

Diagnosis and Clinical Relevance of Depression and Apathy in Alzheimer's Disease

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Abstract Depression is one of the most common psychiatric disorders in Alzheimer's disease (AD), and depression is associated with poorer quality of life, greater disability in activities of daily living, faster cognitive decline, and higher frequency of depression and burden in caregivers. Depression in AD is usually underdiagnosed, which may be related to the lack of validated diagnostic criteria and specific instruments to assess depression in dementia. Left untreated, major depression in AD may last for about 12 months. Apathy is increasingly recognized as a major behavioral disorder in neuropsychiatric diseases, but confusion still exists as to its proper definition and assessment and whether apathy should be considered a symptom or a syndrome. Nevertheless, a variety of instruments have been developed to rate the severity of apathy in dementia, and a structured clinical interview has been recently validated. Moreover, there is now international consensus for a set of standardized diagnostic criteria to diagnose apathy in AD. Finally, apathy is a significant predictor of faster functional, mood, and motor decline.

Depression and apathy are among the most common behavioral and psychological disorders in AD. Both disorders have a strong negative impact on patients' quality of life and are related to increased burden and stress among caregivers. One of the limitations in dealing with apathy and depression in dementia is that their respective diagnoses are not straightforward. Several scales to rate the severity of depression and apathy have been validated for use in AD, but standardized diagnostic criteria have only recently been proposed. This chapter addresses different strategies currently used to diagnose depression and apathy in AD and discusses the diagnostic criteria recently proposed. Another aim of this chapter is to discuss the frequency and clinical correlates of depression and apathy in AD.

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Depression in Alzheimer's Disease

Diagnosis of Depression in AD

One of the major challenges in neuropsychiatry is how to obtain a valid and reliable diagnosis of a psychiatric disorder when its symptoms overlap with the symptoms of the neurological condition. Another limitation is that common disorders such as depression in Alzheimer's disease (AD) are rarely isolated phenomena and usually coexist with other psychiatric conditions such as anxiety, apathy, pathological affective display, psychotic symptoms, and poor insight. These confounding factors may account for the lack of general consensus on the most valid and reliable method to diagnose depression in AD.

Four different strategies have been used to diagnose depression in chronic degenerative disorders. The "inclusive approach" [1] diagnoses depression based on symptoms that may or may not be related to the physical illness. This approach is the most commonly used diagnostic strategy in neuropsychiatry. The "exclusive approach," on the other hand, does not include for diagnosis those symptoms considered to be related to the physical illness [2]. The "substitutive approach" replaces overlapping symptoms of depression with psychological symptoms [3]. Finally, the "specific symptom approach" only considers for diagnosis those symptoms that were identified as belonging to a "depressive cluster" using specific statistical techniques, such as latent class analysis. In a recent study Verkaik and coworkers [4] examined potential confounders for the diagnosis of depression in AD. One main confounder is that some studies diagnosed depression on the basis of a cutoff score on a depression scale (the "continuous method") whereas other studies diagnosed depression using standardized diagnostic criteria (the "categorical method"). Other confounders identified by the authors are (1) the grouping of different types of dementia, (2) different criteria to diagnose AD, (3) different instruments to assess the severity of AD and depression, and (4) heterogeneous samples in terms of size and sociodemographic characteristics.

Diagnostic Criteria for Depression in AD

Lyketsos and coworkers were the first to propose standardized criteria to diagnose depression in AD [5]. They assessed a large sample of individuals living in the community using the Neuropsychiatric Inventory (NPI). A latent class analysis produced three clusters, one of which was characterized by depression, anxiety, irritability, and apathy. Based on this cluster, Lyketsos and coworkers proposed the diagnostic criteria summarized in Table 1. One limitation of the study lies with the use of the NPI,

Table 1 Diagnostic criteria for Alzheimer's disease (AD)-associated neuropsychiatric disturbance (adapted from [5])

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- A. Meeting National Institutes of Neurology and Communicative Disorders/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD.
- B. A prominent disturbance of affect, disruptive to the patient or the care environment, and representing a change from the patient's baseline, as evidenced by the presence of one or more of the following symptoms:
- (1) Depression
 - (2) Irritability
 - (3) Anxiety
 - (4) Euphoria
- C. One or more of the following associated symptoms must be present:
- (1) Aggression
 - (2) Psychomotor agitation
 - (3) Delusions
 - (4) Hallucinations
 - (5) Sleep disturbance
 - (6) 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.
- F. The disturbance cannot be explained in its entirety by another cause (e.g., a general medical condition, medications, life stressors).
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a useful screening instrument but without the phenomenological detail necessary to diagnose depression using diagnostic criteria such as in the DSM-IV.

A workgroup conveyed by the National Institutes of Mental Health (NIMH) proposed standardized diagnostic criteria for depression in AD (NIMH-dAD) based on expert advice [6] (Table 2). These criteria are similar to the DSM-IV criteria for major depression; but with the inclusion of irritability and social withdrawal to replace loss of libido, and loss of pleasure in response to social contact to replace loss of interest. Finally, the NIMH-dAD diagnostic criteria require only three symptoms for the diagnosis of depression, and these symptoms do not have to be present every day.

An early study from our group assessed a consecutive series of AD patients attending a memory clinic using the structured clinical interview for the DSM-III-R (SCID) [7]. The main finding was that the presence of sad mood was significantly associated with most symptoms of depression assessed by the Hamilton depression scale, such as guilt, suicidal ideation, insomnia, loss of interest, psychomotor retardation, worrying, anxiety, loss of libido, and loss of energy. The question arises as to the specificity of symptoms of depression in AD, that is, whether AD patients have symptoms of depression in the absence of sad mood or loss of interest/anhedonia (masked depression). We found that only 2% of 233 AD patients had enough symptoms to meet the DSM-IV criteria for major depression in the absence of sad mood or loss of interest/anhedonia. Moreover, we also found that AD patients who reported no sad mood had no more symptoms of depression than a group of age-comparable healthy controls.

Table 2 Provisional diagnostic criteria for depression of AD (adapted from [6])

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- 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 (1) depressed mood or (2) decreased positive affect or pleasure:
- (1) Clinically significant depressed mood
 - (2) Decreased positive affect or pleasure in response to social contacts and usual activities
 - (3) Social isolation or withdrawal
 - (4) Disruption in appetite
 - (5) Disruption in sleep
 - (6) Psychomotor changes
 - (7) Irritability
 - (8) Fatigue or loss of energy
 - (9) Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
 - (10) Recurrent thoughts of death, suicidal ideation, plan, or attempt
- B. All criteria met for dementia of the Alzheimer type.
- 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 caused by the direct physiological effects of a substance.
- F. The symptoms are not better accounted for by other psychiatric conditions.

Specify if:

Co-occurring onset: if onset antedates or co-occurs with the AD symptoms

Post-AD onset: if onset occurs after AD symptoms

Specify:

With psychosis of AD

With other significant behavioral signs or symptoms

With past history of mood disorders

Taken together, these findings suggest that symptoms of depression are not rife among euthymic AD patients. It is important to note that AD patients may have poor insight into their own depressive symptoms and tend to minimize or deny their presence. Therefore, it is important to obtain collateral information when assessing patients' mood.

In a more recent study we assessed the construct of major and minor depression in a series of 670 patients with AD [8]. In this cross-sectional study, we found that 26% had major depression and an identical percentage had minor depression. The percentage of patients with three or more symptoms of depression (as required by the NIMH-dAD diagnostic criteria) but without sad mood was 22% among patients with mild AD, 23% among patients with moderate AD, and 41% among patients with severe AD, suggesting that the NIMH-dAD may have high sensitivity but poor specificity.

Another strategy to clarify the phenomenology of depression in AD is to assess the pattern of symptom improvement on the remission of depression. To this end, we examined a series of 65 patients with AD and depression who received a follow-up assessment 1–3 years later [9]. At follow-up, 33 patients had a full remission of depression whereas 32 patients continued to be depressed (with major or minor depression). The main finding was that patients with a full remission of depression had a significantly lower score on the Hamilton depression scale for the symptoms of sad mood, guilt,

suicide ideation, insomnia, loss of interest, psychomotor changes, loss of energy, social withdrawal, and loss of appetite/weight as compared to patients with no remission of depression. Moreover, patients on remission also showed a significant decrease in the severity of anxiety. On the other hand, there were no significant between-group differences in the severity of apathy, supporting previous findings that showed that apathy and depression are overlapping but independent syndromes in AD [10].

Frequency of Depression in AD

Before discussing the frequency of depression in AD, it is important to note that estimates of depression in AD depend on sampling issues, diagnostic methods, and clinical manifestations. The prevalence of major and minor depression has been estimated to range between 30% and 50% [3]. Population studies reported a prevalence of dysphoria of 20% and an 18-month incidence of 18% [11, 12]. A population case-report study from the United Kingdom diagnosed major depression in 24% of their sample [13], and similar frequencies were reported in a recent study from Maastricht [14].

Clinical Correlates of Depression in AD

Depression in AD has been associated with worse quality of life, greater impairments in activities of daily living, decrease in caregiver's well-being [15], faster cognitive decline, greater health care utilization [16], higher mortality rates [17], and higher rates of nursing home placement [18]. Our group [8] found that patients meeting DSM-IV criteria for either minor or major depression had more severe social dysfunction and greater impairment in activities of daily living than AD patients without depression. Furthermore, AD patients with major depression had more severe anxiety, apathy, delusions, and parkinsonism than patients with minor depression, suggesting that the severity of psychopathological and neurological impairments in AD increases with increasing severity of depression. On the other hand, patients with either major or minor depression had similar deficits on activities of daily living and social functioning, suggesting that even mild levels of depression are significantly associated with increased functional impairment in AD. Depression among nursing home patients with AD has been associated with relatively more severe malnutrition, behavioral problems, noncompliance with treatment, increased nursing staff time, and excessive mortality rate [19].

Conclusion

Depression is among the most frequent psychiatric disorders in AD. One important limitation to the diagnosis of depression in AD is the lack of valid and reliable criteria.

Recent studies proposed standardized diagnostic criteria for depression in AD for empirical validation. Our group demonstrated the validity of the DSM-IV criteria for major depression in several studies [7, 8]. Depression is associated with a poor quality of life for both patients and caregivers [15]. Depressed AD patients have a faster functional decline, earlier admission to nursing homes, and higher mortality. Future studies should examine whether the successful treatment of depression in AD may have a beneficial impact upon the comorbid conditions of depression.

Apathy in AD

Apathy is defined as a psychiatric syndrome characterized by deficits in goal-directed behaviors as manifested by the simultaneous diminution of cognitive and emotional concomitants of goal-directed behavior [20]. A similar division of apathy into emotional, cognitive and behavioral domains was proposed by van Reekum and coworkers [21]. More recently, Levy and Dubois suggested that apathy should be defined as an observable behavioral syndrome consisting of a quantitative reduction in self-generated voluntary and purposeful behaviors [22].

One of the limitations for the diagnosis of apathy in AD is that this syndrome is subsumed under different terms such as athymormia, psychic akinesia, abulia, and the negative syndrome. There is also a paucity of structured interviews to diagnose apathy in dementia, and specific diagnostic criteria have only recently been validated. We discuss here the different instruments and strategies to diagnose apathy in AD, and we also discuss the major comorbid disorders of apathy in dementia.

Diagnosis of Apathy in AD

Although the ICD-10 makes no reference to apathy, the DSM-IV mentions apathy as a subtype of personality disorder caused by a General Medical Condition. Our group has validated a set of standardized criteria for the diagnosis of apathy in AD [23]. To this aim, we assessed a series of 319 patients with AD using the apathy scale (a severity rating scale) and found that 13% of the sample met our ad hoc criteria for apathy. These criteria have been recently updated by Starkstein and Leentjens [24] (Table 3). On the other hand, none of a series of 46 age-comparable healthy controls demonstrated apathy. It is important to note the overlap between depression and apathy in AD: 13% of the AD sample had apathy and no depression, but 24% had both depression and apathy. AD patients with apathy only and patients with neither apathy nor depression had similar scores on the Hamilton depression scale, suggesting that apathy does not artificially increase depression scores in this population.

The European Psychiatric Association Task Force on apathy has recently published standardized diagnostic criteria for apathy in AD [25]. These criteria

Table 3 Diagnostic criteria for apathy (adapted from [24])

A. Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture as indicated either by subjective account or observation by others.

B. Presence *for at least 4 weeks, during most of the day*, of at least one symptom belonging to each of the following three domains:

Diminished goal-directed behavior

- (1) Lack of effort or energy to perform everyday activities
- (2) Dependency on prompts from others to structure everyday activities

Diminished goal-directed cognition

- (3) Lack of interest in learning new things, or in new experiences
- (4) Lack of concern about one's personal problems

Diminished concomitants of goal-directed behavior

- (5) Unchanging or flat affect
- (6) Lack of emotional responsivity to positive or negative events

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not caused by diminished level of consciousness or the direct physiological effects of a substance.

follow the same general structure as the standardized criteria published by Starkstein and Leentjens, but were made more sensitive by requiring symptoms on two of the three domains rather than symptoms in each of the three domains. Regardless of which criteria are used, it is important to note the suggestion by Marin and Wilkosz [26] that apathy should be diagnosed only after a comprehensive mental state examination, which should include assessments of the individual's social and physical environment, variability in human goals, interests, emotional displays, and activities, as well as their level of education, social status, age cohort, and other cultural factors.

Several instruments are currently used to measure the severity of apathy in AD. Marin and coworkers were the first to develop a specific scale to measure the severity of apathy. The apathy evaluation scale (AES) [27] has three versions: a self-rated scale, a caregiver version, and a clinician version. Starkstein and coworkers developed the apathy scale [28], an abridged and modified version of Marin's scale. This scale has been validated for use in AD, Parkinson's disease, and stroke. Cummings and coworkers developed the NPI [29], an instrument administered to caregivers that includes a specific module on apathy. The dementia apathy interview and rating [30] assesses dementia-related changes in motivation, emotional responsiveness, and engagement. Finally, Robert and coworkers developed the apathy inventory [31], which rates several dimensions of apathy such as emotional blunting, lack of initiative, and loss of interest.

To our knowledge, there is one single structured interview for apathy in AD. Starkstein and coworkers developed the structured clinical interview for apathy (SCIA) to screen for symptoms of apathy into standardized diagnostic criteria [23]. The SCIA includes a series of questions to assess the domains of lack of motivation, lack of effort, dependency on others, lack of interest and concern, and blunted affect. Based on responses to these questions, a diagnosis of apathy may

be made using the Starkstein and Leentjens' or the European diagnostic criteria for apathy.

Differential Diagnosis of Apathy in AD

The first differential diagnosis to be considered is abulia, defined by Ribot as a "loss, lack or impairment of the power of the will to execute what is in mind" [32]. Marin considered abulia and apathy to be on a continuum of motivational and emotional deficits, with abulia as the most severe manifestation [20]. Marin defined abulia as poverty of behavior and speech output, lack of initiative, loss of emotional responses, psychomotor slowing, and prolonged speech latency [20]. Akinetic syndromes have been described to range from psychic akinesia (defined as the lack of goal-directed activities among patients who are fully responsive), to akinetic mutism (defined as a state of immutability caused by lack of voluntary movement, mutism, and vigilant gaze) [33]. Laplane and Dubois [34] described the "auto-activation deficit," which is characterized by inertia, mental emptiness, stereotyped activities, flat affect, and blunted emotional responses. A full reversal of the negative state on external stimulation was suggested as the main difference between this syndrome and abulia.

Frequency of Apathy in AD

In a recent study, Starkstein and coworkers [35] examined the frequency of apathy in a series of 319 patients with AD, 117 patients with depression but no dementia, and 36 age-comparable healthy individuals. Apathy was diagnosed in 37% of the AD patients, in 32% of the depressed patients, and in none of the healthy controls. A Latin American study [36] examined 60 AD patients with the NPI, reporting a frequency of apathy of 53%. A similar frequency (59%) was recently reported by an American study [37].

Clinical Correlates of Apathy in AD

In a recent series of longitudinal studies, our group examined the predictive validity of apathy in AD. The first study included a series of patients who were followed for 1–4 years [38]. At baseline, apathy was significantly associated with older age and depression (both major and minor). The frequency of apathy increased from 14% in the stage of very mild AD to 61% in the stage of severe AD. Therefore, cognitive deficits are not sufficient to produce apathy in AD because about half the patients with moderate or severe dementia did not show apathy. Whether cognitive deficits

are necessary to produce apathy has not been yet determined, but most studies assessing patients with a variety of neurological conditions such as stroke and Parkinson's disease found a significant association between greater apathy and more severe cognitive impairments [39, 40]. At follow-up, patients with apathy at baseline or patients who developed apathy during follow-up had a significant increase in Hamilton depression scale scores compared to AD patients with no apathy at baseline. Moreover, patients with apathy at baseline or those who developed apathy during follow-up had a significantly greater functional and cognitive decline and more severe parkinsonism than patients without apathy at baseline [41]. Based on these findings, we proposed that apathy may be a behavioral marker of a more "malignant" type of AD, with more severe behavioral problems and a faster cognitive, functional, and motor decline.

Conclusions

Apathy is present in about half of patients with AD and is significantly related to more severe dementia. There is a variety of instruments to rate the severity of apathy in AD, but structured clinical interviews have been developed only recently. There is now a consensus among international researchers on a common set of standardized criteria to diagnose apathy in AD. Apathy is associated with poor prognosis. Patients with apathy and dementia have a faster functional, cognitive, and motor decline than patients without apathy. Future studies should aim at finding successful therapies for apathy in dementia.

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