OFF-LABEL DRUG USE: RISK VS. BENEFIT

Off-label drug use (OLDU) involves using a medication for an indication not currently approved by the Food and Drug Administration (FDA). It can also refer to marketing of a drug to a patient population other than the population it was approved for, or marketing a drug in a dosage or dosage form other than what it was approved by the FDA. This issue of CLIPS briefly summarizes an article that answers the ten most common questions regarding OLDU. If you need further information, please contact the Samford University Drug Information Service at (205) 726-2659.


OLDU in Practice

- Health care providers consider OLDU because they desire to utilize a drug for a specific population (e.g., pediatric, geriatric, pregnancy) that has not yet been studied or approved by the FDA, a possibly terminal medical condition that is not responding to conventional therapies, or use of drug for an indication that has been approved for other drugs in the class, but not yet for this particular drug.
- OLDU use is very common.
  - For instance, one study found that nearly 80% of children were discharged from pediatric hospitals with a prescription for at least one off-label medication.
  - In another study of a headache specialty clinic, off-label use represented nearly 50% of prescriptions written for patients. Studies report off-label use as high as 36% in hospital intensive care units. Off-label use of antidepressants, anticonvulsants, and antipsychotic medications has been shown to increase with patient age.

OLDU as standards of care

- Certain drugs or classes of drugs may be used off-label as the primary treatment for many medical conditions.
  - Examples include tricyclic antidepressants for neuropathic pain, aspirin for coronary disease prophylaxis in diabetic patients, morphine for pain treatment in children, and indomethacin for closing of persistent, symptomatic patent ductus arteriosus in newborns. All of these examples represent indications not currently approved by the FDA.
  - Some drug classes are also often used off-label for rare or difficult-to-study disorders, such as seen with use of Selective Serotonin Reuptake Inhibitors (SSRIs) for borderline personality disorder, stuttering, pathologic gambling and alcoholism.
- Unfortunately, many medications are prescribed for OLDU with poor clinical evidence. One study reports that 73% of medications prescribed for off-label use had poor to no scientific evidence to support the decision. OLDU was used without appropriate evidence nearly 50% of the time in a study of critical care patients. Due to the increased use of off-label drugs and the absence of supportive literature, increases in medication errors may occur.

Patient Perceptions of OLDU

- A nationwide poll conducted in 2006 found that over half of the patients polled were unaware that a drug could be prescribed for a use other than the original one approved by the FDA.
- Additionally, many of those polled felt that physicians should not be allowed to prescribe drugs for off-label use. Almost two-thirds of poll respondents stated that OLDU should only be allowed in clinical trials and that it should be banned in everyday prescribing.

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Approval for Off-label Indications
- FDA approval is not sought for new indications for these drugs because the process is expensive and time-consuming.
- A supplemental drug application must be filed with the FDA to add additional indications to an already approved drug. Many times the revenues gained for approval for a new indication may not offset the cost of obtaining the approval. Therefore, drug companies may never seek supplemental approval for new drug indications.

Prescriber liability
- Food, Drug and Cosmetic Act of 1938 will not be involved in regulating the practice of medicine by creating physician liability for OLDU.
- If medications are not to be used in research, then they can be used off-label without regulation by the FDA.
- A 1996 Ohio court case ruled that physicians may be subject to professional liability for medical negligence involving OLDU but that they would not be held liable for nondisclosure.
- Before prescribing medications for OLDU, physicians should determine if the drug has FDA approval, has the off-label use been substantially reviewed by peers (is the use evidence-based), and is the use of the drug non-experimental.
- FDA requirements state that physicians prescribing medications for off-label use should be well informed about the drug and base all treatment on evidence-based research. Physicians are also advised to keep records of product use and effects noted.

Evidence-based Knowledge of OLDU
- Review articles that address widely applied OLDU are welcomed by medical journals and offer prescribers a chance to review evidence-based research regarding off-label usage for many different drugs.
- While pharmaceutical companies are not allowed to promote OLDU, the Accreditation Council for Continuing Medical Education states that as long as evidence-based research was consulted, OLDU can be discussed during continuing education courses.
- The FDA prohibits pharmaceutical manufacturers from promoting OLDU, however, the medical affairs division may respond to questions from health care professionals regarding off-label use and may distribute peer-reviewed literature on OLDU upon request.
- The 1997 FDA Modernization Act allowed pharmaceutical companies to distribute literature regarding OLDU to health care providers. In 2009, the FDA ruled that OLDU literature must be accurate, presented in an unabridged format, and that any relationship between the drug manufacturer and distributor of the literature, be disclosed.
- In 2010, the FDA created the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program to assist in reporting of prohibited OLDU promotion by healthcare professionals and consumers. However, even with FDA legislation, off-label marketing of drugs has been the cause of many costly lawsuits for pharmaceutical companies.

Orphan Use of Drugs
- Medications created and used for very rare diseases are called orphan drugs.
- Physicians generally use medications off-label to treat rare conditions due to the limited availability of medications approved for treatment of the diseases.
- Thus, orphan drugs are considered a form of off-label drugs.
- The Orphan Drug Act of 1983 provided the FDA a special approval process for development and promotion of orphan drugs.
- Because of the lack of profitability associated with orphan drugs, the law provides incentives (e.g., tax breaks, marketing rights, reduced application fees) for pharmaceutical companies to off-set the costs incurred and encourages development of these medications.

Summary:
- While some risk exists, the benefits of OLDU can be numerous.
- Health care professionals must remain educated regarding OLDU in order to provide exceptional care for their patients and limit liability.
- OLDU should be used only when it is in the best interest of the patient and when it is based on current drug literature.