

The Clinical Interface of Depression and Dementia

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The interface between depression and dementia is complex and has been studied primarily in Alzheimer's disease. This article discusses several aspects of this intriguing area of clinical research, including depressive pseudodementia and the possibility that depression may be a risk factor for the expression of Alzheimer's disease in later life and that depression may occur as a prodrome for this most common dementing disorder. In addition, the treatment challenges faced by clinicians when depression complicates the course of Alzheimer's disease are addressed. It is likely that a combination of behavioral treatment and use of antidepressant medication will provide the optimal management of depression in Alzheimer's disease. *(J Clin Psychiatry 1998;59[suppl 10]:9-12)*

The clinical interface of depression and dementia is a rich and complex topic. For the purposes of this article, *dementia* is defined as a syndrome of acquired impairment of memory and other cognitive functions secondary to structural brain damage. In Alzheimer's disease, the most common cause of dementia in later life,¹ structural brain damage is diffuse and includes neuronal loss, intraneuronal neurofibrillary tangles, and extracellular neuritic plaques.¹ Because most of the literature addressing the interface of depression and dementia relates to older persons with Alzheimer's disease, a discussion of the interface of depression and Alzheimer's disease will form the bulk of the subject matter covered in this article.

The precise definition of *depression* in the context of Alzheimer's disease is problematic. The overlap of signs and symptoms between Alzheimer's disease and major depressive episode (e.g., apathy and loss of interest, sleep disturbance, agitation, difficulty thinking and concentrating) makes the use of DSM-III or DSM-IV criteria confusing. Various authors have used the term *depression* to denote major depressive episode, dysthymia, nonsyndromal depressive signs and symptoms, or a mixture of these diagnostic entities. The following discussion will address these questions: (1) What is depressive pseudodementia, and how can it be distinguished from Alzheimer's disease?

- (2) Can depression be a prodrome of Alzheimer's disease?
- (3) Is depression a risk factor for eventual expression of Alzheimer's disease?
- (4) Do neurobiological variables intrinsic to Alzheimer's disease affect the expression of depression as a complicating feature of Alzheimer's disease?
- (5) How should the clinician treat a complicating depression occurring in the context of Alzheimer's disease?

DEPRESSIVE PSEUDODEMENTIA

The term *depressive pseudodementia* is used to describe substantial but reversible cognitive impairment caused by an episode of severe major depression.² It can be argued that depressive pseudodementia phenomenologically and etiologically more closely resembles delirium, a syndrome of impaired attention and level of consciousness secondary to reversibly disrupted brain physiology. To further complicate categorization, the prominent lack of motivation and poor cooperativeness of the typical depressive pseudodementia patient does not neatly fit into either the dementia syndrome or the delirium syndrome. Nonetheless, this rare but treatable cause of reversible late-life cognitive impairment is important to recognize and treat vigorously.

Depressive pseudodementia can be distinguished from Alzheimer's disease by the following criteria. In depressive pseudodementia, depressive signs and symptoms are the first expression of the disorder, and the patient usually has a history of affective illness with prior episodes of depression and sometimes mania. In Alzheimer's disease, impairment of recent memory and executive function usually occurs before substantial depressive signs and symptoms develop (but not always; see discussion below of depression as a possible prodrome for Alzheimer's disease). The patient with depressive pseudodementia is uncooperative with mental status testing, and his or her cognitive capacity fluctuates with the examiner's ability to elicit moti-

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vation. In contrast, the patient with Alzheimer's disease is usually cooperative with the examiner but manifests persistent cognitive deficits despite clearly attempting to perform cognitive tasks to the best of his or her ability. The patient with depressive pseudodementia does not have an aphasic language disturbance or an apractic inability to perform well-learned motor activities. In Alzheimer's disease, aphasia and apraxia are common problems, particularly in the middle and later stages of the disorder. The patient with depressive pseudodementia fails to respond positively to pleasurable or interesting environmental stimuli. The patient with Alzheimer's disease, even if apathetic, usually responds positively to environmental situations that he or she previously has found pleasurable or interesting. Finally, the patient with depressive pseudodementia almost always responds well to aggressive antidepressant therapy, and remission of cognitive deficits is the rule as the underlying depression resolves. In the patient with Alzheimer's disease, cognitive deficits do not substantially improve with antidepressant therapy even if depressive signs and symptoms are alleviated.³ When depressive pseudodementia is suspected, a careful review of the patient's drug regimen and general medical status to detect and eliminate medications or underlying medical illness that can produce depressive signs and symptoms is essential. If no remediable underlying adverse drug effect or medical illness is detected, aggressive treatment with antidepressant drugs and occasionally electroconvulsive therapy is warranted.

DEPRESSION AS A PRODROME OF ALZHEIMER'S DISEASE

Depression that occurs in the several years immediately preceding the onset of Alzheimer's disease can be a prodrome of Alzheimer's disease, that is, an early expression of the underlying pathobiology of the disorder. Such a depression can also be a coincidental event related temporally but unrelated pathobiologically to Alzheimer's disease. Another possibility is that such an episode of depression, even though independent of the pathobiology of Alzheimer's disease, is a risk factor for the ultimate expression of Alzheimer's disease. Whether depression preceding Alzheimer's disease is a prodrome of this dementing disorder or is an independent event has been debated at least since the time of Kraepelin. On the basis of careful longitudinal observation, Kraepelin⁴ considered depression a common prodrome of Alzheimer's disease in the older patient. Later Scandinavian and British studies in which persons with late-life depression were followed longitudinally could detect no greater likelihood of eventual dementia in persons with a severe late-life depression than in older persons free of affective disorders.⁵

A recent carefully designed study gives support to Kraepelin's initial observation. Devanand et al.⁶ assessed

depression and cognitive impairment in more than 1000 individuals over 60 years of age in the Washington Heights community of Manhattan, New York. These individuals underwent annual follow-up examinations. In subjects not meeting criteria for dementia, depressed mood was more common in individuals with greater cognitive impairment. In a follow-up study of those subjects without dementia at baseline, the effect of baseline depressed mood on the endpoint diagnosis of dementia (over 90% of these dementia patients met criteria for Alzheimer's disease) was evaluated. Baseline depressed mood was associated with a moderately increased risk for incident dementia at follow-up examination. These data are consistent with the idea that depressed mood can be a prodrome of Alzheimer's disease. These data also are consistent with the possibility that depression is independent of Alzheimer's disease but increases susceptibility to expression of Alzheimer's disease through another mechanism.

DEPRESSION AS A RISK FACTOR FOR ALZHEIMER'S DISEASE

If an association could be demonstrated between Alzheimer's disease and episodes of depression occurring and resolving many years before the onset of Alzheimer's disease, such a finding would be more consistent with depression as a risk factor for Alzheimer's disease than as a prodrome of Alzheimer's disease. Speck et al.⁷ used a case-controlled design to evaluate the strength of the association between reported history of depression and onset of Alzheimer's disease in a large community-based sample of older persons. When data were stratified by depression onset year, an increased risk for development of Alzheimer's disease was noted in persons with depression occurring more than 10 years before the onset of the cognitive and behavioral symptoms of Alzheimer's disease. They found no increased risk for depression onset within 10 years of the onset of Alzheimer's disease symptoms. In their study, depressive episodes occurring well before Alzheimer's disease symptom onset appeared to increase the risk of Alzheimer's disease. A pooled analysis of existing case-controlled studies examining the association between history of depression and Alzheimer's disease came to similar conclusions, except that the association held for episodes of depression occurring more than 10 years before the onset of dementia as well as for those occurring within a decade of dementia onset.⁸

There is a possible neuroendocrine mechanism for depression as a risk factor for Alzheimer's disease. Late-life depression is associated with increased activity of the hypothalamic-pituitary-adrenal axis,⁹ and this increased activity results in increased exposure of the brain to higher-than-normal levels of glucocorticoids. In the aged rat, increased corticosterone concentrations lower the threshold for aging-associated degeneration of hippocam-

pal pyramidal neurons.¹⁰ In humans, these hippocampal pyramidal neurons are severely affected in Alzheimer's disease.¹¹ Whether increased cortisol concentrations lower the threshold for the expression of Alzheimer's disease in humans remains speculative, but studies recently have demonstrated an association between high plasma cortisol concentrations and cognitive decline in nondemented older persons.¹² The possibility of subtle neurotoxic effects of the hypercortisolemia associated with late-life depression provides an additional rationale for the aggressive treatment of depression in older persons.

DEPRESSION COMPLICATING ALZHEIMER'S DISEASE

That depressive signs and symptoms are common in Alzheimer's disease is broadly accepted. However, when DSM-III-R or DSM-IV criteria are applied to prevalence studies of depression complicating Alzheimer's disease, rates vary tremendously.¹³ This broad prevalence range suggests that the diagnosis of major depressive episode in Alzheimer's disease is in the eye of the beholder. How investigators interpret the confounding overlap of signs and symptoms of depression and those of Alzheimer's disease, how much weight they give to the pervasiveness criteria of depressive symptoms, and how the history of depressive signs and symptoms is obtained given the inability of patients with Alzheimer's disease to provide a reliable history all affect the diagnosis of depression complicating Alzheimer's disease. There is little doubt, however, that the often fluctuating depressive signs and symptoms complicating Alzheimer's disease are important problems for the patients and their caregivers.¹⁴ Adding credibility to the existence of a depressive syndrome complicating Alzheimer's disease is the consistent finding of a relationship between degenerative changes in brain stem aminergic nuclei and antemortem depression in Alzheimer's disease.^{15,16}

Guidelines for treating depression complicating Alzheimer's disease are only beginning to emerge from the still low number of placebo-controlled clinical trials for this problem. Only 2 small placebo-controlled outcome trials of antidepressants available in the United States have been conducted in persons with Alzheimer's disease who meet diagnostic criteria for depression. Reifler et al.¹⁷ randomly assigned 28 outpatients meeting criteria for Alzheimer's disease and DSM-III major depression to treatment with either imipramine or placebo for 8 weeks. Depression ratings substantially improved in both treatment groups, with no difference between imipramine- and placebo-treatment conditions. Imipramine treatment was associated with only subtle decrements in cognitive function compared with placebo.¹⁸ Petracca et al.¹⁹ randomly assigned 24 patients meeting criteria for Alzheimer's disease and DSM-III-R depression to treatment with either clomipramine or placebo in a randomized, double-blind,

placebo-controlled crossover study. As in the imipramine trial reported by Reifler et al.,¹⁷ both active drug (in this case, clomipramine) and placebo were associated with improvement in depression ratings. However, in this study, the improvement in depression in the active-drug group was modestly greater than that in the placebo group. One subject in the clomipramine group dropped out of the study because of an acute confusional episode. These 2 placebo-controlled trials of tricyclic antidepressants in depression complicating Alzheimer's disease clearly illustrate that depression is substantially responsive to nonpharmacologic components of participation in a clinical outcome trial. Clomipramine may have modestly complemented this nonpharmacologic effect. The adverse effects of tricyclic antidepressants including orthostatic hypotension, central anticholinergic delirium, and peripheral anticholinergic dry mouth, constipation, and urinary retention often make these drugs difficult to use in elderly patients with Alzheimer's disease.

The serotonin selective reuptake inhibitor (SSRI) antidepressants offer the advantage of a more benign adverse effect profile than the tricyclic antidepressants. Unfortunately, the only data currently available concerning SSRI efficacy in depression complicating Alzheimer's disease come either from studies of agents not currently available in the United States or from anecdotal reports. A multicenter Scandinavian study compared the SSRI citalopram with placebo in patients with Alzheimer's disease and patients with vascular dementia manifesting depressed mood as well as other signs of "emotional disturbance."²⁰ In the subjects with Alzheimer's disease, citalopram was more effective than placebo in treating depressed mood, restlessness, fear/panic, and irritability. Treatment differences favoring citalopram were not apparent in the subjects with vascular dementia. Adverse effects were mild in this study. These investigators suggested that this SSRI had a broader effect than other antidepressants and that it be categorized as an "emotional stabilizer."²¹ Volicer et al.²¹ reported that the SSRI sertraline improved depressed affect and also decreased food refusal in 10 severely demented institutionalized patients with Alzheimer's disease. These reports provide rationale for future placebo-controlled trials of SSRIs in patients with Alzheimer's disease with depression and other noncognitive problem behaviors.

The pronounced improvement of depressive signs and symptoms in patients randomly assigned to the placebo groups in the imipramine and clomipramine trials described above^{17,19} strongly suggests that behavioral and interpersonal approaches to the treatment of depression complicating Alzheimer's disease are effective. This prediction recently has been confirmed in a controlled clinical trial of behavioral treatment of depression in Alzheimer's disease. In this study, patients with Alzheimer's disease who met DSM-III-R criteria for either major or minor depressive disorder and had a Hamilton Rating Scale for

Depression score of at least 10 were randomly assigned to 1 of 2 active behavioral treatments (1 emphasizing pleasurable events and 1 emphasizing caregiver problem solving) or to comparison treatments that included a typical care condition and a wait-list control condition.²² Patients in both of the active behavioral treatment groups showed significantly greater improvement in depression compared with those in the control groups. These gains were maintained at 6-month follow-up. In addition, caregivers in each of the active behavioral conditions showed significant improvement in their own depressive symptoms as compared with caregivers in the control groups.

CONCLUSION

The interface between depression and Alzheimer's disease is complex. Depression may be a risk factor for the expression of Alzheimer's disease in later life and also may occur as a prodrome for this most common dementing disorder. Depression complicating the course of Alzheimer's disease presents treatment challenges for the clinician. Therapeutic efforts should be instituted to improve quality of life both for the patient and his or her caregivers. It is likely that a combination of behavioral treatment and judicious use of antidepressant medication will provide the optimal management of depression in Alzheimer's disease.

Drug names: clomipramine (Anafranil), imipramine (Tofranil and others), sertraline (Zoloft).

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