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Abuse deterrent technology

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ABSTRACT

Many pharmaceutical active ingredients, in addition to having excellent activity in their appropriate application, also have potential for abuse, i.e. they can be used by an abuser to bring about effects other than those intended. Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria. The abuse-deterrent composition prevents the immediate release of a substantial portion of drug, even if the physical integrity of the formulation is compromised (for example, by chopping with a blade or crushing) and the resulting material is placed in water, snorted, or swallowed. However, when administered as directed, the drug is slowly released from the composition as the composition is broken down or dissolved gradually within the GI tract. "Abuse-deterrent composition" or "abuse-deterrent formulations" are used interchangeably herein to refer to compositions that reduce the potential for improper administration of drugs but that deliver a therapeutically effective dose when administered as directed. Improper administration includes tampering with the dosage form and/or administering the drug by any route other than instructed. The object of this review is to provide an overview of the various types of premarketing tampered and abuse drug studies.

Keywords: Abuse; deterrent; Opiates; Formulations

INTRODUCTION

Misuse refers to an exposure resulting from the improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. Abuse refers to a deliberate exposure to a substance (including alcohol and illicit drugs) on which the person is dependent, or in order to achieve a euphoriant or psychotropic effect. The misuse and abuse of prescription medicines is a growing public health problem. In addition to the tragic toll on families and communities, prescription drug abuse results in increased costs to the health care and the criminal justice systems.[1]Abuse of prescription medications is being combated with the advent of novel formulations designed to prevent or discourage tampering and misuse.[1] The ability of these abuse-deterrent and tamper-resistant formulations to impact abuse, and the test methods used to determine their lowered abuse potential is becoming more important. There are three main reasons for the need to access these formulations to determine if a formulation itself can impact abuse of a product, for standardized methods that can be used to support product labeling, and to evaluate both new and generic products for tamper-equivalence.[1,2]

The treatment of pain and patients access to needed opioid analgesics has always been in conflict with preventing the misuse and abuse of these potentially addictive medications. With prescription drug abuse growing to epidemic proportions in the United States, as shown in Fig.1, it is now becoming significantly important to find effective

solutions that lower abuse. Recent strategies have been proposed and implemented with efforts to specifically help curb abuse of prescription medications.[2]One strategy gaining increasing attention is the development of novel dosage forms that are engineered to be more resistant to tampering and abuse when compared to traditional formulations already on the market. These tamper-resistant and abuse-deterrent medications have recently entered the clinical setting over the last three years, and their effectiveness at deterring abuse in the real-world is now being examined. [2,3]

The development of abuse deterrent dosage forms is in its early stages and the study methods used to evaluate products that have gained FDA approval are few, and not always designed properly to show the effect of important variables. In addition to the typical drug safety, efficacy, pharmacokinetic, and performance studies of most products, abuse deterrent formulations are often first evaluated in-vitro for their resistance to physical and chemical tampering. These methods include how the product performs under stresses such as being crushed, grated, ground, mixed with solvents, frozen, heated, drawn up and out of a syringe, and the effects of ethanol on accelerating dissolution. Since different drugs and formulation types have been associated with very different probabilities in their routes of abuse and tampering [4], manipulation studies should focus on the most apparent abuse methods for a particular product.

The need to evaluate how these novel formulations perform is primarily fuelled by three main reasons. The first, and probably the most obvious, is to determine if they have an impact on public health. Studies that can show these formulations are associated with less abuse, less "liked" by abusers, have lower street value or are associated with decreased overdoses and or deaths would define that a product's formulation plays a major role in preventing its abuse. Additionally, studies with positive outcomes may drive legislation that requires tamper-resistance to be incorporated into all prescription drugs having abuse potential.[5] The STOPP (Stop Tampering of Prescription Pills) Act is one example of federal legislation that, if passed, would require pharmaceutical manufactures to produce tamper-resistant formulations of specific drugs, and would prohibit sales of previously approved non-tamper resistant formulations if a new safer version of the drug is approved by the Food and Drug Administration (FDA) [1,6].

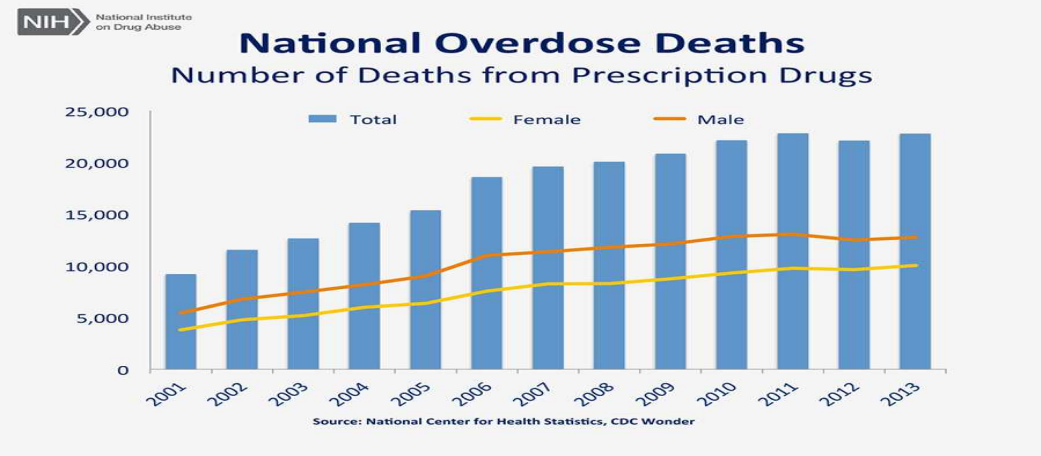

Fig.1 Number of deaths due to overdose of prescription drug without supervision of expertise

2.Objectives:

FDA laid down various objectives to study the drug abuse by opoids, their agenda is to reduce abuse of drug including opiods is by

a)Improving the use of opioids through careful and appropriate regulations.
b)Improving the use of opioid through education of prescribers and patients.
c) Improving the safe use of opioids through partnership and collaboration.
d)Improving the use of opioids through improved science

2.1 Drugs are misused or abused:

1. Opioids prescribed for pain relief
    a. Hydrocodone
    b. Hydromorphone
    c. Morphine
    d. Oxycodone
2. CNS depressants: Barbiturates and Benzodiazepines
3. Stimulants prescribed for ADHD, sleep disorders, obesity

3.Abuse-deterrent products:

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. As a general framework, abuse-deterrent formulations can currently be categorized as follows: [7, 8]

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse. [9]

2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted. [10, 11]

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted. [12]

4. *Delivery System* (including use of depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.[13,14]

5. *New molecular entities and prodrugs*– The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).

6. *Combination* – Two or more of the above methods could be combined to deter abuse. [15]

7. *Novel approaches* – This category encompasses novel approaches or technologies that are not captured in the previous categories.[16]

3.1 Different Strategies Limiting Drug Abuse/Misuse:[17]

1. Pharmacological strategies:
- Antagonist

2. Drug delivery strategies:
- Repulsive Agent
- Gelling Agent
- Hardener Agent/Process

A) **Repulsive agent:**

I. Irritant e.g. Capsaicin as irritant is used to limit snorting abuse as well as to some extent the oral abuse (chewing), intravenous abuse and injection failure.

II. Bittering agent e.g. Denatonium benzoate is used as bittering agent to limit oral abuse as well as helpful to reduce snorting.

III. Colorant e.g. Rohypnol® Reformulation responded to concerns about the drug's role in sexual assaults.

New formulation containing a blue core that dyes liquid blue (Indigotin) which limit snorting and chewing/sucking abuses.

B) **Gelling agent:**

I. Highly viscous gel:

e.g of Remoxy® (Oxycodone HCl) it limits snorting and extraction/ injection abuses due to high-viscosity components helps in limiting crushing and drug extraction.

II. Gelation induced by water:

e.g of Concerta® (Methylphenidate HCl) helps to limit mainly snorting and extraction and injection abuses.

III. Gelation induced by shear-stress:

Gelation induced systems generally limits extraction and injection abuses. The major example of this system is the Trigger Lock™ technologies which are with coated microparticles, in which polymer combination increases drastically solvent viscosity after crushing the formulation.

C) **Resistance to crushing**:

I. Mechanical resistance: Example of OxyContin® reformulation. It is of great success as because of the use of excipients and addition of a curing step after compression to strengthen the tablets,as shown in Fig.2[18].It causes difficulty to crush the tablet into powder gives limitation of snorting, extraction and injection abuses whereas no dose dumping in alcoholis seen.

Fig.2 Tablets with hardness that difficult the crushing to avoid abuse

3.2 M**arketed Formulations:**

Product	Abuse deterrent property	Company
Nucynta® ER (tapentadol ER tab)	Mechanical resistance	Johnson & Johnson / Janssen Pharmaceuticals
Oxycontin® (oxycodone CR Tab)	Mechanical resistance Gelling in the solvents	Purdue Pharma
Exaglo® (hydromorphone ER tab)	OROS technology, hard outer shell Gelling in the solvent	Mallinckrodt
Opana® ER (oxymorphone ER tab)	Crush resistant "Intac technology" by Grunenthal	Endo Pharmaceuticals
Oxecta® (oxycodone tab)	Gels in liquid Nasal irritant	Pfizer Inc. (formerly King Pharmaceuticals)

Table 1: Current availability of marketed formulations having abuse deterrent properties

CONCLUSION

Challenges with evaluation of ADF are seen because Premarketing studies have their limitations. It is difficult to measure consequences of non-medical use. Standard data collection or measures used in population based epidemiological studies may not apply to measuring abuse. Current surveillance systems have their limitations; new

surveillance systems may be needed. Defining population of abusers can be difficult. Even when decrease in abuse of one product is demonstrated, the overall impact on the abuse problem may not be observed until more abuse-deterrent products are on the market. The concept of abuse deterrence is viewed as the introduction of some limits or impediments to abuse, as opposed to the outright elimination of the target for developers:To limit the attractiveness of their formulations to abusers, LockTab® is a flexible and well-adapted formulation to limit drug abuse by crushing or breaking tablets and swallowing (with and without alcohol)or by crushing and snorting and injecting.

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