Recent advances in the treatment of opioid use disorders–focus on long-acting buprenorphine formulations

Michael Soyka, Andreas G Franke

Abstract

Oral methadone or sublingual buprenorphine are first-line medications for pharmacotherapy of opioid use disorders (OUDs). Three long-acting buprenorphine depot or implant formulations are currently available for the treatment of OUDs: (1) CAM 2038 (Buvidal) for subcutaneous weekly and monthly application; (2) RBP-6000 (Sublocade™) as a monthly depot formulation; and (3) A six-month buprenorphine implant [Probuphine™]. The pharmacology, clinical efficacy and prospects of these medications are discussed.

Key Words: Opioids; Opioid dependence; Maintenance treatment; Methadone; Buprenorphine; Depot; Implant

Core Tip: Although opioid maintenance therapy with methadone or buprenorphine is the widely accepted first line treatment in opioid use disorders (OUDs) the risk of diversion and low retention rates limit its use. While previous attempts to introduce long-acting methadone analogues have failed due to cardiac side effects in recent years, three different long-acting buprenorphine formulations have been developed and successfully studied in opioid users, two weekly or monthly depot injections (CAM 2038, RBP-6000) and one implant (probuphine). The prospects of these new medications are significant by optimizing retention and compliance and minimizing the risk of diversion. Thus these novel medications can facilitate treatment of OUDs significantly.

Citation: Soyka M, Franke AG. Recent advances in the treatment of opioid use disorders–focus on long-acting buprenorphine formulations. World J Psychi 2021; 11(9): 543-552

URL: https://www.wjgnet.com/2220-3206/full/v11/i9/543.htm
Opioid use disorder (OUD) is defined as a chronic relapsing substance use disorder that causes psychological and physical harm. The economic burden and health costs of OUD are also very significant.[1-4]

PREVALENCE

OUD has a prevalence of approximately 0.2%-0.4% in the adult population in many countries.[5-7] In Europe, heroin is the most frequently abused opioid. However, in other countries, the use of synthetic opioids and opioid pain killers, such as fentanyl or oxycodone, has been exploding and is the predominant form of opioid use. In particular, the United States is facing an epidemic of opioid pain killer abuse[8]. Recent data indicate that in Europe, there are 1.3 million high-risk opioid users and 644000 opioid users in substitution treatment[5]. Opioid use accounts for 40% of all drug requests in the European Union.

The high mortality in opioid dependence remains a significant problem. Opioids are involved in 82% of fatal drug-related overdoses[5]. Most opioid-related deaths are caused by overdose and respiratory depression. Other frequent causes of death include suicide, accidents, injuries, and numerous somatic disorders, such as infectious diseases (human immunodeficiency virus, hepatitis, others). In many fatal drug intoxications, polysubstance abuse is involved, especially alcohol or other sedative drugs[9].

TREATMENT AIMS

Opioid maintenance treatment (OMT) and psychosocial interventions are key elements in the treatment of OUD[2,8,10,11]. Major aims in the treatment of OUD are reduction of opioid use or even abstinence[12,13] as measured by self-reports or toxicological analysis, reduction of other substance use, improved social functioning and health outcome and reduction of criminal behavior[12,14,15].

There are numerous clinical and longitudinal studies on treatment outcomes in OUD. However, many long-term studies only address substance use or abstinence rates, whereas other outcome parameters are less often reported. An interesting study on outcome criteria has recently been described by Wiessing et al[16], who assessed reported outcome domains in 27 Longitudinal studies (Table 1). Data indicate that many domains, especially social functioning or health economics, are often neglected as outcome parameters.

Several medications are currently available for the treatment of OUDs (Table 2). For approximately 5 decades, OMT has been the established and widely accepted first-line treatment of OUD[11,14,17-20]. In addition, a number of pharmacological options are available. Medications used in OMT control craving for opioids and withdrawal symptoms. The two widely examined gold standards in OMT are methadone and buprenorphine[21].

Oral methadone (standard doses 60-100/120 mg daily) and sublingual buprenorphine (standard doses 8-12, max 24-32 mg daily) are the primarily used drugs in the treatment of opioid dependence. Its efficacy has been shown in many clinical studies.[17-19]. Some distinct pharmacological differences are noted between methadone and buprenorphine.

Methadone is a pure nonselective opioid receptor agonist of the mu, delta and kappa opioid receptors. Methadone induces the typical clinical effects of full opioid agonists, such as analgesia, sedation, respiratory depression, euphoria and tolerance. Methadone causes a significant physical dependence. Methadone has a half-life of approximately 22 h (13-50 h). Methadone blocks the opioid receptor for approximately 24 h, so it is suitable for daily dosing. Methadone suppresses opioid withdrawal symptoms for 24 h. There is broad evidence for the efficacy of methadone in OMT[14, 17-19]. The drug is widely accepted and used.
Table 1 Large variations in outcome measures in longitudinal studies of opioid dependence[16]

| Domain                        | Reported among 27 studies included |
|-------------------------------|------------------------------------|
| Drug use                      | 21 of 27                           |
| Crime                         | 13 of 27                           |
| Health                        | 13 of 27                           |
| Treatment-related outcomes    | 16 of 27                           |
| Social functioning            | 13 of 27                           |
| Harms                         | 8 of 27                            |
| Mortality                     | 13 of 27                           |
| Economic estimates            | 2 of 27                            |

Results are based on 27 studies included. Eight domains were defined. Each domain was reported x-times among 27 studies.

Table 2 Pharmacological options in the treatment of opioid use disorders

| Drug                        | Onset of action, duration | Route of administration | Clinical use |
|-----------------------------|---------------------------|-------------------------|--------------|
| Opioid antagonists          |                           |                         |              |
| Naloxone                    | Few minutes               | i.v., nasal (spray)     | Opioid overdose |
| Naltrexone                  | Daily                     | Oral                    | Abstinence    |
| Naltrexone (depot)          | One month                 | i.m.                    | Abstinence    |
| Partial agonists            |                           |                         |              |
| Buprenorphine               | Daily                     | Sublingual              | Maintenance  |
| Buvidal                     | Weekly, monthly           | Subcutaneous            | Maintenance  |
| RB_6000 (sublocade)         | Monthly                   | Subcutaneous            | Maintenance  |
| Probuphine                  | 6 mo                      | Implant                 | Maintenance  |
| Full agonists               |                           |                         |              |
| Methadone                   | Daily                     | Oral                    | Maintenance  |
| Heroin                      | Hours                     | i.v.                    | Maintenance  |
| Morphine sulfate (retarded) | Daily                     | Oral                    | Maintenance  |
| Heroin¹                     | Twice daily (?)           | i.v.                    | Maintenance  |
| Morphine sulfate            | Daily                     | Oral                    | Maintenance  |

¹In combination with methadone?

Buprenorphine, being a partial agonist at the m-opioid receptor[11,19], has to be administered sublingually because of a strong first pass effect. Regarding opioid receptors, the use of buprenorphine is associated with a ceiling effect at these receptors. Compared to methadone, buprenorphine is at lower risk to induce depression of respiration. Numerous studies indicate that buprenorphine is associated with fewer fatal intoxications or overdose deaths than methadone. Other full opioid agonists used for the treatment of OUD include morphine sulfate and diacetylmorphine (heroin). Both are second line medications for OMT[11,14,22].

There are some significant problems in OMT. The most important factor is the risk of diversion of methadone or buprenorphine. Other major problems are concomitant opioid or other substance use as well as limited compliance and retention in treatment [20,23,24]. The latter is of great importance. A recent systematic review on retention in OMT[25] included 4 randomized clinical trials and 63 observational cohort studies with a total of 294592 patients. The overall findings indicate a 1-year retention rate of 57% and a 3-year retention rate of 38.4%. The retention rate is higher in patients with older age and depends on an adequate dose of the maintenance drug. Several studies
Soyka M et al. Depot buprenorphine in opioid dependence

indicate that a too low dosage is associated with a higher dropout rate[26].

Dosing issues are of great relevance in OMT. Adherence to treatment depends on adequate dosing, and retention can be improved by adequate dosing[15,27-29]. Too low doses of methadone or buprenorphine are associated with low retention and risk of further substance use.

Methadone remains the most frequently used medication in OMT. The other first-line medication is buprenorphine[18,19,24,26,30,31]. The retention rate for buprenorphine was reported to be lower than that of methadone in some studies[19,26,30]. The risk for respiratory depression by buprenorphine in cases of overdose is lower than that for full opioid agonists[24,32].

Buprenorphine is used as a sublingual tablet. It is marketed as a monoprodut or in combination with naloxone (buprenorphine:naloxone ratio 4:1)[9,27]. Naloxone is a short-acting opioid antagonist and is pharmaceutically active only as an i.v. medication and as a nasal spray for the prevention of overdose death. Naloxone will rapidly induce opioid withdrawal. The risk of precipitated opioid withdrawal should prevent the patient from injecting buprenorphine and thus reduce the risk of diversion or i.v. use of buprenorphine.

Both methadone and buprenorphine are administrated as once a day doses, and both suppress symptoms of opioid withdrawal for 24 h. Longer dosing intervals have been a major aim in OMT research. A long-acting methadone analog was previously studied but had to be withdrawn over potential adverse cardiac effects[33,34].

Clinical and social reasons for long-acting opioids in OMT include a reduced risk of diversion, improved compliance, easier home dosing and longer treatment intervals. The recent coronavirus disease 2019 (COVID-19) epidemic has demonstrated that prolonged dosing and treatment intervals and consequently less time spent in the outpatient clinic or at the office-based physician, respectively, and reduced use of social and medical resources are important goals for many clinicians.

Recent developments

Exciting developments have occurred in recent years: Three different long-acting buprenorphine formulations have been developed, approved and in part introduced into clinical practice in many countries. These agents will be reviewed briefly.

**RBP-6000 (Sublocade™)**

RBP-6000 is a buprenorphine depot injection. It has been marketed in the United States since 2018 and will soon be available in Europe. Medication and dosing intervals: Monthly s.c. injections are available with dosages of 100 and 300 mg. Dosages recommended for the treatment of OUD (www.sublocade.com) include two initial 300 mg injections monthly followed by monthly 100 mg injections.

RBP-6000 has been studied in several pharmacological and clinical studies. Nasser et al[35] studied the effects of RBP-6000 in patients with opioid dependence. RBP was found to block the effects of a strong opioid, hydromorphone, such as opioid cravings. Other studies showed effective µ-opioid receptor blockade with different dosages of RBP-6000[35,36]. These findings suggest that RBP-6000 is a suitable medication for OMT. A recent combined analysis of phase II and III trials with 570 subjects[37] showed that therapeutic concentrations can be achieved from the first injection. These therapeutic concentrations were achieved during the entire treatment duration. The data suggest that the drug provided therapeutic plasma concentrations over the entire treatment duration.

Clinical data indicate that RBP-6000 is effective in OMT. Haight et al[38] performed a multicenter phase III study being double-blind and placebo-controlled. Dosing regimen among the opioid dependent patients was as follows: One group received monthly injections of RBP-6000 subcutaneously (6 × 300 mg or 2 × 300 mg) followed by 4 × 100 mg, the other group received placebo. Abstinence rates as a major outcome in both buprenorphine depot groups (n = 203 and n = 201 patients, respectively) were significantly higher than those in the placebo group (n = 100) (41.3% and 42.7% in the respective buprenorphine groups compared to 5.0% in the placebo group; P < 0.0001 for both buprenorphine groups). No differences in outcome were noted between the buprenorphine groups. Both studied dosing regimens were equally effective. In addition, the rate of hospital admissions was also lower in both buprenorphine groups compared with the placebo group[39]. Overall, these data indicate that RBP-6000 is effective. Andorn et al[40] performed an open-label multicenter study in 257 patients. A total of 13.2% of OUD patients had injection-site adverse events. Although these events are usually mild and transient, they may affect acceptance of this or other depot injections. Otherwise, the safety profile was good with fewer adverse events in the second 6 mo of treatment vs the first 6 mo. The retention rate was approximately 50%
after 12 mo.

**CAM 2038 (Buvidal)**

CAM 2038 is another novel depot buprenorphine injection. The drug is injected subcutaneously. Buvidal is approved in Europe\(^1\). Dosing regimen: Four different dosages are available: 8, 16, 24 or 32 mg for weekly injections and 64, 96, 128 or 160 mg for monthly injections. CAM 2038 treatment is typically initiated with weekly injections. Later, the patient can be transferred from weekly to monthly depot injections.

Several pharmacological studies have been conducted to explore the pharmacological effects of RBF-6000\(^2\). In sum, adequate plasma concentrations and bioavailability were demonstrated for the compound. Albayat et al\(^3\) showed that monthly or weekly subcutaneously administered depot of CAM 2038 (dosages: 96 mg and 192 mg) exhibited 5.7- to 7.7-fold increased bioavailability than sublingual buprenorphine (8, 16 or 24 mg). In addition, 24 mg and 32 mg Buvidal block the subjective effects of intramuscularly administered hydromorphone\(^4\).

The efficacy of Buvidal has also been demonstrated in several clinical trials. In a phase III study being double-blind with double-dummy, with 428 patients\(^5\), flexible weekly injections of CAM 2038 were used in the first 12 wk rather than monthly injections in the following 12 wk and tested against sublingual buprenorphine (flexible dose up to 24 mg daily maximum). Buvidal was found to be noninferior to sublingual buprenorphine with respect to opioid use (primary outcome) and opioid-free urine (secondary outcome). The average weekly CAM 2038 dosages were 24 mg, and monthly injections ranged over 100 mg. No novel adverse events were noted. The side effect profile of RBF-6000 is similar to that of sublingual buprenorphine\(^6\). With respect to the injection, mild local reactions were reported by 18%–22% of the participants. In a very recent study, injection site reactions of mild intensity were the most frequent adverse drug reaction\(^7\). Further safety data are being collected in an ongoing nonrandomized prospective observational study\(^8\).

**Buprenorphine implant (Probuphine™, Sixmo)**

The third long-acting buprenorphine is an implant\(^9\). Probuphine was approved by the Food and Drug Administration (FDA) in 2016 for the long-term treatment of opioid dependent patients who were on a stable medication regimen of 8 mg buprenorphine sublingually or less. Buprenorphine (8 mg) is typically considered a moderate dose in OMT with an upper limit of daily sublingual buprenorphine dose of 24–32 mg. In Europe, the implant was approved by the European Medicine Agency in 2019. Buprenorphine is linked to a polymer that delivers the drug steadily to the body. Four implants are inserted. The dose of the buprenorphine released by the implant is equivalent to 8 mg sublingual buprenorphine or less\(^10\). Subdermal insertion of the implant requires minimal surgery. The implant is inserted in the upper arm and remains there for 6 mo before it is removed again. Plasma concentrations peak 12 h after the implant is inserted. Steady state conditions were noted after 3–4 wk\(^11\).

Several relevant clinical studies of Probuphine are available. The efficacy of the buprenorphine implant was demonstrated in three double-blind studies (309 patients included) with a follow-up of up to 6 mo.

In a randomized controlled trial Ling et al\(^12\) assessed 163 participants with opioid dependence over a period of 6 mo. After initial treatment with sublingual buprenorphine, the patients were transferred to either 4 × 80 mg buprenorphine or placebo implants. The retention rate in the implant group (71 of 108 patients) was significantly higher than that in the placebo group (17 of 55 patients; 65.7% vs 30.9%, \(P < 0.001\)). In the buprenorphine implant group, the number of opioid-free urine samples was higher.

Rosenthal et al\(^13\) conducted a placebo-controlled randomized clinical trial in opioid-dependent patients who either received 4 × 80 mg buprenorphine (\(n = 114\)) or 4 placebo implants (\(n = 54\)). In an open design, the control group was treated with sublingual buprenorphine at a dose of 12-16 mg daily. In total, 119 participants were included in the control group. Compared to the placebo group, the retention rate of the implant group was significantly higher (\(P < 0.0001\)) (64 vs 26%). Furthermore, regarding the mean number of urine samples being opioid-free, the implant group was also found to be superior to the placebo group and noninferior to the sublingual buprenorphine group. Side effects: Negligible (local) reactions among the patients of the implant group were more or less frequent (25%-27%).

Furthermore, Rosenthal et al\(^14\) studied OMT patients being stably adjusted to a sublingual dose of 8 mg (or less). Patients were given sublingual placebo plus four buprenorphine implants or sublingual buprenorphine plus four placebo implants over
a period of 24 wk. In total, 177 patients were included. Over a time period of 6 mo, the rate of abstinence among patients in the buprenorphine implant group was found to be noninferior to that in the control group treated with sublingual buprenorphine (85.7% vs 71.9%). The retention rate was 93%. The response rate was 96.4% in the buprenorphine implant group and 87.6% in the control group ($P < 0.01$). In addition, 85% of patient in the implant group were opioid free compared to 72% of the patients of the control group.

According to the FDA there is the necessity of a special risk management for this treatment. The “Probuphine Risk Evaluation and Mitigation Strategy” program was initiated (https://probuphinerems.com).

In addition, Titan Pharmaceuticals announced discontinuing United States Probuphine implant sales on October 15, 2020. No specific medical reasons were given for this decision.

### DISCUSSION

OMT is the established first-line treatment in OUD, and methadone and buprenorphine serve as the pharmacological “frontrunners”[21]. Buprenorphine has a good safety profile[56] but modest and somehow lower retention rates than methadone. Retention to treatment is of overwhelming importance for treatment outcome and mortality in OUD, especially the induction phase and the period after leaving treatment[15]. Other common problems include diversion and i.v. use of buprenorphine[3,57]. Whether the combination of buprenorphine and naltrexone lowers the risk of buprenorphine diversion is controversial[58].

Emerging or approved long-acting buprenorphine (depot or implant) formulations significantly widen the therapeutic arena in OMT[42,59]. Weekly and monthly s.c. buprenorphine injections as well as 6-mo depot formulations are available or will be available in the near future. It is clear and self-evident that the retention to treatment in patients with a depot formulation will be greater than that noted in patients in conventional OMT, and the risk of diversion is especially minimal to nonexistent. The data reviewed indicate that long-acting buprenorphine formulations are as efficient as sublingual buprenorphine with respect to opioid use with a similar side effect profile—with the exception of effects linked to injection or insertion of the compound. To date, some other observational studies on these medications are ongoing to provide further safety data[49,60].

**The clinical question is: Who will benefit?**

With the long-term French buprenorphine experience in mind, Vorspan et al[61] suggest prolonged-release buprenorphine depot formulations, such as Buvidal, as a promising treatment option in the following scenarios: (1) OMT initiation, including in nonspecialized medicine care; (2) Discharge from prison or hospital; (3) Diversion /Misuse of buprenorphine or methadone; and (4) Patients.

In addition, clinically stabilized patients wishing to receive an injection or implantation of the compound can be transferred to a buprenorphine depot.

This covers a wide range of patients. Other authors have similar views. Ling et al[39] stated that “Anyone with an OUD who can benefit from oral buprenorphine can benefit from the injectable”.

Patients who want to avoid daily oral intake of the medication may be attracted by the prospect of more personal freedom.

In addition to benefits at the individual level, this novel medication also provides public health benefits. Retention rates may be increased—which has to be shown in future studies—and the risk for diversion may be reduced. In addition, the utilization of health care resources will be reduced. These effects are relevant, especially during the COVID-19 pandemic when social distancing is required[42].

Arunogiri and Lintzeris[62] argued that the use of long-acting buprenorphine formulations may help during the COVID-19 pandemic, and some health care organizations have advocated its use[42]. For example, a rapid upscaling of Buvidal use in custodial settings occurred in Australia during the COVID-19 epidemic[63].

Depot formulations are already used in prisons or forensic psychiatry settings to avoid diversion of the drug[61]. Broad empirical evidence suggests that OMT can reduce criminality in OUD[64-68] as reported in a meta-analysis by Moore et al[69]. The risk of diversion and misuse of opioid medication is significant in prison settings. Depot medications may reduce this risk significantly.
There are also some practical aspects to be considered. Although transfer from sublingual to depot buprenorphine will likely not represent a major problem, the introduction of depot buprenorphine to a patient previously treated with methadone is more complicated. Moreover, there are no studies on this issue. Switching the patient from methadone to sublingual buprenorphine first before transferring him to a depot formulation seems to be the most appropriate method at present.

Patient preferences and attitudes toward treatment are of great relevance for OMT. Many patients prefer certain OMT medications. There are very few qualitative studies on this issue. Patient preferences and attitudes toward treatment are of great relevance for OMT. There are very few qualitative studies on this issue. There are also some practical aspects to be considered. Although transfer from sublingual to depot buprenorphine will likely not represent a major problem, the introduction of depot buprenorphine to a patient previously treated with methadone is more complicated. Moreover, there are no studies on this issue. Switching the patient from methadone to sublingual buprenorphine first before transferring him to a depot formulation seems to be the most appropriate method at present.

CONCLUSION

In conclusion, novel depot buprenorphine formations are a promising therapeutic option in OMT. There is no doubt about the efficacy of these compounds, but the practical value has to be shown in real life conditions.

REFERENCES

1. Degenhardt L, Charlson F, Mathers B, Hall WD, Flaxman AD, Johns N, Vos T. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction* 2014; 109: 1320-1333 [PMID: 24661272 DOI: 10.1111/add.12551]

2. Degenhardt L, Grebely J, Stone J, Hickman M, Vickereman P, Marshall BD, Bruneau J, Atice FL, Henderson G, Rahimi-Movaghar A, Larney S. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. *Lancet* 2019; 394: 1560-1579 [PMID: 31657732 DOI: 10.1016/S0140-6736(19)32229-9]

3. Neusser S, Treutner A, Pomorin N, Wasem A, Neumann A. Krankheitskosten der Opioidabhängigkeit in Deutschland. *Suchtmed* 2020; 22: 205-216

4. Schuckit MA. Treatment of Opioid-Use Disorders. *N Engl J Med* 2016; 375: 1596-1597 [PMID: 27797302 DOI: 10.1056/NEJMMe1610830]

5. EMCDDA. European Monitoring Centre for drugs and Drug addiction (2020) European Drug Report. Lisbon: EMCDDA. [cited 10 January 2021]. Available from: https://www.drugsandalcohol.ie/33049/

6. Merz F. United Nations Office on Drugs and Crime (2017) World Drug Report. SIRIUS-Zeitschrift für Strategische Analysen 2017; 85-86 [DOI: 10.1515/sirius-2018-0016]

7. United Nations. United Nations Office on Drugs and Crime (2020) International Standards on Drug Use Prevention. Second updated Edition. [cited 10 January 2021]. Available from: https://www.unodc.org/

8. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *Lancet* 2019; 393: 1760-1772 [PMID: 30878228 DOI: 10.1016/S0140-6736(18)32078-2]

9. Soyka M, Batra A, Heinz A, Moggi F, Walter M. Suchtmédizin. München: Elsevier, 2019. 177-202

10. Volkow ND, Frieden TR, Hyde PS, Chá SS. Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med* 2014; 370: 2063-2066 [PMID: 24758595 DOI: 10.1056/NEJMp1402780]

11. Volkow ND, Blanco C. Medications for opioid use disorders: clinical and pharmacological considerations. *J Clin Invest* 2020; 130: 10-13 [PMID: 31763992 DOI: 10.1172/JCI134708]

12. Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug Alcohol Depend* 2001; 62: 255-264 [PMID: 11295330 DOI: 10.1016/s0376-8716(00)00211-8]

13. Bell J. Pharmacological maintenance treatments of opiate addiction. *Br J Clin Pharmacol* 2014; 77: 253-263 [PMID: 23210630 DOI: 10.1111/bcp.12051]

14. Bell J, Strang J. Medication Treatment of Opioid Use Disorder. *Biol Psychiatry* 2020; 87: 82-88 [PMID: 31420089 DOI: 10.1016/j.biopsych.2019.06.020]

15. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, Ferri M, Pastor-Barriuso R. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* 2017; 357: j1550 [PMID: 28446428 DOI: 10.1136/bmj.j1550]

16. Wiessing L, Ferri M, Darke S, Simon R, Griffiths P. Large variation in measures used to assess outcomes of opioid dependence treatment: A systematic review of individual observational studies. *Drug Alcohol Rev* 2018; 37 Suppl 1: S123-S138 [PMID: 28971544 DOI: 10.1111/dar.12688]

17. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments vs agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev* 2011; CD004147 [PMID: 21975742 DOI: 10.1002/14651858.CD004147.pub4]
18 Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy vs opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2003; CD002209 [DOI: 10.1002/14651858.cd002209]

19 Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance vs placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2014; CD002207 [DOI: 10.1002/14651858.cd002207]

20 Soyka M, Strehole J, Rehm J, Bühringer G, Wittchen HU. Six-Year Outcome of Opioid Maintenance Treatment in Heroin-Dependent Patients: Results from a Naturalistic Study in a Nationally Representative Sample. *Eur Addict Res* 2017; 23: 97-105 [PMID: 28376505 DOI: 10.1159/000468518]

21 Crotty K, Freedman KI, Kampman KM. Executive Summary of the Focused Update of the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder. *J Addict Med* 2020; 14: 99-112 [PMID: 32299915 DOI: 10.1097/ADM.0000000000000635]

22 Strang J, Groshkova T, Uchtenhagen A, van den Brink W, Haasen C, Schechter MT, Lintzeris N, Bell J, Pirona A, Oviedo-Joekes E, Simon R, Metrebian N. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction?. *Br J Psychiatry* 2015; 207: 5-14 [PMID: 26135571 DOI: 10.1192/bjp.bp.114.149195]

23 Bell J. The global diversion of pharmaceutical drugs: opiate treatment and the diversion of pharmaceutical opiates; a clinician's perspective. *Addiction* 2010; 105: 1531-1537 [PMID: 20626373 DOI: 10.1111/j.1360-0443.2010.03144.x]

24 Bell J, Trinli L, Butler B, Randall D, Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. *Addiction* 2009; 104: 1193-1200 [PMID: 19563562 DOI: 10.1111/j.1360-0443.2009.02627.x]

25 O'Connor AM, Cousins G, Durand L, Barry J, Boland F. Retention of patients in opioid substitution treatment: A systematic review. *PLoS One* 2020; 15: e0232086 [PMID: 32407321 DOI: 10.1371/journal.pone.0232086]

26 Hser YI, Saxton AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, West K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction* 2014; 109: 79-87 [PMID: 23961726 DOI: 10.1111/add.12333]

27 Fareed A, Vayalapalli S, Casarella J, Drexler K. Effect of buprenorphine dose on treatment outcome. *J Addict Dis* 2012; 31: 8-18 [PMID: 22356665 DOI: 10.1080/10550887.2011.642758]

28 Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend* 2014; 144: 1-11 [PMID: 25179217 DOI: 10.1016/j.drugalcdep.2014.07.035]

29 Greenwald MK, Johansen CF, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubiena JK. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 2003; 28: 2000-2009 [PMID: 12902992 DOI: 10.1038/sj.teen.1502511]

30 Hser YI, Evans E, Huang D, Weiss R, Saxton A, Carroll KM, Woody G, Liu D, Wakim P, Matthews AG, Hatch-Maillette M, Jelstrom E, West K, McLaughlin P, Ling W. Long-term outcomes after randomization to buprenorphine/naloxone vs methadone in a multi-site trial. *Addiction* 2016; 111: 695-705 [PMID: 26599131 DOI: 10.1111/add.13238]

31 Jordan CJ, Cao J, Newman AH, Xi ZX. Progress in agonist therapy for substance use disorders: Lessons learned from methadone and buprenorphine. *Neuropsychopharmacology* 2019; 158: 107609 [PMID: 31009632 DOI: 10.1016/j.neuropharm.2019.04.015]

32 Kimber J, Larney S, Hickman M, Randall D, Degenhardt L. Mortality risk of opioid substitution therapy with methadone vs buprenorphine: a retrospective cohort study. *Lancet Psychiatry* 2015; 2: 901-908 [PMID: 26384619 DOI: 10.1016/S2215-0366(15)00066-1]

33 Deamer RL, Wilson DR, Clark DS, Pritchard JG. Torsades de pointes associated with high dose buprenorphine: a retrospective cohort study. *PLoS One* 2015; 10: e0232086 [PMID: 32407321 DOI: 10.1371/journal.pone.0232086]
VR, Ling W, Heidbreder C; RB-US-13-0001: Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2019; 393: 778-790 [PMID: 30792007 DOI: 10.1016/S0140-6736(18)32259-1]

39 Ling W, Shoptaw S, Goodman-Meza D: Depot Buprenorphine Injection In The Management Of Opioid Use Disorder: From Development To Implementation. Subst Abuse Rehabil 2019; 10: 69-78 [PMID: 31819701 DOI: 10.2147/SAR.S155843]

40 Andora AC, Haight BR, Shinde S, Fudala PJ, Zhao Y, Heidbrecher C, Learned SM, Fox NL, Nadpelli VR, Hassman D, Rutrick D: Treating Opioid Use Disorder with a Monthly Subcutaneous Buprenorphine depot Injection: 12-Month Safety, tolerability, and Efficacy Analysis. J Clin Psychopharmacol 2020; 40: 231-239 [DOI: 10.1097/jcp.0000000000001195]

41 Coe MA, Lofwall MR, Walsh SL: Buprenorphine Pharmocology Review: Update on Transmucosal and Long-acting Formulations. J Addict Med 2019; 13: 93-103 [PMID: 30531584 DOI: 10.1097/ADM.0000000000000457]

42 Soyka M: Novel Long-Acting Buprenorphine Medications for Opioid Dependence: Current Update. Pharmacopsychiatry 2021; 54: 18-22 [PMID: 33212514 DOI: 10.1055/a-1298-4508]

43 Haasen C, Linden M, Tiberg F: Pharmacokinetics and pharmacodynamics of a buprenorphine subcutaneous depot formulation (CAM2038) for once-weekly dosing in patients with opioid use disorder. J Subst Abuse Treat 2017; 78: 22-29 [PMID: 28554599 DOI: 10.1016/j.sjat.2017.04.008]

44 Walsh SL, Comer SD, Lofwall MR, Vince B, Levy-Cooperman N, Kelsh D, Coe MA, Jones JD, Nuzzo PA, Tiberg F, Sheldon B, Kim S: Effect of buprenorphine weekly depot (CAM 2038) and hydromorphone blockade in individuals with opioid use disorder: a randomised clinical trial. JAMA Psychiatry 2017; 74: 894-902 [PMID: 28655025 DOI: 10.1001/jamapsychiatry.2017.1874]

45 Alhayaty M, Linden M, Olsson H, Johnsson M, Strandgarden K, Tiberg F: Pharmacokinetic evaluation of one-weekly and once-monthly buprenorphine subcutaneous injection depot (CAM 2038) vs intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockade: an open-label phase 1 study. Adv Ther 2017; 34: 560-575 [PMID: 28070862 DOI: 10.1007/s12325-016-0472-9]

46 Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, Frost M, Tiberg F, Linden M, Sheldon B, Oosman S, Peterson S, Chen M, Kim S: Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial. JAMA Intern Med 2018; 178: 764-773 [PMID: 29799968 DOI: 10.1001/jamainternmed.2018.1052]

47 Frost M, Bailey GL, Lintzeris N, Strang J, Dunlop A, Nunes EV, Jansen JB, Frey LC, Weber B, Haber P, Oosman S, Kim S, Tiberg F: Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM2038) in the treatment of adult out-patients with opioid use disorder. Addiction 2019; 114: 1416-1426 [PMID: 31013390 DOI: 10.1111/add.14636]

48 Lintzeris N, Dunlop AJ, Haber PS, Lubman DL, Graham R, Hutchinson S, Arunogiri S, Hayes V, Hjelmaström P, Svedberg A, Peterson S, Tiberg F: Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA Netw Open 2021; 4: e219041 [PMID: 33970256 DOI: 10.1001/jamanetworkopen.2021.9041]

49 Schulte B, Lehmann K, Schmidt CS, Rühlung E, Weber B, Schäfer I, Reimer J, Verhein U: Addiction Recovery Among Opioid-Dependent Patients Treated With Injectable Subcutaneous Depot Buprenorphine: Study Protocol of a Non-randomized Prospective Observational Study (ARIDE). Front Psychiatry 2020; 11: 580863 [PMID: 33363483 DOI: 10.3389/fpsyt.2020.580863]

50 Barnwal P, Das S, Mondal S, Ramasamy A, Maiti T, Saha A: Probuphine® (buprenorphine implant): a promising candidate in opioid dependence. Ther Adv Psychopharmacol 2017; 7: 119-134 [PMID: 28348732 DOI: 10.1177/2045125316681984]

51 Itzoe M, Guarnieri M: New developments in managing opioid addiction: impact of a subdermal buprenorphine implant. Drug Des Devel Ther 2017; 11: 1429-1437 [PMID: 28546740 DOI: 10.2147/DDDT.S109331]

52 White J, Bell J, Saunders JB, Williamson P, Makowska M, Farquharson A, Beebe KL: Open-label dose-finding trial of buprenorphine implants (Probuphine) for treatment of heroin dependence. Drug Alcohol Depend 2009; 103: 37-43 [PMID: 19403243 DOI: 10.1016/j.drugalcdep.2009.03.008]

53 Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, Rosenthal RN, Beebe KL: Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA 2010; 304: 1576-1583 [PMID: 20940383 DOI: 10.1001/jama.2010.1427]

54 Rosenthal RN, Ling W, Casadonte P, Voci F, Bailey GL, Kampman K, Patkar A, Chavoustie S, Blasey C, Sigmon S, Beebe KL: Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. Addiction 2012; 108: 2141-2149 [PMID: 22919595 DOI: 10.1111/j.1369-1660.2012.03479.x]

55 Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Voci FJ: PRO-814 Study Group. Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial. JAMA 2016; 316: 282-290 [PMID: 27434441 DOI: 10.1001/jama.2016.9382]

56 Pendergrass SA, Cris RC, Jones LK, Hoch JR, Berrettini WH: The importance of buprenorphine research in the opioid crisis. Mol Psychiatry 2019; 24: 626-632 [PMID: 30617273 DOI: 10.1038/s41380-018-0329-5]
55 Soyka M, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis 2016; 35: 22-35 [PMID: 26467975 DOI: 10.1080/10550858.2016.1100960]

56 Keilty E, Cumming C, Troeung L, Hulse G. Buprenorphine alone or with naloxone: Which is safer? J Psychopharmacol 2018; 32: 344-352 [PMID: 29433352 DOI: 10.1177/0269881118756015]

57 Allikmets S, Vink JP. Clinical applications of buprenorphine depot injection for opioid use disorder. Addiction 2020; 115: 190 [PMID: 31521065 DOI: 10.1111/add.14818]

58 Larance B, Byrne M, Lintzeris N, Nielsen S, Grebely J, Degenhardt L, Shabbari J, Shanahan M, Lancaster K, Dore G, Ali R, Farrell M; CoLAB study team. Open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: protocol for the CoLAB study. BMJ Open 2020; 10: e034389 [PMID: 32737087 DOI: 10.1136/bmjopen-2019-034389]

59 Vorspan F, Hjelmlström P, Simon N, Benyamina A, Dervaux A, Brousse G, Jemain T, Kosim M, Rolland B. What place for prolonged-release buprenorphine depot formulation Buvidal® in the treatment arsenal of opioid dependence? Expert Opin Drug Deliv 2019; 16: 907-914 [PMID: 31364884 DOI: 10.1080/17425247.2019.1649252]

60 Arunogiri S, Lintzeris N. Depot buprenorphine during COVID-19 in Australia: Opportunities and challenges. J Subst Abuse Treat 2021; 124: 108221 [PMID: 33303254 DOI: 10.1016/j.jsat.2020.108221]

61 Roberts J, White B, Attalla D, Ward S, Dunlop AJ. Rapid upscale of depot buprenorphine (CAM2038) in custodial settings during the early COVID-19 pandemic in New South Wales, Australia. Addiction 2021; 116: 426-427 [PMID: 32888226 DOI: 10.1111/add.15244]

62 Bukten A, Skuttveit S, Strangeland P, Gossop M, Willersrud AB, Waal H, Havnes I, Clausen T. Reductions in convictions for violent crime during opioid maintenance during a 3-year period prior to opioid maintenance treatment: a longitudinal national cohort study. J Subst Abuse Treat 2012; 41: 407-414 [DOI: 10.1016/j.jsat.2011.06.006]

63 Havnes I, Bukten A, Gossop M, Waal H, Stangeland P, Clausen T. Reductions in convictions for violent crime during opioid maintenance treatment: a longitudinal national cohort study. Drug Alcohol Depend 2012; 124: 307-310 [PMID: 22382045 DOI: 10.1016/j.drugalcdep.2012.02.005]

64 Soyka M, Träder A, Klotsche J, Haberthür A, Bühringer G, Rehm J, Wittchen H-U. Criminal behavior in opioid-dependent patients before and during maintenance therapy: 6-year follow-up of a nationally representative cohort sample. J Forensic Sci 2012; 57: 1524-1530 [DOI: 10.1111/j.1556-4029.2012.02234.x]

65 Russolillo A, Moniruzzaman A, McCandless LC, Patterson M, Somers JM. Associations between methadone maintenance treatment and crime: a 17-year longitudinal cohort study of Canadian provincial offenders. Addiction 2018; 113: 656-667 [PMID: 28970868 DOI: 10.1111/add.14059]

66 Vorma H, Sokero P, Aaltonen M, Turtiainen S, Hughes LA, Savolainen J. Participation in opioid substitution treatment reduces the rate of criminal convictions: evidence from a community study. Addict Behav 2013; 38: 2313-2316 [PMID: 23584191 DOI: 10.1016/j.addbeh.2013.03.009]

67 Moore KE, Roberts W, Reid IH, Smith KZ, Oberleitner LMS, McKee SA. Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review. J Subst Abuse Treat 2019; 99: 32-43 [PMID: 30797392 DOI: 10.1016/j.jsat.2018.12.003]

68 Kenney SR, Anderson BJ, Bailey GL, Stein MD. Buprenorphine treatment formulations: Preferences among persons in opioid withdrawal management. J Subst Abuse Treat 2018; 94: 55-59 [PMID: 30243418 DOI: 10.1016/j.jsat.2018.08.011]

69 Larance B, Degenhardt L, Grebely J, Nielsen S, Bruno R, Dietze P, Lancaster K, Larney S, Santo T Jr, Shanahan M, Memedovic S, Ali R, Farrell M. Perceptions of extended-release buprenorphine injections for opioid use disorder among people who regularly use opioids in Australia. Addiction 2020; 115: 1295-1305 [PMID: 31860767 DOI: 10.1111/add.14941]

70 Tompkins CNE, Neale J, Strang J. Opioid users’ willingness to receive prolonged-release buprenorphine depot injections for opioid use disorder. J Subst Abuse Treat 2019; 104: 64-71 [PMID: 31370986 DOI: 10.1016/j.jsat.2019.06.007]

71 Neale J, Tompkins CNE, Strang J. Prolonged-release opioid agonist therapy: qualitative study exploring patients’ views of 1-week, 1-month, and 6-month buprenorphine formulations. Harm Reduct J 2019; 16: 25 [PMID: 30943990 DOI: 10.1186/s12954-019-0296-4]
