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MINIREVIEWS

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

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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

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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.

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INTRODUCTION

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 five 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. Their 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
Morphine sulfate	Daily	Oral	Maintenance

Buprenorphine, being a partial agonist at the mu-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 four 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 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[13,27-29]. 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 monoproduct or in combination with naloxone (buprenorphine:naloxone ratio 4:1)[9,27]. Naloxone is a short-acting opioid antagonist and is pharmacologically 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 administered 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[41,42]. 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 RBP-6000[43-45]. In sum, adequate plasma concentrations and bioavailability were demonstrated for the compound. Albayaty *et al*[45] showed that monthly or weekly subcutaneously administered depots 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[44].

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[46], 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 RBP-6000 is similar to that of sublingual buprenorphine[47]. 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[48]. Further safety data are being collected in an ongoing nonrandomized prospective observational study[49].

Buprenorphine implant (Probuphine™, Sixmo)

The third long-acting buprenorphine is an implant[1]. 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[50-52]. 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[52].

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*[53] 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*[54] 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*[55] 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 naloxone 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) Clinically stabilized patients wishing to avoid daily oral taking of the medication.

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 few 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[70-73]. Patients cite spending less time with drug-treatment services, having more time for other activities and avoiding the stigma of being in OMT as reasons for preferring depot medications[39].

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.

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