

Virtual Mentor

American Medical Association Journal of Ethics
July 2012, Volume 14, Number 7: 576-581.

OP-ED

Informed Consent for Off-Label Use of Prescription Medications

Zain Mithani, MD

In the 1960s, British pharmacologist John Vane made a very interesting discovery in his laboratory at the University of London. Vane found that aspirin, a drug that for many years was used primarily to relieve minor pain and fevers, could disrupt a pathway needed for platelet aggregation. Further studies in the 1980s showed that this effect could be used for the prevention of heart attacks and stroke. Despite the evidence, the Food and Drug Administration (FDA) prevented manufacturers from advertising this information until more convincing clinical trials of aspirin's anticoagulant action had been completed. Doctors, in the meantime, were allowed to prescribe aspirin for this purported use. In fact, it was not until 1998 that the FDA finally approved aspirin for the prevention of cardiovascular events [1].

Should manufacturers be allowed to advertise off-label uses of their drugs for which they have credible research? Would this use of aspirin have prevented the deaths of patients who would have asked to be put on it had they seen it advertised as an anticoagulant? Conversely, should physicians be allowed to prescribe drugs that a governing body like the FDA has not determined to be unequivocally safe for use by the general public? This article is in favor of transparency and examines what reasonable people would want to know about the drugs they are being prescribed.

Once a drug has been approved by the FDA for one purpose, a physician can prescribe that drug for any purpose. The practice of prescribing a drug for a purpose other than that for which it is approved is known as "off-label" use [2]. Off-label use is legal and does not necessarily mean that the drug is being used inappropriately [2]. In fact, many physicians prescribe a drug off label because they believe it is the best treatment for a specific condition even though it has not yet been formally tested for use in that condition [2, 3]. Off-label use becomes an ethical, not a legal, issue when the principle of informed consent is introduced.

The concept of informed consent as it is currently understood arose in response to the many medical research abuses of the middle half of the twentieth century—from the mid-1930s through the mid-1970s—in Nazi Germany and the United States. Simply put, informed consent demands that patients give their consent to any treatment or research protocol that a clinician proposes. The "informed" part of the term forces us to ask: how much information must patients receive in order to be able to give "informed" consent?

Given the status that the principle of informed consent enjoys in U.S. medicine today, it should seem strange that physicians commonly prescribe drugs without informing patients that these drugs have not been approved for the use in question. Most patients believe, rightly, that all drugs prescribed by physicians have been approved by the FDA [4]. What most patients do not know or question is whether a given drug has received FDA approval for a specific purpose. It is interesting to note that, despite being such a controversial issue, relatively little has been published about informed consent for off-label use.

Arguments for Requiring Consent for Off-Label Use

Informed consent is a principle that is observed to ensure that patient autonomy is preserved, requiring that competent patients are made aware of and understand enough about the intended benefits and possible risks of proposed treatment to make an informed decision [5]. This consent can be implied by the patient's lack of protest, and, in the case of many routine medical interventions, it is. The FDA requires explicit written consent for drugs being used experimentally or as a part of research, but no explicit consent is required for any off-label drug use if it can be argued that, like any other treatment, the drug is being used in the patient's best interests [6].

Nearly all physicians prescribe drugs for off-label purposes without informing their patients that the drug has not been approved for the purpose they intend [4]. Is it acceptable for a physician to neglect to tell patients of a drug's off-label status? It could be argued that the physician who withholds that information is violating the ethical duty to secure the patient's informed consent [4].

FDA panels have found that some off-label uses can be dangerous. The example of fenfluramine emphasizes this point. Eighteen million prescriptions for the off-label use of fenfluramine as a weight-loss drug were written before it was concluded that it had caused heart-valve damage in thousands of people [4].

A recent survey seemed to increase safety concerns [7]. The survey looked at 150 million prescriptions for off-label use in the United States and found that 73 percent had little to no scientific backing. The study concluded that "off-label medication use is common in outpatient care, and most occurs without scientific support" [7].

Doctors are legally bound to inform patients of risks. The fact that there is a lack of research for off-label use should be considered a risk to the patient. Hence, physicians should follow legal standards that require them "to obtain informed consent from a person before performing a test or stating a treatment—particularly a treatment that involves some uncertainty" [4]. It should follow then that physicians be required to inform patients of off-label use, but this does not seem to be the case.

Doctors are often encouraged to practice an approach known as shared decision making, a model that many consider to be the best guide for the patient-physician relationship. In short, shared decision making requires that both the physician and

patient share information and work together to decide on a treatment plan [4]. Clearly, withholding the intent to prescribe a drug for off-label use fails to honor this approach to the relationship.

To investigate a new use of a drug, a manufacturer has to apply for the investigational new drug (IND) process, which requires that the drug undergo monitored clinical trials to prove its safety in off-label uses. In the meantime, the drug can be prescribed off-label if explicit consent is given by the patients prescribed it [8]. If the drug proves to be safe for a new use, the manufacturer could then submit a new drug application to the FDA, after the approval of which the drug can be used without explicit informed consent for its new use. It is notable that consent is required of participants in a drug trial because the drug's effects have yet to be shown, but consent is not required for a drug prescribed in a clinical setting for a purpose that has not been fully studied.

It could be argued that, given the documented lack of scientific support, off-label drug use should be considered experimental or investigational; the use supports a theoretical assumption on the physician's part. If off-label use were classified as experimental, physicians would be required to obtain explicit consent from patients, most commonly in the form of written consent.

The Argument for Not Requiring Consent for Off-Label Use

One may wonder why, even though the ethical and legal principles of informed consent and shared decision making are not being upheld, off-label use has become so prevalent in the daily practice of medicine. The lack of scientific support for most drug use of this type should serve to heighten these concerns. Some contend, however, that there are logical reasons not to inform patients of a drug's off-label status and instances in which off-label use is actually beneficial.

The most commonly used defense of off-label drug use is that acquiring FDA approval for all uses is not economically feasible. This is especially true in pediatric care, in which three-fourths of prescription drugs are used off label [2, 6]. It is not cost-effective for pharmaceutical companies to get drugs reapproved for children or for other uses [6]. Once a drug is determined to be safe and effective for one use, the pharmaceutical industry relies on the off-label market to expand its sales potential.

Some have contended that the risks involved in using drugs off label are no different than the risk of any medical intervention [2, 8]. Any intervention requires, at the least, an implied consent. Proponents of this argument claim that the "mere fact of off-label use, however, is a matter solely of FDA regulatory status and cannot logically be considered a medical risk of a drug or medical device" [8], suggesting that off-label status is irrelevant to the actual medical risks posed. It has also been argued that a lack of FDA approval does not preclude the drug's being effective or being standard care [3].

The argument is that informing patients of the off-label status would “confound patient decision making by diverting attention to medically irrelevant information” [5]. Proponents of the position argue further that forcing physicians to “learn and discuss legal/administrative (rather than medical) facts [could be] potentially to their detriment and to the detriment of their patients” [8].

It may alarm some that “current practice does not require or even suggest that doctors disclose any of these facts to their patients” [4]. This practice has been amplified by court decisions on the matter. The case of *Alvarez v. Smith* is a good example of courts’ take on the use of a medical device off label. This case was a class-action suit by patients whose surgeons had implanted in their spines screws that had been approved for use in long bones (i.e., arms and legs) only. Many surgeons used the screws off label, and more than 2,000 patients claimed that they had suffered postoperative injuries as a result.

The courts, which have a history of being lenient on off-label use, relied upon past precedent to decide the case in the physicians’ favor [9]. In an earlier ruling, the court had determined that “while patients might have some assurance that uses actually appearing on labeling are safe and effective, they cannot imply from a label’s silence that a particular use recommended by their physician is unsafe, risky, novel, or untried” [5].

Another angle that proponents of off-label drug use take is pointing out that FDA approval is not a guarantee of safety [9]—despite FDA approval, drugs like Vioxx have had serious health implications for *on-label* use. This supports the argument that specifically discussing the off-label status of a drug may wrongly imply that “on-label” means “guaranteed safe,” and could distract patients and clinicians from the real conversation that needs to occur about risks. To complicate matters, different jurisdictions within the United States have different concepts of what constitutes informed consent [10]. Without a clear stance taken by the legal establishment, the medical establishment is less able to set up a model of best practice on this issue and has less incentive to do so.

Although it would be a stretch to do so, physicians might invoke “therapeutic privilege” to excuse them from the legal principle of informed consent [10]. Therapeutic privilege allows physicians to circumvent informed consent when “full disclosure would be detrimental to a patient’s total care and best interests” [4]. A physician who wished to use therapeutic privilege to justify not informing a patient of off-label drug use would have to prove that telling the patient would be detrimental to the patient’s health [4]. A patient with end-stage disease, perhaps, might refuse a treatment upon learning that it was not approved by the FDA, and the physician might judge that refusal of the drug would have serious implications for the patient.

Therapeutic privilege, as one can imagine, is a hotly debated issue. Many argue that it too often allows physicians to set aside legal requirements and ethical principles in

order to provide the treatments that they see as best, but that are not necessarily what their patients want. The American Medical Association *Code of Medical Ethics* takes a much narrower stance, stating that “physicians may withhold information about a patient’s diagnosis or treatment when disclosing it would pose a serious psychological threat, so serious a threat as to be medically contraindicated” [11]. Clearly, this would limit the number of cases that could justify the use of therapeutic privilege.

Whether or not to inform patients of off-label drug use has been the subject of heated debate for a long time, with convincing arguments made on both sides of the issue and no consensus reached. What must be said is that physicians should follow evidence-based standards of care constructed from comprehensive studies looking at health outcomes, patient satisfaction, and the feasibility of the proposed methods.

References

1. Jeffreys D. *Aspirin: The Remarkable Story of a Wonder Drug*. New York: Bloomsbury; 2004.
2. Gazarian M, Graudins LV, Kelly M, McPhee FR, Ward RL, Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust*. 2006;185(10):544-548.
3. Meadows WA, Hollowell BD. “Off-label” drug use: an FDA regulatory term, not a negative implication of its medical use. *Int J Impot Res*. 2008;20(2):135-144.
4. Wilkes M, Johns M. Informed consent and shared decision-making: a requirement to disclose to patients off-label prescriptions. *PLoS Med*. 2008;5(11):e223.
5. Veatch RC. *Medical Ethics*. 2nd ed. Sudbury, MA: Jones and Bartlett Publishers; 1997.
6. Committee on Drugs, American Academy of Pediatrics. Uses of drugs not described in the package insert. *Pediatrics*. 2002;110(1 Pt 1):181-183.
7. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166(9):1021-1026.
8. Beck JM, Azari ED. FDA, off-label drug use, and informed consent: debunking myths and misconceptions. *Food, Drug, Cosmetic Law J*. 1998;53(1):71-104.
9. Mehlman MJ. Off label prescribing. *The Doctor Will See You Now*. <http://www.thedoctorwillseeyounow.com/content/bioethics/art1971.html>. Accessed June 14, 2012.
10. Wear S. *Informed Consent: Patient Autonomy and Physician Beneficence within Clinical Medicine*. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1993.
11. Wynia M. Invoking therapeutic privilege. *Virtual Mentor*. 2004;6(2). <http://virtualmentor.ama-assn.org/2004/02/msoc1-0402.html>. Accessed June 14, 2012.

Zain Mithani, MD, is a resident in internal medicine at the University of Colorado Denver.

Related in VM

[Selective Paternalism](#), July 2012

[Neurontin and Off-Label Marketing](#), June 2006

[Risks and Benefits of Innovative Off-Label Surgery](#), February 2010

[New Devices and Truly Informed Consent](#), February 2010

[Technical Skill and Informed Consent](#), February 2010

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

Copyright 2012 American Medical Association. All rights reserved.