Chronic pain remains one of the most ubiquitous international healthcare problems. Some figures estimate that 90 million Americans—nearly one third of the population—are affected by chronic pain. This number surpasses those affected by diabetes, heart disease, and cancer combined. Opioid medications are widely (but not universally) believed to have an integral role in treating pain. Though controversial, there is considerable evidence to suggest the efficacy of opioids in pain management.

Though opioids are generally regarded as helpful, the debate about their benefits and risks has persisted for many years. Indeed, documentation of this debate is recorded as far back as 300 BC. With the recent passing of high profile public figures and rising rates of death from opioid overdose, opioid misuse/abuse has garnered great media and political attention and prompted several features in both print and video journalism referencing an “opioid epidemic.”

Opioid misuse has been defined as the intentional therapeutic use of a prescription opioid analgesic in an inappropriate way, excluding events that qualify as abuse. Opioid abuse has been defined as the “intentional, non-therapeutic use of a prescription opioid analgesic to achieve a desirable psychological or physiological effect, for example euphoric, sedative, or anxiolytic effects.” Common strategies for opioid abuse include taking larger amounts of the medication than previously intended orally, crushing the pills and insufflating (“snorting”) the resulting powder nasally, or dissolving the pills in a solvent and then injecting the medication intravenously.

Among the several potential strategies to mitigate the potential harms of opioid abuse have been proposed, the development of abuse deterrent formulations (ADF) of opioids has gained recent attention. The FDA has supported the development of ADFs as a modality to combat abuse and misuse of opioids. ADFs most commonly contain variables that deter abuse by acting via these improper means of administration; either (a) acting through physical barriers that confer resistance to tablet tampering, (b) combining the opioid agonist with an antagonist, or (c) incorporating an aversive ingredient intended to cause discomfort when abused by the nasal route.

This article will examine the demand, development, and potential utility of these agents in pain management, offering examples of each of several types of ADFs.

**PHYSICAL BARRIERS**

Physical barriers, as their name states, deter abuse by rendering certain improper routes of administration inaccessible or difficult for a given product. Typically this involves a mechanical or chemical barrier to crushing or pulverizing a medication. Oxycodone is a commonly abused opioid mediation, and as such has been a target for reformulation to attempt to make it more abuse deterrent. One early example was the reformulation of Oxycontin (Purdue), which was reformulated with a polymer matrix to provide a physical barrier to breaking and crushing. As such, it was approved by the FDA in 2010.

Nucynta, for example, an FDA approved (2011) extended release iteration of Tapentadol (Ortho-McNeil-Janssen Pharmaceuticals), has formulated a polyethylene oxide matrix coating that makes it difficult to be crushed and then insufflated. Tramadol Extended Release (TheraQuest
Biosciences) has a formulation that makes it both crush resistant and also difficult to dissolve in alcohol.11 Morphine biosciences ER is also resistant to being crushed, cut or dissolved by a solvent when compared to its counter-part morphine sulfate ER.12 It was FDA approved for use in October 2015.

Opana (Oxymorphone, Endo Pharmaceuticals) contains a coating made of a polyethylene matrix which makes the tablet crush resistant but does not affect its extended release properties. When Opana is exposed to a solvent, it forms a gel. The viscosity of this gel makes it difficult to be drawn into a syringe and therefore dissuades intravenous use of the drug.8 Opana was FDA approved in Dec 2011. Research in this area remains robust, including a new formulation of an extended release oxycodone, Xtampza ER (Collegium Pharmaceuticals). Xtampza consists of capsules containing tiny beads of medication. Each of these beads contains the drug uniformly dispersed in a tamper-resistant matrix. The beads are made of a hydrophobic, waxy material with a high melting point that cannot be drawn into a syringe for injection when melted.9,12,13 Xtampza was FDA approved in April, 2016.

Hydrocodone is also named as one of the most frequently abused opioid medications.14 Hysingla ER is an extended release formulation that is taken once a day and offers a coating resistant to crushing or chewing the tablet. Furthermore research suggest this medication offers abuse deterrent benefits while offering equivalent analgesic effects.15,16 Hysingla was FDA approved for distribution in November 2014.

CHEMICAL BARRIERS

Other drugs make use of chemical barriers, including the addition of opioid antagonists. These antagonist compounds may mitigate the desired effect of the opioid medication when the drug is misused or abused. They may either be sequestered or freely available. When a freely available antagonist is used, the ideal antagonist will have low bioavailability by the intended route (ex: oral or sublingual) and higher bioavailability through an inappropriate route of administration (ex: intravenous). One such compound is naloxone. Naloxone has low oral bioavailability and thus has little antagonist activity when used by the prescribed sublingual route. However, intravenous abuse of the drug will result in higher levels of naloxone that are likely to antagonize the abusers intended opioid effects.8

Suboxone employs buprenorphine as an opioid (partial) agonist with naloxone as an antagonist and was approved by the FDA in 2003 for the treatment of opioid dependence but is commonly used off-label as a pain medication and is widely regarded to be abuse deterrent.17 Embeda, approved in August 2009, contains both extended release morphine and sequestered naltrexone. Because naltrexone has higher oral bioavailability than naloxone, it must be sequestered or it may produce opioid antagonist effects when used appropriately by the oral route. When swallowed whole as prescribed, the morphine is released over an extended period of time and the naltrexone remains isolated behind a physical barrier. However, if crushed or chewed, the naltrexone embedded in the core of the medication is released alongside the morphine, mitigating its effect.8 Another ADF that utilizes naltrexone is OxyNal, a sustained-release capsule containing beads of Oxycodone and Naltrexone. When ingested whole, only the Oxycodone is absorbed with negligible absorption of the Naltrexone. When the capsule is otherwise manipulated, the beads of Naltrexone are released thereby antagonizing the desired effects of the opioid agonist.11 Troxyca ER also features this oxycodone/naltrexone combination and was approved by the FDA in June 2016.

INCORPORATION OF AVERSIVE INGREDIENTS

Other ADF opioids contain agents that will create adverse effects when administered improperly. These opioids are formulated with an additional agent that is expected to be inert when taken as prescribed, but may cause an undesired unpleasant effect when abused by a non-oral route of administration. This unpleasant effect is expected to deter use of these agents by non-oral routes such as intravenous injection and insufflation.

Oxaydo (Egalet Corporation), combines immediate release oxycodone with sodium lauryl sulfate. This compound may irritate the nasal mucosa when abused by the nasal route.8,18,19 Research suggests that ADF versions of oxycodone can demonstrate very similar oral bioavailability when compared to non-ADF immediate release Roxicodone.20

Regulation and development of abuse deterrent opioids

As opioids have become a topic of increasing interest in our society, the Center for Disease Control (CDC) and the Food and Drug Administration (FDA) have begun to issue guidelines and protocols to help improve the safety of opioid medications in our community. The FDA has developed a study protocol with which pharmaceutical compa-
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FDA Study Categories for the Abuse Deterrent Opioids

Category 1: Examining in vitro manipulation of the medication, these studies evaluate the ease with which the abuse deterrent technology can be bypassed. Possible bypass methods include crushing, grinding, or using solvents to separate the opioid from the abuse deterrent technology.

Category 2: Studies at this stage go further and examine the in vivo properties of the medication and its abuse deterrent mechanism. Often in category 2, there is a comparison of the medication’s plasma concentrations before and after manipulation. These data may then be compared to the same molecule without abuse deterrent technology.

Category 3: These pre-market studies evaluate the clinical abuse potential of the novel compound and compare this potential to that of similar medications without abuse deterrent technology. These studies commonly focus on the likability of the investigational drug among abusers.

Category 4: Performed post-market, these studies evaluate whether or not the abuse deterrent technology in the medication has resulted in effective reduction of the abuse, misuse, addiction, and overdose rates associated with the medication. Presently, there is limited data for most products in this category and it will take several years before useful data is gathered and analyzed.

CONCLUSIONS AND FUTURE DIRECTIONS

The future of ADFs will likely see more products come to market that fall into one of the three categories described here, and will likely also witness the proliferation of opioid prodrugs. Since the abuse of opioids commonly occurs via routes of administration other than the gastrointestinal tract, opioid prodrugs may be a useful ADF development target. This drug would be ingested in an inactive form that would only obtain opioid activity when metabolized in the GI tract. If it were abused by another route (e.g., intravenous or intranasal), it would not produce the usual opioid effect. Additionally, if the specific metabolic systems required for activation were saturable, further biotransformation to active forms may not occur above a certain ceiling dose, which may reduce euphoria and the risk of respiratory depression in case of overdose.

Another modality currently being developed is that of opioids with slower kinetics of CNS entry. NKTR-181 (Nektar Pharmaceuticals) is a novel opioid agonist that enters the central nervous system at a rate 90 percent slower than typical opioid medications. Using small molecule delivery technology, NKTR-181 has been shown to exhibit lower abuse than oxycodone in preclinical studies. This slower delivery system also decreases the risk for respiratory distress in a rat model, even at the five times the equipotent lethal dose of oxycodone. As of 2012, this formulation has been accepted into an FDA fast-track development program but has not yet been approved by the agency.

Once available, these ADFs must be accepted and used by physicians if they are to have a chance at combatting opioid abuse. Lower Controlled Substances Act scheduling of these drugs compared to their non-abuse deterrent counterparts could make them more available and encourage physicians to prescribe them. Moreover, increased pressure on insurance companies to include ADFs in their formularies without barriers to access (such as high co-pays and burdensome designated step through medications) may also encourage the use of ADFs.

Regardless of the specific modality of ADF that a physician seeks to employ, the resourceful abuser will likely continue to find ways to circumvent or offset the deterrent features of abuse deterrent opioids. The increased availability of ADFs may partially ameliorate the opioid abuse problem that we face, but it will not eliminate the problem on its own. Indeed, no single modality, law, or practice mandate is likely to be a panacea for the scourge of opioid abuse.

Access to new, potentially safer opioid medications is expected to be a challenge for both patients and physicians. Continued vigilance and effort will be required from patients, family members, legislators, and payers in order to continue to provide compassionate, judicious pain management therapies for patients in need of care.
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