Safer use of medications through risk evaluation and mitigation strategies: Academy perspectives

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Pharmacists are essential to REMSs

In practice, we regularly assess whether patients should take certain medications. This risk-versus-benefit analysis comes as second nature to many of us as we simultaneously factor in the disease to be treated, expected benefit/length of treatment, and extent of potential adverse effects. Similarly, the Food and Drug Administration (FDA) and pharmaceutical manufacturers work together to focus on risk assessment on a more global scale, constantly determining whether a medication's benefit outweighs its risk.

Hennessy

For every product approved by FDA, package inserts are the primary tool for communicating safety to patients. Sometimes, however, FDA may determine that the level of risk for a medication is greater than that which is considered normally acceptable and that the package insert alone cannot ensure safe use. FDA will then work with manufacturers to develop more sophisticated and robust safety tools such as a risk evaluation and mitigation strategy (REMS) to ensure that a medication's benefit exceeds its risk. Because of our placement in the health care delivery process, we are perfectly positioned to work with the various REMS programs that are currently mandated to ensure that patients are educated, safe, and well treated.

REMS concept: Familiar to the practice of pharmacy

Although REMSs, most recently identified as risk minimization action plans (RiskMAPs), may seem to represent a new regulatory hurdle, they are not new. Granted, "REMS" is a relatively new term, but from a practice perspective, pharmacists have been working with these risk management programs for years. Regardless of whether they realize it, many pharmacists are already working within the various REMS requirements associated with a number of commonly used medications and classes of medications.

Since the Food, Drug, and Cosmetic Act of 1962, which was spurred by the misprescribing of thalidomide to inappropriate patients, FDA has been mandating risk management systems in some fashion to help improve medication safety. As of mid-August 2010, FDA lists 134 REMS programs on its website, with most programs containing at least one requirement that enlists the expertise of pharmacists. Many of these REMS programs affect commonly used medications such as the fluoroquinolone antibiotics, erythropoiesis-stimulating agents (ESAs), and isotretinoin.

Understanding REMS practice requirements

Of important note, not all REMSs are on the same level. FDA seems to be taking a risk-stratification approach and lumping affected products into three general categories. Fortunately, for the most part, these categories have fairly standard requirements for

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pharmacists that range in complexity from minimal involvement to complex design and implementation characteristics. The algorithm that FDA has been using to determine the REMS category for a particular medication, and hence the complexity of its use, has been somewhat mysterious. However, the requirements are clear after a medication's REMS is approved.

For example, fluoroquinolones fall into the least complex type of currently approved REMS. For the fluoroquinolone REMS, pharmacists simply must ensure that patients receive a medication guide (MedGuide) designed to educate them on the tendonitis risks associated with this class of antibiotics. On the opposite end of the spectrum, isotretinoin and its corresponding iPledge management system is much more onerous for all stakeholders. Pharmacies, prescribers, patients, and wholesalers must be registered with the program or access to the product is restricted. The goal of this REMS program is to eradicate fetal exposure to isotretinoin. The REMS for ESAs falls in the middle of the complexity spectrum, with a heavy emphasis on formal education for pharmacies and prescribers but no restriction in product distribution. The goal of the program is to reduce the risk of decreased survival and poorer tumor outcomes associated with the ESA class.

Practice of pharmacy is ready for REMS

Safe use issues during the past several years involving Vioxx, Fen-Phen, Avandia, and OxyContin have created a public health crisis. The public is pressuring Congress, Congress is pressuring FDA, FDA is pressuring the pharmaceutical manufacturers, and the manufacturers are pressuring pharmacists. REMS will fundamentally change the way pharmacists deliver care to our patients and may open new revenue streams for pharmacy. This is a prime opportunity for the profession to ensure that patients remain safe and benefit from high-risk medications when indicated.

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With the every-5-year reauthorization of the Prescription Drug User Fee Act in 2007, Congress took the opportunity to amend the Food, Drug, and Cosmetic Act to provide FDA with, among other things, new safety-related responsibility, authority, and resources.[1] The FDA Amendments Act authorizes FDA to initiate a REMS whenever accumulating information reveals safety-related concerns that place medication risks at an unacceptably high level. A REMS is a detailed plan to minimize risks associated with prescribing, dispensing, and patient use of medications. Although FDA's approach is still evolving, its authority now goes well beyond manufacturers, pharmacists, and of course patients, extending now to prescribers as well. Similar to any new regulatory program, substantial change will involve controversy.

Williams

Communication and safety

During the previous 2 decades, many drugs have been removed from the market because their risks were not adequately being assessed at the prescribing stages or adequately managed once in patients' possession. Notable examples include cyclooxygenase-2 antagonists, cisapride, bromfenac, terfenadine, and astemizole. The experience illustrates that safety data may change dramatically in the postmarketing phase and that improving communication and increasing education is crucial to minimizing newly discovered risks of medication therapy, thus permitting safe use. Also of note, our society invests tremendous resources in placing a medication on the market; one goal of REMS is to keep medications available that might otherwise be lost.

New tools

The new law provides that, based on evolving safety information, any time FDA determines that the risks of using a medication are beginning to outweigh its benefits, the Agency has authority and responsibility to require submission of a proposed REMS by the manufacturer. For a medication already on the market, "new safety information" may be "derived from a clinical trial, an adverse event report, a post-approval study, or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system ... or other scientific data deemed appropriate" by FDA.[2] For an investigational new drug, the law requires FDA to consider the size of the affected population, seriousness of indicated diseases, expected benefit and duration of treatment, risks and rates of adverse events, and whether the medication is a new molecular entity. After FDA identifies the risk and contacts the manufacturer, it has 120 days to submit its proposal, which then undergoes review. The proposal is judged based on how well it addresses the risks under the particular circumstances of use. After approval by FDA, the sponsor (manufacturer) is required to submit an assessment of its effectiveness (minimally) 180 days, 3 years, and 7 years after approval; however, more frequent assessments may be required.

A REMS may include tools that are now familiar to pharmacists: a MedGuide and/or patient package insert (PPI). Long required at the time of dispensing, this is in essence a patient communication plan. In addition, a communication plan for health care providers may be required; such plans are designed to provide education about risks, possibly including letters, sponsored communication through professional societies, and other dissemination plans. As of August 9, 2010, 134 REMSs have been approved by FDA. Of those, 132 required dispensing a MedGuide and 35 required a professional communication plan. Congress recognized that for some medications, the inherent risks required additional "elements to assure safe use" (ETASUs) to allow continued marketing.