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Abuse-Deterrent Opioids: Advances in Technology

(Part 1 of a 3-Part Series)

Introduction

Chronic pain is a serious medical condition that affects more than 100 million American adults, affecting many to the point where they are unable to work, maintain relationships, or even participate in daily tasks.¹ It is one of the most common reasons individuals seek medical care, resulting in up to \$635 billion in direct medical costs and lost productivity on an annual basis.¹ There are a number of treatment options for chronic pain including both nonpharmacologic and pharmacologic modalities.^{2,3} Pharmacologic options may include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants, adjuvant therapies (eg, antidepressants, antiepileptics, or benzodiazepines), and opioid analgesics.³ While opioids represent an important treatment option, abuse and misuse of these drugs are significant concerns that negatively affect their appropriate use, as well as the health of patients.⁴⁻⁶

Opioid Abuse and Misuse

Multiple factors have contributed to the severity of opioid abuse and misuse in the United States, including a substantial increase in the number of opioid prescriptions written and dispensed, from an estimated 76 million in 1991 to more than 200 million in 2013; greater acceptability for prescribing opioid medications for different indications; greater awareness of risks associated with alternative treatments (gastric, cardiovascular, and renal effects of NSAIDs); more time spent during training (medical school, residency, and fellowship) on the appropriate use of opioids; and an increase in the marketing of medications.^{7,8} According to the Centers for Disease Control and Prevention, opioids are the leading cause of drug overdose deaths in the United States with approximately 17,000 opioid overdose deaths reported in 2010.⁹ For every one opioid overdose death, there are¹⁰:

- 10 treatment admissions for abuse
- 32 emergency department visits for abuse or misuse
- 130 people who abuse or who are dependent; and
- 824 nonmedical users

Opioids can be abused in a variety of ways (Table).^{6,11,12} By altering the prescribed dosage formulation, the abuser hopes to create a “dump” effect (ie, an increased maximum serum concentration over a shorter duration of time), which is associated with the occurrence of a rapid high.^{13,14} The primary routes of opioid abuse are oral, inhaling (eg, snorting), parenteral (IV,

Table. Primary Routes of Opioid Abuse and Manipulation Methods

Routes of abuse	Inhalation (eg, snorting)
	Oral
	Parenteral (ie, IV, intramuscular, or subcutaneous)
Manipulation methods	Smoking
	Crushing or grinding into a powder or small particles
	Dissolving in a solvent such as alcohol
Manipulation methods	Extracting through exposure to hot or cold temperatures

Based on references 6, 11, and 12.

intramuscular, subcutaneous), and smoking. The primary methods of opioid manipulation are crushing or grinding into small particles of powder, dissolving into a solvent (eg, alcohol), and extraction by hot or cold temperatures.¹² Although extended-release (ER) formulations may be manipulated to achieve the desired “dump” effect, the greater attraction (also known as likability) for potential abusers has been with immediate-release formulations. There has been a rise in abuse seen with long-acting opioids in recent years, driving industry to begin investing in approaches to help mitigate this challenge.

The societal epidemic of opioid abuse requires a multifaceted approach, with the goal of mitigating risk to ensure safe and effective pain management. Advances are being made in education, guidance, and resources, but a recent strategy in this area is development of abuse-deterrent (AD) opioids as one way to mitigate the risk for opioid abuse and misuse.¹¹

Approaches to the Development of Abuse-Deterrent Opioids

When developing an AD opioid, researchers need to maintain the efficacy of the original formulation while improving the ability to deter abuse. In January 2013, the FDA issued a draft guidance document to assist the pharmaceutical industry in developing new formulations of opioid drugs with AD properties. The document explains the FDA’s current thinking about studies designed to demonstrate AD properties of a given formulation, how studies will be evaluated, and labeling claims that may be proposed based on study results. The draft guidance also outlines that AD technology approaches can be classified into 6 categories⁶:

1. Physical/chemical barriers
2. Agonist/antagonist combinations
3. Aversion
4. Prodrug
5. Delivery system
6. Combination of 2 or more of the above

Physical/Chemical Barriers

Physical barriers can prevent “chewing, crushing, cutting, grating, or grinding” of an approved opioid formulation, whereas chemical barriers can “resist extraction of the opioid using common solvents such as water, alcohol, or other organic solvents.”⁶ These barriers can alter the physical form of the oral opioid, thereby making it less likely to be abused.⁶ Examples of AD formulations that may use physical and/or chemical barriers include crush-resistant pills and tablets, high-viscosity gelatin capsules (Figure 1), and extruded pellets.¹⁵ As AD technology evolves, there may be products introduced that seek to include both physical and chemical barriers to further strengthen the AD potential to deter abuse. Oral opioid formulations that are crush resistant or more difficult to crush deter abuse by making the crushed remains of the product challenging to inject or snort (Figures 2A and 2B). In the event the crushed remains of the product are snorted, injected, or consumed orally, opioid formulations that also are chemically resistant may affect the likability.

Finally, another potential physical barrier to opioid abuse is the use of extruded pellets. With this formulation, tampering with the opioid results in predominantly coarse particles that are generally less desirable to inhale via snorting.¹⁶



Figure 1. Crushed gelatin capsule.



Figure 2A. Crush-resistant tablet.

Agonist/Antagonist Combinations

With agonist/antagonist combinations, an opioid antagonist, such as naloxone or naltrexone, is added to the formulation to “interfere with, reduce, or defeat” the euphoria associated with opioid abuse (Figure 3).⁶ In these AD formulations, the opioid antagonist is isolated from the opioid and only released if the prescribed formulation is manipulated in some way.⁶ If the product is swallowed or the pellets are sprinkled on food, there is no notable antagonistic effect. However, if it is crushed or chewed, the antagonist is released and mixed with the opioid, resulting in the prevention of the high sought by the abuser by preferentially binding to opioid receptors, which may result in withdrawal symptoms in the abuser.¹³

Aversion

Aversion technology refers to adding a noxious component to a formulation to produce an unpleasant effect if manipulation occurs before administration, or when a higher dose than prescribed is consumed.⁶ Examples of potential aversive agents may include the following:

- The addition of a nasal irritant so that snorting of a manipulated opioid would result in nasal passage discomfort (burning and irritation); or
- If excessive oral consumption of the aversive agent occurs, the abuser may experience unpleasant symptoms (eg, flushing, chills, sweating, itching, and headache).¹³

These unpleasant symptoms may deter abuse and may be of interest for opioid products in development.

Prodrugs

Prodrugs are biologically inactive substances that are metabolized inside the body to their active form.¹¹ Development of a prodrug that lacks opioid activity until it has been metabolized in the gastrointestinal (GI) tract may be an attractive option to prevent IV or intranasal routes of abuse.^{6,11} Although there are no opioids currently available that use this approach, the effects have been observed with stimulant medications.¹¹

Delivery Systems and Combinations

According to the draft guidance, the method of drug delivery or certain drug-release designs offer resistance to opioid abuse.⁶ Examples of drug delivery systems that may deter abuse and misuse include subcutaneous implants, depot injectable formulations, beads within a capsule, and erodible matrix technology.⁶ These drug delivery systems release the medication slowly over time, are inherently difficult to manipulate, are dependent on GI tract activity for diffusion of the medication, or require surface erosion of a matrix for the medication to be released, respectively.

The draft guidance also contains a “combination” category as an AD technology approach. Using this approach, 2 or more of the above methods would be utilized in order to decrease the potential for abuse.⁶

Conclusion

Opioids are a cornerstone of the pharmacologic management of chronic pain for many patients. However, abuse and misuse of opioids remain significant concerns. The goal of each of the



Figure 2B. Non-crush-resistant tablet.

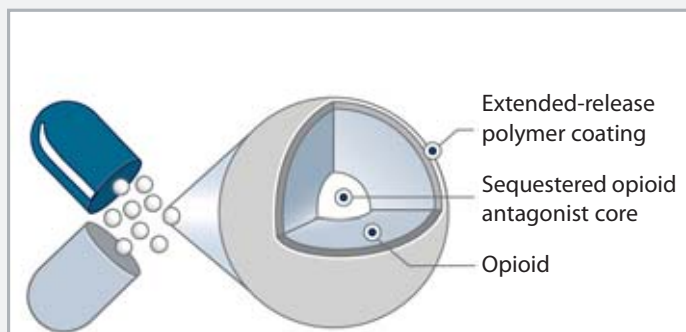


Figure 3. An agonist/antagonist combination.

approaches to AD technology reviewed in this article is to maintain efficacious analgesia while reducing the risk for potential abuse and misuse. Not all AD technologies are the same. With AD being a fairly recent development, and limited real-world experience, time may tell how these AD technologies may contribute in mitigating the risk for opioid abuse.

In the next installment of this 3-part series on AD opioids, the types of studies outlined by the FDA to evaluate AD formulations

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