Author Contributions: Dr Doshi had full access to the request log file used in the study and takes responsibility for the accuracy of the data analysis. Study concept and design: Doshi and Jefferson. Acquisition of data: Doshi. Analysis and interpretation of data: Doshi and Jefferson. Drafting of the manuscript: Doshi and Jefferson. Critical revision of the manuscript for important intellectual content: Doshi and Jefferson. Statistical analysis: Doshi. Conflict of Interest Disclosure: Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society’s September 2012 annual congress, where he gave an invited talk on oseltamivir. Dr Jefferson receives royalties from his books published by Blackwell and IL Pensiero Scientifico Editore, none of which are on clinical study reports. In 2011-2012, Dr Jefferson acted as an expert witness in a litigation case related to an antiviral (oseltamivir phosphate; Tamiflu [Roche]). Dr Jefferson is on a legal retainer for expert advice on litigation for influenza vaccines in health care workers. Drs Doshi and Jefferson also personally know some European regulators who share an interest in this topic.

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Online-Only Material: The eAppendix and eFigure are available at http://www.jamanetwork.com.

Additional Contributions: David Mackay, BVetMed, MSc, PhD, MRCVS, of the European Medicines Agency, closely reviewed the manuscript for accuracy and provided many clarifications about the EMA’s policy. Dr Mackay received no compensation for his assistance.


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Using Information Technology to Improve the Monitoring of Outpatient Prescribing

Adverse drug events (ADEs) and medication nonadherence are common and reduce the potential benefit of medications. Adverse drug events, defined as poor health outcomes caused by medications, occur in up to 25% of ambulatory care patients prescribed a medication, medication nonadherence, defined as patients not taking their medications as directed, can occur in 25% of new prescriptions. Improved monitoring and communication could reduce ADEs and nonadherence to minimize medication-associated problems.

See Invited Commentary at end of letter

We designed the ISTOP-ADE system (Figure), an information technology-based approach to monitor ambulatory patients receiving incident prescriptions. This system automatically called patients 3 and 17 days following a prescription and allowed patients to request a pharmacist phone call. The purpose of this study was to determine this approach’s potential effectiveness.

Methods. We conducted a prospective cohort study of patients receiving incident prescriptions from 1 of 70 primary care physicians in Montreal and Quebec City, Canada. Practices were selected if they used the Medical Office of the 21st Century web-based electronic prescribing and integrated drug management system. Eligible pa-
patients received an incident prescription for at least 1 new medication. We excluded patients who could not speak English or French; had a telephone number with an extension; or were deemed inappropriate for the study by their primary care physician.

Twenty-one days after their prescription, we contacted all patients and used a structured interview to elicit information about medication use, symptoms, changing health state, and health care visits. We then collated these responses with electronic health record and automated call data into case record forms. Using standard methods, 2 physicians independently reviewed cases to determine whether patients experienced ADEs or primary nonadherence.

Results. We recruited 628 patients from 76 practices (median patient age, 66 years; interquartile range, 57-73 years). The 3 most common medication classes were antilipemic agents (n=146; 22.2%), antidiabetic agents (n=122; 18.5%), and inhaled corticosteroids (n=91; 13.8%). We completed the study protocol on 568 of 628 patients (90%) and found no statistically significant differences between completers and noncompleters.

On the day-3 and day-17 calls, the system successfully connected with 465 (82%) and 475 patients (84%), respectively. Of patients connecting to the system, one-third required follow-up from the pharmacist. On the day-3 contact, the most common reason for pharmacist assistance was the patient not starting to take the medication (n=65; 44%); at day 17, the most common reason was new problems starting since the patient started taking the medication (n=81; 50%).

Overall, we identified 125 ADEs experienced by 125 patients (22% [95% CI, 19%-26%]). The ISTOP-ADE system identified 58 of 125 ADEs (46.4% [95% CI, 38%-55%]). In 23 of the 58 patients who experienced an ADE (40% [95% CI, 27%-53%]), the pharmacist modified the patient’s medication regimen in response to their interaction. For patients whose ADE was identified by the ISTOP-ADE system, 20 of 58 had symptoms lasting 7 days or longer (35%); in contrast, patients whose ADE was not identified by the system, 33 of 67 had symptoms that lasted 7 days or longer (49%) (P = .04). Thirty-three patients reported primary nonadherence (5.8% [95% CI, 4%-8%]), of which the system identified and potentially influenced the management of 10 (30%).

Comment. The ISTOP-ADE system successfully connected with over 80% of patients, one-third of whom requested personal contact with a pharmacist. The system identified 46% of ADEs and influenced the management of 40% of these. Those ADEs identified by our system were of shorter duration than those not identified. Finally, the system identified one-third of all primary nonadherence events. It is possible that the identification of ADEs and nonadherence events led to modifications in treatment that had positive health benefits.

Our approach for improving safety was to monitor all patients. When we identified patients experiencing an ADE or being nonadherent, we were able to intervene in a timely manner by connecting them to a pharmacist who called to personally provide help. We believe that this approach reduced the duration of ADEs, most of which were not preventable.

It is notable that our intervention did not identify all ADEs and primary nonadherence. We believe that certain enhancements could improve the system, including an inbound function to allow patients to call, an online data entry form for patients, improved education, and improved scripting and dialogue design.

Because our study was nonexperimental, one should not conclude that our intervention will improve patient health status. However, these preliminary results suggest a potential benefit and warrant further study.

In conclusion, our intervention allowed successful monitoring of most patients and identified many medication-related problems. The system led to important treatment modifications in a significant proportion of patients, suggesting that it has the potential to positively impact health outcomes. Before widespread implementation, we recommend controlled clinical trials.


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M any millions of dollars have been spent on preventing adverse drug reactions at the point of prescribing. Automated systems help identify drug-drug interactions and excessive drug doses. Computerized alerts warn prescribers about potentially inappropriate drugs in older adults. However, only one-quarter of adverse drug reactions can be prevented by catching errors or problems at the time of prescribing.1 The remainder of adverse drug reactions are not the result of prescriber error but simply represent the known adverse effects of drugs. Some patients who take calcium channel blockers will develop peripheral edema. Some patients who take selective serotonin reuptake inhibitors will experience marked sexual dysfunction. For some drugs, risk factors have been identified that place a patient at higher risk of developing an adverse event. However, in most cases, we cannot predict who will develop an adverse drug reaction and who will not. We prescribe and hope for the best.

Unfortunately, physicians do not do a good job of identifying and appropriately managing adverse reactions when they occur. Many patients do not tell their physicians when they are experiencing an adverse event, and we often do not ask.2,3 Moreover, physicians often misattribute the symptoms of an adverse drug reaction to an underlying disease, leading to diagnostic workups and a prescribing cascade of new medications rather than treating the problem at its source by discontinuing the offending drug.4 On a broader level, only a small fraction of adverse drug reactions are reported to the US Food and Drug Administration Adverse Event Reporting System (http://www.fda.gov/Safety/MedWatch/), hindering efforts for postmarketing surveillance of drug safety.5 These problems with recognizing and managing adverse drug reactions occur not because physicians are incompetent, but because we lack the systems that would allow us to systematically identify and address medication-related problems.

The research described by Forster and Auger3 in this issue of *JAMA Internal Medicine* shows a promising approach to bridge this quality gap. Building on past studies that have shown the benefits of reaching out to patients to identify adverse drug reactions, the authors developed a hybrid system. Three days after a drug was newly prescribed, the system generated a phone call to the patient. Using interactive voice response technology, the system asked the patient 4 simple questions about problems they may be having with their drugs and whether they wanted to talk to a pharmacist. The process was repeated 2 weeks later. One-third of contacted patients needed a follow-up call from the pharmacist. Overall, the system identified slightly under half of the 22% of patients who experienced an adverse drug reaction. In addition, it identified one-third of the 6% of patients who were nonadherent to their medications.

This is exciting and highly promising. It is also not ready for widespread implementation. While the system detected a number of medication-related problems, it missed more than half of adverse drug reactions and two-thirds of episodes of nonadherence in patients — and would likely have done worse outside the controlled environment of a research setting. For most patients, the simple act of reaching out is necessary but not sufficient. People do not develop adverse drug reactions — they develop symptoms, which may be mistakenly attributed to causes other than drugs (including “getting old”), and which they may be hesitant to disclose. (Other adverse reactions may be completely asymptomatic but nonetheless serious, such as progressive hyperkalemia or anemia.) Outreach calls may also be asynchronous with when the patient develops a medication-related problem. These challenges bedevil the widespread practice of calling patients several days after hospital discharge to inquire on their well-being and to identify problems with their medications. While a wonderful idea, relatively little is known about how well these follow-up procedures actually identify problems, and although there is some evidence that these interventions are effective, the benefits are not as great as one might hope.6

What might be most helpful is a multifocal approach in which the surveillance strategies being developed by Forster and Auger3 and like-minded colleagues are coupled with efforts to educate and encourage patients to be active partners in monitoring adverse reactions and nonadherence to their medications.7 This latter approach is best exemplified by health-coach based approaches pioneered by Coleman et al8 and others in which impressive improvements in health resulted not from bringing services to patients but by helping patients be engaged participants in their own care. These interventions are complex, and their potential benefits do not diminish the substantial contribution of surveillance-based approaches. Nonetheless, the solution to the problems of adverse drug reactions and nonadherence cannot solely rest on bringing the health care system closer to the patient. We need to empower our patients to come closer to us.

Michael A. Steinman, MD

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INVITED COMMENTARY

**Reaching Out to Patients to Identify Adverse Drug Reactions and Nonadherence: Necessary but Not Sufficient**