Commentaries

Challenges Involved in the Development and Delivery of Abuse-deterrent Formulations of Opioid Analgesics

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ABSTRACT

Purpose: This commentary examines the development, regulatory, and reimbursement challenges facing abuse-deterrent formulation (ADF) products.

Methods: In January 2017, the Tufts Center for the Study of Drug Development convened a roundtable to explore clinical development, regulatory, and reimbursement challenges with respect to ADFs of opioid analgesics. Roundtable participants, who included a range of pharmaceutical industry and other experts, discussed multiple challenges.

Findings: First, several key clinical development challenges were identified and discussed. These challenges pertain to prodrug development and development of deterrents against oral abuse. Second, experts suggested that more clarity is needed from regulatory authorities regarding standards for proving ADF labeling claims and for being rewarded with 3-year data exclusivity. Similarly, given the substantial burdens associated with the development of postapproval evidence generation, experts raised the need for a consistent regulatory policy related to postapproval evidence generation for all ADFs (branded and generic). Third, despite the public health benefits of certain ADF products, current coverage and access policies impede patient access. Payer justification for restrictive policies appears to be based more on budget impact considerations than cost-effectiveness. Fourth, there remains a need to further expand the evidence base regarding clinical and cost-effectiveness as well as abuse deterrence in a real-world setting for all ADF products.

Implications: Clinical development challenges need to be overcome with respect to novel ADF technologies, such as prodrugs and deterrents against oral abuse. More clarity is needed from regulatory authorities on labeling claims and data exclusivity eligibility with respect to ADFs. Ensuring prescriber training and awareness of various options for treating pain, including ADF products, is an important step, as is educating payers about the public health benefits of ADFs in appropriate subpopulations of pain patients. In addition, physicians may need to incorporate appropriate risk stratification methods. Finally, it is important to establish a level playing field between coverage of ADF and non-ADF products so that non-ADF products are not given preferred formulary placement. (*Clin Ther*. 2018;40:334–344)

Key words: opioids, abuse-deterrent formulations of opioid analgesics, chronic pain, drug development, payer reimbursement.

INTRODUCTION

Opioid abuse, misuse, and diversion are major public health concerns.* Overdoses attributed to prescription opioids, counterfeit opioids, and heroin continue to increase. In 2016, >33,000 opioid-related deaths were recorded (from licit and illicit opioids).[1] The aggregate medical and productivity loss costs associated with prescription opioid analgesic misuse, abuse, and diversion are estimated to be $78.5 billion annually.[2–5]

*Abuse is the intentional non-therapeutic use of a drug to achieve a desirable effect. Misuse is the intentional therapeutic use of a drug in an inappropriate way. Diversion is the intentional removal of a medication from legitimate distribution and dispensing channels.

Accepted for publication January 2, 2018.
https://doi.org/10.1016/j.clinthera.2018.01.003
0149-2918/$ - see front matter

The pharmaceutical industry is addressing this crisis through the development of abuse-deterrent formulations (ADFs) of opioid analgesics, addiction treatments, medications to treat opioid overdose, and development of nonopioid analgesic drugs. This commentary, based on a roundtable held in January 2017 at the Tufts Center for the Study of Drug Development, examines on the development, regulatory, and reimbursement challenges facing ADF products.

The goal of ADFs is to maintain effective pain relief while reducing the potential for abuse. This goal can be achieved by hindering extraction of the active ingredient, preventing administration through alternative routes or making abuse of the manipulated product less rewarding, and using extended-release (ER) methods or controlled delivery systems to provide pain relief to patients while deterring patients from abusing opioids by crushing, snorting, or injecting them.[6] The most common form of abuse is oral ingestion. Other methods of abuse include inhaling and injecting. Table I lists current ADF technologies.

Table II lists the 10 ADF products that have been approved thus far. Four ADF products have been launched. Note, 9 of 10 ADF approvals are ER formulations. The current regulatory framework is geared toward ER/long-acting rather than immediate-release (IR) ADFs.

There are 25 to 30 New Drug Applications of ADF products pending US Food and Drug Administration (FDA) review. Table III lists selected ADF products that are currently under FDA review, including several IR products.

METHODS

In January 2017, the Tufts Center for the Study of Drug Development convened a roundtable to explore clinical development, regulatory, and reimbursement challenges with respect to ADFs of opioid analgesics. Roundtable participants, who included a range of pharmaceutical industry and other experts, discussed multiple challenges. Below we report on roundtable proceedings and key findings from the discussion.

Table I. ADF technologies.

ADF Technology	Advantages	Limitations
Physical and chemical barriers	May prevent chewing, crushing, or extraction by solvents	Does not deter abuse of intact tablets
Agonist/antagonist combinations	Antagonist (eg, naloxone or naltrexone) may be formulated to be clinically active only when manipulated (crushing, chewing, or dissolving)	Does not deter abuse of intact tablets
Aversion	Aversive agents may be combined with the opioid to create unpleasant adverse effects	Potential for unpleasant adverse effects in adherent patients who take product as directed
Delivery system	Method of drug delivery can prevent abuse (eg, drug release design)	May still be possible to extract opioid from formulation
Prodrug: new molecular entity that lacks opioid activity until transformed in the gastrointestinal tract. This can deter intravenous injection or intranasal routes of abuse.	Properties of prodrugs would include different receptor bindings, and slower penetration into the central nervous system. This will cause a lack of opioid activity until in the gastrointestinal tract. This makes intravenous injection or intranasal routes less appealing.	Still possible to ingest too many oral doses

ADF = abuse-deterrent formulation.