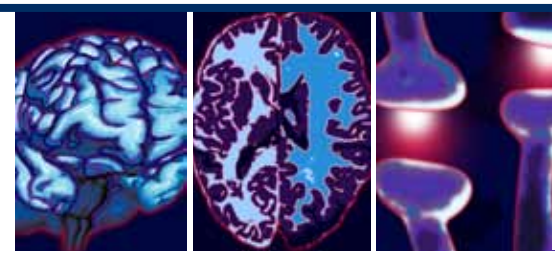
REVIEW



The diagnosis of depression in Alzheimer's disease: review of the current literature

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Practice points

- The diagnosis of depression in Alzheimer's disease (AD) should be carried out considering the overlap of symptoms.
- The 'specific approach' is the best diagnostic strategy for depression in AD.
- Depression scales should be used to rate the severity of depression but not to make diagnoses.
- Depression in AD should be diagnosed using standardized criteria using information provided by structured interviews.
- Recent studies showed the diagnostic and statistical manual of mental disorders (DSM-IV) criteria for major depression may be used unmodified to diagnose depression in AD.
- Anxiety and apathy are frequent comorbid symptoms of depression in AD.

SUMMARY Depression is among the most common psychiatric disorders in Alzheimer's disease (AD). Nevertheless, given the overlap between the symptoms of depression and the symptoms of dementia, diagnosing depression is still problematic. Several depression rating scales have been validated for use in AD. Both the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale have been used for screening purposes, to measure the severity of depression, and for assessing response to treatment. The recommendation to diagnose depression in AD is by using structured psychiatric interviews, such as the Structured Clinical Diagnostic Interview for DSM-IV or the Mini International Neuropsychiatric Interview. Based on information obtained from the structured interviews, depression is diagnosed using DSM-IV criteria. Consensus groups suggested specific changes to the diagnostic criteria to account for the overlap of symptoms between depression and dementia, and recent studies validated the DSM-IV criteria for major depression for use in AD.

Depression has been recognized as one of the most frequent psychiatric comorbidities in Alzheimer's disease (AD), with a negative impact on patients' quality of life and carers' psychological well being [1]. Many studies have been carried out in an attempt to quantify

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the rates of depression in this group, however, the results of these studies vary widely. This lack of consensus can in part be explained by the fact that there are currently no standardized methods to diagnose depression in AD, and few instruments exist that have been specifically designed for this undertaking. Other methodological issues compounding this problem include the overlap between symptoms of depression and symptoms of dementia.

The aim of this review article is to provide a critical review of the main strategies and instruments to diagnose depression in AD, and to discuss current methods used to diagnose subtypes of depression in dementia.

Scales & structured psychiatric interviews used to assess depression in dementia

A variety of depression rating scales and structured psychiatric interviews have been used to assess depression in AD. Some of them have been validated for use in dementia, but their psychometric attributes have not been thoroughly examined.

■ Rating scales for depression in AD

There is only a single scale that has been specifically adapted to rate depressive symptoms in AD. Most scales currently in use have been primarily designed to assess depression in nondemented individuals, and some of them have been validated for use in AD. A brief review of the most frequently used instruments is provided below.

Depression rating scales

Cornell Scale for Depression in Dementia

This instrument was specifically developed to assess signs and symptoms of major depression in patients with dementia. Information is elicited through independent interviews with the patients and an informant. Because of potential discrepancies between the patient and the informant, the Cornell Scale for Depression in Dementia (CSDD) represent the rater's clinical impression. The CSDD includes 19 items and takes approximately 20 min to complete [2].

Geriatric Depression Scale

The Geriatric Depression Scale (GDS) is a short screening instrument for depression in the elderly that focuses on psychosocial aspects of depression, avoiding symptoms that may potentially overlap with medical disorders or aging [3]. The most commonly used version of this instrument includes 15 items that are rated by the individual and takes approximately 5–10 min to complete.

Montgomery-Asberg Depression Rating Scale

This is a ten-item rating scale that covers all the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depression with the exception of psychomotor changes. The Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician rated scale that includes physical, emotional and cognitive items [4]. This instrument has been specifically designed to measure change in severity of depressive symptoms during clinical trials with antidepressants, but may also be used for screening purposes.

Hamilton Depression Rating Scale

The most commonly used version of the Hamilton Depression Rating Scale (HAM-D) includes 17 items that are administered by a trained-clinician [5]. The HAM-D does not rate several symptoms that are necessary for a DSM-IV diagnosis of major depression or dysthymia, but rates symptoms of anxiety, psychosis, and cognition.

Beck Depression Inventory

The Beck Depression Inventory (BDI) was designed as a test for the intensity of depressive symptoms in healthy adult patients who receive psychoanalytical psychotherapy as treatment for depression, and to measure the change of intensity over time [6]. This is a self-assessed instrument rating the existence and severity of depressive symptoms. The BDI includes 21 items and tends to be weighted towards psychological symptoms of depression. The BDI-II is a revised version which corresponds better with DSM-IV criteria for major depression.

Neuropsychiatric Inventory

This instrument assesses the following ten behavioral disturbances: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy and aberrant motor activity. Screening questions are used to minimize administration time, and this instrument is assessed with an examiner and a suitable informant. Both the frequency and severity for every item are determined. The main advantage of

the Neuropsychiatric Inventory (NPI) is that it rates a wide range of psychopathological problems in dementia [7].

Cambridge Examination for Mental Disorders of the Elderly

This instrument was designed to diagnose and measure dementia and other mental disorders in the elderly. The Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) consists of three sections rating the individual's current mental state, personal and familial psychiatric history, a mini-neuropsychological battery, and a structure interview assessed with an informant to obtain independent information [8].

■ Structured psychiatric interviews

The main aim of structured psychiatric interviews is to provide information in order to make psychiatric diagnoses based on standardized criteria. The interviews most commonly used in dementia are described below.

Structured Clinical Interview for DSM-IV

The Structured Clinical Interview for DSM-IV (SCID)-I is a semi-structured interview for making the major DSM-IV axis I diagnoses, and was designed to be administered by a clinician [9]. The administration time may range from 15 min to 2 h, depending on how many modules are administered, the complexity of the patient's psychiatric history, and the patient's ability to provide clear and concise answers. Based on the SCID answers, psychiatric diagnoses are made based on DSM-IV criteria [10]. The DSM-IV has long been considered the gold standard for the diagnosis of mood disorders. It specifies that a major depressive episode should have five persistent symptoms out of a list of nine **(Box 1)** including depressed mood or loss of interest/anhedonia.

Mini International Neuropsychiatric Inventory

The Mini International Neuropsychiatric Inventory (MINI) is a short diagnostic structured interview to explore 17 DSM-IV axis I and II disorders [11]. This instrument assesses the existence of current and lifetime psychiatric disorders. The MINI includes screening questions to rule out the diagnoses when answered negatively.

While structured clinical interviews are the most valid and reliable instruments to diagnose depression in dementia, their use in a clinical setting is complicated given their length. Therefore, future studies should develop and validate specific diagnostic instruments for clinical use.

Methodological problems to diagnose depression in AD

One of the main limitations to diagnosing depression in AD is how to determine the specificity of depressive symptoms when these may be shared between the psychiatric and the neurological condition. For instance, while loss of interest, poor concentration, psychomotor retardation, low self-esteem and insomnia are key criteria to diagnose major depression among individuals with no neurological conditions (i.e., 'primary depression'), patients with AD often present with loss of interest because of their inability to engage in activities they used to enjoy but can no longer perform. Similarly, concentration problems are essential manifestations of dementia, and low self-esteem usually results from the patients' increasing incapacity to perform their usual chores. Insomnia is a frequent complaint of AD patients, who may oversleep during the day and have frequent awakenings during the night. Finally, bradyphrenia or slow thinking is a common manifestation of dementia, and motor retardation is seen in more than a third of AD patients.

Several strategies have been recommended to deal with the overlap between depression and neurological symptoms in neurological conditions. For the 'inclusive approach' [12], symptoms are counted towards the diagnostic criteria regardless of whether they may be secondary to the physical illness. One limitation of this approach is that it may overdiagnose depression. For the 'exclusive approach', symptoms significantly associated with depression are counted, unless the examiner feels these are related to the physical condition [13]. The main limitation of this approach is that it may underdiagnose depression. For the 'substitutive approach' nonoverlapping symptoms of depression (e.g., psychological symptoms) are substituted for the overlapping criteria [14]. Main limitations of this approach are that psychological symptoms of depression may relate to the presence of cognitive decline and impairments in activities of daily living (e.g., self-depreciation, worrying, loss of pleasure). Psychological symptoms replacing

Box 1. Criteria for major depressive episode.

- Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure:
  - Depressed mood most of the day, nearly every day
  - Markedly diminished interest or pleasure in most activities
  - Significant weight loss or gain, or decrease or increase in appetite
  - Early insomnia or hypersomnia nearly every day
  - Psychomotor agitation or retardation nearly every day
  - Fatigue or loss of energy nearly every day
  - Feelings of worthlessness, or excessive or inappropriate guilt
  - Diminished ability to think or concentrate, or indecisiveness
  - Recurrent thoughts of death, recurrent suicidal ideation

Adapted from the Diagnostic and Statistical Manual of Mental Disorders.

somatic symptoms of depression have not been validated for use in AD. Finally, the 'specific symptom' approach only considers those symptoms which are significantly more frequent in patients with sad mood, and the diagnostic criteria may be modified to include only specific symptoms [15]. There are no relevant limitations for this approach, which provides the most valid way of diagnosing depression in AD and other neurological conditions.

Strategies to diagnose depression in AD

DSM-IV criteria

The main DSM-IV category to diagnose depression in AD is "mood disorder due to a general medical condition". This diagnostic category included four subtypes:

- Mood disorders with depressive features
- Mood disorders with major depressive-like episodes
- Mood disorders with manic features
- Mood disorders with mixed features

One limitation of this diagnostic category is that it does not provide more specific criteria to diagnose the mood disorder (e.g., the subtype with depressive features only requires the presence of a predominantly depressed mood, but lacks full criteria for major depression), which may result in including patients with heterogeneous depressive conditions. Thus, a patient with sad mood but no other symptoms of depression could be diagnosed under this category. Given the lack of specific criteria and a required number of symptoms, this diagnostic category is difficult to implement in research studies and several studies used the DSM-IV criteria for a major depressive episode **(Box 2)**.

National Institutes of Mental Health criteria

A workshop organized by the National Institutes of Mental Health (NIMH) [14] proposed provisional diagnostic criteria to better characterize depression in AD and to avoid some of the potential overlap between the mood disorder and the symptoms produced by dementia **(Box 2)**. The NIMH criteria for depression in AD (NIMH-dAD) are similar to the DSM-IV criteria for major depression, but with the following changes:

- Loss of interest was revisited to indicate loss of pleasure in response to social contact
- Irritability and social isolation were included to replace loss of libido
- The NIMH-dAD criteria require three or more symptoms of depression, compared with five or more for the diagnosis of major depression following the DSM-IV criteria
- Depressive symptoms are not required to be present nearly every day

Several limitations of the NIMH-dAD should be discussed. First, only requiring three criteria of depression, whose symptoms are not required to be present every day, may increase the risk of over diagnosing depression, particularly in the late stages of AD. Furthermore, the specificity of depressive symptoms may be reduced by the severity of concomitant cognitive and motor impairments. Second, the NIMH-dAD criteria may allow the inclusion of heterogeneous samples of AD patients with various subtypes of depression (i.e., major depression, dysthymia or minor depression). Finally, the NIMH-dAD criteria are yet to be validated, and as the authors acknowledged, validation is critical before definite criteria can be adopted. Another strategy for diagnosing

depression in AD was proposed by Lyketsos and coworkers (Box 3) [16]. Similarly to DSM-IV and NIMH criteria, these diagnostic criteria are yet to be empirically validated.

International Classification of Diseases-10

The International Classification of Diseases (ICD)-10 criteria have rarely been used to diagnose depression in dementia. Engedal and coworkers assessed 112 patients with AD using the Cornell Scale for Depression in Dementia [17]. Depression was diagnosed based on DSM-IV, ICD-10 or Provisional Criteria for Depression in Alzheimer's Disease (PCD-dAD) criteria. The main finding was that there were significant differences in the frequency of major depression depending on which criteria was used (e.g., 53% for PDC-dAD, 47% for ICD-10 and 35% for DSM-IV). Vilalta-Franch and coworkers assessed depression in 491 patients with probable AD using the CAMDEX [18]. An important finding was that the frequency of depression showed wide variability depending on the diagnostic criteria applied (e.g., from 5% according to ICD-10 criteria to 27% according to the PDC-dAD criteria). Teng and coworkers carried out a similar study that included 101 patients with probable AD who were assessed with the Cornell Scale for Depression in Dementia [19]. They found that the NIMH-AD criteria had high sensitivity and specificity for the DSM-IV criteria for major depression.

Phenomenology & specificity of depressive symptoms in AD

Our group has examined the phenomenology and validity of depression in AD in a series of studies. Chemerinski and coworkers examined the specificity of depressive symptoms in patients with AD [20]. This study was composed of a series of 233 patients with AD, 47 patients with depression but no dementia, and 20 age-comparable healthy controls. A number of important findings were found in this study. First, depressed patients with AD had significantly higher scores on most items of the HAM-D scale than nondepressed patients (both within the physical and psychological symptoms of depression). Second, the number of symptoms of depression in the nondepressed patients with AD, were no more frequent than those found in the age-comparable healthy controls. Finally, depressed patients with AD, rated their depression severity on the HAM-D as less severe than their respective caregivers, suggesting that patients may minimize the severity of their depression. Similar findings were reported by Engedal and coworkers [17], who found that sadness, anxiety, suicidal thoughts, poor self esteem, multiple physical complaints and pessimism, were the symptoms that most significantly distinguished AD patients with depression from those without depression. Together, these findings suggest that dementia does not produce the symptoms of depression in

Box 2. Provisional diagnostic criteria for depression in Alzheimer's disease.

- A: Three or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either depressed mood or decreased positive affect:
  - Clinically significant depressed mood
  - Decreased positive affect or pleasure in response to social and daily activities
  - Social isolation
  - Changes in appetite
  - Changes in sleep
  - Psychomotor changes
  - Irritability
  - Fatigue or loss of energy
  - Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
  - Recurrent thoughts of death, suicidal ideation, plan or attempt
- B: All criteria met for dementia of the Alzheimer type (based on DSM-IV criteria)
- C: The symptoms cause clinically significant distress or disruption in functioning
- D: The symptoms do not occur exclusively during the course of a delirium
- E: The symptoms are not due to the direct physiological effects of a substance
- F: The symptoms are not better accounted for by other psychiatric conditions

DSM: Diagnostic and Statistical Manual of Mental Disorders.
Adapted with permission from [14].

Box 3. Diagnostic criteria for Alzheimer's disease-associated neuropsychiatric disturbance.

- A: Meeting NINCDS/ADRDA criteria for probable Alzheimer's disease
- B: A prominent disturbance of affect, and representing a change from the patient's baseline, as evidence by the presence of one or more of the following symptoms:
  - Depression
  - Irritability
  - Anxiety
  - Euphoria
- C: One or more of the following associated symptoms must be present:
  - Aggression
  - Psychomotor agitation
  - Delusions
  - Hallucinations
  - Sleep disturbance
  - Appetite disturbance
- D: Symptoms from B and C co-occur most days, and the disturbance has a duration of at least 2 weeks
- E: The disturbance has its first onset within 2 years, or after the onset of dementia

ADRDA: Alzheimer's Disease and Related Disorders Association; NINCDS: National Institute of Neurological and Communicative Disorders and Stroke.
Adapted with permission from [16].

the absence of sad mood, and that the symptoms of depression are specific for a mood disorder and not due to the underlying disease.

Subtypes of depression in AD

Migliorelli and coworkers demonstrated that major and minor depressions have different correlates among patients with AD [21]. These authors reported that major depression usually begins before the onset of dementia; it is associated with poor perfusion in specific brain areas (as assessed with single photon emission computed tomography) [22]; it is associated with more severe anosognosia than patients with minor depression [21]; and has a significantly longer duration than minor depression [23]. On the other hand, minor depression most often begins after the onset of cognitive decline; it is most frequent in the early stages of dementia, and is related to better awareness and less cognitive impairment than major depression.

In a study that included a consecutive series of 670 patients with AD, Starkstein and coworkers examined whether major and minor depression are valid constructs in AD, and also assessed the threshold at which depression should be diagnosed [15]. One of the main findings was that patients with either minor or major depression (as per DSM-IV criteria) were more impaired in their activities of daily living and were more severely socially dysfunctional, than nondepressed AD patients. Additionally, AD patients with major depression had more severe anxiety, apathy, delusions and parkinsonism than patients with minor depression, suggesting that the severity of depression is significantly associated with the severity of psychopathological and neurological impairment. When patients were diagnosed using the NIMH-dAD criteria, 44% of the patients in the stage of severe dementia had no sad mood, suggesting that the NIMH-dAD criteria may have low specificity for depression in the advanced stage of dementia. Moreover, the finding that loss of interest was more frequent in both major and minor depression argues against the NIMH-dAD recommendation that loss of interest should not be used to diagnose depression in AD. The NIMH-dAD criteria also suggest that affective lability should be excluded from the depression syndrome of AD and be better classified as "affective dysregulation of dementia". Nevertheless, Starkstein and coworkers found that depressed AD patients had significantly higher scores on the crying subscale of the Pathological Laughing and Crying Scale (PLACS) than nondepressed patients, suggesting that affective lability may be a manifestation of depression in AD [24].

Phenomenology & longitudinal evolution of depression in AD

Starkstein and coworkers [23] examined the longitudinal changes of depressive symptoms in a series of 65 AD patients with major or minor depression assessed twice, with a mean interval of 17 months. All patients had either major or minor depression at baseline, while at follow-up 28%

had major depression, 21% had minor depression and 51% were no longer depressed. Patients with depression at baseline but no depression at follow-up (i.e., full remission) showed a significant improvement on the following depressive symptoms: sad mood, guilty ideation, suicide ideation, insomnia, loss of interest, psychomotor retardation, loss of energy, loss of appetite and social withdrawal. Moreover, remitted patients also showed a significant decrease on scores of anxiety, but there were no significant changes on scores of irritability or apathy. Taken together, these findings support the validity of diagnosing depression in AD using DSM-IV criteria and suggest that symptoms of anxiety may be attributable to the depressive condition. On the other hand, both apathy and irritability seem to be independent from the construct of depression in AD.

■ Latent Cluster Analysis of depressive symptoms in AD

In a recent study, Starkstein and coworkers assessed depressive symptoms in a consecutive series of 971 patients with AD, and the results were analyzed with Latent Cluster Analysis to determine whether there are latent classes for which depression symptom data arise [25]. The aim of the study was to use Latent Cluster Analysis to enable the adoption of diagnostic criteria for depression in AD based on solid empirical and statistical grounds. The main result from this study was that all nine DSM-IV diagnostic criteria for major depression identified a class (labeled 'major depression') with high statistical significance. A second class (labeled 'minor depression') included patients with an intermediate frequency of depressive symptoms, and a third class (labeled 'no depression') had a very low frequency of depressive symptoms. Another relevant finding from this study was that both apathy and anxiety, but not irritability, were significant predictors of depression in AD. Additionally, between-group differences for the nine DSM-IV criteria for major depression were all significant. Moreover, whilst 96% of patients in the 'major depression' class met unmodified DSM-IV criteria for major depression, none of the patients in the 'no depression' class met diagnostic criteria for major depression, whilst 62% of the patients in the 'minor depression' class met DSM-IV criteria for minor depression.

Barca *et al.* assessed 1159 elderly individuals residing in nursing homes with the CSDD [26]. A factor analysis of this scale showed a single factor that included the symptoms of sadness, pessimism, poor self esteem, anxiety suicidal ideation and delusions. These symptoms were unrelated to the presence and severity of dementia, providing further support for the validity of these symptoms for the diagnosis of depression in dementia.

Conclusion & future perspective

Studies over the past 10 years have helped to provide diagnostic instruments with increasing validity for diagnosing depression in AD. Scales are being developed to rate the severity of depression in AD, and diagnostic criteria are progressively refined and validated.

Over the next 5–10 years we should see valid instruments to rate and diagnose depression in the different stages of AD. Diagnosing depression in the severe stages of dementia still remains a big challenge. The concept of depression will probably be widened to include other common behavioral and psychological problems in AD such as anxiety and apathy. Once the phenotype of depression in AD is fully characterized, we should be better able to test pharmacological and psychotherapeutic treatments for this condition.

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