

Drug Tampering and Abuse Deterrence

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Abstract

There has been a growing response from governments, industries, and academic institutions to address the worldwide incidence of prescription drug abuse. These organizations have addressed this prominent public health concern in different ways. One crucial step has been research and development into developing medications that are considerably more resistant to abuse. These novel medications prevent or discourage abuse and tampering, and consequently referred to most often as abuse-deterrent or tamper-resistant formulations. While prescription drugs used to treat insomnia, anxiety, and behavioral disorders are commonly abused, prescription opioids are most significant. Attempts to produce more rapid "high" or euphoria have resulted in various tampering techniques by abusers. Swallowing multiple dosage forms at once, either intact or crushed (chewed), is relatively considered the most common form of tampering, followed by nasal insufflation and injection. However, the prevalent route used can greatly depend on the drug or dosage form. The simultaneous use of prescription opioids with alcohol has also become a dangerous form of tampering that can lead to serious adverse effects and even death. The objective of this paper is therefore to provide a summary of the types of tampering commonly performed during abuse of prescription drugs that can be useful in developing dosage forms more resistant to multiple forms of abuse.

Keywords: Ethanol co ingestion; Formulation; Opioids; Prescription drug abuse

Introduction

There has been a growing response from governments, industries, and academic institutions to address the worldwide incidence of prescription drug abuse. These organizations have addressed this prominent public health concern in different ways. However, the ability to reduce abuse of prescription drugs while still allowing for their ease of access to patients for legitimate use has been a challenging endeavor. One approach has been to develop medications that can deter or even prevent abuse and tampering. These products are often referred to as abuse-deterrent or tamper-resistant formulations. Some have tried to better define tamper-resistant formulations as those having some type of physical resistance to tampering and abuse-deterrent formulations as those having added ingredients that reduce desirability in abusers [1]. However, no classification or naming system exists and other titles such as abuse-proof, tamper-proof, and abuse-resistant are used without distinction though recently, "Abuse-Deterrent Formulations" (ADFs) seem to be the preferred wording by regulatory agencies for all types.

While prescription drugs used to treat insomnia, anxiety, and behavioral disorders are commonly abused, prescription opioids are still the most significant. Attempts to produce more rapid "high" or euphoria have resulted in various tampering techniques by abusers. Swallowing multiple dosage forms at once, either intact or crushed (chewed), is relatively considered the most common form of tampering, followed by nasal insufflation and injection. However, the prevalent route used can greatly depend on the drug or dosage form. The simultaneous use of prescription opioids with alcohol has also become a dangerous form of tamper that can lead to serious adverse effects and even death. Therefore, ADFs must strive to be resilient to the many forms of tampering in order to be the most effective at deterring abuse. In the following paragraphs we briefly highlight prescription drug abuse and the movement towards ADFs. Additionally, the tampering methods most commonly used by abusers are discussed to help formulation scientists gain a better understanding of the scope and nature of this epidemic.

Prescription Drug Abuse Epidemic

Prescription medications are considered safe and effective therapies to treat a variety of medical conditions when used for legitimate purposes. However, their growing misuse was generally overlooked for a number of years as most early studies address their tendency for abuse were conducted over short periods of time [2]. Eventually, large-scale long-term studies drew attention to the high prevalence of prescription drug abuse and its major impact on public health. Overall, abuse of prescription drugs has risen to such high levels that in 2011 the White House Office of National Drug Control Policy classified it as a national "epidemic" [3]. Currently, it is estimated that 6,700 people (aged >12) each day decide to try a prescription medication for the first time for nonmedical purposes; over half the time being obtained free of charge from relatives and friends [4].

The United States has been affected in many ways by this large increase in prescription drug abuse. For example, the number of emergency room visits and unintentional deaths due to controlled prescription drugs increased sharply from 1998 to 2008 [5]. Also, for the first time in our history, it is reported that deaths due to drug poisoning and overdoses now kill more Americans than car accidents, largely because of misuse and abuse of prescription medications [6]. The increased incident of prescription drug abuse has impacted many healthcare related areas as well. From 1999 to 2008, there has been an increase in the number of individuals seeking treatment for substance abuse related to prescription pain medications [7]. The prescription drug abuse problem has also led to rising medical costs. The overall

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direct cost to health insurers resulting from the nonmedical use of prescription painkillers estimated to be up to \$72.5 billion annually [8]. Government has even acted to amend the Federal Food, Drug, and Cosmetic Act to withdraw, suspend, or refuse approval of medications having abusable drugs in formulations not resistant to abuse [9].

Furthermore, the abuse and misuse of prescription medications is not limited to the United States. According to a United Nations World Drug Report, the demand for cocaine, heroin, and cannabis (all illicit drugs) has declined or stayed the same while the production and abuse of prescription opioid pain medications has grown [10].

Drugs Most Commonly Abused

It may be apparent that not all drugs or dosage forms have the same potential for abuse. Medications containing certain families or classes of drugs have been more abused than others. Overall, the top classes of prescription drugs most associated with abuse are [11,12]:

- i) Opioid analgesics (e.g. codeine, morphine, hydrocodone, oxycodone),
- ii) Central nervous system depressants (e.g. phenobarbital, alprazolam, zolpidem)
- iii) Central nervous system stimulants (e.g. amphetamine, dextroamphetamine, methylphenidate)

Opioids are medications similar to morphine, which commonly produce a sense of well-being or euphoria in the user making them prone to abuse. CNS depressants can cause drowsiness and a calming effect while stimulants produce alertness, energy, and an overall elevation in mood. The opioid analgesic class itself is of major concern as these medications have been attributed to more overdose deaths than all other drugs combined, accounting for approximately 74% of all prescription overdose deaths [8].

The type of dosage form a medication is formulated as also plays a role in the likelihood of abuse. Although a variety of dosage forms (e.g.; tablets, transdermal patches, nasal sprays) are known to be abused, tablets and capsules are the most common. This is likely due to the high frequency at which they are prescribed and therefore easy to access. Certain extended release medications containing large amounts of drug have also been sought after, particularly those in which the controlled release mechanism can be easily defeated. The addicted person may simply chew or crush the medication to release the entire drug content all at once to gain a “high” or “rush”.

The Abuse-Deterrent Movement

The first types of ADFs were often developed using narcotic antagonists added into the formulation to discourage intravenous (I.V.) drug abuse and tampering. Examples include Talwin® NX (approved in 1982) and Suboxone® (approved in 2002) which both added naloxone to prevent I.V. abuse of extracted product, and Embeda® (approved in 1999) which used sequestered naltrexone to discourage product crushing. Furthermore, it is common to see products being reformulated into an ADF after the original product display widespread abuse in the general population (e.g.; Talwin® NX, Oxycontin®, Opana® ER). Today, more emphasis is placed on preventing widespread abuse of products before they enter the market by incorporating abuse deterrent technologies at the start to prevent future tampering and misuse. Additionally, there are more technologies focusing on using inactive ingredients (excipients) and various manufacturing processes to design abuse resilient products without pharmacologically active agents [13]. Recent formulations that did choose to incorporate active

substances (e.g.; opioid antagonist, aversive agents) with their sole intention to deter abuse have been faced with more regulatory scrutiny and manufacturing challenges (e.g., Acurox® with niacin, Embeda®) [14].

The primary focus and use of ADF technologies has been for opioid pain medications, particularly long-acting and extended-release products. Although long-acting opioids are appropriate for chronic pain, a greater number of prescriptions are written for short-acting and immediate release products for management of acute and breakthrough pain. This has provided greater access and availability of immediate release medications for abuse. Particularly because short-term pain medications are often left over by patients after treating acute symptoms, producing a serious source of unused medication for abusers [15]. However, only a very small number of ADFs are formulated with immediate release properties and approved to treat acute pain. This is even in light of the fact that immediate release opioid pain medications have been found to be more misused, abused, and diverted than extended release products [16].

Drug Product Tampering

When a drug taken orally no longer gives the same high or euphoric feeling, abusers may take more (overdose), take it in a different way, or manipulate the medication to produce a better or more rapid euphoria [17]. Altering the medication from its original form for this purpose can be defined as a form of tampering. In this regards, tampering can be generally defined in this paper as an intentional chemical or physical manipulation of a dosage form. For example, a drug displaying heightened effects, when given parenterally compared to orally, will likely see high rates of product tampering specifically for intravenous abuse. Additionally, understanding the tampering methods in the following section better help researchers develop *in-vitro* testing methods that simulate real world abuse conditions. The *in-vitro* evaluation of a products resistance to abuse is important not only for quantifying its resistance to tampering, but also for product labeling and evaluating generic versions of a reference listed drug [18].

Methods of Tampering

Overall, tampering is typically done for two reasons, 1) allow for faster rate of drug absorption, and 2) modify the dosage form to be given by alternate routes. Crushing the dosage form is often the first step done when abusing a medication. Once a medication is reduced to fine particles or powder, it may then be taken orally, smoked, nasally insufflated, or mixed with a solution for extraction and injection. More complex and multistep methods of tampering also exist and include processes involving heating, cooling, and separation of the active drug from product excipients using household or industrial solvents [19]. Examples of the most common forms of tampering are listed below in Table 1.

Ethanol Co-ingestion

The acute ingestion of alcohol with abusable medications is another important type of abuse that can be considered a form of tampering. Certain drugs and excipients used in manufacturing are ethanol soluble, and can readily be dissolved or extracted in hydroalcoholic solutions. This may lead to the drug being rapidly absorbed and produce intensified effects when taken orally with alcohol. This is a major concern with long-acting medications as they may contain lethal amounts of drug if absorbed all at once. When tampering or unintentional means causes the entire dose to rapidly release out of a long-acting medication, it is referred to as “dose-dumping” [20]. Quick

Method	Techniques	Equipment
Mechanical	crushing shearing grinding pulverizing	mortar and pestle, coffee grinder, hammer, blender, worm drive clamp, cheese grater
Chemical	dissolution solvent extraction	water, beer, wine, spirits, soda, lemon juice, household cleaners
Thermal	heating freezing	oven, microwave, freezer, liquid nitrogen, dry ice
Oral	chewing multiple administration	saliva, masticatory force
Parenteral	syringeability injectability filtration	needle, syringe, cotton filter, cigarette filter, spoon, heat source
Insufflation	crush	straw, bill, pen, spray bottle
Inhalation	burn or heat	lighter, stove, candle, aluminum foil

Table 1: Common Tampering Methods.

exposure to high levels of opioids can cause severe adverse effects such as altered mental status, severe sedation, respiratory depression, and even death. The mixture of ethanol and prescription drugs is well-recognized in the college party scene. In the United States, it is estimated that 1.1 million undergraduate students each year combine prescription drugs and alcohol [21].

Multiple Administrations

The practice of taking more than the prescribed amount of a drug at once is a dangerous form of tampering done by abusers that can lead to an overdose with deadly consequences. To date, no single drug formulation has been able to successfully prevent or significantly decrease this form of fatal abuse. Thus other forms of prevention have been utilized. For example, community overdose prevention programs have been started to distribute take-home injectable naloxone to cut down on the number of lives lost to overdose [22].

The Future of ADFs

Development and research of ADFs has been evolving rapidly in response to the high levels of prescription abuse over the last decade. Such efforts seem to have made an impact in decreasing abuse and lowering product tampering by abusers [23]. Because it is impossible to tell which drugs will become abused and have higher rates of tampering and diversion after entering the market, the best approach is to formulate all high risk medications with abuse deterrence capability. However, if these formulations are not affordable compared to their non-abuse resistant counterparts, they will unlikely be clinically prescribed to a large enough degree to show a sensible impact on abuse. Therefore, we are left with two choices. First, research and development of ADFs must focus on finding ways that make products resistant to tampering but at an economical price of manufacturing. Second would be for regulatory agencies to recall or ban the sale and distribution of non-ADFs when a comparable product is approved having abuse deterrent properties. These steps could greatly benefit public health by reducing prescription abuse, reduce transmission rates of HIV and Hepatitis C infections in injection users, and lower overdose deaths from prescription opioids.

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