J. Med. Toxicol. (2012) 8:400–407

DOI 10.1007/s13181-012-0270-y

REVIEW ARTICLE

Abuse-Deterrent Formulations, an Evolving Technology Against the Abuse and Misuse of Opioid Analgesics

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Published online: 17 October 2012

# American College of Medical Toxicology 2012

Abstract The increased use of opioid pain medication has been mirrored by the increased misuse and abuse of these drugs. As part of a multidisciplinary approach to this epi-demic, pharmaceutical companies, with the encouragement of the Food and Drug Administration, have increased the development of abuse-deterrent formulations. While all have the goal of treating pain while mitigating misuse and abuse, there are different technologies utilized to impart the abuse-deterrent properties. The goal of this paper is to review the basis of abuse-deterrent formulations, the differ-ent types and approaches of some of the abuse-deterrent products, and their current regulatory status in the USA.

Keywords Abuse deterrent formulation . Opioid abuse . Opioid misuse

Introduction

The use of opioid analgesics continues to increase in the USA [1–3]. From 1998 to 2007, outpatient prescriptions dispensed for oxycodone rose 166 % from 15.9 to 42.3 million, while hydrocodone rose 94 % from 63.6 to 123.3 million [4]. The significant use of opioids for pain has led to the increased availability of these medications in the popu-lation [5]. An unintentional effect of this was the increase of the abuse and misuse of these drugs which has become a recognized public health concern [6, 7]. In 2009, there were seven million people in the USA aged greater than 12 who

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used prescription-type psychotherapeutic drugs within the last month. Nearly one third of those who first used drugs for nonmedical reasons in 2009 began by using prescription pain medication nonmedically [8]. The strategy to combat this epidemic requires a multidisciplinary approach as out-lined by the White House report of the proposed drug abuse prevention plan. This plan includes education, tracking and monitoring, proper medication disposal, and enforcement with one of the goals being the issuance of a “guidance document on developing abuse-deterrent formulations and on post-market assessment of their performance” [9].

The aim of this paper is to review the basis of abuse-deterrent formulations (ADF), the different types and approaches of the various ADFs by way of some examples, and their current regulatory status in the USA.

Abuse and Tampering of Opioid Analgesics

The potential for abuse of an opioid is essentially predicated on its pharmacokinetic (PK) profile. Drug abusers prefer those drugs that give them a large brain concentration (high Cmax) in the shortest time (low Tmax) [ [1](#page7)0]. The PK properties of in-creasing Cmax and decreasing Tmax correlate with the pharma-codynamic property of the euphoria, or the high, and is referred to as the attractiveness quotient (AQ). The euphoria reinforces the reward behavior, resulting in further misuse or abuse [ [1](#page7)1]. While some formulations may already have a high AQ based on their existing PK profile, some preparations may be rendered more attractive by tampering with the drug deliv-ery system to allow for more rapid and easily accessed drug [ [1](#page7)2]. Extended release and controlled release both refer to drug delivery systems that allow for slow, steady drug release over a longer period of time. This is usually based on the coating, or drug containing matrix. Although often used inter-changeably, they are not the same with the main difference being appropriate laboratory testing to determine confor-mance to the specifications for the rate of release of each

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| J. Med. Toxicol. (2012) 8:400–407 | 401 |
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active ingredient required to receive Food and Drug Admin-istration (FDA) designation of controlled release [ [1](#page7)3,  [1](#page7)4]. Both of these, in theory, should be less attractive due to delivery systems that slow and control release. However, the increase in active ingredient per pill or capsule may make it more attractive depending on the ease with which the drug delivery system might be defeated. Tampering is common with more than 80 % of a group of prescription drug abusers entering a treatment facility admitting that they had altered the drug delivery system by tampering in some way [ [1](#page7)5]. The major forms of tampering other than ingestion (which includes chew and swallow) are inhalation, parenteral use, and smoking [ [1](#page7)5,  [1](#page7)6].

Abuse-Deterrent Formulations

ADFs were formulated to address the tampering with those drugs that might be manipulated resulting in easy misuse or abuse. The first ADF was released in 1983 in response to the crushing, then parenteral use of the combination of Talwin (pentazocine) with tripelennamine HCl (antihistamine) to im-part a heroin-like high. The drug was reformulated to Talwin NX (pentazocine 50 mg and naloxone 0.5 mg). The naloxone would not be clinically active when taken orally; however, if taken parenterally, it would cause withdrawal-type symptoms or decrease the expected euphoria. While there appeared to be a significant decrease in pentazocine abuse after the release of the new product [ [1](#page7)7], it has been suggested that this may have been partially due to the increased availability of heroin during the same time period [ [1](#page7)8].

Formulations

There is no generally accepted categorization of ADFs. While it seems reasonable to categorize them by formula-tion, some utilize more than one technology. This paper breaks them down into four different categories with exam-ples of each: physical or mechanical barrier, aversion or the addition of a noxious component, agonist/antagonist combi-nations, and prodrug. Some of the drugs described are FDA-approved, while others have either submitted a New Drug Application (NDA) or are in the process of answering a complete response letter (CRL) (Table 1).

Much of the technology remains proprietary, so informa-tion is limited. All information below is based on clinical studies (many sponsored by the respective pharmaceutical company), FDA materials, and promotional material when no other information was available. Because some of these are a reformulation of a well-studied drug, efficacy studies were not always required by the FDA for NDA approval.

Physical or Mechanical Barrier

These types of ADFs employ a physical barrier or char-acteristic that would limit tampering, thus restricting ac-cess to active compound. Although this would not limit abuse by excess doses or pills, the increased difficulty and time necessary to access the drug may make it less appealing [ [1](#page7)9].

Solid

This form of a physical barrier limits access to the active compound by resisting chewing, grinding, crushing, or drug extraction. This is accomplished by way of an external shell or by the drug delivery system.

Oxycodone Extended Release (Oxycontin, Purdue Phar-ma) Oxycodone extended release (OC-E) is a semisynthetic opioid approved in 2010 for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time [ [2](#page7)0]. When the original oxycodone extended-release preparation was released in 1995, the FDA and Purdue both felt that due to the extended-release delivery system, there was less abuse liability than with the immediate-release preparation of oxycodone [6]. Not long after its approval and release, however, reports of abuse were noted which increased con-siderably over the next few years [6,  [2](#page7)1]. Users discovered that if they chewed, ground, or otherwise manipulated the pill, they would defeat the delivery system presumably releasing more drug rapidly [ [2](#page7)2].

The reformulated OC-E consists of a controlled-release tablet covered by a cosmetic film coat. The composition includes a polymer used previously in approved tablet formulations. During the manufacturing process, the controlled-release tablet is heated above the melting point of the polymer. On cooling, the polymer fuses to impart plastic-like properties to the tablet [ [2](#page7)3]. Extraction is described to be very limited. It is reported to be much more difficult to grind or crush with resultant large pieces that would be difficult to nasally insufflate. Even if crushed, a viscous gel forms when added with a solvent, decreasing a user’s ability to draw it up into a syringe for intravenous use [ [2](#page7)3]. Bioequivalence of OC-E was shown with the original formulation in both the fasted and fed state across different doses [ [2](#page7)4,  [2](#page7)5].

Purdue stopped making and distributing all dosage forms of the old formulation in August 2010. The FDA has requested post-marketing and epidemiologic studies to bet-ter evaluate the new preparation.

Oxymorphone Extended Release (Opana ER, Endo Phar-maceuticals) Oxymorphone extended release (OX-ER) is a

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| 402 |  |  |  | J. Med. Toxicol. (2012) 8:400–407 | |  |
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| Table 1 Abuse-deterrent formulations | | |  |  |  |  |
|  |  |  |  |  |  |  |
| Formulation | Trade name | Active drug/generic | Technology | Pharmaceutical company | FDA approval |  |
|  |  |  |  |  |  |  |
| Physical Barrier |  |  |  |  |  |  |
| Solid | Oxycontin | Extended-release | Fused polymer creating | Purdue Pharma | Yes, 2010 |  |
|  |  | oxycodone | plastic-like coating |  |  |  |
|  | Opana ER | Extended-release | Polyethylene INTAC process | Endo Pharmaceuticals | Yes, 2011 |  |
|  |  | oxymorphone | (Grunenthal) |  |  |  |
| Gel | Remoxy | Controlled release | SAIB creating a viscous, gel | Pfizer; Pain | No, denied 2011. No |  |
|  | XRT | oxycodone | matrix (ORADUR by | Therapeurics | resubmission date |  |
|  |  |  | DURECT Corporation) |  | for NDA |  |
|  | Oxecta | Immediate-release | Functional excipients causes | Pfizer; Acura | Yes, 2012 |  |
|  |  | oxycodone | gel-like consistency with | Pharmaceuticals |  |  |
|  |  |  | tampering, also causes local |  |  |  |
|  |  |  | irritant symptoms (Acurapharm) |  |  |  |
| Aversion | Acurox | Immediate-release | Functional excipients as above | Acura Pharmaceuticals | No, denied 2010. No |  |
|  |  | Oxycodone with | with subtherapeutic niacin to |  | resubmission date |  |
|  |  | niacin | cause adverse events |  | for NDA |  |
|  |  |  | (Acurapharm) |  |  |  |
| Agonist/Antagonist | Embeda | Extended-release | Pellets of morphine surrounding | King Pharmaceuticals | Yes, 2009 but recalled |  |
|  |  | Morphine sulfate/ | sequestered naltrexone which |  | for quality concerns |  |
|  |  | naltrexone | can be released with tampering |  |  |  |
|  | Suboxone | Buprenorphine/ | Naloxone becomes active if | Reckitt Benckiser | Yes, 2003 |  |
|  |  | naloxone | utilized parenterally, not | Pharmaceuticals |  |  |
|  |  | Lisdexamfetaminea | sublingually |  |  |  |
| Prodrug | Vyvanse | Becomes active in GI tract | Shire Pharmaceuticals | Yes, 2007 |  |

limiting parenteral abuse, saturation kinetics may limit oral misuse

SAIB sucrose acetate isobutyrate, NDA New Drug Application

a Not an opioid, an amphetamine used in the treatment of attention deficit/hyperactivity disorder

semisynthetic opioid approved by the FDA originally in 2006 for the treatment of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time [ [2](#page7)6]. Because of concerns of abuse and misuse, a reformulated OX-ER was developed and FDA-approved in December of 2011. The reformulated OX-ER utilizes an extrusion process including the polyeth-ylene oxide INTAC matrix offering certain physical and physicochemical tamper-resistant properties. The tablet is dif-ficult to crush and will turn into a viscous gel when combined with fluids [ [2](#page7)7].

Bioequivalence was shown between OX-ER and the original formulation with similar oxymorphone plasma con-centration versus time for 5 and 10 mg doses of both formulations [ [2](#page7)8]. A study on the effects of ethanol on the pharmacokinetics of both the old and new formulations suggests that minimal or modest ethanol exposure is unlike-ly to cause a meaningful change in oxymorphone plasma concentration in either formulation. However, significant ethanol exposure may produce maximum oxymorphone concentration with increases in Cmax and decreases in Tmax of both formulations. There was a stable plasma concentra-tion AUC, suggesting total exposure was the same despite ethanol exposure [ [2](#page7)9].



Gel

This formulation has a structure that is highly viscous or semisolid. It also includes solids that become viscous and gelatinous upon adding water or attempting an extraction. A gel formulation may also limit abuse if it is deemed too difficult to overcome the delivery system.

Oxycodone Controlled Release (Remoxy XRT, Pfizer/Pain Therapeutics) Oxycodone controlled release (OC-R) is a long-acting oxycodone in a gelatin matrix. It utilizes ORA-DUR technology by DURECT Corporation. This proprie-tary formulation uses a base component such as sucrose acetate isobutyrate which is a highly hydrophobic, water insoluble, fully esterified sucrose derivative [ [3](#page7)0]. This high-ly viscous matrix provides the controlled release for the oxycodone that may also limit dose dumping should there be an attempt at tampering [ [3](#page7)1]. Extraction was limited with “common household solvents”, while syringeability was low. There was minimal volatilization with the OC-R char-ring after heating and low yield of oxycodone [ [3](#page7)2].

OC-R had a statistically significant improvement in pain and quality of life score in patients with osteoarthritis [ [3](#page7)3]. Long term efficacy as well as an adverse event profile

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| J. Med. Toxicol. (2012) 8:400–407 | 403 |
|  |  |

similar to other opioids and tolerability was also reported in a study of patients with osteoarthritis [ [3](#page7)4]. It is important to note that the control in the efficacy study was placebo, not another oxycodone product. There is no reported study that compares OC-R to other oxycodone products. Bioavailabil-ity was reported in preclinical testing as consistent across multiple studies for a 40 mg dose [ [3](#page7)2].

An abuse potential study showed significantly lower drug likeability and thus potentially decreased abuse po-tential for both whole and crushed OC-R compared to both whole and crushed oxycodone immediate and extended-release preparations [ [3](#page7)5].

After resubmission of a prior NDA that was denied, Pain Therapeutics again received a CRL from the FDA in June 2011, signifying that their NDA had not been approved. The FDA indicated that there were concerns in the Chemistry, Manufacturing, and Controls (CMC) section of the NDA, specifically that some of the lots showed inconsistent release during in vitro testing. There is currently no resubmission date announced.

Oxycodone Immediate Release HCl (Oxecta, Pfizer/Acura Pharmaceuticals) Oxycodone HCl 5 mg (OC-O) was ap-proved by the FDA in June 2012 for the treatment of acute and chronic, moderate to severe pain. It was for-mulated using Acurapharm’s Aversion Technology which includes a proprietary essential composition of functional inactive excipient [ [3](#page7)6,  [3](#page7)7]. These excipients are utilized to limit the potential for abuse as the crushed tablet causes nasal irritation such as stuffiness, lacrimation, dryness, rhinorrhea, and throat irritation. The drug is also designed to minimize syringeability as it becomes a viscous gel if there is an attempt at extraction or addition of a solvent [ [3](#page7)6].

OC-O showed bioequivalence to a similar approved oxy-codone product [ [3](#page7)8]. Based on the well-described properties of approved oxycodone, the FDA did not require further safety or clinical efficacy studies. There were safety and CMC studies for the proprietary excipients, which were deemed acceptable by the FDA [ [3](#page7)6].

Although the FDA agreed that a descriptive analysis of the decreased likeability of snorting OC-O versus conventional oxycodone was significant, statistical and blinding concerns precluded them from agreeing that there was a statistically significant difference leading to a description as abuse deterrent. There was more diffi-culty snorting the OC-O than the conventional oxyco-done product as well as more adverse events such as nasal irritation, nasal blockage, sore throat, and lacrimation with the OC-O [ [3](#page7)6].

The FDA decided that OC-O’s decreased likeability was significant enough to allow labeling, pointing out that the difference may lead to potential decreased abuse liability.

The FDA is requiring post-marketing and epidemiologic studies to define the actual abuse liability of OC-O [ [3](#page7)6].

Aversion

Aversion technology utilizes a noxious component added to the formulation to discourage abuse because of unwanted adverse events.

Acurapharm also utilized Aversion Technology to formu-late an immediate-release oxycodone product with subther-apeutic niacin (Acurox, Acurapharm). The premise of this formulation was that as the excipients decreased abuse po-tential via the IV or IN routes as previously described, the subtherapeutic niacin would cause unpleasant flushing and other adverse events as the oral dose was increased by taking too many tablets. The FDA did not approve this drug with concerns that with 60 mg of niacin, which was the equivalent of two tablets, patients had an increased risk of adverse events. It was also noted that food would attenuate the niacin flush, as would aspirin and nonsteroidal anti-inflammatories. The decision was made that the risk of the adverse events in the compliant population was not worth the potential added benefit that may be gained by the addi-tion of the niacin [ [3](#page7)9]. There are currently no similar-type products approved by the FDA.

Agonist/Antagonist

Morphine Sulfate and Naltrexone HCl, Extended Release Tablets (Embeda, King Pharmaceuticals)

Morphine sulfate and naltrexone HCl, extended release tab-let (MS-N) was approved by the FDA in August 2009 for the management of moderate to severe pain when a contin-uous, around-the-clock opioid analgesic is needed for an extended period of time [ [4](#page7)0]. MS-N contains pellets of morphine sulfate surrounding a central core of sequestered naltrexone hydrochloride in a ratio of 100:4 (morphine/ naltrexone). Each morphine pellet has an outer polymer layer that provides the extended-release delivery while also not allowing the release of the naltrexone.

Efficacy was shown in a multicenter, randomized, double-blind, crossover study comparing MS-N to extended release morphine sulfate (ERMS) in chronic osteoarthritis patients. Efficacy outcomes for pain were similar for MS-N and ERMS with most patients rating both treatments as good, very good, or excellent. Steady-state plasma concentrations indicated comparable bioavailability between MS-N and ERMS. Nal-trexone was adequately sequestered with plasma concentra-tions of naltrexone and its major metabolite, 6-b-naltrexol, low or below the limit of quantification for most patients and did not affect pain [ [4](#page7)1].



404 J. Med. Toxicol. (2012) 8:400–407

If the capsules are chewed, ground, or otherwise tam-pered, the orally available naltrexone will be released, caus-ing the decrease in the euphoria expected by the morphine. In a study of experienced, non-addicted recreational opioid users, there was a lower Cmax and a longer Tmax with intact MS-N than a morphine sulfate solution (MSS). In crushed capsules, morphine concentrations over time were the same for crushed MS-N capsules and MSS, but with decreased euphoria and “liking” for both the whole and crushed MS-N versus the MSS [ [4](#page7)2].

Since its release, MS-N has had multiple recalls primarily because of stability issues. The inadvertent release of nal-trexone in non-tampered capsules could cause potential adverse events in those taking the medication appropriately [ [4](#page8)3]. In March 2011, King Pharmaceuticals, a subsidiary of Pfizer, initiated a voluntary recall of all dosage forms of MS-N. The company stated that although the stability issue would likely not cause a safety issue, the failure of routine stability tests resulted in the recall [ [4](#page8)4]. It remains unavail-able with no return date announced.

Buprenorphine/Naloxone (Suboxone, Reckitt Benckiser

Pharmaceuticals)

Buprenorphine/naloxone (BUP-N) is a sublingual capsule and film combination product of buprenorphine, a partial mu opioid agonist, and naloxone, an opioid antagonist, in a 4:1 ratio [ [4](#page8)5]. It has been available in the USA since 2003 for the maintenance of opioid dependence. BUP-N was approved at the same time as buprenorphine (BUP) alone after multiple reports of IV BUP abuse in Europe were published since its initial approval in France in 1996 [ [4](#page8)6]. Since naloxone is not significantly bioavailable sublin-gually, it would cause no effects if taken appropriately. If the BUP-N were to be injected, the naloxone would be biologically active either mitigating the euphoria from the opioid or potentially precipitating withdrawal symptoms.

BUP-N and BUP were noted to be equally effective in office-based opiate treatment, both of which were signifi-cantly more effective than placebo [ [4](#page8)7].

BUP-N has been reported to have reduced abuse liability in various opioid-dependent patients [ [4](#page8)8– [5](#page8)0]; however, post-marketing results have shown variable success. A study in Malaysia that evaluated the continued IV use of BUP-N after the discontinuation of BUP reported that 98 % either injected the same amount or more after the change with only 2 % decreasing their injection [ [5](#page8)1]. In Finland, 68 % of respondents in a survey at a needle exchange clinic reported that they had tried injecting BUP-N; 45 % used it more than once, and 8 % used it regularly. However, 80 % reported that experience of BUP-N was “bad” compared to BUP and they were willing to pay significantly less for BUP-N than for BUP. Only 2 % of those were in active treatment [ [5](#page8)2].



Another Finnish study of a population of drug abusers in active treatment that were changed over to BUP-N from BUP, however, reported minimal abuse and misuse [ [5](#page8)3].

Prodrug

Prodrugs are biologically inactive substances that are me-tabolized in vivo to their active form. This is generally accomplished by the hydrolysis of an ester or an amide group. There are two types of prodrugs: Type I in which the biotransformation occurs intracellularly and Type II in which the biotransformation occurs extracellularly. There are further subsets based on the specific extracellular site, with the gastrointestinal (GI) tract being Type IIA [ [5](#page8)4]. If an oral formulation needs to be in the GI tract to become active, this would theoretically minimize the abuse from the intra-nasal or intravenous routes. Although it does not specifically address abuse by ingesting multiple doses, the GI biotrans-formation is the rate-limiting step. Therefore, if the enzymes become saturated after a large dose over a short period of time, absorption would be delayed, thereby potentially de-creasing the Cmax and increasing the Tmax. This may de-crease the euphoria that reinforces the behavior [ [1](#page7)1,  [1](#page7)9].

Lisdexamfetamine (Vyvanse, Shire Pharmaceuticals)

Although not an opioid, lisdexamfetamine (LDX) is the inactive prodrug to dexamphetamine utilized in the treat-ment of attention deficit/hyperactivity disorder. After oral ingestion, (LDX) is metabolized in the GI tract L-lysine and the active D-amphetamine. There is no active D-amphet-amine in the parent formulation; therefore, manipulation by crushing or extraction will not result in the active drug. In studies of stimulant abusers, there was no difference in abuse-related liking between IV LDX and placebo [ [5](#page8)5]. Also, likeability was significantly decreased with LDX ver-sus D-amphetamine although that difference disappeared at higher LDX doses [ [5](#page8)5].

Currently, there are no opioids utilizing this technology; however, a prodrug form of hydrocodone has been sug-gested with a covalently bonded moiety such as an amino acid or carbohydrate. The prodrug would theoretically de-crease bioavailability if injected or snorted, with the same saturable kinetics that might limit the euphoria [ [1](#page7)9].

ADFs and the FDA

In response to the increased misuse and abuse of opioids, the FDA in 2009 announced a requirement to develop a Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting (ER/LA) opioid products. REMS was finalized and released in July of 2012 with the goal being

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| J. Med. Toxicol. (2012) 8:400–407 | 405 |
|  |  |

to reduce serious adverse outcomes resulting from inappro-priate prescribing, misuse, and abuse of ER/LA opioid anal-gesics while maintaining patient access to pain medication [ [5](#page8)6]. While not specifically discussing ADFs in the REMS, the FDA has encouraged their formulation with the January 2010 release of a draft guidance for industry on assessing the abuse potential of drugs. In this guidance, the FDA recommends a three tier approach to the determination of the abuse potential of drugs to be submitted in an NDA: (1) in vitro manipulation and extraction studies to evaluate the ease with which the abuse-deterrent mechanism can be defeated; (2) clinical pharmacokinetic studies compared to reference products, including effects of food or alcohol; and

(3) human abuse liability studies to compare the subjective effects of the whole or tampered test product in comparison to whole or tampered reference product [ [5](#page8)7].

Based on the assessment, the determination of abuse liability must be submitted to the FDA with the NDA. These factors, along with other criteria, also contribute to the determination of a drug being scheduled by the DEA under 21 U.S.C.812 [ [5](#page8)8].

For a new drug wanting to make a claim of “abuse deterrent,” the FDA specifically recommends that the new drug be studied for relative abuse potential with a previously approved product as the positive control. The guidance also calls for vigorous assessment of efficacy, safety, biopharma-ceutical, and epidemiologic studies. Included in this would be the aforementioned primary determination of abuse lia-bility as well as post-marketing and robust epidemiologic studies [ [5](#page8)7]. Currently, there are no FDA-approved drugs labeled as “abuse deterrent”.

Making an Impact on the Abuse and Misuse of Prescription Opioids

ADFs have the potential to allow for treatment of pain while minimizing certain types of abuse [ [1](#page7)2]. As part of a com-prehensive plan that includes regulatory, educational, and industry intervention, ADFs may offer an advantage if they can reduce the likelihood of worsening addiction in pain patients and recreational users, minimize the complications from those already addicted, and minimize the morbidity and mortality of unintentional ingestion or overdose [ [5](#page8)9].

After approval of the new formulation of oxycontin, a study was undertaken to evaluate the effect of the ADF on the use oxycontin and other opioids. The results showed that oxycontin as a primary drug of abuse decreased significant-ly while the selection of other opioids such as hydrocodone, other oxycodone agents, hydromorphone, and fentanyl rose markedly. Of all opioids used to get high within the prior month, oxycontin dropped dramatically while the selection of heroin doubled. Although 24 % reported finding a way to

defeat the abuse-deterrent component, many more merely switched to another opioid [ [6](#page8)0]. While the ADF appeared to decrease the use of the target drug, there was no evidence that the users stopped their drug use; they just substituted another. ADFs will likely have a much better chance of making a significant difference when other non-abuse-deterrent formulations of opioids are no longer available [ [1](#page7)2]. Recently, new legislation has been proposed to address this issue as well as direct pharmaceutical companies and the FDA to further the research, development, and release of abuse-deterrent opioids [ [6](#page8)1].

The FDA views abuse deterrence as setting limits or impediments to abuse rather than being able to outright eliminate abuse [ [5](#page8)7]. This may speak to the fact that there may not be a formulation that is completely abuse-proof. There are numerous websites and threads dedicated to defeating the new drug delivery systems as well as the potential effect these may have on the end user’s goals of abuse and misuse. The results are mixed but the efforts continue [ [6](#page8)2– [6](#page8)4]. Extensive studies are needed to define the potential benefit (or lack of benefit) of ADFs. Many different individuals are exposed to opioids, and they are used, misused, and abused in so many ways that there can never be one study design or scale that will define the change in abuse liability of all ADFs for all popula-tions. The studies will require a broad variety of research design and will need to evaluate variables such as abuse liability in different populations, post-marketing epidemi-ologic data, and pain treatment efficacy [ [5](#page8)9]. This will allow for the most robust result that will be useful as these formulations and strategies continue to be developed and improved.

Conclusion

Opioid analgesic use continues to increase in the USA, and their high rate of abuse and misuse require the aggressive development of a comprehensive approach to minimize this while appropriately treating pain. ADFs are a relatively new but potentially promising component of this strategy. As these drugs are designed and approved, robust pre- and post-marketing studies will be imperative to better evaluate the success of these novel formulations.

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406 J. Med. Toxicol. (2012) 8:400–407

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