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Re-scheduling of hydrocodone: deterring abuse or pain control?

Yevgeniy Lyutov; Mitchelle Rodriguez; Minh Trinh; Tam Tran, PharmD Candidates; Marcus W. Campbell PharmD, BC-ADM

Hydrocodone is a semisynthetic opioid agonist which works by binding to opiate receptors in the CNS, altering the perception of and response to pain as well as suppress the cough in the medullary center. Hydrocodone is commonly prescribed for analgesia in combination with non-analgesic pain relievers (eg. acetaminophen or ibuprofen) or as an antitussive in combination with chlorpheniramine.[1] In addition to these therapeutic effects, hydrocodone can also cause drowsiness, mental clouding, euphoria and changes in mood as do all centrally-acting opioid agonists.[2]

The Controlled Substance Act (CSA) was developed to regulate the manufacturing, importation, possession, use, and distribution of certain substances. In the United States, drug formulations that contain only hydrocodone are listed in Schedule II of the CSA. Hydrocodone combination products containing specified amounts of hydrocodone and one or more therapeutically active non-narcotic ingredients are listed in Schedule III of the CSA. More specifically, these combination products cannot contain more than 3 mg per 1 ml or more than 15 mg of hydrocodone base per dosage form in combination with an active non-narcotic ingredient to be listed in Schedule III.[3,4]

The controversy over the scheduling of hydrocodone combination products is not a new one. The Drug Enforcement Administration (DEA) received a citizen's petition in 1999 requesting that hydrocodone combination products be moved to Schedule II. This led to a request by the DEA to the Secretary of Health and Human Services (HHS) to investigate the issue in 2004. In March of 2008, the HHS recommended to the DEA that hydrocodone combination products should remain in Schedule III of the CSA.[5] This decision was based on the finding that hydrocodone combination products have less potential for abuse than the drugs in schedule II because less hydrocodone will be needed to treat pain in comparison with lower doses of single entity scheduled II opioids. Although acetaminophen does decrease the amount of hydrocodone needed for its therapeutic effect, it is perceived that the toxic effect of high doses of acetaminophen acted as a deterrent for abuse. This was found to be untrue when hydrocodone combination products were compared to oxycodone. They possessed a higher number of toxic exposures and fatalities which demonstrates its misuse and abuse.[3]

In response to the 2008 recommendation, the DEA collected more data regarding the abuse and diversion of hydrocodone combination products and submitted a request to the FDA's Center for Drug Evaluation and Research (CDER) to reconsider up-scheduling all hydrocodone containing products. On January 25, 2013, an FDA advisory committee voted 19-10 in favor of rescheduling hydrocodone combination products from Schedule III to Schedule II.[3] Now the FDA has to decide whether to follow the committee's recommendation.

Some of the evidence supporting the committee's decision includes data on abuse potential and epidemiological data. According to IMS Institute for Healthcare Informatics, hydrocodone and acetaminophen combination products were the most prescribed medication in 2010. The DEA reports that combination products of hydrocodone and other medications have been prescribed to 47 million patients and included in 131 million prescriptions in 2011.[3] This volume of prescribing and use far exceeds other opioids and this increased availability has the potential for increased abuse.

In addition, scientific literature review showed that hydrocodone and hydrocodone combination products produced similar effects to those of Schedule II drugs such as morphine, oxycodone and hydromorphone in a dose-related manner. These opioid effects include "high" and "drug-liking" as well as nausea and dizziness and were observed when hydrocodone doses were 15 mg or higher. In terms of epidemiological data analysis, hydrocodone combination products were involved in less emergency room visits. However, there was a higher prevalence of use of hydrocodone containing products by high school students. This is likely due to the fact that hydrocodone combination products are prescribed more often and more readily available which increases the opportunity for experimentation.[3,6]

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Bates et al. performed a study by doing a survey of patients 2-4 weeks post-operation in the University of Utah Urology center. In this study, 63% of the prescriptions were for hydrocodone. Of the 47% of patients that participated in the post-op survey, only 58% of the patients consumed their pain medication, 67% of the respondents had leftovers from the initial prescription. Then 92.2% of patients indicated that no instructions were given on how to properly dispose of unused medications and of those patients 90.8% indicated that they had kept the extra medication at home. The study supports the idea that limiting the oversupply of prescription opioids and properly educating patients on proper drug disposal will minimize the potential source of prescription diversion.[7]

Leftover medications, including narcotics, become readily accessible to all household members. More specifically, teenagers and young adults have access to prescription medications that can be easily diverted. In 2010 the National Survey on Drug Use and Health data showed that nonmedical use of prescription pain relievers in youths (12-17 years of age) and young adults (18-25 years of age) was the second most prevalent illicit drug use category, with marijuana being first. It demonstrated that 55% of the prescription pain relievers were given free by a friend or relative, 11.4% of prescription pain relievers were bought from a friend or relative and 4.8% of prescription pain relievers were taken from a friend or relative. This was true in regards to all opioids whether schedule II or III.[8]

Rescheduling hydrocodone from schedule III to schedule II will affect prescribers, pharmacists and patients. One potential benefit of re-scheduling hydrocodone is more restrictive prescribing. The restrictions associated with schedule II medications would allow for a decrease in the quantity, frequency and prescribers of hydrocodone. As pointed out by one of the bill's sponsors, US Senator Joe Manchin (D-WV) "patients would need an original prescription for refills, pills would be stored and transported more securely, and traffickers would be subject to increased fines and penalties." Overall, this may lead to potential decrease in diversion, misuse and abuse of hydrocodone.

However, the change from schedule III to schedule II would not come without implications for patients and healthcare professionals. The rescheduling of hydrocodone products will affect its availability to numerous patients currently managing their pain with these products. Patients will not be able to have refills on their prescriptions and the prescriptions will be limited to a three month supply. Only written prescriptions from a physician would be allowed and this would also prohibit nurse practitioners and physician assistants in the majority of states from prescribing the drug. Patients would have to visit their physicians more frequently to get additional prescriptions which would increase cost and make it harder for patients in underserved rural areas to get their medications .[4,9]

Rescheduling hydrocodone may also result in increased co-pays and higher costs to patients. A potential increase in prescriptions of less effective medications may lead to more patients suffering from inadequate pain management.

Prescribing alternative medications at a lower controlled level to avoid regulatory restrictions may increase adverse effects, possibly making treatments unsafe for patients. For example, tramadol may cause seizures and serotonin syndrome when used in higher doses. Codeine has an unpredictable genetic predisposition that can cause a variation in treatment which may result in treatment failure or lead to an overdose. Then non-steroidal anti-inflammatory drugs (NSAIDs) may cause gastrointestinal, renal, and hematological side effects which can be detrimental in some patients. Mortality risk may increase if patients are switched from short-acting hydrocodone to a long-acting opioid product because a majority of deaths related to opioids included long-acting dosage forms. When methadone, a long acting opioid is used as a substitute for hydrocodone as a pain reliever, it resulted in about 33% of opioid related deaths in 13 states.[9]

The rescheduling of hydrocodone will also impact the administrative procedure in pharmacy service. Additional steps are required when pharmacists process a Schedule II medication compared to a Schedule III medication. Refill requests are no longer faxed to medical offices as, prescribers are unable to call pharmacies to send refill authorization and additional administrative documentation will be mandated. [9] Not to mention, prescribers and pharmacists face an increased risk of penalties when incorrectly prescribing and dispensing schedule II medications.[4,9,10]

The proposed changes to hydrocodone combination products scheduling intend to curtail the current prescription drug abuse problems present in the United States. New York has already implemented the new policy as of February 23, 2013. The new policy will not allow the pharmacist to dispense hydrocodone that exists in the pharmacy file before the new policy was implemented. The new policy will also mandate that hydrocodone prescriptions written after the new policy was put in effect, will need to be filed with the other Schedule II substances and a physical inventory will be necessary. However, a DEA-222 form will not be required for placing an order for hydrocodone because as of October 10, 2012, it is still listed as a schedule III controlled substance in the Federal Code of Regulations. As current and future health care providers it is imperative we are aware and current on all laws and regulations regarding medications such as hydrocodone due to the impact this has on so many current and future patients.[11]

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Accessibility of Abuse Deterrent Formulations

Yevgeniy Lyutov, PharmD Candidate; Mitchelle Rodriguez, PharmD Candidate; Katherine Tromp, PharmD

Prescription drug abuse is the intentional use of a medication without a prescription, in a way other than as prescribed, or for the experience or feeling it causes.[1] Prescription drug misuse can consists of using a medication in a manner or at a dose that was not recommended by a healthcare professional.[2] The misuse and abuse of prescription drugs is a growing epidemic in the United States. It is estimated that over 20% of Americans have abused prescription drugs.[3]

The National Institute on Drug Abuse (NIDA) reports the most commonly abused medications are pain relievers, tranquilizers, stimulants, and sedatives. They also state that among these medications, pain relievers are the most frequently abused prescription drug. The CDC reported 1 in 20 US individuals have used painkillers for non-medical use in 2010.[4]

Among adolescents, prescription and over-the-counter medications account for most of the commonly abused illicit drugs. The 2011 Monitoring the Future Study (MTF) from NIDA and National Institute of Health (NIH) showed that 1 in 12 high school seniors reported nonmedical use of Vicodin®; 1 in 20 reported abuse of OxyContin®. They also reported that when high school students were asked how prescription narcotics were obtained for nonmedical use, 70% of 12th graders said they were given to them by a friend or relative.[6]

Prescription opioid analgesics are an important component of pain management. Abuse and misuse of these products, however, have created a serious and growing public health problem. As a result of this growing drug problem, the Food and Drug Administration (FDA) and several drug companies have taken on the task of formulating abuse deterrent formulations for opioids, the most commonly abused painkillers.

In January 2013, the FDA issued a draft guidance document that is meant to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties. Abuse deterrent formulations (ADFs) should mitigate abuse liability, reduce dependence potential, and decrease public health risk. In the guidance document from the FDA they have categorized abuse-deterrent formulations based on the mechanism by which they deter abuse [Table 1].[7] In recent years, several products have gained, are in the process of achieving or have attempted approval from FDA.

Table 1: Abuse Deterrent formulations of opioids by deterrent mechanism

Category of Abuse deterrent formulation	Mechanism	Products
Physical/Chemical Barriers	Physical barriers can prevent chewing, crushing, cutting, grating, or grinding. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents. Physical and chemical barriers can change the physical form of an oral drug rendering it less amenable to abuse	Remoxy®(Oxycodone) capsules. Extended release (ER) formulation. ORADUR™ sustained release gel-cap technology, which deters abuse via physical/chemical barriers that resist crushing, freezing and dissolving [8]
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 tampering	Embeda® (morphine sulfate/naltrexone hydrochloride) capsules an ER formulation that deters abuse by releasing an antagonist when product is tampered therefore deterring crushing, chewing, or dissolving of the tablets.[9]
Aversion	Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used	Acurox® (oxycodone HCl/niacin) tablets an immediate-release (IR) combination product utilizing an aversive agent (Niacin), gel forming polymer and mucosal irritating surfactant to deter abuse.[10]
Delivery System	Certain drug release designs or the method of drug delivery can offer resistance to abuse. These include depot injectable formulations and implants	Probuphine® (buprenorphione HCl) subdermal implant formulation designed using its ProNeura™ technology to deliver six months of medication following a single treatment.[11]
Prodrug	A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for intravenous injection or intranasal routes of abuse	NRP-290 (conditionally bioreversible derivative (CBD) of hydrocodone) is a lysine-modified opioid prodrug that requires a biotransformation in the GI to become active, deterring intravenous and intranasal administration.[12]
Combination	Two or more of the methods mentioned can be combined to deter abuse.	Acurox® (oxycodone HCl/niacin) contains aversive agent and physical/chemical barriers.

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Overall, the development of opioids that are formulated to deter abuse is a step in the right direction. The use of ADFs in the management of chronic pain has the potential to curb the growing abuse of opioids but in order to truly make a difference; these products must be readily available. The recent guidance document released by FDA is meant to help generic drug companies meet the requirements brand name ADFs do.

There are various obstacles that ADFs need to overcome, including availability and efficacy. The majority of the ADFs are still in the approval process, have failed to prove they deter abuse, or have been taken off the market (voluntarily or mandated) [Table 2]. ADFs have demonstrated abuse deterrent capacity theoretically but lack clinical evidence supporting their abuse deterring properties. ADFs also face the availability of less expensive, more bioavailable opioids. Additionally, ADFs have not been able to deter the most common form of abuse, swallowing a number of intact pills or tablets to achieve a feeling of euphoria. Due to the pharmacologic nature of opioid analgesics and their need for the management of pain, the extent to which an abuse-deterrent product is able to reduce abuse will never be absolute.

<Click for references>

Table 2: Market Availability of Abuse Deterrent Opioids

Product	Approval status	Market status
Remoxy® (oxycodone)	Re-submission of NDA FDA Response letter issued June 24, 2011[13]	Not on market.
Oxytrex® (oxycodone/naltrexone)	Phase III trials in October 2005. No NDA application submitted[15]	Not on market
Acurox® (oxycodone/niacin)	NDA submitted December 2008. FDA Response letter issued June 2009[9]	Not on market
Probuphine® (buprenorphine HCl)	NDA application will be reviewed March 21, 2013[18]	Not on market
NRP290	IND submitted June 28, 2005[12]	Not on market
Embeda® (morphine/naltrexone)	Approved August 13, 2009[16]	Voluntary recall: March 10, 2011 due to stability requirements not met during routine testing.
Talwin®Nx (pentazocine/naloxone)	Approved December 16, 1982[17]	Voluntary recall: December 2009, in response to FDA inspection of manufacturing site.
Suboxone® (buprenorphine/naloxone)	Approved October 28, 2002[19]	Currently on market
Oxecta® (oxycodone)	Approved June 17, 2011[14]	Currently on market

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Managing Editor: Marcus W. Campbell, PharmD, BC-ADM

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LECOM Bradenton
5000 Lakewood Ranch Blvd.
Bradenton, FL 34211-4909

941-756-0690 Phone
941-782-5721 Fax

LECOM
SCHOOL OF PHARMACY
CENTER FOR DRUG INFORMATION AND RESEARCH

LECOM Erie
1858 West Grandview Blvd/
Erie, PA 16509-1025

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