dian, 79 vs 47; P < .001). Aggregating drugs by medical specialty, we found ADEs to be highest in medications associated with neurology (n = 168), psychiatry (n = 116), and rheumatology (n = 111). Looking at date of approval, we found that newer medications had significantly more labeled ADEs than older medications, with drugs approved during the 1980s and 1990s having the highest overall number of ADEs.

Structured Product Labels formatted in accordance with the 2006 labeling guidelines contained a greater number of ADEs than other SPLs (72 vs 47; P < .001). To control for the possibility that this differential was due simply to new format labels being associated with newer drugs, we repeated the comparison looking only at medications approved since 1980. Again, we found a significantly higher number of ADEs in new-format SPLs than in older label formats (113 vs 72; P < .001).

Comment. The goal of our research was to survey the current landscape of ADE labeling. We found the volume of ADEs to be remarkably high, particularly in newer and more commonly prescribed medications as well as in psychiatric and neurologic drugs. These patterns are not entirely unexpected. Newer drugs may face more rigorous clinical trials and postmarketing surveillance compared with older medications. Similarly, commonly prescribed drugs, by sheer volume of patient exposures, are likely to generate more ADE reports than less common drugs. The high volume of ADEs found in neuropsychiatric medications may relate as much to patient population as to the effects of the drugs themselves. Yet while a high number of labeled ADEs is not necessarily indicative of drug's true toxicity, the presence of such excess data still may induce information overload and reduce physician comprehension of important safety warnings.

Recent FDA guidelines do not appear to have reduced overwarning. Structured Product Labels formatted in compliance with the 2006 regulations actually contained more ADEs than other labels. This finding underscores the tremendous challenge faced by the FDA in reversing the long-standing trend toward overwarning. It is our hope that the baseline data provided by this study will inform the design and evaluation of future efforts to decrease the complexity of adverse event labeling.

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INVITED COMMENTARY

Prescription Drug Label Adverse Events: A Call for Prioritization

In 2006, the FDA unveiled the first major revision of the prescription drug label in more than 25 years. This format, the Physicians Labeling Rule (PLR), was intended to make the drug label easier to read and understand by reorganizing and prioritizing drug information that had become overwhelmingly detailed, complex, and difficult to interpret. In this issue of the Archives, Duke and colleagues describe the first quantitative analysis of listed ADEs in the drug label. Extracting more than 330,000 ADEs from 5602 drug labels indexed on the DailyMed Web site, the investigators observed that the median number of unique ADEs had steadily increased from 43 events per label for drugs approved in the 1960s to 63 events per label for drugs approved within the past decade. Almost 600 drugs listed more than 150 ADEs, and 84 listed more than 300. In addition, drugs that conformed to the PLR were documented to have even more ADEs than older drug labels. Although the authors did not address the possibility of bias associated with inclusion of multiple labels for the same drug (eg, methotrexate has 10 labels indexed in DailyMed and amiodarone has more than 20 labels), they have provided us with a glimpse of the overwhelming numbers of ADEs that health care providers must sift through to make informed decisions toward the safe, effective use of a drug for an individual patient.

What risks should be included in the product label? How should the information be presented? While it is...
important to disclose risk information, overwarning without appropriate context is not helpful. Prescribers ignore vague, difficult-to-interpret warnings, even for risks that have been deemed serious. In addition, dizzying lists of all known and theoretical ADEs, regardless of severity, frequency, or causality may discourage prescribers and patients from using a valuable drug. As proof, risk communications have been shown to reduce prescribing of drugs, often with poor health outcomes.4,5

The FDA guidance document on the presentation of information in the “Adverse Reactions” section of the drug label offers a framework for selecting, characterizing and organizing adverse event information.6 The document suggests that ADEs that occur at the same rate as placebo, should generally not be included. Vague terms such as “common,” “rare,” “infrequent,” or “frequent” should be avoided unless linked to specific frequencies. An example of a specified frequency for “common” ADEs would be those that occurred in at least 10% of treated patients and at a rate at least twice that of placebo. Furthermore, ADEs should be reported in a hierarchical manner, with those that occurred with higher frequency first, followed by those that caused therapy discontinuation and those that occurred with lower frequency but were serious (eg, fatal, life threatening, or caused or prolonged hospitalization). In all cases, only those ADEs for which there is plausible causality should be included.

Since these guidelines are not legally binding, it is not known to what extent drug labels follow these recommendations. A consistent approach to the selection and risk characterization of ADEs in the drug label is needed, particularly with the documented proliferation of ADEs that now reside in the drug label. At the minimum, drug labels should present ADE information in a standardized format using common terminology and definitions so that health care providers can systematically process and manage the deluge of clinical data. The recommendations set forth by FDA guidance documents provide an excellent starting point.

As with all quality health care improvement initiatives, a validation process for drug labels linked to outcomes—including health care provider comprehension, perception of drug benefits, and risks and usability—as a decision-making tool are needed. The information within the drug label must receive regular, rigorous evaluation for currency and clinical relevance to health care providers of varying background, training, and experiences. While studies exist evaluating modes of effective risk-benefit communications to patients, little has been published regarding communication of drug information to health care providers. Responsible oversight on the development and revision of drug labels is necessary to ensure the effective delivery of unbiased, comprehensive, accurate, up-to-date, and user-friendly drug information.

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Process Changes to Increase Compliance With the Universal Protocol for Bedside Procedures

Wrong site, wrong procedure, and wrong patient events can be devastating to patients. Between 1300 and 2700 such events are estimated to occur annually in the United States. These are also called “never events” because processes can be implemented to prevent them. In 2004, The Joint Commission (TJC) created the Universal Protocol (UP) as a mandatory safety standard in an attempt to eliminate wrong procedures through a preprocedure verification process, procedure site marking, and a “time-out” (correct site, procedure, and patient). Up to 70% of wrong site procedures may be prevented if the time-out process is used.

Although a number of publications have documented successful interventions for improving compliance with the UP in the operating room, to our knowledge there are no data on compliance with this protocol for bedside procedures. In fact, wrong site/wrong patient events outside the operating room constitute a significant problem and result in substantial harm. We developed an innovative reengineered process for bedside procedures with an aim to improve compliance with the UP.

Methods. This pre- and postintervention study focused on medical inpatient bedside procedures (lumbar puncture, paracentesis, and thoracentesis) at a large academic medical center from July 2008 to May 2010. The Northwestern University institutional review board determined this project exempt.