Off-Label Prescribing: Fundamental Considerations

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http://www.thedoctorwillseeyounow.com/content/bioethics/art1971.html
Off-Label Prescribing

• The physician practice of prescribing a drug or medical device for a purpose different from one of the indications for which the product is approved by the Food and Drug Administration

• Possibly, as high as 60 percent of all drug prescriptions in the U.S. are off-label (as well as a large proportion of chemotherapy and pediatric prescribing).
Off-Label Prescribing

• Delicate balance between protecting patients from possibly unsafe/unapproved drugs or devices versus the right of physicians to decide how to treat patients
• Off-label prescribing (OLP) does not violate FDA law: “Any approved product may be used by a licensed practitioner for uses other than those stated in the product label.”
• FDA is not in the practice of medicine
• FDA has to regulate but not “directly interfere” with the practice of medicine
OLP

- OLP may often occur in advance of the FDA’s regulatory activities and possibly constitute “state of the art” practice in some cases: “In some circumstances, an off-label use of a particular drug or device may even define the standard of care.” (Richardson v. Miller, Tenn. Ct. App. 2000)

- Yet, a physician doing OLP will lack the information on use, dosage, and route of administration that is provided on the package labeling for approved indications.

- Also, the safety and efficacy of the OLP will not have been established by FDA approved methods, i.e., clinical trials; obviously, safe and efficacious in one clinical context does not necessarily generalize to another.
In Richardson v. Miller, the court held that a physician could be held liable for deviating from the standard of care by using a drug (terbutaline) off label.

“Given the risk of liability for using a product for an unapproved purpose, physicians should do so only when they are convinced that the unapproved status of the use is outweighed by the potential benefit to the patient.” (Mehlman)
Levels of Evidence

• I  Meta Analytical Studies
• II  Randomized, double blinded, multicenter, placebo controlled trials
• III  Controlled, nonrandomized trials
• IV  Case controlled cohort studies
• V  Comparative, Correlational Case Series or Studies
• VI  Single Case Reports
• VII  Clinical Anecdotes

Most EBPs are based on level IV - VII studies.
OLP

• OLP largely not considered “experimentation” as it doesn’t seek to secure generalizable knowledge but rather is therapeutically intended

• If the primary intent is to benefit the patient, the intervention is therapy

• But the line can be blurry because sometimes the physician is motivated by an interest in generalizable knowledge and sometimes has a financial interest motivating his or her OL use
FDA focus on product promotion

- GSK agreed to plead guilty to a three-count criminal information, including two counts of introducing misbranded drugs, Paxil and Wellbutrin, into interstate commerce and one count of failing to report safety data about the drug Avandia to the Food and Drug Administration (FDA). Under the terms of the plea agreement, GSK will pay a total of $1 billion, including a criminal fine of $956,814,400 and forfeiture in the amount of $43,185,600. (Dept. of Justice, July 2, 2012; http://www.justice.gov/opa/pr/2012/July/12-civ-842.html.)
The manufacturer can distribute reports of clinical studies on unapproved use if

- The manufacturer:
  - Filed an application with the FDA to approve the new indication
  - Sponsored the trials
  - Filed the reports it wanted to distribute with the FDA 60 days in advance
  - Noted via a disclaimer that the new use had not been approved by the FDA
The pros and the cons of promotion

• Pros:
  – Makes info available to physicians, perhaps promoting better patient care
  – Postpones costs of obtaining FDA approval, thus accelerating an off-label use for patient care
  – Benefits patients with orphan diseases

• Cons:
  – Undermines FDA’s interest in ensuring safety and efficacy
  – Removes incentives for clinical trials
  – Encourage seeking FDA approval for in slam dunk cases, where research overwhelming demonstrates benefits
Is a physician required to tell a patient that the drug or device is OL?

- Courts have said “No.”
- Maybe they should be: After all, if the drug or device is not approved, that would by definition attest to a “lack of knowledge” about safety and efficacy
- But is that true? Is there a serious “lack of knowledge” about the drug or device just because it doesn’t have FDA approval?
- The problem will be settled in the courts
Last considerations

• The manufacturer’s liability for OLP: In Proctor v. Davis (Ill. Ct. App. 1997), Upjohn was held liable for knowing that Depo-Medro was dangerous for periocular use; not only did Upjohn fail to alert physicians to this but actively promoted Depo-Medro for periocular use

• Should insurance companies provide coverage for OLP? (Is it experimental? Some state legislatures have required reimbursement, however.)