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Innovative Drug Delivery and Formulation Designs To Deter Drug Abuse/Misuse Related To Suicide

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Abstract

Patients with a history of abuse/misuse of pain and psychotic medications are at high risk for suicide. Novel drug delivery and formulation approaches have been explored to reduce the potential of drug abuse/misuse and to improve patient compliance. This chapter reviews the design and mechanism of five successful products in the opioid and anti-psychotic categories. Embeda™ is an extended release capsule containing morphine pellets with a sequestered core of naltrexone; naltrexone acts as an aversive agent and is released only when the product is crushed. Remoxy® is an extended release oxycodone capsule with a highly viscous liquid fill content which is resistant to most common methods of tampering. Suboxone® is a sublingual tablet or film strip of buprenorphine with naloxone as an aversive agent; naloxone has poor sublingual/oral bioavailability and does not exert its activity unless the product is abused by the injectable route. Risperidal® Consta®, is a biweekly intramuscular injection of risperidone based on a biodegradable polymer microsphere technology. Invega® Sustenna® is a once-monthly intramuscular injection of paliperidone based on the water insoluble prodrug approach. The review of these five new drug products showcases the novel formulation tools and technologies available to deter drug abuse/misuse in patients who are at high risk of suicide.

Introduction

Prescription and OTC drugs contribute to suicide in three general ways.

1. Some CNS-active drugs, such as the anti-depressants, have been linked to suicidal ideation and behavior as treatment emergent adverse events.[1]
2. A number of prescription drug classes, such as opioid analgesics, stimulants, and anti-psychotics, have high potentials for abuse/misuse. Drug abusers and non-compliant psychotic patients are at high risk for suicidal ideation and behavior.[2,3]
3. Prescription and OTC drugs are often used directly and intentionally in suicidal attempts via overdosing.[4]

This chapter provides a review of recent innovations in drug delivery and formulation designs to address issue 2, i.e. the abuse and misuse of prescription drugs. Selected new products are

discussed as examples to showcase the novel drug delivery and formulation approaches. Issue 1 is related to the intrinsic pharmacological properties of the active drugs, which typically cannot be overcome by any drug delivery or formulation approaches. Issue 3 is difficult to address by product design due to the vast availability of prescription and OTC drugs, especially in developed countries. Some long-acting injectable or implantable drug products do reduce their potentials for being used directly in suicidal attempts. However, a determined suicidal patient can simply choose other alternative drug products as a means of suicide. Therefore, this chapter will focus solely on the formulation innovations intended to deter drug abuse/misuse in patients who are at high risk of suicide.

Oral Opioid Products

Opioid medications play an essential role in the management of moderate-to-severe pain in patients. The number of prescriptions for opioid medications has increased significantly over the last two decades.[5-7] Due to this increased accessibility, especially for the oral dosage forms, the opioid products are often abused by patients and channeled into illicit distribution chains. Most opioid drug abusers prefer intense and rapid onset of action, and they often choose products which have high drug contents and can be tampered easily to attain rapid drug release and exposure. Many novel formulation designs have been explored to reduce the potential for misuse/abuse and diversion.[7-9] Currently the most promising approaches can be classified in two general categories: (i) physical barriers are introduced to prevent tampering, such as crushing and solvent extraction; (ii) a deterrent or aversive ingredient is incorporated in the formulation, and it remains inactive unless the product is being misused or tampered. Three new opioid products are discussed below to illustrate the utility and application of these novel formulation designs.

1. Embeda™, an extended release capsule of morphine pellets with sequestered naltrexone

   Morphine is a pure opioid receptor agonist, and it has been used for over a century as the gold standard to treat moderate-to-severe pain.[10-11] It is available commercially as both injectable and oral dosage forms.[11] Due to the increased accessibility, the oral products present high potentials for abuse, especially the extended release capsules and tablets which contain a high drug content in each product unit.[12-13] The individuals may chew the capsules or tablets to destroy the extended release mechanism and attain a quicker and higher exposure of the drug. Another common way of abuse is to extract the drug in a solvent followed by injection.

   A new abuse deterrent formulation, Embeda™, was developed by King Pharmaceuticals (now Pfizer) and approved by US FDA in 2009.[14,15] Embeda™ is an extended release capsule formulation containing pellets of morphine and naltrexone at a ratio of 100:4.[14] Naltrexone is an opioid receptor antagonist, and it is normally well absorbed via the oral route. In

Embeda™ capsules, however, naltrexone is sequestered in the pellet core. When used as directed, the Embeda™ capsules deliver morphine over an extended period of time similar to the previous extended release capsule products, and the naltrexone remains sequestered within the core. Tampering with the capsule pellets by crushing or chewing (still swallowed orally) leads to rapid release and absorption of naltrexone which counteracts the euphoric effect of morphine.[14-16] If the crushed pellets are dissolved or extracted followed by injection, the naltrexone is also released into the systemic circulation which achieves the same deterrent effect.[16]

While the Embeda™ product design reduces the potential for abuse/misuse, it does not completely eliminate it. For example, the sequestered naltrexone has no deterrent effect if the patient takes extra capsules as prescribed to get an increased drug exposure. It is also unknown whether naltrexone is effective (bioavailable) if the crushed pellet powder is snorted via the nasal route.

2. Remoxy®, an extended release oxycodone capsule with a high viscosity matrix

Oxycodone is an opioid agonist with an abuse liability similar to morphine, and both are classified as CSA (Controlled Substances Act) schedule II.[17] The first generation extended release oral tablet, OxyContin®, was developed by Purdue Pharma and approved by FDA in 1995.[11] OxyContin® was launched in 1996, and many patients responded well to this extended release opioid formulation. Initially FDA and Purdue Pharma did not expect OxyContin® to have high potential for abuse due to the controlled release formulation design.[18] By 2001, the product grew to be the most prescribed brand name narcotic medication for treating moderate-to-severe pain. Ironically, this product also became extremely popular among opioid abusers.[18] Aside from the increased accessibility, the drug abusers also realized that OxyContin contained high drug content in each tablet and that the controlled release formulation could be easily manipulated to obtain a rapid release of drug for the oral or injectable route.
Purdue Pharma reformulated the OxyContin and obtained approval from FDA in April 2010.[19] However, the new formulation appeared to offer only incremental improvement on abuse deterrent features, based on the limited technical information available.[19,20] The company stated that "there is no evidence that the reformulation of OxyContin is less subject to misuse, abuse, diversion, overdose, or addiction." [21]

A separate effort has been undertaken by King Pharmaceuticals (now Pfizer) to develop an abuse deterrent extended release capsule of oxycodone. The new drug application (NDA) of this product, Remoxy®, has been filed to FDA and is currently under review.[22] The Remoxy® capsule formulation employs a novel proprietary Oradur™ sustained release gel cap technology. [23-25] The oxycondone is suspended in a water-insoluble, highly viscous, and

hydrophobic fluid matrix, which is subsequently filled into the regular capsule shells. This unique fluid matrix is designed to deter the four common routes of abuse - oral ingestion, snorting, injection, and inhalation. [23-25] In an aqueous medium, such as the gastrointestinal fluid, the viscous liquid transforms into an elastic matrix, which maintains the controlled drug release but prevents rapid drug extraction. The viscosity of the Oradur™ fluid matrix is extremely high (~ 60,000 centipoise), which renders it impossible for direct injection. This high viscosity also serves as a barrier for volatilization of the drug by heat for inhalation. The matrix remains as a liquid even at subzero temperatures. Therefore, it cannot be frozen to facilitate crushing or grinding to obtain solid powder for snorting. The tamper resistance features of Oradur™ have been demonstrated by several *in vitro* studies.[23-25] A recent clinical study also showed that the abuse potential of Remoxy when taken whole or chewed was much lower than the regular immediate and extended release dosage forms of oxycodone.[26]

Similar to the limitation of Embeda™, the Remoxy® product design does not reduce the potential of an abuser to overdose the product via the intended oral route.

3. Suboxone®, a sublingual tablet or film strip of buprenorphine with deterrent naloxone

Buprenorphine is a partial agonist at the mu-opioid receptor.[27] It was first approved as an injectable analgesic in 1981.[11] The tablet formulations, Subutex® and Suboxone®, were later developed by Reckitt Benckiser and approved in US in 2002 for office-based treatment of mild-to-moderate opioid dependence.[11,27] Subutex® and Suboxone® are sublingual tablets, which means that the drug is absorbed through the veins under the tongue. Subutex® contains only buprenorphine at 2 mg and 8 mg strengths; it is used during the induction phase of the treatment. [27] Suboxone® contains a combination of buprenorphine/naloxone at 2 mg /0.5 mg and 8 mg/2 mg strengths; it is used for the maintenance phase of the treatment. [27]

Based on its unique pharmacological properties, buprenorphine has a less abuse potential than full mu-opioid agonist[28] and hence a CSA schedule III status.[17] However, Subutex® and Suboxone® are prescribed to patients with existing opioid dependence and are therefore subjected to high risk for potential misuse. There were also concerns that these sublingual tablets dissolve rapidly in aqueous media and can be manipulated easily to allow abuse via injection. The second ingredient naloxone in Suboxone was specifically added as a deterrent for potential abuse by injection.[27,28] Naloxone is a potent antagonist at mu-opioid receptor. It has no clinically significant effect when administered sublingually or orally due to poor bioavailability.[27,28] However, if an abuse attempts to extract the active ingredient buprenorphine by a solvent vehicle, the deterrent naloxone will also dissolve in the vehicle. Once injected, naloxone will exert full antagonist activity, attenuate the buprenorphine effect, and lead to withdrawal in patients with opioid dependence. As expected, the withdrawal effect depends on the ratio of buprenorphine/naloxone. Several clinical studies were

conducted to identify the optimal dose ratio in patients with existing full agonist opioid dependence. In a pivotal clinical study using morphine stabilized subjects, IV injections of 2:1 and 4:1 ratios resulted in the most intense withdrawal effect.[27,28] Hence, the ratio of 4:1 buprenorphine/naloxone was chosen for the final product.

Since the launch of Subutex® and Suboxone® tablets, encouraging clinical results have been reported and published.[28-31] The buprenorphine/naloxone combination tablets, Suboxone, were found to offer a safe and effective treatment for opioid dependence with similar or better outcomes than methadone or clonidine, respectively. Moreover, Suboxone tablets were available through office based treatment with patient friendly dispensing frequency, which improved the overall patient accessibility and retention. Both Subutex and Suboxone had documented abuse cases, but the numbers were low relative to the number of prescription dispensed.[29] The incidence for abuse/misuse were reported as 0.08 and 0.16 abuse cases per 1,000 prescriptions dispensed for Subutex® and Suboxone®, respectively.[29] The higher rate of abuse for Suboxone® over Subutex® was not expected. A few possibilities were proposed as follows: Suboxone was prescribed to a broader spectrum of patients; Suboxone® was diverted and used by non-opioid dependent abusers via the sublingual route; the deterrent effect of naloxone for the iv route of abuse is only partial and short-lived in nature.[29,10.]

Most recently a new formulation, Suboxone® sublingual film strip, was approved and launched in US in late 2010.[11,32] The buprenorphine and naloxone strengths are kept the same as in the tablets. The pharmacokinetic behavior of the film is similar to that of the tablet, although not all doses are bioequivalent.[32] Interestingly, the company decided not to pursue the single ingredient buprenorphine film product. Only the combination buprenorphine/naloxone film is marketed.

Several new features have been incorporated in the Suboxone film product to further address the abuse/misuse and diversion issues.[32,33] Suboxone film strips are individually packaged as unit-dose child-resistant pouches. In contrast, the previous sublingual tablet products are packaged as 30 tablets per bottle.[27] This unit-dose pouch packaging also reduces the potential for being used directly as a means for suicide, serving as a primary prevention mechanism similar to the blister packaging approach described in Chapter 7a of this book. A 10-digit code is printed on each pouch which facilitates medication counts and deters diversion.[32,33] The manufacturer also states that the film formulation makes it difficult to be crushed into a powder for snorting.[33]

In addition to reduced potential for abuse/misuse, the film strips offer several improved product attributes over the tablets, which should aid in patient compliance. In short, the films adhere better to the oral mucosa in the sublingual region, dissolve faster, and taste better than the tablets.

Unfortunately, neither the sublingual tablet nor the film reduces the potential for overdosing via the intended sublingual route. Naloxone has poor oral bioavailability. Even when overdosed orally, the amount of naloxone in Suboxone does not result in the necessary systemic concentration to elicit the antagonist effect. The Suboxone tablets or films also do not deter the non-opioid dependent abusers from taking the product via the sublingual or oral route.

Long-Acting Injectable Anti-psychotic Products

Psychotic disorders, such as schizophrenia and bipolar disorder, are a major risk factor for suicide.[2,34] Studies also suggest that 25 – 60% psychotic patients do not take their medications as prescribed; some are non-adherent, some partial adherent, and some excess fillers.[35-37] All these non-compliant behaviors of antipsychotic drug treatment are strongly linked to relapse, rehospitalization, and potentially suicide. In addition to strengthening the social support and medical supervision, much effort has been directed to novel formulation designs to improve patient compliance.

The long-acting injectable antipsychotics have been recognized as an effective approach to address the non-compliance issue for psychotic patients who require long-term medications.[38] These injections are administered via the intramuscular route by the health care providers. Upon injection, the product forms an *in situ* depot of drug, which is released slowly over an extended period of time, typically 2 – 6 weeks. In comparison to the oral product, the long-acting injectable formulation reduces the fluctuation of plasma drug concentration, which can improve the safety and efficacy of the antipsychotic medication. In addition, the long-acting formulations eliminate the need for patients to keep large quantity of pills for maintenance therapy and reduce the potential for these oral products to be used as a means of suicide. Some early generation of depot injection products were formulated in oil which could lead to undesired side effects over time, such as nodules at the injection site. Two recent products with distinct mechanisms of depot formation and drug release are described below.

1. Risperidal® Consta®, extended-release microspheres of risperidone

Risperidone is an atypical (second generation) antipsychotic drug, and it is one of the most commonly prescribed medications to treat schizophrenia and bipolar disorder.[39-41] This drug was first approved by FDA in 1993 as an immediate release oral tablet.[11] An oral solution and orally disintegrating tablets were later developed and approved to for patients who cannot swallow tablets or are resistant to taking medications.[11]

A long-acting injection formulation, Risperdal® Consta®, was developed by Janssen Pharmaceuticals and approved by US FDA in 2003. This was the first long-acting atypical antipsychotic product on the market. Risperdal® Consta®, is a twice-monthly intramuscular depot injection. The drug is encapsulated in poly(lactic-co-glycolic acid) (PLGA) microspheres at a concentration of ~38% w/w.[39] PLGA is a biodegradable and biocompatible polymer excipient. Prior to injection, the microspheres are suspended using an aqueous diluent provided in a pre-filled syringe. Once injected, the microspheres form a depot in the muscular tissue at the injection site. The PLGA copolymer undergoes hydrolytic degradation progressively and releases risperidone over several weeks. According to the prescribing information from the manufacturer,[39] significant release of risperidone from the microspheres starts at week 3, is maintained from week 4 to week 6, and subsides by week 7. Therefore, supplemental oral antipsychotic medication should be given to the patient during the first 3 weeks of treatment with Risperdal® Consta®. Steady-state plasma concentrations are achieved after 4 biweekly injections.

The hydrolysis of PLGA gives back the lactic acid and glycolic acid monomers. These two acids are normal by-products of various metabolic pathways in the body. Therefore, the PLGA microsphere depot injections are generally safe and well tolerated with low incident rate of injection site pain or irritation.

The efficacy and tolerability of Risperdal® Consta® were investigated in a number of clinical studies in schizophrenic and bi-polar patients.[39-42] The data suggested that the Risperdal® Consta® treatment regimen offered similar efficacy as the long-term oral dose regimen with minimal increase in injection related adverse effects. As the first long-acting atypical antipsychotic product, Risperdal® Consta® offered a new mode of treatment with improved patient compliance and long-term outcomes.

2. Invega® Sustenna®, extended-release injectable suspension of paliperidone palmitate

Paliperidone is an active metabolite of risperidone discussed above.[43,44] This drug was first approved by FDA as an extended release oral tablets in 2006 for treating schizophrenia and in 2009 for schizoaffective disorders.[11] Paliperidone has improved pharmacokinetic properties over the parent drug risperidone, which reduces the risk for hepatic drug-drug interactions.[44] The unique OROS® tablet formulation technology also provides steady drug release rate and smooth drug plasma level, which allows once-daily dosing with no need for dose titration.[43,44]

In 2009, a long-acting injectable formulation, Invega® Sustenna®, was approved by FDA for once-monthly dosing.[11,45] Invega® Sustenna® is also an intramuscular injection which serves a depot function similar to Risperal® Consta® described above. However, it employs a prodrug approach instead of the microsphere approach.[43] Invega® Sustenna® contains paliperidone palmitate, which is an ester prodrug of paliperidone. In the body, the palmitate

prodrug is converted to paliperidone via hydrolysis catalyzed by esterase. The product is formulated as a ready-to-use aqueous based suspension, so it does not require a reconstitution step as Risperal® Consta® prior to injection. Paliperidone palmitate is extremely insoluble in water. Therefore, the prodrug particles form an *in situ* depot after the intramuscular injection, and the prodrug dissolves slowly to provide the extended release mechanism. The dissolved prodrug is rapidly hydrolyzed to the parent drug paliperidone and absorbed into the systemic circulation.[45] Following a single intramuscular dose, the drug plasma concentration rises gradually to reach a maximum at day 13. The drug release starts as early as day 1 and lasts for as long as 126 days. Even though Invega® Sustenna® is intended for once-monthly injection, an initial regimen of two injections on day 1 and day 8 is recommended to rapidly attain the steady-state drug concentration without the use of oral supplementation.[45] As a relatively new product on the market, there are limited clinical data on Invega® Sustenna® in the literature besides the studies conducted by the manufacturer for registration. It remains to be seen whether this long-acting depot product provides any improvement in efficacy, safety, and patient compliance over the long-term oral therapy and/or the risperidone long-acting depot product.

In theory, the long-acting injectable product designs can also be applied to opioids (discussed earlier in this chapter) to reduce abuse/misuse. However, this approach is not applicable to all drugs, especially the ones with high doses and/or undesirable physicochemical properties. In addition, opioid drug therapy requires careful dose titration, and there are sometimes needs to switch drugs for the same patient to improve outcomes. There are also concerns about dose dumping from some of these long-acting formulations, which can lead to life threatening adverse effects. On a positive note, several injectable and implantable products of buprenorphine have been developed and are currently in different stages of clinical trials.[9] One of these products, Probuphine, is a 6-month sustained-release implant and has recently demonstrated positive results in Phase 3 clinical studies.[46]

Conclusions

This chapter provides a review of recent innovations in drug delivery and formulation designs to reduce drug abuse/misuse in patients who are at high risk of suicide. These include the use of aversive agents, unique physical properties to resist tampering, and long-acting depot injections. All these approaches provide exciting opportunities for the development of future abuse deterrent drug products. Meanwhile, each approach has its limitations and needs to be balanced with the potential benefits.

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