Why off-label isn't off base

Douglas Mossman, MD

Dear Dr. Mossman:
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?

Submitted by "Dr. W"

Dr. W wants to know how he can minimize malpractice risk when prescribing a medication off label and 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 hopefully help you avoid—the medicolegal pitfalls of off-label prescribing.

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—such as sildenafil for women with antidepressant-induced sexual dysfunction.[1]

Other examples are prescribing a drug:

- at an unapproved dose
- in an unapproved format, such as mixing capsule contents with applesauce
- outside the approved age group
- for longer than the approved interval
- at a different dose schedule, such as 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

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DO YOU HAVE A QUESTION ABOUT POSSIBLE LIABILITY?

- Submit your malpractice-related questions to Dr. Mossman at douglas.mossman@dowdenhealth.com.
- Include your name, address, and practice location. If your question is chosen for publication, your name can be withheld by request.
- All readers who submit questions will be included in quarterly drawings for a $50 gift certificate for Professional Risk Management Services, Inc's online marketplace of risk management publications and resources (www.prms.com).

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Clinical Point

The fact that a drug is not FDA-approved for a particular use does not imply that the drug was prescribed negligently

Box

4 reasons why off-label prescribing can be controversial

Limited testing for safety and effectiveness. Experiences such as "Fen-phen" for weight loss[11] and estrogens for preventing vascular disease in postmenopausal women[12] 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.[13,14] Many studies ostensibly designed and proposed by researchers show evidence of "ghost authorship" by commercial concerns.[15]

Study bias. Even published, peer-reviewed, double-blind studies 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.[16,17] Even for FDA-approved indications, a selective, positive-result publication bias and non-reporting of negative results may make drugs seem more effective than the full range of studies would justify.[18]

Legal use of labeling. Though 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."[4] 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. It places the burden of proof on the defendant physician to show how an off-label use met the standard of care.[19]

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 1 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 U.S. Supreme Court has concluded that off-label prescribing "is an accepted and necessary corollary of the FDA's mission to regulate."[5]

Is off-label use 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 and valproate for bipolar mania. Though fluoxetine is the only FDA-approved drug for treating depression in adolescents, other SSRIs may have a favorable risk-benefit profile.[6]

Numerous studies have shown that off-label prescribing is common in 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 human guinea pigs?

Some commentators have suggested that off-label prescribing amounts to human experimentation.[10] Without FDA approval, they say physicians lack "hard evidence" that a product is safe and effective, so off-label prescribing is 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 institution review board approval and special consent forms.

Although this argument sounds plausible, off-label prescribing is not experimentation or research (***Box***).[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 1 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]

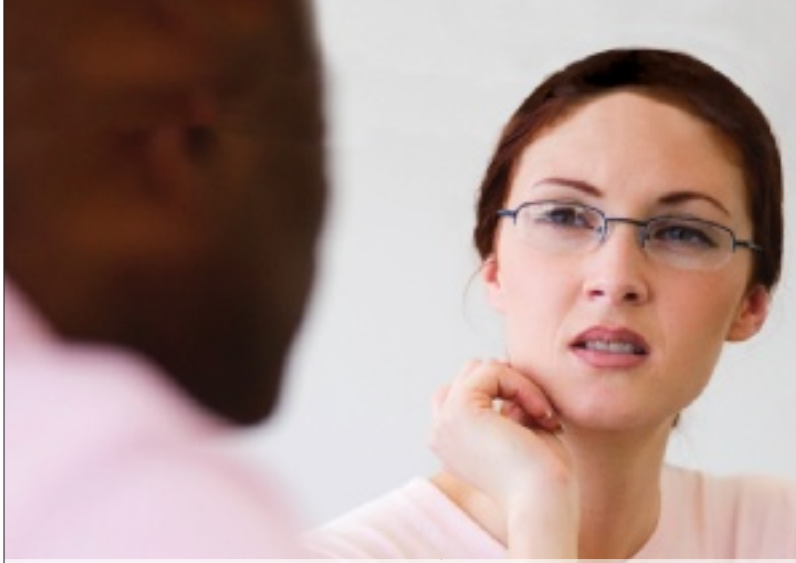
Courts also have said that off-label use does not require special informed consent. Just because a drug is prescribed off-label doesn't mean it's risky. FDA approval "is not a material risk inherently involved in a proposed therapy which a physician should have disclosed to a patient prior to the therapy."[20]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

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 (such as hormone therapy for sex offenders).[22]

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.

Know why an article applies to your patient. If you are sued for malpractice, you can use an



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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. For example, if you prescribe a second-generation antipsychotic for a nonpsychotic patient, you wouldn't want your patient to think you believe he has schizophrenia when he reads the information his pharmacy attaches to his prescription.

Engage in ongoing informed consent. Uncertainty is part of medical practice and is heightened when doctors 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.[23]

Clinical Point

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Related Resources

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- Spiesel S. Prozac on the playground. October 15, 2008. Slate. www.slate.com/id/2202338.

Drug Brand Names

Fenfluramine and phentermine • Fen-phen
Fluoxetine • Prozac
Sildenafil • Viagra
Valproate • Depakote

Bottom Line

Prescribing medications for indications not approved by the FDA is legal, widespread, and often the accepted standard of care. Most physicians cannot and should not avoid prescribing drugs for off-label indications. But when you prescribe off-label, take extra steps to keep your patients safe and reduce your risk of a malpractice judgment.