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

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Submitted to World J Psychiatry (revised)

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Abstract

For pharmacotherapy of opioid use disorders oral methadone or sublingual buprenorphine are first-line medications. Three long-acting buprenorphine depot or implant formulations are available now for treatment of opioid use disorders; a.) CAM 2038 (buvidal) for subcutaneous weekly and monthly application, b.) RBP-6000 (Sublocade™) as a monthly depot formulation and c.) 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

Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing substance use disorder. causing psychological and physical harm. The economic burden and health costs of opioid use disorder is also very significant (1,2,3,4).

Prevalence

OUD has a prevalence of about 0.2-0,4 % in the adult population in many countries (5,6,7). In Europe heroin is the most frequently abused opioid but in other countries the use of synthetic opioids resp opioid pain killers such as fentanyl or oxycodon has been exploding and is the predomanting cause of opioid use. Especially the US is facing an epidemic of opioid pain killer abuse (8). Recent date 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 is still a significant problem. In 82% of fatal drug-related overdoses opioids are found (5). Most opioid related deaths are caused by overdose and respiratory depression. Other frequent causes of death are suicide, accidents, injuries, and numerous somatic disorders such as infectious diseases (HIV,hepatitis,others). In many fatal drug intoxications polysubstance abuse is involved, especially of alcohol or other sedative drugs (9).

Treatment aims

Opioid maintenance treatment (OMT) and psychosocial interventions are key elements in 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 outcome in OUD but many long-term studies only adress substance use or abstinence rates while other outcome parameters are less often reported. An interesting study on outcome

criteria has recently been studied by Wiessing et al (16) who studied reported outcome domains in 27 longitudinal studies (see tab 1). Data indicate that many domains, especially social functioning or health economics, are often neglected as outcome parameter.

Several medications are available now for treatment of opioid use disorders (see tab. 2). For about 5 decades OMT is the established and widely accepted first line treatment of OUD (11,14,17,18,19,20). Meanwhile there are a number of pharmacological options available. Medications used in OMT shall control craving for opioids and withdrawal symptoms. The two widely examined gold standards in OMT are methadone and buprenorphine (21).

Oral methadone (usual doses 60-100/120 mg daily) and sublingual buprenorphine (usual 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 (17,18,19). There are some distinct pharmacological differences between methadone and burprenorphine.

Methadone is a pure nonselective opioid receptor agonist at the mu, delta and kappa opioid receptor. 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 about 22 hours (13-50h). By blocking the opioid receptor for about 24 hours methadone is suitable for daily dosing. Methadone suppresses opioid withdrawal symptoms for 24 hours. There is broad evidence for the efficacy of methadone in OMT (14,17,18,19). The drug is widely accepted and used.

Buprenorphine is a partial agonist at the μ-opioid receptor (11,19). Due to a strong first pass effect buprenorphine has to be given sublingually. Buprenorphine has a ceiling effect at the opioid receptor and therefore a lesser risk of respiratory depression compared to methadone. Numerous studies indicate that there are less fatal intoxications or overdose death associated with buprenorphine compared to methadone. Other full opioid agonists used for treatment of OUD are morphine sulfate and diacetylmorphin (heroin). Both are second line medications for OMT (11,14,22).

There are some significant problems in OMT. The probably most important one is the risk of diversion of methadone or buprenorphine. Other major problems are cocommitant 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 randomised clinical trials and 63 observational cohort studies with in sum 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 higher age and depends on an adequate dose of the maintenance drug Several studies indicate that too low dosage is associated with higher dropout rate (26).

Dosing issues are of great relevance in OMT. The adherence to treatment depends on adequate dosing and retention can be improved by adaquate dosing (13.27,28,29). Too low doses of methadone or buprenorphine are associated with low retention and risk of further substance use.

Methadone is still 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 in some studies compared to methadone (19,26,30). The risk for respiratory depression for buprenorphine in case of overdose is lower compared to 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 i.v. medication, and as a nasal spray for prevention of overdose death. Naloxone will rapidly induce opioid withdrawal. The risk of precipitated opioid withdrawal shall prevent the patient from injecting buprenorphine and thus reduce risk of diversion or i.v. use of buprenorphine.

Both methadone and buprenorphine are given as once a day doses and both suppress symptoms of opioid withdrawal for 24 hours. Longer dosing intervals have been a major aim in OMT research. Previously, a long-acting methadone analogue (LAAM) was studied but had to be withdrawn over potential adverse cardiac effects (33,34).

Clinical and social reasons for long-acting opioid in OMT are a reduced risk of diversion, improved compliance, easier take home dosing and longer treatment intervals, among others. The recent COVID 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 lesser use of social and medical ressources are important goals for many clinicians.

Recent developments

There is an exciting development in recent years: Three different long-acting buprenorphine formulations have been developed, approved and in part introduced into clinical practice in many countries. Those will be reviewed briefly.

RBP-6000 (Sublocade™)

RBP-6000 is a buprenorphine depot injection. It is marketed in the US since 2018 and will be available in europe soon. Medication and dosing intervals: There are monthly s.c. injections available with dosages of 100 and 300 mg. Dosages recommended for the treatment of OUD (www.sublocade.com) are 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 craving for opioids. Other studies showed an 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 in phase III trials therapeutic concentrations were achieved from the first injection and maintained over 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 double-blind placebo-controlled multicentre phase-III-study. Dosing regimen: Monthly RBP-6000 s.c. injections (6 x 300 mg or 2 x 300 mg), followed by 4 x 100 mg injections, or placebo were given in patients with opioid dependence. Abstinence rates as major outcome in both buprenorphine depot groups (N=203 resp. N=201

patients) were significantly higher compared to the placebo group (N=100): 41,3 % % resp. 42,7 % in the buprenorphine groups compared to 5,0 % in the placebo group ($p<0.0001$ for both buprenorphine groups). There were no differences concerning outcome for both buprenorphine groups. Both studied were equally effective. In addition, the rate for hospital admissions was also lower in both burprenorphine groups compared to placebo (39). Overall these data indicate that RBP-6000 is effective. Andorn et al (40) performed an open-label multicentre study in 257 patients. 13.2% of OUD patients had injection-site adverse events. Although these are usually mild and transient they may affect acceptance of this or other depot injections. Otherwise the safety profile was good with less adverse events in the second 6 month of treatment versus first 6 months. The retention rate was about 50% after 12 months.

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: There are 4 different dosages available: 8, 16, 24 or 32 mg for weekly injections, 64, 96, 128 or 160 mg for monthly injections. Usually, treatment with CAM 2038 is initiated with weekly injections. Later on 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 (43,44,45). In sum, adequate plasma concentrations and bioavailability was demonstrated for the compound. Albayaty et al (45) showed that monthly or weekly s.c. depots of CAM 2038 (dosages of 96 und 192 mg) had a 5.7 to 7.7-fold higher bioavailability compared to sublingual buprenorphine (8, 16 or 24 mg). In addition, Buvidal 24 und 32 mg were found to block the subjective effects of hydromorphone i.m. (44).

The efficacy of buvidal has also demonstrated in several clinical trials. In a double-blind, double-dummy, randomized phase-III-study with 428 patients (46) Flexible weekly injections of CAM 2038 were used in the first 12, than monthly injections in

the following 12 weeks 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 urines (secondary outcome). The average weekly CAM 2038 dosages used were 24 mg, monthly injections ranged over 100 mg. No novel adverse events were noted. The side effect profile of RBP-6000 is similar to sublingual buprenorphine (47). With resepect 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 the most frequent adverse drug reaction (48). Further safety data are collected in an ongoing non-randomized prospective observational study (49).

Buprenorphine implant (Probuphine™, Sixmo)

The third long-acting buprenorphine is a buprenorphine implant[1]. Probuphine has been approved in the US by the FDA in 2016 for long term treatment of patients with opioid dependence who are on a stable medication of 8 mg buprenorphine sublingual or less. 8 mg buprenorphine is usually considered as a moderate dose in OMT with an upper limit of daily sublingual buprenorphine dose of 24-32 mg. In Europe the implant has been approved by the European Medicine Agency (EMA) in 2019. Buprenorphine is linked to a polymer that delivers the drug steadily in the body. 4 implants are inserted. The dose of the buprenorphine implant released is equivalent to 8 mg sublingual buprenorphine or less (50,51,52). The subdermal insertion of the implant requires minimal surgery. The implant is inserted in the upper arm and remains there for 6 month before it is removed again. Plasma concentrations peak 12 hours after the implant is inserted. Steady state conditions were noted after3-4 weeks (52).

There are several relevant clinical studies available for probuphine. The efficacy of the buprenorphine implant was demonstrated in three double-blind studies (309 patients included), with a follow-up of up to 6 months.

[1] siehe auch: https://www.titanpharm.com/pipeline/probuphine

Ling et al (53) performed a 6-month randomized controlled trial in 163 participants with opioid dependence. After initial treatment with sublingual buprenorphine the patients were transferred to either 4x80mg buprenorphine or placebo implants. The retention rate in the implant group (71 of 108 patients) was significantly higher compared to the placebo group (17 of 55 patients; 65.7% vs. 30.9%, $p<0.001$). The number of opioid-free urine samples was also higher in the buprenorphine implant group.

Rosenthal et al (54) conducted a placebo-controlled randomised clinical trial in opioid dependent patients who either received 4x 80 mg buprenorphine (N=114) or 4 placebo implants (N=54). The control group in an open design was treated with sublingual buprenorphine in a dose of 12-16 mg daily. 119 participants were included in the control group. The retention rate was significantly higher ($p<0.0001$) in the implant group compared to the placebo group (64 vs 26%). In addition, the implant group was also found to be superior to the placebo group and non-inferior to sublingual burprenorphine with respect to mean number of opioid-free urine samples. Side effects: Smaller local reactions at the implant site were rather frequent (25-27 %).

Rosenthal et al (55) also studied OMT patients stable on a sublingual dosage of 8 mg or less. They received either sublingual buprenorphine plus 4 placebo implants or a sublingual placebo plus 4 buprenorphine implants over 24 weeks. 177 patients were included. The abstinence rate in the buprenorphine implant group over 6 months was found to be non-inferior to the control group treated with sublingual buprenorphine (85.7% vs. 71.9%). The retention rate was 93 %. The number of responders was 96.4 % in the buprenorphine implant group and 87.6 % in the control group ($p<0.01$). In addition, 85 % of the patients in the implant group were opioid free compared to 72 % in the control group.

The FDA had requireq a special risk management for this treatment. The „Probuphine Risk Evaluation and Mitigation Strategy“ (REMS) program was initiated (https://probuphinerems.com).

Meanwhile Titan Pharmaceuticals on oct 15, 2020 announced to discontinue its US propupine implant sales. No specific medical reasons have been given for this decision.

Discussion

OMT is the established first line treatment in OUD with methadone and burprenorphine as the pharmacological frontrunners (21). Buprenorphine has a good safety profile (56) but modest and somehow lower retention rates compared to 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 are essential in this respect (15). Other common problems are diversion and i.v. use of buprenorphine (23,57). Whether the combination of buprenorphine and naloxone lowers the risk of diversion of buprenorphine is controversial (58).

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

The clinical question is: Who will benefit?

Vorspan et al (61), with the long French buprenorphine experience in mind, suggest prolonged-release buprenorphine depot-formulations such as buvidal as a promising treatment option in

- OMT initiation, including in non-specialized medicine care
- Discharge from prison or hospital
- Diversion/Misuse of buprenorphine or methadone
- patients

In addition, clinically stabilized patients wishing 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) in their review stated that „Anyone with an opioid use disorder 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.

Apart from the individual level there are also public health aspects with this novel medication. Retention rates may be incesaed – which has to be shown in future studies – and the risk for diversion may be reduced. In addition, the utilization of health care ressources will be reduced. This is of relevance especially in times of pandemic COVID infections when social distancing is required (42).
Arunogiri and Lintzeris (62) argued that during the COVID-19 pandemic the use of long-acting buprenorphine formulations may help, and in fact some health care organizations have advocated its use (42). For example. there is a rapid upscale of buvidal use in custodial settings 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). There is broad empirical evidence that OMT can reduce criminality in OUD (64,65,66,67,68), 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. While transfer from sublingual to depot buprenorphine will probably be no major problem introducing depot buprenorphine in a patient previously treated with methadone is more complicated and 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 way at present.

Patients preferences and attitudes to treatment are of great relevance for OMT. Many patients allocate themselves to certain OMT medications.
There are very few qualitative studies on this issue (70,71,72,73). Patients arguments for depot medications are: Spending less time with drug-treatment services, having more time for other activities and avoiding the stigma of being in OMT (Ling et al 2019).

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.

Conflict of interest

For the past three years MS has worked as a consultant or has received speakers fee from Lundbeck, Camurus und Indivior.
The manuscript is the sole work of the single author

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