

Staying on Track When Prescribing Off-Label

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Using medications or medical devices for patient populations, symptoms, or diseases not officially approved by the U.S. Food and Drug Administration (FDA) is a practice commonly called off-label use. Off-label prescribing is legal in the United States under the premise that regulatory agencies do not have authority to control the practice of medicine. It occurs for many reasons, including advances in medicine that outpace the FDA's and manufacturers' ability to approve or relabel medications and devices (e.g., aspirin use for acute coronary syndromes prior to FDA approval), limited availability of study data in certain populations (e.g., children, pregnant women), limited FDA-approved alternatives (e.g., fibromyalgia symptoms), and documented effectiveness without formal approval (e.g., beta blockers for congestive heart failure). For these and other reasons, off-label use is common, accounting for approximately 10% to 20% of prescriptions.^{1,2}

Most physicians would likely agree that off-label prescribing is an acceptable choice when there is published scientific evidence supporting it, and when the medication has a low likelihood of adverse effects and a moderate to strong likelihood of benefit. For example, the only beta blocker approved for migraine prophylaxis is propranolol, but metoprolol has been found to be equally effective and is commonly used.³ This type of off-label use is generally considered consistent with sound scientifically based medical practice, regardless of the FDA status of indications.

Most physicians would also agree that off-label use is unacceptable when there is

little scientific evidence, especially if there is a moderate or high likelihood of adverse effects and only a low likelihood of benefit. For example, one trial studied the use of carbonic anhydrase inhibitors for migraine prophylaxis. The trial did not find any increased effectiveness over placebo and was stopped early because of adverse effects.⁴ Prescribing carbonic anhydrase inhibitors for migraine prophylaxis could be deemed inappropriate off-label use.

The ethics surrounding off-label use become more complicated when considering medications with less clear-cut positive or negative risk-benefit ratios. This is the gray area where physicians individually weigh the translational gaps in evidence between effectiveness, available research, and the complexities of real-world clinical practice. Particular scrutiny is suggested when using off-label medications with red flags, such as new medications, medications with known serious adverse effects, or high-cost medications, or when considering novel off-label use.⁵ For example, case reports suggest that anticoagulants might play a role in migraine prophylaxis.^{6,7} Should a physician consider prescribing warfarin (Coumadin) for migraine prophylaxis? There are no randomized controlled trials and scant published literature, and the mechanism of warfarin's effect on migraines is not well understood. Most physicians would not prescribe warfarin for migraine prophylaxis. At the individual patient level, however, this might seem more plausible if a patient has already tolerated warfarin that was prescribed for a different indication, has reported a decreased incidence of migraines while taking it, cannot tolerate other prophylaxis medications, and is at low risk of adverse effects. In this more nuanced case, the novel use of a known drug with patient-reported effectiveness, a known adverse-effect profile, and only moderate costs could be deemed reasonable.

Physicians are responsible for integrating detailed information about individual

patients, disease states, best available evidence, and variation in medication responses to determine appropriate medication choices. The FDA website <http://www.fda.gov/Drugs/default.htm> is a helpful resource for the latest medication information. When information is not available through federal channels, physicians rely on professional organizations, peer-reviewed medical journals, and consensus guidelines to help with the decision-making process. Although journals strive to publish specific recommendations and general guidelines to readers,^{8,9} practicing physicians must use their best judgment to balance effectiveness and safety when choosing a medication for an individual patient.

Ideally, in the context of a strong physician-patient relationship, patients should be notified of the uncertainties of off-label prescribing and share in the complex decision-making process. In the era of electronic databases, medical records, and clinical decision support, physicians have the opportunity to minimize unnecessary risk while optimizing care with off-label prescribing when appropriate.

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REFERENCES

1. Egualé T, Buckeridge DL, Winslade NE, Benedetti A, Hanley JA, Tamblin R. Drug, patient, and physician characteristics associated with off-label prescribing in primary care. *Arch Intern Med.* 2012;172(10):781-788.
2. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med.* 2006;166(9):1021-1026.
3. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society [published correction appears in *Neurology.* 2013;80(9):871]. *Neurology.* 2012;78(17):1337-1345.
4. Vahedi K, Taupin P, Djomby R, et al.; DIAMIG investigators. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomized placebo-controlled trial. *J Neurol.* 2002;249(2):206-211.
5. Largent EA, Miller FG, Pearson, SD. Going off-label without venturing off-course: evidence and ethical off-label prescribing. *Arch Intern Med.* 2009;169(19):1745-1747.
6. Maggioni F, Bruno M, Mainardi F, Lisotto C, Zanchin G. Migraine responsive to warfarin: an update on anticoagulant possible role in migraine prophylaxis. *Neurol Sci.* 2012;33(6):1447-1449.
7. Asherson RA, Giampaulo D, Singh S, Sulman L. Dramatic response of severe headaches to anticoagulation in a patient with antiphospholipid syndrome. *J Clin Rheumatol.* 2007;13(3):173-174.
8. O'Malley PG. What does off-label prescribing really mean? *Arch Intern Med.* 2012;172(10):759-760.
9. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc.* 2012;87(10):982-990. ■

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