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Why off-label isn't off base

You don't bring greater liability upon yourself in a malpractice suit just because the case includes your off-label Rx

Douglas Mossman, MD

Dr. Mossman is director, Glenn M. Weaver Institute of Law and Psychiatry, University of Cincinnati College of Law, and volunteer professor of psychiatry and associate program director, Institute for Psychiatry and Law, University of Cincinnati College of Medicine.

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CASE

A physician speaking with a colleague expressed his anxiety and uncertainty over off-label prescribing:

"When I was a resident, attending physicians occasionally cited journal articles in their consultation notes to substantiate their treatment choices. Since then, I've done this at times when I've prescribed a drug off label.

"Recently, I mentioned this practice to a physician who is trained as a lawyer. He thought citing articles in a patient's chart was a bad idea, because by doing so I was automatically making the referred-to article the 'expert witness.' If a lawsuit occurred, I might be called upon to justify the article's validity, statistical details, methodology, etc. My intent is to show that I have a detailed, well-thought-out justification for my treatment choice.

"Am I placing myself at greater risk of incurring liability should a lawsuit occur?"

This physician wants to know how he can minimize malpractice risk when prescribing a medication off label. He wonders if citing an article in a patient's chart is a good—or bad—idea.

In law school, attorneys-in-training learn to answer very general legal questions with "It depends." There's little certainty about how to avoid successful malpractice litigation because few, if any, strategies have been tested systematically. However, this article will explain and, I hope, help you avoid the medicolegal pitfalls of off-label prescribing.

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4 reasons why off-label prescribing can be controversial

Limited testing for safety and effectiveness. Experiences such as the fen-phen (weight loss) controversy[1] and estrogens for preventing vascular disease in postmenopausal women[2] remind physicians that some untested treatments may do more harm than good.

Commercial influence. Pharmaceutical companies have used advisory boards, consultant meetings, and continuing medical education events to promote unproven off-label indications for drugs.[3,4] Many studies that were, ostensibly, designed and proposed by researchers show evidence of so-called ghost authorship by commercial concerns.[5]

Study bias. Even peer-reviewed, double-blind studies that are published in the medical literature might not sufficiently support off-label prescribing practices because sponsors of such studies can structure them or use statistical analyses to make results look favorable. Former editors of the ***British Medical Journal*** and ***The Lancet*** have acknowledged that their publications unwittingly served as "an extension of the marketing arm" or "laundering operations" for drug manufacturers.[6,7] Even for FDA-approved indications, a selective, positive-result publication bias and nonreporting of negative results may make drugs seem more effective than the full range of studies would justify.[8]

Legal use of labeling. Although off-label prescribing is accepted medical practice, doctors "may be found negligent if their decision to use a drug off label is sufficiently careless, imprudent, or unprofessional."[9] During a malpractice lawsuit, plaintiff's counsel could try to use FDA-approved labeling or prescribing information to establish a presumptive standard of care. Such evidence usually is admissible if it is supported by expert testimony. The burden of proof is then placed on the defendant physician to show how an off-label use met the standard of care.[10]

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Off-label: Accepted and necessary

Off-label prescribing occurs when a physician prescribes a medication or uses a medical device outside the scope of FDA-approved labeling. Most commonly, off-label use involves prescribing a medication for something other than its FDA-approved indication. An example is sildenafil [Viagra] for women who have antidepressant-induced sexual dysfunction.[1]

Other examples are prescribing a drug:

- at an unapproved dose
- in an unapproved format (e.g., mixing capsule contents with applesauce)
- outside the approved age group
- for longer than the approved interval
- at a different dose schedule (e.g., qhs instead of bid or tid).

Typically, it takes years for a new drug to gain FDA approval and additional time for an already-approved drug to gain approval for a new indication. In the meantime, clinicians treat their patients with available drugs prescribed off label.

Off-label prescribing is legal. FDA approval means drugs may be **sold** and **marketed** in specific ways. But the FDA does not tell physicians how they can use approved drugs. As each edition of the *Physicians' Desk Reference* explains, "Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling."[2] Federal statutes state that FDA approval does not "limit or interfere with the authority of a health care practitioner to prescribe" approved drugs or devices

"for any condition or disease."[3]

Courts endorse off-label prescribing. As one appellate decision states: "Because the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment."[4] The US Supreme Court has concluded that off-label prescribing "is an accepted and necessary corollary of the FDA's mission to regulate."[5]

Does off-label constitute malpractice?

Off-label use is not only legal—it's often wise medical practice. Many drug uses that now have FDA approval were off label just a few years ago. Examples include using selective serotonin reuptake inhibitors (SSRIs) to treat panic disorder and obsessive–compulsive disorder. Fluoxetine is the only FDA-approved drug for treating depression in adolescents, but other SSRIs may also have a favorable risk–benefit profile.[6]

The practice is common—we know that

Numerous studies have shown that off-label prescribing is common in, for example, psychiatry[7] and other specialties.[8,9] Because the practice is so common, the mere fact that a drug is not FDA-approved for a particular use does not imply that the drug was prescribed negligently.

Are patients guinea pigs?

Some commentators have suggested that off-label prescribing amounts to human experimentation.[10] Without FDA approval, they say, physicians lack hard evidence, so to speak, that a product is safe and effective—making off-label prescribing a small-scale clinical trial based on the doctor's educated guesses.

If this reasoning is correct, off-label prescribing would require the same human subject protections used in research, including institutional review board approval and special consent forms.

Although this argument sounds plausible, off-label prescribing is not experimentation or research (see "4 reasons why off-label prescribing can be controversial," page e2).[4,11–19] Researchers investigate hypotheses to obtain generalizable knowledge, whereas medical therapy aims to benefit individual patients. This experimentation–therapy distinction is not perfect because successful off-label treatment of one patient might imply beneficial effects for others.[10] When courts have looked at this matter, though, they have found that "off-label use… by a physician seeking an optimal treatment for his or her patient is not necessarily…research or an investigational or experimental treatment when the use is customarily followed by physicians."[4]

Courts also have said that off-label use does not require special informed consent. Just because a drug is prescribed off label doesn't mean it's risky. FDA approval "is not a material risk inherently involved in a proposed therapy which a physician should have disclosed to a patient prior to the therapy."[20] In other words, a physician

Advice on protecting yourself in practice

› **Know why an article applies to your patient.** If you are sued for malpractice, you can use an article to support your treatment choice by explaining how this information contributed to your decision-making.

› **Tell your patient that the proposed treatment is an off-label use** when you obtain consent, even though case law says you don't have to do this. Telling your patient helps him understand your reasoning and prevents surprises that may give offense.

› **Engage in ongoing informed consent.** Uncertainty is part of medical practice and is heightened when physicians prescribe off label. Ongoing discussions help patients understand, accept, and share that uncertainty.

› **Document informed consent.** This will show—if it becomes necessary—that you and your patient made collaborative, conscientious decisions about treatment.[1]

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is not required to discuss FDA regulatory status—such as off-label uses of a medication—to comply with standards of informed consent. FDA regulatory status has nothing to do with the risks or benefits of a medication and it does not provide information about treatment alternatives.[21]

What should you do?

For advice on protecting yourself when you prescribe off label, see the box on page e3.

In addition, you should keep abreast of news and scientific evidence concerning drug uses, effects, interactions, and adverse effects, especially when prescribing for uses that are different from the manufacturer's intended purposes.[22]

Last, collect articles on off-label uses, but keep them separate from your patients' files. Good attorneys are highly skilled at using documents to score legal points, and opposing counsel will prepare questions to focus on the articles' faults or limitations in isolation.

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