The timely article by Murray et al. prompts me to write. We have produced nearly 30 risk minimization plans to permit the safer use of medicines by patients and to enhance the benefit to risk ratio. A key part of such plans, which are now enshrined in the United States under the Food and Drug Administration Amendments Act of 2007 (Pub L No. 110-85), within Risk Evaluation and Mitigation Strategies (REMS) and Risk Minimisation Action Plans, and also the Risk Management Plan of the European Medical Evaluation Agency (EMEA) in the European Union, are measures to minimize the effect of any identified and potential risks.

We have appreciated for some time that many of the most effective risk minimization measures for new medicines are centered around the activities of the pharmacist and the relevant interface with both patients and prescribers. Relevant tools can relate to pharmacist education and also to the role of pharmacist as educator, as well as prescriber restrictions based on the pharmacist acting as a gatekeeper for access. We have also explored physician and health care professional behavior during the prescribing decision making process for particular medicines using a Web-based decision support algorithm and how the pharmacist can mitigate risks that can subsequently arise. This technology can easily be adapted for other related uses, such as consumer and patient decision support, compliance, and adverse event reporting.

Another key area that we are exploring is how risk minimization measures lead not only to improved safety for patients but also to better and more targeted prescribing, such as adhering to the label, which is of relevance already in Europe and is likely to become so in the United States. The pharmacist is likely to play a key role in both risk benefit and risk share schemes in the future.

The work of Murray et al. has led to further key evidence in this important debate and is therefore to be applauded.

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In reply

Dr Banerjee describes the need for improved risk minimization plans for marketed drugs and the relevance of appropriate prescribing, pharmacist education, and technology in improving medication safety. Because of the complexity of pharmacotherapy and our modest understanding of the risks of marketed drugs, approaches to risk minimization involving health care providers (physicians, pharmacists, and nurses) and technology, such as the Internet, could reduce threats to medication safety. These efforts are of global importance and have captured the attention of drug policy experts and regulatory agencies, particularly in the European Union, the Middle East, and the United States.

Nonetheless, because of limited support to improve prescribing practices, limited time spent by health care providers educating patients about their medications, and a still evolving informatics infrastructure, patients often slip through the existing safety net and experience drug-related problems. As indicated by the results of our study, pharmacists may play an important role in improving medication safety. Such improvements are most notable when patients receive careful instructions on their medications in health care systems that encourage communication among all health care providers and the patients they serve. Thus, I would agree with Dr Banerjee that in addition to thoughtful risk minimization plans, core components of improved benefit to risk profiles for medications include salient technology to imple-
ment these plans and more time spent instructing patients. While physicians and nurses play key front-line roles enhancing the benefits and reducing the risks of medicines, pharmacists are especially well poised to make a difference improving medication safety. Finally, I appreciate Dr Banerjee’s enthusiasm for our work.

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Adverse Events in Patients Receiving Cholinesterase Inhibitors Due to Dissimilar Follow-up Periods

The study by Gill et al1 suggested a higher risk of adverse outcomes including syncope, bradycardia, pacemaker insertions, and hip fractures in community-dwelling adults with dementia receiving cholinesterase inhibitors compared with well-matched controls. These findings have important implications, as the agents in question remain the mainstay of symptomatic treatment for an otherwise debilitating illness.

It is interesting to note that while the incidence of hospital visits for syncope are comparatively higher in the cholinesterase inhibitor cohort (2.2% vs 1.5% in controls, see Table 3 in Gill et al1), the incidences for all other adverse outcomes are actually almost identical between cholinesterase inhibitor and control groups (hospital visits for bradycardia, 0.5% vs 0.4%; pacemaker insertions, 0.3% vs 0.3%; and hospitalizations for hip fractures, 1.6% vs 1.6%). The significant difference noted in the event rates and subsequent hazard ratios are therefore mainly influenced by the shorter follow-up periods reported for the cholinesterase inhibitor group (hospitalization due to hip fractures, mean follow-up times were 252 days and 302 days for the cholinesterase inhibitor and control cohorts, respectively.) Unfortunately, there was no clarification for this disparity in the article text.

Based on the authors’ description of their method in determining follow-up duration, one could offer the following possible explanations for the discrepancy: (1) subjects in the cholinesterase inhibitor group experienced adverse events much earlier compared with controls, thereby shortening their follow-up time; (2) there was a high rate of drug discontinuation in the cholinesterase inhibitor cohort, resulting in a high number of dropouts from the study; and (3) mortality rate was higher in the cholinesterase inhibitor group compared with controls, resulting in the observed disparity. Any of these scenarios would have important clinical implications that should be explored further.

Previous reviews have identified the clinical benefits of treatment with cholinesterase inhibitors for patients with dementia, especially in patients with Alzheimer disease.2,3 However, as highlighted in the study by Gill et al,1 the possibility of significant adverse events cannot be ignored. Physicians considering their use in frail elderly patients with dementia should be clearly aware of their treatment goal (the preservation of cognitive function) and the need for follow-up monitoring to ensure drug safety.

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We thank Dr Chan for his interest in our study,2 and we agree that cholinesterase inhibitors may provide clinical benefits for some patients with Alzheimer disease. The goal of our study was to better characterize underrecognized adverse effects of these medications. Dr Chan highlights the shorter mean follow-up time among cholinesterase inhibitor users compared with nonusers in our study, which was detailed in Table 3 of our article.1 These findings are similar to those in randomized trials, in which it has been consistently demonstrated that there is a higher dropout rate for patients assigned to treatment with cholinesterase inhibitors than for patients assigned to placebo.2 Clinical experience supports this observation, which appears to be due primarily to adverse drug effects such as nausea and diarrhea. Thus, the patients who used cholinesterase inhibitors in our study had less opportunity to develop syncope-related outcomes compared with the control subjects. As a result, the number of events per 1000 person-years provides a more accurate reflection of harm than do crude event rates. Nonetheless, we presented both figures in Table 3.1

Our findings may underestimate the true burden of harm. Observational studies of medical interventions such as ours have been found to provide conservative estimates of the absolute risks of harm compared with randomized trials.3 Unfortunately, randomized trials alone are often inadequate to fully characterize the adverse effects of medications in the real-world setting. As a result, postmarketing surveillance studies are necessary to complement adverse event data from randomized trials. We look forward to further studies to confirm and clarify the risks identified in our article.

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