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US Food and Drug Administration's Risk Evaluation and Mitigation Strategy for Extended-Release and Long-Acting Opioids

Pros and Cons, and a European Perspective

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Abstract

Prescriptions for opioid analgesics to manage moderate-to-severe chronic non-cancer pain have increased markedly over the last decade. An unintentional consequence of greater prescription opioid utilization has been the parallel increase in misuse, abuse and overdose, which are serious risks associated with all opioid analgesics. In response to disturbing rises in prescription opioid abuse, the US Food and Drug Administration (FDA) has proposed the implementation of aggressive Risk Evaluation and Mitigation Strategies (REMS). While REMS could dramatically change the development, release, marketing and prescription of extended-release opioids, questions remain on how these programmes may influence prescribing practices, patient safety and ultimately patient access to these agents. The extent of the availability and misuse of prescription opioids in Europe is difficult to assess from the data currently available, due in large part to the considerable differences in prescribing patterns and regulations between countries. Balancing the availability of prescription opioids for those patients who have pain, while discouraging illicit use, is a complex challenge and requires effective efforts on many levels, particularly in Europe where policies are quite different between countries.

1. Background

Chronic pain is prevalent in 5–33% and 22% of US and European populations,[1,2] respectively. This highly prevalent condition places a substantial burden on patients in terms of personal suffering, reduced productivity and healthcare costs. Chronic pain remains inadequately treated in many patients. Successful management of chronic pain should be individually tailored to each patient, taking into account his or her pain intensity and duration, disease state, tolerance of adverse events and risk of medication abuse or diversion. A number of long-acting (LA) opioids have demonstrated sustained

improvements in pain intensity and pain-related sleep disturbances in appropriately selected patients with moderate-to-severe chronic pain, particularly when used as part of a comprehensive pain management plan.[3] Prescriptions for extended-release (ER) opioid analgesics for moderate-to-severe chronic non-cancer pain have increased markedly over the last decade,[4] as have postmarketing reports of adverse events associated with opioids. Two percent of the US population use opioids regularly,[5] with a 19% increase in the number of patients from 2000 to 2005. The increased use of prescription opioids over the last decade has been mirrored in an increase in the reported misuse, abuse and diversion of these agents, as well as overdose and death.[6,7] Clinicians can implement procedures such as careful patient screening and on-going monitoring to minimize the risk of opioid abuse without interfering with appropriate use in patients with legitimate chronic non-cancer pain.

There is significant concern regarding the misuse and abuse of opioid prescriptions, and that this problem has a huge impact on public health.[8] This article briefly reviews health issues related to opioid prescription, describes the Risk Evaluation and Mitigation Strategies (REMS) for ER opioids, the possible limitations and the existing situation in Europe.

2. Health Issues Related to Opioid Use for Chronic Non-Cancer Pain

Moderate-to-severe pain is the US FDA-approved indication for nearly all opioids when pain relief is needed for a long stretch of time. Such overly broad indications imply that the FDA has established that long-term use of opioids is safe and effective. Many clinicians may be under the false impression that chronic opioid therapy is an evidence-based treatment for chronic pain and that dose-related toxicities can be avoided by slow upward titration. These misinterpretations lead to over-prescribing and high-dose prescribing.[9] An increased body of medical literature suggests that long-term use of opioids is problematic, especially when prescribed in high doses.[10]

It has been shown that the rate of addiction in patients receiving opioids for chronic pain conditions is high, and estimates of the prevalence of abuse range from 12% to 43%, four times higher than rates for the general population.[11,12] Moreover, the most dramatic increase in drug overdose deaths has been observed with the prescription of opioid medications. The risk of overdose is increased in patients prescribed higher doses of oral morphine equivalents.[13]

In an attempt to prevent abuse, pharmaceutical companies are engineering medications with several fundamentally different technologies, each with its own strengths and weaknesses. Tamper resistance impedes efforts to break an ER pill down and extract its active ingredients in a fast-acting form. Some formulae guard only against crushing. Others resist many manipulations. Chemical combinations mix standard analgesics with antidotes that block the 'high' or with irritants that annoy users. Some formulations only release the second drug if the pill is crushed or otherwise manipulated. Others are engineered to resist over-ingestion. Prodrugs replace standard analgesics with chemicals that only activate when processed in the digestive system, which means they do nothing if smoked, snorted, injected or otherwise routed around the digestive system. Finally, novel delivery systems do away with pills. Patches worn on the skin have medication woven into the material so that it is very hard to extract. Implantable analgesic delivery systems can have a 1-month supply packed into a device inserted under the skin. Before approving any new formulation designed to resist manipulation or curb abuse, the FDA has to see that it works as advertised, and the manufacturer must earn the right to market the drugs as 'safer' by meeting targets set as part of multi-year REMS assigned to each drug at approval. Without labels that proclaim greater safety, there can be little justification to force patients or insurers to pay extra for the new formulations, and yet the only way to test the downstream benefits of the new medications will be to pay extra.[14]

These issues stress the clinical value of utilizing risk assessment prior to initiating opioid therapy, appropriate prescribing practices, and counselling patients. Patients may be overwhelmed by information about drugs with REMS requirements, which could discourage the use of potentially beneficial therapies.[15]

In response to disturbing rises in prescription opioid abuse, the FDA has proposed the implementation of aggressive REMS when a question exists as to whether the benefits of a drug outweigh its risks.[16] The US FDA Amendments Act of 2007 was signed into law on 27 September 2007. This act authorizes the FDA to require pharmaceutical manufacturers and distributors to ensure that the safety of their products continues to outweigh the risks. The new powers ascribed to the FDA are notable, as they add enforceability to safety strategies that were not part of the FDA's prior risk management tools: risk minimization action plans. Failure to comply with REMS can lead to financial penalties of up to $US10 million, and a drug could be deemed misbranded if the REMS is not followed. The new approach to risk management via the FDA has elevated the rigor with which manufacturers must fulfil postmarketing safety commitments.[17] The FDA has recently been petitioned to tighten label restrictions for opioid analgesics as a way to combat the epidemic of addiction and fatal overdoses associated with these drugs.[9]

3. Possible Benefits

A REMS may ensure that the benefits of an opioid medication outweigh the risks. The FDA indicated a need for a class-wide REMS for ER opioids as early as 2009. A REMS for ER opioids was developed by the FDA in April 2011 as a result of stakeholder, industry, public and advisory committee meetings held over several years,[18,19] although the provider participation in this REMS is currently voluntary. This project was designed to mitigate the serious risks of opioid-related adverse outcomes through provider training and patient education. Unlike many of the FDA safety warnings and communications that are often ignored, REMS programmes for LA/ER opioids uniquely provide education and enrolment prior to dispensing and prescribing. Therefore, an opioid REMS is more likely to impact how these agents are prescribed and dispensed than any of the previously released FDA warnings.[20]

Potential components of REMS include medication guides, patient package inserts, communication plans for healthcare providers and elements to ensure safe use (e.g. special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, use of patient registries).[6,21]

3.1 Medication Guide

The purpose of a medication guide is patient education. It provides specific information about risks and safe use of the particular opioid to be prescribed and products in the class. This guide outlines symptoms of overdose and the risks associated with manipulating the product (e.g. breaking or crushing the tablet) or sharing medications with others. Patients are advised to store medications in a safe place and to dispose of unused or expired medications. Patients are also warned of the risks associated with combining them with other substances that act on the central nervous system, or with alcohol or illegal drugs.

3.2 Communication Plan

The purpose of a communication plan is provider education. It underlines the importance of REMS, informs about product-specific risks, and provides protocols for safe use and patient monitoring.

3.3 Elements to Assure Safe Use

The purpose of REMS is the safe access to otherwise unavailable medications. Education programmes should include general information for safe opioid prescribing, product-specific information and patient counselling, as well as information on dispensing, monitoring and follow-up, and enrolment in a registry.

3.4 Implementation System

The purpose of an implementation system is to pre-emptively ensure compliance. It includes certification prior to prescribing or dispensing, and restricting dispensing and distribution to authorized people or entities.

3.5 Timetable for Submission of Assessments

The purpose of the assessments is to determine whether REMS is meeting desired goals through

periodic effectiveness assessments of the overall programme and each component.

4. Possible Limitations

The FDA has publically stated that a REMS for LA/ER opioids was necessary due to the potentially increased risks from dosage forms with possibly lethal amounts of opioids (e.g. oxycontin 80 mg), which could pose increased risks versus immediate-release (IR) products, which typically contain less drug per dosage form (tablet, capsule, etc.). This approach has been criticized because it implies that the IR forms are 'safer' than the ER/LA opioids.[8]

It seems to be necessary to include all opioids in a REMS because if REMS exist only for ER/LA opioids, then prescribers will naturally stop prescribing them and shift to IR opioids, which do not have a REMS requirement. Interestingly, although the Centers for Disease Control and Prevention (CDC) have recently released a report on increased deaths from methadone, no data indicate that ER/LA are more dangerous than IR opioids.[22]

Critics of the FDA's REMS for ER/LA opioids are chiefly concerned with its voluntary prescriber education, as well as the fact that that education will be underwritten by the drug makers.[21] More than 20 opioid manufacturers will be available to provide continuing education programmes to prescribers on the proper use of these drugs. It should be clear that these programmes, sponsored by drug manufacturers, are not based on evidence, and in some cases fail to provide appropriate information. A coalition of experts complained of the overly broad indications for all IR opioids as well as ER opioid formulations and the lack of mention of the risk of addiction to or dependence on the drugs,[9] and that aggressive marketing by drug companies may be responsible for over-prescribing. Indeed, an increasing body of evidence suggests that long-term use of opioids, especially when prescribed in high doses, may be neither safe nor effective for many patients. Thus, they propose (i) striking the term 'moderate' from the indication for non-cancer pain; (ii) that the maximum daily dose be equivalent to 100 mg of oral morphine; and (iii) that the maximum duration for continuous daily use be 90 days. In their opinion, the label changes would not prevent physicians from prescribing opioids at doses and durations that they deem appropriate on a case-by-case basis.

It is expected that once the programme is fully implemented, the number of clinicians prescribing ER/LA opioids is likely to decline. Physicians could stop prescribing ER opioids because of the perception that their prescribing practices will be more closely monitored.[20] A substantial proportion of primary care physicians would not be willing to prescribe opioids controlled by the new REMS, which could have the unintended effect of decreasing access to these medications for legitimate medical purposes.[23] Patients may be overwhelmed by information about drugs with REMS requirements, which could deter the use of potentially beneficial therapies.[15] Thus, these issues could not address the needs of a multitude of patients who have been appropriately prescribed opioid medications. Other voices suggest that the availability of these drugs should be ensured for patients who can benefit from them and concrete approaches to limiting abuses and misuses should be established.[9]

While it is obvious that more education on chronic pain and the use of opioids is mandatory, and information should not be influenced by industry, it is also clear that physicians should be given responsibility for prescribing opioids in proper indications, prescription and monitoring. Demonizing the drug could mean ignoring the responsibility of the prescriber.

Other possible sources of drugs are not included in the education process. The majority of people who are currently abusing opioid analgesics receive them from a friend or neighbour.[24] Any attempt to address the rising problem of drug-related overdose deaths that focusses only on educating patients, providers and pharmacists may have a limited impact, as friends, parents, children and others with whom the patient comes in contact are not involved in this programme.[20] It is likely that REMS will not be influent for patients able to find an approved prescriber and enrolled pharmacy. However, given the existing disparity, patients who have insufficient healthcare resources may find these medications no longer available to them. This programme could change how chronic therapy is delivered. While the REMS programme may have theoretical

capabilities for evaluating and addressing problematic drug use among prescribed patients, it is unlikely to reduce the bulk of prescription drug abuse that occurs with non-patients.[25]

Finally, any effective opioid REMS programme should include all opioids, including IR opioids, particularly in combination with other drugs, and highlight the risks associated with combining them with other substances acting on the central nervous system (e.g. benzodiazepines, anticonvulsants, antidepressants and alcohol).[20]

5. European Perspective

The extent of the availability and misuse of prescription opioids in Europe is difficult to ascertain from the data currently available. Moreover, direct comparisons between the EU and other parts of the world are difficult, due in large part to the considerable differences that exist in prescribing patterns and regulations. There are huge discrepancies in the access to and consumption of opioids between EU countries, with northern countries having the largest opioid consumption.[26] Formulary deficiencies and excessive regulatory barriers interfere with appropriate patient care in many European countries, raising an ethical and public health imperative to address these issues.[27] Whether or not general practitioners prescribe opioids for persistent non-cancer pain is mainly determined by their personal beliefs about appropriateness of opioids for this indication.[28]

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was established in 1993. Inaugurated in Lisbon in 1995, it is one of the EU's decentralized agencies. The EMCDDA exists to provide the EU and its member states with a factual overview of European drug problems and a solid evidence base to support the drugs debate. Today it offers policy makers the data they need for drawing up informed drug laws and strategies. It also helps professionals and practitioners working in the field pinpoint best practice and new areas of research. However, most data concern injection drugs and illicit use or clients of maintenance programmes. Despite a dramatic increase in treatment availability over the years, the number of users dying of drug overdose in Europe has remained the same. Reducing overdose fatalities therefore represents a major challenge for drug services across Europe.[29]

6. Expert Opinion

REMS could dramatically change the development, release, marketing and prescription of LA/ER opioids. However, the direction of these changes is unpredictable. Questions remain on how these programmes may influence prescribing practices, patient safety and, ultimately, patient access to these agents. The impact of any opioid REMS programme should be determined with an appropriate audit. While it is important to provide the best care for patients, the primary obligation of all healthcare providers is to appropriately address and manage pain. The challenge of balancing the availability of prescription opioids to treat patients who have pain while discouraging illicit use is complex and requires effective efforts on many levels. REMS requirements are challenging, but the FDA is cognizant of the need to balance the goals of ensuring drug safety and providing patient access to drugs without placing an undue burden on the health system.[23] Similar processes should be performed in Europe, where the different healthcare systems restrict the ability to gather systematic data and to create homogeneous solutions.

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