MAYO CLINIC

SPECIAL ARTICLE

Ten Common Questions (and Their Answers) About Off-label Drug Use

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Abstract

The term *off-label drug use* (OLDU) is used extensively in the medical literature, continuing medical education exercises, and the media. Yet, we propose that many health care professionals have an underappreciation of its definition, prevalence, and implications. This article introduces and answers 10 questions regarding OLDU in an effort to clarify the practice's meaning, breadth of application, acceptance, and liabilities. Off-label drug use involves prescribing medications for indications, or using a dosage or dosage form, that have not been approved by the US Food and Drug Administration. Since the Food and Drug Administration does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (eg, pediatric, pregnant, or psychiatric patients). Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has lead to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient. In addition, health care professionals should educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

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The term *off-label drug use* (OLDU) is used extensively in the medical literature, continuing medical education (CME) exercises, and the media. It is a polarizing term because it can be associated with great benefit or harm to patients.[1] In addition, OLDU, along with allegations of pharmaceutical company promotion of OLDU, has been the cause of major lawsuits and historically large out-of-court legal settlements.[2-7] Therefore, all health care professionals have likely heard the term *OLDU* used, yet we propose that many have an underappreciation of its definition, prevalence, and implications. This article introduces and answers 10 questions regarding OLDU in an effort to clarify the practice's meaning, breadth of application, acceptance, and liabilities.

QUESTION 1: WHAT IS THE DEFINITION OF OLDU?

The most common form of OLDU involves prescribing currently available and marketed medications but for an indication (eg, a disease or a symptom) that has never received Food and Drug Administration (FDA) approval.[8,9] Hence, the specific use is "off-label" (ie, not approved by the FDA and not listed in FDA-required drug-labeling information). The term *OLDU* can also apply to the use of a marketed medication in a patient population (eg, pediatric), dosage, or dosage form that does not have FDA approval.

The current role of the FDA is to control which medications are available commercially. Historically, the Food, Drug, and Cosmetic Act of 1938 required only that a new medication be safe.[9] In 1962, the Kefauver-Harris Amendment mandated that FDA-approved new drugs also must have evidence that they are effective.[9] Therefore, the FDA approves new medications that have been shown to be safe and effective for specific indications (ie, "on-label" prescribing). The FDA does not limit or control how the medications are prescribed by physicians once the medications are available on the market. By definition, OLDU is prescribing for an indication, or employing a dosage or dosage form, that has not been approved through the FDA process.

Off-label drug use can be motivated by several factors. First, a medication may not have been studied and approved for a specific population (eg, pediatric, geriatric, or pregnant patients).[10] Second, a life-threatening or terminal medical condition may motivate a health care professional to give any treatment that is logical and available, whether approved by the FDA or not. Third, if one medication from a class of drugs has FDA approval, physicians commonly use other medications in the same class without specific FDA approval for that use for the same indication.[8,9] In addition, if the pathologic or physiologic features of 2 conditions are similar, a physician may use a medication approved for 1 of these conditions for both (eg, diabetes and metabolic syn-

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drome; psychiatric diseases such as anxiety and posttraumatic stress disorder).[8]

QUESTION 2: IS OLDU COMMON?

Indeed, OLDU is common. Radley et al[1] reported in 2006 that in a group of commonly used medications, 21% of prescriptions were for an off-label use. In certain subpopulations of patients, this rate may be even higher. For example, a study by Shah et al[11] found that 78.9% of children discharged from pediatric hospitals were taking at least 1 off-label medication. In addition, in a pediatric emergency department, the rate of OLDU was estimated to be 26.2%.[2] The off-label use of antidepressant, anticonvulsant, and antipsychotic medications is high and is more prevalent with increasing patient age.[12] In an intensive care unit, Lat et al[13] reported that 36.2% of medication orders were for an off-label use. In addition, β-adrenergic blocking agents are commonly prescribed for an off-label indication, and specialists may more commonly prescribe for off-label β-blocker use than primary care physicians.[10] In a headache specialty practice, Loder and Biondi[14] reported that off-label use accounted for 47% of prescriptions written.

QUESTION 3: CAN AN OLDU FOR A GIVEN DRUG BECOME A WIDELY ACCEPTED PRACTICE OR EVEN A STANDARD OF CARE?

Off-label drug uses can become widely entrenched in clinical practice and become predominant treatments for a given clinical condition. For example, tricyclic antidepressants do not have FDA approval as a treatment for neuropathic pain, yet this class of drugs is considered a first-line treatment option.[15] The use of aspirin provides another interesting example of OLDU. Aspirin was widely used before the introduction of the Food, Drug, and Cosmetic Act of 1938. Therefore, aspirin was grandfathered and approved as an existing drug without the rigorous testing that modern medications undergo. Currently, aspirin is FDA approved for use in patients with pain, fever, rheumatic diseases, cardiovascular diseases (eg, acute myocardial infarction, previous myocardial infarction, angina pectoris, and previous cerebrovascular disease), and a history of a revascularization procedure (eg, coronary artery bypass grafting and carotid endarterectomy).[16] However, aspirin does not have an indication for coronary disease prophylaxis in diabetic patients, yet guidelines recommend its use in these patients.[8] Therefore, aspirin prophylaxis for coronary disease in high-risk patients is an off-label use.

Elsewhere, medications are often prescribed for OLDU with poor or absent clinical evidence. Radley et al[1] reported that 73% of medications prescribed for an off-label use had poor or no scientific support. In critical care patients, OLDU was without adequate evidence 48.3% of the time.[13] Because OLDU is typically less critically evaluated than is on-label drug use, OLDU may be associated with an increase in medication errors.[17] Rinke et al[17] studied pediatric antidepressant drug use in a national error-reporting database and found that 77% involved off-label prescribing.

QUESTION 4: WHAT ARE SOME EXAMPLES OF WIDELY PRACTICED OLDUs?

There are examples of widely practiced OLDUs in every specialty of medicine (Table). Since the patient population in pediatrics is often excluded from clinical drug studies, examples of OLDU are especially abundant. For example, morphine has never received an FDA indication for pain treatment in children, but it is extensively used for this indication in hospitalized pediatric patients.[11] In another example, researchers discovered in the 1970s that the nonsteroidal anti-inflammatory agent indomethacin was efficacious as a medical therapy for closing a persistent, symptomatic patent ductus arteriosus in newborns.[18] Thus, a trial of indomethacin became the treatment of choice for many affected newborns in an attempt to avoid curative surgery. Indomethacin has never been approved for this indication and, as such, this use remains an OLDU. In addition, many inhaled bronchodilators, antimicrobials, anticonvulsants, and proton pump inhibitors are often used in the pediatric population without formal FDA approval.[30]

The FDA has attempted to lessen the gap between FDA approval and contemporary drug-prescribing practices in pediatrics through the FDA Modernization Act of 1997. This Act created incentives, including exclusive marketing and patent extension, for pharmaceutical companies to test medications on children.[31]

Medications for psychiatric disorders are also frequently used for unapproved indications.[12,32] Patients with psychiatric disorders are often excluded from clinical trials, and these disorders are inherently difficult to study. Moreover, there is often crossover in symptoms from disease state to disease state, which has lead physicians to use psychiatric medications approved for one psychiatric condition for additional unapproved indications. For example, selective serotonin reuptake inhibitors have been used off-label for rare or difficult-to-study disorders, such as borderline personality disorder, stuttering, pathologic gambling, and alcoholism.[16] Moreover, selective serotonin reuptake inhibitors (eg, paroxetine, sertraline, and fluoxetine) are considered first-line treatments for premature ejaculation, another off-label use.[33] In recent years, antipsychotic drug use

Mayo Clin Proc. ■ Month 2012;xx(x):xxx ■ http://dx.doi.org/10.1016/j.mayocp.2012.04.017
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TABLE. Examples of Common Off-label Uses of Drugs

Category and drug	Off-label use(s)[a]
Allergy	
Diphenhydramine	Chemotherapy-related emesis, insomnia[16]
Anesthesiology	
Propofol	Intracranial hypertension
Dexamethasone, propofol	Postoperative nausea
Meperidine	Postanesthetic shivering
Cardiology	
Amiodarone	Supraventricular tachycardia[16]
Aspirin	Antithrombosis in atrial fibrillation, Kawaskai disease[16]
Atorvastatin, simvastatin	Extended-interval dosing for hyperlipidemia[16]
Indomethacin	Pharmacologic closure of patent ductus arteriosus[18]
Dermatology	
Azathioprine	Atopic dermatitis, pemphigus; psoriasis[19]
Biologic agents (eg, etanercept, infliximab, intravenous immunoglobulin, rituximab)	Alopecia areata, atopic dermatitis, Behçet disease, dermatomyositis, hidradenitis suppurativa, pemphigoid, pityriasis, vasculitis[20]
Gastroenterology	
Erythromycin	Gastroparesis[21]
Omeprazole	Reflux-related laryngitis[16]
Hematology/oncology	
Alendronate	Hypercalcemia of malignancy[16]
Dabigatran	Venous thromboembolism prophylaxis after orthopedic surgery[22]
Doxorubicin	Refractory multiple myeloma[16]
Furosemide (nebulized)	Dyspnea[16]
Rituximab	Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia[16]
Infectious disease	
Linezolid	Infective endocarditis[16]
Sulfamethoxazole-trimethoprim	Sinusitis[16]
Nephrology	
Acetylcysteine	Prevention of contrast nephrotoxicity[16]
Albuterol	Hyperkalemia[16]
Erythropoietin	Anemia of chronic disease[16]
Neurology	
Atenolol, metoprolol, propranolol	Migraine prophylaxis[10]
Isoflurane	Seizure, status epilepticus
Donepezil	Frontotemporal dementia[23]
Gabapentin	Bipolar disorder, diabetes, fibromyalgia, neuropathic pain symptoms, headache, hiccups, hot flashes, restless leg syndrome[24]
Lidocaine	Postherpetic neuralgia[24]
Tricyclic antidepressants	Bulemia, insomnia, irritable bowel syndrome, neuropathic pain symptoms[15,16,24]
Obstetrics	
Magnesium sulfate	Premature labor[16]
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Intraoperative uterine contraction
Pediatrics	
Amoxicillin (high dose)	Otitis media in children[16]
Atenolol	Hypertension in children[16]
Intranasal desmopressin	Nocturnal enuresis[25]

(continued)

TABLE 1. Continued

Category and drug	Off-label use(s)[a]
Pediatrics (continued)	
Morphine	Pain in children[11]
Sildenafil	Pulmonary hypertension in children[16]
Pulmonary	
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Status asthmaticus[26]
Psychiatry	
Atypical antipsychotics (eg, risperidone, olanzapine, quetiapine)	Anxiety, dementia, eating disorders, obsessive-compulsive disorder, personality disorders, posttraumatic stress disorder, substance abuse[27]
β-Blockers	Social phobia, public speaking[28]
Citalopram	Alcoholism, fibromyalgia, irritable bowel syndrome, obsessive-compulsive disorder, pathologic gambling, stuttering[16]
Fluoxetine	Borderline personality disorder, diabetic neuropathy, fibromyalgia, hot flashes, premature ejaculation[24]
Trazodone	Insomnia in elderly patients[16]
Urology	
Sildenafil	Sexual dysfunction symptoms in women[29]

[a] This table is not comprehensive and is not intended as an endorsement of these off-label drug uses.

for unapproved FDA indications has increased. Alexander et al[32] estimated that the cost of off-label antipsychotic drug use in 2008 was $6.0 billion.

During the 1970s and 1980s, there was a proliferation of cardiac surgery to repair or replace diseased heart valves. Disease in many of these patients was the result of rheumatic abnormalities in patient populations with inadequate or no antibiotic drug treatment of infections earlier in their lives. In these patient populations, hemodynamic stability was of utmost concern during anesthesia, surgery, and the immediate postoperative course. Lowenstein[34] reported that high-dose morphine, combined with amnestic agents, could provide the type of stable anesthetic required for these patients and that the beneficial effects of the anesthetic would continue into the postoperative intensive care period. With the later introduction of the short-acting opioid fentanyl, it was infused in doses much greater than approved by the FDA, thus converting a short-acting drug into a long-acting drug. High-dose morphine- and fentanyl-based anesthetics, highly favored therapy for valve replacement surgery, were retained as core anesthetics with the introduction of coronary artery bypass graft surgery. Today, patients are typically brought to surgery much earlier in the disease course (hence, they tend to be more stable hemodynamically), and there is a focus on shortening stays in the intensive care unit after cardiac surgery. In addition, improvements in surgical technique have shortened operation times. For these reasons, high-dose opioid anesthesia is less common than in the past, although it is still used. These high doses of morphine and fentanyl have never been approved by the FDA, and, therefore, their use has always been off-label.

Postoperative nausea and vomiting in surgical patients can add to patient morbidity and the cost of health care. Postoperative nausea is common, occurring in nearly 70% to 80% of high-risk patients.[35] Because of this, practitioners have empirically explored a variety of antiemetic therapies. In patients at high risk for postoperative nausea and vomiting, bolus or infused propofol and bolus dexamethasone have gained favor as antiemetic regimens. However, these treatments have never been approved by the FDA for this indication. As such, they represent OLDUs.

QUESTION 5: IF EFFICACIOUS, WHY IS GOVERNMENT APPROVAL NOT OBTAINED TO CONVERT OFF-LABEL USES OF DRUGS TO ON-LABEL USES?

Obtaining a new FDA approval for a medication can be costly and time-consuming. To add additional indications for an already approved medication requires the proprietor to file a supplemental drug application, and, even if eventually approved, revenues for the new indication may not offset the expense and effort of obtaining approval.[8] Finally, generic medications may not have the requisite funding foundations needed to pursue FDA-approval studies.[8] For these financial reasons, drug proprietors may never seek FDA approval for a new drug indication.

Mayo Clin Proc. ■ Month 2012;xx(x):xxx ■ http://dx.doi.org/10.1016/j.mayocp.2012.04.017
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QUESTION 6: DO PHYSICIANS EXPOSE THEMSELVES TO LEGAL VULNERABILITY FOR INCLUDING OLDUs IN THEIR CLINICAL PRACTICES, PARTICULARLY IF THE PATIENT EXPERIENCES AN ADVERSE REACTION RELATED TO AN OLDU?

Physicians have been involved in legal claims due to an adverse reaction related to a medication prescribed for an off-label use.[8,36] The legal theories used in these lawsuits include unregulated use of a research drug, failure to provide adequate informed consent for an OLDU, and medical negligence.[37] In developing legal precedents for off-label therapies, the courts have typically treated drugs and devices as coequals. As such, many of the courts' views on OLDU have evolved from decisions regarding off-label uses of medical devices.

Research vs Practice

The FDA makes it clear that it does not regulate the practice of medicine and that the federal Food, Drug, and Cosmetic Act of 1938 will not play a role in creating physician liability for OLDU.[38] However, the FDA requires stringent review before drugs and medical devices are involved in research to ensure that steps are taken to properly protect human study participants. When not classified as tools involved in research, medications can be prescribed and medical devices can be used in an off-label manner without FDA regulatory oversight. Regarding this point, during its evaluation of possible harm arising from placement of an orthopedic spine medical device, an Ohio appellate court stated that "the off-label use of a medical device is merely a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment, but off-label use of a medical device is not barred by the U.S. Food and Drug Administration."[38,39] By way of legal precedent and similar FDA regulatory processes, the same standard would apply to OLDU.

Drawing a clear line of demarcation between a drug's use in research vs practice can often be difficult. Prescribing a drug in a new and yet untested manner does not alone brand it as an interest of research.[38] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has attempted to define whether a drug's use might be classified as a practice or research tool, and their definitions follow. The goal of medical practice is to "provide diagnosis, preventative treatment or therapy."[38] Research, on the other hand, is "designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge."[38] When not deemed research, legal claims brought solely on the basis of failure to gain adequate FDA approval before prescribing an off-label drug will likely be struck down. However, physicians may not be sheltered from other forms of liability theories.

Medical Malpractice: Informed Consent

No court decision to date has mandated that a physician must disclose, through an informed consent process, the off-label use of a drug.[40] Two arguments are often voiced by those who oppose any routine requirement for disclosure: (1) disclosure may unduly frighten patients and (2) the extensive burden placed on physicians to constantly review and communicate medication risk and benefit information may divert attention away from other more important patient care issues.[40]

Perhaps the most cited modern legal case involving the medical informed consent process is *Canterbury v Spence*.[41] The Canterbury court held that "the test for determining whether a particular peril must be divulged is its *materiality* to the patient's decision."[41] A material risk is one in which "a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy."[41]

Many courts have not considered OLDU to be an independent material issue requiring disclosure during the consent process.[38] A 1996 Ohio court held that off-label use of medical devices was a "matter of medical judgment."[38,42] According to the court, physicians may be subject to professional liability for medical negligence involving OLDU but will not be held liable for nondisclosure.[38,42]

The results of a 2006 nationwide poll on the public's view of OLDU may precipitate concerns for future court challenges not fully appreciated by previous legal opinion. Half of the poll's respondents falsely believed that a drug could be prescribed only for its primary FDA-approved use.[43] An almost similar percentage felt that physicians should be prohibited from prescribing drugs for off-label use. Nearly two-thirds of those responding felt that except for use in clinical trials, OLDU should be completely banned.[43] This is a remarkable aggregate response given that a considerable fraction of those responding negatively to OLDU had likely benefited from the practice at some point in their lives (although they were probably unaware).

Although many courts do not require physicians to disclose OLDU, patients may have a different belief and concern regarding their use. Whether these matters will develop into a greater expectation for adequate disclosure remains unknown. Some physicians have suggested that providing patients with information about OLDU may afford greater protection from future liability suits.[38]

Medical Malpractice: Negligence

Medical malpractice is a broad term that includes the action of negligence. In fact, 4 elements of tort law dealing with negligence must be proved before liability can be found to exist: (1) the prescribing physician must have a duty to the patient, (2) that duty must be breached, (3) there must be some injury requiring compensation, and (4) there must be a causal link between the breech and that injury.

A physician's duty of care is defined as the same degree of care provided by other physicians practicing under similar circumstances. Use of off-label medication alone does not result in liability under negligence standards.[44] When a patient believes that he or she was harmed by an off-label use of a medication, it must be established that the prescribing physician deviated from the standard of practice.[38] Because the FDA prohibits manufacturers from sponsoring physician education for off-label use of their medications, physicians may find it difficult to establish how others in their field are using medications outside their FDA-approved uses.[37] As peer-reviewed published evidence focusing on a drug's off-label use grows over time, new standards of practice involving the off-label use of a drug begin to develop.[38]

To help determine whether the standards of practice are being met when prescribing medications for OLDU, physicians should first ask themselves several questions[38,45,46]: (1) Does the native drug have FDA approval? (2) Has the off-label use been subjected to substantial peer review? (3) Is the off-label use medically necessary for treatment? (4) Is the use of the medication nonexperimental? To mitigate the risk of liability, physicians should always prescribe off-label drugs in "good faith, in the best interest of the patient, and without fraudulent intent."[45] This 3-pronged approach to prescribing medications will also ensure that the tenets of the FDA's requirement are met; specifically, physicians prescribing medications for off-label use should "be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."[47]

QUESTION 7: WILL INDEXED MEDICAL JOURNALS PUBLISH ARTICLES ON OLDU?

Reports on OLDU, particularly original observations, are not only tolerated by indexed medical journals but also may actually be encouraged. The most welcomed reports may follow several patterns, the 2 most common of which are described in the following subsections.

Reports to Evaluate New Drug Therapies Seeking FDA Approval

Before a drug use can be approved by the FDA, drug utilization for this specific application must undergo extensive studies of efficacy and safety in humans. The data from multiple phases of study are needed for the drug's proprietor to file a New Drug Application to the FDA. Studies of new drugs or studies involving expanded use of an existing drug are, by definition, "off-label" indications until FDA approval is obtained. These studies may take the form of phase 0 (pharmacokinetic and pharmacodynamic studies of subtherapeutic drug doses in small numbers of patients), phase 1 (small studies of drug pharmacodynamic properties in healthy volunteers), phase 2 (larger studies of drug pharmacology, safety, and efficacy in volunteers and patients), and phase 3 (large, randomized, multicenter trials of drug safety and efficacy; drug compared with a placebo or an existing treatment standard) trials.[48] In addition, phase 4 trials are completed after FDA approval to further delineate the drug's effects and adverse reactions.[48]

Although preliminary research on drug pharmacology and safety intended to support a petition for FDA approval may be important to the proprietor and the FDA, articles based on these data may be difficult to publish in competitive biomedical journals because the data may not be of interest to the journal's target audience. As such, initial research may not pass peer review because of journal priorities. However, as subsequent trials evaluate drug efficacy and safety using methods that mimic the drug's use in clinical practice, journals' interest in the research will be piqued. The more novel the therapy (eg, a new class of drug for a common application, in contrast to a "me too drug"), the more likely the research data will be competitive for publication in better-quality medical journals. In fact, journals may introduce the reports with editorials and engage in media promotion of the discoveries, both testaments to the value the journals place on the research.

Reports to Evaluate Off-label Uses, or Describe Adverse Effects, of Drugs Approved for Other Indications

As previously described, a large fraction of drug use is off-label, and these indications may even become the standard of care (see Question 3). In these instances, the FDA will have previously approved the drug for clinical practice but for an indication other than the one under question. Medical journals and their readers may have a keen interest in original observations related to this form of drug use. Articles may not only become accepted for publication but may also get journal promotion (editorials and media promotion) reserved for the highest-priority articles. Clearly, a journal's enthusiasm for these types of articles is coupled with the quality and statistical power of the data, the novelty of the obser-

Mayo Clin Proc. ■ Month 2012;xx(x):xxx ■ http://dx.doi.org/10.1016/j.mayocp.2012.04.017
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vation, the generalizability of the results, and the relevance of the observations to the intended audience's interests. As such, a journal may publish OLDU articles on drugs' effects and adverse effects related to indications for which FDA approval may never be sought.

Prospective trials of drug use in humans must conform to federal regulations, be approved by the institutional review boards of all participating institutions, and be registered in one of many appropriate registries (eg, ClinicalTrials.gov) to be considered for publication in biomedical journals.[49,50] Retrospective OLDU observations in patients, whether of a drug's effects or adverse effects, also must have accompanying institutional review board approval before reporting the observations to a biomedical journal. However, the standards of approval for retrospective observations are much less stringent than for prospective research.

Indexed biomedical journals are less likely to publish review articles on drugs that are seeking FDA approval for a first use. Reviews with the best probability of getting published are those that describe novel drug mechanisms or success in treating conditions in which other drugs have limited efficacy. Articles primarily intended to support a marketing angle for the proprietor (ie, seeding reports)[51] have difficulty getting published in the most competitive medical journals. In contrast, journals may welcome review articles that address a widely applied OLDU. As information on a given OLDU grows, journals may even welcome updated reviews or new reviews that address novel aspects of the OLDU experience (eg, new information on a drug's effects or adverse effects, updates on the operant mechanisms of action, and articles on drug-use adherence and economics).

QUESTION 8: CAN SPEAKERS DISCUSS OLDU DURING ACCREDITED CME COURSES?

Speakers at accredited CME courses are allowed to discuss OLDU during their presentations. The Accreditation Council for Continuing Medical Education historically required that all discussions of OLDU be disclosed during the CME presentation. However, current Accreditation Council for Continuing Medical Education requirements state that all clinical presentations should be based on "evidence that is accepted within the profession of medicine."[52] If the discussion of OLDU conforms to this mandate, no specific disclosure is required.

QUESTION 9: CAN DRUG COMPANIES PROMOTE OLDU?

The 1938 Food, Drug, and Cosmetic Act gave the FDA the power to regulate promotional materials on medications.[53] Two provisions from the FDA prohibit most promotion of off-label uses of medications by pharmaceutical manufacturers and marketers. First, the FDA requires approval before distribution into interstate commerce of all medication labeling (including the package insert, print and broadcast advertisements, brochures, and patient education materials).[53] Second, the FDA prohibits "misbranding" of medications. Misbranding includes labeling a medication with misleading information, including off-label uses.[53]

Although pharmaceutical manufacturers are not allowed to promote off-label uses of medications, they are allowed to respond to unsolicited questions from health care professionals about off-label use and to distribute peer-reviewed publications regarding off-label use.[53] Responses to questions regarding off-label use must be completed by the manufacturer's medical affairs office and not their sales representatives, and interactions with the questioner must be documented.[53]

Historically, the 1997 FDA Modernization Act allowed manufacturers to distribute to health care providers peer-reviewed journal articles about unapproved uses of medications.[54,55] If a given drug company chose to engage in distribution of this type of information, it was required to submit an application for approval of that indication within a rigid and prespecified period. These requirements were subsequently revised in 2009 with the approval of new FDA guidelines.[53] The new guidelines clarified existing rules and allowed distribution of information on off-label uses by pharmaceutical manufactures if specific regulations were followed.[53] After 2009, pharmaceutical manufacturers could distribute information, including journal articles and textbook chapters, describing unapproved uses for their medications. The FDA demanded that the information in these OLDU publications be accurate, the relationship between the distribution of information and the sponsoring drug manufacturer be disclosed, and the published material not be edited or presented in an abridged form.[53] In addition, the manufacturer is no longer required to submit an application for approval for that indication.[53]

With the increase in direct-to-consumer marketing by pharmaceutical manufacturers, in 2010 the FDA introduced the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program. This program provides a mechanism by which health care professionals and patients can report illicit OLDU promotion to the FDA.

Despite regulations that ban pharmaceutical manufacturers and marketers from promoting OLDUs, some have ignored this mandate. In fact, one study found that off-label marketing by drug companies was one of the most common causes of

Medicaid fraudulent claim investigations.[2,56] In addition, marketing of off-label uses has been the source of costly lawsuits and out-of-court penalties for pharmaceutical manufacturers. In 2012, GlaxoSmithKline paid a record $3 billion to settle a dispute, including alleged illegal off-label marketing involving paroxetine in children (approved only for use in adults), the antidepressant bupropion as a weight loss aid, and failure to report safety information about the antidiabetes medication rosiglitazone.[5] In 2012, Abbott paid $1.6 billion in penalties for alleged off-label marketing of valproic acid.[7] In 2009, Eli Lilly paid $1.4 billion in a settlement for alleged off-label marketing of olanzapine for dementia.[3] That same year, Pfizer paid $2.3 billion for alleged off-label marketing of 4 of its medications.[4]

QUESTION 10: WHAT IS THE DIFFERENCE BETWEEN OLDU AND ORPHAN USE OF DRUGS?

Orphan drugs are medications that are developed and used for rare, or orphan, diseases. Owing to a drug's limited clinical use for an orphan indication, it will typically generate insufficient profitability for the drug's sponsor to seek FDA approval for the narrow indication. As such, practitioners are typically forced to use medications in an off-label manner to treat orphan diseases. Therefore, orphan drugs are often a subtype of OLDU. However, in 1983, the FDA implemented the Orphan Drug Act, which offered incentives to pharmaceutical manufacturers that developed and marketed new drugs for rare diseases.[57] Incentives include tax breaks, exclusive marketing rights, and reduced drug application fees. In addition, the FDA has offered grants for the development of drugs for rare diseases. These measures have been successful in increasing the development of new, FDA-approved (ie, "on-label") drugs for orphan diseases.[57] Examples of off-label uses of medications for orphan disease include aspirin for Kawasaki disease and rituximab for Behçet disease.[16,20]

OLDU SUMMARY

Off-label drug use involves prescribing medications for an indication, or using a dosage or dosage form, that has not been approved by the FDA. Since the FDA does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (eg, pediatric, pregnant, or psychiatric patients). Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has lead to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient on the basis of the most credible available evidence. In an era of global exchange of medical information, this approach to physician prescribing practices may have greater utility than restricting practices solely to indications approved by a US-based pharmaceutical labeling system. Health care professionals should continually educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

Abbreviations and Acronyms: **CME** = Continuing Medical Education; **FDA** = Food and Drug Administration; **OLDU** = off-label drug use

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