

# Buprenorphine: A New Alternative in the Treatment of Opioid Addiction

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## ÖZET:

Opioid bağımlılığı tedavisinde yeni bir alternatif: buprenorfin

Opioid agonistleri, opioid bağımlılığı tedavisinde detoksifikasyon ve idame tedavileri olarak sıklıkla kullanılır. Uzun etkili bir opioid agonisti olan metadon, yüksek bağımlılık ve kötüye kullanım riski olması, ve ayrıca sadece belli merkezlerde kullanılabilmesi nedeniyle günümüzde oldukça artan opioid bağımlılarının tedavi ihtiyacına cevap verememektedir. Bir parsiyel opioid agonisti olan buprenorfin, metadona göre daha güvenli profili, uzun etkisi ve muayenehane ortamında kullanılabilmesi sayesinde 2000li yılların başından beri hekimler tarafından opioid detoksifikasyon ve idame tedavisinde tercih edilmektedir.

**Anahtar Kelimeler:** Opioid agonist, opioid bağımlılığı, buprenorfin, ayaktan tedavi, opioid idame

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## ABSTRACT:

Buprenorphine: a new alternative in the treatment of opioid addiction

Opioid addiction is a complex disease with severe biological, psychological, and social impacts in the life of the individual, his family and the society. Besides heroin, misuse and abuse of prescription opioid pain medications are rising. Current pharmacological maintenance therapy with methadone accompanied by appropriate psychosocial treatments is a highly effective treatment for opioid addiction. However, due to strict regulations, limited availability, and abuse risk of methadone, new and practical approaches are required. Buprenorphine, a high affinity partial  $\mu$  opioid agonist, allows qualifying physicians to offer treatment in office-based settings for the detoxification or maintenance of individuals with opioid addiction.

**Key words:** Opioid agonist, opioid addiction, buprenorphine, office-based treatment, opioid maintenance

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## Bağıntı beyanı:

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## INTRODUCTION

Opioid addiction is a chronic, relapsing condition effecting many people all over the world, and its prevalence has been increasing (1). In the United States, 1.7% of people aged 19-30 have tried heroin at some point in their lives (2,3). According to the American Office of National Drug Control Policy (ONDCP), an estimated 810,000 to 1,000,000 individuals in the United States were addicted to heroin in the year 2000 (4).

Not only is heroin abuse increasing, the misuse and abuse of prescription opioid pain medications are also on the rise (5). Although usage of opioids for pain treatment in medical practice is common and safe when monitored closely (6), data showed that in 2006, 2.2 million Americans 12 years and older non-medically used prescription opioids for the first time within the past 12 months (7). Hydrocodone (Vicodin®, Lortab®, Lorcet®) and oxycodone (OxyContin®, Percocet®) are the two most popular opioid prescription drugs. Even in adolescents, 9.6% of 12th graders reported taking

Vicodin® without a prescription, making opioids second to marijuana in rates of illicit drug use among high school students (8). The incidence of emergency department visits related to prescription opioid pain medications has more than doubled between 1994 and 2001, and narcotic pain medications—primarily oxycodone and hydrocodone—were ranked among the 10 most common drugs involved in drug abuse deaths (9). As rates of prescription opioid use continue to climb, clinicians are considerably more likely to encounter opioid abusers in their practices.

Moreover, the economic cost of opioid addiction is enormous; in 1996, the United States spent approximately \$20 billion dollars on addiction expenses associated with medical, economic, social, and criminal impact caused by heroin use (10). A 2005 study by White et al. found that opioid abusers are associated with 8.7 times higher mean annual direct health care cost than non-abusers (11) (costs are significantly higher because frequent psychiatric comorbidities (i.e. depression) are taken into account. Thus, treatments that address comorbid issues associated

with higher retention, longer abstinence post-treatment completion, and decreased economic impact (loss of productivity, criminal activities, and welfare) would be beneficial.

#### **Methadone in Maintenance Treatment:**

Opiate-substitution pharmacotherapy provided by “methadone clinics” has been shown to reduce the use of illicit opioids (12), especially heroin. Along with dispensing methadone, these programs offer several counseling services, vocational resources, referrals, and appropriate drug monitoring which improve physical and mental health, related crime, increase employment, and decrease the incidence of human immunodeficiency virus (HIV) related to needle sharing. Unfortunately, methadone is permissible only in federally approved and strictly regulated methadone clinics because of concern about the diversion of methadone to illicit use. Methadone can only be dispensed, not prescribed, with limited permission for take-at-home dosing. In addition; methadone maintenance treatment system capacity has not kept pace with the rise in the prevalence of opioid addiction. These factors discourage many addicted persons from seeking help.

#### **Buprenorphine in Maintenance Treatment:**

In October 2002, the American Food and Drug Administration (FDA) agency approved buprenorphine monotherapy product, Subutex®, and a buprenorphine/naloxone combination product, Suboxone®, for use in opioid addiction treatment in office-based settings (13,14). This revolutionary step was an important decisive moment because the use of opioid medications to treat opioid addiction became permissible in the medical office by qualifying physicians

#### **Chemical Properties of Buprenorphine:**

Buprenorphine, is classified as a partial  $\mu$  opioid agonist and a weak  $\kappa$  antagonist (15). It has a high affinity for the  $\mu$  receptor, with slow dissociation resulting in a long duration of action. The high-affinity blockade of  $\mu$  receptors limits the effect of subsequently administered opioid agonists (i.e. heroin). In lower doses, buprenorphine is 25 to 40 times more potent than similar milligram dosages of morphine (16). In higher doses, however, its analgesic effect reaches to a plateau (ceiling effect) due to it is a partial agonistic property, resulting in

receptor antagonism. This antagonist property limits the maximal analgesic effect and provides a favorable safety profile, and a low level of physical dependence. The long duration of action causes mild withdrawal symptoms on cessation after prolonged administration. These qualities make buprenorphine advantageous for the treatment of opioid dependence.

Buprenorphine is taken sublingually with a bioavailability of 60% to 70% (17). Oral use is not recommended because it is quickly metabolized by the liver. Its peak plasma concentration is in 90 minutes with a half-life of 4 to 5 hours. It is highly bound to plasma protein, and due to its lipophilic properties it provides a high brain tissue level. Buprenorphine is then converted to inactive conjugated metabolites (80% to 90%), by enzymatic transformation (15).

#### **Clinical Use of Buprenorphine:**

Buprenorphine has been successfully used for opioid detoxification and maintenance. A regimen of 8 to 12 mg sublingual daily has been used for 5 to 7 days for opioid detoxification (18). The slow release of buprenorphine from the  $\mu$  receptor allows mild withdrawal symptoms during detoxification. The introduction of buprenorphine (“induction”) should be done in the presence of a physician due to the potential risk of precipitating withdrawal symptoms with the first dose of buprenorphine. In a patient with a recent use of heroin or methadone, the antagonist effect of buprenorphine may prevail. Depending on the type and duration of action of the abused opioids, an initial opioid-free period (at least 24 hours from the last opioid use) must elapse before initiating buprenorphine. Several supportive medication treatments such as clonidine and ibuprofen may be offered during the initial opioid-free period to ease initial withdrawal symptoms. Patients should then be started on a low dose of buprenorphine (without naloxone) which can be administered on a schedule or as needed by using a withdrawal protocol such as The Clinical Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms (19).

Upon completion of detoxification patients may be started on buprenorphine maintenance. One of the earlier studies by Schottenfeld et al. showed the effectiveness of administration of buprenorphine in an average daily dose of 16 mg in a 12-week trial involving 92 participants who met diagnostic criteria for opioid dependence (20)

(Fig). Patients may need to be seen more frequently in the first week for medication adjustments to find the maintenance dose which is individual (stabilization phase). Maintenance doses up to 32 mg/day have been shown to prevent withdrawal symptoms and cravings for opioids (18,21,22), thus reducing illicit opioid use. In our clinic, most of the patients are maintained with 12-24mg/day doses divided to 2-3 times. It is not rare that patients frequently request increment in buprenorphine doses. However, this is mostly due to the nature of the addiction and patients' concern that they will experience withdrawal symptoms which are painful, unpleasant experiences for all. Unlike other opioids, users of buprenorphine rarely develop a tolerance to the drug. Maintenance dosages can remain at the same moderate level and in many cases even lowered, without causing withdrawal symptoms.

Physical dependence to buprenorphine is considered milder than methadone or heroin. Consistent with its agonist action at opioid receptors, buprenorphine has a risk of abuse, however is lower than the other full opioid agonists. Intravenous, intranasal, even rectal administrations of pills were reported by patients who mostly prefer Subutex® which does not contain naloxone. A formulation containing buprenorphine in combination with naloxone (Suboxone®) has been developed to decrease the potential for abuse via the injection route. Naloxone in the combination has poor absorption when administered sublingually and orally, but blocks the opioid action if administered parenterally.

Due to the potential for serious drug–drug interactions, buprenorphine must be used cautiously with certain other types of medications, particularly benzodiazepines, sedatives, opioid antagonists, and P450 3A4-metabolized medications. Norbuprenorphine, a product of N-dealkylation by the cytochrome P-450 3A4 enzyme, has more potent respiratory depressive effects than the parent drug (23). Therefore, medications that induce 3A4, such as phenobarbital, carbamazepine, and phenytoin, could increase the levels of norbuprenorphine (24-27). The clinical effects of these interactions are unknown.

All patients who receive buprenorphine for opioid detoxification or maintenance should be screened for substance-related problems, and are regularly monitored for diversion of prescription medications and other illicit drug use. Urine toxicology screening remains the most common method of drug testing. Several class-specific

immunoassay drug panels for urine “dip-stick” testing are available for a rapid testing at lower cost (25). Unfavorable drug test results should not be used punitively but should be seen as an opportunity to discuss and modify the treatment approaches accordingly.

Treatment of addiction disorders are a long term and complicated process requiring additional training and familiarity with addiction disorders and with common comorbid psychiatric disorders. In the United States physicians who are interested in using buprenorphine for opioid detoxification and maintenance must receive specialized training and experience (26), as well as notify Department of Health and Human Services by applying for a special Drug Enforcement Administration (DEA) number. They should also have appropriate counseling and other services available for opioid abusing patients. A maximum of 100 patients are allowed to be treated per physician in the office-based settings. At the present time Subutex® and Suboxone® or approved generic versions of these products are the only Schedule III substances to have received Food and Drug Administration (FDA) approval for opioid addiction treatment. Thus, they are the only opioid medications that may be prescribed or dispensed for this indication. Buprenex® is not approved for treatment of opioid addiction.

#### **Conclusion:**

Opioid dependence, including prescription analgesics and heroin, affects not only the individual's health, but also adds to the psychosocial burden of their families and society. It is imperative that opioid dependent people get the treatment that they need. Office-based buprenorphine treatment has been successfully implemented in the practice for opioid detoxification and maintenance in the hands of well trained physicians who excel in treatment of opioid dependent individuals.

#### **Pearls:**

#### **4 Phases of Clinical Use of Buprenorphine in an Office Setting:**

1. Intake
2. Induction
3. Stabilization
4. Maintenance

**Potential Benefits of Buprenorphine:**

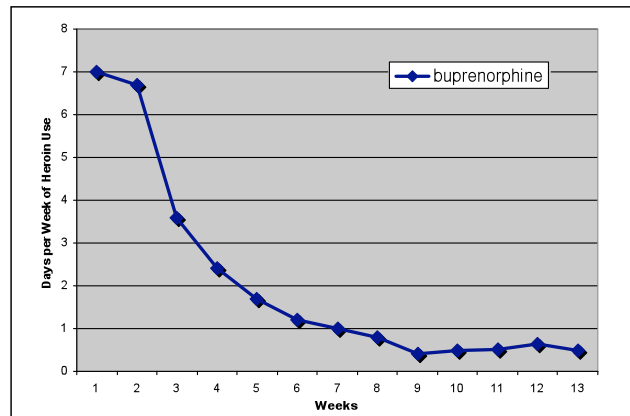
- Low abuse potential
- High safety profile
- Relatively mild withdrawal symptoms
- May attract more addicts into treatment

**Further reading:**

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**Buprenorphine Yield Declines in Days of Heroin Use**

Patients in treatment for opioid addiction received an average daily dose of 16 mg of buprenorphine showed reductions in reported days of heroin use during a 12-week trial. (modified from: Schottenfeld et al. *Biological Psychiatry* 47(12):1072-1079, 2000)(20).

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