Opioid Abuse and Deterrence: Buprenorphine Products
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Abstract
Abuse of opioid based prescription drugs is an ongoing global health concern that affects millions of individuals worldwide. The economic burden from this abuse has led to the development of treatment programs and the use of methadone maintenance in clinics. Yet, methadone itself has abuse liability and is misused in ways such as crushed for nasal insufflation or dissolved for subsequent intravenous injection. Later, a newer synthetic opioid working as a partial agonist at the mu-opioid receptor, buprenorphine (Subutex®), became available for outpatient use. This new opioid produces restricted euphoria, decreases withdrawal symptoms, and can prevent displacement of buprenorphine should the user decide to take illicit opioids. Due to high risk of abuse, the product was discontinued and now only available as a combination (Suboxone®) with the opioid antagonist naloxone. Users who abuse the combination product by parenteral routes will have euphoric effects cancelled by the presence of naloxone. Such novel dosage forms having additional physical and/or pharmacological barriers can provide a safe and effective option for medication-assisted treatment of opioid addiction with increased access to care.

Introduction
In recent times, a global health concern has emerged regarding the illicit use and subsequent dependence to opiates and prescription opioid analgesics. In 2010, the most common forms of illicit drug dependence worldwide were attributed to opioid and amphetamine drugs [1]. According to the United Nations Office on Drugs and Crime (UNODC), Opiate Abuse (OA) affected between 12 and 21 million individuals aged 15-64 worldwide in 2009 [2]. Additionally, these individuals used opiates at least once over a year (2008-2009) with an annual prevalence rate ranging from 0.3% to 0.5%. It is important to note that substance abuse can lead to addiction, where an individual’s behavior is dominated by the procurement of opioids/opiates. Dependence to opioids initially emerged as a concerning problem in the United States during the Civil War, where it was widely prescribed on the battlefield for pain, discomfort, and stress. Heroin was later introduced in 1898 as a cough suppressant, and eventually misused for its euphoric properties [3]. With the advent of the hypodermic drug administration technique in the 1910s, opioid/opiate addiction continued into the 20th and 21st century [3].

Opiates and semi-synthetic derivatives such as heroin, work at the opiate receptors μ (mu), κ (kappa), and δ (delta). Opiates inhibit adenylate cyclase, which modulates the release of nociceptive neurotransmitters (dopamine, acetylcholine, norepinephrine, substance P, and GABA), by decreasing intracellular cyclic adenosine monophosphate [4]. Opiates are powerful pain relievers that do not have a ceiling dose for their analgesic effect. However, in addition to analgesia, these drugs can produce a feeling of euphoria or a “high” in the user that can lead to addiction. Furthermore, the stimulation of μ receptors also produces respiratory depression, decreased gastric motility, cough suppression, hypotension, miosis, and physical dependence.

Economic Burden
In a study by Hansen et al. [5] the economic cost of non-medical prescription opioid use was evaluated across the United States. When accounting for OA treatment programs, loss of productivity, medical complication, and criminal justice, the economic burden of nonmedical use of prescription opioids was estimated at $53.4 billion. Seventy-nine percent of which was accounted by productivity loss, followed by costs of criminal justice, OA treatment programs, and lastly medical complications [5].

History of Treatment for Opioid/Opiate Abuse
The economic burden associated with OA led to effective treatments starting in the 1960s when methadone gained recognition in the treatment for opioid/opiate addiction, gaining US Food and Drug Administration (FDA) approval in treating opiate addiction in 1972 [6]. In an effort to de-stigmatize and establish opiate addiction as a legitimate medication treatment, methadone treatment has undergone regulation changes. Currently, methadone is federally regulated under the Substance Abuse and Mental Health Services Administration (SAMHSA), and can only be provided by specialized clinics registered by the Attorney General [7]. Methadone became an appropriate agent in the management of opioid/opiate addiction due to its slow onset and long duration of action, which creates a blunted euphoric effect [4].

In 1948 Levo-Alpha Acetyl Methadol (LAAM) was developed as an alternative to methadone for suppressing opioid withdrawal symptoms. The drug was approved by the FDA in 1993 under the brand name Orlaam (levo methadyl acetate hydrochloride) for opioid addiction treatment. A longer duration of action requiring less frequent dosing compared to daily methadone was believed to be its major benefit. The effect achieved by LAAM lasted for 48 to 72 hours versus just 24 hours with methadone [3]. However, by 2001 LAAM became a less desirable alternative due to cardiac-related disturbances. And by 2002, only 3% of patients enrolled in US opioid addiction treatment programs were receiving LAAM, and production was finally ceased by 2004 [3].

Another treatment option for opioid dependence is the use of opioid antagonists such as naltrexone. Naltrexone is a pure opioid

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antagonist that binds to mu-opioid receptors with a higher affinity than morphine, methadone, or heroin and which therefore can displace these drugs from the receptor. In 1984, the FDA approved naltrexone to treat opioid addiction primarily in highly motivated patients after detoxification. Patients need to have a high desire to take the drug as compliance is very poor. This is due in part because the drug itself does not ease cravings or produce any type of withdrawal symptoms upon missed doses. Consequently, it is often seen combined together with other drugs used to treat OA in a single dosage form. Combination products containing of opioid receptor antagonists are also seeing benefits currently in abuse-deterrent pharmaceutical dosage forms, which are further discussed below.

In 2000, Congress passed the Drug Addiction Treatment Act (DATA 2000) that changed the prescribing practices of medical doctors by allowing patients to have access to opiate treatment outside of federally approved Opioid Treatment Programs [6]. Under this act, medical doctors can prescribe schedule III to V narcotic medications for opioid addiction.

Buprenorphine (Subutex®) is a newer synthetic opioid working as a mixed agonist-antagonist narcotic by acting as a partial agonist at the mu-opioid receptor, an agonist at the delta-opioid receptor, an antagonist at the kappa-opioid receptor, and a partial agonist at the ORL-1 (nociception/orphanin FQ) receptor [4]. Buprenorphine is a schedule III drug FDA approved in 2002 as Subutex®. Reckitt Benckiser Pharmaceuticals discontinued the manufacturing of Subutex® in 2012 due to its high risk of misuse, abuse and diversion. The combination product Suboxone® (buprenorphine/naloxone) uses the addition of naloxone (formulations listed in Appendix A) to create a product with less potential for parenteral abuse. Suboxone® has a fixed ratio of 4:1 buprenorphine/naloxone and was available in sublingual tablets having 2 mg buprenorphine/0.5 mg naloxone or 8 mg buprenorphine/2 mg naloxone. In 2012 the sublingual tablets were discontinued and the more favorable and safer sublingual films are currently available in four different strengths ranging from 2 mg/0.5 mg to 12 mg/3 mg. Subutex® and Suboxone® become the first medications eligible for use under the DATA 2000 [6]. This enabled approved medical doctors to prescribe up to 30 patients buprenorphine containing medication treatment for opioid dependence, with the ability to treat up to 100 patients after holding certification for one-year with approval [4].

Since buprenorphine is only a partial agonist at the mu-opioid receptor, it produces a less intense high or “rush” as experienced with other opioids. However, its ability to decrease withdrawal symptoms and prevent cravings makes it a good product for maintenance therapy. Additionally, buprenorphine binds tightly to the mu-receptor, which causes blockade of the full effects of other mu-receptor agonists (for instance heroin or oxycodone) [4].

Abuse Potential of Products

Substance-addicted users have several routes and methods of administration for oral opioid medications. These methods involve techniques such as crushing to a fine powder for nasal insufflation, chewing (mastication), or dissolution in aqueous liquids for subsequent intravenous injection. All these administration techniques can provide rapid absorption to produce a “quicker rush”. Since many of these products are intended solely for oral ingestion, excipients and other inactive ingredients can become hazardous to the body if injected or snorted.

The advent of abuse deterrent formulations provided both physical and pharmacological barriers in dosage forms. Physical barriers can be formulations with enhanced mechanical properties that prevent crushing or having excipients that inhibit aqueous dissolution or syringeability. Examples of physical barriers are high viscosity gel capsules or insoluble coated microcapsules. Pharmacological barriers are substances added to the formulation that cause a pharmacological effect to discourage abuse. This most often includes the use of opioid antagonist (e.g. naloxone). For example, Suboxone® contains the pharmacological barrier of naloxone in combination with buprenorphine to deter abuse. A combination of barriers can also be used in a formulation. For example, Aversion® technology makes the extraction of the active ingredient difficult by causing irritation to the body (formulations containing niacin) or by changing its physical properties when mixed with water or alcohol into a gelatinous material preventing injection [8].

Mechanism of Action of Buprenorphine and Naloxone

As opioids from the bloodstream attach to mu-receptors in the brain, the stimulation of these receptors leads to a release of dopamine, which is a catecholamine responsible for the euphoria feeling of opioids. Upon repeated opioid use, the body becomes accustomed to the exogenous source of opioids and develops a biochemical balance. Once opioid use is discontinued, norepinephrine is released from the brain which presents as withdrawal symptoms.

Buprenorphine acts as partial-agonist to the mu-receptors in the brain enabling some dopamine release, but producing restricted euphoria. This is due to the high affinity of buprenorphine to the mu-receptors, limited intrinsic activity once attached, and slow dissociation from the mu-receptor [4]. This mechanism also prevents displacement of buprenorphine, should the user decide to take illicit opioids. These actions all result in decreased withdrawal symptoms and prevention of craving.

Naloxone is a (primarily) mu-receptor antagonist, working to stop both the clinical and toxic effects of opioid via competitive antagonism [4]. Naloxone has limited protein binding and a relatively short half-life of 30-80 minutes [4]. Since naloxone has limited bioavailability when taken orally, it has been included in combination with buprenorphine products as a deterrent to intravenous abuse. Since Suboxone® is taken orally, the antagonistic effects of naltrexone do not cancel out the effects of buprenorphine. However, if the user chooses to abuse Suboxone® by self-administering it intravenously, the pharmacokinetic profile of naloxone allows its effects to cancel out the euphoric effects of buprenorphine.

Pharmaceutical Dosage Forms of Abuse-Deterrence/Resistance

There are several mechanisms in which buprenorphine and its combination product deter abuse and make it a good alternative to other opioid treatments. Since buprenorphine acts as a partial mu-receptor agonist and exhibits a ceiling effect on its analgesic properties, it may be less dangerous with respect to overdoses and toxicity [4]. Buprenorphine is formulated with the opioid antagonist, naloxone. Naloxone has very little absorption when taken sublingually and studies have shown similar effects to buprenorphine alone when taken sublingually [9,10].

In the combination formulation of buprenorphine and naloxone, if the sublingual tablet or film is tampered with for administration intravenously, the naloxone component will precipitate an immediate withdrawal effect making it a deterrent for future abuse. Withdrawal
symptoms occur as mu-receptors become tolerant to repeated use of an opioid, which necessitates higher doses of opioid to create the same effect. Withdrawal symptoms commonly experienced can be divided into early and late stages. Early symptoms include agitation/anxiety, muscle aches, sweating, yawning, lacrimation, and insomnia. Late symptoms may include diarrhea, mydriasis, nausea and vomiting.

However, buprenorphine/naloxone still carries with it some abuse liability. Due to the pharmacodynamic properties of Subutex® and Suboxone®, if taken within 6 and 24 hours of short and long-acting periods respectively, withdrawal symptoms may occur. As a result of its high mu-receptor affinity and slow dissociation from its receptors, it may prevent withdrawals from naloxone as opposed to other opioids that have a shorter dissociation and weaker affinity allowing naloxone to give its withdrawal effects [9].

In patients dependent on short-acting opioids, it is recommended by the U.S. Department of Health and Human Services Consensus Panel to be inducted to the buprenorphine/naloxone combination product starting at the 4-1 mg dose at the onset of early withdrawal symptoms to give its withdrawal effects [9].

It may prevent withdrawals from naloxone as opposed to other opioids. Additionally, increasing accessibility to treatment programs can be a viable option for patients with high-risk for buprenorphine IV use. While there is abuse liability in all OA treatment options, buprenorphine/naloxone, has shown potential for decreasing buprenorphine IV abuse.

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In another study by Alho et al. [12] 176 participants (30%) returned a survey handed out during needle-exchange programs in Finland questioning buprenorphine and combination buprenorphine/naloxone intravenous (IV) abuse. While the most frequently abused drug was buprenorphine (73%), a majority of the participants tried the buprenorphine/naloxone combination at least once (68%). Of the respondents who have tried buprenorphine/naloxone, most of them have used it again or regularly, however, 80% reported a “bad” experience [12]. The survey also included the maximum street prices respondents have paid for buprenorphine and buprenorphine/naloxone tablets. The survey results also indicated that combination buprenorphine/naloxone is on average less than half the street price of buprenorphine [12].

These studies show combination buprenorphine/naloxone may be a viable option for patients with high-risk for buprenorphine IV abuse. Additionally, increasing accessibility to treatment programs using buprenorphine/naloxone combination could reduce IV abuse of buprenorphine, and hence reducing the abuse liability of buprenorphine via the pharmacological barrier of naloxone.

Conclusion

The growing rate of opioid/opiate abuse worldwide is a concern that has many implications to public health. Additionally, OA is a growing concern that affects many aspects of the economy. The majority of these costs are attributed to loss of productivity and criminal justice.

With the introduction of OA treatment programs, medications such as methadone, LAAM, buprenorphine, and buprenorphine/naloxone became options in the battle against OA. The advent of abuse-deterrent/resistant changes in pharmaceutical dosage forms provided physical and pharmacological barriers in drug formulations. While there is abuse liability in all OA treatment options, buprenorphine/naloxone, has shown potential for decreasing buprenorphine IV abuse.

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