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Editorial

Path to Deter Drug Abuse

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There has been major concern across the nation regarding the pharmacological treatment of pain and other medical conditions (e.g., anxiety, insomnia, attention deficit disorder) with medications having high abuse liability. This concern is largely due to the rapid increase in prescription drug abuse, particularly of opioid based analgesics. Although these medications have been used for legitimate medical conditions, opioids are well known for their high potential for abuse and are commonly seen used for recreational and non-legitimate purposes. The non-medical practices of abuse often involve methods that help to further heighten the euphoric effects of a drug. For example, tablets or other solid dosage forms may be physically tampered with in ways that promote drug release at faster than intended rates. This may involve simply chewing or crushing the tablet before ingesting or more advanced methods of grinding such as the use of a blender or coffee grinder. The small particles produced allow for more rapid dissolution of drug if taken orally and also make the tablet suitable for nasal insufflation (snorting) or inhalation by vaporization (smoking). Additionally, mixing the crushed tablet with a suitable solvent that is capable of dissolving the drug creates a solution that can be filtered and parenterally injected for a rapid effect. A great concern to public health has been the abuse of potent long-acting pain medications containing high drug dose that are made to be safely delivered over an extended period of time. When taken intact and as directed, these formulations have been used without harm. However, if the control release mechanism is not robust and can be destroyed by simple crushing, a large amount of drug can be rapidly released after oral ingestion leading to dangerous blood levels.

Historically, abuse of prescription medications has been deterred with the addition of pharmacological agents (e.g., opioid antagonists) into the product or with the development of less addictive drug moieties. Today, more emphasis is being placed on using inactive ingredients (excipients) and various manufacturing processes to design what are best known as abuse-deterrent formulations.

In the past, the most well-known attempts to develop prescription dosage forms that deter, discourage, or prevent non-medical use have occurred only after rampant abuse of the product created a need for reformulation. The first attempts at making such dosage forms involved the addition of narcotic antagonists into the formulation, particularly to prevent parenteral abuse. One early example was the reformulation of a prescription product containing pentazocine (Talwin®) that was being injected by abusers along with the antihistamine tripelennamine to gain a high similar to heroin [1]. The product was originally approved by the FDA in 1967, a few years before widespread parenteral abuse prompted a reformulation that came out in 1982 [2]. In the United States, the reformulated product include the opioid antagonist naloxone and was renamed Talwin®Nx. The addition of a small amount of naloxone (0.5 mg) is sufficient to block the effects of pentazocine when injected, yet have limited effects when the tablet is taken orally as prescribed. A more recent example of where prevalent abuse prompted a reformulation is with the popular extended release pain medication Oxycontin®. This potent pain medication came to the market at the end of 1995 and was found to be easily crushed, destroying the slow release mechanism and delivering the entire drug at once. By 2000, abuse was far reaching and Purdue Pharma L.P. (Stamford, CT, USA) the makers of the product, began working out a formulation that would be less susceptible to abuse. In April of 2010, a new formulation was approved which relied on inactive ingredient properties and manufacturing processes to produce a tablet more difficult to abuse. The new tablet looks almost identical to the original formulation but resists crushing and milling into a fine powder. Additionally, if crushed, the resultant pieces form a viscous solution when mixed with water and are more resistant to chemical extraction, making the parenteral abuse more difficult [3]. The reformulated version has proven itself to be more deterrent to tampering suggesting that this type of formulation approach can significantly reduce abuse [4]. Furthermore, the reduction in abuse was sufficiently shown to the FDA to allow the manufacturer to be the first to claim in the product labeling that physical and chemical properties of the tablet are expected to make abuse via injection difficult and reduce abuse via the intranasal route (snorting) [5].

Similar to the shift from curative care to preventive medicine, a shift from simple drug formulations to ones having abuse prevention is becoming more common. Prescription medications containing drugs known or suspected to be abused are now entering the clinical arena prepared to handle multiple types of tampering and abuse that can occur after reaching the general population. Examples of these formulations include extended release analgesics such as Exaglo®, Opana ER®, and Nucynta ER, which are formulated with excipients that make them hard to crush, inject, and/or snort. Immediate release formulations include Oxecta® which has gelling agents in the tablet that activate when wet and also includes a substance that causes nasal irritation when insufflated [6]. These new formulation and technology approaches are rapidly expanding and include a number of products and proprietary formulations that are in development, but also include some that have had manufacturing issues, or were denied regulatory approval [7].

The future of drugs is entering a time where we are looking not only at the pharmacodynamics and pharmacokinetics of the active drug, but also are placing emphasis on how the formulation itself can affect these parameters. Furthermore, the ability of a formulation itself to change the abuse liability of a product through innovative technologies can help prevent drug abuse related morbidity, mortality

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and healthcare expenses. It is worthwhile to remember that a drug product must be kept safe and efficacious throughout its use. This must include keeping it safe when inadvertent tampering occurs all the way to intentional abuse, yet still remain effective as a therapeutic agent for its intended purpose. Abuse-deterrent formulations are capable of achieving this by housing medicinal agents in formulations that show promise in lowering prescription drug abuse worldwide.

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