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Medication-assisted treatment for opioid addiction: methadone and buprenorphine

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Abstract

Among agents for treatment of opioid addiction, methadone is a full mu-opioid receptor agonist, whereas buprenorphine is a partial agonist. Both are long-acting. Buprenorphine has a superior safety profile. Methadone is formulated for oral administration and buprenorphine for sublingual administration. A subdermal buprenorphine implant with a 6-month duration of action is being considered for approval by the U.S. Food and Drug Administration. Both medications reduce mortality rates and improve other outcomes. Data from a recent randomized controlled comparison of both medications (N = 1269) show better treatment retention with methadone but reduced illicit opioid use early in treatment with buprenorphine. Human immunodeficiency virus (HIV) risk behaviors were measured using the Risk Behavior Survey at baseline, 12 weeks, and 24 weeks for study completers. In the 30 days prior to treatment entry, 14.4% of the completers randomized to treatment with buprenorphine (n = 340) and 14.1% of the completers randomized to methadone treatment (n = 391) shared needles. The percent sharing needles decreased to 2.4% for buprenorphine and 4.8 for methadone in the 30 days prior to Week 24 ($p < 0.0001$). In the 30 days prior to treatment entry, 6.8% of the completers randomized to buprenorphine and 8.2% of the completers randomized to methadone had multiple sexual partners, with only 5.2% and 5.1%, respectively, reporting multiple partners at Week 24 ($p < 0.04$).

Keywords

opioid addiction; methadone; buprenorphine; medication-assisted treatment

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1. Introduction

Most patients with opioid use disorder require pharmacotherapy for effective treatment. The most frequent medications used in this treatment are methadone and buprenorphine. This paper summarizes the basic pharmacology and clinical use of these medications, as well as some of the findings from a large, open-label randomized controlled trial comparing the two medications on liver health, treatment retention, and changes in risk behavior.

2. Methdadone Treatment for Opioid Use Disorder

Methadone absorption occurs rapidly after oral ingestion[1]. Methadone has a typical oral bioavailability of about 80%, with a range of 41–95%[2]. Initial effects occur within 30 minutes, but peak effects and peak plasma levels are obtained on average about 4 hours after ingestion, with a range of 1–6 hours[3]. Methadone has an average terminal half-life of 22 hours, with a range of 5 to 130 hours [4].

Methadone metabolism is complex and not yet fully understood. Most available data indicate that the liver enzyme CYP 450 3A4 is the primary catalyst of methadone metabolism [5]. There is growing evidence that other enzymes, including CYP2B6, CYP2D6, CYP1A2, CYP2C9, and CYP2C19, also contribute to methadone metabolism [4,6]. These enzymes exhibit wide inter-individual variation in activity based mainly upon genetics but also upon environmental factors, so every patient's body handles methadone a bit differently and dosing must be individualized.

Methadone's long half-life makes it a highly effective pharmacologic intervention for opioid use disorder. For most patients, a once-daily oral dose prevents opioid withdrawal symptoms, which are a strong driver for ongoing illicit opioid use. Finding the best dose for each individual patient often involves a clinical balancing act because the doses needed to establish adequate tolerance and diminish illicit opioid can cause some side effects. Clinical trial evidence shows that methadone doses of 80–100 mg per day have significant advantages over lower doses in reducing illicit opioid use and retaining patients in treatment [7]. For most patients, a stable dose ranges from 80–120 mg per day. However, given inter-individual differences, some patients stabilize on lower doses and some need higher doses.

3. Burprenorphine Treatment for Opioid Use Disorder

Buprenorphine has a unique and complex pharmacology, but, in contrast to methadone, one of its defining characteristics is its safety profile. Buprenorphine has poor oral bioavailability, so in the formulations currently approved for treatment of opioid use disorder it is ingested via the sublingual route. As with methadone, its gradual onset and long half-life contribute to its efficacy. Buprenorphine acts as a partial agonist with high affinity and slow dissociation at the μ-opioid receptor and also functions as an antagonist at the κ-opioid receptor [8,9]. As a partial μ-opioid agonist, it has a ceiling effect on its activity, such that after a modest dosage is received, further doses do not lead to increasing effects and, thus, the risk of respiratory depression and overdose is very low [10,11].

Currently marketed buprenorphine for opioid use disorder comes in three sublingual formulations: (1) buprenorphine sublingual tablets, (2) buprenorphine/naloxone sublingual tablets, and (3) buprenorphine/naloxone sublingual film. The buprenorphine/naloxone formulation is intended to prevent misuse of the medication by injection. Naloxone, a μ-opioid antagonist, has minimal sublingual bioavailability, that is to say, when the medication is taken by the sublingual route, the amount of naloxone absorbed is too little to have any clinically observable effect. However, since naloxone has very good parenteral bioavailability, crushing and injecting the buprenorphine/naloxone tablet results in the co-administration of both a partial agonist and an antagonist. The naloxone will reduce any of the parenteral effects of buprenorphine and also possibly precipitate opioid withdrawal if full agonist opioids are present [12].

The buprenorphine-only tablets are supplied as 2 mg and 8 mg tablets. The buprenorphine/naloxone tablets are supplied as 2 mg (buprenorphine)/0.5 mg (naloxone) and 8 mg (buprenorphine)/2 mg (naloxone). The buprenorphine/naloxone film has two additional dosage forms: 4 mg/1 mg and 12 mg/2.5 mg. An experimental formulation of buprenorphine, a subdermal implant which releases active medication over a 6-month time frame is still being studied but appears safe and efficacious [13].

After sublingual ingestion of buprenorphine, absorption proceeds promptly [14]. Sublingual bioavailability shows large inter-individual variability but is generally around 35% for the tablet [14–16]. Initial effects appear within 30 minutes, with peak effects and peak plasma levels reached on average about 1 hour after ingestion [14,17–18]. Buprenorphine has an estimated average terminal half-life of 32 hours [14]; however, there is wide variation across studies and individuals [19]. Buprenorphine undergoes both glucuronidation and N-dealkylation. Most available data indicate that N-dealkylation is catalyzed by the liver enzyme CYP 450 3A4 [14]. The product of N-dealkylation is an active metabolite, nor-buprenorphine [14,18].

As a partial μ-opioid agonist with high affinity for the receptor, buprenorphine has the potential to cause precipitated opioid withdrawal if administered when a full agonist occupies the receptors because it can displace the full agonist and immediately reduce activation of the receptors [20]. To avoid the risk of precipitated opioid withdrawal, induction on buprenorphine requires the patient to abstain from short-acting opioids for a period of about 24 hours and enter a state of moderate opioid withdrawal prior to the administration of the first dose of buprenorphine. When the patient arrives for induction, the physician must witness the presence of objective signs of opioid withdrawal such as lacrimation, rhinorrhea, yawning, sneezing, coughing, piloerection, restlessness, or tremor. Induction can begin with a low buprenorphine dosage of 2 mg or 4 mg. This first buprenorphine dosage will likely ameliorate most of the withdrawal signs and symptoms within 30–60 minutes. Once the withdrawal improvement occurs, additional doses can be safely administered until any lingering withdrawal symptoms resolve, usually within a day or two at doses of 8 to 16 mg per day. Final stabilization doses of buprenorphine range from 2 mg to 32 mg per day.

4. Efficacy of Opioid Agonist Medications

In regard to the efficacy of opioid agonist medications, a buprenorphine study randomly assigned 40 subjects to a year's treatment with 16 mg per day or to a 6-day taper followed by placebo. All subjects received intensive behavioral interventions; 75% of buprenorphine-treated subjects remained in treatment for 1 year versus none of the placebo-treated subjects. Seventy-five percent of urine specimens collected from the buprenorphine-treated subjects were negative for illicit drugs. Four of the placebo-treated subjects died during the year versus none of the buprenorphine-treated subjects [21]. A similar controlled, though not blinded, trial randomly assigned 34 heroin addicts either to receive methadone treatment or to a control group that offered psychosocial treatment only. The control group had a mortality rate of 11.8% within 2 years compared to 0% in the methadone group [22].

Methadone and buprenorphine both can produce many of the side effects typical of opioid medications, including sedation, nausea, constipation, weight gain, lowered libido, edema, and headache. Methadone can also prolong the cardiac QT interval. Many side effects can be resolved or reduced in severity by incremental dose reductions of methadone 5–10 mg or of buprenorphine 2–4 mg every 5 to 7 days.

A large (N = 1269), open-label, randomized clinical trial, "Starting Treatment with Agonist Replacement Therapies (START)," that compared buprenorphine/naloxone to methadone primarily on effects on liver health but also on treatment retention, illicit substance use, and HIV risk behavior was recently completed [23]. After providing baseline liver indices, participants were randomly assigned to receive buprenorphine/naloxone (mean maximum daily dose = 22.2mg, SD = 9.3) or methadone (mean maximum daily dose = 93.2mg, SD = 43.9) for 24 weeks. Repeat liver tests occurred at weeks 1, 2, 4, 8, 12, 16, 20, and 24. Urine drug screens were obtained weekly. Self-reported drug use data were collected every 4 weeks.

Participants who completed 24 weeks of medication and provided at least 4 blood samples for post-baseline liver transaminase testing (n = 340 buprenorphine/naloxone; n = 391 methadone) were considered "evaluable." Changes in transaminase levels did not differ by medication condition. Baseline infection with hepatitis C or B was the only significant predictor of moving from low to elevated transaminase levels.

Among methadone patients, 74% completed 24 weeks of treatment versus 46% for buprenorphine/naloxone ($p < 0.01$); the rate among methadone patients increased to 80% when the maximum dose reached 60mg/day or more. Thirty percent of buprenorphine/naloxone patients dropped out within 30 days of starting treatment, and the completion rate increased linearly, with 60% of those taking higher doses (30–32mg/day) completing treatment [24]. Of those remaining in treatment, positive opiate urine results were significantly lower among those taking buprenorphine/naloxone, compared to methadone patients during the first 9 weeks of treatment. Higher medication dose was associated with lower rates of illicit opiate use with both medications, but more so among the buprenorphine/naloxone patients.

HIV risk behaviors were measured using the Risk Behavior Survey at baseline, 12 weeks, and 24 weeks for study completers. In the 30 days prior to treatment entry, 14.4% of the evaluable participants who were randomized to buprenorphine/naloxone and 14.1% of the evaluable participants who were randomized to methadone (n = 391) shared needles. The proportion sharing needles decreased to 2.4% for those taking buprenorphine/naloxone and 4.8% for those taking methadone in the 30 days prior to Week 24 ($p < 0.0001$). In the 30 days prior to treatment entry, 6.8% of the completers randomized to buprenorphine/naloxone and 8.2% of the completers randomized to methadone had multiple sexual partners, with only 5.2% and 5.1%, respectively, reporting multiple partners at Week 24 ($p < 0.04$).

5. Conclusions

In summary, both methadone and buprenorphine are highly effective and relatively well tolerated treatments for opioid use disorder when provided in adequate doses. Buprenorphine has a lower risk for overdose, but methadone seems to retain patients in treatment longer. Both help to reduce HIV risk behaviors.

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