CONTINUING EDUCATION CREDIT

A Review of Abuse-Deterrent Opioids For Chronic Nonmalignant Pain

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Educational Objectives

After reviewing this article, readers should be able to:

- Explain the purpose and use of the NAVIPPRO database.
- Describe and differentiate between abuse-deterrent technologies.
- Compare and contrast the new agents for use in chronic nonmalignant pain with older agents.

Introduction

Chronic nonmalignant pain is a silent epidemic in the U.S. that affects approximately 116 million Americans.[1] It is also the most common reason patients seek medical care, resulting in $635 billion annually in both medical costs and decreased work productivity.[1]

Although the physiology of chronic pain continues to be poorly understood, it has been identified as a disorder associated with many psychosocial conditions, including lack of appetite, depression, and sleep disturbances. Therefore, the use of a multimodal therapeutic plan is imperative in the treatment of patients experiencing chronic pain. Health care practitioners should ensure that all aspects of the chronic pain syndrome, including pathophysiology, functional impairment, and psychosocial needs, are addressed.[2] Nonpharmacological options, such as massage therapy, physical and occupational therapy, biofeedback, guided imagery, and cognitive–behavioral therapy, have been shown to help decrease some of the overall pain complaints. Interventional therapies, such as nerve blocks, transcutaneous electrical nerve stimulation (TENS), and injectable medications, are also used in various situations. However, a therapeutic plan typically employs the use of non-opioid and opioid analgesics to help control the pain.

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Opioid Use

An ongoing debate has revolved around the long-term use of opioids in the treatment of chronic nonmalignant pain.[3] Some of the discussion stems from the lack of data supporting long-term opioid use because of a lack of efficacy, ongoing concerns about adverse effects, and the potential for opioid misuse and abuse.[4] Abuse and misuse of these medications remains a public health challenge, with abuse rates having quadrupled in the decade from 1990 to 2000.[5,6] In addition, more than 70% of illegal users obtain opioids by stealing them, purchasing them illegally, or receiving them from family or friends.[7] These individuals seek to achieve a "high" from prescription medications by taking an excess number of pills orally or by crushing the pills, followed by snorting, smoking, or injecting the new altered formulation.

By altering the prescribed formulation, many abusers seek to create what is known as the "dump" effect, or an acceleration associated with a rapid "high." The effect results in a much higher peak serum concentration (C_{max}) over a shorter duration of time (T_{max}). This pharmacokinetic change results in a pharmacodynamic response or in the abuser's desired "reward" of euphoria. Therefore, each opioid should be examined for its potential abuse quotient ($AQ = C_{max}/T_{max}$). The abuse quotient can be reviewed to assess the rate of rise achieved by the drug in the blood and brain when the formulation is manipulated by an abuser.[8]

Extended-release (ER) formulations hold a greater attraction

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for abusers than immediate-release (IR) formulations because of their per-dose level of drug.[9] ER opioid formulations provide higher drug concentrations that can be manipulated. When ER formulations are altered, not only is there a more rapid onset of action (a shorter T_{max}) than that proposed by the manufacturer; there is also greater euphoria or anxiolysis, an effect that abusers desire.[9]

Development of Abuse-Deterrent Formulations

The concept in developing an abuse-deterrent formulation (ADF) is similar to that of developing any new opioid. General goals include producing a drug that is safe and effective for the intended population, one that does not easily cause serious harm to the potential abuser, and a medication that is economically feasible.[10] The only additional component added to the development of an ADF is that it must also deter abuse by potential abusers.

Research aimed at finding reliable data on the most commonly abused drugs and their preferred routes of administration by abusers can be very helpful in determining which drugs need an ADF and which characteristics the new drug will most likely exhibit. The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) database was created to track drugs of abuse, their current popularity, and their preferred method of use by abusers.[11] The NAVIPPRO database further breaks down each drug of abuse into percentages showing the drug's use within the previous months and the routes by which it is most often abused. A thorough examination of this database would help the pharmaceutical industry to focus on the drugs of abuse that cause the most concern and to identify routes of delivery that new formulations should specifically strive to deter. For example, after a review of the database, it would be simple to conclude that investing large amounts of time and money into developing a new formulation of hydrocodone that deters injection would be a waste of resources, because only 1% of hydrocodone users inject the drug.[11]

After an innovation for an ADF is under development, the next step is to show that the drug is safe and effective for the treatment of pain and that it deters abuse. The current "gold standard" in clinical trials is to compare the abuse liability of a new opioid or opioid formulation with that of an opioid of known abuse liability in volunteers who have a history of previous drug abuse.[10] If the trial shows a low abuse liability within this population, the abuse liability in the general population can also be expected to be low.

Clinical trials can lead manufacturers to make FDA-approved implicit or explicit claims, which can be included in the product's labeling. Implicit claims may indicate that the new formulation *might* have some impact on abuse but has not yet been proven.[10] Explicit claims may be made when clinical trials establish that the new formulation has been shown to deter abuse.[10] These claims and any materials promoting the new formulation, although they are closely monitored by the FDA, are among the few incentives that drug companies receive for investing their time and money in products that some would consider unnecessary or that would serve only to protect the public from itself.

One method of creating an ADF is to add a pharmaceutical or a chemical component to the opioid. An example is the addition of naloxone to decrease the user's response to an abused substance or to provide an adverse reaction when the user alters the formulation. This type of modification is made in an attempt to decrease the abuse quotient of the particular opioid formulation. Another method is to deter the user's ability to physically alter the drug's original manufactured form to extract the active ingredient through various methods, such as crushing, chewing, or mixing with a solvent, such as alcohol.[8]

This article discusses available opioids that include abuse-deterrent mechanisms as well as such agents currently in development.

Agents Currently on the Market

Buprenorphine/Naloxone (Suboxone)

Suboxone (Reckitt Benckiser) is a combination of the partial opioid agonist-antagonist buprenorphine and the opioid antagonist naloxone. Buprenorphine acts as a partial agonist at the mu-opioid receptors and as an antagonist at the kappa-opioid receptors. This combination of partial mu-receptor agonism and kappa-receptor antagonism makes buprenorphine useful as an analgesic while also providing some abuse deterrence. To increase the level of abuse deterrence, naloxone was added to buprenorphine to prevent injectable exploitation. As a Schedule CIII controlled substance, Suboxone is indicated for the treatment of opioid dependence.[12] Buprenorphine and naloxone are combined in a 4:1 ratio and are available in only two doses, 2:0.5 mg and 8:2 mg.[12]

Although the oral bioavailability of buprenorphine is poor, its high lipid solubility allows exceptional sublingual bioavailability.[13] The naloxone component of Suboxone displays virtually no sublingual absorption and very little oral absorption.[13] For this reason, Suboxone is available as both a sublingual tablet and a sublingual film. Plasma concentrations of buprenorphine remain comparable whether or not naloxone is added, thereby indicating that naloxone does not alter buprenorphine's pharmacokinetic profile.[12]

Because of naloxone's poor absorption, it has a clinical effect only when a patient abuses the product by administering it intravenously or intramuscularly.[13] When Suboxone is injected, the effect of naloxone is no longer impeded by low oral and sublingual absorption. In fact, when Suboxone is injected, it can produce opioid antagonistic actions similar to those of naloxone alone.[12] This antagonistic action, produced by the naloxone contained in Suboxone, causes opioid-dependent patients to experience withdrawal, thereby deterring abuse.[14]

Today, Suboxone plays a minor role in the treatment of pain, but it can be helpful in treating chronic pain in patients with a history of opioid addiction.

Morphine/Naltrexone (Embeda)

Embeda (King Pharmaceuticals) consists of a combination of extended-release morphine sulfate (used for moderate-to-severe pain) with naltrexone HCl (a mu-opioid antagonist) in a ratio of 100:4 mg. This ADF was developed to limit the potential for crushing and dissolving the ER morphine product. An extra gelatin capsule in a sequestered core separates the morphine from naltrexone. When Embeda is taken orally or when its pellets are sprinkled over applesauce, naltrexone has

no significant effect on morphine, even though it is detectable at very low steady-state levels.[15,16] However, if the tablet is crushed, naltrexone is released and exerts opioid antagonism, which may cause symptoms of withdrawal.[15,16]

Because of manufacturing problems, Embeda was recalled several times and was voluntarily withdrawn by the manufacturer in March 2011.[17]

Oxymorphone (Opana)

Oxymorphone, a Schedule II controlled substance, was approved by the FDA in 2006 for the treatment of moderate-to-severe chronic pain. It is currently available as an ER preparation, Opana ER, and as an IR preparation, Opana IR (Endo Pharmaceuticals). In December 2011, a New Drug Application (NDA) was approved for the ER formulation of oxymorphone HCl. This formulation includes the Grünenthal Group's INTAC Technology, which preserves the ER characteristics of the medication while imparting crush-resistant properties. The FDA's approval verified that the addition of the INTAC Technology did not significantly affect the rate of absorption of the active ingredient. The newly approved Opana ER has the same name, color, and dosage strength as the IR formulation.

Opana ER is available in 5-mg, 7.5-mg, 10-mg, 15-mg, 20-mg, 30-mg, and 40-mg tablets.[18,19] This medication should be used only for the treatment of chronic pain. It is not indicated for use in postsurgical pain or for as-needed use.[20]

OROS Hydromorphone (Exalgo)

In 2010, the FDA approved the Osmotic extended-Release Oral delivery System (OROS) of hydromorphone (Exalgo, Mallinckrodt) for the treatment of moderate-to-severe pain in patients who are opioid-tolerant and who require around-the-clock analgesia.[21] IR hydromorphone has been available in many formulations (e.g., oral solutions, tablets, powder for compounding and injection, a solution for injection, and rectal suppositories) for many decades. Hydromorphone is a synthetic mu-opioid agonist that is similar to morphine; however, oral hydromorphone is 5.0 to 7.5 times more potent than oral morphine.[22]

In 2004, the FDA approved an ER formulation of hydromorphone (Palladone, Purdue Pharma). However, within 6 months of Palladone's release onto the market, overdoses associated with alcohol use were reported. Alcohol has the potential to cause a rapid release of hydromorphone (known as "dose dumping"), which leads to elevated blood levels of the drug and an increased risk of overdose. Palladone was withdrawn from the market in July 2005.[23]

OROS hydromorphone is now the only ER form of hydromorphone available in the U.S. OROS technology allows hydromorphone to be delivered at a constant rate over a period of 24 hours, thereby providing more stability in pain control compared with the IR formulation, which is given every 4 hours.[24] OROS technology consists of an osmotically active bilayer core enclosed in a semipermeable tablet shell membrane, which is eventually eliminated in the feces.[23] This technology has also proved to be tamper-deterrent because the tablet is difficult to crush or extract for injection.[25]

The use of OROS hydromorphone is approved only for patients who are opioid-tolerant (i.e., patients who took 60 mg of oral morphine equivalents per day for the previous 7 days). This includes patients who are currently receiving transdermal fentanyl (Duragesic, Janssen) 25 mcg/hour, oral oxycodone (OxyContin, Purdue Pharma) 30 mg/day, oral hydromorphone 8 mg/day, or oral oxymorphone 25 mg/day for the previous 7 days. Failure to adhere to this recommendation could lead to an overdose and possibly to respiratory depression, death, or both, in opioid-naive patients who take this formulation.[21] OROS hydromorphone should be used only for the treatment of chronic pain. It is not indicated for use in postsurgical pain, and it should not be prescribed on an as-needed basis.[21]

Oxycodone Controlled Release (OxyContin)

In April 2010, the FDA approved a new controlled-release (CR) formulation of OxyContin, another popular opioid drug of abuse that has been associated with drug-related mortality.[26,27] This CR opioid received the FDA's approval for an NDA for product reformulation. The NDA was granted based on the drug's diminished potential for tablet manipulation for purposeful abuse or misuse. However, without formal ADF studies, Purdue Pharma was not able to market this new formulation as an "abuse-deterrent" drug. Although no studies have indicated that the CR formulation has true ADF qualities, the package insert states that the ease of cutting, breaking, chewing, crushing, and dissolving this new formulation is diminished.[26]

According to the manufacturer, the new OxyContin formulation of oxycodone is bioequivalent to the original OxyContin (oxycodone HCl CR), which is a mu-receptor and kappa-receptor agonist. The newer formulation, which has a slightly longer T_{max} and a slightly higher C_{max}, may be identified by the designation "OP" on the tablets ("OC" appears on the older formulation).[26] This medication should be used only for the treatment of chronic pain. It is not indicated for use in postsurgical pain, and it should not be prescribed on an as-needed basis.[28]

Aversion Technology

Acura Pharmaceuticals, Inc., is one of the leading companies working on the development of abuse-deterrent products. Acura has patented Aversion Technology in an attempt to decrease the abuse of common oral opioid analgesics. Common pharmaceutical ingredients are used to change the consistency of the drug product into a form that is not favorable for administration through frequently used routes during opioid abuse. For example, if the active ingredient is crushed, it forms crumbled chunks that cause irritation when the product is snorted. Furthermore, if the active ingredient is mixed with a liquid, the product forms a gel that prevents it from being injected.[29,30]

Aversion Technology has three main goals:

1. To make it more difficult to extract the active ingredient from the tablet, thus preventing it from being abused parenterally. When the tablet is mixed with a common solvent, such as water or alcohol, it is changed into a gelatinous mixture. This makes it difficult to draw the drug into a syringe for parenteral administration.
2. To cause increased burning and irritation to the nasal

passages, compared with previous formulations, when the tablet is crushed and nasally snorted.
3. To decrease excess tablet swallowing.

Acura's objective was to incorporate niacin into opioid tablets so that when the tablets are consumed in excess, the person would experience uncomfortable symptoms, such as flushing, itching, sweating, chills, and headache. It is anticipated that the niacin-induced discomfort would begin within 15 minutes after excess consumption and would resolve 75 to 90 minutes later.

Although Acura patented the technology, it does not necessarily mean that all pain products developed in association with the company will contain all three methods of deterrence. Acura is working with Pfizer on these products. Pfizer is ultimately in control of product development, and therefore only parts of Acura's Aversion Technology may be used if Pfizer so desires.[31]

Oxycodone (Oxecta)

Oxecta (oxycodone HCl, USP; Pfizer), formerly known as Acurox, was originally a new IR formulation of oxycodone HCl that also contained niacin, thus using Aversion Technology. The FDA did not approve Acurox; therefore, the company later submitted an NDA for a niacin-free version of Acurox in December 2010. This newly formulated product was given a fast-track status for FDA approval.[32] After the NDA for the new niacin-free form was submitted, King Pharmaceuticals was acquired by Pfizer, which renamed the niacin-free version of Acurox as Oxecta. The FDA approved Oxecta for the management of acute and chronic moderate-to-severe pain on June 17, 2011.[33]

In a double-blind, active-comparator, crossover study, the "drug-liking" responses to crushed Oxecta tablets were compared with those of crushed IR oxycodone tablets when 40 nondependent recreational opioid users administered the drugs intranasally. Thirty percent of subjects exposed to Oxecta responded that they would not take the drug again, whereas only 5% of subjects exposed to IR oxycodone shared that opinion. The Oxecta group had a higher incidence of nasopharyngeal and facial adverse events and a decreased ability to completely insufflate two crushed tablets within a fixed period when compared with the oxycodone group. Although these results are promising, there is no evidence that Oxecta has a reduced abuse potential when compared with IR oxycodone.[34]

Because Oxecta is not amenable to crushing or dissolution, it may obstruct feeding tubes and should not be administered to patients via this route.[34]

Agents Under Development

Aversion Technology

Oxycodone HCl/Acetaminophen (Acuracet)

Acuracet is a recent IR formulation of oxycodone HCl and acetaminophen. This product was developed by Acura Pharmaceuticals, which patented the Aversion Technology. Although the drug was licensed in December 2007, it is still undergoing formulation and stability testing. The only available information about the product's abuse-deterrent ability is that the formulation should reduce nasal snorting and intravenous injection.[35]

Hydrocodone Bitartrate/Acetaminophen (Vycavert)

Acura's Vycavert, an IR opioid analgesic, is similar to Acuracet. The drug was licensed in December 2008 and is still undergoing formulation and stability testing. Like that of Acuracet, the goal of this new formulation is to reduce nasal snorting and injectable abuse of the product.[36]

Oxytrex Science and Technology

Oxycodone/Naltrexone (Oxytrex)

Oxytrex is an orally administered, abuse-deterrent opioid drug that was initially developed by Pain Therapeutics, Inc. The recent literature indicates that this product is in late-stage clinical development for the treatment of moderate-to-severe chronic pain. The formulation combines a therapeutic amount of oxycodone with a very low dose of the opioid antagonist naltrexone.

Data from animal studies suggested that the abuse-deterrent component, naltrexone, works at ultra-low doses by reducing the development of opioid tolerance and dependence.[37,38] In phase 3 clinical trials, patients showed reduced dependence on opioids along with levels of pain relief that were comparable to those obtained with the non–abuse-deterrent formulation.[39] The reduction in opioid tolerance with this drug was thought to lessen the propensity of patients to self-medicate and possibly to avoid opioid abuse. However, Pain Therapeutics has returned the rights for Oxytrex to Albert Einstein College of Medicine.

DETERx Technology

COL-003

Collegium Pharmaceutical designed DETERx Technology to preserve the ER property of a medication even if someone has tampered with it by crushing or dissolving it.[40] Because ER products contain larger amounts of active ingredients than IR formulations do, ER products have been highly sought after by drug abusers. Traditional ER formulations do not protect the ER property of the drug after a user has tampered with it. Therefore, crushing or dissolving these products allows the release of all active ingredients at once, making the agents attractive for drug abusers.

DETERx preserves the ER component, thereby causing ER products to be less attractive to abusers because the drug is still released slowly into the body even if the product has been tampered with. Unlike many other ADF technologies, DETERx does not contain an antagonist or irritating agent to minimize a drug's abuse potential.[40] The benefit of not including these agents is a decreased risk of withdrawal or uncomfortable side effects in patients taking the drugs for a legitimate purpose.[40]

A medication using the DETERx formula consists of small beads inside a capsule. Each bead contains drug molecules that are uniformly dispersed in an ER tamper-resistant matrix. A standard spray-congealing process is used to prepare the matrix.[40] A drug/fatty acid–ionic complex is formed, allowing the product to be a solid solution within the beads.[41] The beads are made of a hydrophobic, waxy material that has a high melting point.[41] Each bead has tamper-resistant and ER formulations; therefore, the capsule may be opened and sprinkled on food for patients who have trouble swallowing.[40]

Collegium has conducted studies of chewing, crushing, and extraction and of the ability of the product to be drawn into a

syringe to demonstrate the efficacy of the DETERx Technology. Two studies were conducted to evaluate the effect of chewing on the time-release formulation.[40] The chewed version was shown to be bioequivalent to the intact product, and it even had a slightly lower C_{max}.[42]

To evaluate the effect of crushing and extraction on the DETERx beads in COL-003 (a form of oxycodone), a mortar and pestle was used to crush the product, which was then exposed to household solvents to determine whether there was a dose-dumping effect.[42] Compared with a traditional ER product, the DETERx beads were able to maintain their time-release property.

In another test, researchers melted DETERx beads at a high temperature and then attempted to draw up beads into a syringe. As a result of the high melting point, the formulation solidified, demonstrating its resistance to heat.[42]

Collegium used DETERx Technology to develop COL-003. In September 2011, the company announced a successful meeting with the FDA in regard to a proposed phase 3 clinical trial of the drug. Collegium plans to conduct a 12-week, placebo-controlled study in opioid-naive and opioid-experienced patients with chronic low back pain to demonstrate the drug's efficacy. Collegium has also filed an Investigational New Drug (IND) application for COL-172, an oxymorphone product with DETERx Technology. Both COL-003 and COL-172 have been granted fast-track designations by the FDA.[43] Two more pain products using DETERx Technology, COL-195 and COL-196, are undergoing preclinical development.[44]

Small-Molecule Delivery

NKTR-181

Developed by Nektar Therapeutics, NKTR-181 is a mu-opioid analgesic product currently undergoing phase 1 clinical trials. In preclinical studies, this product demonstrated analgesia equivalent to that of oxycodone, one of the most commonly abused opioids.[45] NKTR-181 is designed to reduce abuse by entering the central nervous system (CNS) at a rate that is 90% slower than that of traditional opioid drugs.[45]

The technology used to develop NKTR-181 involves small-molecule polymer conjugates.[45] In addition to slowing delivery to the CNS, the polymer conjugate design also prevents NKTR-181 from being converted into an opioid that can be easily abused. NKTR-181 was compared with oxycodone and morphine in a validated primate model to determine the product's abuse liability.[45] Even at a 100-fold higher dose, NKTR-181 had a lower abuse potential than its equivalent analgesic counterpart, oxycodone.[45]

Because the delivery of NKTR-181 to the brain is slowed, euphoria is decreased, thus making the product less desirable for drug abusers. Another benefit for patients with legitimate analgesia needs is that the drug's slowed delivery to the brain also decreases the potential for dangerous adverse effects, such as respiratory depression.[45] Even at five times the lethal dose of oxycodone, NKTR-181 did not result in death from respiratory depression in rats.[45]

In December 2011, Nektar announced positive data from a phase 1 trial that evaluated increasing doses of oral NKTR-181 (100, 200, 300, and 400 mg), administered over an 8-day period in 60 healthy adults.[46] In this study, NKTR-181 showed an extended analgesic response, supporting a twice-daily dosing schedule.[46] The purpose of this study was to determine a safe and effective dosing scheme for NKTR-181. Full results from the study were presented at the 2012 American Academy of Pain Medicine's annual meeting in February 2012.[44] Phase 2 trials were scheduled to begin this month.[46] Human abuse liability will also be studied in phase 2.

NKTR-181 has been accepted into the FDA's fast-track development program.[47]

Bio-Activated Molecular Delivery and Multi-Pill Abuse Resistance Technology

PharmacoFore, Inc., has developed an abuse-deterrent technology, Bio-Activated Molecular Delivery (Bio-MD), that is aimed at preventing opioid abuse at the molecular level.[45] Unlike most other ADFs, Bio-MD technology is not based on sequestering a drug with a physical barrier. Instead, opioid release is possible only when the medication is exposed to specific physiological conditions.[48]

After a Bio-MD–formulated product reaches the small intestine, the amino acid mask on the opioid particles is cleaved off by the enzyme trypsin.[49] Opioid medications made with Bio-MD technology do not create the desired "high" that abusers seek, because the formulation is essentially inactive in the blood if it has not passed through the small intestine first.[45] Bio-MD technology prevents the medication from being converted into the active drug if it enters the systemic circulation alone, such as through injection. In addition, systemic exposure is not increased by chewing, crushing, or dissolving the tablets. Limiting systemic exposure not only decreases the desired "high" but also minimizes undesirable side effects.[48]

In addition to the Bio-MD system, which prevents the active drug from being released until it has been exposed to the intestine, Multi-Pill Abuse-Resistance (MPAR) technology was developed to protect against excessive ingested overdoses.[45] MPAR technology works in conjunction with Bio-MD through the Bio-MD system's mechanism of action.[48]

With the addition of MPAR technology, taking 10 MPAR pills produces the same systemic exposure as taking two or three non-MPAR pills.[48] PharmacoFore has many opioids in the pipeline that are scheduled to be produced with both the Bio-MD and MPAR technologies. The three delivery technologies that are to be used on specific opioids include PF03, to be used with hydromorphone, oxymorphone, and morphine; PF06, to be used with oxycodone and hydrocodone; and PF16, to be used with tapentadol (Nucynta, Janssen).[48]

PF329

PharmacoFore's leading drug, compound PF329, is an ER hydromorphone agent formulated with Bio-MD and MPAR technologies. A phase 1 proof-of-concept study in 51 healthy subjects demonstrated that dose-proportional hydromorphone release is a safe and efficient mechanism.[48] Subjects received PF329 solution (dosage range, 1–48 mg) and IR hydromorphone.[50] The T_{max} of PF329 was approximately 2 hours, which was slower than that of IR hydromorphone. The half-life of the compound should allow twice-daily dosing, a much less frequent schedule compared with that of current hydromorphone forms.[48]

During this study, the compound was dissolved in solution to show the effect of the Bio-MD technology. This demonstration highlighted the fact that Bio-MD technology does not involve the reformulation of existing opioids in matrices that might be susceptible to extraction.[48] As a result of this specialized technology, crushing, chewing, and injecting the medication does not create the opioid "high" that abusers are looking for.

Oradur Technology

Extended-Release Oxycodone (Remoxy)

Remoxy (Pain Therapeutics/King/Pfizer) is an ER formulation of oxycodone in a high-viscosity, hard-gelatin (water-insoluble) matrix capsule. It was developed to deter breaking, chewing, snorting, or thermal extraction for injection. Oradur Technology (Durect Corp.) is designed to transform short-acting oral capsule dosage forms into sustained-release oral products, thereby providing a mechanism that is less prone to abuse.[43] The area-under-the-curve (AUC) concentration for the Remoxy formulation is significantly lower than that of oxycodone (OxyContin). The efficacy of Remoxy is similar to that of oxycodone when taken with food, but the administration of Remoxy under fasting conditions provides a significantly lower plasma oxycodone concentration (41% without food, 102% with food).[51]

Studies in which Remoxy was crushed and extracted with 40% alcohol compromised the formulation by producing a 10% increase in the C_{max}. However, this was still a significantly lower drug level at 1 to 2 hours when compared with that of oxycodone.[8]

In June 2011, the FDA declined to approve this new formulation.[51]

Conclusion

The various types of pain and their treatment options continue to pose challenges in the U.S. health care system. Opioids are effective therapies for various chronic nonmalignant pain conditions, although further studies are needed to confirm the utility of using these agents in the long term. The introduction of new formulations has improved management options for clinicians who develop treatment plans. However, abuse continues to cause uneasiness among clinicians when opioids are prescribed, and this may result in the prescription of inadequate doses for pain control.

In response to the clinical concerns about drug abuse, many manufacturers are developing opioid products that have abuse-deterrent qualities. It is imperative that clinicians understand the characteristics of these agents if they are to improve the care of their patients with chronic nonmalignant pain.

References

1. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, D.C.: National Academies of Science; June 29, 2011. Available at: www.iom.edu/~/media/Files/Report%20Files/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research/Pain%20Research%202011%20Report%20Brief.pdf. Accessed December 16, 2011.
2. Argoff CE, Albrecht P, Irving G, Rice F. Multimodal analgesia for chronic pain: Rationale and future directions. *Pain Med* 2009;10(S2):S52–S66.
3. Fine PG, Mahajan G, McPherson ML. Long-acting opioids and short-acting opioids: Appropriate use in chronic pain management. *Pain Med* 2009;10(S2):S79–S88.
4. Bernstein D, Stowell AW, Haggard R, et al. Complex interplay of participants in opioid therapy. *Pract Pain Manage* 2007;7:10–36.
5. National Institute on Drug Abuse (NIDA). *NIDA Community Drug Alert Bulletin: Prescription Drugs*. Bethesda, Md.: U.S. Department of Health and Human Services, 2005. NIH Pub. No. 05-0580. Available at: http://archives.drugabuse.gov/prescripalert/. Accessed November 1, 2011.
6. Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain* 2006;22(2):173–181.
7. Webster LR, Bath B, Medve RA. Opioid formulations in development designed to curtail abuse: Who is the target? *Exp Opin Investig Drugs* 2009;18(3):255–263.
8. Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. *Drugs* 2010;70(13):1657–1675.
9. Webster L. Update on abuse-resistant and abuse-deterrent approaches to opioid formulations. *Pain Med* 2009;10(S2):S124–S133.
10. Katz NP, Adams EH, Chilcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain* 2007;23(8):648–660.
11. Katz N. Abuse-deterrent opioid formulations: Are they a pipe dream? *Curr Rheumatol Rep* 2008;10:11–18.
12. Suboxone (buprenorphine and naloxone) Sublingual Tablets, prescribing information. Richmond, Va.: Reckitt Benckiser; December 2011. Available at: www.suboxone.com/pdfs/SuboxonePI_tablet.pdf. Accessed February 3, 2012.
13. Helm S, Trescot A, Colson J, et al. Opioid antagonists, partial agonists, and agonists/antagonists: The role of office-based detoxification. *Pain Physician* 2008;11:225–235.
14. Orman JS, Keating GM. Buprenorphine/naloxone: A review of its use in the treatment of opioid dependence. *Drugs* 2009;69(5):577–607.
15. Embeda (morphine sulfate and naltrexone HCl) Extended Release Capsules, prescribing information. Bristol, Tenn.: King Pharmaceuticals, Inc.; July 2010. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=694. Accessed February 3, 2012.
16. Duggan ST, Scott LJ. Morphine/naltrexone. *CNS Drugs* 2010; 24(6):527–538.
17. Morphine/naltrexone combo temporarily withdrawn. Medscape News. Available at: www.medscape.com/viewarticle/739008. Accessed November 1, 2011.
18. FDA approves tamper-resistant oxymorphone formulation. Medscape News. Available at: www.medscape.com/viewarticle/755260?src=rss. Accessed December 1, 2011.
19. Grünenthal Group. Grünenthal's INTAC technology. Available at: http://grunenthal.com/grt-web/Grunenthal_Group/Research_&_Development/Preclinical_R&D/Novel_drug_delivery_systems/Intac%E2%84%A2_/127701579.jsp;jsessionid=6129785B71A327F8D837E62F62B7B7DE.drp1. Accessed December 1, 2011.
20. Opana ER (oxymorphone HCl) Extended-Release Tablets, prescribing information. Chadds Ford, Pa.: Endo; December 2011. Available at: www.endo.com/pdf/products/Opana%20ER%20PI%2020111212.pdf. Accessed February 3, 2012.
21. Exalgo (hydromorphone HCl) Extended-Release Tablets, prescribing information. Hazelwood, Mo.: Mallinckrodt; November 2010. Available at: www.exalgo.com/media/pdf/EXALGO–FullPrescribingInformation.pdf. Accessed December 23, 2011.
22. Carter N, Keating G. OROS hydromorphone prolonged release: A review of its use in the management of chronic, moderate to severe pain. *CNS Drugs* 2010;24(4):337–361.
23. FDA. Information for healthcare professionals: Hydromorphone hydrochloride extended-release capsules (marketed as Palladone). Available at: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288.htm. Accessed December 1, 2011.

24. Sathyan G, Xu E, Thipphawong J, Gupta SK. Pharmacokinetic investigation of dose proportionality with a 24-hour controlled-release formulation of hydromorphone. *BMC Clin Pharmacol* 2007;7(3):1–8.
25. Palangio M, Northfelt DW, Portenoy RK, et al. Dose conversion and titration with a novel, once-daily, OROS osmotic technology, extended-release hydromorphone formulation in the treatment of chronic malignant or nonmalignant pain. *J Pain Symptom Manage* 2002;23(5):355–368.
26. New OxyContin (oxycodone controlled-release) formulation. *Pharmacist Lett Prescriber Lett* 2010;26(12):261201.
27. Schneider JP, Matthews M, Jamison RN. Abuse-deterrent and tamper-resistant opioid formulations: What is their role in addressing prescription opioid abuse? *CNS Drugs* 2010; 24(10):805–810.
28. Oxycontin (oxycodone HCl) Controlled-Release Tablets, prescribing information. Stamford, Conn.: Purdue Pharma LP; November 2007. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2009/020553s060lbl.pdf. Accessed January 1, 2012.
29. Fiore K. FDA okays new abuse-resistant opioid. *MedPage Today,* June 20, 2011. Available at: www.medpagetoday.com/ProductAlert/Prescriptions/27157. Accessed December 23, 2011.
30. FDA approves tamper-resistant oxycodone. Medscape Medical News, WebMD; June 20, 2011. Available at: www.medscape.com/viewarticle/744935. Accessed December 23, 2011.
31. Aversion technology. Acura. Available at: http://acurapharm.com/research-development/aversion-technology. Accessed December 23, 2011.
32. Oxecta Tablets. Available at: http://acurapharm.com/products/acurox-without-niacin-tablets. Accessed December 23, 2011.
33. Adams B. FDA approves Pfizer pain drug Oxecta. *InPharm,* June 21, 2011. Available at: www.inpharm.com/news/160392/fda-approves-pfizer-pain-drug-oxecta. Accessed December 14, 2011.
34. Oxecta (oxycodone HCl, USP) Tablets, prescribing information. Bristol, Tenn.: King Pharmaceuticals, Inc.; June 2011. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=620. Accessed December 23, 2011.
35. Acuracet tablets. Acura. Available at: http://acurapharm.com/products/acuracet-tablets. Accessed December 23, 2011.
36. Vycavert tablets. Acura. Available at: http://acurapharm.com/products/vycavert-tablets. Accessed December 23, 2011.
37. Largent-Milnes TM, Guo W, Wang HY, et al. Oxycodone plus ultra-low-dose naltrexone attenuates neuropathic pain and associated mu-opioid receptor-Gs coupling. *J Pain* 2008; 9(8):700–713.
38. Webster LR. Oxytrex: An oxycodone and ultra-low-dose naltrexone formulation. *Exp Opin Investig Drugs* 2007;16(8):1277–1283.
39. Webster LR, Butera PG, Moran LV, et al. Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *J Pain* 2006; 7(12):937–946.
40. Collegium Pharmaceutical. Technology introduction. Available at: www.collegiumpharma.com/technology-introduction. Accessed December 13, 2011.
41. Collegium Pharmaceutical. DETERx formulation design. Available at: www.collegiumpharma.com/deterxatrade-formulation-design. Accessed December 13, 2011.
42. Collegium Pharmaceutical. DETERx tamper resistance. Available at: www.collegiumpharma.com/deterx-tamper-resistance. Accessed December 13, 2011.
43. Collegium Pharmaceutical, Inc., announces successful type A meeting with FDA for tamper-resistant, extended-release opioid. *Business Week*, September 26, 2011. Available at: http://investing.businessweek.com/research/stocks/private/snapshot.asp?privcapId=7490189. Accessed December 23, 2011.
44. Collegium Pharmaceutical. Products/pipeline. Available at: www.collegiumpharma.com/productspipeline. Accessed December 23, 2011.
45. Nektar Therapeutics, Product Fact Sheet, 2011. CNS/PAIN—NKTR-181: New mu-opioid analgesic with novel molecular structure in clinical development as a safer, abuse-deterrent pain therapeutic. Available at: www.nektar.com/pdf/pipeline/NKTR-181/product_fact_sheet.pdf. Accessed December 13, 2011.
46. Nektar announces positive clinical data from second phase 1 clinical study of NKTR-181, a novel opioid analgesic molecule to treat chronic pain. *Daily Markets* December 13, 2011. Available at: www.dailymarkets.com/stock/2011/12/13/nektar-announces-positive-clinical-data-from-second-phase-1-clinical-study-of-nktr-181-a-novel-opioid-analgesic-molecule-to-treat-chronic-pain. Accessed December 13, 2011.
47. Nektar/PR Newswire. Nektar announces that FDA grants fast track designation to NKTR-181, a new oral opioid analgesic molecule for the treatment of moderate-to-severe chronic pain, June 7, 2012. Available at: http://ir.nektar.com/releasedetail.cfm?ReleaseId=681109. Accessed June 18, 2012.
48. PharmacoFore. Pipeline: Moderateto severe pain. Available at: www.pharmacofore.com/view.cfm/39/Moderate-to-Severe-Pain. Accessed December 13, 2011..
49. Fiore K. Companies attempt abuse-proof opioids. *MedPage Today,* April 13, 2011. Available at: www.medpagetoday.com/Psychiatry/Addictions/25888. Accessed December 13, 2011.
50. PharmacoFore. PharmacoFore, Inc. announces positive results from a phase I clinical study of its hydromorphone Bio-Activated Molecular Delivery™ system and upcoming presentation at the 2011 BIO Business Forum during the annual BIO International Convention in Washington, D.C.; June 23, 2011. Accessed December 14, 2011.
51. Durect Corp. Primary endpoint of pivotal phase III clinical trial achieved for Remoxy, December 6, 2007. Available at: www.durect.com/wt/durect/page_name/pr_1196960615. Accessed December 7, 2011.

Continuing Education Credit for Physicians and Pharmacists

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ACPE Program # 0079-9999-12-019-H04-P
Expiration Date: July 31, 2013

Topic: A Review of Abuse-Deterrent Opioids for Chronic Nonmalignant Pain

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Topic: A Review of Abuse-Deterrent Opioids for Chronic Nonmalignant Pain

ACPE Program # 0079-9999-12-019-H04-P

CE Evaluation: Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to The Jefferson School of Population Health, Thomas Jefferson University, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

Multiple Choice

Select the one correct answer.

1. **Which of the following is *not* a necessary component of the development of an abuse-deterrent formulation (ADF)?**
   a. The drug must be safe and effective for the intended population.
   b. The drug must deter abuse by potential abusers.
   c. The drug must be crush-proof.
   d. The drug must be economically feasible.

2. **Which of the following medications contains naloxone, an opioid antagonist?**
   a. Suboxone
   b. Embeda
   c. Oxecta
   d. None of the above

3. **What is the major difference between the Acurox (not FDA-approved) and Oxecta formulations of oxycodone?**
   a. the presence of naloxone
   b. the presence of naltrexone
   c. the presence of niacin in Acurox
   d. There is no difference.

4. **Oxecta deters the following routes of drug abuse:**
   a. injection
   b. crushing/snorting
   c. oral overdose
   d. more than one of the above

5. **What information on drugs of abuse can be gained from the NAVIPPRO database?**
   a. the number of controlled prescriptions filled by a patient
   b. the preferred method of use by abusers
   c. information on patients who are doctor-shopping
   d. none of the above

6. **Aversion Technology is designed to deter abuse through the following mechanisms *except:***
   a. side effects of flushing, itching, and sweating when excess tablets are swallowed.
   b. increased burning and irritation when the tablet is crushed and nasally snorted.
   c. side effects of nausea and vomiting when excess tablets are swallowed.
   d. increased difficulty in extraction of the active ingredient.

7. **This opioid formulation is a combination of hydrocodone bitartrate and acetaminophen and uses Aversion Technology to deter abuse:**
   a. Oxytrex
   b. Vycavert
   c. Acuracet
   d. none of these

8. **DETERx technology works to deter abuse by the:**
   a. preservation of the extended-release component.
   b. addition of niacin to increase side effects of excess tablet swallowing.
   c. addition of a substance that prevents extraction of active ingredient.
   d. reformulation of active ingredient that decreases euphoria and makes the product less desirable to abusers.

9. **Bio-Activated Molecular Delivery (Bio-MD) differs from other abuse-deterrent technologies by:**
   a. preventing abuse at the molecular level.
   b. increasing side effects when medication is exposed to specific physiological conditions.
   c. reformulating the active ingredient to decrease euphoria and to make the product less desirable to abusers.
   d. adding an ingredient that increases side effects in the case of excess tablet swallowing.

10. **The opioid formulation with abuse-deterrent technology that has received FDA approval is:**
    a. Remoxy.
    b. Oxytrex.
    c. Vycavert.
    d. none of these

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CE Registration and Evaluation Form

Date of publication: **July 2012**
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Submission deadline: **July 31, 2013**
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Registration

Name: _____ Degree: _____

Street address: _____ Last 4 Digits of Social Security No. (Web ID): _____

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NABP ID # (required for pharmacists only): _____ Date of birth (MM/DD): _____

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Signature (required) Date

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1.	a ☐	b ☐	c ☐	d ☐	6.	a ☐	b ☐	c ☐	d ☐
2.	a ☐	b ☐	c ☐	d ☐	7.	a ☐	b ☐	c ☐	d ☐
3.	a ☐	b ☐	c ☐	d ☐	8.	a ☐	b ☐	c ☐	d ☐
4.	a ☐	b ☐	c ☐	d ☐	9.	a ☐	b ☐	c ☐	d ☐
5.	a ☐	b ☐	c ☐	d ☐	10.	a ☐	b ☐	c ☐	d ☐

Evaluation

Rate the extent to which:	Very High	High	Moderate	Low	Very Low
1. Objectives of this activity were met	☐	☐	☐	☐	☐
2. You were satisfied with the overall quality of this activity	☐	☐	☐	☐	☐
3. Content was relevant to your practice needs	☐	☐	☐	☐	☐
4. Participation in this activity changed your knowledge/attitudes	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
5. You will make a change in *your practice* as a result of participation in this activity. Specify the changes you plan to make. _____	☐	☐	☐	☐	☐
6. This activity presented scientifically rigorous, unbiased, and balanced information	☐	☐	☐	☐	☐
7. Individual presentations were free of commercial bias	☐	☐	☐	☐	☐
8. Adequate time was available for Q&A	☐	☐	☐	☐	☐

9. Which ONE of the following best describes the impact of this activity on your performance:
   - ☐ This program will not change my behavior because my current practice is consistent with what was taught.
   - ☐ This activity will not change my behavior because I do not agree with the information presented.
   - ☐ I need more information before I can change my practice behavior.
   - ☐ I will immediately implement the information into my practice.

10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   - ☐ Discuss new information with other professionals
   - ☐ Discuss with industry representative(s)
   - ☐ Other _____
   - ☐ Consult the literature
   - ☐ Participate in another educational activity
   - ☐ None

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