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Early Alzheimer's disease - Reply

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## CORRESPONDENCE



## Early Alzheimer's Disease

**TO THE EDITOR:** In the Clinical Practice article about early Alzheimer's disease, Dr. Kawas (Sept. 11 issue)<sup>1</sup> discusses testing for reversible causes of dementia. More than 15 years ago, it was conclusively shown that true reversibility of dementia, especially in the elderly, was extremely rare.<sup>2,3</sup> More recent work has confirmed these findings, revealing improvement in less than 1 percent of cases.<sup>4</sup>

On the basis of the evidence, one should be quite conservative, and decisions about testing should be directed primarily by the clinical clues available from the history and physical examination. Kawas cites the American Academy of Neurology's universal neuroimaging policy but does not refer to other authoritative bodies that have published more conservative recommendations, such as those from Canada.<sup>5</sup> These guidelines have even been tested and found to do no harm.<sup>6</sup>

Geriatricians long ago learned that it is often in the patient's best interest to make haste somewhat slowly. This is especially true in the case of a frail elderly patient who presents with cognitive decline.

A. Mark Clarfield, M.D.

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**TO THE EDITOR:** Dr. Kawas enumerates causes of dementia to be ruled out before one makes a diagnosis of Alzheimer's disease. Among the tests for ruling out other causes, serologic tests for syphilis and human immunodeficiency virus (HIV) infection should be recommended as part of the differential diagnosis, especially in patients who are less than 65 years old, because both causes can improve with specific treatment.

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**TO THE EDITOR:** Paroxetine is highlighted for the treatment of depression in patients with dementia, but the drawbacks of this medication should be considered. First, of the selective serotonin-reuptake inhibitors, it has the highest binding affinity for the muscarinic acetylcholine receptor<sup>1,2</sup> (equivalent to that of nortriptyline), and such a medication should be used cautiously for the treatment of a disease marked by acetylcholine deficiency; cognitive symp-

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toms may be exacerbated or may arise and be mistaken for progression of the illness. Second, of the selective serotonin-reuptake inhibitors, paroxetine is associated with the highest incidence of the antidepressant discontinuation syndrome,<sup>3,4</sup> which may occur after even a single dose has been omitted. The memory loss in patients with early Alzheimer's disease places them at particular risk for this syndrome. The quality of life is affected by this syndrome, but also, some of its cardinal symptoms (disequilibrium, headache, and agitation) may be mistakenly attributed to other medical conditions (e.g., transient ischemic attack), prompting the performance of unnecessary diagnostic procedures. Antidepressants with negligible anticholinergic activity and a negligible incidence of the antidepressant discontinuation syndrome (e.g., fluoxetine, mirtazapine, and bupropion) generally may be preferable for patients with dementia who have depression.

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**TO THE EDITOR:** Recommendations regarding the use of risperidone (Risperdal) for treatment of the symptoms of dementia (Table 3 of the article by Kawas) require reconsideration, for several reasons. First, risperidone has been studied in a number of controlled trials for the treatment of agitation and psychosis in patients with dementia.<sup>1-3</sup> This experience suggests that a target dose of 0.5 to 2.0 mg per day (half the dose listed in Table 3) may be associated with the best ratio of benefit to tolerability. Second, it may be misleading to state that risperidone has been associated with an increased risk of stroke. Although a recent change in the U.S. prescribing information noted that, in controlled trials, more "cerebrovascular adverse events" were reported among patients with dementia who were taking risperidone than among those taking placebo, it is important to note that the majority of these events were not strokes. When "serious" events as defined in the Code of Federal Regulations — a category

that includes stroke — are considered, there is no statistically significant difference between risperidone and placebo. In the United States, neither risperidone nor any other drug is approved for the treatment of dementia-related psychosis.

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**TO THE EDITOR:** In the article by Kawas, the case vignette highlighting safety issues with respect to an older patient with cognitive decline focuses on the ability to carry out activities of daily living, driving, and orientation. We are concerned about hazards in the home environment, capacity, and decision-making ability in this group of patients, including issues related to the safe care of an infant.

One of us and a colleague have reported the case of a woman with a score on the Mini-Mental State Examination of 18 (maximal possible score, 30) who was caring daily for her grandchild.<sup>1</sup> This experience has led us to look in more detail at the group of patients in our day hospital, among whom are many older people (some with cognitive impairment) who are involved in the regular care of young children. Although responsibilities such as child care may be very important to an older person's self-esteem and may be valuable in the maintenance of independence, we need to address this issue as a safety concern. Perhaps the time has come to include a carefully worded question about child care in the assessment of older patients in order to ensure optimal safety.

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**DR. KAWAS REPLIES:** Dr. Clarfield describes studies showing that potentially reversible dementias oc-

cur in approximately 3 to 5 percent of patients and that documented reversibility is exceedingly rare. The data come from a variety of sources, including tertiary care clinics, primary care settings, and population studies. Several studies involved prevalent cases, although reversible disease would be more likely in incident cases. I agree with Dr. Clarfield's points. However, it is difficult to generalize these data to the care of an individual patient. Every patient surely does not need every test, but the possibility of treatable conditions that may underlie dementia should be carefully considered. I obtain a computed tomographic scan and measurements of thyroid function and vitamin B<sub>12</sub> in virtually all patients with a recent onset of symptoms. On the basis of the Canadian guidelines cited by Dr. Clarfield, neuroimaging would be indicated for the patient in the vignette because she had had symptoms for two years or less.

Dr. Ruiz-Ruiz notes that HIV infection and syphilis can cause reversible dementia; other illnesses, including cancers and collagen vascular disorders, can also cause this condition. These diagnoses should be considered particularly in the case of patients who are young or who present with an atypical or rapid course. Decisions about specific laboratory studies should be directed by clinical suspicion.

Dr. Hausner notes some important potential disadvantages of paroxetine. The choice of an antidepressant for use in elderly patients with Alzhei-

mer's disease is a difficult one. I included paroxetine as a treatment option because in my clinical practice I have found it to be useful for some patients, particularly those with agitation or sleep disorders, which can be exacerbated by some antidepressant agents.

Drs. Mahmoud and Greenspan point out that risperidone at a dose of 0.5 to 2.0 mg per day (half the final dose recommended in Table 3 of my article) has the best ratio of benefit to tolerability in clinical trials involving patients with dementia. Selected patients may benefit from more medication if tolerability is not an issue.

Finally, Drs. O'Dwyer and O'Shea remind us that we should not forget safety issues involving the care of children by cognitively impaired adults. I agree that clinicians should assess the safety of all activities, while respecting the patient's autonomy and preserved abilities.

Since the publication of my Clinical Practice article, the Food and Drug Administration has approved memantine, an N-methyl-D-aspartate antagonist, for the treatment of moderate-to-severe Alzheimer's disease. At present, there are no data showing the efficacy of this drug in patients with milder disease. Memantine can be used alone or in combination with cholinesterase inhibitors and should be available in the United States by early 2004.

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## Suspected Pulmonary Embolism

**TO THE EDITOR:** In their Clinical Practice article on suspected pulmonary embolism, Fedullo and Tapson (Sept. 25 issue)<sup>1</sup> state that a positive computed tomographic (CT) angiogram in patients with a low clinical probability of pulmonary embolism confirms the diagnosis. Although probably consistent with current practice, this recommendation is not supported by Bayesian analysis.

The authors define a low clinical probability of pulmonary embolism as a prevalence of 5 to 10 percent. Even if CT angiography is assumed to have a sensitivity and a specificity of 95 percent (which is much higher than many published estimates<sup>2,3</sup>), with a positive CT angiogram, the post-test probability is only 50 to 68 percent. This is at least 20 percent lower than the recommended threshold for an-

ticoagulation for venous thromboembolism.<sup>4</sup> Since 25 to 65 percent of patients with suspected pulmonary embolism have a low clinical probability of embolism,<sup>1</sup> relying solely on the CT angiogram, as the authors recommend, will result in many false positive diagnoses.

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