where: (1) subjects were not human; (2) buprenorphine was given or explored only in any preparation form other than LAI (i.e., oral, sublingual, transdermal, or implantable); and (3) participants were not diagnosed with active or historic OUD (e.g., persistent pain).

2.3. Data extraction and synthesis

The study extracted the following information from included studies and tabulated: study design, location, participant demographics, interventions, outcomes including participant perspectives on LAIB, and data on the SDH. The team did not consider meta-analysis appropriate due to the heterogeneity of data collected across identified studies, including the intervention selected, study design, duration of treatment, and outcome measures. Furthermore, we required a qualitative framework to address the research objectives.

The team selected a framework analysis to synthesize identified qualitative information; this approach combines deductive and inductive logic to address a priori research questions while enabling attention to unanticipated material (Bryman & Burgess, 1994). To ensure analytical rigor, the co-authors followed the five-step process, first becoming familiar with material through repeated reading of included studies. The team coded findings into themes to identify relevant psychosocial impacts of LAIB. Identified themes were then coded into categories of SDH as per the WHO to ensure the development of a contextualized summary of findings. The co-authors did the coding independently before a critical discussion to ensure appropriate categorization, and to determine if data fell into more than one category.

2.4. Quality assessment

Included studies were subjected to quality appraisal. For randomized studies, the team used the Revised Cochrane Risk-of-bias tool (Sterne et al., 2019). The study assessed qualitative studies using the Critical Appraisal Skills Programme (CASP) tool (Critical Appraisal Skills Programme, 2018). The team assessed observational studies using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016). To facilitate comparison between the different quality appraisal tools, and account for those instruments that yielded no rating, the team took a tripartite approach to provide an overall quality rating of either good, fair, or poor. The team reached these ratings through discussion to achieve consensus. Given the recency of LAIB and the nature of thematic analysis, the team decided that it would include low quality studies in the context of exploring relevant insights important for overall interpretation in an emerging area of literature.

3. Results

3.1. Included studies

The search strategy yielded 9258 studies, with 15 meeting inclusion criteria after full-text review (Fig. 1). Three papers included randomized control trials (Haight et al., 2019; Ling et al., 2019; Lofwall et al., 2018). Ling et al. (2020) reported on a non-randomized, open-label safety study. Our search also yielded a second non-randomized trial (Frost et al., 2019), six semi-structured qualitative interviews (Neale, Tompkins, McDonald, & Strang, 2018a, 2018b; Neale, Tompkins, & Strang, 2019a, 2019b; Saunders et al., 2020; Tompkins, Neale, & Strang, 2019), two surveys (Gilman et al., 2018; Larance et al., 2020), one case series (D'Agnone, 2019), and one case report (Farahmand, Kim, Twark, & Suzuki, 2020).

Two of the randomized trials, Ling et al. (2019) and Haight et al. (2019) examined the same trial (NCT02357901) but reported on different outcomes. These participants were invited to participate in the trial (NCT02510014) examined by Ling et al. (2020) though the paper only reported on the de novo participant group and excluded those already reported on by Ling et al. (2019) and Haight et al. (2019).

The team identified qualitative papers in which two participant groups had been reported on in multiple studies. Two papers had reported on the first group (Neale et al., 2018a, 2018b) and three papers reported on the second group (Neale et al., 2019a, 2019b; Tompkins et al., 2019). The authors, EM, HM and KYC, determined that the papers had their own individual merit with regard to SDH and warranted independent inclusion and analysis.

Seven studies (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Haight et al., 2019; Ling et al., 2019, 2020; Lofwall et al., 2018) reported on outcomes of LAIB treatment. Eight studies evaluated LAIB-naïve participants' perspectives (Gilman et al., 2018; Larance et al., 2020;Neale et al., 2018a, 2018b, 2019a, 2019b; Saunders et al., 2020; Tompkins et al., 2019). The most geographically diverse study was conducted across 26 outpatient sites in the United States, United Kingdom (UK), Hungary, Denmark, Sweden, Germany, and Australia (Frost et al., 2019). All other studies were conducted in either the United States (Farahmand et al., 2020; Haight et al., 2019; Ling et al., 2019, 2020; Lofwall et al., 2018; Saunders et al., 2020), the UK (D'Agnone, 2019; Gilman et al., 2018; Neale et al., 2018a, 2018b, 2019a, 2019b; Tompkins et al., 2019), or Australia (Larance et al., 2020). No studies included countries from South America, Asia, or Africa. See Appendices 2 and 3 for a summary of included studies and outcomes.

3.2. Participant information

This systematic review included a total of 2293 participants with either historical or current OUD. The average age of participants ranged from 36 to 52 years. Most participants (approximately 60%) were male and of Caucasian ethnicity (>50%), with the remainder comprising other ethnic backgrounds including Asian, Black, Hispanic, and Latino. Occupational status was not consistently reported across all studies; however, for those that did, employment (full or part-time) ranged from 32% to 56% (D'Agnone, 2019; Frost et al., 2019; Gilman et al., 2018; Haight et al., 2019; Larance et al., 2020; Ling et al., 2019, 2020; Lofwall et al., 2018; Saunders et al., 2020).

3.3. Risk of bias and quality assessment

The methodological quality of the studies ranged from poor to fair, with only one study (Saunders et al., 2020) rated as good (see Appendix 4). Regarding risk of funding bias, eleven studies were either directly or indirectly funded by pharmaceutical companies involved in LAIB development (Frost et al., 2019; Haight et al., 2019; Larance et al., 2020;

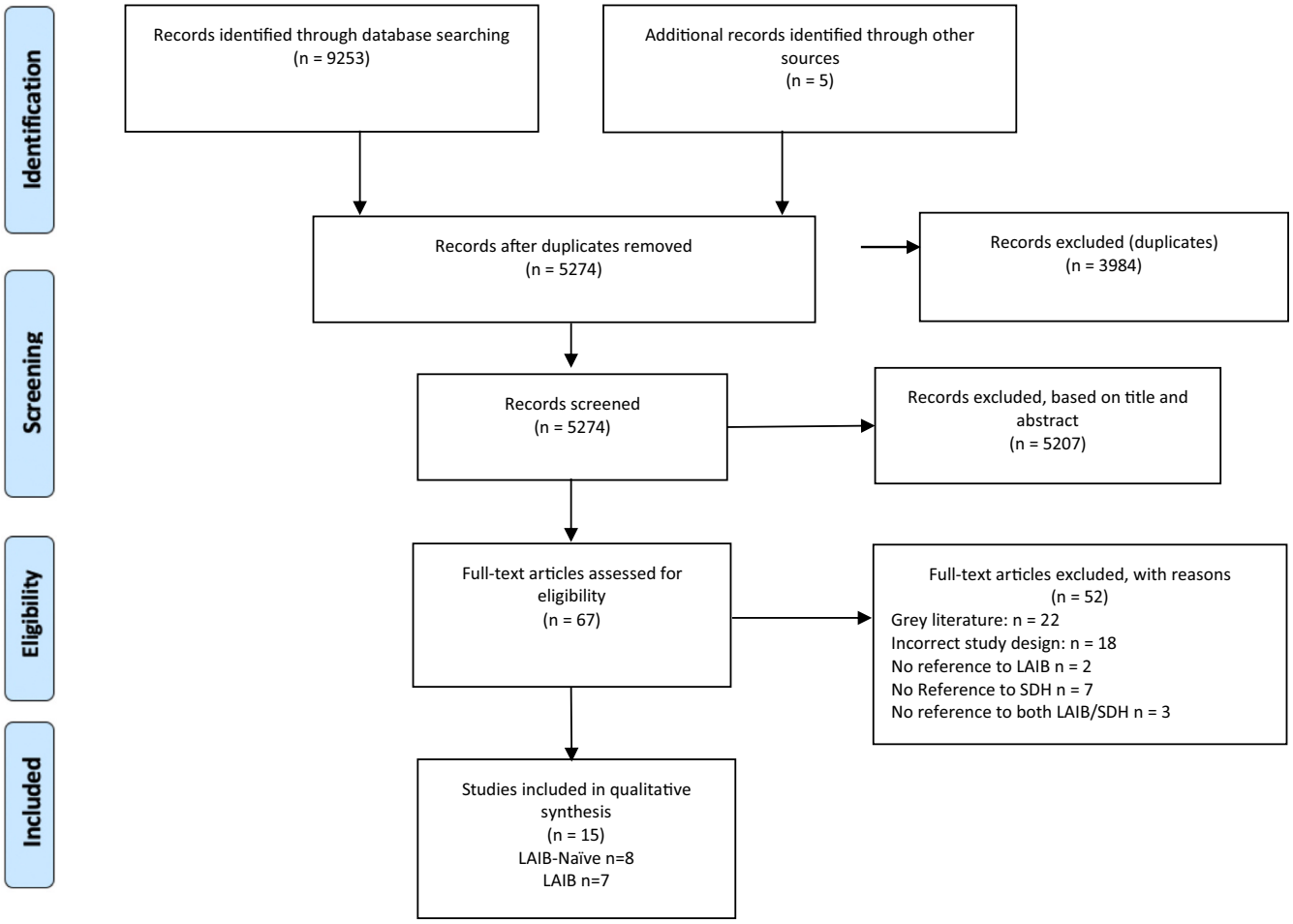

Fig. 1. PRISMA flow diagram.

Ling et al., 2019, 2020; Lofwall et al., 2018; Neale et al., 2018a, 2018b, 2019a, 2019b; Tompkins et al., 2019). Within the qualitative studies, the use of focus groups (Neale et al., 2018a, 2018b) and interviewers (Neale et al., 2018a, 2018b, 2019a, 2019b; Saunders et al., 2020; Tompkins et al., 2019) potentially introduced group-think and interviewer biases, which may have influenced their results. The only study (Lofwall et al., 2018) that directly compared LAIB to SLB did not have a measure of compliance in the SLB treatment arm, which presented a significant confound to the interpretation of their results. Multiple studies reported on three unique participant groups (Haight et al., 2019; Ling et al., 2019; Neale et al., 2018a, 2018b, 2019a, 2019b; Tompkins et al., 2019), constraining generalizability of overall results.

3.4. Results of thematic analysis

The psychosocial impact of LAIB was summarized in six identified themes utilizing the SDH Framework. These included abstinence, accessibility, employment, forensic, gender, and social relationships (see Table 2 and Table 3). Of note, the team did not identify themes relating to globalization and urbanization as SDH. No studies explored practical implications for the introduction of LAIB into health systems. Studies underutilized measurement tools relating to SDH or psychosocial factors, with only four measures identified including: 36-item Short-Form Health Survey (SF-36v2) (Ware et al., 2008), 5-Level EQ-5D (EQ-5D-5L) (Herdman et al., 2011), Addiction Severity Index-Lite (ASI-Lite) (McLellan, Luborsky, Woody, & O'Brien, 1980), or the Treatment Effectiveness Assessment (TEA) (see Appendix 3; Ling, Farabee, Liepa, & Wu, 2012).

3.5. Abstinence

The study divided abstinence as a theme into subcategories of: (1) reduction or cessation of illicit opioid use; (2) cravings; and (3) treatment satisfaction of LAIB, as these were considered important elements in identifying an individual's ability to have their clinical and psychosocial needs met and engage in an MAT program. Fourteen out of the 15 studies examined abstinence (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Gilman et al., 2018; Haight et al., 2019; Larance et al., 2020; Ling et al., 2019, 2020; Lofwall et al., 2018; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019).

3.5.1. Opioid reduction or cessation

Thirteen studies directly discussed opioid reduction or cessation (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Gilman et al., 2018; Haight et al., 2019; Larance et al., 2020; Ling et al., 2020; Lofwall et al., 2018; Neale et al., 2018a, 2018b; Neale et al., 2019b; Saunders et al., 2020; Tompkins et al., 2019). Gilman et al. (2018) described abstinence from illicit substances as the most common goal for engaging in MAT. Seven studies (Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019) identified that LAIB-naïve participants believed the LAIB would have a positive impact in supporting their autonomy to reduce illicit opioid-use, as illustrated by the comment "*if it is going to give me three months away from street drugs, then of course I'm going to embrace it*" (Neale et al., 2018a). However, some participants also saw the irreversibility and stable dose effect as a negative. They indicated that they would miss the daily ritual, or that LAIB would erode their

Table 2
Summary of identified themes and the SDH implications.

Themes	Identified impact	The SDH as per WHO
Abstinence	+ High satisfaction + Improved abstinence + Reduction in all substance use except alcohol + Stable or reduced cravings +/− Reduce ability to use illicit substances	Employment Health systems Social exclusion
Accessibility	+ Prison population + Reduction in hospitalisation and overdose + Unintended interruptions with treatment + Reduced risk of diversion + Reduced travel burden + Reduced Stigma +/= Retention rates +/− Misinformation and fear relating to LAI preparation − Belief LAI may reduce access to psychological and social supports of MAT − Health insurance rates − Mistrust of literature from pharmaceutical companies	Health systems Public health programmes Social exclusion
Employment	+ Increase participation in workforce + Increase productivity + Increased flexibility (time)	Employment Social exclusion
Forensic	+ Reduction in crime secondary to OUD (acquisition and use) + Reduction in involvement in active legal issues + Reduces risk of withdrawal during incarceration	Health systems Social exclusion
Gender	+ Females: privacy +/− Females: previous experience with contraceptive LAI − Males: some may have reluctance to receive LAI formulation	Gender equality
Social relationships	+ Increased ability to prioritise family and children + Improvement in family relationships + Improvement in social status + Reduced stigma + Reduced travel burden − Loss of daily support from pharmacy/ dispensary − Reduction in contact with holistic MAT − Reduction of engagement with community (specific to those with mental illness)	Early child development Employment Social exclusion

Abbreviation: + positive impact, − negative impact, +/− positive and negative impact, +/= positive or neutral impact.

autonomy by holding them '*hostage*' (Neale et al., 2018a) and prevent them from using additional opioids (Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019).

Six studies evaluated the impact of LAIB on the reduction or cessation of illicit opioids (D'Agnone, 2019; Farahmand et al., 2020;Frost et al., 2019; Haight et al., 2019; Ling et al., 2020; Lofwall et al., 2018). All four patients described in the case report (Farahmand et al., 2020) and case series (D'Agnone, 2019) had abstained from opioids following the commencement of LAIB, which was confirmed by urine drug screening (UDS). Three studies (Frost et al., 2019; Haight et al., 2019; Lofwall et al., 2018) found a reduction in illicit opioid use via self-report and negative UDS in those on LAIB. These studies found abstinence rates ranged from 35 to 82% in LAIB groups (Frost et al., 2019; Haight et al., 2019; Lofwall et al., 2018), 28% for SLB intervention (Lofwall et al., 2018), and 5% for placebo (Haight et al., 2019). Lofwall et al. (2018) compared LAIB to SLB and found that at 24 weeks a significant reduction in illicit opioid use occurred ($p < 0.02$) in the LAIB arm. However, these results must be interpreted with caution given unclear compliance in the SLB arm. Ling et al. (2020) found significant improvements from baseline in all substance use areas except for alcohol ($p < 0.05$) in LAIB participants.

3.5.2. Cravings

The team identified opioid cravings as a further subtheme with regard to abstinence in nine studies (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Haight et al., 2019; Larance et al., 2020; Lofwall et al., 2018; Neale et al., 2019b; Saunders et al., 2020; Tompkins et al., 2019). In the studies examining LAIB-naïve participants, two studies (Neale et al., 2019b; Tompkins et al., 2019) identified concerns that the LAI preparation may not adequately treat participants throughout the dosing window, which may lead to an increase in cravings. Conversely, three studies (Larance et al., 2020; Neale et al., 2019b; Tompkins et al., 2019) found participants viewed the dosing window and its ability to reduce cravings as a positive. The potential for the LAIB syringe to trigger cravings was also identified as a negative (Larance et al., 2020; Saunders et al., 2020).

While LAIB-naïve participant perspectives were mixed, this review found reduction in cravings with LAIB treatment in five studies (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Haight et al., 2019; Lofwall et al., 2018). In the study examining LAIB against placebo (Haight et al., 2019), cravings scores were consistently lower in the LAIB arm; however, that study did not complete statistical analysis. When LAIB was compared to SLB, cravings were reduced in both intervention arms, with no statistical difference found (Lofwall et al., 2018). Three LAIB intervention studies allowed for dose titration or supplementation based on clinical judgement (Frost et al., 2019; Ling et al., 2020; Lofwall et al., 2018). One study found that 5.8% of participants required intervention to ensure optimization of dose (Frost et al., 2019).

3.5.3. Treatment satisfaction

Six studies (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019;Haight et al., 2019; Ling et al., 2019, 2020) showed that LAIB groups had high satisfaction rates with the treatment. Frost et al. (2019) found 68.4% of those converted from SLB found LAIB '*much better*' than their previous treatment. They also noted participants receiving LAIB rated ease of travel, daily adherence, lack of need for daily medication, or regular trips to the pharmacy as '*extremely important*' to treatment satisfaction throughout the study.

3.6. Accessibility

The study team interpreted accessibility to include factors that may positively or negatively reflect on individuals' ability to access OUD health programs. Thirteen studies discussed the accessibility of LAIB (D'Agnone, 2019; Frost et al., 2019; Gilman et al., 2018; Haight et al., 2019; Larance et al., 2020; Ling et al., 2020; Lofwall et al., 2018; Neale et al., 2018a, 2018b, 2019a, 2019b; Saunders et al., 2020; Tompkins et al., 2019), with regard to retention rates, implications of dosing route, and patient education.

3.6.1. Retention

Four studies explored retention as an outcome of LAIB treatment and found it to range between 50 and 73% in those receiving LAIB (Frost et al., 2019; Haight et al., 2019; Ling et al., 2020; Lofwall et al., 2018). Lofwall et al. (2018) found retention rates were similar between the LAIB and SLB interventions, with retention rates being approximately 70% at 24 weeks. Haight et al. (2019) reported retention rates were significantly higher in LAIB intervention when compared to placebo ($p < 0.0001$) also at 24 weeks.

3.6.2. Implications of dosing route

Eight studies (Frost et al., 2019;Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020;

Table 3
Summary of identified themes using framework analysis.

		Abstinence			Accessibility			Employment	Forensic	Gender	Social relationships	
		Opioid reduction/ cessation	Cravings	Treatment satisfaction	Retention	Implication of dosing route	Patient education				Social function	Care of children
Randomized studies	Haight et al., 2019*	+	+	+	+	•	•	+	•	•	•	•
	Ling et al., 2019*	•	•	+	•	•	•	+	•	•	+	•
	Lofwall et al., 2018	+	+	•	+	•	•	•	+	•	•	•
Observational studies	D'Agnone, 2019	+	+	+	•	•	•	+	•	•	+	+
	Farahmand et al., 2020	+	+	+	•	•	•	•	•	•	•	•
	Frost et al., 2019	+	+	+	+	+	•	•	•	•	+	+
	Ling et al., 2020	+	•	+	+	•	•	+	+	•	+	•
Qualitative studies	Gilman et al., 2018	+/−	•	•	•	+/−	•	•	•	•	+	•
	Larance et al., 2020	+/−	+/−	•	•	+/−	•	+	•	+	+	+
	Neale et al., 2018a#	+/−	•	•	•	+/−	+	+	•	+	+	+
	Neale et al., 2018b#	+/−	•	•	•	+/−	•	+	•	•	+	+
	Neale et al., 2019a^	•	•	•	•	•	+	•	+	•	•	•
	Neale et al., 2019b^	+	+/−	•	•	+/−	•	+	+	•	+	•
	Saunders et al., 2020	+	−	•	•	+/−	•	+	•	•	+	+
	Tompkins et al., 2019^	+/−	+/−	•	•	+/−	+	•	•	•	+	+

Abbreviations: + indicates positive findings, − indicates negative findings, +/− positive and negative impact, • indicates not reported.
*/#/^ indicate individual participant groups reported on in multiple papers.

Tompkins et al., 2019) explored how the LAI formulation would impact treatment engagement when compared to current MAT. Participants positively described the LAIB treatment regimen as a way to break the routine or "ritual" of illicit substance use and/or daily administered MAT (Neale et al., 2018a, 2018b; Tompkins et al., 2019). LAIB also offered a contingency against some of the hurdles of MAT such as lost doses (Neale et al., 2018a), the inability to attend the pharmacy (Neale et al., 2018a), and the potential risk of diversion (Neale et al., 2019b; Saunders et al., 2020). Conversely, six studies (Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b; Saunders et al., 2020; Tompkins et al., 2019) found participants expressed concern that cessation of daily dosing may lead to a reduction in access to support from MAT services, pharmacists, or social engagement with the community, thereby impairing their recovery. Neale et al. (2018a) specifically identified reduced supports as a greater concern in those with mental illness. Needle aversion was also found to be a potential barrier to LAIB-based MAT in seven papers (Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019). One participant expressed their concerns as '*I wouldn't even go there, not even think about it, because I don't like needles*' (Neale et al., 2018a). With respect to weekly or monthly dosing frequency, LAIB-naïve participants believed: (1) discussions about individual preferences were important (Tompkins et al., 2019); (2) either frequency was acceptable (Larance et al., 2020; Neale et al., 2019b; Saunders et al., 2020; Tompkins et al., 2019); and (3) that there was a preference for weekly administered LAIB during the initiation phase of therapy to ensure access to MAT supports (Neale et al., 2019b).

3.6.3. Patient education

Three studies found participants' desire for inclusive and relevant patient education (Neale et al., 2018a, 2019a; Tompkins et al., 2019), as fear surrounding the process, potential drug interactions, or impact of treatment on other conditions was identified as a barrier to uptake of LAIB. Participants identified that a variety of modes of information delivery prior to commencement, such as leaflets, videos, and advice from professionals or patients who were already on LAIB, would positively impact patients' ability to make an informed decision (Neale et al., 2019a). The same study found that medication information generated by pharmaceutical companies may be perceived as biased and unreliable to participants (Neale et al., 2019a).

3.7. Employment

Nine of the 15 studies examined employment (D'Agnone, 2019; Haight et al., 2019; Larance et al., 2020; Ling et al., 2019, 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020). When examining participants' perspectives, seven studies (D'Agnone, 2019; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019) identified that removing the need for daily pickups from the pharmacy was or would be helpful in engaging in the workforce "*people… wouldn't have to worry about, 'Oh I've got to leave work' or 'going to have to tell my manager [when needing to access dose]*'" (Neale et al., 2019b). D'Agnone (2019) described how the LAI preparation allowed patients to apply themselves at work due to improvement in their mood. Three studies that examined the impacts of LAIB demonstrated stable or improved employment rates ranging from 44 to 51% at study completion (Haight et al., 2019; Ling et al., 2019, 2020). Ling et al. (2019) found that employment rates were nonsignificantly lower at 33% in the placebo group compared to LAIB interventions.

3.8. Forensic implications

Four studies examined the forensic implications of LAIB treatment (Ling et al., 2020; Lofwall et al., 2018; Neale et al., 2019a, 2019b). In two studies, LAIB-naïve participants indicated LAIB may be beneficial within the prison setting given the potential for withdrawal with short-acting opioid replacement (Neale et al., 2019a, 2019b). Furthermore, studies identified that the potential reduction in opioid cravings could reduce the need to commit OUD-related crime (Neale et al., 2019b). Ling et al. (2020) found a reduction in the legal domain scores of the ASI-Lite with LAIB treatment, which indicated a reduction in active legal issues such as charges, pending trials, and parole (0.017, 95% CI: 0.001, 0.032). Lofwall et al. (2018) had one case of a non-fatal overdose after a participant was jailed for several days without access to their SLB and used heroin to treat their withdrawal symptoms.

3.9. Gender

No study specifically explored the relationship between LAIB and gender equity. However, two studies examined gender differences in perceptions of LAIB (Larance et al., 2020; Neale et al., 2018a). Neale et al. (2018a) found that females had a preference for LAI formulations as they were '*discreet*', '*invisible*', and had '*less stigma*' associated with them. Larance et al. (2020) also found that females were statistically more likely to believe LAIB was a good treatment (OR = 1.67, 95%CI = 1.04–2.69; $p = 0.034$).

3.10. Social relationships

Studies assessed the impact of LAIB on social relationships with regard to social function and care of children.

3.10.1. Social function

Twelve studies explored social function (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Gilman et al., 2018; Larance et al., 2020; Ling et al., 2019, 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019). In eight studies (Frost et al., 2019; Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019), participants felt that LAIB would offer '*freedom*' from being '*chained to services*' (Tompkins et al., 2019) allow them to '*get on with life*' (Neale et al., 2018a), and spend their time on other activities of living (Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b; Saunders et al., 2020; Tompkins et al., 2019). Two studies (Neale et al., 2019b; Tompkins et al., 2019) identified positive social implications with participants stating that they would be '*more normal*' (Tompkins et al., 2019) when visiting friends, and LAIB would allow them to have a social life. Six studies (D'Agnone, 2019; Gilman et al., 2018; Larance et al., 2020; Neale et al., 2018a, 2018b, 2019b) found moving to a long-acting formulation would allow participants to feel they were being treated as '*normal*' rather than stigmatized or as an '*addict*' (Neale et al., 2018a).

Ling et al. (2019) examined social functioning using the SF-36v2 and found that at 25 weeks a statistically significant improvement occurred in the LAIB group receiving the 300 mg/300 mg dose protocol ($p = 0.037$) but not the 300 mg/100 mg dose protocol ($p = 0.117$). The follow up study by Ling et al. (2020) examined the effects of 12 months of LAIB treatment and found statistically significant improvements in the domains of social functioning using the measurement tools SF-36v2 (95% CI: 2.81, 10.89) and ASI-Lite ($p < 0.05$). However, the study did not conduct analysis between LAIB dosages.

3.10.2. Care of children

The role of participants as caretakers for children was reported on in seven studies, which all identified views that LAIB would increase participants' ability to focus on family responsibilities including childcare, by reducing the burden of pharmacy visits and clinic appointments (D'Agnone, 2019; Frost et al., 2019; Larance et al., 2020; Neale et al., 2018a, 2018b; Saunders et al., 2020; Tompkins et al., 2019). Tompkins et al. (2019) identified the participants' perspective that LAIB would allow them to '*get on*' and focus on family responsibilities. Frost et al. (2019) found that participants believed that the prevention of accidental exposure to children of oral forms of MAT was an important factor for treatment satisfaction with LAIB.

4. Discussion

4.1. Summary of main findings

This review has qualitatively summarized fifteen studies to characterize the psychosocial impact of LAIB. Using the SDH framework, this review examined perspectives of participants who were either LAIB-naïve or who had received this intervention (D'Agnone, 2019; Farahmand et al., 2020; Frost et al., 2019; Gilman et al., 2018; Haight et al., 2019; Larance et al., 2020; Ling et al., 2019, 2020; Lofwall et al., 2018; Neale et al., 2018a, 2018b, 2019a, 2019b; Saunders et al., 2020; Tompkins et al., 2019). The benefits of LAIB described by participants related to abstinence, employment, social relationships, reduced forensic issues, and accessibility of OUD treatment. Only the LAIB-naïve studies identified negatives aspects of the intervention. These included: diminished self-determination (due to constrained ability to administer illicit opioids and control over their dosing compared to oral or sublingual alternatives), anticipated reduced access to psychological and social supports of MAT, lessened social connection with both pharmacy and community at large, and the potential for misinformation with regard to the release of the novel agent. Those with a comorbid mental illness or new to services were most concerned about a reduction in health service contacts.

4.2. Comparison to treatment as usual

This systematic review found that when compared to the literature on treatment as usual (TAU) MAT, LAIB treatment had comparable rates of employment (44–51%) (Rosic, Worster, Thabane, Marsh, & Samaan, 2020; Zippel-Schultz et al., 2016), retention (50–73%) (O'Connor et al., 2020), and abstinence (35–82%) (Brunisholz et al., 2020; Carew & Comiskey, 2018; Teesson et al., 2008). Specific identified benefits of LAIB compared to TAU MAT were: (1) the reduced risk of intentional or accidental diversion of buprenorphine to others including children in the community; (2) the dosing flexibility with regard to unanticipated treatment interruptions, including incarceration; and (3) reduction in time lost and stigma associated with frequent medication collection. Participants also saw LAIB to have several potential disadvantages when compared to TAU MAT, including: (1) the invasive injectable route of administration; (2) reduced support with services; and (3) a reduced need to leave home for dosing resulting in an overall loss in social connection. These findings illustrate the heterogeneous views in the OUD population with regard to the acceptability of LAI when compared to TAU MAT. Overall, this review suggests that LAIB may positively impact psychosocial outcomes for some individuals with OUD; although, others prefer TAU MAT.

4.3. Clinical implications

The findings of this review offer insight into the importance of patient selection for the treatment of OUD with LAIB to optimize psychosocial outcomes. LAIB will not be appropriate for all patients with OUD nor all OUD providers given varying service approaches to harm minimization and the balance between encouraging ease of access and engagement with services with that of abstinence from illicit opioids. Gryczynski et al. (2014) found that in patients who disengaged from treatment within six months, 61% were unable to adhere to the service framework, and 4% ceased due to desire to return to illicit opioid use.

These findings are consistent with that of our review, which found that some patients may view the inability to use illicit opioids in conjunction with MAT as a barrier to LAIB. Our findings suggest that a subpopulation of patients exist who will have a preference for more frequent or flexible dosing regimens that cannot be met by LAIB.

The review also found that vulnerable groups such as those new to MAT or those living with mental illness may prefer daily dosing as a safeguard to ensure a connection with health services and the broader community. Findings support the view that LAIB may be beneficial for those for whom employment and abstinence is a priority, have childcare responsibilities, or those incarcerated or at risk of incarceration, thereby breaking the cycle of social exclusion and the socioeconomic downward drift in some patients with OUD (Hurst, 2012; Lofwall et al., 2018; Neale et al., 2019a, 2019b). Treatment providers, therefore, must engage patients in shared decision-making when determining their treatment plan to respect patients' autonomy and remain in line with recovery-orientated practices. Patients' preferences should always be weighed with that of the prescriber's clinical opinion, which may warrant consideration of a risk-benefit analysis to support their recovery (Connery, 2015).

The review identified a range of factors that services must consider when introducing this novel treatment. These include ensuring a wide range of educational resources to encourage patients' participation to better enable supported decision-making and development of shared treatment goals, as well as ensuring services consider vulnerable populations who may benefit from more support. This would arguably include structural determinants of SDH such as those of culturally and linguistically diverse backgrounds (such as First Nation People) where OUD has been shown to exacerbate high rates of health inequity and social exclusion (Gisev et al., 2014), and those where domestic violence can act as a barrier to OUD treatment (Stone & Rothman, 2019). Available studies did not address how implementation would impact existing services, such as legislative requirements, clinical upskilling, and practical aspects, such as reallocating resources or other access barriers that smaller or more regional sites may encounter.

4.4. Strengths and limitations

This is the first systematic review that characterizes the psychosocial impacts of LAIB as a novel treatment for OUD within the SDH framework. The strength of this review is the rigorous methodology and comprehensive analysis of the perspectives and experiences of both those LAIB-naïve and those who had received LAIB within this emerging body of literature. Utilization of the SDH framework allowed the team to explore the psychosocial impacts of LAIB. Because of the recent release and diversity of terms used to describe LAIB, the authors used broad search terms coupled with searching references and citations to strengthen search rigor.

A limitation of this systematic review is the recency of the release of LAIB. In the release of any new treatment, early reporting bias is possible, which may inflate results leading to an increased risk of iatrogenic harm (Heyman, Alaszewski, Shaw, & Titterton, 2010). Additionally, eleven studies were either directly or indirectly funded by pharmaceutical companies involved in LAIB development (Frost et al., 2019; Haight et al., 2019; Larance et al., 2020; Ling et al., 2019; Ling et al., 2020; Lofwall et al., 2018; Neale et al., 2018a, 2018b, 2019a, 2019b; Tompkins et al., 2019). Pharmaceutical involvement impacted quality ratings with only one study being rated as good. Another limitation of this systematic review was the decision to include studies reporting on the same patient population groups (Haight et al., 2019; Ling et al., 2019; Neale et al., 2018a, 2018b; Tompkins et al., 2019). While the studies had multiple, shared participants, the nature of the thematic analysis and the different outcomes reported by these studies meant that no anticipated impact on the qualitative analysis occurred. Furthermore, their inclusion allowed for a comprehensive understanding of patient experiences and LAIB-naïve participant perspectives of LAIB.

This review has been unable to definitively identify that any reported positive or negative psychosocial impacts are directly attributable to the LAI formulation when compared to TAU MAT. The only study that compared LAIB to SLB had no measure of compliance for the SLB arm (Lofwall et al., 2018). Of note, unlike the LAIB-naïve studies, no negative psychosocial impacts existed in LAIB intervention groups, which may indicate self-selection bias. Additionally, four interventional studies (Frost et al., 2019;Haight et al., 2019; Ling et al., 2020; Lofwall et al., 2018) were clinical trials for non-inferiority, safety, or efficacy, with three of these studies (Haight et al., 2019; Ling et al., 2020; Lofwall et al., 2018) excluding participants if they had received treatment for OUD within at least 60 days of enrollment, which may limit the generalizability of findings (Rehal, Morris, Fielding, Carpenter, & Phillips, 2016; Shrimanker, Beasley, & Kearns, 2018).

The research field relating to LAIB is rapidly evolving and growing. The authors are aware of two recent papers that provide a quantitative and qualitative perspective of those with OUD and the introduction of LAIB in Australia, which have demonstrated impacts on SDH by LAIB (Barnett et al., 2021; Lintzeris et al., 2021). The qualitative study by Barnett et al. (2021) explored patient views after receiving LAIB and found it allowed for more freedom in dosing, increased time to dedicate to education, and reduced economic burdens associated with treatment. However, some patients found the lack of control in their dosing, and lack of daily support and routine as a result of the LAIB a negative. These findings were consistent with the overall findings of this systematic review with regard to improved accessibility and potential for decreased social connection. These findings further highlight the need for shared decision-making in commencing LAIB to ensure individually tailored treatment options. The quantitative open-label randomized trial by Lintzeris et al. (2021) examined patient-reported outcomes in 119 participants and compared TAU SLB to those who transitioned to LAIB. It found that the LAIB arm had greater global satisfaction, found LAIB more convenient and the LAIB preparation was a less burdensome treatment. This study supports the findings of this systematic review with regard to improved accessibility.

4.5. Implications for future research

This emerging area of research would benefit from longitudinal, real-world, head-to-head, randomized clinical trials comparing LAIB to current MAT, utilizing validated quality of life measurement tools. This systematic review has shown that the use of validated measurement tools such as the SF-36v2, EQ-5D-5L, ASI-Lite, or the TEA are underutilized for OUD treatment outcomes. This review also demonstrated that the current literature had limited diversity with regard to culture, urbanization, geographical regions, or health care settings, which may obscure relevant issues related to globalization such as challenges of differing regulatory bodies internationally, issues with affordability, varied availability on a global scale, cultural acceptability, and the clinical prioritization of LAI preparation in those countries. These areas would benefit from further research to advance our understanding of the relationship between patient characteristics and LAIB treatment outcomes, as well as the implementation of LAIB across a diverse population in health systems and health programs.

5. Conclusion

This review demonstrated that LAIB appears to have positive psychosocial impacts with regard to social exclusion and employment, and may (albeit indirectly) benefit the children of individuals with OUD. The most salient impact described within the literature was that of social exclusion, with positive improvements reported in abstinence, social relationships, and reduction in crime. Health programs and health systems should consider adapting services to include this novel agent. However, further methodologically rigorous research, without

conflicting interests, is necessary to further our understanding of the longer-term biopsychosocial benefits and shortcomings associated with this intervention. The patients' perspectives considered here highlight that shared decision-making represents an important aspect of treatment planning, particularly given the complex nature of OUD. Using SDH measurement tools is crucial to understanding the psychosocial consequences of evidence-based treatments, and, as such, we strongly recommend their universal implementation.

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CRediT authorship contribution statement

Emily Martin: Conceptualization, Formal analysis, Methodology, Project administration, Data curation, Software, Writing – original draft, Writing – review & editing. **Hayley Maher:** Conceptualization, Formal analysis, Methodology, Project administration, Data curation, Software, Writing – original draft, Writing – review & editing. **Gemma McKeon:** Writing – review & editing. **Sue Patterson:** Writing – review & editing. **Julie Blake:** Writing – review & editing. **Kai Yang Chen:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

None.

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Appendix 1. Search terms

Pubmed

(buprenorphine[MeSH Terms]) AND ("opioid-related disorders"[MeSH Terms])

Embase

('opioid use disorder'/exp OR 'opioid use disorder' OR 'opiate addiction'/exp AND ('buprenorphine'/exp OR buprenorphine) AND [2010-2020]/py

Scopus

TITLE-ABS-KEY((opioid AND dependence) OR (opioid AND use AND disorder) AND buprenorphine) AND PUBYEAR >2009 AND PUBYEAR <2020

Appendix 2. Summary of included studies

Study population	Author, year (country)	Study design and aim	Intervention	Setting	Main inclusion/exclusion criteria[a]	Participants
LAIB exposed	D'Agnone, 2019 (UK)	Case series reporting treatment with LAIB	LAIB monthly varying dose	Not stated	Not stated	*Enrolled/completed*: 3/3 *Mean age*: 52 *Percentage female*: 33.3% *Ethnicity*: 66.66% Caucasian, 33.33% unknown
	Farahmand et al., 2020 (USA)	Case study reporting treatment with LAIB	LAIB 300 mg monthly	Tertiary Hospital	Not stated	*Enrolled/completed*: 1/1 *Mean age*: 38 *Percentage female*: 100% *Ethnicity*: Latino
	Frost et al., 2019 (United States, United Kingdom, Hungary, Denmark, Sweden, Germany, Australia)	Non-randomized trial assessing long-term safety of weekly and monthly LAIB in adults with OUD	LAIB weekly or monthly (clinical judgement used for dose)	26 outpatient sites	*Inclusion criteria*: Age 18–65; current or past diagnosis of OUD; currently treated with SLB[b] or seeking to initiate MAT and no buprenorphine treatment for >60 days *Exclusion criteria*: chronic pain requiring opioid treatment	*Enrolled/completed*: 227/167 *Mean age*: 41.3 *Percentage female*: 37.4% *Ethnicity*: NA
	Haight et al., 2019 (USA)	Randomized control trial assessing efficacy of two LAIB dosing regimens in the treatment of OUD	LAIB 300 mg/300 mg or 300 mg/100 mg compared with placebo	36 outpatient treatment centres	*Inclusion criteria*: 18–65 years; OUD for at least 3/12; seeking MAT *Exclusion criteria*: MAT within 90 days of enrolment; current diagnosis other than OUD requiring chronic opioid treatment	*Enrolled/completed*: 665/288[c] *Mean age*: 39.6 *Percentage female*: LAIB 300 mg/300 mg 33%, LAIB 300 mg/100 mg 34%, Placebo 35% *Ethnicity*: LAIB 300 mg/300 mg 71% Caucasian, African descent 28%, other 1%; LAIB 300 mg/100 mg Caucasian 68%, African descent 29%, other 3%; Placebo Caucasian 78%, African descent 20%, other 2%
	Ling et al., 2019 (USA)	Evaluation of patient-centred outcomes during a phase 3, randomized, double blind	LAIB 300 mg/300 mg or 300 mg/100	36 outpatient treatment centres	*Inclusion criteria*: 18–65 years; OUD for at least 3/12; seeking MAT	*Enrolled/completed*: 487/487[c] *Mean age*: 40

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Study population	Author, year (country)	Study design and aim	Intervention	Setting	Main inclusion/exclusion criteria[a]	Participants
		study comparing LAIB dosing regimens	mg compared with placebo		*Exclusion criteria*: MAT within 90 days of enrolment; current diagnosis other than OUD requiring chronic opioid treatment	*Percentage female*: LAIB 300 mg/300 mg 33%, LAIB 300 mg/100 mg 34%, Placebo 35% *Ethnicity*: LAIB 300 mg/ 300 mg 71% Caucasian, African descent 28%, other 1%; LAIB 300 mg/ 100 mg Caucasian 68%, African descent 29%, other 3%; Placebo Caucasian 78%, African descent 20%, other 2%
	Ling et al., 2020 (USA)	Non randomized trial characterising the effects of 12 months of treatment with LAIB on those with OUD	LAIB (clinical judgement used for dose)	Outpatient	*Inclusion criteria*: 18–65; seeking treatment; diagnosis of OUD in previous 3/12 *Exclusion criteria*: diagnosis other than opioid use disorder requiring chronic opioid treatment; received MAT in the 90 days prior to study	*Enrolled/completed*: 412/ 206 *Mean age*: 38.4 *Percentage female*: 36.2% *Ethnicity*: Caucasian 71.6%
	Lofwall et al., 2018 (USA)	Double blind randomized control trial to determine if weekly and/or monthly LAIB is non-inferior to daily SL buprenorphine/naloxone combination for the treatment of OUD	LAIB (dose at clinician discretion) weekly weeks 1–12, monthly weeks 12–24) + sublingual (SL) placebo	Outpatient	*Inclusion criteria*: 18–65 years; diagnosed with and seeking treatment for OUD *Exclusion criteria*: receiving pharmacotherapy for OUD within 60 days; chronic pain requiring opioid therapy	*Enrolled/completed*: 428/ 303 *Mean age*: 38.4 *Percentage female*: 38.6% *Ethnicity*: 74.6% Caucasian of LAIB arm, 76.3% Caucasian of SLB arm
LAIB-naïve	Gilman et al., 2018 (UK)	Qualitative survey assessing the opinion of those with lived experience to inform future medication choices for MAT	Self-directed structured digital survey	National Conference aimed at involving service users with treatment providers	*Inclusion criteria*: experience of using drug treatment services for OUD; self-reported treatment experience *Exclusion criteria*: Nil	*Enrolled/Completed*: 35/35 *Mean age*: NR *Percentage female*: 31% *Ethnicity*: NR
	Larance et al., 2020 (Australia)	Qualitative survey examining perceptions on LAIB among people who regularly use opioids	Computer-assisted structured survey	Outpatient	*Inclusion criteria*: 18+, using illicit or prescription opioids regularly (used at least 21 out of last 28 days) or currently on MAT (or both) *Exclusion criteria*: not meeting inclusion criteria	*Enrolled/Completed*: 402/ 382 *Mean age*: 42 *Percentage female*: 36% *Ethnicity*: 85% Australian born, 32% Non-Australian (32% north/west Europe, 19% Oceania, 19% south east Asia, 11% south/east Europe, 10% North Africa and 5% other regions)
	Neale et al., 2018a (UK)	Qualitative interview to evaluate the views of those who do or have used heroin on novel MAT delivery systems	Semi-structured interview via focus groups	Drug and alcohol services, peer support recovery service, homeless hostel	*Inclusion criteria*: All current or former heroin users *Exclusion criteria*: Nil	*Enrolled/Completed*: 44/44 *Mean age*: 48 *Percentage female*: 36% *Ethnicity*: Caucasian 66%, Asian 0%, African descent 18%, Mixed 8%, Other 8%
	Neale et al., 2018b (UK)	Qualitative interview to evaluate the views of those who do or have used heroin on novel MAT delivery systems to identify factors influencing preferences	Semi-structured interview via focus groups	Drug and alcohol services, peer support recovery service, homeless hostel	*Inclusion criteria*: All current or former heroin users *Exclusion criteria*: Nil	*Enrolled/Completed*: 44/44 *Mean age*: 48 *Percentage female*: 36% *Ethnicity*: Caucasian 66%, Asian 0%, African descent 18%, Mixed 8%, Other 8%
	Neale et al., 2019b (UK)	Qualitative interview assessing patient's preference for weekly, monthly or six-monthly LAIB	Semi-structured interview	Community addiction treatment services, homeless hostel, peer support service	*Inclusion criteria*: 18+; using prescribed oral methadone, or prescribed buprenorphine, or using heroin daily but not taking any MAT *Exclusion criteria*: Nil	*Enrolled/Completed*: 36/36 *Mean age*: 45 *Percentage female*: 28% *Ethnicity*: Caucasian 67%, black 14%, Asian 3 &, Mixed 8%, other 8%
	Neale et al., 2019a (UK)	Qualitative interview assessing information needs and information preferences with regards to LAI buprenorphine	Semi-structured interview	Community addiction treatment services, homeless hostel, peer support service	*Inclusion criteria*: 18+; using prescribed oral methadone, or prescribed buprenorphine, or using heroin daily but not taking any MAT *Exclusion criteria*: Nil	*Enrolled/Completed*: 36/36 *Mean age*: 45 *Percentage female*: 28% *Ethnicity*: Caucasian 67%, Black 14%, Asian 3&, Mixed 8%, other 8%
	Saunders et al., 2020 (USA)	Qualitative interview assessing patient preferences for long acting MAT (LAIB or implant) compared to short-acting (oral) MAT	Semi-structured telephone interview	Outpatient	*Inclusion criteria*: 18+; currently or previously on MAT; English-language proficient; residing in USA;	*Enrolled/Completed*: 40/40 *Mean age*: 36.5 years Percentage female: 40% *Ethnicity*: 90% Caucasian, 10% African descent

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Study population	Author, year (country)	Study design and aim	Intervention	Setting	Main inclusion/exclusion criteria[a]	Participants
	Tompkins et al., 2019 (UK)	Qualitative interview assessing willingness to receive LAI buprenorphine and factors which influence this	Semi-structured interview	Community addiction treatment services, two hostels for homeless people, peer support service	OUD (screening via TAPS) *Exclusion criteria*: NA *Inclusion criteria*: 18+; using prescribed oral methadone, or prescribed buprenorphine, or using heroin daily but not receiving MAT *Exclusion criteria*: Nil	*Enrolled/Completed*: 36/36 *Mean age*: 45 *Percentage female*: 28% *Ethnicity*: Caucasian 67%, Black 14%, Asian 3 &, Mixed 8%, other 8%

[a] Full inclusion/exclusion criteria can be found in original studies.
[b] Sublingual buprenorphine.
[c] 665 enrolled but only 489 participants were analysed due to: site closure (n = 15), run in failures (n = 160), randomisation error (n = 1).

Appendix 3. Summary of included studies main outcomes with regards to the SDH

Study population	Author, year (country)	Outcome measures	Duration	Outcome
LAIB exposed	D'Agnone, 2019 (UK)	UDS, Clinical judgement	3–4 months	LAIB was safe and effective treatment option with reduction in cravings and withdrawals, improved ability to engage in employment and social relationships and supports abstinence from opioids.
	Farahmand et al., 2020 (USA)	UDS, Clinical judgement	3 weeks	LAI preparation ceased cravings for and use of illicit opioids. Patient perspective positive on 'steady' nature of dosing regimen. Supported patient in returning to the community. Patient expressed desire to pursue role supporting others with OUD in future.
	Frost et al., 2019 (United States, United Kingdom, Hungary, Denmark, Sweden, Germany, Australia)	UDS, self-reported opioid use, retention rates, opioid withdrawal scales, desire to use VAS,[a] need to use VAS, patient reported experience measures (ease of travel, daily adherence, privacy, lack of need for daily medication or regular trips to pharmacy, accidental paediatric exposure and access by others to medications)	48 weeks	LAIB was tolerated and safe when compared to SL buprenorphine. Both weekly and monthly LAIB resulted in high retention rates, lower levels of illicit opioid use when compared to baseline, as well as reducing and maintaining opioid cravings and withdrawals throughout this study. Participant survey showed favourable views on LAIB effect on travel, medication adherence, privacy, medication burden, prevention of accidental exposure, prevention of others accessing medications, and saving time by avoiding pharmacy. Majority supported that LAIB was 'much better' than SL buprenorphine.
	Haight et al., 2019 (USA)	% abstinence from week 5–24; 'treatment success' (80% opioid abstinence during weeks 5–24); retention, COWS,[b] opioid craving VAS[b] scores	24 weeks	Abstinence and retention rates were higher in both LAIB groups compared to placebo group. LAIB was well tolerated, with high satisfaction rates (88% for active group compared to 46% with placebo). LAIB was seen to have low and stable cravings compared to placebo groups which were higher and increased as study progressed. Active treatment groups had improved employment rates whereas they fell in placebo group. Overall, found LAIB safe and well tolerated.
	Ling et al., 2019 (USA)	EQ-5D-5L,[c] SF-36 V2,[d] MSQ,[e] employment/insurance status	24 weeks	Participants receiving LAIB had statistically significant changes in EQ-5D-5L, physical component summary score, satisfaction rates when compared to placebo. Employment rates improved in the LAIB groups and reduced in placebo group.
	Ling et al., 2020 (USA)	EQ-5D-5L, SF-36v2[e], TEA,[f] ASI-Lite,[g] employment/ insurance questionnaire, MSQ[e]	12 months	Participants showed improvements in: SF-36v2 mental health component scores, TEA scale, ASI-Lite for all problem areas including family, social status, legal status, psychiatric status, health status, drug reduction except for alcohol use. There was no change in the SF-36v2 physical component scores. EQ-5D-5L scores increased from screening to baseline and remained stable across the LAIB intervention. Improvements were seen in employment and health insurance status. Retention rates were 50%.
	Lofwall et al., 2018 (USA)	UDS, self-report of substance use, retention, VAS[d] (desire and need to use), opioid withdrawal scales, frequency of supplemental LAI	28 weeks	Retention rates were similar between the intervention groups. Compared with SL buprenorphine, LAIB resulted in higher rates of opioid negative urines with reductions in opioid cravings and withdrawals with comparable safety profile. SL buprenorphine group had more hospitalisation and overdoses. No overdoses seen in LAIB arm. SL buprenorphine had one participant jailed which resulted in withdrawal and accidental overdose post release to '*self-medicate*'.
LAIB-naïve				

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Study population	Author, year (country)	Outcome measures	Duration	Outcome
	Gilman et al., 2018 (UK)	7-Point Likert scales to rate statements describing elements of MAT including LAIB	Not reported	Majority of participants were willing to receive prescribed buprenorphine in either oral, injectable or implantable preparations. Provision of education around differing preparations may increase willingness to try novel forms of buprenorphine. Participants supported the views that LAIB would: make life easier; reduce stigma of treatment; and release time for preferred activities. Participants disagreed with views that loss of contact with pharmacy, loss of control over therapy and loss of ability to use illicit substances were barriers to accessing LAI. It was found that those actively in MAT were more likely to agree to the statement "I would have less control over my therapy with a depot medication".
	Larance et al., 2020 (Australia)	Computer-assisted structured survey	60 min	Participants expressed positive perspectives that LAIB would result in: reduced requirement to attend services, more time to do other things, allow for work and holidays, prevent cravings for opioids, feel in control of treatment, suppress withdrawal symptoms, cost savings, increased convenience, enhanced self-determination, enhanced privacy, reduction of sigma, missing fewer doses and reducing challenge of daily dosing for those with children. Participants expressed negative perspectives that LAIB would result in: inadequate dosing effect, prevent ability to use other opioids (both prescribed and illicit) and that the use of a syringe may trigger cravings for illicit use. Overall, the majority believed it would be a good treatment for them and expressed no preference for dosing frequency.
	Neale et al., 2018a (UK)	Semi-structured interview via focus groups	41–63 min	Participants expressed positive perspectives that LAIB would result in: increased ability and time available to engage in education, employment, parenting roles, social engagement; reduce social stigma; assist in reduction of illicit substance use by breaking the ritual of use, reduce ability to use illicit opioids; be protective against withdrawal by preventing missed/lost doses; and reduce overall disruption to life from regular pharmacy collection. Participants expressed negative perspectives that LAIB would result in: reduction in service engagement; reduction in motivation for sobriety due to potential for reduced service engagement (seen in new to treatment participants); loss of social connection associated with regular pharmacy collection; difficulty with irreversibility/ flexibility of dose; loss of intoxication and withdrawal symptoms (seen as desirable for some); concerns regarding negative impacts on acute pain management if required; and potential for syringe to be a trigger for opioid cravings.
	Neale et al., 2018b (UK)	Semi-structured interview via focus groups	41–63 min	Participants were cautious, but willing to consider, novel routes of buprenorphine administration. Anticipated benefits included: reduced pharmacy burden allowing for increased work/travel/childcare, reduction of stigma secondary to daily dosing and reduced cravings. Reduced pharmacy visits and daily dosing was also viewed as a negative, particularly in those with lived experience of mental illness. The inability to use illicit substances on top of LAIB (ability to 'self-medicate') and route of administration (fear of needles) was also expressed. There was no clear preference for a specific novel agent in those explored. Participant views demonstrated a need to align participant treatment goals with route of buprenorphine.
	Neale et al., 2019a (UK)	Semi-structured interview	37–100 min	Participants expressed that in order to determine if LAIB was appropriate for them they would require: information on safety, treatment process, LAI delivery, illicit substance use and ceasing treatment. Participants expressed the view point that they would want information from trusted and reliable sources including health professionals and patients with LAIB treatment experience. Participants felt that this information should be provided in printed, verbal and electronic forms. One participant speculated that LAIB may be useful in prison settings.

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Study population	Author, year (country)	Outcome measures	Duration	Outcome
	Neale et al., 2019b (UK)	Semi-structured interview	37–100 min	Participants identified LAIB may result in increased opportunities for employment, recreation and building relationships (family and friends). The potential for reduction in diversion and need for crime to fund illicit substance habit was seen to be positive, as was the reduction in cravings/withdrawals and stigma associated with treatment. The reduction in contact with services was both a positive and negative. It was speculated LAIB may also be beneficial for use in prisons. There was no definitive preference for weekly or monthly dosing. However, there was a preference for the patient's own treatment goals to be considered.
	Saunders et al., 2020 (USA)	Semi-structured telephone interview	45–60 min	A majority of participants were not willing to receive injection or implant based buprenorphine. Participants identified positive impacts of the LAIB to be: reduced medication collection burden; reduced risk of diversion; and reduce the impact of treatment on family/children/work/travel. Participants identified negative impacts of LAIB to be: loss of control; potential for reduction in support from services; and potential harms due to invasive nature of injectable treatment. Prior experience of LAI medications was also demonstrated to positively impact patient acceptability of LAIB. Overall, participants endorsed the importance of shared decision making may support patients in selection of the treatment modality best aligned with their experiences and treatment goals.
	Tompkins et al., 2019 (UK)	Semi-structured interview	37–100 min	Participants found increase choice and flexibility to be a positive when compared to current MAT. Specifically, participants identified LAIB would allow for improved ability to engage in work and family responsibilities, and reduction in stigma associated with treatment. It also found that there was a willingness to use LAIB if it enables them to reduce their illicit drug use and facilitates recovery. Reduced access to pharmacies and treatment centres was viewed as both positive and negative.

[a] Visual Analogue Scale (VAS).
[b] Clinical opioid withdrawal scale.
[c] 5-Level EQ-5D.
[d] Short-form 36 Health Survey Version 2.
[e] Medication Satisfaction Questionnaire.
[f] Treatment Effectiveness Assessment.
[g] Addiction Severity Index-Lite.

Appendix 4. Summary of included study quality assessments

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Intention to treat analysis (yes/no)	Group similarity at baseline	Incomplete compliance with intervention	Additional bias	Overall quality rating
Haight et al., 2019	Low	Low	Low	Low	Unclear	Unclear	Low	Yes	Unclear	High	Yes	Poor
Ling et al., 2019	Low	Low	Low	Low	Unclear	High	High	Yes	Unclear	Unclear	Yes	Poor
Lofwall et al., 2018	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Unclear	Unclear	Yes	Poor

Randomised Studies: Revised Cochrane Risk-of-bias (Sterne et al., 2019)

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias due to measurement of outcomes	Bias in selection of the reported results	Overall quality rating
Frost et al., 2019	Moderate	Low	Low	Low	Serious	Moderate	Low	Fair

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Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias due to measurement of outcomes	Bias in selection of the reported results	Overall quality rating
D'Agnone, 2019	Serious	Serious	Low	Low	Low	Serious	Serious	Poor
Farahmand et al., 2020	Serious	Serious	Low	Low	Low	Serious	Serious	Poor
Ling et al., 2020	Low	Serious	Low	Low	Serious	Low	Low	Fair

Observational Studies: Risk of Bias in Non-Randomised Studies of Interventions (Sterne et al., 2016)

Study	Clear statement of aims	Qualitative methodology appropriate	Appropriate research design	Appropriate recruitment strategy	Appropriate data collection	Relationship between researcher & participants considered	Ethical issues considered	Sufficiently rigorous data analysis	Clear statement of findings	Addition-al bias	Overall quality rating
Gilman et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Larance et al., 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Neale et al., 2018a	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Unclear	Yes	Yes	Poor
Neale et al., 2018b	Yes	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Poor
Neale et al., 2019a	Yes	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Fair
Neale et al., 2019b	Yes	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Fair
Saunders et al., 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Good
Tompkins et al., 2019	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Fair

Qualitative Studies: Critical Appraisal Skills Programme (Critical Appraisal Skills Programme, 2018).

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