Literature Review

Current Impact and Application of Abuse-Deterrent Opioid Formulations in Clinical Practice

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Background: Abuse-deterrent formulations (ADFs) represent one novel strategy for curbing the potential of opioid abuse.

Objective: We aim to compare and contrast the characteristics and applications of current abuse-deterrent opioid products in clinical practice.

Methods: Literature searches were conducted in databases (Pubmed Medline, International Pharmaceutical Abstracts, Google Scholar) and official reports. Relevant data were screened and organized into: 1) epidemiology of opioid abuse, 2) mitigation strategies for reducing opioid abuse, 3) development of ADFs, and 4) clinical experience with these formulations.

Results: Increasing trends of opioid abuse and misuse have been reported globally. There are 5 types of abuse-deterrent opioid products: physical chemical barrier, combined agonist/antagonist, sequestered aversive agent, prodrug, and novel delivery system. The advantages and disadvantages of the 5 options are discussed in this review. A total of 9 products with abuse-deterrent labels have been approved by the Food and Drug Administration (FDA). The rates of abuse, diversion, and overdose deaths of these new products are also discussed. A framework for collecting in-time data on the efficacy, benefit and risk ratio, and cost-effectiveness of these new products is suggested to facilitate their optimal use.

Limitations: The present review did not utilize systematic review standards or meta-analytic techniques, given the large heterogeneity of data and outcomes reviewed.

Conclusions: ADFs provide an option for inhibiting the abuse or misuse of oral opioid products by hindering extraction of the active ingredient, preventing alternative routes of administration, or causing aversion. Their relatively high costs, uncertain insurance policies, and limited data on pharmacoeconomics warrant collaborative monitoring and assessment by government agencies, pharmaceutical manufacturers, and data analysis services to define their therapeutic role in the future.

Key words: Opioid abuse, abuse-deterrent formulations, ADF, post-marketing, FDA guidance, cost impact, abuse liking, physician attitude, generic abuse-deterrent formulation, clinical application

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The development of strategies for the rational use of opioids has become an emergent need globally, in response to the escalating crisis of prescription opioid abuse and misuse. Prescription opioids are the second most prevalent type of abused medicine after marijuana (1). The opioid prescription volume increased 7-fold from 1997 to 2007 (2). The International Narcotics Control Board (INCB) revealed that almost two-thirds of opioid abusers obtain their pain analgesics from physicians (Fig. 1) (1-4). Similar

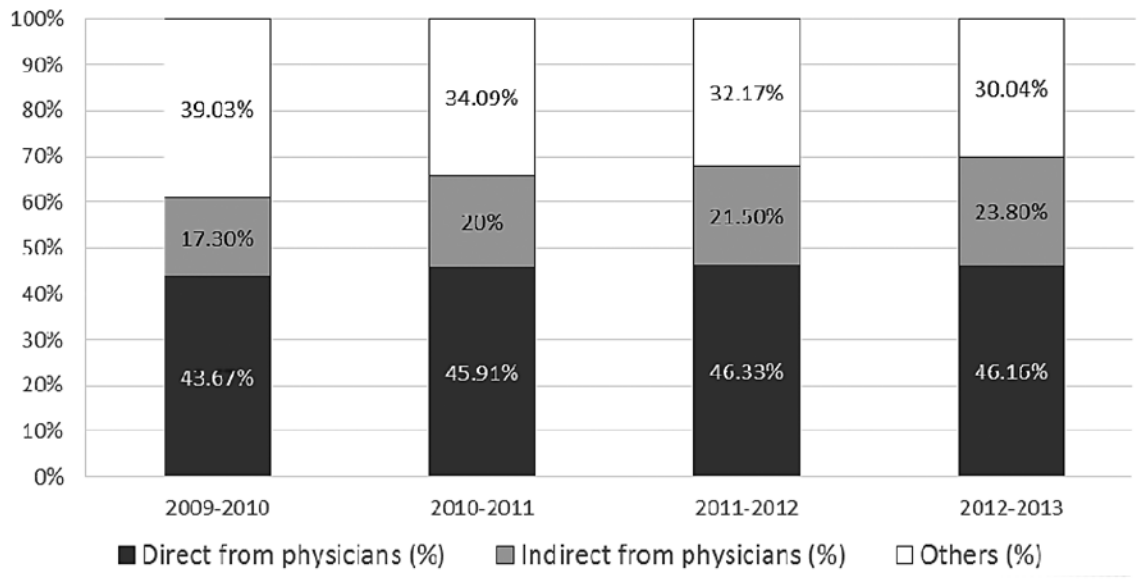

Fig. 1. *Annual sources for most recent nonmedical users aged 12 years or older obtaining pain relievers: 2009-2013 (1-4).*
The category of direct from physicians includes the sources where users obtained "From One or More physician;" the category of indirect from physicians includes free sources where friend/relative obtained "From One or More Physicians;" the others category includes the sources "Bought On Internet," "Drug Dealer/Stranger," "Bought/Took from Friend/Relative," "Free from Friend/Relative," "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

patterns of opioid abuse have been reported in Canada, Australia, Germany, Italy, Spain, and the United Kingdom (5-7). Innovative pharmaceutical formulations, proper coordination with multidisciplinary pain management, and well-designed continuum of care systems are essential to lessen trends of opioid abuse.

Abuse-deterrent formulations (ADFs) of opioids represent a major new strategy for combating the trend of increased illicit opioid prescriptions and overdose deaths. The abuse of immediate-release (IR) formulations generally involves over-ingestion of intact doses (8). Extended-release (ER) and sustained-release (SR) opioid analgesics were more frequently associated with abuse by crushing or dissolving in a liquid in the past (8-10). ADFs render the active drug less likely to be abused by 3 different mechanisms: 1) to impede the extraction of the active ingredient from the formulation, 2) to prevent administration of the drug by alternative routes, or 3) to make the manipulated product less attractive, less rewarding, or even aversive to those who might intend to misuse or abuse the product (11,12). The results of post-marketing surveillance suggest that the introduction of ADF opioids might reduce tampering with controlled-released formulations, while not totally preventing or eliminating the abuse of opioids by the oral route.

A lack of medication reconciliation puts patients who are treated by multiple physicians and doctor shoppers at a greater risk of opioid abuse (12). A national survey identified that among those using opioids for nonmedical purposes, 20% of individuals received opioids from more than one physician, while the remaining received opioids from their friends, family, drug dealers, or strangers (13). A 2008 US survey reported that the average "doctor shopper" obtained 32 opioid prescriptions from 10 different prescribers (14). In 2013, one state prescription drug monitoring program (PDMP) revealed that over half of the prescriptions were received by doctor shoppers, and hydrocodone was the most frequently prescribed medication associated with deaths (15). Opioid-involved treatment for non-malignant pain in the emergency department (ED) was reported to have a 1.8 times increase from 2000 to 2010 (27.4% to 48.9%, $P < 0.0001$) (16). These results highlight the need for effective policies to prevent opioid abuse across caregivers.

The purposes of this review are to analyze the trend in opioid abuse, compare and contrast different opioid mitigation policies and ADF products that have already been developed, and explore the applications, implications, and practical considerations of ADF therapy as an abuse-deterrent strategy.

Methods

Literature searches were conducted in databases (Pubmed Medline, International Pharmaceutical Abstracts, Google Scholar) and official reports. The searching keywords included: opioid analgesics, opioids/pain killer prescription, prevalence/epidemic/epidemiology of opioid illicit use/abuse/misuse, opioid overdose death/ED visit, social cost/burden of opioid abuse, sources of opioid abuse, abuse-deterrent/tamper-resistant technology, abuse-resistant, misuse prevention, agonist/antagonist, aversive, crush-resistant, abuse prodrug, transdermal delivery system, opioid abuse-deterrent, and clinicians/physicians attitudes/beliefs. Articles in English pertaining to opioid abuse and ADFs were identified, and relevant information was extracted and organized into 4 main categories: 1) epidemiology of opioid abuse, 2) mitigation strategies for reducing opioid abuse, 3) development of ADFs, and 4) clinical experience with ADFs.

Results

Epidemiology of Opioid Abuse

According to the National Survey on Drug Use and Health (NSDUH) and Centers for Disease Control and Prevention (CDC), the prevalence of opioid abuse is slightly higher in men (2.3%) than women (1.7%), and the rate of overdose deaths is 1.55 times greater for men (1,17). However, from 1999 to 2010, the rate of overdose deaths among women increased more rapidly than for men (17). The age of an individual and a prior history of substance abuse are also related. According to a 2013 national survey, one-percent of people aged over 65 years were reported to engage in illicit drug use, compared to 8.9% in the population aged 12 years and older (2). Furthermore, young adults aged 18 to 25 years had a higher rate of abuse (21.5%) than the 12 to 18 years age group (10.1%) (1). A prospective cohort survey revealed that in addition to younger age and male gender, factors that correlated with opioid misuse behavior were previous cocaine abuse (OR, 4.3), conviction for driving under the influence of drugs or alcohol (OR, 2.6), and a history of alcohol abuse (OR, 2.6) (18). Persistent high pain scores was not a predictor of misuse behavior.

The escalation of prescribed opioid abuse and misuse exerts a substantial economic burden on health care and adversely affects society. Approximately 75% of new heroin users were first addicted to opioid pain relievers (19). In 2016, the US economic burden that resulted from prescription opioid overdose, abuse, or dependence was estimated to be $78.5 billion, of which $28.9 billion can be attributed to health care and substance abuse treatment (20). A national report revealed that the prevalence of ED visits for opioid overdoses increased by 183% from 2004 to 2011 (21). A 2016 Morbidity and Mortality Weekly Report (MMWR) indicated that from 2000 to 2014, there was a 140% increase in drug overdose deaths, driven largely by opioids (22). In 2014, 61% of the 47,055 drug overdose deaths in the US involved opioids, representing a 14% increase from the previous year (22,23). Natural and semi-synthetic opioids, such as morphine, oxycodone, and hydrocodone have been associated with the highest rates of overdose mortality (22).

Strategies for Mitigating Opioid Abuse and Misuse

State and federal agencies continue to develop strategies aimed at stemming the growing trend of prescription opioid abuse (19,24). According to the US Department of Health and Human Services (HHS), efforts are focused on decreasing the prevalence of opioid use disorder, overdose events, and related mortality by targeting opioid prescribing practices and expanding the use of opioid antagonists or substitutions (25). The Food and Drug Administration (FDA) has taken a series of actions aimed at changing how opioids are approved, labeled, and prescribed (26,27). The FDA Opioids Action Plan, released in 2016, (1) expanded the use of advisory committees for opioid's new drug applications without abuse-deterrent properties, (2) enhanced IR opioid labeling to provide safe prescribing guidance, (3) strengthened post-marketing monitoring and reporting requirements with an emphasis on long-term analysis, (4) improved access to generic forms of ADFs, (5) enhanced opioid overdose treatment, including broadened access to naloxone, (6) updated the opioid-related requirements, and (7) reassessed the risk-benefit approval framework for the use of opioids (27). It is hoped that the ongoing implementation, assessment, and modification of these actions will have a major impact on reducing opioid abuse and misuse in the future.

Legislative Enforcement

Regulatory and legislative action have focused on rescheduling opioid analgesics, increasing the use of naloxone, and promoting more complete reporting of overdose events (25,28,29). In 2014, one of the most prescribed opioid analgesics, hydrocodone in combination, was rescheduled from schedule III to schedule II, thereby eliminating refills without a new, hand-written prescription (28,30). Legislation has been enacted to provide greater access to naloxone, an opioid antagonist, by allowing it to be distributed to opioid users, their families, friends, and even potential bystanders (25,31). Over 152,000 laypersons have received naloxone kits and been trained in the proper use of the drug, and more than 26,000 opioid overdose events were managed with naloxone from 1996 to 2014 (29,32). As of June 2016, legislation encouraging access to naloxone has been passed by 48 states in the US (33).

Good Samaritan laws are designed to encourage witnesses of potential overdose situations to contact emergency medical services (34,35). A survey of opioid users reported that up to 42% had witnessed an opioid overdose within the previous year, but 911 was called in only half of the incidents, possibly due to the fear of law enforcement action (29,34,36,37). Good Samaritan laws provide limited criminal immunity for bystanders, so as to encourage the summoning of emergency medical assistance in response to an overdose (19,29). As of April 2016, 35 states and the District of Columbia had enacted such a law, with varying scopes of criminal immunity (19,35); however, the impact remains unclear. A 2011 survey of 355 opioid abusers and 245 police officers in Washington revealed that only a third of opioid users and 16% of police were aware of the law, though 88% of opioid abusers responded that they would be more likely to request EMS assistance in the future due to the protections offered (36).

Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMPs) are state-by-state electronic databases of controlled substance prescriptions to detect doctor- or pharmacy-shopping behaviors, with different selected controlled substances (25,38-40). In 36 states that have enacted PDMPs, when patients exceed an established threshold for a targeted substance, a series of actions are triggered to notify prescribers, pharmacies, and patients to initiate a law enforcement investigation (24,41). PDMPs enable physicians to base their decisions on an accurate portrayal of the patient's drug use, rather than having to rely solely on the patient's explanation (14). The programs are reportedly associated with less opioid abuse and higher rates of opioid treatment admissions (42). As of October 2016, every state but Missouri had established a PDMP, though the inability to share information between states remains a limitation (19,39-41).

Risk Evaluation and Mitigation Strategies

The FDA Amendments Act, which was passed into law in 2007, led to the FDA requiring opioid manufacturers to establish Risk Evaluation and Mitigation Strategies (REMS) to optimize the benefit vs. risk of prescription opioids (43). In July 2012, the FDA mandated a new REMS requirement for manufacturers to provide continuing education about the risks and benefits of ER/long-acting (LA) opioids to prescribers (9,27,44). There is concern, however, that the REMS requirements could dissuade some physicians from prescribing opioids for patients with a legitimate need for pain management, simply to avoid the REMS training requirement (45-47). After the REMS program was launched, a paucity of the carryover persisted. One report indicated that 13.4% of 259 physicians surveyed would consider discontinuing the practice of prescribing an opioid if forced to complete the continuing education (46). A careful examination of REMS training expectations seems warranted (9,47,48).

Development of ADFs

The development of ADFs has provided prescribing options to discourage abuse (11). ADFs are therapeutically equivalent to the original formulation in terms of release rate, dose, chemical stability, clinical efficacy, and safety, while incorporating abuse-deterrent effects (49,50). Ideally, an opioid ADF might also function by mitigating the severity of medical consequences that result from misuse (Table 1, Table 2) (51).

Consideration of Formulation and Routes of Administration

Understanding opioid abuser preferences of route of administration can help to develop suitable ADFs. The leading routes of administration for opioid abuse are ingestion (both chewing and swallowing intact), inhalation (snorting, inhaling, or smoking), and injection (intravenous (IV), intramuscular, or subcutaneous) (8,52,53). According to US data from 2002 to 2012, oral ingestion was the most prevalent route of administration (59%), with 21% administered via inhalation and 17% via injection of the drug after manipulation (54).

Table 1. *Potential of various types of ADF mechanisms to deter abuse or misuse based on the route of administration* (10,11).*

Type of ADF	Ingestion multi-intact dose	Ingestion by manipulation	Inhalation	Injection
Physical and chemical barriers	—	X	X	X
Agonist/ antagonist	—	X (naltrexone)	X (naltrexone)	X (naltrexone, naloxone)
Aversion	X (niacin, emetic)	X (bitter agent, dye, mucous membrane irritants)	X (mucous membrane irritants)	X (mucous membrane irritants)
Prodrug	X	X	X	X
Delivery system	—	X	X	X

*This table is intended to demonstrate the potential on deterring different routes of abuse and misuse according to the type of ADF, depending upon the mechanism of the formulation. "X" indicates potential benefit, and "—" indicates little or no potential benefit, in terms of deterring abuse and misuse.

Table 2. *Advantages and disadvantages of different types of ADFs (66,111).*

Type of ADF	Advantages	Disadvantages
Physical and chemical barriers	1) Potential to prevent abuse routes requiring manipulation 2) No risk of adverse events for users 3) Benefit to prevent patients from misuse 4) Formulations in microsphere can be benefit for patients with difficulty in swallowing	1) Not able to deter swallowing multiple intact doses 2) Potential teeth breaking from excessive bite force 3) Crush-resistant tablets may not be suitable for dysphagia or phagophobia patients with needs to cut or crush tablets
Agonist/ antagonist	1) Potential to deter euphoric effect with routes requiring manipulation 2) Active neutralizing effect only when manipulated	1) Not able to deter swallowing multiple intact dose 2) Decrease efficacy and risk in causing withdrawal symptoms to compliant patients if misuse
Aversion	1) Prevent abuse by crushing or chewing 2) Potential to deter swallowing multiple intact dose	1) Deterrence effect may be limited for those abusers rather enduring the physical discomfort of aversive agents to reach goal 2) Potential risk of compliant patients with need to cut or crush tablets in unwanted aversive effects 3) Potential risk of patients with a legitimate need in taking higher doses to compensate the tolerance in unwanted aversive effects
Prodrug	1) Limit the non-oral routes (e.g., IV and intranasal) of abuse through the required activation process by GI enzymatic cleavage 2) Potential to deter swallowing multiple intact dose	1) No current available products of opioid analgesics
Delivery system	1) Offer resistance and increasing difficulty in intention to abuse	1) Possible to extract the opioid ingredient form the formulation by motivated abusers

Methods of manipulation include crushing or grinding into a powder or small particles, dissolving in a solvent such as alcohol or water, or extraction via exposure to hot or cold temperatures (8). In a survey of experienced abusers, the major factors affecting preference included formulation, availability, ease of extraction, onset of action, and duration of effect (55).

The route of administration might also be influenced by patient factors, such as duration of abuse, age, and geographic location (51,56,57). Less experienced or young abusers prefer the oral route, with the prevalence of non-oral administration increasing with the duration of abuse (8,56). The most common route of administration for experienced abusers was inhalation (62.4%), followed by IV (25.6%) and oral ingestion (14.3%) (56). Geographic location and active ingredients of opioids can also influence the route of abuse (51,58). A study of 212 recreational prescription drug abusers showed ingestion to be the preferred route in urban areas, in contrast to an inhalation preference in rural areas (51). Preferred routes of administration also vary by opioid. A retrospective survey of 59,792 patients enrolled in abuse treatment programs demonstrated that hydrocodone, oxycodone, and oxymorphone were more likely to be abused by inhalation, whereas hydromorphone and morphine were more prone to be abused by injection (58). However, opioid abusers often utilize multiple routes of administration to achieve

euphoria, thereby exacerbating the medical outcome beyond what would be expected from the direct effects of the drug (8,53,59).

Regulation of ADFs

The FDA announced requirements to be met when labeling ADF opioid products in 2015 (60). Health Canada also issued guidance for tamper-resistant formulations of opioid products, which include the same 4 categories of testing as the FDA. Category one includes laboratory-based in vitro manipulation and extraction studies to demonstrate a significant decrease in the ability to tamper with the product; category 2 includes pharmacokinetic studies to ensure that the deterrent feature adversely affects absorption, distribution, or elimination; category 3 includes clinical abuse potential studies to assess the product's attractiveness to abusers; category 4 includes post-marketing epidemiology studies to determine the impact of marketed products in reducing abuse-related adverse clinical outcomes in practice (60,61). Nine opioid ADF products have been approved by the FDA as of January 2016, with more than 30 ADF products in various phases of development (62-64).

ADFs that Contain Physical or Chemical Barriers

Some ADFs rely on physical or chemical barriers to resist extraction of the active drug by water or organic solvents, thereby limiting abuse by mechanical manipulation techniques, such as chewing, crushing, cutting, grinding, snorting, or injecting (10-11,60). Examples of physical or chemical barriers include crush-resistant pills, waxed-combined microspheres, and high-viscosity gelatin capsules (65). These products pose little risk of adverse consequences, but do not serve as effective deterrents for abusers who tend to swallow multiple intact doses (11,66). Likewise, some barrier products are not suitable for patients with dysphagia or phagophobia, who have a legitimate need to crush or chew tablets (66).

ER oxycodone (OxyContin, Purdue Pharma LP, Stamford, CT) was reformulated in a polymer matrix, which makes tampering by chewing or crushing difficult. It also forms into a viscous gel when extracted to prevent intravenous injection (67). Although the high-dosage strength and potency of reformulated OxyContin make it potentially attractive to abusers, the peak plasma concentrations of this ADF product are lower and more delayed, rendering it less desirable to recreational abusers than the original ER oxycodone formulations (68,69). This new formulation received FDA approval and replaced the original ER oxycodone in 2010. It was subsequently granted ADF status by the FDA in 2013 (70). In the first 11 months after being released, post-marketing data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) showed a 49% (95% CI: 46-53%) decline of ER oxycodone abuse by any administration route (from 24% to 12%) (71).

HYDER (Hysingla, Purdue Pharma LP, Stamford, CT) is an ER form of oxycodone bitartrate that applies RESISTECTM technology to form a combined polymer that enhances tablet hardness and increases viscosity when dissolved in aqueous solutions (72). Two phase III and 2 post-hoc analysis studies have demonstrated its efficacy and safety in patient cohorts that had previously received hydrocodone/acetaminophen or ER morphine for chronic pain (73-76). HYDER deters abuse via chewing, snorting, or injection (8,72). A randomized, double-blind, placebo-controlled study performed in recreational opioid abusers who relied on intranasal administration demonstrated that HYDER (both fine and coarsely crushed) produced a lower mean hydrocodone C_{max}, a longer T_{max}, and a significantly lower favorability score of intranasal use compared to IR hydrocodone powder (65.4 versus 90.4, $P < 0.001$) (77). HYDER was approved as an ADF in November 2014 (78). Post-marketing studies of HYDER are scheduled for completion in 2018 (79).

A novel ER tablet of morphine (Morphine ARER; MorphaBond, Inspirion Delivery Technologies, LLC, Valley Cottage, NY) contains inactive ingredients that inhibit physical manipulation or chemical extraction, while maintaining ER characteristics (80). Unpublished laboratory testing of Morphine ARER confirms the product's resistance to tampering via cutting, crushing, and breaking. A viscous material forms after the tablet is subjected to liquid, preventing passage through a needle (80). Compared to ER morphine sulfate, Morphine ARER produced lower mean scores for drug favorability and a decreased potential for intranasal abuse (81). Morphine ARER was approved in October 2015 as the first ER morphine without an antagonist, but as of August 2016, it had not been marketed (8,82).

A new oxycodone ADF approved in April 2016, (Xtampza ER, Collegium Pharmaceuticals, Inc., Canton, MA) is formulated using DETERx® microsphere-in-capsule technology (65,83). When the microspheres are melted or dissolved, they combine with fatty acids and waxes in the capsule, thus preventing abuse by chewing, crush-

ing, insufflation, or extraction for IV injection (82). The product demonstrated superior pain relief in a phase III, enriched enrollment randomized withdrawal study to compare opioid-naïve (defined as taking 0–10 mg/d morphine sulfate equivalent (MME) for more than 2 weeks) and opioid-experienced adults (those who once received 30–240 MME for more than 2 weeks) for moderate-to-severe chronic low back pain (0.29 versus 1.85 in pain intensity score, $P < 0.0001$), compared to active placebo (84). It should be noted, however, that Xtampza ER must be administered with food (83). Its absorption increases in the presence of a high-fat meal (85,86).

The FDA has approved 2 more ADFs with physical/chemical barrier properties in January, 2017: Arymo ER (Egalet Corporation, Wayne, PA) and Vantrela ER (Teva Pharmaceutical Industries, Ltd. USA, North Wales, PA) (87-88). Both of them are indicated for the management of severe pain. Arymo contains morphine sulfate and Vantrela consists of hydrocodone bitartrate in ER dosage forms (64,87,88).

It should be noted that the approach of physical and chemical barriers can be applied to multiple, as well as single, ingredient products. A fixed-dose combination product of oxycodone and acetaminophen (Xartemis XR, Mallinckrodt Pharmaceuticals, St. Louis, MO) is an example indicated for acute pain management in an IR/ER formulation (89). The polyethylene oxide (PolyOx) inactive ingredient transforms the tablet into an unpalatable, gelatinous mixture, resulting in difficult extraction for injection and other intentional use (90). Moreover, with the biphasic-layered matrix design, the combination formulation contains a relatively small amount of opioid (7.5 mg oxycodone/tablet), making it less attractive for abuse (91).

ADFs that Combine an Agonist and Antagonist

The functionality of a formulation that combines an opioid agonist with an antagonist is derived from the sequestration of the antagonist, such that it does not become active to neutralize the agonist unless the product is manipulated for illicit use (66). Naloxone and naltrexone are the 2 antagonists used in ADFs. Naltrexone, being more bioavailable than naloxone, offers the additional advantage of deterring misuse via chewing or snorting (10,11). Antagonizing the pharmacologic effect of the active ingredient opioid tends to neutralize the euphoric effect when tampered in a way that activates the antagonist (51). The drawback of such ADFs is that there is no deterrent effect when intact tablets or capsules are swallowed (66). These products also carry the risk of precipitating withdrawal symptoms due to misuse or manipulation. Accidental chewing might also precipitate withdrawal symptoms and reduce analgesic efficacy in compliant individuals (92,93).

Targiniq ER (Purdue Pharma LP, Stamford, CT) is an ADF that contains ER oxycodone and naloxone in a fixed 2:1 ratio (8,94). Three randomized, double-blind phase III studies have demonstrated its efficacy and safety after 12 weeks in patients with moderate to severe, chronic, non-malignant pain (94). Despite having only about 3% oral bioavailability, a clinical abuse study of 29 opioid-dependent individuals demonstrated a deterrent effect when the product was chewed or swallowed intact. Two studies of intranasal and IV injection in opioid nondependent individuals, also showed significantly lower mean scores of drug favorability compared to hydrocodone HCl ($P < 0.001$) (94,95). Targiniq ER was approved in July 2014, but it is not yet available on the market (95).

Embeda (Pfizer Inc., New York City, NY) is an ER pellet formulation of morphine sulfate with a core of sequestered naltrexone (96,97). In clinical abuse studies of nondependent opioid abusers, it had significantly lower "drug liking" and "drug high" scores than morphine without naltrexone, whether administered orally, intranasally, or intravenously (98,99). Initial approval of the product was in 2009, but due to several reported cases of acute withdrawal syndrome and concerns about its stability, the manufacturer voluntarily recalled it in March 2011 (92-93,100). A reformulated ER morphine/naltrexone was approved in October 2014 and the new product was relaunched in the US in 2015 (100). A phase 4 clinical trial (NCT02101554) is being conducted and will be completed in 2019 (101).

In August 2016, a combination product of oxycodone and naltrexone (Troxyca ER, Pfizer Inc., New York City, NY) was approved by the FDA with ADF labeling (102). Designed in capsules containing pellets with oxycodone hydrochloride that are surrounded by naltrexone hydrochloride, the effect of oxycodone will be counteracted by sequestered naltrexone if the capsules are crushed (103). As the third ADF combining an agonist and antagonist, Troxyca ER is expected to reduce abuse when crushed and administered by the oral and intranasal routes. However, caution should be raised that abuse of Troxyca ER by these routes is still possible (103).

ADFs that Contain Sequestered Aversive Agents

ADFs with aversion technology allow noxious compounds mixed with opioid to induce unpleasant

effects when the product is manipulated or multiple doses are consumed (10,66). Aversive agents used in ADFs include niacin, emetics, bitter agents, and dyes, as well as mucous membrane irritants to deter snorting, inhalation, and parenteral administration (10,104-106). The aversive effects produce a lower dosage ceiling, discouraging abusers from taking larger doses (66). Nevertheless, the effectiveness of these ADF opioids remains questionable. Observation studies suggest that abusers might endure the unpleasantness of physical discomfort in order to reach a state of euphoria (66). The flushing effect of niacin could be relieved by food, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs) (107). The new drug application of an IR oxycodone HCl product with both niacin and sodium lauryl sulfate (Acurox, Acura Pharmaceuticals Inc., Palatine, IL) was rejected by the FDA in 2010 due to this concern. Furthermore, patients with swallowing difficulty might inadvertently be subjected to aversive effects from cutting or crushing tablets (11,66). A similar circumstance could occur for patients who legitimately require larger analgesic doses (106).

None of the currently approved opioid ADFs that apply aversion technology have received FDA approval for ADF labeling. IR oxycodone HCl tablets (Oxaydo, Egalet Corporation, Wayne, PA) was first approved in June 2011 under the trade name of Oxecta from Pfizer (108). This formulation incorporates sodium lauryl sulfate to generate mucous membrane irritation when the product is chewed or inhaled (109,110). A randomized, double-blind, active-controlled cohort with histories of intranasal oxycodone abuse showed significantly decreased drug favorability (47.8 vs 87.4, $P < 0.0001$) and desire to take the drug again (45.9 vs 91.3, $P < 0.0001$) than the traditional IR oxycodone formulation (70). However, aversive IR oxycodone was associated with a greater occurrence of nasopharyngeal and facial adverse effects (70).

ADFs that are Prodrugs

Prodrug ADFs contain inactive precursors that must be biochemically converted into an active form in vivo (111). Requiring biotransformation in the gastrointestinal tract can prevent abuse by inhalation (insufflation, intranasal, snorting), injection, chewing/crushing, or taking extra doses (11,51,111). Saturation of metabolic enzymes inhibits the rate of biotransformation when a large dose is taken, resulting in a reduction in maximum euphoria, along with a reduced risk of overdose symptoms, such as respiratory depression (11).

Benzhydrocodone hydrochloride (KP201), a chemical prodrug of hydrocodone, has a covalent benzoic acid group attached. It was developed by KemPharm (KemPharm Inc., Coralville, IA) in combination with acetaminophen (KP201/APAP) as a potential ADF (112). KP201, which utilizes ligand-activated therapy (LAT), is only activated by gastrointestinal enzymes that cleave the ligand from hydrocodone to release the active ingredient (113). The safety and tolerability of KP201 was tested in healthy individuals and confirmed by a group of opioid-naïve subjects (patients who are not chronically receiving opioid analgesics on a daily basis) in clinical studies (114,115). Three human clinical abuse potential studies showed that KP201/APAP produced a significantly lower C_{max}, a delay in T_{max}, a decreased total exposure to hydrocodone, and a lower incidence of hypoxia at high doses, as compared to a hydrocodone bitartrate and APAP combination for both intranasal and oral administration (112,116). The manufacturer received new drug application approval and priority review from the FDA in February 2016 (117). If approved, KP201/APAP could become the first IR hydrocodone combination product with ADF properties to be released on the market.

ADFs with Novel Delivery Systems

Another potential strategy for deterring opioid abuse is the development of new delivery systems, such as subcutaneous implants and depot injections that provide sustained and gradual opioid release (51,60). One example is the buprenorphine transdermal delivery system (BTDS; Butrans, Purdue Pharma LP, Stamford, CT) (118). The high affinity for the μ-receptor and partial agonist properties make buprenorphine a suitable opioid choice as an agent for abuse deterrence (119). Evidence from 5 programs in the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) system showed the lowest rates of abuse and diversion for BTDS, compared to other forms of buprenorphine, fentanyl patches, ER opioid formulations, and ER tramadol (120).

Implants could be used to treat patients with comorbid chronic pain and substance abuse, which accounts for 32% of chronic pain patients who require prescription opioids (11,18). The first subdermal implant of buprenorphine (Probuphine, Titan Pharmaceuticals, San Francisco, CA) was approved by the FDA in May 2016 for the maintenance treatment of opioid dependence (121). This product provides continuous low dosing of buprenorphine for up to 6 months, obviating the need

for daily medication and safeguarding against illicit drug use (121-123). Pharmacokinetic data suggests that implant buprenorphine produces lower peak plasma concentrations than sublingual administration (123). A small study of heroin-dependent abusers showed that implant buprenorphine resulted in fewer positive urine tests for opioids, less withdrawal symptoms, and fewer craving events after 6 months (124). An unpublished phase III trial demonstrated after 6 months that implant buprenorphine was non-inferior to sublingual buprenorphine/naloxone in maintaining clinical stability, with no evidence of illicit opioid use (63.2% versus 53.9%, $P = 0.21$) (125). Despite the promising potential of implant buprenorphine, a monthly cost of about $1,000 may discourage widespread use (126).

Experience with ADFs

Measuring the clinical and economic outcomes of ADF products is essential to better define the future role of opioid ADFs in clinical practice (62). Recruiting recreational opioid abusers for clinical studies can confound the results, as the effects of the product to reduce abuse-liking under a research setting might not accurately reflect the effectiveness among a "real-life" population (49). Therefore, post-marketing surveillance data in real users is critical to adequately assess the utility of opioid ADFs, as well as their economic impact.

Post-Marketing Data

A growing body of post-marketing evidence supports the contention that the use of opioid ADFs reduces rates of abuse without sacrificing safe, effective pain management (71,127-131). The efficacy and safety of ADFs for morphine sulfate and naltrexone HCl ER, oxycodone HCl controlled-release, and oxycodone HCl ER have been studied in systemic reviews and meta-analyses, and both ADF (-0.21; 95% CI -0.35 to -0.07) and non-ADF (-0.59; 95% CI -0.94 to -0.24) were found to be superior for efficacy, but no direct comparison was made of ADF to non-ADF for pain relief, compared to placebo (127). Overdose deaths associated with abuse-related behavior has decreased to 86% (95% CI:-92, -75) during the 3-year period following the release of reformulated ER oxycodone (128). A large observational study of over 140,000 individuals undergoing substance abuse treatment showed that reformulated ER oxycodone significantly decreased the prevalence of past-30-day abuse to 41% (95% CI: -44 to -37), as compared to the original formulation (129). Similar results were reported in a 2014 prospective study in Australia that included 552 individuals, of which 81% had a recent history of oxycodone abuse (130). The 3-month rate of abuse with this product was found to be 12%. It should be noted, however, that confounding effects from other abuse reduction strategies cannot be excluded (62,128).

The use of ADFs in clinical practice warrants the consideration of some limitations. First, their use in deterring the swallowing of multiple intact doses, the most common abuse route, has not yet proven successful. To date, the primary mechanism of ADFs is to increase difficulty in product manipulation and administration via different routes (132). The properties of ADFs produce a reduced risk of abuse rather than the elimination of risk. Furthermore, experience with reformulated ER oxycodone has shown that ADF properties can be overcome when using the oral route, illustrating that the effectiveness of ADFs in deterring abuse behaviors is limited (133).

The availability of an ADF for one opioid might cause abusers to shift their use to different prescription products or even to heroin (71,131,134,135). In 2010, during the first 11 months after the introduction of reformulated ER oxycodone, abuse with ER oxymorphone increased 139% (95% CI: 102-183%) (71). A large cross-sectional study among 33 states showed no significant decrease in overall abuse, but significant increases in abuse of both oxymorphone ER (RR 2.91, 95% CI 1.29-1.64) and buprenorphine (RR 1.85, 95% CI 1.74-1.96) after the introduction of reformulated ER oxycodone (131). A 2015 survey from the RADARS System indicated an increasing prevalence of heroin abuse, along with decreased abuse trends of reformulated ER oxycodone (134).

Physician Attitudes toward ADFs

Continuing education in pain management and the dissemination of information to physicians about the potential benefits and availability of ADF opioids is important to maximize the benefits of these products. A 2009 survey reported that primary care physicians account for 42% of IR and 44% of ER/LA opioid prescriptions (136). Turk et al (137) conducted a cross-sectional survey of a nationally representative sample of 1,535 practicing physicians using the Clinician's Attitudes about Opioids Scale (CAOS) questionnaire. Five factors (impediments, effectiveness, education, schedule of opioids, and tamper-resistant formulations and dosing of ADF) were used to predict physician acceptance and the likelihood of prescribing an ADF opioid (138).

Table 3. *Comparative cost of 30-days of ADF opioid treatment with an equivalent dosing regimen (67,78,82,83,87,88,95,99,102,181-183).*

Trade Name	OxyContin®	Targiniq® ER	Embeda®	Hysingla™ ER	MorphaBond™	Xtampza™ ER	Troxyca® ER	Arymo™ ER	Vantrela™ ER
Active Ingredient	Oxycodone HCl	Oxycodone HCl/ naloxone HCl	Morphine sulfate/ naltrexone	Hydrocodone bitartrate	Morphine sulfate pentahydrate	Oxycodone base	Oxycodone HCl / naltrexone HCl	Morphine sulfate	Hydrocodone bitartrate
Manufacturer	Purdue Pharma LP	Purdue Pharma LP	Pfizer Inc.	Purdue Pharma LP	Inspirion Delivery Technologies LLC	Collegium Pharmaceuticals	Pfizer Inc.	Egalet Corporation	Teva pharmaceutical
Final Approval	2010	2014	2014	2014	2015	2016	2016	2017	2017
Dosage Form	ER tablet	ER tablet	ER capsule	ER tablet	ER tablet	ER capsule	ER capsule	ER tablet	ER tablet
Category of ADF	Physical/ chemical barrier	Agonist/ antagonist	Agonist/ antagonist	Physical/ chemical barrier	Physical/chemical barrier	Physical/chemical barrier	Agonist/ antagonist	Physical/chemical barrier	Physical/ chemical barrier
Dosing Regimen§	10 mg/BID	10 mg/5 mg BID	20 mg/0.8 mg QD	20 mg QD	15 mg BID	9 mg BID with food	10 mg/1.2 mg BID	15 mg BID or TID	15 mg BID
Cost/30-Day#	$183.92	N/A*	$178.48	$215.83	N/A*	$202.2	N/A*	N/A*	N/A*

Abbreviations: ADF = abuse-deterrent formulation; ER = extended-release;
§ The smallest recommended initial dosing regimen for opioid-naive and opioid non-tolerant patients.
* Wholesaler acquisition cost (WAC) price corresponded to the recommended initial dosing strength. Data obtained from. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers. As of January 2017, 5 out of 9 products with approved ADF labelling have not yet been marketed.
# Approximate cost for 30 day's treatment at the recommended initiate dosing regimen for opioid-naive and opioid non-tolerant patients.
Cost for IR Oxycodone 5 mg QID is $30.09.

Results showed that major predictors of physician willingness to prescribe ADFs were believing in the effectiveness of opioids (B = 0.43, $P < 0.001$), concern about diversion of opioids and impediments to use (B = 0.22, $P < 0.001$), percentage of chronic non-cancer pain patients prescribed opioid analgesics (B = 0.1, $P < 0.001$), being board certified in pain medicine (B = 0.05, $P < 0.05$), and being satisfied with training and education in pain management (B = 0.05, $P < 0.05$) (137).

Economic Impact of ADFs

Careful consideration of prescribing options may maximize the cost-benefit ratio of ADF products. The high costs of brand ADF opioids might not be justifiable for patients with low-abuse risk (49,137). It is estimated that the average additional cost for ADF opioid prescriptions would be in the range of about $600 – $2,800 per month (Table 3) (139). However, cost savings of reformulated ER oxycodone was realized from significant reductions in opioid abuse, with an estimated annual medical cost savings of $430 in the US (140). In another study, Kirson et al (141) estimated $1.035 billion annual cost savings associated with reformulated ER oxycodone, stemming from the combination of direct medical cost savings ($33 million) and indirect cost savings of $1 billion, which include costs associated with the workplace, criminal justice, and caregiving. In contrast, greater Medicaid health care expenditures were noted in 2013 and 2014 for patients prescribed ADF opioid prescriptions than traditional products ($24,979 vs. $15,043 per patient, $P < 0.01$), but there was no significant difference in the number of ED visits between the formulations (142). The economic impact can be further clarified by considering overall health care expenditures and the cost impact of patients shifting to other opioids, as well as the careful selection of patients in need of ADF products.

State Legislation Regarding ADFs

Some state legislatures have explored legislative support for ADF implementation as a means of curbing the rising trend of opioid abuse (143). The goal of such legislation is to ensure that patients have access to ADF opioid products by overcoming barriers to ADF prescribing (49,144-146). States such as Massachusetts, Maryland, and Florida have passed legislation to ensure insurance coverage of

opioid ADFs with limited cost-sharing responsibilities for patients (146-150). Other states are considering bills to assess the effect of ADFs and the potential adoption of legislation to require insurance coverage. As of May 2016, there were about 30 ADF bills pending among 20 states (146).

Market Challenge and the Future of Generic ADFs

The market share of reformulated ER oxycodone accounted for only 25% of ER/LA opioids in 2014, and ER/LA opioids accounted for about 10% (63). The low market share indicates the need for generic ADFs (8,145). In March 2016, the FDA launched a drafted guidance for the industry to evaluate the abuse deterrence of generic opioid drug products. Recommendations include conducting comparative in vitro studies to demonstrate non-inferiority or superiority of generic ADF opioid products in comparison to reference listed drugs (RLD) (151,152). To apply for an abbreviated new drug application (ANDA), a sponsor is required to propose bioequivalence to the RLD in terms of active ingredient(s), dosage form, routes of administration, strength, and labeling. The drafted guidance also provides more detailed requirements about routes of abuse, comparative in vitro studies, and other factors to consider regarding abuse-deterrent generic opioids (151). With the high expectations of cost containment and abuse reduction that go along with the development of generic ADF products, a rigorous process of evaluating applications and analyzing post-marketing data is warranted.

Oversight and Monitoring of ADFs

The benefits and risks of ADF opioids need to be assessed from the perspective of practical applications and actual efficacies in clinical practice, within the context of multi-faceted strategies to combat opioid abuse. The high costs of ADFs and the limited amount of post-marketing data further complicate the process of assessing their role in therapy (7,49,62). Governments, insurance agencies, and manufacturers have leading roles in the development and marketing of new ADF products (Fig. 2). Quality, efficacy, and safety standards, as well as proper labeling of brand and generic ADF products are crucial responsibilities of regulatory agencies and pharmaceutical companies. Adequate insurance coverage and reasonable product pricing are also important issues.

Big data analysis is an important factor in the systemic control of ADF products. In-time referral and adverse data reporting to government agencies or big data analyzing services provide direct evidence of market patterns. Studies that assess abuse-deterrence efficacy, product safety, cost-effectiveness, and pharmacoeconomic impact can provide useful data upon which to base adjustments in reimbursement, pricing policies, and practice guidelines. Aside from manufacturers, which are responsible for post-marketing reporting, such as periodic safety update reports (PSUR), academic researchers, professional associations, or government surveillance agencies might also evaluate the outcomes produced by ADF products. One such example is the Narcotics Information Management System (NIMS) in Korea (153). Overall, results from post-marketing surveillance should be integrated into ADF pricing structures, reimbursement policies, and practice guidelines to optimize the therapeutic benefit and reduce trends of opioid abuse.

Discussion

Factors to Consider When Prescribing ADFs

The manner in which ADFs are utilized in clinical practice will impact the success of this formulation-based strategy in combatting the opioid epidemic. Generally, prescribing an ADF for every patient with legitimate need optimizes the level of protection and minimizes potential resistance, thereby increasing the likelihood that abuse trends will be mitigated (66,138). However, high costs and risks of adverse events may discourage the widespread use of ADFs (11,49). Below are factors of benefit versus risk to consider when prescribing ADFs in current practice.

Analyzing the Potential Risk of Abuse

To deter opioid abuse in clinical practice, the first step is to classify patients according to each individual's risk of abuse (154). Understanding drug-taking behavior can be helpful in the diagnosis of addiction and should be assessed before making a decision to prescribe an opioid. Tools for assessing the potential for abuse, such as the Current Opioid Misuse Measure (COMM), have been validated in specialty pain management patients for identifying the degree of abuse-related behavior relating to opioid pain management (155). A 24-item self-administered screening tool, the Screener and Opioid Assessment for Patients with Pain (SOAPP), is a validated device with sufficient sensitivity and specificity to predict the risk of future drug-related behaviors among patients with chronic pain, 6 months

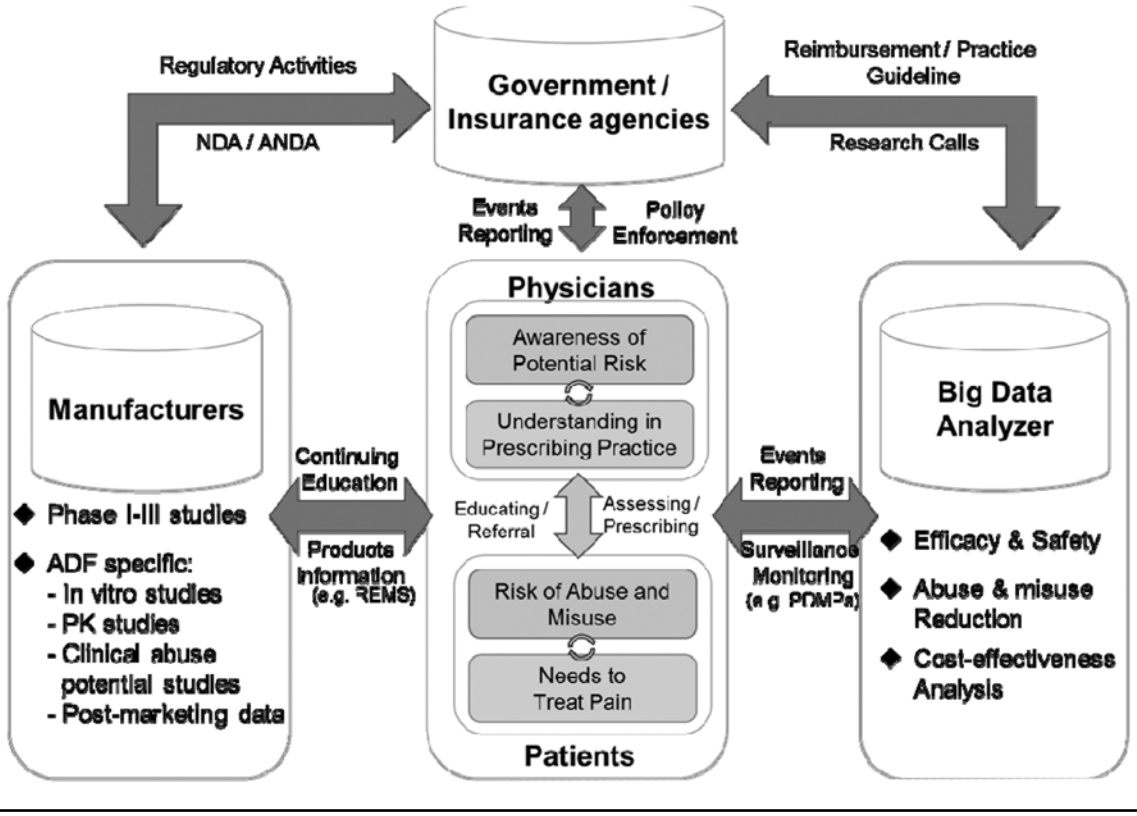

Fig. 2. *Framework and roles of managing ADF strategy in the health care system.*

after screening (156). Another risk assessment method, the Opioid Risk Tool (ORT), also demonstrates a high sensitivity and specificity for determining the probability that opioid patients will display aberrant behavior (157). Compared to the SOAPP, the ORT is simplified but may be less comprehensive when assessing patients who are at high-risk for abuse (154).

Behaviors suggestive of possible opioid abuse or addiction include compulsive opioid use with impaired control, disregarding the adverse consequences of abuse, and opioid craving (158). Additional aberrant drug-taking behaviors reported by pain management physicians include selling and forging prescriptions, consuming drugs by a route other than as prescribed, tampering with the delivery system, concurrent abuse of related illicit drugs, obtaining drugs via theft or manipulation, frequently reported prescription losses, unsanctioned dosing, and insistent demands for more drugs (159). Nevertheless, it is difficult to diagnose opioid abuse by merely observing patient behaviors. In some cases, behavior can be misinterpreted as being related to addiction when the patient is suffering from inadequately treated pain or manifests signs of a cognitive or psychiatric disorder (50,160). In such circumstances, confirmatory urine toxicology testing focusing on 5 substance categories (marijuana, cocaine, opiates, phencyclidine, amphetamines) can serve as an objective and reliable tool with which to detect abuse potential (161,162). Confirmation of urine drug testing was reported to reduce possible substance abuse and diversion in opioid patients by up to 50% and has been recommended as standard practice for patients requiring long-term pain treatment, though some physicians find it difficult to interpret the results of a confirmatory urine drug test (163,164). Misleading interpretations of a urine drug test can involve either false-negatives (lack of drug detection) or false-positives (e.g., detection of a metabolite of codeine) (161).

The potential for opioid abuse or drug-taking behavior might also be predicted by considering the

potential attraction of a particular prescription (55). Butler et al (55) used the Opioid Attractiveness Technology Scaling (OATS) as a tool to demonstrate the attractiveness to abuse of an opioid prescription. Factors on the scale include abuse liability of various compounds, formulation and availability of the drug, ease of extraction, rapid onset, and duration of the effect. Other relevant factors include cost, media attention toward a specific drug, and peer preferences (55). By estimating the likely attractiveness of a new ADF product, assessment tools such as OATS can be used to better predict the effectiveness of the product before it is brought to market (165). However, further study is warranted to ensure the validity of such abuse potential assessment tools.

Physicians should also be cognizant of the possibility that addressing abuse potential concerns or acting on suspicions of abuse can harm the clinician-patient relationship (166). Patients might feel that they are being unfairly or inappropriately stigmatized as drug abusers when the physician is merely assessing abuse potential (167). Therefore, efforts should be made by healthcare professionals to build honest and positive relationships with their patients and carefully explain the risks of opioid abuse and the steps that must be taken with all patients to minimize the risks. Patients need to understand their responsibilities, which could involve a signed opioid agreement with the clinician (77,168).

Tailoring ADF Therapy to the Risk of Abuse

Prescribing a specific ADF opioid product for patients with a significant risk of abuse should be accomplished as part of a well-defined abuse-deterrent strategy. In 2005, a panel of experts on opioid abuse and diversion proposed the categorization of opioid prescription abusers into 6 categories (50). Based on features of abuse history, targeted substances and typically utilized routes of administration, opioid abusers were classified as the following: experienced heroin addicts, experienced prescription opioid addicts, polydrug abusers, rave abusers, inexperienced abusers, and patient abusers (Table 4) (50). Generally, abusers who are more experienced in abuse have greater tolerance and tend to prefer a non-oral route of administration. In contrast, abusers with less experience or fear of thrombotic events prefer orally ingested opioids combined with other addictive substances. Although this classification system requires further validation and patients may fit into more than one group, the information provides physicians with insight into the most likely routes of administration for abuse when contemplating the use of an ADF opioid product (8,50). For low-risk patients, the decision of whether or not to use an ADF product should be weighed more carefully (50,66). Although a less costly generic formulation without ADF properties may be more appropriate for low-risk patients, one should not assume that to always be the case. Some low-risk patients may prove to be suitable candidates for therapy with an ADF product. The decision should be individualized based on a variety of patient-specific factors (50).

Considerations Prior to Initiating ADF Opioid Therapy

Factors to consider before initiating opioid therapy for chronic non-cancer pain include a history of sub-

Table 4. *Types of abusers and related pattern of abuse (50).*

Type of Abuser	Abusing Feature	Targeted Medicine	Preferred Route
Experienced heroin addict	Having a high tolerance for euphoric effect; seeking other drugs when heroin is not available	Intense of heroin-like high medicine (methadone, BZDs) when heroin is not available	IV
Experienced prescription opioid addict	Adopting multiple opioids to achieve immediate-released effect	Tampered controlled-release opioids	Oral, intranasal
Polydrug abuser	Highly tolerated to multiple CNS-acting drugs	Opioids and many other CNS-acting drugs	Oral, intranasal
Rave abuser	Seeking the longest-lasting high	ER opioids	Ingest multiple intact dose
Inexperienced abuser	Having little drug tolerance, most probably are students	Mixed ER prescription drugs with alcohol or marijuana	Ingest by chewing
Patient abuser	Having a substance abuse history or other aberrant drug-taking behaviors	Depended on individuals	Depended on individuals

stance abuse, verification of the diagnosis of chronic pain, assessment of the level of pain and disability, and related impacts on quality of life (169). The risk of developing iatrogenic opioid addiction or dependence may increase after prolonged exposure to opioids, even for patients who represented a low risk during a period of compliant screening and monitoring (48,168,170). In a study of acute pain resolution after discharge from an ED, more than 20% of patients reportedly developed either an unresolved pain problem or a worsening of pain during the time since discharge (170). Effective opioid treatment reduces drug exposure for extended periods and lowers the risk of eventually developing abuse (154).

The overprescribing of opioids for short-term analgesia can increase the risk of subsequent abuse or diversion. Two-thirds of patients in a postoperative survey admitted to being in possession of leftover pain medication (n = 213), with more than 90% having stored medication that was no longer needed (171). Another prospective longitudinal study that evaluated a cohort of 192 patients aged 21 to 26 years, found that 89% had received opioids in the past for acute pain, 27% of patients diverted their pain analgesics, and 63% of them were over-users at risk of diverting (172). The increasing risk of opioid diversion or abuse as a possible consequence of drugs that are leftover following short-term opioid therapy highlights the need for cautious pain management.

A strategy of multimodal analgesic therapy, which is recommended for managing acute pain, includes drugs other than opioids, such as acetaminophen, NSAIDs, gabapentin-like drugs, and other neuropathic drugs. Local anesthesia has been shown to shorten patients' length of stay, improve pain control, and reach therapeutic pain goals sooner, with less opioid consumption than therapy that relies exclusively on opioids (173,174). Based on the different mechanisms as designed, when a regimen of multimodal analgesics is used to manage acute pain, the adoption of ADF opioids with multiple active ingredients may represent an effective strategy for deterring opioid abuse (154). Although IR formulations are typically prescribed as management of acute pain, there is a limited selection of ADF opioids from which to choose for acute pain management (48). As of August 2016, only 2 opioid products with abuse-deterrent properties existed for treating acute pain: an oxycodone HCl/acetaminophen ER tablet combination (Xartemis XR) with a physical barrier and oxycodone HCl with an aversive agent (Oxecta), but neither of the products had approved ADF labeling (175,176).

When prescribing ADF opioids, some consideration needs to be given to the specific patient population. Populations that are generally considered to be at greater risk include the elderly, patients with dysphagia, patients with theft potential, and opioid-dependent or opioid-tolerant patients. For elderly patients, the potential exists for misuse of an ADF product by chewing or crushing. Crush-resistant opioids may be preferred. Conversely, sequestered agonist/antagonist and aversive agents may not be appropriate for the elderly due to the potential of withdrawal symptoms or adverse effects (11,93). Patients with dysphagia or with an enteral feeding tube present a unique challenge for administering opioid therapy (66). Developing ADF products that can be sprinkled onto soft food for these patients are important (83). An IR dosage form given on a timed schedule based upon half-life is theoretically the best choice. However, IR formulations have limitations on the frequency of administration. Instead, it is best to avoid ADF tablets that contain chemical barriers that form into a gel when dissolved with liquids. Excipient polymer ingredients, such as polyethylene oxide, may become too sticky to be swallowed after hydration (177-179).

An ADF product may be appropriate for patients who are not at risk for abuse themselves, but who might be victimized by theft or diversion perpetrated against them. In such circumstances, prescribing a traditional, non-ADF opioid product could increase the likelihood of the drug being diverted away from the intended patient. Therefore, consideration should be given to prescribing an ADF product for compliant patients who are at risk of being targeted by an abuser intent on diverting the medication, perhaps a family member or friend who would have access to the drug (1,180).

For patients who are prescribed chronic long-term opioid therapy, it can be difficult to differentiate between tolerance, dependence, and addiction. Unlike recreational abusers, patients with opioid tolerance often have a legitimate need to take higher doses for adequate pain management (66). When selecting an ADF opioid for this patient population, it is best to avoid sequestered agonist/antagonist products due to the risk of withdrawal symptoms caused by the neutralization of the active opioid ingredient.

Thus far, post-marketing data provide no conclusive evidence with regard to the effectiveness of different types of ADF products in terms of abuse liability, safety, or cost-effectiveness among various patient groups. As

additional information becomes available about the effectiveness of ADFs in clinical practice, their role in therapy should become clearer.

Conclusion

When opioid analgesia is indicated, ADFs provide an oral therapeutic option that can lower the likelihood of abuse or misuse by hindering extraction of the active ingredient, preventing alternative routes of administration, or causing aversion. There are currently 9 opioid analgesic products with approved abuse-deterrent labeling, though a number of other products are in various stages of development. A growing body of post-marketing evidence in the US confirms the association of ADF opioids with decreasing rates of abuse, diversion, and overdose deaths. Nevertheless, the high-cost of ADF products and conflicting reports about benefit versus risk raise legitimate concerns about their role in therapy. Legislative efforts and the development of generic ADFs have been undertaken to facilitate greater acceptance.

When considering an ADF product, clinicians should be familiar with the risks of opioid abuse based on differences in formulation and route of administration. Other considerations include type of pain, duration of treatment, insurance coverage, and whether the patient has dysphagia, is elderly, or is opioid-dependent or tolerant. The goal is to ensure legitimate pain relief and minimize the risk of abuse with an ADF product that is suitable, from the perspective of both the prescriber and the patient. In the face of an ever-increasing opioid abuse problem, ADFs represent a promising therapeutic option for curbing abuse, though the role of opioid ADFs remains to be defined.

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