C-SSRS itself is demonstrated to be valid and reliable in the diverse patient populations to which its use has been extended.

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Dr. Chappell and Dr. Stewart are full-time employees of Pfizer. Dr. Feltner has received consulting fees from Astellas, Ironwood, Merck, National Institute of Neurological Disorders and Stroke, Novartis, Ono, Takeda, and Toyama; he is consulting chief medical officer at and holds stock options in Embera Neurotherapeutics; he has equity interest in Eli Lilly and Pfizer; and he is a former employee of Pfizer. Dr. Makumi is a full-time employee of GlaxoSmithKline.

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Response to Large and Nielssen and Chappell et al. Letters

TO THE EDITOR: Drs. Large and Nielssen dispute a claim in the introduction of our article. We wrote that studies of risk factors predicting suicide consistently suggest that suicidal ideation and a history of suicide attempt are among the most salient risk factors for suicide, and we provide four citations summarizing the relationships of attempts and ideation to suicide. The first citation does not refer to an association between ideation and suicide but between attempts and suicide (1). The fourth shows a relationship between ideation and attempts (2). Our second and third citations refer to studies with the Scale for Suicidal Ideation. As shown by Beck et al. (3), worst point suicidal ideation as indicated by the total score of 19 items predicted subsequent deaths by suicide. Brown et al. (4) reported that current suicidal ideation as measured by the total score on the Scale for Suicide Ideation contributed "unique risk estimates of eventual suicide." Although not all studies agree, many large studies show that suicidal ideation predicts both suicide and suicide attempts (5, 6). Although the association between suicidal ideation and suicidal behavior is modest, we know of no other risk factors that are stronger, with the possible exception of impulsivity/aggression (see Oquendo et al. [7] for a review of the prospective literature), that may be more important at a younger age range. Furthermore, since our paper was published, Gibbons et al. (8) reported that the antisuicidal effect of antidepressants such as fluoxetine and venlafaxine in adults is mediated through amelioration of depression severity. This means that even though suicidal ideation may be a modest predictor of risk in adults, it is important to monitor because it is also a modifiable risk factor.

We appreciate the comments by Dr. Chappell and colleagues and agree that further research is required, as we noted in our paper. We anticipate that the instrument will provide clarity to the field of suicide research by providing comparable data in different populations.

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Does the Neurotoxicity of Haloperidol Explain the Higher Mortality in Dementia Patients Compared With the Second Generation Agents?

TO THE EDITOR: The study by Kales et al. (1) in the January 2012 issue of the *Journal* provides yet another set of data confirming the relatively higher risk of mortality with the first-generation antipsychotic haloperidol compared with the second-generation antipsychotics olanzapine, quetiapine, and risperidone in elderly persons with dementia.

We have also reported a significantly higher mortality risk with haloperidol compared with risperidone and olanzapine in a veteran population over age 65 (2). Our sample was assessed in 1998 and 1999, which partially overlaps with the sample dates in the Kales et al. study (1998–2008), with very similar findings.

Kales et al. do not address the possible reasons for the higher mortality *risk* with haloperidol; however, published studies show that haloperidol induces apoptosis and is neurotoxic (3, 4).

In contrast, studies over the past decade indicate that atypical antipsychotics are neuroprotective (4), inducing neurogenesis and increasing levels of neurotropins such as nerve growth factor and brain-derived neurotrophic factor. Haloperidol's neurotoxicity may be particularly lethal for the degenerating brains of dementia patients. For several years, I have urged our trainees not to use haloperidol to treat psychosis in any patient, young or old. Other conventional antipsychotics, such as perphenazine, have also been reported to be neurotoxic (5), suggesting that serious consideration should be given to avoiding the first-generation antipsychotics for patients at any age, although their efficacy on psychotic symptoms is well established.

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Dr. Nasrallah has received research grants from Eli Lilly, Forest, Otsuka, Roche, and Shire and has received honoraria for serving as a consultant, advisory board member, or speaker for Alkermes, Boehringer-Ingelheim, Genentech, Gruenthal, Janssen, Lundbeck, Merck, Novartis, and Sunovion.

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Response to Nasrallah Letter

To the Editor: As Dr. Nasrallah notes, our data provide confirmation of the higher mortality associated with haloperidol when compared with atypical antipsychotics in patients with dementia (1). The main finding and unique contribution of our paper, however, is that there are mortality risk differences between atypical antipsychotics, with risperidone and olanzapine having higher mortality rates than quetiapine. Since the publication of our article, our findings of differential mortality among individual antipsychotics have been confirmed in another sample (2).

Dr. Nasrallah also brings his pilot study (3) to our attention. This retrospective study at a single center reported higher rates of 2-year mortality for patients taking haloperidol in comparison with those taking atypical antipsychotics. However, as noted in a letter to the editor regarding that paper (4), the study did not control for the known selection biases that occur in patients treated with haloperidol compared with atypical antipsychotics. Haloperidol tends to be prescribed for patients older and sicker than those treated with atypical antipsychotics (5). In our study, we analyzed a wide array of potential confounding factors in addition to using propensity methods to control for potential treatment-by-indication bias. In doing so, we observed the mortality action of haloperidol occurring within the first 30 days of treatment. Therefore, it is unclear that one could conclude that neurotoxicity is the mechanism of mortality risk.

In light of our data, the evidence from randomized controlled trials, and a number of retrospective database studies, we find no support for the idea that atypical antipsychotics are neuroprotective in patients with dementia. Randomized trials have shown atypical antipsychotics to have 1%–2% higher risk than placebo over 10- to 12-week study periods (6). Over the longer 6-month follow-up in our cohort, olanzapine and risperidone showed mortality rates of approximately 27 deaths per 100 person-years of treatment compared with 18.6–21 deaths per 100 person-years with quetiapine and valproic acid. In addition, we previously showed (7) that the absolute mortality risk over 12 months in patients taking atypical antipsychotics was 4.8% higher than in those not taking medication, which corresponds to a number needed to harm of 20.8. Therefore, if atypical antipsychotics are to be prescribed, then they should be used in conjunction with a risk-benefit approach taking into account the efficacy and safety evidence base for the agents under consideration.

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