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The Missing Patient Voice in Drug-Safety Reporting

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A patient wants to know about symptoms she may experience from a prescription drug she is taking. Consulting the label's "Adverse Reactions" section, she finds a wealth of data. Little does she realize that this information, largely collected during clinical trials, is based almost entirely on clinicians' impressions of patients' symptoms — not on patients' own firsthand reports of their experiences with the drug.

Current drug-labeling practice for adverse events is based on the implicit assumption that an accurate portrait of patients' subjective experiences can be provided by clinicians' documentation alone. Yet a substantial body of evidence contradicts this assumption, showing that clinicians systematically downgrade the severity of patients' symptoms, that patients' self-reports frequently capture side effects that clinicians miss, and that clinicians' failure to note these symptoms results in the occurrence of preventable adverse events.^{1,2}

Prospectively collecting data directly from patients about symptoms they experience while taking a drug (so-called adverse symptom events) is an alternative approach that could add valuable information to current practice. Self-reports are more sensitive to underlying changes in patients' functional status than are clinicians' reports and tend to reflect symptoms occurring earlier during a course of treatment (see graphs).³ Current methods for detecting adverse events in clinical trials are acknowledged to lack sensitivity,⁴ and concerning symptoms might well come to light earlier in the drug-development cycle if patient reporting were standard practice.

Before a drug has received marketing approval from the Food and Drug Administration (FDA), direct patient reporting could be used in phase 2 trials to screen for unexpected reactions and then in phase 3 trials to follow up on any detected signals and to characterize the incidence and severity of additional potential adverse symptom events. Although other inherent limitations of preapproval safety evaluations, such as narrow eligibility criteria and limited follow-up, would persist, the ability to detect adverse symptom events among study participants would improve. After FDA approval, both general screening to detect signals in observational cohorts and more targeted assessments in controlled trials could be used.

Such methods might have resulted in earlier detection of some serious adverse events that have been widely publicized, including suicidal ideation related to the use of selective serotonin-reuptake inhibitor (SSRI) antidepressants in younger patients and severe constipation and ischemic colitis associated with the use of the 5-hydroxytryptamine type 3 antagonist alosetron, which resulted in temporary withdrawal of the drug from the market.

Why isn't patient reporting of such events a standard component of drug evaluation? Although safety evaluation once predominated over efficacy evaluation in the regulatory review of drugs, over time the rigor of efficacy measurement has progressed, while safety screening has remained largely dependent on ad hoc and retrospective reporting. It is in this

milieu that the current clinician-based approach to adverse symptom reporting has evolved. This model remains in place largely because of inertia — but today's patients are vocal partners in decisions about their own care, and there are commonly available technologies that permit reliable collection of information from them. Optimizing tactics for collecting this information is especially important because adverse symptom events are common, accounting for a large proportion of the adverse reactions listed in drug labels (see table).

Objections to adopting a patient-focused approach to safety monitoring have included perceived regulatory constraints and concerns about feasibility, added administrative requirements, cost, and limitations of the available questionnaires. But these objections no longer seem insurmountable.

After all, there are no regulatory requirements that clinicians rather than patients report potential adverse symptom events in clinical trials. The FDA mandates only that sponsors provide safety data during drug development and approval. In fact, patient self-reporting as a data-collection method was recently embraced by the FDA in its “Guidance for Industry: Patient-Reported Outcome Measures Use in Medical Product Development to Support Labeling Claims,” in which “patient-reported outcomes” — a term that broadly refers to any data directly reported by patients without interpretation by someone else — are characterized as the gold standard for assessing subjective phenomena that are best described by the patient, such as symptoms. But the scope of the FDA guidance is limited to the collection of data to support labeling “claims” (e.g., claims of efficacy based on comparative data); it stops short of recommending patient-reported outcomes for adverse-event screening. For example, the guidance establishes that if a claim is sought for a symptom-based effect such as reduced shortness of breath in asthma or pain palliation in metastatic cancer, the end-point data should be reported directly by patients and not interpreted by anyone else. But if shortness of breath or pain is measured as a suspected adverse effect of a drug, the standard approach is still for clinicians, not patients, to interpret and document it. Nonetheless, the FDA guidance reflects substantial progress in bringing the patient's voice into regulatory reporting and paves the way for similar methods to be adopted for general screening for adverse symptom events.

Questions about the feasibility of collecting adverse-event information from patients have been raised, given the complexity of collecting data at disparate sites and times. Yet in myriad trials, patient-reported–outcome instruments have been demonstrated to be a practicable means of collecting data on health-related quality of life, compliance with a drug regimen, and patient satisfaction with care. Although capturing patients' reports does require administrative resources, most of the necessary infrastructure is already in place, since adverse-event reporting is standard in clinical trials. Incremental costs can be minimized by using widely available, inexpensive reporting technologies that rely on the Internet or patients' telephones. In fact, administrative efficiency might actually improve if patients' self-reports were shared with clinicians, saving time that investigators would otherwise have to spend eliciting that information.

As for the availability of patient-reported–outcome questionnaires, the field of instrument development has advanced substantially in recent years, with standards that are now encoded in the FDA guidance. There are multiple measures that could be immediately adopted or modified for this purpose, including the Patient-Reported–Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which my colleagues and I developed as part of a National Cancer Institute (NCI) initiative to introduce patient-reported outcomes as a standard component of adverse-event monitoring in NCI-sponsored trials (<http://outcomes.cancer.gov/tools/pro-ctcae.html>).

Responsibility for including patient-reported measures of adverse symptom events in a trial's design before approval would fall to the study's industry sponsor. Questionnaires would be administered by local site personnel, and the sponsor would analyze and report this information to the FDA and include it in the submitted label. After approval, responsibility for including these end points would again fall to an industry sponsor if a trial were part of its postmarketing commitment to the FDA or related to seeking a new indication for an agent. In investigator-initiated studies, the principal investigator would take on these responsibilities.

The limitations of current safety-reporting mechanisms are well documented^{4,5} and have led the FDA to develop its recently announced Safe Use Initiative to reduce preventable harm from medicines. Patient self-reporting offers one solution that would enhance the capture of subjective elements of safety information. Given the clinical and scientific value of patient-reported adverse symptom events as well as the feasibility of collecting this information, one can make an ethical argument that patients are entitled to know the impressions of their peers — and that scientists, regulators, and clinicians should have access to those impressions when evaluating drugs. Such a change would lend all of us extra confidence when we reach into the medicine cabinet.

References

1. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and their documentation in the medical record. *Am J Manag Care* 2008;14(8):530–9. [PubMed: 18690769]
2. Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. *Arch Intern Med* 2005;165(2):234–40. [PubMed: 15668373]
3. Basch E, Jia X, Heller G, et al. Adverse symptom reporting by patients versus clinicians: relationships with clinical outcomes. *J Nat Cancer Inst* 2009;101(23):1624–1632. [PubMed: 19920223]
4. Institute of Medicine, National Academy of Sciences. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. National Academies Press; Washington, DC: 2006.
5. Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004 Nov 16;141(10):781–8. [PubMed: 15545678]

Table

Proportion of Adverse Events Listed in U.S. Drug Labels That Would Be Amenable to Patient Self-reporting (“Symptoms”).*

Indication	No. of U.S. Approved Drug Labels Examined	No. of Unique Adverse Events Listed in Labels	Average No. of Adverse Events per Label	Proportion of Adverse Events That Are Symptoms
Asthma	35	368	54	198/368 (54%)
Breast cancer	32	617	83	234/617 (38%)
Gastroesophageal reflux disease	18	475	121	221/475 (47%)
Hyperlipidemia	28	375	86	172/375 (46%)
Osteoarthritis	39	685	94	296/685 (43%)

* The data on adverse events were abstracted and categorized by two physicians, with arbitration by a third in cases in which the first two disagreed.