

ETHICS CASE

Prescribing “Off-Label”: What Should a Physician Disclose?

Commentary by Katrina Furey, MD, and Kirsten Wilkins, MD

Abstract

This case highlights clinical dilemmas faced by physicians when treating patients with conditions for which there are limited or no FDA-approved treatment options. First, it raises questions about when it is appropriate to prescribe medications for “off-label” indications and what might be the ethical and legal implications of doing so. It also prompts us to consider why pharmaceutical companies might or might not pursue FDA approval for new indications when a drug has already been approved for use in another condition. Finally, this case demonstrates the importance of employing shared decision making when discussing complex clinical decisions and how such techniques might have led to different outcomes and better understanding between Dr. Shannin, Maxine, and Heather.

Case

Heather brings her 89-year-old mother, Maxine, to the office of her psychiatrist, Dr. Shannin, for an evaluation. Maxine lives with Heather’s family, and though she has been diagnosed with dementia, she still sees Dr. Shannin in his office by herself while Heather waits for her in his office lobby. During her last visit with Dr. Shannin three months ago, Maxine reported that whenever she got confused, she began to think that the people around her were going to harm her. Heather also expressed concerns about Maxine’s confusion and paranoia, since Maxine would typically respond to those feelings by acting out as if she were being threatened. Maxine was unable to remember these outbursts, but she did remember feeling agitated and did note that Heather seemed very upset when she felt that way. At that time, Dr. Shannin suggested that Maxine try an atypical antipsychotic, olanzapine, to help control her agitation and paranoia. He explained the risks and benefits in detail and also explained that while he’d had good results with several patients with this medication in the past, managing confusion, agitation, and paranoia was not what this medication is really for. Maxine felt confident that Dr. Shannin had used this medication to manage these symptoms for his other patients, however, and so she agreed to begin taking olanzapine, which has managed her symptoms well for the last three months.

Maxine’s dementia has progressed significantly since her last visit with Dr. Shannin, and she is having a particularly bad day today: she doesn’t recognize her longtime physician

and is unable to correctly answer questions about being oriented to time and place. It seems that from this point forward, Maxine will no longer be able to participate meaningfully in decisions about her own care, so Heather now takes a more active role in Maxine's care planning and accompanies Maxine during her appointment with Dr. Shannin.

Dr. Shannin asks Heather if she has any questions for him about Maxine. "Yes," she says, "What's olanzapine? I know she's been taking that for a while, but when I looked it up, it seems to be used for treating psychosis. I'm puzzled. My mother's not psychotic." Dr. Shannin explains his rationale. Heather follows his explanation closely and confirms that while Maxine's memory and functioning have declined over the last three months, she appreciates that she has been less confused, agitated, and paranoid. However, Heather worries about her mother continuing to take a drug that's "off-label" and contains a black box warning in the package. "It just doesn't seem safe, particularly since the black box warning notes an increased risk of death," she explains to Dr. Shannin. "I assume you explained the risks to her when she consented to take this medication three months ago. You've taken good care of my mom and I don't doubt your good intentions. But, as a physician, I guess I don't understand how you're really even allowed to prescribe medications in ways that aren't approved by the Food and Drug Administration."

Dr. Shannin wonders how to respond.

Commentary

Approval by the Food and Drug Administration (FDA) implies that available evidence shows that a drug is safe and effective for the specific indication (disease or symptom) for which it was tested [1]. "Off-label" drug use commonly refers to prescribing currently available medication for an indication (disease or symptom) for which it has not received FDA approval [1, 2]. Off-label use also includes prescribing a drug for a different population or age range than that in which it was clinically tested and using a different dosage or dosage form [1, 2]. Contrary to what patients might assume, off-label drug use is not the same as [experimental or research use](#). Once a drug is FDA-approved for a specific indication, legally it can be used for any indication [3, 4]. Off-label prescribing is common; it accounts for 10 to 20 percent of all prescriptions written [5], although the practice is more common in specific patient populations like children and the elderly [1, 2, 5]. Physicians also might be more likely to prescribe off-label medications for patients facing life-threatening or terminal medical conditions for which there are limited or no FDA-approved alternatives [1, 5].

There are several reasons why off-label prescribing is so common. Advances in clinical medical practice often outpace the FDA's ability to approve new drugs or relabel previously approved drugs with new indications [1, 2, 5]. The FDA approves only 40 to 60 percent of all drugs submitted for review, and it can take six to eight years and approximately \$1.7 billion to get a new drug approved [4]. Moreover, the revenue

associated with relabeling a drug with additional indications might not offset the expense required to conduct the necessary clinical trials, which discourages most pharmaceutical companies from relabeling drugs once they have already been FDA-approved for one indication [1].

Another reason that off-label prescribing is common is that there is limited evidence of the effectiveness of “on-label” use in certain patient populations frequently excluded from clinical trials, such as children, pregnant women, the elderly, and psychiatric patients [1, 2, 5]. In psychiatric patients, in particular, symptom similarity between disease states might contribute to use of one medication off-label for various conditions [1]. Specifically, off-label use of antidepressants, anticonvulsants, and antipsychotics is high and such use increases in prevalence with patients’ advancing age [1, 6]. Elderly patients with dementia, like Maxine, belong to two of the aforementioned groups.

It is important to note that there are no FDA-approved treatment options for dementia-related behavioral disturbances (e.g., psychosis, agitation) [7]. However, randomized controlled trials suggest modest efficacy of atypical antipsychotics in reducing these symptoms [7], and expert consensus and professional guidelines support the use of antipsychotic medications like olanzapine in clinically appropriate circumstances when nonpharmacologic management has failed [8, 9]. In fact, the use of off-label atypical antipsychotics for conditions like dementia has increased in recent years [1]. In Maxine’s case, if medications are deemed necessary for behavioral symptom management (i.e., nonpharmacologic management has failed or her symptoms have become significantly distressing or dangerous), it is reasonable from clinical and ethical standpoints for Dr. Shannin to prescribe olanzapine off-label for her.

Legalities of Off-Label Prescription Drug Marketing and Use

Physicians like Dr. Shannin might worry about legal implications of prescribing off-label. It is important to remember that though FDA approval is based on available evidence of the effectiveness and safety of a drug for the specific indication for which it was tested, it does not guarantee either, even for on-label uses [4]. For example, the FDA has approved drugs, like Vioxx, that were actually unsafe for on-label uses [3]. Because of the associated risks, the FDA has limited manufacturer [marketing of off-label uses](#) of FDA-approved drugs [1, 4]. The FDA Modernization Act of 1997 [10] ruled that manufacturers are allowed to distribute peer-reviewed journal articles about off-label uses of medications to health care professionals upon request [1]. Such off-label drug use publications must be accurate and unedited, and the relationship between information distribution and the sponsoring pharmaceutical company must be clearly disclosed in the marketing materials [1]. The FDA has continued to ban direct-to-consumer marketing of off-label uses by preventing such indications from being advertised in package inserts, TV advertisements, or patient education materials [1]. Nevertheless, off-label marketing by pharmaceutical companies has been one of the most common causes of Medicaid fraudulent claim investigations [11].

The FDA does not prohibit physicians from prescribing drugs off-label [4], and Congress has repeatedly taken legal steps to prevent the FDA from interfering with the practice of medicine [4]. Although many malpractice lawsuits have been filed on behalf of patients arguing that they did not give [informed consent](#) to take a drug because they were not informed that use for their particular condition was actually off-label, the law has generally sided with physicians in finding that they have no legal duty to inform patients of a drug's regulatory status [3, 4]. Such rulings enforce that off-label is an FDA regulatory term that denotes nothing about clinical risks or benefits [4]. The physician's duty is to provide *clinical* information and some have argued that taking the time to explain the legal complexities of FDA approval versus off-label drug use could distract from shared clinical decision making [3, 4].

Weighing the Evidence

Because physicians often treat clinically complex patients, they must balance a patient's needs and individual characteristics with available scientific evidence when deciding whether to prescribe medications off-label [5]. Off-label use is appropriate when it is in the best interest of the patient on the basis of credible, published scientific data supporting the use of the drug in that manner [1, 5]. Furthermore, the risks of using a medication off-label should not outweigh the benefits, although this distinction might be less clear in complicated situations or for patients with many comorbidities [5].

Atypical antipsychotics used off-label to treat dementia-related behavioral disturbances carry significant risks, which, some have argued, outweigh their benefits [12]. The risks posed to Maxine by using olanzapine include general risks to all patients taking antipsychotics (e.g., parkinsonism, akathisia, tardive dyskinesia, metabolic syndrome) as well as risks specific to patients with dementia (e.g., stroke) [13]. In addition, all antipsychotic medications carry a [black-box warning](#) of increased risk of death compared to placebo in patients with dementia [13]. In this case, the risks of using olanzapine off-label must be weighed against the risks of not treating Maxine's escalating paranoia and agitation. Untreated behavioral symptoms of dementia have been associated with an increased risk of nursing home placement and higher rates of caregiver burden, which could lead to decreased quality of life for Maxine and her daughter [7]. Some studies have also shown that dementia-related psychosis and agitation have been associated with more rapid cognitive decline and an increased mortality risk [7].

Shared Decision Making

A key question in this case is whether Maxine had decisional capacity to consent to the initial prescription of olanzapine. She accepted the medication after a discussion of risks and benefits, likely because of her trust in Dr. Shannin. The power dynamic in physician-patient relationships can be such that patients and families trust their physician implicitly; this has its merits and drawbacks, from clinical and ethical standpoints. Although Dr. Shannin indicated to Maxine that he was using olanzapine to treat a

condition for which it was not originally intended, he did not specifically disclose to Maxine its lack of FDA approval to be used to treat her specific symptoms. As discussed above, he is not legally required to do so, but, from an ethics point of view, we might still wonder how his nondisclosure might have affected his alliance with Maxine and Heather. For example, Heather was surprised to learn that her mother had been prescribed a medication typically used in patients with psychotic disorders. Given Maxine's cognitive decline, Heather will likely be assuming a much greater role in medical decision making. Will she trust Dr. Shannin to fully disclose treatment risks in the future? A potential worry is that if nondisclosure undermines Heather's trust in Dr. Shannin, she might not feel comfortable reaching out to him in a crisis or when her mother's treatment needs escalate.

The practice of patient-centered medicine requires that patients and families experience medical treatment decisions as a collaborative and shared process. In his initial discussion with Maxine about olanzapine, Dr. Shannin could have employed additional communication strategies that are key to [shared decision making](#). Whether or not a patient with dementia has decision-making capacity, it is reasonable to ask the patient's permission to include a trusted family member in discussion of treatment options. Maxine might not later recall specific details of the conversation, and, given the typical progressive decline of patients with dementia, she will likely need increasing family involvement in the future. Bringing a family member into the discussion allows a physician to inquire about the effects of the symptoms on the patient's and family's quality of life and to ascertain specific treatment goals of a patient and her family, which might not always be congruent with those of the physician. In this case, Dr. Shannin's goal could be to ensure Maxine's safety and to reduce caregiving burden on Heather. However, Maxine might want a medication to calm her nerves or help her sleep, and Heather might want to reduce familial stress or delay Maxine's placement in a nursing home.

How can shared decision making be implemented? Elwyn et al [14] propose a practical three-step communication model for shared decision making: (1) "choice talk," the step at which patients are made aware that reasonable options exist; (2) "option talk," the step at which patients are provided information about the options; and (3) "decision talk," the step at which patients are supported in considering preferences and making a decision. In this case, if Maxine had not yet been treated for her symptoms, choice talk might include making Maxine and Heather aware that both nonpharmacologic and pharmacologic treatment options exist for agitation and paranoia in dementia. Option talk could include Dr. Shannin's noting that pharmacologic options are limited and that no medications are FDA-approved for this indication. He could then discuss the risks, benefits, and off-label use of olanzapine, and provide a lay summary of the scientific evidence and practice standards that guide use of this medication despite its lack of FDA approval in dementia. Dr. Shannin could also explain nonpharmacologic alternatives (e.g.,

patient reassurance and redirection) and pharmacologic alternatives (e.g., antidepressants) to olanzapine. Option talk might also make use of decision support aids such as pamphlets, videos, or reputable websites, which have been shown to lead to improved patient knowledge, more accurate perception of risks and benefits, and greater participation in decision making [15]. The idea is that patients are supported in the deliberation process throughout and given ample time to make a final decision, which can take more than one encounter [14].

Conclusion

Off-label prescribing is a common and legal practice in medicine. This practice is justified when scientific evidence suggests the efficacy and safety of a medication for an indication for which it does not have FDA approval and when the practice is supported by expert consensus or practice guidelines. Through shared decision making, patients and families are equal partners in clinical decision-making processes, which can help a physician carefully weigh risks and benefits of a given treatment according to the patient's unique circumstances.

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