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Review Article

Recent Advances in the Treatment of Opioid Use Disorders

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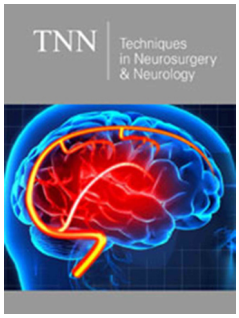

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Abstract

For pharmacotherapy of opioid use disorders treatment with oral methadone or sublingual buprenorphine are established first-line treatments. Recently three novel long-acting buprenorphine depot or implant formulations have been studieD and in part approved for treatment of opioid use disorders: for subcutaneous weekly and monthly application the depot formulations CAM 2038 [Buvidal®], the monthly depot formulation RBP-6000 [Sublocade™] and the six-month buprenorphine implant [Probuphine™]. The pharmacology and efficacy of these novel medications will be reviewed and discussed

Keywords: Opioids; Opioid dependence;Maintenance treatment;Methadone;Buprenorphine;Depot;Implant

Introduction

Opioid use disorder (OUD) is defined as a chronic relapsing substance use disorder causing significant psychological and physical harm. The econmic burden of opioid use disorder is also very significant [1,2]. OUD has a prevalence of about 0.2-0,4 % in the adult population (EMCDDA 2010; United Nations Office on Drugs and Crime 2017,2020) but trends in opioid use are somehow shifting. While in Europe heroin by far still is the most frequently abused opioid – with some synthetic opioids such as fentanyl catching up - , the US is facing an epidemic of opioid pain killer abuse. In Europe, there are 1.3 million high-risk opioid users and 660000 people receive opioid substitution treatment (European Monitoring Centre for Drugs and Drug Addiction 2020). Mortality in opioid dependence is still a significant problem. In 82% of fatal drug-related overdoses opioids are involved (European Monitoring Centre for Drugs and Drug Addiction 2020). Most opioid related deaths are caused by respiratory depression, often in combination of opioids with alcohol or other sedative drugs. Other frequent reasons for death are accidents, injuries, suicides, and numerous infectious disaeses (HIV,hepatitis,others). Major targets in the treatment of opioid use disorders are cessation or reduction of opioid use [3,4] and other substance use, better social integration and reduction of criminal behavior [4,5]. For decades opioid maintenance therapy (OMT) is the established first line treatment of OUD [5-9] A number of opioids are available for OMT so far. The two gold standrads in OMT are methadone and buprenorphine. Oral methadone (usual doses 60-100/120mg) and sublingual buprenorphine (usual doses 8-12, max 24-32mg) are the two gold standards in treatment of opioid dependence. Their efficacy has been shown in many clinical studies [6,10]. There are clear pharmacological differences between methadone and burprenorphine. Methadone is a pure nonselective opioid receptor agonist at the mu, delta and kappa opioid receptor, causing the typical effects of opioids: analgesia, sedation, respiratory depression, euphoria and tolerance. The drug has a high addictive profile. Methadone has a half life of about 22 hours (13-50h) and blocks opioid withdrawal symptoms for 24 hours. There is overwhelming evidence for the efficacy of methadone in OMT [3,6,10]. Buprenorphine is a partial agonist at the μ-opioid receptor [9,11]. Due to a strong first pass effect the drug has to be given sublingually. Buprenorphine also has a ceiling effect at the opioid receptor and therefore a much lesser risk of respiratory depression compared to methadone. Other full opioid agonists such as morphine sulfate and diacetylmorphin are second line medications for OMT [3,9]. There are persistent problems in OMT, including the risk of diversion of methadone or buprenorphine, compliance and retention in treatment [8,12]. Especially the

retention rate in OMT is crucial. A very recent systematic review on this issue by O'Connor et al (2020) included 4 randomised clinical trails and 63 observational cohort studies (N=294592) and reported a 1-year retention rate of 57% and a 3-year retention rate of 38.4%. Important factors modifying retention to treatment are age, substance use, dosing of the maintenance drug, legal issues and attitudes towards OMT. Previous reserach has already shown than adherence to treatment can be improved by adaquate dosage [13,14] Methadone was the first and still is the most widespread drug to be used in OMT. The other first line medication for OMT [15,16] is buprenorphine. The retention rate for buprenorphine in some studies is lower as for methadone [10]. The major advantage of buprenorphine is the lower risk for respiratory depression in case of overdose compared to full opioid agonists. The drug is used as a sublingual tablet, either as a monoproduct or in combination with naloxone (buprenorphine:Naloxone ratio 4:1) [16,17]. Naloxone is pharmacologically active only as i.v. medication. The combination of buprenorphine plus naloxone (4:1 ratio) should prevent diversion or i.v. use of buprenorphine. Both methadone and buprenorphine are given as once a day doses. The development of long-acting opioids for long has been a major goal in OMT research to reduce risk of diversion, improve compliance and to make lives easier the patient does not have to show up daily or – in case of take home dosing – et least weekly in the outpatient clinic or at the physician. Previously, a long-acting analogue of methadone, LAAM, had been developed and tested successfully but LAAM was withdrawn over potential adverse cardiac effects [18].

New developments

In recent years, three different long-acting buprenorphine formulations have been developed and in part introduced into clinical practice.

RBP-6000 (Sublocade™)

This is a buprenorphine depot injection, marketed in the US since 2018. It will very probably introduced in europe soon. There are monthly s.c. injections available with dosages of 100 and 300mg. Dosages recommended for the treatment of OUD (www.sublocade.com) are two initial 300mg injections monthly followed by monthly 100mg injections. The depot formulation has been studied in several experimental and clinical trials. Nasser et al. [19] demonstrated that RBP-6000 blocks hydromorphone induced effects in patients with opioid dependence (such as craving for opioids). In other experiments an effective μ-opioid receptor blockade was shown with different dosages of RBP-6000 [20]. The most relevant clinical study on the efficacy of RBP-6000 was performed by Haight et al. [21]. This was a double-blind placebo-controlled multicentre Phase-III-study. Monthly RBP-6000 s.c. injections (6 x 300mg or 2 x 300mg, followed by 4 x 100mg injections) were given in opioid dependent people. Abstinence rates in both verum groups (N=203 resp. N=201 patients) were significantly higher compared to the placebo group (N=100). 41,3 % % resp. 42,7 % in the verum groups compared to 5,0 % in the placebo group were drug free (p<0.0001 for both verum groups). Both buprenorphine concentrations were equally effective. The rate for hospital admissions was also lower in the two burprenorphine groups, among others Ling et al. [22].

CAM 2038 (Buvidal®)

CAM 2038 is a s.c. depot buprenorphine injection. Buvidal is approved in Europe Coe et al. [23]. There are 4 different dosages available for either weekly (8,16,24 or 32mg), or monthly injections (64,96,128 or 160mg). Typically, treatment is initiated with weekly injections. Several pharmacological studies are available [24,25] The latter group showed that monthly or weekly s.c. depots of CAM 2038 (dosages of 96 und 192mg) had a 5.7 to 7.7-fold greater bioavailability compared to sublingual buprenorphine (8, 16 or 24mg). As for RBP-6000, it has been shown that 24 und 32mg Buvidal s,c. block the effects of hydromorphone i.m. Walsh et al. [25]. The efficy of buvidal has also been shown in clinical trials. In a double-blind, double-dummy, randomized phase phase-III-study N=428) Lofwall et al. [11] CAM 2038 (flexible weekly injections in the first 12, than monthly injections in the following 12 weeks) was tested against sublingual buprenorphine (flexible dose up to 24mg daily). The depot was noninferior to sublingual buprenorphine with respect to the primary outcome parameters (opioid use) and superior with respect to secondary parameters (opioid-free urine). Average weekly CAM 2038 dosages used were 24mg, monthly injections ranged over 100mg. In general, the side effct profile of RBP-6000 is similar to sublingual buprenorphine Frost et al. [26]. Mild local reactions at the injection sites were reported by 18.-22% of participants.

Buprenorphine implant (PROBUPHINE™, Sixmo)

Another alternative is the use of a buprenorphine implant which 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 8mg buprenorphine sublingual or less. 8mg buprenorphine is a moderate dose in OMT. In Europe the implant has been approved by the European Medicine Agency (EMA) in 2019. The insertion of the implant requires minimal surgery in the upper arm where the implant remains for 6 month. The dose of the buprenorphine implant released is equivalent to 8mg sublingual buprenorphine or less [27-29] Ther peak of buprenorphine plasma concentration is reached 12 hours after implant. Steady state conditions are noted after3-4 weeks. There are several relevant clinical studies on the efficacy oft he buprenorphine implant. Data are available from three double-blind studies (N=309), with a follow-up of up to 6 months. There is a 6-month randomized controlled trial in 163 adults with opioid dependence who after initial treatment with sublingual buprenorphine were transferred to either 4x80mg or placebo implants Ling et al. [30]. The retention/completion 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). in addition, the number of opioid-free urine samples was also higher in the buprenorphine implant group. Another important study was conducted by Rosenthal et al. [31]. In this

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placebo-controlled RCT opioid dependent patients either received 4 80mg buprenorphine or placebo implants (N=114) or 4 placebo implants (N=54). The control group in an open design received sublingual buprenorphine (12-16mg daily, N=119). The retention rate was higher in the implant compared to the placebo group (64 vs 26% , p<0.0001). The implant group was also superior to the placebo condition and non-inferior to sublingual burprenorphine with respect to mean number of opioid-free urine samples. Smaller local reactions at the implant site were rather frequent (25-27 %). In addition, Rosenthal et al (2016) studied patients stable on a sublingual dosage of 8mg or less who received either sublingual buprenorphine plus 4 placebo implants or a sublingual placebo plus 4 buprenorphine implants over 24 weeks (N=177). The abstinence rate in the buprenorphine implant group over 6 months was non-inferior to the sublingual buprenorphine control group (85.7% vs. 71.9%) with a retention rate of 93 %. The number of responders was 96.4 % in the buprenorphine implant group compared to 87.6 % in the control group (p<0.01). 85 % of the patients in the implant group were abstinent from opioids compared to 72 % in the control group. The FDA requires a special risk management for this treatment. The Probuphine Risk Evaluation and Mitigation Strategy (REMS) program was initiated.

Discussion

OMT is a well established first line treatment in opioid use disorders. Methadone and burprenorphine are the two widespread used medications in this area Crotty et al. [32]. Buprenorphine is a promising medication with a good safety profile Pendergrass et al. [33] but diversion and i.v. use of buprenorphine is still a widespread problem. The combination of buprenorphine and naloxone has not changed this situation Kelty et al. [34]. The recently introduced or emerging new long-acting buprenorphine (depot or implant) formulations are a major progress in OMT [35-37]. There will be weekly and monthly s.c. buprenorphine injections, or even 6-month depot formulations. While pharmacological progress is sometimes fast, clinical progress has not necessarily the same speed. The treating physician delivering OMT to the patient and the patient himself must be convinced from the new therapeutic options. What type of patient will benefit from these new medications? Ling et al. [22] in their review stated that Anyone with an opioid use disorder who can benefit from oral buprenorphine can benefit from the injectable. The stable patient on sublingual buprenorphine is definitely the primary candidate or treatment with long acting buprenorphine formulations. Switching the medication from sublingual bupreNorphine to depot IS easy to do, and the depot medication will allow the patient to spend less time traveling to the physician or outpatient clinic and to be more actice, have a less restricted social life. Introdocing depot buprenorphine in a patient previously treated with methadone is more complicated and there are no studies on this issue. Switching patient to sublingual buprenorphine first before transferring him to a depot formulation seems to be the most appropriate way at present. Depot formulations may also be used in prisons or forensic psychiatry settings to avoid diversion of the drug Vorspan et al. [38].

Patients preference and attitude to treatment are always of great importance

There are very few qualitative studies on this issue [39-42]. Spending less time with drug-treatment services, having more time for other activities and avoiding the stigma of being in OMT may be key points for patients decision to change medication Ling et al. [22]. At this point these novel formations, despite having some cons such as the surgical procedure for the implant, risk of infection and fixed dosage regimen appear to be attractive for many patients-and health care providers - and offering new therapeutic options for management of OUD [42-55].

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