

An adverse drug reaction as defined by the World Health Organization (WHO) is a noxious and unintended reaction to a drug at doses normally used in humans for prophylaxis, diagnosis, and treatment.<sup>1</sup> In a meta-analysis, Lazarou et al. estimated that ADRs cause 106,000 deaths per year, ranking between the fourth and sixth leading cause of death in the United States.<sup>2</sup> In 2002, it was estimated that 800 ADR reports were due to off-label uses.<sup>6</sup> Brennan et al. found that 10-20% of hospitalized patients experience at least one ADR for the duration of their stay.<sup>3</sup> This increases the length of stay and hospital costs by 2.2 – 3.2 days and \$3244 – \$4655, respectively.<sup>4,5</sup>

A six-month investigation by Knight Ridder, a news organization with over 31 news publications nationwide, reports 115 million prescriptions in 2002 were written for unapproved indications, which doubled from 5-years ago.<sup>6</sup> Physicians were routinely prescribing medications that do not have FDA-approved indications for the conditions they were treating. This sparked controversy and recent media attention as to whether there is an increase in patient morbidity and mortality with off-label prescribing.

The Department of Veterans Affairs (VA), the largest integrated healthcare system in the U.S. that treats close to 5 million veterans each year, established the Center for Medication Safety (VAMedSAFE), a Patient Safety Center of Inquiry. It is the Center's aim to improve the safety of medication prescribing and administration by identifying, tracking, and addressing preventable adverse drug events, focusing on adverse drug reactions (ADRs). To address off-label prescribing in the VA, VAMedSAFE established a guideline in conjunction with the VA Pharmacy Benefits Management Strategic Healthcare Group and the VA Medical Advisory Panel that recommends an evidence-based approach in weighing the risk and benefits of off-label prescribing. Further evaluation of the risks of off-label prescribing is of particular interest to the Center for Medication Safety and the VA system.

In cooperation with VAMedSAFE, the findings of this project will be used to help inform VA National Policy on the safety of off-label drug use in a given facility. In concordance with VAMedSAFE, the findings will be disseminated throughout the system to increase knowledge and awareness and promote patient safety.

Before marketing a new drug, the Food and Drug Administration (FDA) requires manufacturers to demonstrate through clinical testing the safety and efficacy in the medical conditions and the patient population the drug purports to have. This information is contained in the proposed "label" submitted. With the FDA approval, the drug label identifies only the uses for which the evidence showed safety and efficacy. Physicians use a drug "off-label" when they prescribe an FDA-approved drug for indications other than those specified on the label.

Currently there is no organization devoted to monitoring off-label uses. According to the FDA, "...Congress did not intend to interfere with the practice of medicine. Thus, once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed on the FDA approved labeling..."

The extent to which off-label use is prevalent in the different areas of medicine is not clear. However, there are studies that show extensive use in AIDS patients, cancer patients, the pediatric population, and pregnant women. The reason behind this is that during clinical trials these patient populations are generally excluded. The use in the general population is still somewhat unclear, but a newspaper reports that 21% of the prescriptions in 2002 were written for off-label uses and some drugs had non-FDA approved uses as high as 90%.<sup>6</sup> For the elderly, a population with multiple comorbidities, its extensive use is not clear. The adverse drug reactions (ADRs) that result from such practice are currently unknown, but we predict it to be more serious, particularly in the elderly.