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**Opioid users' willingness to receive prolonged-release buprenorphine depot injections
for opioid use disorder**

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Declaration of interests

Joanne Neale has received honoraria and research grants from pharmaceutical companies: Camurus AB and Mundipharma International Ltd.

John Strang is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He has also worked with a range of governmental and non-governmental organizations, and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (King's College London) have received honoraria, travel costs, and/or consultancy payments. This has included discussions with Camurus AB, Indivior and Molteni Farma (all three of whom have developed ultra-long-acting buprenorphine formulations) and also an oversight role for the UK part of a safety trial of CAM2038, the product discussed in this paper. For a fuller account, see John Strang's web-page at: <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>

Charlotte Tompkins received salary support from Camurus AB whilst undertaking this study. She previously received salary support from Mundipharma International Ltd.

Abstract

Aims: Prolonged-release implantable and depot injection formulations of buprenorphine are very recent developments in the treatment of opioid use disorder. Such formulations remove the need for daily dosing and provide patients with sustained concentrations of buprenorphine over a period of weeks or months. We explored opioid users' personal willingness to receive prolonged-release buprenorphine depot injections and factors influencing their interest.

Methods: The study took place in London during 2018, before depot buprenorphine was licensed for use in Europe. Thirty-six face-to-face, semi-structured qualitative interviews were conducted with people who were: i) using heroin daily and not receiving any treatment for opioid use (n=12); or ii) prescribed daily oral buprenorphine (n=12); or iii) prescribed daily oral methadone (n=12). Participants were asked about their willingness to receive depot buprenorphine and were encouraged to discuss factors that might alter their opinions. Interview data were analysed following the stages of Iterative Categorization.

Findings: Participants expressed a high level of willingness to receive depot buprenorphine. Their views were influenced both positively and negatively by six key features of depot buprenorphine: i) reduced contact with pharmacies and drug treatment services; ii) impact on illicit drug use and recovery; iii) the perceived effectiveness of depot buprenorphine; iv) the duration and dosage of depot buprenorphine injections; v) clinical administration of the depot buprenorphine injection; and vi) potential for side effects associated with the depot buprenorphine injection.

Conclusions: Willingness to receive a given medication is complex, individual and changeable. Opioid users seem likely to welcome greater choice and flexibility in respect of opioid agonist medications and appear more likely to accept and adhere to depot buprenorphine if it enables them to reduce their illicit drug use and facilitates their recovery. Research is now needed to assess whether patients' reported willingness to receive depot buprenorphine translates into actual uptake and adherence.

Keywords: Buprenorphine; depot injection; extended-release; opioid agonist treatment; prolonged-release; qualitative

Abbreviations

Opioid use disorder (OUD)

Opioid agonist treatment (OAT)

Highlights

- Qualitative interviews explored opioid users' willingness to receive prolonged-release buprenorphine
- Opioid users both in and out of treatment expressed interest in receiving depot buprenorphine
- Six key features affected interest in receiving depot buprenorphine
- Opioid users wanted more information to improve their decision-making

Opioid users' willingness to receive prolonged-release buprenorphine depot injections for opioid use disorder

1. Introduction

Opioid use disorder (OUD) affects millions of people worldwide (EMCDDA, 2017; United Nations, 2018), with detrimental health and social consequences including premature mortality, opioid-related overdose, infectious disease transmission, and crime (Rudd et al., 2016). Pharmacotherapies for OUD commonly include the prescription of opioid agonists (e.g. methadone) or partial agonists (e.g. buprenorphine) (Clinical Guidelines on Drug Misuse and Dependence (Update) 2017; NIDA, 2018a; Stotts, Dodrill & Kosten, 2009). The antagonist naltrexone can also be considered when a person is opioid-free in order to support abstinence and prevent relapse.

In England, treatment for OUD includes the use of methadone and buprenorphine. Commonly prescribed through primary care and specialist addiction treatment services at no cost to the patient, consumption is usually supervised for a length of time appropriate to an individual's needs and risks (Clinical Guidelines on Drug Misuse and Dependence (Update) 2017). Methadone and buprenorphine are typically prescribed in oral form, and for daily administration until stability established. Whilst naltrexone is available orally, it is rarely prescribed, often due to a lack of interest from patients and issues with adherence (Clinical Guidelines on Drug Misuse and Dependence (Update) 2017).

Evidence from numerous randomized controlled trials and observational studies confirms that opioid agonist treatment (OAT) is effective in reducing opioid use, overdose, the risk of infectious disease transmission, and drug-related criminal behaviour (Bell, 2012; NIDA, 2018b; The American Society of Addiction Medicine, 2013). Attending a clinic to receive OAT also helps to provide structure to people's lives, increases access to other therapies and can

be a source of psychosocial support (Clinical Guidelines on Drug Misuse and Dependence (Update) 2017; NIDA, 2018b). Despite this, drugs such as methadone and buprenorphine have known negative side effects which include physical dependence (Brunton, Knollmann & Hilal-Dandan, 2017; Itzoe & Guarniei, 2017). In some countries, OAT remains controversial, politically divisive and disliked, even amongst people who use it (Neale, 2013). This constitutes a major obstacle in the treatment of OUD given that uptake and adherence are both likely to be poor if patients have negative views and expectations about the medications being offered to them.

Over the years, oral methadone has been the most extensively explored OAT from the patient perspective. Some people prescribed oral methadone have repeatedly described it as a stigmatizing, restrictive and punitive treatment (Crawford, 2013; Harris & McElrath, 2012; Radcliffe & Parkes, 2013; Strike et al., 2013). Indeed, patients have likened it to a form of social control because it can tie them to strict medication-related rules and monitoring systems, such as urinalysis and daily attendance at services (Chandler et al., 2013; Crawford, 2013; Neale, 2013; Strike et al., 2013; Treloar & valentine, 2013). Studies have compared patients' views of oral methadone with oral buprenorphine (Hill et al., 2015; Kelly et al., 2012; Schwartz et al., 2008; White et al., 2007). However, findings from this research have been inconsistent and inconclusive; for example, there is evidence that patients prefer methadone on some criteria and buprenorphine on others (White et al., 2007).

Oral (sublingual) buprenorphine lasts around 24–60 hours. As a partial agonist, buprenorphine activates the mu-opioid receptors in the brain, but to a lesser extent than full opioid agonists (Walsh & Eissenberg, 2003). In so doing, it latches onto opioid receptors with high receptor affinity, and reduces or 'blocks' the rewarding effects of illicit opioid use (Barnwal et al., 2017; Walsh & Eissenberg, 2003). In the UK, daily supervised dosing is recommended and sometimes required by regulators or treating clinicians, at least until good adherence is established. After which time, supervised dosing should be reduced or stopped providing that

stability is not jeopardised (Clinical Guidelines on Drug Misuse and Dependence (Update) 2017). Nonetheless, as with oral methadone, the burden and perceived stigma of having to constantly attend services can undermine patient satisfaction and compliance (Barnwal et al., 2017; Neale et al., 2018a). Further, there is evidence that patients sometimes forget or choose to miss oral buprenorphine doses; divert, snort or inject the tablets; 'misuse' the medication in other ways; or drop out of treatment prematurely and then return to illicit opioid use (Awgu, Magura & Rosenblum, 2010; Fareed et al., 2014; Itzoe & Guarniei, 2017; Middleton et al., 2011; Rosenthal & Goradia, 2017; Sordo et al., 2017).

Poor and non-adherence to oral medications have been important drivers behind the development of prolonged-release (also known as extended-release) implantable and depot injection formulations for OUD (Compton & Volkow, 2016; Hegde, Singh & Sarkar, 2013; Rosenthal & Goradia, 2017; Sigmon & Bigelow, 2016). These new formulations remove the need for daily dosing and provide patients with sustained concentrations of medication over a period of weeks or months. Even though injectable and implantable formulations of other OUD medications (e.g. naltrexone) have been developed and are available in other countries, no such licensed products have been introduced in the United Kingdom (UK).

Since 2016, various prolonged-release buprenorphine products have been licensed. First, the United States (US) Food and Drug Administration (FDA) approved Probuphine[®] (Titan Pharmaceuticals, San Francisco and Braeburn Pharmaceuticals, Inc. Princeton, NJ, USA), a 6-month buprenorphine sub-dermal implant (Barnwal et al., 2017; Sigmon & Bigelow, 2016; Voelker, 2016). The FDA then approved Sublocade[™] (investigational name RBP-6000) (Indivior, Richmond, VA, USA), a monthly subcutaneous depot buprenorphine (Lorman, 2018). In addition, European Commission and the Australian Therapeutic Goods Administration approved Buvidal[®] (investigational name CAM2038) (Camurus AB, Lund, Sweden), a weekly and monthly subcutaneous injection (Camurus AB, 2018a, 2018b). In December 2018, the FDA also issued tentative approval of weekly and monthly Brixadi[™] (the

same CAM2038 product approved in Europe as Buvidal) (Braeburn, Camurus' US partner) (Camurus AB, 2018c). Most recently (April 2019) the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a marketing authorisation for the buprenorphine implant, Sixmo, the brand name for Probuphine in the European Union (EMA, 2019).

The safety and efficacy of buprenorphine implants have been reported (Ling et al., 2010; Rosenthal et al., 2013). Although research into depot buprenorphine injections is still relatively new (Albayaty et al., 2017; Haasen, Linden & Tiberg, 2017; Haight et al., 2018; Nasser et al., 2016; Walsh et al., 2017), findings indicate promising results regarding its therapeutic effectiveness and tolerability (Lofwall et al., 2018). Indeed, the safety profile of depot buprenorphine appears generally consistent with that of oral buprenorphine, apart from some mild-to-moderate injection-site reactions (Haight et al., 2018; Lofwall et al., 2018). In terms of patient perspectives, a focus group study (Neale et al., 2018a, 2018b) and a survey (Gilman et al., 2018), both conducted with people with a history of opioid use in the UK shortly before prolonged-release buprenorphine was licensed, found that participants liked the anticipated convenience, reduced stigma, and opportunity to live more 'normally' which they believed prolonged-release OAT would offer. Nonetheless, the focus group participants expressed concerns about its irreversibility, administration, and reduced contact with treatment services once received (Neale et al., 2018a, 2018b); these issues were not reported by the survey participants (Gilman et al., 2018).

In terms of patients' interest in receiving new OAT formulations, a quantitative survey of 338 people entering inpatient opioid withdrawal management programs in the US found that 185 (54.7%) reported that they were willing to be prescribed buprenorphine in the future and, of these, 48.6% said that they preferred daily oral formulations, 23.1% preferred a weekly or monthly injection, and 26.6% preferred a bi-annual implant (Kenney et al., 2018). Beyond this study, however, there has been little research exploring whether opioid users are personally

willing to receive prolonged-release buprenorphine. Responding to this information gap, we undertook a qualitative interview study to ascertain opioid users' stated willingness to receive depot injection buprenorphine and the factors that influenced their responses. We focused on the depot injection rather than the implant as the first depot buprenorphine injection was nearing approval for use in Europe. This gave the topic immediacy and real-world relevance.

2. Methods

The study was conducted in London (UK), in two community addiction treatment services, two hostels for homeless people, and a peer support service. The research was undertaken with financial support from Camurus AB, one of the developers of Buvidal and Brixadi (CAM2038). To the best of our knowledge, Camurus AB are the only developers of weekly and monthly injectable forms of depot buprenorphine. Approval to conduct the study was obtained from King's College London Research Ethics Committee and separately from the participating services. Fieldwork took place between June and October 2018, before any form of prolonged-release depot buprenorphine was available in Europe.

To ensure that participants were all people who might be eligible for depot buprenorphine in the future, we purposively recruited people who were: i) using heroin daily and not receiving any treatment for opioid use; or ii) prescribed at least 8mg oral buprenorphine/ day; or iii) prescribed at least 60mg methadone/ day. To facilitate recruitment, one of the researchers (CT) visited the services and hostels to introduce the study to staff. Posters about the study were also displayed in the services. Staff liaised with keyworkers and searched electronic patient records to identify service users who seemed to meet the eligibility criteria. They then verbally outlined the study to those service users and introduced them to the researcher if they were interested in taking part. Of the 63 people approached by staff, 59 expressed interest.

CT next completed a screening questionnaire with all interested individuals to check their eligibility and obtain demographic information (gender, age, ethnicity), details on illicit opioid use (age of first heroin use, current heroin use), current and previous OAT, and history of depot medications. Using the screening information, CT purposively sampled 12 individuals from each of the 3 groups (daily user of heroin, daily buprenorphine patient, daily methadone patient), taking care to include people with different demographic characteristics and medication histories. She then contacted them to arrange interviews. Despite reminders, nine (3 people who used heroin, 5 methadone patients, 1 buprenorphine patient) did not attend for interview. Three interviews were successfully re-arranged (1 person who used heroin, 2 methadone patients), but 6 individuals could not be contacted.

Prior to each interview, CT gave participants verbal and written information about the study, assured them of their confidentiality, and obtained written informed consent. To ensure their understanding, she outlined the hypothetical nature of the study and stated that depot buprenorphine was not currently available as a treatment in England. CT then interviewed each participant in private in the services using a semi-structured topic guide. This explored participants' personal circumstances; their drug use and treatment history; their understanding of, and views on, depot buprenorphine; their personal willingness to receive depot buprenorphine; and factors that might alter their opinions of depot buprenorphine. To aid discussions, participants received basic verbal information on the concept of injectable depot buprenorphine, covering the potential duration, administration, dosing, and side effects (see Box 1). At the end of the interviews CT reminded participants that depot buprenorphine was not an available treatment option and that the discussions about whether they were willing to receive depot buprenorphine would not be interpreted beyond their early thoughts.

Box 1

Interviews were audio-recorded and lasted between 37 and 100 minutes. Participants received a £20 shopping voucher for taking part. Thirty-six individuals (26 men, 10 women) were interviewed. Participants were aged between 24 and 63 years. Most (n=23) were White British. Nine participants reported that they had received contraceptive medications, anti-psychotic treatments, or testosterone replacement therapy via a depot injection in the past. Table 1 provides more information about the participants.

Table 1

All interviews were transcribed verbatim. Data coding and analyses were guided by the stages of Iterative Categorization (Neale, 2016). First, a coding frame was developed based on the interview guide and supplemented by codes emerging from the interviews. The interview transcriptions and the coding frame were then imported into the specialist qualitative software programme MaxQDA (version 11) for systematic, line-by-line coding, whereby all text was assigned to one or more of the codes.

For this paper, data coded to the 'personal interest in receiving depot buprenorphine' code and its sub-codes ('factors that might increase interest in receiving depot buprenorphine' and 'factors that might decrease interest in receiving depot buprenorphine') were exported into Microsoft Word documents and systematically reviewed to identify themes and patterns. During this process, any similarities and differences between sub-groups of participants were explored.

3. Findings

Early in the interviews, participants were asked if they would personally be willing to receive depot buprenorphine if offered it as a treatment. Participants mostly expressed a high level of willingness, using phrases such as '*jump at the chance*', '*snap it up*', and '*be over the moon*'.

Some even said that they would be willing to receive depot buprenorphine as '*a guinea pig*' or '*without the licence*'. Several participants stated that they would want more information to help them decide, but only a few (all male) expressed a definite reluctance to try it. These included a participant who said that he was satisfied with his current methadone treatment and a participant who reported a dislike of needles and injections. Only one of the people who had previously received a medication via a depot injection expressed reluctance to receive depot buprenorphine. This man explained that although he had found receiving an anti-psychotic depot 'painful' and 'degrading,' his reluctance was because he liked, and was habituated to, the daily ritual and effects of taking oral buprenorphine.

Towards the end of the interviews, participants were again asked if they would be personally willing to receive depot buprenorphine. There was no evidence of any participant changing their view, although several said that they still had questions and required more information. Despite their enthusiasm, analyses also revealed that participants' willingness was influenced both positively and negatively by six key features of depot buprenorphine: i) reduced contact with pharmacies and drug treatment services; ii) impact on illicit drug use and recovery; iii) the perceived effectiveness of depot buprenorphine; iv) the duration and dosage of depot buprenorphine injections; v) clinical administration of the depot buprenorphine injection; and vi) potential for side effects associated with the depot buprenorphine injection. These are described below and illustrated using pseudonymised quotations.

3.1 Reduced contact with pharmacies and drug treatment services

Patients with extensive treatment histories who reported current stability on OAT frequently explained that they would welcome depot buprenorphine if it reduced how often they would need to attend treatment services or pharmacies. Elaborating on this, they stated that collecting OAT from a pharmacy every day was habit-forming, time-consuming, and stigmatising; whereas long-acting depot buprenorphine offered them '*freedom*' from '*being chained*' or '*tied*' to services and would be '*easier*' and '*more convenient*', particularly during

times of opioid withdrawal, forgetfulness, physical ill health, and transport problems. Some participants also reported that depot buprenorphine could disrupt the cycle of drug-taking behaviours which attending services and daily supervised dosing reinforced.

You get caught up going... once a week to the [drug] project [for your OAT prescription], every day to the doctor or the chemist, to pick it [OAT medication] up. Like it takes over your life, you don't have any free time. Whereas that [weekly depot buprenorphine injection] sounds good, because... you've got seven days free until you have to go back [to the drug project]. (Bob, 47 years, heroin)

In contrast, people who use heroin not in treatment and patients less well-established in their current treatment expressed concerns at the prospect of having reduced contact with treatment services. Their anxieties centred on losing the structure, 'safety net,' and emotional and practical support provided by visiting treatment services and by meeting with keyworkers. These participants reported being less willing to receive depot buprenorphine as they said that taking medication in isolation was 'not enough' to 'recover' and 'only half the job' and they worried that their psychosocial and other support needs would be overlooked or neglected.

The important thing is how you engage back in the services again once you've got it [depot injection]... If I was on a depot, I would want someone... [to] find out exactly how I really am... whether I'm going to be using or not... or whether I'm alright on it... so you're not falling by the wayside. (Simon, 40 years, methadone)

Relatedly, a few participants emphasized that collecting OAT from a pharmacy gave opioid users somewhere to go, provided them with structure, enabled social interaction with pharmacy staff, and thereby also generally promoted recovery. They worried about losing such benefits if they received depot buprenorphine.

3.2 Impact on illicit drug use and recovery

Participants who described themselves as being motivated to stop using heroin or ‘*serious*’ about recovery said that they would be very willing to receive depot buprenorphine, stating that they felt certain that their drug use would cease for the duration of the injection. These participants reported that buprenorphine reduced cravings for, and ‘*blocked*’ the effects of, opioids; therefore, there would be ‘*no point*’ in using heroin anymore. Depot buprenorphine would, they said, help them to ‘*break cycles*’ of drug use and achieve stability. Moreover, it would enhance their opportunities to ‘*get on*’ and live ‘*normal*’ lives, which they characterised by work and family responsibilities rather than using illicit drugs.

What’s more nicer than somebody who was a hardcore junkie can have a social life, can sit in a park, talk to people, can sit in the pub... If I can use that [depot buprenorphine] and get back a normal life, that would be clean, that would be good... I would love to get back into work... if that can keep you away for three or four months, become normal. (Earl, 54 years, heroin)

Participants (particularly current buprenorphine patients who said that they had sometimes deliberately missed or reduced oral doses in order to use heroin and participants who stated that they were committed to not using heroin on top of prescribed medication) additionally liked the fact that depot buprenorphine injections would be harder to manipulate and circumvent than oral OAT formulations. However, the extended ‘*blocking*’ properties of depot buprenorphine did not appeal to all participants and led some, including those who wanted to continue to use heroin, to report less willingness to receive depot buprenorphine.

It’s got a blocker in there that stops me from being able to use. And so once it’s done it’s done, there’s no taking it back... the junkie in me, the drug addict in me might be a little concerned because he can’t get high. (Jack, 39 years, heroin)

3.3 The perceived effectiveness of depot buprenorphine

Participants often emphasised that they would need to be confident that depot buprenorphine 'worked' before they committed themselves to receiving it. When asked what they meant by 'worked', participants said that they would need to be certain that the medication would guarantee them stability, prevent opioid craving and withdrawal symptoms, and block illicit opioids. Following on from this, some also stated that they would feel more confident that depot buprenorphine worked, and they would therefore be more willing to try it, if they had more information about the treatment or if they had spoken to other opioid users who had already had a depot buprenorphine injection and experienced positive outcomes.

I would want to talk to somebody who has already tried it, I would, because I would want to listen to their experiences, i.e. did it work? That's the main thing, did it work? And just because it works for you, doesn't mean it's going to work for me. So yeah, I would like to talk to somebody who's tried it. (Darren, 53 years, heroin)

Generally, participants who had themselves previously had good experiences with oral buprenorphine seemed more willing to try a depot injection, noting that '*it's still the same drug you're pumping into your system, just in a different method*' (Helen, 44 years, buprenorphine). Furthermore, some current methadone patients and people who use heroin who had no personal prior experience of buprenorphine expressed interest in depot buprenorphine as they said that buprenorphine was a less stigmatising, less addictive, and more effective medication than methadone. Conversely, other participants reported a reluctance to receive depot buprenorphine because they had doubts about oral buprenorphine's effectiveness and had heard negative reports of oral buprenorphine from other patients. In addition, methadone patients were sometimes worried about experiencing opioid withdrawal if they transferred from methadone to depot buprenorphine as they recognised that they would probably have to firstly reduce, and then stop current doses of methadone for a period of time to comfortably transition.

[Methadone patients] would probably be more frightened [about having depot buprenorphine], because it's a known fact in users that swapping from methadone to buprenorphine can be painful. (Clare, 52 years, buprenorphine)

3.4 Duration and dosage of depot buprenorphine injections

Frequently, participants across all three sample groups explained how having different duration (weekly and monthly) depot injections and different strength dosages increased their personal willingness to receive depot buprenorphine because this afforded them more choice and flexibility in treatment. For example, participants said that they appreciated having the option of a shorter duration injection at start of treatment to facilitate '*dipping your toe in gently*' as a '*trial run*' to '*see how you get on with it*' before committing to the longer monthly treatment.

Something that stays in your body for 28 days, that's a hell of a half-life that. If something goes wrong, that's awful. Even seven days, that's a hell of a half-life. Have a one or two-day injection... then worst case scenario you're ill for 24 hours, but at least you know then that you don't want to take the seven day one... that would encourage me a lot more. (Nick, 24 years, methadone)

Indeed, participants (including those who had received depot medications for other conditions in the past) mostly viewed the idea of a monthly injection of buprenorphine as '*daunting*' and '*a big step*' and expressed reluctance to '*jump straight in*'. However, they reported that they would be more willing to consider a monthly depot injection if they had tried out and were satisfied with a shorter duration depot, or if they were already accustomed to oral buprenorphine. Once confidence and trust in the depot buprenorphine injection had been established, participants said that they would prefer a longer duration depot injection as this would allow them more freedom from services, so enabling them to pursue their recovery and live a more '*normal*' life.

According to many participants, again from all three sample groups, having the ability to transfer between depot buprenorphine injections of different durations and to 'top up' insufficient doses increased their willingness to receive depot buprenorphine. Conversely, concerns about depot buprenorphine injections 'running out early' or not lasting for the intended duration if not 'topped up' in time made them wary. In particular, participants worried that they would then experience opioid withdrawal but may not be believed by drug service staff. As a result, they would then have to use heroin in order to alleviate withdrawal, so making the depot injection seem pointless.

I don't want to have something that is supposed to make me feel better for a month and after three weeks I'm feeling rough, because it's not, there's no point doing it, no point taking it. (Jim, 46 years, buprenorphine)

Some participants additionally argued that people seeking rapid detoxification from OAT may be less willing to having a depot injection that lasted a month because their treatment would be fixed for that period with no option for reduction. Others explained that the availability of weekly and small doses increased the appeal of depot buprenorphine for people reducing their dose or at the end of treatment as medications could be tapered down in small increments and at a pace that suited the patient.

3.5 Clinical administration of depot buprenorphine injection

Although participants were informed in the interview that the depot injection would be administered by a healthcare professional, participants across all three sample groups still emphasised that their willingness to receive depot buprenorphine would be affected by who administered the treatment. Thus, many explained that they would be more willing to have a depot buprenorphine injection if it was administered by a trained person who 'knew what they were doing'. In this regard, participants mostly stated that trained medical professionals should

administer depot buprenorphine injections as they would know how to do this '*properly*' (that is, in the '*right place*' on the body, using '*clean*' equipment, and with limited complications). Although some participants argued that hostel staff or keyworkers could be trained to administer depot injections, others were less certain. For example, participants who had received medications via depot injections in the past noted that medical professionals had always administered the injections.

You feel safer knowing that they are medical professionals than actually if you went to a service and I had my keyworker administer it to me. I would have more faith and trust in a doctor or a nurse. (Mark, 53 years, heroin)

Some participants (again across all sample groups) reported that they would be willing to receive depot buprenorphine if they could self-administer it. In contrast, others were against allowing people to self-inject the treatment, stating that the medication might be abused. In addition, participants sometimes suggested that people might be reluctant to receive injectable buprenorphine if they were afraid of needles. Despite this, participants who said that they personally did not like needles almost always argued that the benefits of depot buprenorphine outweighed any concerns they had about the administration process.

3.6 Potential for side effects associated with depot buprenorphine injection

The risk of experiencing mild or moderate side effects or reactions from the administration of depot buprenorphine (e.g. pain, swelling, reddening of the skin, or bruising) did not appear to reduce participants' willingness to receive depot buprenorphine. Rather, most described this as '*a small price to pay*' and '*not a big deal*', noting that the longer-term benefits of the treatment would outweigh any short-term side effects.

If the long-term goal is going to make you feel better, it's going to give you a better quality of life, I think you'd accept a little bit of discomfort... If the benefit's outweighing

a little bit of discomfort... I would still give it [depot buprenorphine injection] a go.

(Andrew, 49 years, methadone)

Despite this, participants generally said that prolonged side effects might deter them from continuing with depot buprenorphine, particularly if injected medication could not be removed and if no antidote was available to reverse negative reactions. Additionally, participants commonly explained how the risk of side effects would make them more inclined to try a shorter duration depot in the first instance, and to think carefully about where on their body they would have the injection. For example, some participants said that they would prefer to have the depot injection in the buttock as any complications (redness, bruising or soreness) would only be seen by intimate partners, whereas others expressed concern that any swelling or bruising on the buttock could make it painful to sit down. Others preferred different (and often contradictory) administration sites (arm, stomach or thigh) depending on how well they thought they would tolerate the injection in the particular site/s and how successfully they felt they would be able to cover any visible reactions.

The thigh, buttock area is probably the best... if it swells, red, itching, at least it's somewhere where people are not going to see... whereas if it's on your arm it might stick out, unless you wore long clothes. (Tracey, 50 years, methadone)

4. Discussion

As depot buprenorphine is a very new treatment, research into the medication is developing. We are not aware of any published studies on patients' experiences of receiving depot buprenorphine and limited research appears to have been conducted into their willingness to receive it. From the few studies we identified, quantitative research indicates that people who use opioids will be willing to receive depot buprenorphine (Gilman et al., 2018; Kenney et al.,

2018), even though they recognize that it has both positive and negative features (Gilman et al., 2018). Qualitative research explored opioid users' views of novel opioid pharmacotherapy delivery systems, including depot injections (Neale et al., 2018a, 2018b). Yet, such research was not specific to any specified medication and used focus groups to ascertain general insights from several people at once (Neale et al., 2018a, 2018b). In consequence, we do not yet know the extent to which prolonged-release depot buprenorphine genuinely constitutes a solution to the long-standing problem of OAT compliance. Given this apparent lack of information, we designed an interview study to ask potential patients to consider whether they would be personally willing to receive depot buprenorphine, and then explored the factors influencing their responses.

Analyses of our interview data indicated that people prescribed daily methadone, people prescribed daily buprenorphine and daily users of heroin not in treatment were willing to receive depot buprenorphine. In accounting for this, participants frequently articulated a belief that depot buprenorphine injections would reduce their cravings, withdrawal symptoms, and use of heroin. Moreover, this would in turn enable them to pursue 'constructive', non-drug using lives characterised by reduced stigma and increased 'normality', 'freedom', and flexibility. Participants' high expectations of depot buprenorphine stand in stark contrast to patients' widely-reported criticisms of the inconvenience, stigma, restrictions and burden of taking oral OAT every day (Crawford, 2013; Fraser & valentine, 2008; Harris & McElrath, 2012; Neale, 2013; Neale et al., 2018b; Radcliffe & Parkes, 2013; Strike et al., 2013). Whilst this suggests that depot buprenorphine could potentially overcome key limitations of traditional OAT formulations, people may have unrealistic beliefs about, and hopes for, new medicinal products, particularly if they have not yet experienced the treatment and yet are eager for treatment or want a rapid solution to complex problems. Their views may then change if the new treatment fails to live up to early high expectations (Dolovich et al., 2008; Madden et al., 2018).

During the interviews, participants identified features of depot buprenorphine that both positively and negatively influenced their willingness to receive it. Thus, they tended to be more willing if they believed that it would reduce the stigma and inconvenience of attending pharmacies and drug services; 'block' heroin; enhance their recovery; guarantee stability; prevent withdrawal; provide flexibility in terms of duration and dosage; be administered by an experienced medical professional in a place on their body that was painless and invisible to others; and not cause serious side effects. In contrast, they seemed deterred by concerns that psychosocial support might be removed; the medication would not be effective or would expire early; the injection would be administered by non-medical staff; or the treatment would produce irreversible or prolonged complications. Our analyses also highlighted some differences between participant groups; for example, depot buprenorphine seemed to be more attractive to individuals who were more 'stable' and 'serious about not using' illicit opioids, but less attractive to people who were 'not in treatment', 'new to treatment', 'not stable in treatment', or afraid of needles.

Our findings are consistent with those of previous focus group research into medication delivery systems (Neale et al., 2018a, 2018b). This provides reassurance and increases trustworthiness in our current findings. Furthermore, the findings presented in this paper also support the argument that depot buprenorphine is a complex medication that comprises interacting physical, psychological and social components (Neale et al., 2018a). Thus, it contains a drug (buprenorphine) that potential patients considered in terms of its stigmatizing and addictive properties; an injection that needed to be administered by a competent professional (or other); and a flexible dose and duration of action. To the study participants, depot buprenorphine was also an unfamiliar treatment of uncertain effectiveness with unknown side effects that might offer them either welcome freedom from having to constantly attend services or unwelcome detachment from structure and psychosocial support which they felt they needed. Reflecting this complexity, different medication features seemed to appeal to particular patient subgroups (e.g. patients new to treatment were more likely to prefer

shorter duration injections) but also to particular individuals (e.g. participants expressed preferences for different administration sites). These findings highlight that willingness to receive a given medication is complex, individual and changeable.

Our findings also connect with the wider literature about willingness to receive treatment medications (Alvai et al., 2015; Grebley et al., 2008; Haythornthwaite et al., 2003). For example, we know from existing research that stated willingness to receive a new medication only mediates potential use (rather than actual uptake) of the medication (Grebley et al., 2008; Haythornthwaite et al., 2003) and that there are different degrees of willingness to receive medications (Alvai et al., 2015). Indeed, high willingness is more likely to translate into uptake, as demonstrated in an Australian study whereby injecting drug users with hepatitis C who were willing to receive treatment were more likely to initiate therapy, compared to those with lower treatment willingness (Alvai et al., 2015). At the same time, even when people demonstrate high willingness to receive a medication, factors such as those stemming from economic, personal, provider, and social issues may play a role and influence the uptake of new medications (Alvai et al., 2015; Grebley et al., 2008; Haythornthwaite et al., 2003; Lubloy, 2014).

Our study has both weaknesses and strengths. None of the participants had personally been treated with depot buprenorphine, nor knew anyone who had received it. Although we ascertained willingness to receive a new treatment, this is not a marker of subsequent uptake and we did not explore degrees of willingness (Grebley et al., 2008; Haythornthwaite et al., 2003). Additionally, the study took place in the community in one metropolitan area of the UK. This may limit the transferability of the findings to other treatment settings (e.g. residential treatment), other locations (e.g. countries where OAT is not available freely or that offer unsupervised/ take home doses of oral buprenorphine), and other people (e.g. those following 12 step treatment approaches). Furthermore, the research was supported by funding from a pharmaceutical company involved in developing both weekly and monthly prolonged-release

buprenorphine depot injections and we used the concept of their depot injection (CAM2038) as a basis for the discussions. Although we emphasized our independence from the pharmaceutical company, the potential for social desirability reporting by participants cannot be ruled out.

To the best of our knowledge, we conducted the first qualitative interview study on willingness to receive depot buprenorphine. In so doing, we generated in-depth data from a range of people with diverse treatment experiences who were all potentially eligible for depot buprenorphine. As such, our findings should be reflective of the range of views that clinicians will likely encounter as depot buprenorphine becomes available in practice. Our study also took place at a time of increased international attention into prolonged-release medications, so making the findings particularly topical.

5. Conclusions

Our analyses add to a small but emergent literature on patients' views of prolonged-release buprenorphine (Gilman et al., 2018; Kenney et al., 2018). Findings support the argument that people are likely to welcome greater choice and flexibility in respect of OAT medications and delivery systems (Neale et al., 2018a, 2018b). Opioid users also seem more likely to accept and adhere to this new medication if it frees them from treatment services; helps them to reduce their illicit drug use and facilitates their recovery; is effective and does not 'run out'; offers choice in terms of dose and duration; and does not have any prolonged or irreversible side effects. Nonetheless, reflecting earlier studies, there are aspects of daily treatment that some patients may be concerned about losing, such as structure, routine, and psychosocial support (Neale et al., 2018a). These should be carefully considered by clinicians once depot buprenorphine is available in treatment settings. In addition, we suggest that treatment providers should not assume that a patient's early enthusiasm for depot buprenorphine provides a definitive reason to prescribe it. Clinicians should always offer patients appropriate

information and discuss all treatment options with them so that they are better able to make informed treatment decisions (Neale et al., 2018b; Yarborough et al., 2016). Given recent international approvals for the use of prolonged-release buprenorphine, qualitative and quantitative research is now especially needed to explore whether patients' reported willingness to receive depot buprenorphine translates into actual uptake and adherence.

ACCEPTED MANUSCRIPT

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Box 1: Summary of key features of one of the depot buprenorphine formulations in development (CAM2038/ Buvidal®) as outlined during the interviews

Overview: prolonged-release buprenorphine injection for the treatment of opioid dependence.

Effectiveness: designed to help block the drug-liking effect of opioids in the brain and reduce withdrawal, craving, and patients' use of illicit opioids.

Duration: available as weekly and monthly depot injection. Potential to 'top up' dose (with either oral buprenorphine or a booster injection) if insufficient. Dose reductions only possible at end of the week/ month. Ability to transfer between weekly and monthly injections.

Administration: under the skin (subcutaneous) injection by healthcare professional into patient's arm, buttock, stomach, or thigh.

Dosage: designed to deliver a set dose every day over weekly or monthly duration.

Potential side effects: comparable to daily sublingual buprenorphine, except for mild to moderate injection site reactions, such as pain, itching, red skin, swelling, lump around the site of the injection.

Service attendance: no need for supervised dosing of daily oral medications. May only have to attend a clinic or pharmacy on the day of the injection, either once a week or once a month.

Table 1: Participant demographics

	Methadone (n=12)	Buprenorphine (n=12)	Heroin (n=12)	Total (n= 36)
Gender				
Male	8 (67%)	9 (75%)	9 (75%)	26 (72%)
Female	4 (33%)	3 (25%)	3 (25%)	10 (28%)
Ethnicity				
White/ White British	10 (83%)	9 (75%)	5 (42%)	24 (67%)
Black/ Black British	0 (0%)	2 (17%)	3 (25%)	5 (14%)
Asian/ Asian British	1 (8%)	0 (0%)	0 (0%)	1 (3%)
Mixed or Multiple	1 (8%)	0 (0%)	2 (17%)	3 (8%)
Other	0 (0%)	1 (8%)	2 (17%)	3 (8%)
Age (years)				
Mean (range)	40 (24-50)	47 (26-57)	47 (35-63)	45 (24-63)
Current heroin use				
Yes	6 (50%)	3 (25%)	12 (100%)	21 (58%)
No	6 (50%)	9 (75%)	0 (0%)	15 (42%)
Current OAT				
Methadone	12 (100%)	0 (0%)	0 (0%)	12 (33%)
Buprenorphine	0 (0%)	12 (100%)	0 (0%)	12 (33%)
None	0 (0%)	0 (0%)	12 (100%)	12 (33%)
Time on current OAT (months)				
Mean (range)	97 (6-300)	20 (1.5-120)	N/A	58 (1.5-300)
Supervised consumption				
Yes	7 (58%)	7 (58%)	N/A	14/24 (58%)
No	5 (42%)	5 (42%)	N/A	10/24 (42%)
Frequency of pharmacy				
Daily	9 (75%)	7 (58%)	N/A	16/24 (67%)
2-3 times a week	2 (17%)	3 (25%)	N/A	5/24 (21%)
Weekly	1 (8%)	2 (17%)	N/A	3/24 (13%)
Ever prescribed methadone				
Yes	12 (100%)	8 (67%)	10 (83%)	27 (75%)
No	0 (0%)	4 (33%)	2 (17%)	9 (25%)

Ever prescribed buprenorphine				
Yes	6 (50%)	12 (100%)	11 (92%)	29 (81%)
No	6 (50%)	0 (0%)	1 (8%)	7 (19%)
Ever received depot medication				
Yes – any	4 (33%)	2 (17%)	3 (25%)	9 (25%)
Yes – contraception	2 (17%)	1 (8%)	2 (17%)	5 (14%)
Yes – anti-psychotic	1 (8%)	1 (8%)	2 (17%)	4 (11%)
Yes – other*	1 (8%)	0 (0%)	0 (0%)	1 (3%)
No	8 (67%)	9 (75%)	9 (75%)	26 (72%)
Don't Know	0 (0%)	1 (8%)	0 (0%)	1 (3%)

* testosterone replacement therapy