

Off-label use of medications in medical practice

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Disclaimer: The off-label uses discussed on this website have not been proven by randomized, double-blind, placebo-controlled clinical trials to be either safe or effective for the indications discussed, and no assurance can be made that this will occur.

Off-label use of a medication or a biological is defined as use for an indication, or in a manner, for which FDA approval has not yet been obtained and which is therefore not included on the FDA-approved label or product packaging.

This review is written to correct many common misconceptions regarding off-label use by physicians in the course of their medical practice. In contrast to common misconceptions, off-label use is common, legal, not experimental and in many cases represents the optimal treatment choice for a condition for which approved uses of existing therapeutics have failed to adequately treat a refractory disease or condition.

“FDA approved indications were not intended to limit or interfere with the practice of medicine”[1]. “Off-label use does not imply an improper use and certainly does not imply an illegal use or a contraindication based on evidence”[2]. “It is undisputed that the prescription of drugs for unapproved uses is commonplace in modern medical practice and ubiquitous in certain specialties”[3]. In fact, prescriptions of off-label uses of drugs “may account for more than 25% of the approximately 1.6 billion prescriptions written each year, with some recent estimates running as high as 60%”[4]. For many medical conditions, including cancer, heart and circulatory disease, AIDS, kidney diseases requiring dialysis, and osteoporosis, the standard treatments are off-label uses of medications or medical devices[5]. By some estimates, 80% of drugs used in the pediatric setting are prescribed “off-label,” [6] due in large part to the ethical issues surrounding the performance of clinical trials in children. The majority of medical treatments are also provided off-label for patients with “orphan” diseases (those that affect fewer than 200,000 patients), because there is no profit incentive for manufacturers to develop and perform clinical trials for such diseases[7]. “The approved indications for a drug can be driven as much by politics and business as by medicine”[8].

Off-label use is not proscribed by the Federal Food, Drug & Cosmetics Act, and a licensed physician is allowed to prescribe FDA approved drugs for off-label uses[9]. In 1982, the FDA Drug Bulletin informed the medical community that “once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling” [10]. This policy has been restated by FDA representatives[11]. Additionally, the Physicians’ Desk Reference has perennially stated in each annual volume’s Foreword that off-label use is clearly permissible:

The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling[12].

The AMA has also recognized the importance of off-label prescribing[13]. George Lundberg, then Editor of the Journal of the American Medical Association, testified in

Congress:

Prescribing FDA-approved drugs for off-label (unlabeled) uses often is necessary for optimal patient care. For a product to have the most effective potential benefits, law and regulation should and must follow, not precede, science. There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to practice in these regards when it is medically appropriate[14].

"[A] knowledge of off-label drug use broadens the clinician's ability to relieve the symptoms of patients with diseases that are refractory to standard therapy or for which there is no effective standard therapy"[15]. "Indeed, the practice of medicine may require a practitioner to use drugs off-label to provide the most appropriate treatment for a patient"[16].

"One frequently asked question is whether an off-label use of an approved drug should be viewed as experimentation requiring formalized institutional review and informed consent. This question reflects a misunderstanding of what constitutes research"[17]. The off-label use of an FDA-approved drug in a medical office in an effort to improve the health of a patient is not experimentation. California Health & Safety Code §24174 defines "medical experiment" as: "...the use of a drug or device ... in or upon a human subject in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of the subject or otherwise directly benefiting the subject." Id. Similarly, the FDA regulations define experiment as "any use of a drug except for the use of a marketed drug in the course of medical practice." 21 C.F.R. 312.3

"As one leading medical ethicist explained, 'many drugs and devices approved for use by the FDA are prescribed for uses that are not listed on the FDA-approved package label. This does not mean that all such uses must be made the object of a formal study designed to establish safety and efficacy'[18]. The FDA itself has stated:

Good medical practice and patient interests require that physicians use commercially available drugs, devices, and biologics according to their best knowledge and judgment. ... Use of a product in this manner as part of the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND) or an Investigational Device Exemption(IDE) or review by an IRB ... [19].

As Taborrok has explained, off-label use is often necessary for optimal patient care:

"Such uses come to be accepted through research, discussion, testing, and especially through the publication of peer-reviewed studies. FDA-required clinical trials are often (although not always) among the best sources of scientific information concerning a drug's safety and efficacy, but they are hardly the only sources of such information. ... [W]hat is "safe" and "effective" depends in part on judgment and preferences; safety and effectiveness are not dictated exclusively by objective fact. Off-label prescribing offers patients and doctors a choice between the judgments of the medical and scientific communities and the judgments of the FDA. For at least some of their therapy, most patients and doctors choose the judgment of the medical and scientific communities"[20].

As Sackett et. al. explained in an editorial in the British Medical Journal discussing evidence based medicine,

“...some questions about therapy do not require randomised trials (successful interventions for otherwise fatal conditions) or cannot wait for the trials to be conducted. And if no randomized trial has been carried out for our patient’s predicament, we must follow the trail to the next best external evidence and work from there”[21].

Finally, off-label use represents an important mechanism for discovery of new indications of existing drugs. A recent study documented that 57% of drug therapy innovations were discovered by practicing clinicians through off-label use in their medical practice, rather than by pharmaceutical industry or academic scientists[22]. Off-label use is therefore of critical importance not only for the optimal treatment of patients, but also for the discovery of new uses of existing drugs.

References

1. Weaver v. Reagen (8 Cir. 1989) 886, F.2d 194, 198.
2. American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, Pediatrics, July 2002, Vol. 110, No. 1, p.181-183.
3. Washington Legal Foundation v. Henney (D.C. Cir. 2000) 202 F.2d 331, 333; *see also*, Femrite v. Abbot NW Hospital (1997 Minn.) 568 N.W.2d 535, 540 [“off-label use of medical products is widespread and appropriate.”].
4. Beck, J., and Azari, E., *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, (1998) 53 Food Drug L.J. 71, 80.
5. Id.
6. Fritch, D., *Speak No Evil, ear No Evil, Harm the Patient? Why the FDA Needs to Seek More, Rather Than Less, Speech From Drug Manufacturers on Off-Label Drug Treatments*(2005) 9 Mich. St. J. Med. & Law 315, 335 and n.106. *See also*, Beck, J., *supra*, FN 44 at 80, n.81; American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, Pediatrics, July 2002, Vol. 110, No. 1, p.181-183.
7. Fritch, D., *supra*, FN 46, at 335. *See also*, Beck, J., *supra*, FN 44, at 80, n. 80.
8. Li, V., et al., *Off-Label Dermatologic Therapies: Usage, Risks, and Mechanisms*, Arch. Dermatol., Nov. 1998, Vol 134, 1449-1454.
9. *See* FTC v. Simeon Management Corp. (N.D. Cal. 1975) 391 F. Supp. 697, 706, *aff’d* 532 F. 2d 708; *see also*, Buckman Co. v. Plaintiffs’ Legal Comm. (2001) 531 U.S. 341, 350-51.
10. FDA Drug Bulletin (1982) 12:4-5.
11. *See e.g.*, Femrite v. Abbot NW Hospital (1997 Minn.) 568 N.W.2d 535, 540; 51 Nightingale, S.L., *Use of Drugs for Unlabeled Indications*, American Family Physician, 269 September 1986, Nightingales, S.L., *Unlabeled Use of Approved Drugs*, Drug Information Journal, 26:141-147, 1992.
12. Foreword of the 2004 edition of the Physicians’ Desk Reference.

13. See AMA Policy, H-120.961, *Unlabeled Indications of Food and Drug Administration Approved Drugs*; see also, Tabarrok, Alexander T., *Assessing the FDA Via the Anomaly of Off-Label Drug Prescribing*, The Independent Review, Summer, 2000, pp. 25-53.
14. Statement of George Lundberg, *Promotion of Drugs and Medical Devices for Unapproved Uses: Hearing Before the Human Resources and Intergovernmental Relations Subcomm. of the House Comm. on Government Operations*, 102 Cong., 1 Sess. 103.
15. Li, V., et al., *Off-Label Dermatologic Therapies: Usage, Risks, and Mechanisms*, Arch. Dermatol., Nov. 1998, Vol 134, 1449-1454.
16. American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, Pediatrics, July 2002, Vol. 110, No. 1, p.181-183.
17. American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, Pediatrics, July 2002, Vol. 110, No. 1, p.181-183.
18. Beck, J., *supra*, FN 44, at 82. See also, American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, Pediatrics, July 2002, Vol. 110, No. 1, p.181-183 [“Use of approved drugs in an off-label manner to treat an individual patient does not require an IND application.”]
19. *Id.*, at 71, 82-83.
20. Tabarrok, Alexander T., *Assessing the FDA via the Anomaly of Off-Label Drug Prescribing*, The Independent Review, Summer, 2000, p. 34.
21. Sackett DL, Rosenberg WM, Muir JA, et. al. *Evidence based medicine: what it is and what it isn't*. BMJ 1996;312:71-72 (13 January).
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