HEALTH CARE REFORM

Going Off-label Without Venturing Off-Course

Evidence and Ethical Off-label Prescribing

FOLLOWING US FOOD and Drug Administration (FDA) approval, clinicians may lawfully prescribe a drug or biologic agent for treatment regimens not specified in the approved labeling or package insert. This is known as *off-label use*. A recent study[1] found that for 160 common drugs in the United States, off-label use accounted for 21% of all prescriptions. Many off-label uses are accepted as standard of care, for example, use of β-blockers for congestive heart failure. Many other off-label uses, however, lack evidence of clinical efficacy.[1] In light of growing concerns about appropriateness and cost, off-label use has been identified as 1 aspect of problematic drug prescribing.[2,3]

Currently, there is little guidance to distinguish clearly between off-label uses that are well-supported by evidence and those that are not. In this article, we address that gap at the level of the practicing physician. First, we identify characteristics of off-label use that signal the need for greater scrutiny. Second, we propose a framework that differentiates types of off-label use based on the available evidence and links the level of evidence to specific requirements for ethical prescribing. Although specifically targeted to off-label use, this framework is applicable to the general issue of appropriate prescribing in light of adequate evidence of risks and benefits.

SIGNALS FOR SCRUTINY

Busy physicians should have a means of prioritizing prescribing decisions that require greater reflection, particularly because they will not always readily know if a use is off-label. Four characteristics signal the need for a more rigorous scrutiny of evidence.

New Drugs

Using relatively new drugs off-label poses 2 major problems. First, these off-label uses will usually be unsupported by evidence from randomized controlled trials or other high-quality studies. Second, available data on safety for on- or off-label use of a new drug will always be limited. It is only through observation of large numbers of patients over many years that infrequent but clinically significant adverse effects become apparent. Although there is no empirical way to judge a sufficient duration of time or number of patients beyond which a drug is no longer "new," a prudent rule of thumb is that 3 to 5 years should elapse before much confidence can be placed in judgments of risk for infrequent but potentially serious adverse effects.

Novel Off-label Use

A novel off-label use—one that is new or unusual—is unlikely to be supported by strong evidence regarding efficacy and safety, even if the drug itself has been on the market for more than 3 to 5 years. For example, fenfluramine hydrochloride and phentermine hydrochloride were approved by the FDA as *individual* agents for *short-term* use in the medical treatment of obesity. More than 2 decades later, published data fueled an interest in a long-term regimen of the drugs in combination (Fen-Phen) for treatment of obesity.[4] Sales of the 2 drugs increased dramatically in 1994; heart valve damage was identified as an adverse effect of this off-label use in 1997.[5]

Drugs With Known Serious Adverse Effects

Although it is possible for the risk of serious adverse effects to be counterbalanced by consideration of the severity of the condition and the potential benefits, off-label use of any drug with potential serious adverse effects merits close attention owing to concerns for patient safety.

High-Cost Drugs

Some high-cost drugs are also highly effective when prescribed off-label. However, when limited evidence supports efficacy, or when the evidence suggests no more than marginal benefit, prescribing high-cost drugs off-label may be costly to individual patients and may represent a suboptimal allocation of resources. Many chemotherapeutic drugs, which are often used off-label, are quite expensive.

EVIDENCE LEVELS TO GUIDE OFF-LABEL PRESCRIBING

For off-label uses characterized by 1 or more of these 4 signals for scrutiny, we divide potentially appropriate off-label prescribing into 3 evidentiary categories: *supported*, *suppositional*, and *investigational*. Each of these categories is distinguished by the level of certainty gained through objective assessment of existing evidence that a patient will experience a net health benefit from the treatment. Supported off-label use corresponds with a moderate to high level of certainty in net health benefit, whereas

suppositional off-label use corresponds with a low level of certainty, and investigational off-label use corresponds with a very low level of certainty.

Several evidence review bodies link level of certainty to an assessment of evidence—an approach perhaps best developed by the US Preventive Services Task Force (USPSTF).[6] The USPSTF proposes that judgments of evidence include explicit consideration of the number and size of clinical trials, study design and conduct, generalizability, and the consistency of results. By rigorously evaluating a body of evidence in this way, a judgment can be made of the level of certainty for a particular magnitude of net health benefit to be gained from an intervention.

Most physicians do not have the skills or time to perform their own systematic review of evidence on potential risks and benefits. They should, however, seek out the most rigorous evidence readily available and adopt an objective approach to judgment. Evidence of potential harms should be sought out and considered at least as inclusively and rigorously as the evidence for potential benefit. When available, professional society recommendations or guidelines often reflect rigorous assessment of evidence beyond the capability of any individual physician and thus can play a useful role in determining individual physicians' level of certainty. Although it is well known that the groups that promulgate professional recommendations can have conflicts of interest, professional society recommendations are still likely to represent a deeper understanding and reflection on the evidence than would be feasible for the individual physician.[7]

PHYSICIAN RESPONSIBILITIES AND ACTIONS

Supported Off-label Use

We propose that drugs may be prescribed for a supported off-label use (with moderate to high certainty of net benefit) in the same manner as they would be for an on-label use grounded by scientific evidence. Physicians do not need specifically to disclose to patients that the use is off-label, but, as in all cases of treatment recommendations, they should discuss with patients the nature of the proposed treatment, the perceived benefits and the important risks, and information about alternative courses of treatment. Patients should be engaged in shared decision making. Often informal and educative, we call this conversation *routine therapeutic consent*.

Suppositional Off-label Use

When considering suppositional off-label use (with low certainty of net benefit), physicians must carefully consider whether it would be more appropriate to recommend no active treatment rather than to take the risks of treatment based on weak evidence. Given the low level of certainty associated with suppositional off-label use, physicians should consider seeking input from colleagues either through informal consultation or by a second opinion rendered in a formal meeting with the patient.

Physicians should clearly communicate to the patient the uncertainties in risks and benefits of suppositional off-label use, just as they would for an FDA-approved drug when there is a low level of certainty in net benefit. We call this type of consent *augmented therapeutic consent* because it requires more discussion than routine therapeutic consent but less formality than written informed consent. The following is an example of augmented therapeutic consent for a suppositional off-label use of an antidepressant to treat fibromyalgia:

> I would like to prescribe drug X for your fibromyalgia. Drug X is a new drug. It is normally used to treat depression. As you know, we have tried several different pain medications, but you are still more uncomfortable than we would like. Some recent studies have shown that drug X may be effective for treating the pain associated with fibromyalgia. It may work by blocking nerve signals, but no one knows for sure. From years of using similar drugs to treat depression, doctors know the more common adverse effects, including dry mouth and weight gain, but I think the possible benefits for you outweigh these risks. Another option would be to try a different pain killer, but I think we should try drug X. What questions do you have?

Written documentation of augmented therapeutic consent may consist of a brief note in the patient's medical chart.

Suppositional off-label use should always be linked to data collection. Minimally, physicians should contribute to evidence development by recording and reporting adverse events using MedWatch, the FDA safety information and adverse event reporting program (http://www.fda.gov/safety/MedWatch/default.htm), which is accessible online. Ideally, physicians will seek out registries on off-label uses to capture information on outcomes, adverse effects, and adverse events. Physicians should advocate for their professional organizations, the FDA, and pharmaceutical companies to lead the organization of these registries.

Investigational Off-label Use

Investigational off-label use (with very low certainty of net benefit) generally should be limited to the context of research protocols.[8] Patients should engage in a formal informed consent process with the physician-researcher before receiving drugs for investigational off-label use. Patients must understand that the purpose of investigational off-label use is to generate data to improve medical care for future patients rather than to provide medically indicated treatment, although the patient may benefit.

COMMENT

Several previous articles have addressed the appropriateness of off-label prescribing and the attendant ethical and professional obligations.[9-12] Though useful, these accounts have distinctive limitations. They treat the phenomenon of off-label prescribing as monolithic and require rigorous informed consent for all situations; they address issues related to off-label prescribing at a specific institutional level, such as the hospital formulary, limiting their applicability to diverse practice environments; or they address off-label prescribing at a regulatory level, which does not attend to immediate ethical concerns. Practicing physicians need a comprehensive and workable ethical framework that prioritizes scrutiny of off-label prescrib-

ing and links the certainty of net benefit to physician responsibilities.

These issues have gained even greater importance following the recent issuance by the FDA of revised "Good Reprint Practices."[13] This formal guidance permits pharmaceutical companies to encourage off-label use by distributing peer reviewed articles relating to off-label use of their drugs.[3,14] In addition, a November 2008 rules change made Medicare coverage automatic for a wider array of off-label uses of cancer drugs.[15] New medications reaching the market, aggressive marketing of off-label uses to patients as well as to physicians, patient expectations that physicians will do "something," and concerns regarding rising health care costs underscore the importance of practical guidance for physicians.

In conclusion, off-label use is an important area of practice in which evidence gaps should trigger more reflection and scrutiny. Four characteristics of off-label use signal to physicians the need for a higher level of scrutiny: new drugs, novel off-label uses, drugs with known serious adverse effects, and high-cost drugs. By classifying off-label uses as supported, suppositional, or investigational, this conceptual framework grounds recommendations for prescribing practices in a judgment of the strength of the evidence for net health benefit. This elevates the role of evidence in the otherwise unregulated realm of off-label prescribing and will help physicians in exercising their responsibility for applying evidence in practice in a rigorous fashion.

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