Drug Abuse: Addiction and Recovery

Chapter 3

Abuse Deterrent Formulations for Reducing Misuse and Abuse of Prescription Opioids

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Abstract

Opioids abuse is an epidemic problem in the US, which can be gauged by consumption level. The US constitutes 5% of world population but consumes 75-80% of global opioids. Prescription opioid abuse has negative consequences on social and economic indicators. FDA has also taken a lead among other federal agencies in combating the prescription abuse by promoting the abuse deterrent formulations (ADFs). ADFs have properties that deter the abuse of prescription opioids. Although they are 5- to 15-times more expensive than non-ADFs brand and generic opioid products, their effectiveness in preventing abuse, death and diversion is limited as shown by the published data. This chapter reviews the steps taken at federal and state agencies, and ADFs status, and their advantage and disadvantage.

Key words: Prescription opioids; addiction; abuse; abuse deterrent formulations

1. Introduction

Pain is considered the fifth vital sign and monitored with vigilance as blood pressure, pulse, temperature and respiratory rate in a modern health-care facility [1-2]. About 100 million Americans suffer from acute and chronic pain [3] and opioids are frequently prescribed to alleviate pain. A consensus is lacking among clinicians about the utility of opioids' use in chronic pain management [4-5]. Moreover, opioids are associated with misuse, abuse, diver-

sion, withdrawal, addiction, overdose and death. Prescription of opioids has increased 4 folds from 2002 to 2010 due to healthcare professional standards (Agency for Health Care Research and Quality guidelines and hospital value-based purchasing program) combined with aggressive marketing by pharmaceutical companies [6-7]. Consequently, USA has become number one consumer of opioid drugs in the world. It constitutes only 5% of world population, but consumes 80% of global supply of opioids [8]. In 2015 alone 227 million prescriptions of opioids were written in the USA, which is enough to hand a bottle of pills to nine out of every ten adults [9]. All this led to an epidemic of opioid addiction and death associated with opioids' overdose. According to National Institute on Drug Abuse, two million Americans had a prescription opioids use disorder and 591,000 suffered from a heroin use disorder in 2015 [10]. Drug overdose is the leading cause of accidental deaths in US with 52,404 deaths alone in 2015, surpassing for the first time the number of people killed by gun homicides and car crashed combined [11-12]. Opioids are driving the epidemic of overdose deaths. In 2015 alone, prescription opioids overdose was responsible for 20,101 deaths, and 12,990 death were attributed to heroin [11]. The opioid products prescribed in US are 90% immediate release and 10% extended release/long acting (ER/LA). Most of ER/LA opioids have abuse deterrent property claims on their label [3]. Opioids linked to overdose deaths are Percocet® (oxycodone and acetaminophen), OxyContin® (oxycodone), heroin and fentanyl [12]. Prescription abuse has a tremendous impact on the US economy. The economic cost of prescription abuse is $78.5 billion on healthcare, law enforcement and lost productivity [13]. This chapter reviews multipronged approaches in addressing this very important issue. Multipronged approaches include steps taken by various governmental agencies including abuse deterrent formulations (ADFs), which deter the abuse of prescription opioids.

2. Steps taken at State and Federal Level to Combat Opioids Epidemic

States and federal agencies are aggressively fighting to eliminate the scourge of prescription opioids' misuse, abuse and diversion. Following actions are taken at states and federal levels:

2.1. Mandatory prescriber training

Prescribers play a critical role in preventing the misuse and abuse of opioids. They have a responsibility to help ensure the safe and effective use of opioid products. Prescriber's education is a very important element in the best use of opioids, including when and which patients they should prescribe. FDA requires companies marketing ER/LA opioids to provide risk evaluation and mitigation strategy (REMS) [14]. REMS is a strategy to manage known or potential risks associated with a drug product. It is required for pre- and post-approval of the ER/LA product of opioids since 2012. It includes communication tools (patient package insert and medication guide), communication plan and elements to assure safe use. In the communi-

cation plan, a developed plan of communicating risk of opioids to key audiences is included in REMS. It includes sending information to healthcare providers, disseminating information about REMS to encourage implementation or explain certain safety protocols or disseminating information through professional societies about any serious risks of drug and protocol to assure safe use. Elements delete of assuring safe use are intended to mitigate a specific serious risk. This includes providing medication guide and training/education to prescribers. Training must be provided through accredited continuing education activities supported by independent educational grants from ER/LA opioids analgesic companies. The education/training on opioids should cover all elements of 'FDA's blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics' [15].

2.2. Prescription drug monitoring programs (PDMPs)

It is an electronic database system of controlled drugs prescribed by practitioners and dispensed by pharmacists and run by the state, common wealth or territory of the USA. It is designed to monitor information of suspected abuse or diversion that can give critical information about the patient's controlled substances prescription history. Prescriber and pharmacists can utilize this information in identifying patients at high-risk and recommend early intervention. It is highly effective program in controlling and reducing abuse and division of prescription controlled substances. Electronic data of controlled substances is submitted by pharmacies and dispensing practitioners. Data are used by states for educational efforts, research, enforcement and abuse prevention. Currently, 49 states, District of Columbia and Guam territory of USA have operational PDMPs. Various state agencies are involved in running this program. The state agencies managing the program are consumer protection, substance abuse, law enforcement, professional licensing, department of health and boards of pharmacy. Per the state law, PDMPs monitor the controlled substances as defined by the Federal and State Controlled Substances Laws. Most states PDMP collect information on federal schedules II-IV controlled substances while some states also collect information on federal schedules II-V controlled substances. Access to PDMPs database system is determined by each individual state. Most states allow access to PDMP data of the patients to practitioners and pharmacists under their care. Many states also allow access of PDMPs to other authorized groups. These may include, e.g. law enforcement for drug investigations (open investigations and sometime court orders are required), licensing and regulatory boards of investigating health care professionals who prescribe or dispense prescription controlled substances, state Medicaid programs for Medicaid members, state medical examiners or coroners for cause of death investigations and research organization that may provide de-identified data for analysis and research [16-18].

2.3. Overdose education and naloxone distribution (OEND)

The purpose of OEND programs is to reduce adverse events and risk of life-threatening

opioid overdose and deaths. The programs involve education and training of opioid overdose prevention, recognition of opioid overdose, opioid overdose rescue response, and distribution of naloxone kits. Education involves educating people at risk for overdose and bystanders on how to prevent, recognize and respond to an overdose. Training elements include how to recognize the sign of overdose, seek help, rescue breathe, use naloxone and stay with the person who is overdosing. Naloxone can be administered by the bystander who is also opioids user, a friend, family member, acquaintance or first responder such as police or firefighter. OEND programs of educating and training of bystander through community started in the 1990s and have expanded to 30 states. Many states have changed legal framework to allow wider access to naloxone. The prescriber is allowed to prescribe naloxone to the third-party family member as well as making naloxone available without a prescription in retail pharmacies. Although community based distribution of naloxone is still a common driver of naloxone distribution [19]. Naloxone is a potent opioid antagonist that antagonizes opioid effects by competing for the same opioid receptor, mu receptor. FDA has approved subcutaneous injection (Evzio®) and nasal spray (Narcan®) dosage forms of naloxone for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression [20-21]. The naloxone kits contain either intranasal or intramuscular dosage form of the drug. OEND programs have reduced opioid overdose deaths in the community that has it compared to one that does not have it. Furthermore, this is supported by number of reported studies and observational data [22-25].

2.4. Doctor shopping and pill mills

It is against the federal law for a doctor to prescribe opioids drug without a valid prescription or outside the usual use of the medicine. A doctor will be charged for drug trafficking if the prescription is deemed not valid. “Pill mill’ is a term used primarily by local and state investigators to describe a doctor, clinic or pharmacy that is prescribing or dispensing powerful narcotics inappropriately or for non-medical reasons [26]. Pill mills were most common in pain management clinic of Florida. Furthermore, abusers and drug traffickers were utilizing pain management clinic as a source of prescription controlled substances. Federal and state governments have cracked down on pill mills [27]. In doctor shopping practice, patient visits multiple physicians to get the medical opinion of continuing illness or to obtain prescription drugs illegally [28]. States law require opioid prescriber to check for doctor shopping through PDMPs database [29].

2.5. Drug courts

Drug courts are problem-solving courts that were created to address the underlying problems that result in criminal behavior. It is most effective justice intervention program in treating drug-addicts. The objective of drug courts is to reduce the crime by changing the be-

havior of abusers toward substance abuse. Thus breaking a cycle of drug addiction and crime. It reduces substance abuse, crime, restores lives, saves children, reunites families and saves money [30]. First drug court was established in Miami-Dade County, Florida in 1989 in response to growing crack (cocaine) problem in which court was tired of prosecuting the same individual for the same crime [31-32]. All 50 states of US have more than 3000 functional drug courts as of June 2015 [32]. It combines the intensive judicial supervision, mandatory drug testing, sanctions and treatment to help the drug abusers. The eligible abuser can be diverted to drug courts in various ways and at various stages in the judicial process. This program is offered to the abuser as an alternative to probation or short-term incarceration. The abuser who agrees to appear in drug court will have the possibility of getting charges dismissed or reduced sentence. There are two programs in drug courts: deferred prosecution and post-adjudication programs. In a deferred prosecution or diverting setting, the abuser is diverted to drug court prior to pleading to a charge. Abusers are not required to plead guilty and those who complete drug court programs are not prosecuted further. However, failure to complete the program results in prosecution. In post-adjudication programs of the drug courts, the abusers plead to their charges but their sentences are deferred or suspended until completion of the programs [33]. Successful completion of the program may results in waived or expungement of sentences. However, they will return to criminal court if they fail to meet drug courts requirement. Standard drug program run from six months to one year but many abusers stay longer in order to complete the entire program. The program's requirements include drug and arrest free for specified time, securing housing and/or employment. Abusers receive reward or face sanction based on the drug test, which is conducted frequently. Rewards include verbal praise, certificates or other tokens of approval or moving to next level of supervision which may include a less frequent visit to court. A sanction may include verbal admonishment, writing an essay, jail time, or kicked out from the program and facing traditional sentencing [34]. Eligibility for drug court varies according to state and local guidelines and on the type of drug court model [35-36].

2.6. Medication assisted treatment (MAT)

It involves treatment of opioids addiction with medicines along with counselling and support (behavioral therapy). Medicines developed for the treatment of opioids addiction act on the same receptors as the opioids drug namely opioids receptors. They can have properties of opioids agonists, partial agonists or antagonists. Medication available for the treatment of opioids addictions are methadone (a slow acting opioids agonist, Dolophine® or Methadose™) [37-38], buprenorphine (a partial opioid agonist, Suboxone® and Probuphine®) [39-40] and naltrexone (an opioid antagonist, Revia® (an immediate acting), Vivitrol® (extended release)) [41-42]. To increase patients' compliance, long acting formulation of buprenorphine and naltrexone is also available (Probuphine® and Vivitrol®). World Health Organization included

buprenorphine and methadone in "essential medicines" category [43]. Typical MAT treatment involves following steps: physician consultation, determining suitability of the abuser to MAT, prescribing medication and stabilization/maintenance of medication. The behavioral treatments include assessment of abuser psychosocial needs; counselling, an inclusion of family support and referrals to community services. Published reports indicated that outcomes of medical assisted therapy are better than without it. Data on MAT approach in addiction treatment has shown that it decreases opioid related overdose death, morbidity and mortality, criminal activity, infectious disease transmission and improves social functioning [44-46]. Substance Abuse and Mental Health Services Administration (SAMHSA) increases the access to MAT treatments to abuser based on published outcomes. SAMHSA issued new reporting requirement for the physicians who will be authorized to prescribe or dispense buprenorphine and buprenorphine/naloxone combination for opioid use disorder to a new limit of 275 patients. The new ruling does not apply to methadone, which is a schedule II drug. Only medication covered under this rule is in Schedule III, IV or V [46].

3. FDA Opioids Action Plan

Dr. Robert Califf, the FDA's Deputy Commissioner for Medical Products and Tobacco, along with other FDA leaders, called for a far-reaching action plan to reassess the agency's approach to opioid abuse epidemic on February 4, 2016. The focus of the plan is on policies aimed at reversing epidemic while at the same time providing access to medicine to the patient in need [47-48]. The FDA actions plan includes:

3.1. Expand use of advisory committee

Since 2016, FDA started convening an advisory committee of external experts before approving any New Drug Application (NDA) for an opioid that does not have abuse deterrent properties (ADPs). FDA will consider the reviews and advice from external experts with an opportunity for public input before approval of any new opioids that do not have ADPs. The agency will also consult an advisory committee for the novel issues of ADFs. Similarly, it convenes a Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labelling is approved [48].

3.2. Develop warnings and safety information for immediate release opioids labeling

In March 22, 2016, FDA announced class-wide safety labeling changes for immediate release opioid medications. FDA requires a new-boxed warning about the serious risks of misuse and abuse, which can lead to addiction, overdose and death. The new labelling requirement is similar to ER/LA opioids. This new information helps the prescriber about the risk of opioids and how to prescribe safely [48-49].

3.3. Strengthen postmarket requirements

The long-term impact of opioids product on human is substantially lacking [5,6]. FDA requires the companies to generate post-market data on the long-term effect of ER/LA opioids products. This information will help in better understanding the risks of misuse and abuse of ER/LA opioids and identify predictors of opioid addiction, among other related issues [48,50].

3.4. Update risk evaluation and mitigation strategy program

FDA requires REMS for ER/LA products under which the sponsor is required to fund continuing medical education providers to offer at low or no cost. FDA Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee recommended broadening the scope of REMS in 2016. The recommendation includes [48,51]:

- Expand the FDA Blueprint to incorporate pain management and extending training to other healthcare professionals involved in the management of patients with pain
- Expanding the REMS requirements to include the immediate-release opioid analgesic drug manufacturers
- Evaluating the best approach for implementing mandatory prescriber education on pain management

3.5. Support better treatment

FDA is reviewing the availability of naloxone to over-the-counter to make sure it is more accessible and thus broadening treatment access to opioid overdoses [48]. FDA also supports CDC (Center for Disease Control) guidelines for prescribing opioids for chronic pain management. Some of CDC recommendation includes [48,52]:

- Use opioids only when benefits are likely to outweigh risks
- Start with the lowest effective dose of immediate-release opioids
- Reassess benefits and risks when considering dose increase

3.6. Reassess the risk-benefit approval framework for opioid use

In March 2016, the FDA asked the National Academies of Sciences, Engineering, and Medicine (NASEM) to outline the state of the science regarding prescription opioids abuse and misuse [48,53-54]. NASEM issued recommendations in July 2017 and these include:

- Invest in research to better understand pain and opioid disorder
- Consider potential effects of illicit markets of policies and program for prescription opioids
- Improve reporting of data on pain and opioid disorder
- Invest in data and research to better characterize the opioid epidemic
- Improve access to drug take-back program
- Establish comprehensive pain education materials and curricula for health care providers
- Facilitate reimbursement for comprehensive pain management
- Improve the use of PDMPs data for surveillance and intervention
- Expand treatment for opioid use disorder
- Improve education and treatment of opioid use disorder for health care providers
- Remove barriers to converge of approved medications for treatment of opioid use disorder
- Leverage prescribers and pharmacists to help address opioid use disorder
- Improve access to naloxone and safe injection equipment
- Incorporate public health considerations into opioid-related regulatory decisions
- Require additional studies and collection of analysis data needed for a thorough assessment of broad public health considerations
- Ensure that public health considerations are adequately incorporated into clinical development
- Increase the transparency of regulatory decisions for opioids in light of the commitee's proposed systems approach
- Strengthen the post-approval oversight of opioids
- Conduct a full review of currently marketed/approved opioids
- Apply public health considerations to opioid scheduling decisions

3.7. Expand access to abuse deterrent formulations to discourage abuse

FDA believes that ADFs hold promise in combating abuse and misuse of prescription opioids as the technologies improve with time. US government, regulatory agencies and pharmaceutical companies are making efforts to increase the presence of ADFs in prescription opioids market [48]. Although short term and long-term impact of ADFs in reducing opioids abuse and misuse is limited [55-61].

4. Abuse Deterrent Formulations (ADFs)

FDA defines ADFs as products having ADPs. ADPs are those properties shown to meaningfully deter abuse but do not fully prevent abuse. Literature is using abuse deterrent and tamper resistant terminology interchangeably. However, FDA does not use tamper resistant terminology for abuse deterrent due to use of tamper resistant terminology for packaging requirement for certain classes of drug, devices and cosmetics [62-63]. FDA approved first ADF product with label claim in 2010. Even before the approval of first ADF label claim product, many ADF products were available without official recognition in FDA drug label. FDA approved two such ADF products (Lomotil® and Motofen®) in 1960 and 1978. Lomotil® and Motofen® contain diphenoxylate hydrochloride and difenoxin hydrochloride, respectively, as actives and both contain atropine sulfate as an aversive agent to prevent abuse. A subtherapeutic dose of atropine is added to discourage deliberate overdose of diphenoxylate hydrochloride and difenoxin hydrochloride [64-65]. In 1982, FDA approved Talwin NX® that contains naloxone hydrochloride as an opioid antagonist to prevent abuse of pentazocine hydrochloride by parenteral route [66]. These products do not contain official abuse deterrent properties or temper resistant claim on their labels. Reformulated OxyContin® was first ADF product with label claim in 2010 and it was originally approved in 1995 (first ER product of opioid) [67]. Reformulation of OxyContin® imparts crush resistant property to reduce the potential of abuse by snorting or dissolving by parenteral routes. Recent reports indicate that OxyContin® has captured 90% market value of the total ADFs market [3]. Since then FDA approved nine more ADF products with label claims. Nine ADF products are in the late-stage pipeline (stage III or FDA submission) [3]. ADF products have efficacy and safety profiles similar to non-ADF products. It means the same level of analgesic benefits and same profile of adverse events when used as prescribed [68]. ADF products may deter against chewing, intranasal and intravenous route of administration. However, swallowing multiple pills is a common form of abuse that cannot be deterred by ADFs use [69]. Abuse of ADFs pose same safety issue as the non-ADF product such as precipitated severe withdrawal symptoms, infections through needle sharing [70], thrombotic microangiopathy [71] and other risks associated with tampering of excipients present in ADFs [72].

4.1. Classification

The classification of ADFs is based on mechanism of abuse deterrence and follows as per FDA guidance documents [62-63]:

- Physical/Chemical barriers
- Agonist/antagonist combinations
- Aversion
- Delivery system
- New molecular entities and prodrugs
- Combination
- Novel approaches

The commercially available ADF products are based on either physical/chemical or antagonist-antagonist combination (**Table 1**). FDA requires four type of studies for the approval of NDA (new drug application) of ADF with label claim. These studies are as follows per guidance document [62].

- Premarket studies

  Laboratory manipulation and extraction studies (category 1)
  Pharmacokinetic studies (category 2)
  Clinical abuse potential studies (category 3)

- Postmarket studies (category 4)

Table 1: FDA approved abuse deterrent formulations

Brand name	Opioids	Year of approval	Company	Reported abuse deterrence mechanism	Nature of drug release	Abuse-deterrent route in the label	Commercially available
OxyContin®	Oxycodone	2010	Purdue Pharma LP	Physical-chemical	Extended/long-acting	Intranasal injection	Yes
Hysingla™ ER	Hydrocodone bitartrate	2014	Purdue Pharma LP	Physical-chemical	Extended/long-acting	Oral intranasal injection	Yes
MorphaBond ER™	Morphine sulfate	2015	Daiichi Sankyo Inc	Physical-chemical	Extended/long-acting	Intranasal injection	Yes
Xtampza ER	Oxycodone	2016	Collegium Pharm Inc	Physical-chemical	Extended/long-acting	Intranasal injection	Yes

Arymo™ ER	Morphine sulfate	2017	Egalet	Physical-chemical	Extended/long-acting	Injection	Yes
Vantrela™ ER	Hydrocodone bitartrate	2017	Teva Branded Pharm	Physical-chemical	Extended/long-acting	Oral, intranasal injection	Yes
RoxyBond™	Oxycodone hydrochloride	2017	Inspiron Delivery	Physical-chemical	Immediate release	Intranasal injection	Yes
Embeda®	Morphine sulfate and naltrexone hydrochloride	2014	AlPharma Pharms	Agonist-antagonist	Extended/long-acting	Oral intranasal	Yes
Targiniq™ ER	Oxycodone hydrochloride and naloxone hydrochloride	2014	Purdue Pharma LP	Agonist-antagonist	Extended/long-acting	Intranasal injection	No
Troxyca® ER	Oxycodone hydrochloride and naltrexone hydrochloride	2016	Pfizer Inc	Agonist-antagonist	Extended/long-acting	Oral intranasal	Yes

The comparator product for the approval of NDA can be ADF (if available) or non-ADF (if ADF is not available). Postmarket studies are mandatory for ADF products. However, OxyContin® was approved prior to mandatory requirement of category 4 studies. Post-market FDA approved studies of Hysingla™ ER and Embeda® are scheduled for completion in 2018 and 2019, respectively [3]. So far, no generics of ADF products is approved even though first ADF product was approved in 2010. ANDA (abbreviated new drug application) for ADF approval has to meet FDA equivalence criteria for ADPs (similar ADPs properties between reference and test products) in addition to pharmaceutical- and bio-equivalence requirements, (**Table 2**) [62-63]. Following are ADF products approved by FDA:

4.1.1. OxyContin®

It is the first ADF product with an official label claim of ADP. It is a film coated tablet formulation of oxycodone hydrochloride containing butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate and titanium oxide as inactive ingredients [73]. The manufacturing process involves tablet compression followed by heating above the melting point of the polymer. Polymer particles fuse and impart plastic like properties on cooling. This imparts tremendous mechanical strength to the tablets [68,74-75]. Reformulated OxyContin® is difficult to manipulate compared to Original OxyContin® formulation. The tablet resists crushing, breaking and dissolution using a variety of household and kitchen tools and solvents. It also forms a viscous hydrogel that resists passage through a needle. OxyContin® may reduce abuse by intranasal route as indicated in clinical studies using liking as a marker (OxyContin® label). Possibly, ADPs are imparted by heat pro-

cess and polymers such as polyethylene oxide and hypromellose which forms viscous mass when the tablet comes in contact with the aqueous environment [74-75].

Table 2: Studies requirement for NDA (new drug product) and ANDA (generics) approval of ADFs

NDA (new drug product)	
Types of studies	Description
Premarket	
Laboratory manipulation and extraction studies	To evaluate physiochemical properties, abuse deterrent properties and level of efforts required to defat ADP
Pharmacokinetic studies	Comparative pharmacokinetic studies of intact and manipulated product and comparator
Clinical abuse potential studies	Clinical studies in drug-experienced, recreational user population to assess potential of abuse
Postmarket studies	To assess reduction in abuse, misuse and related adverse clinical outcomes.
ANDA (generics)	Comparative studies to demonstrate pharmaceutical, bio and abuse deterrent properties equivalence

4.1.2. Hysingla™ ER

It is extended release tablet of hydrocodone bitartrate approved by FDA in 2014. The tablets contain the following inactive ingredients: BHT (an additive in polyethylene oxide), hydroxypropyl cellulose, macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyethylene oxide, polysorbate 80, polyvinyl alcohol, talc, titanium dioxide, and black ink. The tablet was assessed by in-vitro and clinical methods for the abuse deterrent potential [76]. In-vitro studies showed that it has physical chemical properties that resist crushing, breaking and dissolution under various conditions of testing such as solvents and manipulations tools. It also forms a viscous gel when exposed to the aqueous environment, which resists passage through the hypodermic needle. Polymers responsible for forming the viscous gel are polyethylene oxide and hydroxypropyl cellulose [74-75]. Clinical studies also indicated that the abuser has less liking and desire to take Hysingla™ ER. Thus, it has physicochemical properties that may reduce intranasal and oral abuse when chewed [76].

4.1.3. MorphaBond ER™

It is a tablet formulation of morphine sulfate and approved in 2015. It has following excipients: hypromellose, xanthan gum, microcrystalline cellulose, sodium alginate, alginic acid, mannitol, colloidal silicon dioxide, magnesium stearate, ethyl acrylate and methyl methacrylate copolymer dispersion, lactose monohydrate, polysorbate 80, titanium dioxide, polyethylene glycol, shellac in ethanol, isopropyl alcohol, iron oxide black, n-butyl alcohol, propylene glycol, and ammonium hydroxide [77]. MorphaBond ER™ is tested by in-vitro methods to assess abuse potential by various routes including oral, intranasal insufflation, injection and

smoking. It has increased resistance to cutting, crushing or breaking relative to morphine sulfate extended release control. Similar to OxyContin® and Hysingla™ ER, MorphaBond ER™ forms a viscous material that resists passage through a needle. Clinical studies data indicated that physicochemical properties of MorphaBond ER™ reduce abuse by intranasal route of abuse [77].

4.1.4. Xtampza ER

It is a capsule dosage form of oxycodone. It is based on DETERx® technology where drug base instead of salt is mixed with an inactive ingredient to form a lipophilic salt. Lipophilic salts of opioids have less potential of drug extraction compared to water soluble salts [78-79]. It contains oxycodone as myristate salt. Following excipients are present in Xtampza ER: myristic acid, yellow beeswax, carnauba wax, stearoyl polyoxyl-32 glycerides, magnesium stearate, and colloidal silicon dioxide [80]. The capsule shells contain titanium dioxide and hypromellose. *In-vitro* physical and chemical manipulation studies indicated that it is less susceptible to the effects of grinding, crushing, and extraction under various conditions of extraction. Furthermore, melted capsule content or microspheres suspended in water resisted the passage through the hypodermic needle. Similarly, pharmacokinetic and human abuse potential studies along with *in-vitro* data indicated that Xtampza is expected to reduce abuse by nasal route [80].

4.1.5. Arymo™ ER

It is ER tablet dosage of morphine sulfate. Inactive ingredients present in Arymo™ ER are polyethylene oxide 400,000, BHT, polyvinyl alcohol, polyethylene glycol 3350, talc, and titanium dioxide [81]. The Egalet Corporation used proprietary Guardian™ technology to deter the abuse of the product. Guardian™ technology utilizes the injection-molding process to produce tablets that are hard and difficult to manipulate for abuse and misuse [82-83]. Physical and manipulation methods were performed to defeat the extended-release properties of the Arymo™ ER. The product is resistant to cutting, crushing, grinding or breaking in comparison to morphine sulfate extended-release tablets using a variety of mechanical and electrical tools. The Arymo™ ER contains polyethylene oxide 400,000, which has property to form hard plastic material after heat exposure above the melting point of the polymer [74-75]. Injection molding is a heat process where formulation components are melted and poured into a die cavity where component takes the shape of dosage forms on cooling. The product also forms a gelatinous mass or viscous hydrogel, which is difficult to pass through the hypodermic needle. Oral pharmacokinetic and oral clinical abuse potential studies showed a difference in drug liking point but difference was not statistically significant [81].

4.1.6. Vantrela™ ER

It is an extended-release tablet of hydrocodone bitartrate. The tablets contain lactose monohydrate, ethyl cellulose, hypromellose, glyceryl behenate, and magnesium stearate as the excipients. Teva uses proprietary technology to make this ADF product. Teva received label claims of parenteral, oral and nasal abuse deterrence. Parenteral abuse deterrence is based on in-vitro data. In-vitro data results indicated that Vantrela™ ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains extended release property despite manipulation. Oral (oral abuse potential and oral pharmacokinetic studies) and nasal (intranasal abuse potential and nasal pharmacokinetic studies) abuse deterrence are based on in-vitro studies and clinical abuse potential data [84].

4.1.7. RoxyBond™

It is first and only immediate release ADF product of oxycodone hydrochloride approved by FDA in 2017. It uses SentryBond™ proprietary technologies of Inspiron Delivery Sciences, LLC to deter abuse of the product [85]. Alginic acid, ammonium hydroxide, colloidal silicon dioxide, dibutylsebacate, dimethylaminoethyl methacrylate copolymer, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, hypromellose, iron oxide black, isopropyl alcohol, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, n-butyl alcohol, polyethylene glycol, polysorbate 80, polyvinyl alcohol, propylene glycol, shellac in ethanol, sodium alginate, talc, titanium dioxide, and xanthan gum are present in the product as inactive ingredients. RoxyBond™ label has parenteral and nasal abuse deterrent claims. The product resists cutting, crushing, grinding or breaking when manipulated with commonly used household tools. Intact product resists drug extraction using selected household tools and commonly used laboratory solvents, including selected pre-treatment of the product. It forms a viscous material that resists passage through the needle. Thus, it is difficult to prepare an intravenous solution for injection of drug from RoxyBond™ compared to oxycodone immediate-release tablets. Clinical abuse potential studies by nasal route indicated that liking and desire to take it again scores were significantly lower than controlled immediate release formulation [86].

4.1.8. Embeda®

It is the first ADF product based on agonist-antagonist approach. It was initially approved in 2009 but received ADF label claim in October 2014. The agonist is morphine sulfate and antagonist naltrexone hydrochloride. The product is capsule dosage form containing pellets of morphine sulfate surrounding a central core of sequestered naltrexone hydrochloride in a ratio of 100:4 [68]. The extended release capsule contains following inactive ingredients: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, sodium chloride, polyethylene glycol, hydroxypropyl cellulose, dibutylsebacate, methacrylic acid copolymer, di-

ethyl phthalate, magnesium stearate, sodium lauryl sulfate, and ascorbic acid. The excipients provide extended release of morphine sulfate but do not release naltrexone hydrochloride in patients. However, inadvertent release of naltrexone from non-tampered capsule produced adverse events. In vitro studies indicated that crushed beads resulted in the extraction of both morphine and naltrexone. Furthermore, pharmacokinetic and clinical studies showed that both drugs were rapidly absorbed from crushed pallets [87]. Thus Embeda® has properties that are expected to reduce abuse by nasal and oral route. Moreover, there are multiple recall of the product due to stability issues since its approval [68].

4.1.9. Targiniq™ ER

It is the second ADF product approved by FDA in July 2014 based on agonist-antagonist approach, however, it received ADF label claim before Embeda®. The product is temporarily discontinued for an unknown reason. It is an extended release tablet of oxycodone hydrochloride (agonist) and naloxone hydrochloride (antagonist). Inactive ingredients of Targiniq™ ER are lactose monohydrate, stearyl alcohol, ethyl cellulose, povidone, talc, magnesium stearate, polyvinyl alcohol partially hydrolyzed, titanium dioxide, and macrogol. In-vitro manipulation data indicated that Targiniq™ ER could be crushed and dissolved. However, both drugs will be released when the abuser tries to extract oxycodone from the product. Clinical abuse potential data indicated that Targiniq™ ER provides deterrence against intranasal and intravenous routes of administration [88].

4.1.10. Troxyca® ER

It is also based on agonist and antagonist approach. It is an extended release capsule dosage form of oxycodone hydrochloride (agonist) and sequestered naltrexone hydrochloride (antagonist). Talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, hydroxypropyl cellulose, polyethylene glycol, dibutylsebacate, sodium lauryl sulfate, diethyl phthalate, magnesium stearate, methacrylic acid copolymer, and ascorbic acid are the excipients of Troxyca® ER. Manipulation of Troxyca® ER results in simultaneous release and absorption of both oxycodone and naltrexone in in-vitro release and oral pharmacokinetic studies, respectively. It has received oral and nasal abuse deterrence claims on the label based on data of oral abuse and nasal abuse clinical studies in which drug liking and take drug again scores were lower in Troxyca® ER administered patients compared to immediate release oxycodone as a controlled formulation [89].

4.2. ADF Products under FDA review

Nine ADF products are either in stage III or submitted to FDA for the review [3]. For example, KP201 IR and Remoxy ER. KP201 IR is an immediate release product of acetaminophen free hydrocodone and submitted by KemPharm Inc. It will be first IR ADF formulation

of hydrocodone. Sponsor of Remoxy ER is Pain Therapeutics [90]. Ensysce Biosciences is developing amino acid based prodrugs of hydromorphone, oxycodone, hydrocodone and morphine based on BIO-MDTM technologies [91].

Exalgo® (Mallinckrodt Pharmaceuticals), Nucynta® ER (Depomed Inc.), Opana® ER (Endo Pharmaceuticals Inc.), Oxaydo™ (Egalet Corporation), Xartemis™ XR (Mallinckrodt Pharmaceuticals) and Zohydro® ER (Pernix Therapeutics) are other FDA approved opioid products and reported to have ADPs. However, they did not receive FDA label claim for ADPs due to not meeting FDA requirements [92-93].

4.3. Effectiveness of ADFs in reducing abuse of prescription opioids

Evidence on the effectiveness of ADF products in reducing the misuse and abuse is mixed and limited. Most of the data is available for OxyContin® as other ADFs are recently approved and studies have indicated that reformulated OxyContin® has reduced the abuse from 12% to 75%. Moreover, there is a steep decrease in abuse by non-oral route compared to oral route that suggests a shift in the route of abuse. Additionally, investigators found a contemporaneous increase in the rate of other prescriptions abuse (ER oxymorphone, ER morphine and IR oxycodone) and heroin during the same period examined [55-56]. Similarly, rates of overdose and overdose death associated with OxyContin® declined by 34% to 65% after introduction of reformulated OxyContin® [57-59]. This is accompanied by either increase or stability in rates of overdose deaths attributed to other prescription or illicit opioids. It suggests that abusers have switched to other opioids products [57,60-61]. For example, data analysis by RAND Corporation and Wharton school indicated that each percentage decrease in OxyContin® after reformulation is accompanied by 3.1 death per 100,000 population [60]. Data on ADF diversion is extremely limited. Three papers published on OxyContin® diversion based on data obtained from RADARS Drug Diversion Program [3,55-56]. Drug Diversion Program publishes quarterly data on the number of new arrests, street buys and sales involving prescription products submitted by law enforcements and regulatory agencies [94]. Rates of diversion decreased to 89% in June 2015 (from 1.95 per 1,000,000 in the year prior to reformulation to 0.21 per 1,000,000 at year 5 following reformulation) following the reformulation of OxyContin® over a period of five years. Diversion of other prescription opioids also decreased during the same period but at a significantly lower rate (from 13.4 to 9.8 per 1,000,000) [55]. Interestingly, OxyContin® prescription sales also declined (40% since 2010) during the same period [95]. Nevertheless, data on reduction of abuse resulting from the use of ADF products is inadequate.

4.4. Health risk of ADFs

There are many reports of tampering of non-ADF Opana® (oxymorphone hydrochloride) [96] and ADF RoxyBond™ (oxycodone hydrochloride) [72] for intravenous route which

led to safety issues. Reformulated Opana® contains high molecular-weight grade of polyethylene oxide that shifted the route of abuse from nasal to parenteral. An outbreak of HIV and Hepatitis C in Indiana was caused by tampered Opana® product with shared needles [96]. A case of thrombotic microangiopathy was discovered in Tennessee, which is thought to be due to intravenous exposure of substance produced on tampering of polyethylene oxide barrier [97]. Other ADF products also contain either polyethylene oxide or high viscosity polymers. They pose similar health risk if abused by the parenteral route. The ADF products are formulated to be hard monolithic tablets with polymers that form gel when exposed to water (polyethylene oxide and hydroxypropyl methyl cellulose etc) [74-75]. This makes the tablet sticky when moistened and difficult to swallow. There are many reports of currently marketed ADF products that tablets are stuck in patient's throat, causing choking, gagging or regurgitation [3,79].

4.5. Federal and state policies on ADFs

CDC presented twelve recommendations for treatment of chronic pain with opioids in the "CDC Guideline for Prescribing Opioids for Chronic Pain" [52]. None of CDC recommendations mention ADFs product for treating patients with pain. Under 2015 National Drug Control Strategy, the Obama administration requested $27.6 billion for the fiscal year 2016 to reduce the use and its effects. ADF is not the part of National Drug Control Strategy [98]. At the federal level, the only place one finds mention of ADFs as a priority in combating the prescription abuse is the FDA [3,48].

State governments have also taken many steps to address the epidemic of opioids abuse e.g. executive led taskforce, physician education, legislation to establish prescription drug monitoring programs, restrict duration and/or quantity available in an opioid prescription, allocate more funding for abuse treatment options, and legislation requiring health insurances to provide coverage of ADFs. Massachusetts became the first state to pass the ADF legislation Chapter 258 in 2014 which requires ADF medications to be covered by insurance companies and limit cost-sharing requirements for patients. It also requires a pharmacist to automatically substitute ADFs for chemically equivalent non-ADF opioid prescriptions. Implementation of Massachusetts legislation order has been delayed because state officials are still establishing regulatory guidance for insurance and pharmacy. Maryland (Chapter 372) in 2015, and Florida (S.B. 422) and West Virginia (H.B. 4146) in 2016 have passed ADF legislations requiring that ADFs should be covered at parity to non-ADFs equivalent and prohibits step therapy with non-ADF opioids. Maine also passed ADF legislation in 2015 which requires health insurance companies to provide coverage for ADFs. However, in order to pass the legislation, legislators voted to override the Governor's veto. Similarly, 30 bills related to ADF were introduced in 20 states in 2016. Delaware, New Hampshire, Oklahoma and Virginia have passed the resolution to further study ADFs. There has been an increase in the number of legislations introduced

in 2016. However, the rate of adoption is fairly low due to budget concern and effectiveness in reducing the abuse [3,99]. Governors in New York and New Jersey vetoed the bill due to budget concern [3,99]. Furthermore, pharmaceutical companies and their associated advocacy groups spent $880 million between 2006 and 2015 on activities and efforts to influence federal and state opioid policies. One of their goal is to promote expensive ADF products [100].

4.6. Healthcare cost of ADFs

ADFs represent 10% of all the prescription opioids [3]. ADF products are relatively more expensive than non-ADF brands and generics. ADF products are 5- to 15-folds expensive than non-ADF products. It will dramatically increase healthcare cost. For example, VA (Veterans Affairs) spent approximately $100 million on overall opioids. It will dramatically increase the cost by 10-fold (average) if all opioids were to be replaced by ADF. The opioid pharmacy bill would be approximately $1 billion which represents 20% of VA pharmacy [3,101]. Due to the higher cost of ADFs, most of the insurance plans require prior authorization. Insurance plans may cover OxyContin®, Xtampza ER™, Hysingla™ ER and Embeda®. Newer ADF products e.g. Arymo™ ER, Vantreal™ ER, Troxyca® ER and RoxyBond™ were not covered by any plans. Insurance plans require patients to try non-DF, generic equivalents or preferred brand first [3].

5. Conclusion

Various actions have been taken at federal and state levels to combat opioids epidemic. One of the actions at the federal level is to encourage pharmaceutical companies to develop opioids product that has abuse deterrent properties. Since 2010, FDA has approved ten opioids products that have abuse deterrent properties. In coming years, more ADF products with better abuse deterrent features are expected to be reviewed by FDA. ADF products do not treat addiction rather deter the abuse to some extent. They are more expensive than brand and generics of non-ADFs. Moreover, the generic versions of ADF have not been approved yet. Limited evidence is available on their effectiveness in reducing abuse, overdose deaths and diversion of opioids. Multipronged approach is effective in preventing the abuse of opioids crisis and ADF is one of the components of that approach.

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