# Diagnosis and Treatment of Depression in Patients With Alzheimer's Disease and Other Dementias

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Depressive disorders—both major depression and other less severe but nonetheless clinically significant depressions—are common comorbidities, components, or complications of dementia. Depression with reversible cognitive impairment may be a prodrome for dementia rather than a separate and distinct disorder. Recent research has demonstrated that both the diagnosis of major depression and the assessment of typical depressive symptoms can be conducted reliably, even in patients with mild-to-moderate levels of cognitive impairment. Self-ratings of depressive symptoms with the Geriatric Depression Scale remain valid in patients with Mini-Mental State Examination scores of at least 15. Among interviewer-administered instruments, the Hamilton Rating Scale for Depression and the Cornell Scale are the best established. Potential difficulties with assessment include problems with ascertainment (because families, in general, report greater depression in patients than do clinicians) and the ambiguity of symptoms (because apathy and related symptoms can result from both depression and Alzheimer's disease). Brain changes due to Alzheimer's disease may lead to fundamental differences in drug responses. Nevertheless, randomized clinical trials have demonstrated that depression in dementia responds to specific psychopharmacologic or psychosocial treatments.
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Although questions about the interrelationships between depression and dementia have been central to the field of geriatric psychiatry for the past 30 to 40 years, clinical approaches continue to evolve. Current knowledge in this area began with the work of Roth[1] and Post,[2] who demonstrated that dementia and depression were separate and distinct disorders. The difficulties in distinguishing between them, however, were emphasized by Kiloh,[3] who wrote about "pseudodementias" that could occur in depression as well as other psychiatric disorders. Subsequent research demonstrating that depression could lead to real, but reversible, cognitive deficits[4,5] led to intensive efforts to distinguish between Alzheimer's disease and the dementia syndrome of depression. Reifler and colleagues[6,7] took a very different view, noting that dementia and depression were not mutually exclusive states; rather, depression frequently existed as a comorbidity, a component, or a complication of the syndrome of dementia.

With this conceptual restructuring, the focus of both clinicians and investigators moved from "either/or" to "and/or." That is, the questions to be answered in diagnostic evaluations shifted from whether a patient has either dementia or depression to whether there is a significant degree of depression in the presence or absence of dementia. More recently, our understanding of the interactions between dementia and depression evolved further as evidence accumulated that depression with reversible cognitive impairment may be a prodrome for dementia rather than a separate and distinct disorder.[8] Questions have been raised about whether depression may be a risk factor for irreversible dementia.[9–11]

## DIAGNOSIS OF DEPRESSION

Although typical depressive symptoms are common (i.e., depressed mood, changes in weight, changes in sleep patterns, fatigue), they do not account for all of the affective disturbances associated with dementia. The mood changes that occur in patients with dementia are most often recurrent but short-lived and shallow, with fragmentary and transient depressive ideation. Moreover, affective lability, as well as depression, can occur among individuals with dementia (and is often considered to be more common in dementia caused by vascular disease).

The current edition of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) of the American Psychiatric Association considers "with depression" to be a subtype that can be applied to the syndrome of dementia, or to specific disorders such as Alzheimer's disease or vascular dementia, but it does not provide operationalized criteria for diagnosis. Nevertheless, there is a consensus among clinicians and investigators that it is possible to establish diagnoses of major depression and dysthymic disorders in patients with dementing disorders. Even though DSM-III specifically excludes the diagnosis

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of a major depressive episode when it is judged to be "due to an Organic Mental Disorder," DSM-IV is consistent with the clinical reality that major depression can coexist with irreversible dementia. Considerable problems remain, however, when one attempts to apply DSM-IV criteria to patients with Alzheimer's disease and related disorders. One problem is the need to modify diagnostic algorithms because "diminished ability to think or concentrate" cannot serve as a criterion for a depressive diagnosis, and because other symptoms (e.g., loss of interest) can be ambiguous. There may also be questions about the methods that should be used for the ascertainment of symptoms that require the recall of recent experiences. In spite of these potential problems, it is possible to achieve high levels of reliability in the clinical diagnosis of major depression among patients with dementia.[12] A structured diagnostic interview, the Cambridge Mental Disorders of the Elderly Examination (CAMDEX), which uses information derived from interviews and direct observations of patients as well as caregiver reports, has been validated for establishing research diagnosis of depressive disorders in patients with dementia[13]; its clinical utility, however, remains to be established.

## RATING DEPRESSIVE SYMPTOMS

A number of instruments have been used to rate the severity of depressive symptoms in populations of older individuals with dementia. Among those specific for depression, the Depressive Sign Scale[14] relies upon the direct observation of subjects' behavior by trained raters, and the Dementia Mood Assessment Scale[15] uses both direct observation of and a semistructured interview with patients. The Behavioral Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease[16] and the Columbia University Scale for Psychopathology in Alzheimer's Disease[17] rate the intensity of a wide variety of psychotic, affective, and behavioral symptoms in patients with dementia on the basis of interviews with caregivers. Although each of the instruments appears promising, the rating scales that have been studied most intensively include a self-rating instrument, the Geriatric Depression Scale (GDS),[18] and 2 closely related interviewer-administered instruments, the Hamilton Rating Scale for Depression[19] (HAM-D), and the Cornell Scale for Depression in Dementia (CS).[20]

The self-rating instrument that has been most extensively studied has been the GDS, available in 30- and 15-item versions with yes/no responses to questions dealing primarily with the affective and ideational (rather than somatic or vegetative) components of depression. The mode of administration varies between settings and studies; some investigators[21–25] ask impaired subjects to complete written test forms, offering assistance only when subjects cannot do so, while others administer the test verbally.[26,27] There has been extensive controversy about the reliability and validity of the GDS in patients with dementia, with some suggesting that the scale remained useful among patients with irreversible cognitive impairment. Others argued that its utility deteriorated in these patients. The current literature, however, is consistent with the conclusions of McGivney et al.,[28] who found that it remained valid and reliable in individuals with Mini-Mental State Examination scores of 15 or greater. Although they have been less well studied, other investigators have suggested that the Beck Depression Inventory,[29] the Zung Self-Rating Scale for Depression,[30] and the Centers for Epidemiological Studies-Depression Scale (CESD)[31] remain valid in patients with mild-to-moderate degrees of dementia. Experience with all of these instruments suggests that patients with milder forms of dementia are able to evaluate and report on their current mood.

Developed to rate symptoms of major depression through information gathered in a semistructured interview, the HAM-D has become the gold standard among outcome measures used in depression treatment studies. In spite of concerns about the ambiguity of somatic symptoms in the elderly, it has proved reliable and valid with geriatric patient populations. High levels of interrater reliability have been confirmed in patients with dementia, as has concurrent validity versus other measures of depressive symptoms. Furthermore, as discussed below, the HAM-D has been utilized to demonstrate specific treatment responses in randomized clinical trials of both pharmacotherapy and behavioral treatments for depression in patients with dementia; however, because it was developed for use in cognitively intact patients, there must be concerns about the reliability of ratings on items that require recall of memory about symptoms and about items where symptoms of depression and dementia may overlap. Dealing with the former problem requires information from collateral sources, and with the latter, operationalized algorithms for evaluating individual symptoms. Thus, optimizing the reliability of the HAM-D among patients with dementia requires that investigators and clinicians carefully consider the procedures that they will use for gathering data and for rating individual items. Frequently, however, research reports have not documented the local conventions used, and it is therefore difficult to determine exactly what is being measured and how ratings are made.

The CS was introduced by Alexopoulos and coworkers[20] to address these concerns. In item content, it is highly similar to the HAM-D. Seventeen of 21 items in the HAM-D can be mapped against the CS, and 17 of 19 items on the CS against HAM-D items. The procedures for ascertainment were modified to derive information from interviews with caregivers as well as direct observations and interviews with patients, and several items were redefined to facilitate the distinction between symptoms characteristic of depression and those due to dementia. In a series of studies,

Alexopoulos and colleagues evaluated the CS in depressed patients and controls, both in cognitively intact and demented patients, and found the scale to have high internal and interrater reliabilities in both groups.[20,32] Both the Cornell group and other investigators[24,33,34] have confirmed that the scale has a high level of concurrent validity relative to other measures of depression in patients with dementia.

## POTENTIAL CONFOUNDS

Mackenzie et al.[35] found that 14% of a sample of patients with Alzheimer's disease met DSM-III criteria for major depression on the basis of data derived from patient interviews, but 50% met diagnostic criteria on the basis of data derived from caregiver reports. A similar increase in the frequency of depressive symptoms in caregiver reports relative to patient interviews or clinical observations were reported by some investigators,[34,36] but not others.[37]

In response to these findings, Schulz and Williamson[38] suggested that the apparent differences between patient and caregiver reports on the prevalence of depression in patients with dementia could be due to overreporting of depression by caregivers as a consequence of their own depression. This hypothesis has subsequently been tested by a number of investigators. Moye and associates[26] confirmed that caregivers reported patients' depressive symptoms more frequently than the patients themselves, but noted that caregiver reports were not affected by either the patient's level of impairment or the caregiver's scores on the Beck Depression Inventory. Teri and Truax[39] found significant but modest correlations between caregivers' own HAM-D scores and their ratings of their impaired relatives, but no association of caregiver depression with their ratings of videotapes of anonymous patients. They noted that all caregivers meeting criteria for major depressive disorder reported patient symptoms severe enough to suggest a depressive illness; however, a high proportion of nondepressed caregivers (61%) also reported patient depression. Thus, there are discrepancies between patient- and caregiver-derived information in the apparent frequencies of depression coexisting with Alzheimer's disease and related disorders are relatively consistent. Available data do not, however, support the hypothesis that this discrepancy can be explained by overreporting on the part of caregivers due to their own depression. An alternative hypothesis is that increased variability in mood and associated symptoms of depression in demented patients could lead to both overreporting of depression in caregiver reports and underrecognition by clinicians who observe behavior that sample behavior over limited periods of time. Therefore, there are still questions about how much of the increased reporting is due to bias and how much to caregivers' more intensive observations and richer understanding of the patient.[40]

Lazarus et al.[41] emphasized the principle that most of the depressions occurring in patients with Alzheimer's disease were mild or minor, and suggested that case identification should emphasize affective and ideational (rather than somatic or vegetative) symptoms. The primary difficulties in distinguishing between symptoms of depression and those associated with underlying dementias, however, are with symptoms such as apathy, passivity, and decreased initiative. Forsell and colleagues[42] found that motivational disturbances increased with the severity of dementia, while mood symptoms peaked among those with mild dementia. Marin and colleagues[40,43] established reliable methods for the evaluation of apathy and have applied them in a number of clinical populations. In spite of significant correlations between ratings of apathy and depression, they conclude that most of the apathy observed in Alzheimer's disease is unrelated to depression. In fact, they note a specific "apathy syndrome" that is distinct from depression and find that it occurs with a high prevalence in Alzheimer's disease. Similar conclusions were reached by other investigators who studied these issues using concepts and measures related to personality and negative symptoms of schizophrenia.[37,44] The conclusion to be drawn from this literature must be that most of the depression seen in mild-to-moderate dementia is, in fact, a disorder of mood and affect. Emphasizing motivational or vegetative symptoms in an attempt to increase sensitivity for the detection of mild-to-moderate depression is likely to lead to decreased specificity and overdiagnosis.

Future advances will most likely depend upon innovative approaches to the assessment of mood in patients with dementia. One particularly promising avenue may be the direct observation of affective expression and of the signs of depression in patients with dementia on multiple occasions by trained observers.[45] Use of these methods may yield new insights into the nature and dynamics of depression among older persons with dementia, even in more impaired cases where self-reports of affect and mood are unreliable.

## CLINICAL FEATURES OF DEPRESSION IN DEMENTIA

Clinical studies reported prevalence rates for depressed mood in patients with Alzheimer's disease in the range of 0% to 87%, with a median of 41%, and for depressive disorders of 0% to 86%, with a median of 19%.[46] Studies of clinical populations vary in findings about the relationship between depression and the severity of dementia. Most,[47,48] but not all,[41,49] investigators find a decrease in the frequency of depression in patients with more advanced dementia; however, findings depend upon assessment methods[50] as well as subject selection factors. Nevertheless, individual case reports demonstrate that treatable depressions can occur in patients with severe dementia,[51] and suggest that clinicians should remain alert to the possibility that demented patients may experience mood disorders, even late in the

disease. In spite of numerous comparisons of Alzheimer's disease and vascular dementia, there are still questions about the relative frequencies of depression in the 2 disorders; relative rates depend upon factors such as the mode of assessment, the type of depression being considered, and the severity of the dementia.[52,53] When depression occurs early in the course of dementia, it is reasonable to hypothesize that it may reflect the patient's reaction to recognition of his or her cognitive deficits; however, it is important to recognize that whether depressed older patients are cognitively intact or impaired, they commonly complain about memory deficits.[54] Some authors have noted a relationship between depression and recognition of deficits in Alzheimer's disease,[55] while others have not.[56,57] Migliorelli et al.[58] have suggested that dysthymia in Alzheimer's disease is related to awareness of deficits, but that major depression is not.

Evidence for a biological contribution to depression as it occurs in Alzheimer's disease and related disorders comes from autopsy studies that demonstrated greater loss of aminergic neurotransmitters in the cerebral cortex and cell loss or histopathologic lesions in brain stem aminergic nuclei in patients who experienced major depression during the course of their dementia relative to those with uncomplicated dementia.[59–63] At present, it is not clear if these findings are specific to depression in Alzheimer's disease or whether they reflect the neuropathology of late-life depression as it generally occurs. The answer to this question must await clinical pathologic correlations from autopsy studies in a wider range of subjects.

Other research, however, suggests that there may be significant differences in the pathogenic mechanisms leading to major depression in patients with Alzheimer's disease relative to those that occur in individuals with other chronic diseases. A number of classical studies distinguish between those late-life depressions that occur as recurrences of mood disorders, with their initial onset earlier in life (early-onset depressions), and those that emerge for the first time when patients are elderly (late-onset depressions). Early-onset depressions, in general, occur in the context of an increased rate of depression among first-degree relatives, while late-onset depressions appear to occur in the presence of increased rates of chronic disease and disability. In patients with Alzheimer's disease, depressions are most often of late onset; nevertheless, some,[64,65] but not all,[58] authors have found an association with family histories of depression, perhaps more often in women than in men.[66]

While older patients with Alzheimer's disease or vascular dementia can experience typical episodes of major depression or dysthymia, they may be more likely to experience episodes that are milder, shallower, and self-limited. Thus, when symptoms appear mild and atypical, a period of "watchful waiting" before instituting treatment for depression may be prudent. Depression in demented individuals may frequently occur together with delusions[57]; however, clinical experience suggests that the delusional depressions that occur in patients with Alzheimer's disease and related disorders are less severe and more responsive to treatment than those in cognitively intact patients. Agitation is another symptom of depression in patients with dementia. It is important to consider depression in the differential diagnosis of agitation in nursing home residents or other patients.[67]

One of the major questions about depressions occurring in Alzheimer's disease must be about its impact on patients, caregivers, and service needs. Although it is clear that depression is associated with greater suffering, its effects on day-to-day functioning have only recently been evaluated. In considering whether depression represents a source of excess disability in patients with dementia, it is important to recognize that comparisons of cognitive performance of patients with Alzheimer's disease with and without depression as they are seen in clinical settings are likely to be affected by biases in the process of referral. However, it should be possible to evaluate the impact of depression by testing for its relationship with disability and functional impairment in analyses that control for the association between cognitive impairment and functional disability. Following this approach, Pearson et al.[68] and Fitz and Teri[69] have observed increased disability in patients with depression after controlling for cognitive impairment.

## TREATMENT

The effects of antidepressant medications have been studied in both unselected patients with dementing illnesses and in those with depressive disorders occurring in the presence of irreversible dementia. In a seminal study conducted at a time when many psychiatrists were concerned that masked depression and pseudodementia could mimic uncomplicated cases of Alzheimer's disease, Reifler et al.[70] demonstrated that patients with Alzheimer's disease without observable signs or symptoms of depression did not benefit from treatment with the antidepressant imipramine hydrochloride. Tariot et al.[71] conducted a placebo-controlled, randomized, clinical trial of the type B-specific monoamine oxidase inhibitor L-deprenyl in patients with Alzheimer's disease and found a drug-placebo difference favoring active medication in the response of the (low-level) affective symptoms found in these patients. In a similar study, Nyth and Gottfries[72] reported a reduction of depressive symptoms after treatment with the serotonin reuptake inhibitor citalopram.

Several double-blind, placebo-controlled studies[73,74] of antidepressants in study samples that included both cognitively intact and demented patients with major depression demonstrated specific drug effects. Moreover, an early placebo-controlled study demonstrated efficacy of the stimulant methylphenidate hydrochloride in the treatment of "withdrawn apathetic geriatric patients."[75] However, the

first placebo-controlled clinical trial of an antidepressant for the treatment of major depression in patients with Alzheimer's disease was that of Reifler et al.,[70] who treated 28 patients with imipramine hydrochloride or placebo for 8 weeks and found no drug-placebo differences. More recently, Passeri et al.[76] treated 122 demented patients who had depressed mood (63 patients with Alzheimer's disease and 59 with vascular dementia) with the serotonergic, dopaminergic, and procholinergic antidepressant miniprine (or placebo) for 90 days, and noted drug-placebo differences favoring miniprine in both types of dementia. Fuchs et al.[77] treated 127 patients who had dementia and mild depression with maprotiline (up to 75 mg/day) or placebo for 8 weeks and found no significant drug-placebo differences either on video observations of behavior or on GDS scores. Petracca et al.[78] conducted a double-blind, placebo-controlled, crossover study of clomipramine hydrochloride versus placebo in 21 depressed patients with major depression or dysthymia and reported benefits of clomipramine hydrochloride relative to placebo during the initial 6-week treatment period. Finally, Roth et al.[79] recently reported on a large-scale clinical trial in which 694 patients with symptoms of depression and cognitive decline were treated with the reversible, type A-specific monoamine oxidase inhibitor moclobemide (400 mg/day) or placebo for a period of 6 weeks; 511 of the subjects met DSM-III criteria for dementia and, in addition, had significant depressive symptoms, and 183 met diagnostic criteria for major depression (but not dementia) and also had symptoms of cognitive decline. Significant benefits of moclobemide relative to placebo were reported in both groups of patients. In addition, Roth et al. report significant benefits of moclobemide in terms of improved performance on the Mini-Mental State Examination, specifically among those patients with depression and coexisting dementia.

Thus, 3 of the 5 published placebo-controlled clinical trials, including 2 of the 3 with more than 30 subjects, reported significant drug-placebo differences. All of these studies utilized the HAM-D; therefore, these findings provided further support for its validity among patients with dementia. The findings from these studies support the value of the treatment for depression in patients with Alzheimer's disease and related disorders; however, neither the inclusion/exclusion criteria for these studies or the analyses presented allow any conclusions about the nature or subtypes of depression that are likely to respond to drug treatment.

Although antidepressant treatment appears to be of specific benefit for depressed patients with dementia as well as in those who are cognitively intact, the presence of dementia appears to have a substantial impact on responses to at least some antidepressants. Both Young et al.[80] and Streim et al.[81] studied the relationship between plasma drug levels and clinical response during treatment with fixed doses of the tricyclic antidepressant nortriptyline. Both groups confirmed the expected relationship of drug level with response in cognitively intact patients, but not in those with dementia. In fact, both research groups found statistically significant differences between intact and impaired patients in the correlation between nortriptyline hydrochloride levels and clinical improvement. The differences in responses between patient groups could not be attributed to either increased drug-related cognitive impairment in the demented patients or to pharmacokinetic differences between patient groups. Thus, these studies suggest that there may be fundamental pharmacodynamic differences underlying drug responses in demented versus intact patients. Moreover, they demonstrate that in evaluating treatments for depression, it is not possible to extrapolate from intact to impaired patients. Accordingly, they suggest the need for further research on the treatment of depression specifically in patients with Alzheimer's disease and related disorders.

In treating depression in patients with dementia, it is important to recognize their increased vulnerability to cognitive toxicity from anticholinergic medications. Drug-related cognitive impairment from the tricyclic antidepressants was, in fact, observed in the studies of clomipramine and imipramine (versus placebo) discussed above,[70,77,82] and in a recent study of amitriptyline hydrochloride versus fluoxetine hydrochloride in the treatment of major depression complicating Alzheimer's disease.[83]

In light of increasing evidence that structured, time-limited psychotherapies can be effective in the treatment of late-life depression, it is important to consider whether psychosocial interventions can be extended to the treatment of depression coexisting with dementia. Teri and Gallagher-Thompson[84] demonstrated that it is possible to modify cognitive-behavioral therapies for depression to allow them to be administered to patients with mild dementia and to modify behavioral therapies to allow them to be provided for those with moderate-to-severe dementia. Recently, Teri et al.[85] conducted a randomized clinical trial that compared 2 behavioral therapies with a typical care condition, in which family caregivers were given information, advice, and support in their efforts to manage patient problems, and a wait list control in 72 individuals who had major depression and Alzheimer's disease. One type of behavioral treatment consisted of teaching caregivers to focus on increasing pleasant events for the patient, while the other focused on improving the caregivers' approach to problem solving. Those in the 2 behavior therapy conditions and those in typical care received the intervention in 9 weekly, 60-minute sessions. The study provided strong support for the efficacy of specific psychosocial treatments; the 2 behavior therapy conditions were equally beneficial in reducing depressive symptoms and were superior to both the typical care and wait list conditions. Outcomes were similar for the typical care and wait list conditions, suggesting that, in the absence of a structured approach to treatment, professional contact alone is not effective.

## Clinical Guidelines

The literature on treatment supports the efficacy of both psychopharmacologic and behavioral therapies for the treatment of depression occurring in patients with Alzheimer's disease and related disorders; however, although the evidence demonstrates the value of specific mental health treatments for the depressive symptoms, it is not possible at this time to provide definitive recommendations about who should be treated with what interventions. Nevertheless, enough research findings and clinical experience have accumulated to allow the formulation of provisional guidelines for treatment.

The 1997 *Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias of Late Life* of the American Psychiatric Association[86] included a review of the literature and recommendations regarding the treatment of depressive symptoms. The literature review was completed before publication of the findings presented above on the efficacy of both moclobemide and behavioral therapy. The guideline concluded that somatic treatments for depression can be used in demented patients to improve mood, functional status, and quality of life. It noted that these treatments should be considered even in patients with depressed mood who do not meet the diagnostic criteria for major depression.

Specific recommendations included in the practice guidelines were (1) Patients with depression should be carefully evaluated for suicide potential. (2) Depressed mood may respond to improvements in the living situation or stimulation-oriented treatments, but patients with severe or persistent depressed mood should be treated with antidepressant medications. (3) The choice among agents is based on the side effect profile and the characteristics of a given patient. Specific serotonin reuptake inhibitors are probably the first-line treatments, although one of the tricyclic antidepressants or newer agents such as bupropion hydrochloride or venlafaxine hydrochloride may be more appropriate for some patients. Agents with significant anticholinergic effects should be avoided. Because of the elevated risk of dietary indiscretions in patients with dementia and the substantial risk of postural hypotension, non-selective monoamine oxidase inhibitors are probably appropriate only for patients who have not responded to other treatments.

Clinical experience suggests that electroconvulsive therapy is effective in the treatment of patients who do not respond to other agents. Twice rather than thrice weekly and unilateral rather than bilateral treatments may decrease the risk of delirium or memory loss.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), clomipramine (Anafranil), fluoxetine (Prozac), imipramine (Tofranil and others), L-deprenyl (Eldepryl), maprotiline (Ludiomil), methylphenidate (Ritalin), venlafaxine (Effexor).



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