Prescription Drug Manufacturer Attempts to Prevent Abuse of Controlled Substances

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Prescription Drug Manufacturer Attempts to Prevent Abuse of Controlled Substances

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-024-H04-P

Objectives:
After completion of this program, the reader should be able to:

1. Identify ways in which manufacturers can prevent abuse of prescription drugs
2. Distinguish between the requirements established by the FDA for generic vs. brand name drug manufacturers
3. Describe how a manufacturer is already making strides to provide tamper-resistant dosage forms for highly abused drugs
4. List ways in which pharmacists can play an important role in determining prescription drug abuse

Abstract
In the United States, prescription drug abuse is on the rise. This trend has impacted the makers of OxyContin®, as well as the manufacturers of other controlled substances, to reevaluate how they formulate their products, resulting in medications that are more difficult to abuse. These abuse-deterrent formulations utilize physical, chemical and aversion barriers, specific delivery systems, and prodrug technology to prevent abuse. Additionally, some manufacturers have implemented the use of risk-management campaigns and education programs to reduce the misuse of their products. Working together with prescription drug manufacturers, pharmacists play an important role in preventing abuse and educating patients on the appropriate use of their prescriptions.

Background
OxyContin, produced by Purdue Pharma since 1995, is a controlled-release narcotic analgesic indicated for moderate to severe pain. With dosage forms containing between 10 mg and 80 mg of oxycodone, OxyContin has become a significant target for abuse. Instead of using the medication as prescribed, abusers chew or crush the tablet and then swallow or snort the powder to release the drug as rapidly as possible. In some cases, abusers will combine the powder with water or other solvent and inject it intravenously to produce a heroin-like effect. It is this relative ease of administration, combined with its ease of accessibility, that has led to the increased instances of abuse. OxyContin is just one of many prescription drugs that demonstrate substance-abuse potential.

Overall, there were 22,400 drug-overdose deaths in the U.S. in 2005, compared with 17,000 in 1999. Since 2006, adults between the ages of 35 and 54 die more frequently from poisonings, including drug overdose, than from automobile accidents. Opioids were involved in 40 percent of all poisonings in 2006. Furthermore, in 2001, narcotic analgesics represented 14 percent of all drug-abuse related emergency room visits. Of these visits, there was a 41.4 percent increase from 1999 to 2001 in hydrocodone mentions and a 186.3 percent increase in oxycodone mentions. These statistics demonstrate why more media attention has been placed on opioid abuse in recent years. This presents a very difficult situation for health care providers as well as patients with legitimate medical needs. Evidence demonstrates the need for prescribers to make decisions on whether a patient needs the drug for a legitimate reason or if they are simply seeking drugs to feed an addiction. Pharmacists must then make the same decision about dispensing the prescribed drug, often with even less information. Because of these implications, drug manufacturers are looking to decrease the abuse potential of certain drugs.

Manufacturers attempt to prevent abuse
To produce abuse-deterrent drugs, manufacturers have used several approaches. The first creates a physical barrier involving the outer shell or coating of a tablet, which can increase the hardness and make the drug more difficult to extract. Extended-release stimulants used for the treatment of attention deficit-hyperactivity disorder (ADHD), extended-release OxyContin, and MarinolTM, a cannabinoid used as an anorectic and appetite stimulant, all utilize this technique to prevent misuse of these compounds.

The second approach used to prevent drug abuse is to create a chemical barrier. In this technique, an opioid is formulated with an antagonist, such as naltrexone or naltrexone, which blocks and reverses the opioid’s effects when present at a high dose. When used appropriately, these formulations provide only low systemic levels of antagonist, which have little effect. Also, if the oral dose is chewed to release the opioid for immediate effect, a larger dose of the antagonist is released, blocking the euphoric effect of the opioid. More importantly, if an attempt is made to abuse this combination by injection, a substantial amount of the antagonist is delivered into systemic circulation, thereby interfering with the abuser’s intended euphoria. Suboxone®, used to treat opioid dependence, utilizes this technology by combining buprenorphine with naltrexone along with other physical barriers, which makes extraction difficult and time-consuming.

Creating an averting barrier is another way to deter abuse. This technique is similar to a chemical barrier; however, the chemical combined with the opioid is used to produce unpleasant effects when taken in excessive amounts. The prototypic drug of this group is LomotilTM, an antidiarrheal containing diphenoxylate and atropine, an anticholinergic drug with objectionable side effects. A delivery system barrier combines chemical and physical deterrents with a novel drug release design, as
Lastly, the application of prodrug technology is utilized to deter prescription drug abuse. Prodrugs require absorption in the gastrointestinal tract, and then bioactivation into the active form of the drug occurs. Utilizing this technology enables manufacturers to produce drugs that cannot be abused by chewing, snorting or injection. Vyvanse, a controlled substance used to treat ADHD, utilizes prodrug technology. Using these technologies alone or in combination gives manufacturers many options to help fight the war on prescription drug abuse.

Implementing risk-management campaigns is another way manufacturers can regulate the use of their drugs. Risk management is often mandated for specific brand-name drug manufacturers by the FDA. Examples include programs for buprenorphine (Suboxone® and Subutex) and extended-release oxycodone (OxyContin). Interviewing patients, utilizing electronic prescription drug-tracking databases, interviewing treatment providers, and interviewing and educating physicians are important elements of a risk-management program. However, these programs vary in level of involvement. Some only require a medication guide to be dispensed with the medication, while others require the implementation of a communication plan and monitoring of elements to ensure safe use in addition to providing a medication guide.

While risk-management campaigns may be helpful in preventing drug abuse, the FDA does not require generic manufacturers to employ them. Generic manufacturers are only required to establish bioequivalence and mail educational brochures out to prescribers. This poses a significant problem when trying to deter drug abuse considering generics are widely dispensed due to their lower costs. For example, 70 percent of the extended-release oxycodone market is currently represented by generics. Additionally, generic companies do not have to conduct any post-marketing surveillance to pinpoint problems and provide risk prevention. With the use of hydrocodone and methadone increasing dramatically, there is no regulation to provide education to the prescribers or to identify problems. Furthermore, generic fentanyl patches exemplify why simply establishing bioequivalence between a brand and generic drug may not be enough. Original brand name fentanyl patches, Duragesic®, utilized a reservoir system to contain the drug in the patch. These patches were rarely abused because inconsistent levels of drug are obtained from them, often resulting in death. However, some generic fentanyl companies produced a product that utilized a matrix patch system, which requires a larger quantity of active drug to be contained in the patch, making it easier to abuse. To address this problem, the FDA could impose stricter guidelines on generic manufacturers of drugs with addictive properties.

Another attempt by manufacturers to deter prescription drug abuse involves the application of education programs. Purdue Pharma, the maker of OxyContin, created a program in 2003, called “Painfully Obvious,” geared toward preventing prescription drug abuse mainly among teenagers. This campaign sought to make parents and other adults aware of what is in their medicine cabinets and the abuse potential of prescription drugs within their own homes. In addition to creating this education program, Purdue Pharma provided funding to four state-wide prevention groups to create their own prevention strategies.

The Road to Reformulation
OxyContin’s developer, Purdue Pharma, has recently pursued a new objective: to reduce the potential for abuse while maintaining the clinical benefits for the patients who need it. To decrease abuse potential, Purdue Pharma investigated different methods of abuse. Their research revealed that of the 1,368 patients from 2001 to 2004 who entered treatment for OxyContin abuse, 72 percent took the crushed tablet orally, 11 percent “snorted” or inhaled the powder after crushing, and 17 percent injected the powder after crushing and combining it with a solvent. Intranasal and IV formulations were found to be the most dangerous due to the rapid increase in drug blood levels. At the onset of reformulation, the FDA, along with Purdue Pharma, agreed to aim for a product that was both tamper-resistant and effective. The tamper-resistant characteristics were defined as a formulation that was resistant to physical crushing, physical milling and chemical extraction and had no increased dissolution in ethanol. The effective product characteristics were defined as a formulation that released the medication at a rate that was bioequivalent to the previous formulation, a process that was robust enough to undergo commercial manufacture, and a tablet that was chemically and physically stable over time.

After pursuing several different platforms, Purdue Pharma settled on a polymer called Remoxy, which has three distinct characteristics. The first characteristic is that it is very resistant to crushing and breaking. Repeated hammer strikes to a tablet reduce it to a single deformed wafer and not a powder. Many abusers reported crushing the old formulation between two spoons before manipulating it further. The new formulation is too hard and simply cannot be crushed in this way. The second characteristic of the new polymer is that, when the tablet is broken, the fragments retain much of its controlled-release (CR) properties. This is important because most abusers try to first physically break down a tablet and then extract the pure drug from the drug/CR membrane complex. This is done using a wide array of solvents and is known as chemical extraction and can be divided into three subsets. These subsets are simple, which is done at room temperatures with readily available solvents, moderate, also done at room temperature but utilizing more complex and harder-to-obtain solvents, and advanced, which employs the use of heat, time and more toxic solvents. Often in advanced extraction, multiple solvents may be used. Physical crushing of the tablet without the use of solvent was found to rapidly release 91 percent of the dose in the old form and 20-49 percent in the new dose (Table 1). Additionally, 100 percent of the dose was released within five minutes using the old tablet. Using the new tablet, only 20 percent was released in the first five minutes, with just over 40 percent released after 40 minutes. For simple extraction, five different solvents were used on both the old and new form of the tablet. The average percentage of drug released across all five solvents was found to be 87 percent for the old formulation and less than 23 percent in the new formulation. Moderate solvents were tested and found to release more than twice as much drug when used with the old formulation compared to the new one. Results were equally positive for the advanced extraction technique. The old formulation was found to release 1.5 to 3 times as much drug as the new formulation when tested with the same solvent. The third and final property that makes the new polymer so promising is that it forms a viscous gel when combined with any of the aforementioned solvents. This makes extraction of the drug for injection nearly impossible. A single insulin syringe could obtain 49-58 percent of the dose from a tablet that had been crushed and dissolved. The new formulation allowed for less than or equal to 4 percent to be extracted using the same process.
Drugs of Abuse

Prescription Drug Manufacturer Attempts to Prevent Abuse of Controlled Substances

All of these changes reduce the abuse potential for OxyContin while maintaining the same bioavailability for patients with legitimate medical needs. Despite these improvements, it is still important for health care providers to monitor and evaluate each patient before prescribing OxyContin. According to the Director of the Division of Anesthesia and Analgesia Products in the FDA's Center for Drug Evaluation and Research, "Although this new formulation of OxyContin may provide only an incremental advantage over the current version of the drug, it is still a step in the right direction. Prescribers and patients need to know that its tamper-resistant properties are limited and need to carefully weigh the benefits and risks of using this medication to treat pain." The FDA also is requiring Purdue Pharma to conduct a post-market study to determine the effectiveness of the new formulation.

Table 1 Absorption of new vs old OxyContin formulations.

<table>
<thead>
<tr>
<th>% Released</th>
<th>Physical Crushing</th>
<th>Simple Solvents</th>
<th>Moderate Solvents</th>
<th>Advanced Solvents</th>
<th>Insulin Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old Formulation</td>
<td>91%</td>
<td>87%</td>
<td>96%</td>
<td>98%</td>
<td>49-56%</td>
</tr>
<tr>
<td>New Formulation</td>
<td>20-49%</td>
<td>23%</td>
<td>50%</td>
<td>60%</td>
<td>&lt;4%</td>
</tr>
</tbody>
</table>

Unfortunately, since the release of the OxyContin reformulation, current drug abusers have been working together to overcome the abuse-deterrent drug. A quick search on the Internet reveals thousands of message board posts over the last year discussing the change in formulation. Abusers are sharing tips, including recipes, techniques and pictures, on how to abuse the new formulation. Therefore, despite the manufacturer's attempt to deter abuse, it is still occurring. As a result, health care professionals, including pharmacists, need to take an active role in preventing prescription drug abuse.

Pharmacists' Role in Preventing Abuse

While manufacturing attempts to decrease the abuse of controlled substances is a major step forward, pharmacists are in a position to play an integral role in preventing drug abuse. Their unique knowledge base allows them to help prevent abuse by educating and providing awareness of its prevalence and assisting those dependent on a drug. Before a pharmacist even dispenses a controlled substance, appropriateness of therapy must be assessed for each patient. A prescription drug-tracking database, Ohio's Automated Rx Reporting System (OARRS), may be utilized to check for drug-seeking behavior in patients who present to the pharmacy with a prescription for a controlled substance. A few characteristics of drug-seeking behavior to watch for include seeing multiple pharmacists, visiting many pharmacies and forging prescriptions. Once the appropriateness of the drug therapy is determined, a pharmacist's primary role in drug-abuse prevention is to educate the patient on the appropriate use of a controlled substance. Topics include informing the patient of its addictive properties, the possibility of dependency, and appropriate storage and disposal. If it is confirmed that a patient is abusing a prescription and wishes to seek help, the pharmacist is a valuable resource for referring patients to rehabilitation services. Additionally, pharmacists can utilize resources at their disposal to improve their knowledge of substance abuse and to educate other health care providers on the topic.

Pharmacists can take a more intensive role by providing education and ensuring prevention through various programs. Participation in public substance-abuse education and prevention programs provided at grade schools, high schools, colleges, churches and civic organizations is encouraged. These programs should focus on the potential adverse health consequences due to the misuse of drugs. Pharmacists also can foster the development of pharmacy school curricula and pharmacy technician education on the topic of substance abuse. Additionally, professional associations should assume responsibility of advocacy, continuing education and publication of pharmacist-driven research in the field.

Conclusion

Encouraging manufacturers to take a leadership role in the prevention of drug abuse is vital. By utilizing abuse-deterrent medication formulations, as well as risk-management campaigns and education campaigns, health care providers can better care for their patients. Pharmacists, working together along with the rest of the health care team, play an imperative role in educating patients on the appropriate use of controlled medications. Informing patients of the risk associated with these medications in an effort to prevent future abuse will positively impact the war on prescription drug abuse and hopefully aid in the deterrence of this unsettling trend.

References:

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Assessment Questions
1. Which is NOT a way in which manufacturers can prevent abuse of their medications?
   a. Formulating a drug with physical, chemical and/or aversion barriers
   b. Creating an immediate release formulation with high levels of active ingredient to ensure a patient gets the most benefit from the drug
   c. Establishing risk-management campaigns and mandating education programs to ensure safe use of a controlled substance
   d. Utilizing prodrug technology when creating a new drug

2. Risk-management campaigns can include which of the following?
   a. Labeling of approved indications for the medication and listing cautions or warnings
   b. Interviewing patients and educating physicians on high-risk drugs
   c. Utilizing electronic prescription drug-tracking devices and dispensing a medication guide with the medication
   d. All of the above

3. Which of the following is NOT true about generic manufacturers compared to brand name manufacturers?
   a. Generic manufacturers are held to the same strict guidelines in relation to risk management pertaining to prescription drug abuse as brand name companies.
   b. It is sufficient for generic manufacturers to establish bioequivalence between a brand and generic drug and mail educational brochures out to prescribers.
   c. Generic companies do not have to conduct any post-marketing surveillance to pinpoint problems.
   d. Both A and B

4. Drug-seeking behavior that pharmacists should be aware of include:
   a. Seeing multiple prescribers
   b. Utilizing one pharmacy to get all medications
   c. Getting angry when a controlled substance is not in stock
   d. Two of the above

5. Drug-abuse prevention is the main responsibility of
   a. Prescribers
   b. Manufacturers
   c. Pharmacists
   d. All of the above

6. Which is NOT a role the pharmacist plays in preventing prescription drug abuse?
   a. Assess appropriateness of this pharmacotherapy for each patient
   b. Educate the patient on the appropriate use of a controlled medication
   c. Informing the patient of a drug's addictive properties and the possibility of dependency with the goal of deterring the patient from taking the medication
   d. If a patient is abusing a prescription drug and wishes to seek help, the pharmacist may recommend a program that will provide help

7. Pharmacists can play a more active part in preventing drug abuse by participating in
   a. The development of pharmacy school curricula and pharmacy technician education on the topic of substance abuse
   b. Education and prevention programs provided at grade schools, high schools, colleges, churches and civic organizations
   c. Both A and B
   d. None of the above

8. Which statement is FALSE?
   a. A pharmacist's primary role in drug-abuse prevention is to make sure the patient is provided a sufficient drug to alleviate all of their pain regardless of the dependence associated with it
   b. Professional associations should assume responsibility of advocacy, continuing education and publication of pharmacist-driven research in the field to provide insight on prescription drug abuse
   c. Pharmacists can utilize resources at their disposal to improve their knowledge of substance abuse and to educate other health care providers on the topic
   d. Education and prevention programs should focus on the potential adverse health consequences due to the misuse of prescription drugs

9. Which of the following methods is most commonly utilized to abuse OxyContin?
   a. Chewing the tablet
   b. Injecting the powder after combining it with a solvent
   c. Taking several doses of CR tablets at once
   d. Snorting the Powder

10. Which of these characteristics is NOT present in the new OxyContin formulation?
    a. Crush resistance
    b. Fragments that retain some CR properties
    c. Viscous Gel formation when combined with a solvent
    d. Heat Resistance

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Phone: __________________ E-mail: __________________
Pharmacy License #: ______________ State: _______ ONU Alumni? Y N

Program Content: Strongly Disagree Strongly Agree
1. The program objectives were clear. 1 2 3 4 5
2. The program met the stated goals & objectives;
   Identify ways in which manufacturers can prevent abuse of prescription drugs. 1 2 3 4 5
3. Distinguish between the requirements established by the FDA for generic vs. brand name drug manufacturers. 1 2 3 4 5
4. Describe how a manufacturer is already making strides to provide tamper-resistant dosage forms for highly abused drugs. 1 2 3 4 5
5. List ways in which pharmacists can play an important role in deterring prescription drug abuse. 1 2 3 4 5
6. The program met your educational needs. 1 2 3 4 5
7. Content of the program was interesting. 1 2 3 4 5
8. Material presented was relevant to my practice. 1 2 3 4 5
9. Comments/Suggestions for future programs:

Thank You!

Answers to Assessment Questions - Please Circle Your Answer
3. A B C D 6. A B C D

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