authors adjusted their analyses for a range of clinically important factors. However, the study did not consider the impact of prescribed drugs.

While the etiology of delirium is multifactorial, psychotropic drugs are common precipitants. If not identified in hospital and communicated to primary care physicians, use of these drugs may be continued or reinitiated following hospital discharge. Antipsychotics (eg, haloperidol) and benzodiazepines are also used to manage in-hospital delirium. Benzodiazepine and opioid analgesic therapies initiated in hospitals are often continued for long periods following discharge.[2,3] Prescription and continued use of these drugs may have contributed to the greater cognitive deterioration observed in those who developed in-hospital delirium compared with those who had no delirium.[4]

The importance of postdischarge education about delirium for clinicians and care givers has been described.[5] Among people with dementia, clinicians may mistake drug-induced cognitive impairment for progression of the underlying disease process. Cognitive deterioration at any time, and particularly following hospital discharge, should prompt a comprehensive review of drug therapy to identify and minimize the use of drugs that may exacerbate cognitive decline.

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Conflict of Interest Disclosures: None reported.

1. Gross AL, Jones RN, Habtemariam DA, et al. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med*. 2012;172(17):1324-1331.
2. Zisberg A, Shadmi E, Sinoff G, Gur-Yaish N, Srulovici E, Shochat T. Hospitalization as a turning point for sleep medication use in older adults: prospective cohort study. *Drugs Aging*. 2012;29(7):565-576.
3. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. *Arch Intern Med*. 2012;172(5):425-430.
4. Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging*. 2012;29(8):639-658.
5. Alici Y. Interventions to improve recognition of delirium: a sine qua non for successful transitional care programs [letter]. *Arch Intern Med*. 2012;172(1):80.

Delirium Admissions in Dementia

Gross and colleagues[1] wrote an interesting article on hospital admissions in patients with Alzheimer disease 65 years or older who visited the Massachusetts Alzheimer Disease Research Center (ADRC) at least 3 times. The key to their article is the accuracy of discharge coding for delirium in hospital medical charts.

The diagnosis of delirium is fraught with problems. In many hospitals clinicians label any elderly patient with acute confusion as delirious even if they do not meet criteria such as Confusion Assessment Method (used by physicians) or *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (used by psychiatrists). I decided to conduct a retrospective analysis in the Wyong Hospital Memory Clinic to replicate the Massachusetts ADRC study by Gross et al.[1] Wyong Hospital has 370 beds and is located 100 km north of Sydney, Australia. Among the 473 patients in the Wyong Hospital Memory Clinic database, I selected 193 with dementia or mild cognitive impairment who had at least 1 hospital admission (Gross et al[1] sampled only patients with dementia and not MCI). Total follow-up at Wyong Hospital was 340.3 patient-years; the median follow-up was 699 days, or 1.91 years, compared with the median follow-up of 3.2 years in Massachusetts.

Twenty of the 193 Wyong Hospital patients with mild cognitive impairment or dementia (10.4%) were readmitted for delirium (I prospectively verified at least 50% at the time of readmission) compared with 148 of 263 (56.3%) in Massachusetts (χ^2 test, $P<.001$). I repeated this analysis for 115 Wyong Hospital Memory Clinic patients with dementia who had at least 1 readmission during a median follow-up or 652 days (1.8 years). Twelve of 115 Wyong Hospital patients with dementia (10.4%) were readmitted for delirium compared with 148 of 263 (56.3%) in Massachusetts (χ^2 test, $P<.001$).

The best explanations for the 46% absolute discrepancy in delirium readmissions between Massachusetts and Australian patients with dementia are the following 4 factors: (1) diagnosis related group inducements to mention delirium are more powerful in America than in Australia; (2) the 263 American patients with dementia had more severe dementia than the 114 Australian patients with dementia; (3) the Wyong Hospital Memory Clinic linked to a community Dementia Support Service offers more care support than the Massachusetts ADRC; and (4) the retrospective medical chart review in Massachusetts was less sensitive to identifying delirium compared with the present analysis, wherein I personally assessed more than 50% of readmissions from the Wyong Hospital Memory Clinic.

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Conflict of Interest Disclosures: None reported.

1. Gross AL, Jones RN, Habtemariam DA, et al. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med*. 2012;172(17):1324-1331.

The Meaning of Delirium

We read with interest the Invited Commentary by Vasilevskis and Ely[1] entitled "The Danger of Delirium" on the article by Gross and colleagues[2] evaluating delirium and long-term cognitive trajectories in patients with dementia. We agree

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with the authors' indication on the need to preserve the "functional integrity of the brain," and we want to highlight the importance to identify the most appropriate means to reach this objective, since we still currently lack information on the pathological basis explaining the negative long-term effects of delirium.

As stated by the authors,[1] it is challenging to clarify if some of the mechanisms involved in delirium pathogenesis such as sepsis, hypotension, or polypharmacy act directly on cognitive outcomes or their effect is mediated by delirium itself. The question is relevant to the understanding of the pathophysiological construct of this syndrome because in the former condition delirium may be seen as a clinical sign accompanying the effect of different noxious stimuli, similarly to fever for pneumonia, whereas in the latter delirium may be regarded as an independent clinical condition with a direct biological effect. In addition, in the first case it could be hypothesized that treatment of delirium may have only a symptomatic value and does not play a critical role to improve the patients' cognitive and clinical conditions, whereas if delirium is a mediator of long-term consequences, its prevention could have a crucial role, synergic with the cure of the causative diseases. In the case of patients with dementia, the need to distinguish these 2 mutually exclusive pathways is of particular relevance owing to the criticism of prescribing drugs to control hyperactive symptoms of delirium (ie, antipsychotics), which may be harmful in patients with impaired brain and low cognitive reserve. These considerations are also of value in the perspective of educating physicians and nurses; in fact, as stated by the authors,[2(p1329)]

> [l]ack of recognition may be attributed . . . to the notion that delirium is unimportant . . . and has no long-term significance in patients with AD.

We need to use existing data and develop further studies to convince the most reluctant colleagues not only on the "danger" but also on the "meaning" of delirium and its implications, especially in an understudied population such as subjects with dementia.

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Conflict of Interest Disclosures: None reported.

1. Vasilevskis EE, Ely EW. The danger of delirium. *Arch Intern Med.* 2012;172(17):1331-1332.
2. Gross AL, Jones RN, Habtemariam DA, et al. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med.* 2012;172(17):1324-1331.

In reply

The letter by Regal offers an interesting comparison to our study. We applaud the author's motivation. Although the study by Regal raises interesting findings, the prevalence estimate for delirium at admission to the Wyong Hospital Memory Clinic is not directly comparable to our study's reported number of new cases during hospitalization for 3 important reasons: differences in time frame of ascertainment, patient populations, and method of delirium ascertainment. Most importantly, with respect to time frame of delirium, the 10.4% figure reported by Regal is an estimate of delirium prevalence at hospital admission. Our 56.3% is a proportion of new delirium cases during hospitalization.

With respect to the patient population, our sample was composed exclusively of patients with diagnoses of definite, possible, or probable Alzheimer disease, whereas 40% of Regal's sample included patients with mild cognitive impairment. Patients with dementia are nearly 3 times more vulnerable to delirium than patients with less impairment.[1] Although the risk of delirium is lower among nondemented patients, we believe, based on previous studies from our group and others,[2] that the deleterious association of delirium we report is similar in other populations. We further wish to clarify that Massachusetts Alzheimer Disease Research Center clinic visits are not hospitalizations, so our sample is not restricted to readmitted patients as is Regal's sample.

With respect to delirium ascertainment, we did not use hospital delirium diagnoses as Regal did. Rather, delirium was rigorously identified using a validated medical chart review method, which is 24 times more sensitive than diagnoses made by International Classification of Diseases, Ninth Revision *diagnosis codes.[3]*

We are grateful for the review by Bellelli and colleagues. We strongly agree with the authors that studies elucidating the pathophysiologic basis for the negative long-term outcomes of delirium are greatly needed. However, we do not agree that the 2 pathways proposed by Bellelli and colleagues are mutually exclusive. We believe that delirium may serve both as a sign of severe illness or noxious insults and as a contributor to poor outcomes. Epidemiologic evidence suggests that delirium may lead to permanent cognitive impairment.[4] In addition, previous studies suggest that delirium may trigger amyloid deposition.[5] We agree with Bellelli and colleagues that this should be a priority for future research, since the clinical implications are far reaching.

We strongly concur with the points made by Dr Bell. Unfortunately, we were unable to examine the important contribution of medications to cognitive trajectory in our study. We completely agree this is a vital area for future research.

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Conflict of Interest Disclosures: None reported.

1. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *J Am Geriatr Soc*. 2002;50(10):1723-1732.
2. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev*. 2004;14(2):87-98.
3. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST Jr, Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc*. 2005;53(2):312-318.
4. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443-451.
5. Xie Z, Xu Z. General anesthetics and beta-amyloid protein [published online August 14, 2012]. *Prog Neuropsychopharmacol Biol Psychiatry*. doi:10.1016/j.pnpbp.2012.08.002.

Correction

Errors in Text. In the Invited Commentary titled "Measuring Diagnostic Errors in Primary Care: The First Step on a Path Forward" by Newman-Toker and Makary, published online February 25, 2013, and in the March 25 issue of *JAMA Internal Medicine* (2013;173[6]:425-426), errors occurred in the text. In the third paragraph on page 425, the fourth sentence through the end of the paragraph should have read, "Nevertheless, with more than half a billion primary care visits annually in the United States,[6] if these data from Singh et al are generalizable, at least 500 000 missed diagnostic opportunities occur each year at US primary care visits, most resulting in considerable harm. If error rates at the half-billion non–primary care visits[6] are similar, the total could be more than 1 million. If even 10% of these (100 000) are easily prevented, and combining this figure with autopsy-based estimates of preventable US hospital deaths from diagnostic errors (40 000/y to 80 000/y[1]), more than 150 000 patients per year in the United States might have undergone preventable misdiagnosis-related harm."

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