Phenomenology of depression in Alzheimer's disease

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Abstract

The aim of this article is to examine using a conceptual framework the current dilemmas in the diagnosis of depression in Alzheimer's disease (AD). Depression is among the most frequent psychiatric comorbid conditions in dementia. There is no strong consensus as to what criteria should be used to diagnose depression in AD. This is at least partially explained by the overlap between symptoms of depression and symptoms of AD. Recent studies using latent class analysis provided clarification to this diagnostic dilemma. All nine DSM-IV symptoms of major depression were found to characterize a class with a high chance (96%) of having a clinical diagnosis of major depression, and symptoms of anxiety were also frequent. Other psychiatric symptoms may also be included under the construct of depression in AD, since both apathy and anxiety are among the most frequent comorbid conditions for major depression in AD. Subtypes of depression should also be validated in this condition. For instance, increased awareness of cognitive and functional deficits is significantly associated with dysthymia but not with major depression, suggesting that different depressive syndromes in AD may have different aetiology.

Key-words: Alzheimer's disease, dementia, depression, anxiety, apathy, delusions.

1. Introduction

Depression is one of the most frequent comorbid psychiatric disorders in Alzheimer's disease (AD). Up to 50% of patients with AD will suffer from depression at some stage during the progression of dementia [1]. Depression is associated with earlier nursing home placement [2, 3], faster cognitive decline [4], greater impairment in quality of life [5, 6], increased disability in activities of daily living [7], physical aggression toward caregivers and increased depression in caregivers [8], increased morbidity and mortality [9], and increased direct costs [10].

Several studies addressed the phenomenology of depressed mood and depressive syndromes in AD [1, 11, 12] but important issues still remain to be clarified such as what are the most reliable criteria to diagnose depression in AD, and what are the best diagnostic instruments and depression rating scales to use in this population. Significant discrepancies in estimates of frequency, main clinical correlates, and response to treatment [1] may be partially explained by methodological limitations, such as using different instruments to assess depression[11], lack of specific diagnostic criteria, and reliance on information provided by either caregivers or patients [13]. Difficulties with diagnosis may also explain the finding that depression in AD is largely underdiagnosed and undertreated [14].

This review article will examine diagnostic dilemmas and discuss the phenomenology of depression in AD. First, we provide a historical review of the construct of depression in dementia; second, we examine the most commonly used diagnostic criteria and rating instruments for depression in AD; third, we discuss on the most relevant phenomenological attributes of depression in AD, and finally, we address the most frequent comorbidities influencing the diagnosis of depression in this condition.

2. Method

A detailed search of the literature was conducted using the PubMed services database with the words *Alzheimer's disease*, *depression* and *phenomenology* spanning the period January 1980 to April 2014. The search produced 19 citations, and the three citations that

were not in English were not further considered. Relevant journals were also hand-searched, and the references of relevant articles were searched for further publications (this strategy resulted in three additional publications). Papers reporting empirical findings or proposing conceptualization of depression in AD were chosen for discussion. All the articles were revised for potential inclusion by both authors. Inclusion/exclusion criteria were not applied, with selection of publications being mostly based on expertise. It is important to note that the aim of this review is to provide a conceptual critique to the nosology and diagnostic methodology of depression in AD rather than summarizing findings from all available sources.

3. Historical Aspects

Up to the first decade of the 19th century, the term dementia was used as a general designation to define states of insanity [15]. Pinel [16] considered dementia as a specific form of insanity, and his disciple, Esquirol [17] defined dementia as an “acquired, irreversible and severe form of dilapidation secondary to organic brain disorder and chronic insanity”. Later, the French alienist Mairet [18] studied a group of patients with a “mixture of depressive delusions and organic dementia”, a condition he called “melancholic dementia”, characterized by “weakening of intelligence... more or less soon after the onset of the condition (depressive syndrome).” Patients with melancholic dementia showed “remissions...more or less complete and more or less long lasting,” and the cause was believed to be organic, with depressive delusions resulting from changes in the “temporal regions as sites for depressive ideas (*idées de tristesse*), particularly the sphenoidal area” (as cited in [15]). Mairet’s descriptions were re-examined by Berrios [15] who found in his cohort that some cases followed a chronic progression to dementia while others had a fluctuating course.

For decades, dementia was defined based on the “cognitive paradigm”, which considers dementia as a disorder of intellectual function only, whereas delirium, psychotic symptoms and personality changes were described as mere epiphenomena [15]. In the early 20th

century, Kraepelin [19] remarked that either depression or excitement could be present at the beginning of what he termed “senile imbecility,” when “the end will always be a high degree of mental and emotional feebleness”. In the late 20th century depression was recognized as a frequent comorbid condition of AD, especially in the early stages of the illness [15].

Based on several reports of patients with depressive “pseudodementia”, who continued to suffer cognitive decline after the successful treatment of depression, and the finding that depression may precede cognitive changes in dementia, Mahendra [20] conceptualized depression in AD as “the superimposition of ‘functional’ psychiatric illness on an ‘organic’ degeneration”.

Whereas advances in neuroimaging, neurochemistry and molecular biology led to new knowledge about the potential mechanism of depression in AD [11], the overall concept of depression in dementia is still under discussion, and there is no general consensus on the best method to diagnose this psychiatric condition.

3. Assessment of depression in AD

Depression in AD is underdiagnosed [14, 21], which may be explained by the lack of instruments specifically designed to assess depression in dementia, and the lack of consistency in the use of diagnostic criteria. Possible biases in reports by patients and caregivers should also be considered. Several authors found that patients tend to underrate depressive symptoms [22, 23], whereas caregivers may have difficulties distinguishing symptoms of dementia from those due to depression [22]. Both depression and burden in caregivers may also influence depression ratings of patients [24].

The question then arises as to what is the best method to assess depression in AD. An adequate assessment of depression in AD should be based on a structured psychiatric interview that includes questions assessing a variety of behavioral and emotional symptoms, and specific items to assess observed abnormal behaviors. Information should be collected from both the patient and their respective caregivers. The Structured Clinical Interview for

DSM-IV (SCID) is a semi-structured psychiatric interview for making the major Axis I diagnoses on the DSM IV [25]. This instrument includes an overview of the present psychiatric complaint and past episodes of psychopathology. The SCID is administered by the clinician using all sources of information available at the time of the evaluation and uses her/his own judgement about the presence of a given symptom. This instrument has long been considered the gold standard for the diagnosis of mood disorders and has been validated for use in AD [13]. After the release of the DSM-5, new versions of the SCID are being prepared and should be validated for use in AD. The Mini International Neuropsychiatric Inventory (MINI) [26] is a structured interview used to assess current and lifetime psychiatric disorders based on DSM-IV criteria. Finally, the Geriatric Mental State Examination is a semi-structured interview for assessing psychopathology in elderly patients. It is administered by a trained interviewer in a session of less than one hour. This instrument has been validated in different cultures [27], but has yet to be validated for use in AD.

Depression rating scales are useful to screen patients for depressive disorders, to determine the relative severity of depressive symptoms, and to quantify changes in depression after specific treatment, but should not be used for diagnosis.

The Cornell Scale for Depression in Dementia (CSDD) is the only scale specifically developed to assess depression in AD. The CSDD is a clinician-administered instrument based on information provided by a caregiver and the patient on independent interviews [28]. Final scores are based on the examiner's clinical impression. When symptoms are considered to be secondary to the cognitive deficits, potentially overlapping items are excluded. An initial study in AD suggests that the CSDD may have stronger psychometric attributes than the Hamilton Depression Rating Scale (HAM-D) [29].

Other scales that were designed to examine depression in non-demented individuals have been used in AD. The HAM-D is a 17-item interviewer-rated scale that assesses both psychological symptoms of depression, such as self-esteem, suicidal ideation, interests in daily life activity and work productivity, and worrying; and somatic symptoms, such as sleep, appetite, psychomotor changes, and loss of energy [30]. The Geriatric Depression Scale

(GDS) is a short screening instrument for depression in the elderly composed by 15 items. This scale focuses on psychosocial aspects of depression, avoiding symptoms that may overlap with medical disorders or aging [31]. One limitation of the GDS is that it is a self-report instrument, and some of the questions may be difficult to answer reliably for patients with moderate or severe dementia. Nevertheless, the validity of this instrument has been demonstrated for patients with a MMSE score of 10 or more [32]. The Beck Depression Inventory (BDI) [33] is a self-assessed instrument that includes 21 items. The BDI was designed to measure the severity of depressive symptoms in adults and clinical changes during psychotherapy. Therefore the BDI is more weighted towards psychological than somatic symptoms of depression. The Neuropsychiatric Inventory (NPI) [34] is an instrument designed to assess the frequency and severity of neuropsychiatric symptoms based on information provided by a valid informant. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C) is a new version of the NPI created in order to overcome patient's and caregiver's biases when providing information. The NPI-C is based on the clinician judgement using information from caregiver and patient interviews, and any other relevant available data [35].

4. Diagnosis of depression in AD

4.1. Diagnostic criteria

The nosology of depression in AD is still in need of conceptual and empirical clarification. Lyketsos and Olin [11] raised relevant questions regarding the conceptualization in AD, such as whether depression in AD should be defined as a syndrome, or as a dimensional construct related to stress in the context of a progressive and irreversible neurodegenerative condition. A major limitation to the diagnosis of depression in AD is the potential overlap between symptoms of depression and symptoms resulting from the cognitive and functional decline. Thus, insomnia may be confounded with the change in sleeping pattern frequent in AD, loss of interest may be related to the inability to engage in prior activities and declined capacity, psychomotor retardation and concentration deficits are obvious problems with the

progression of AD, poor appetite and loss of weight may be explained by the patients' inability to cook and forgetting to eat, and low self-esteem may be related to increased social dysfunction.

Four main approaches have been proposed to diagnose depression in neuropsychiatric disorders. For the 'inclusive approach' [36, 37] symptoms which may or may not be related to the physical illness are counted towards the diagnostic criteria. This approach may provide the greatest sensitivity but with the lowest specificity, although this has not yet been empirically examined in AD. However, this approach will suggest treatment to most patients in need of it and is currently the strategy of choice. For the 'exclusive approach', those symptoms that the interviewer believes are related to the physical illness are not counted [38]. Approaches with this strategy may underdiagnose depression and ratings are more subjective. For the 'substitutive approach' non-overlapping symptoms of depression (e.g. psychological symptoms) are substituted for the overlapping diagnostic criteria (e.g. somatic symptoms) [39]. The problem with this strategy is the unclear validity, since psychological symptoms of depression may be related to the cognitive and functional decline of dementia rather than depression. Finally, the 'specific symptom approach' only considers those symptoms that are a valid component of a depressive syndrome in the specific neuropsychiatric disorder, thus providing the most accurate diagnosis [40]. For instance, Starkstein et al [24] found anxiety to be a significant component of a major depressive class in AD, and this symptom may be added to the diagnostic criteria for depression in AD.

Lyketsos and co-workers [41] suggested that the "individual symptom approach" may ignore the high comorbidity of psychiatric symptoms and syndromes in AD and should not be used. Based on these findings, they proposed specific diagnostic criteria for AD-associated affective disorder (Table 1). This group [42] was the first to suggest an empirically-based taxonomy for psychiatric disorders in AD based on a large series of AD patients living in the community. They used latent class analysis (LCA) and identified three classes, with the larger one including mostly symptoms of depression, irritability or anxiety, and about half of

the individuals in this class also exhibited apathy and aberrant motor behaviour. This class was labelled “affectively disturbed.”

A workgroup convened by the National Institutes of Mental Health (NIMH) proposed standardized diagnostic criteria for depression in AD (NIMH-dAD) based on the “inclusive approach” [39]. These are similar to the DSM-IV criteria for major depression [43], but with the inclusion of irritability and social isolation replacing loss of libido, and with loss of pleasure in response to social contact replacing loss of interest. The NIMH criteria require three symptoms for the diagnosis of depression in AD instead of the five required by the DSM-IV criteria for major depression, and symptoms are not required to be present nearly every day (Table 2). The workgroup recommended that information about depressive symptoms should be obtained in separate interviews from the patient and a caregiver. Additional information may be obtained from medical records and other sources. The examiner has to make a clinical judgment regarding differences between sources of information, and should also consider the patient’s impaired cognition, cultural factors, denial from patients and caregivers, and their education level. Depressed mood has to be distinguished from apathy and ‘emotional incontinence’ (i.e. sudden episodes of crying and/or laughing which may be mood congruent or mood non-congruent). Social withdrawal is diagnosed based on the patient’s desire to socialise, and sociability when with others. Agitation is rated as the inability to sit still, pacing, and/or hand-wringing, and these signs should be distinguished from anxiety. Irritability is only rated when it represents a change from premorbid personality, while excluding simple frustration over functional deficits. Finally, depressive symptoms should be severe enough to cause significant distress or disruption in social, occupational or psychological functioning. The NIMH criteria are yet to be validated, and several limitations may be pointed out. The lower threshold and modified criteria may result in a reduced specificity, particularly in the stages of severe AD as “loss of positive affect” may allow the inclusion of heterogeneous syndromes such as apathy. Starkstein et al [44] found that 41% of AD patients with severe dementia diagnosed with depression based

on the NIMH-dAD criteria had no sad mood. Another limitation is that subtypes of depression such as dysthymia, minor depression and subsyndromal depression are not considered in the NIMH criteria. Finally, there is equivocal empirical support for including irritability as a diagnostic criterion [45]. Starkstein et al [46] examined the temporal stability of symptoms of depression in a study that included 65 AD patients with depression. At 18-months follow-up, about half of the sample was no longer depressed. No significant longitudinal changes were found on scores of irritability or apathy, suggesting that these symptoms should not be construed as valid criteria for depression in AD. Teng et al [47] found that neither social isolation/withdrawal nor irritability was predictive of depression. They also found that the symptoms that most strongly predicted depression were the DSM-IV criteria of guilt/worthlessness, loss of energy, and psychomotor retardation.

The adequate DSM-IV category to diagnose depression in AD is “Mood disorder due to a General Medical Condition”. However, this category has the limitation of being too broad in scope, with the risk of including heterogeneous syndromes with poor specificity for depression in dementia. In the DSM-5, the category of Dementia of the Alzheimer type was retained, and depressive symptoms are diagnosed as in the DSM-IV (Table 3). The International Classification of Diseases 10 (ICD-10) classifies depressive syndromes as “Dementia in Alzheimer Disease, with other symptoms, predominantly depressive”. The validity of these criteria has been poorly explored.

Engedal, et al. [48] examined the specificity of depressive symptoms in 231 patients with dementia recruited from geriatric or psychiatric hospitals and nursing homes, using the NIMH-dAD, DSM-IV and ICD-10 criteria. The frequency of depression was 53% using the NIMH-dAD criteria, 47% when using ICD-10 criteria, and 34% when using DSM-IV criteria. A logistic regression analysis demonstrated that poor self-esteem, delusions and multiple physical complaints were the best predictors of depression when using NIMH-dAD criteria, whereas sadness, suicidal thoughts and poor self-esteem were the best predictors of depression as diagnosed with ICD-10 or DSM-IV criteria. Using a structured psychiatric interview, the most common symptoms of depression were sadness, loss of interest and

agitation/retardation. On the other hand, irritability had a similar frequency among depressed and non-depressed patients with dementia. The authors concluded that using DSM-IV-TR or ICD-10 criteria for major depression (but not the NIMH-dAD criteria), provides a syndromal profile of depression for AD patients that is similar to the profile of depression for individuals without dementia. Vilalta-Franch et al [49] examined agreement between diagnostic criteria for depression in a series of 491 AD patients using the Cambridge Examination for Mental Disorder of the Elderly, and the NPI. The frequency of depression ranged from 5% based on ICD-10 to 44% when using the NPI depression screening question. Moreover, the diagnostic agreement for depression between DSM-IV and NIMH-dAD was only 44%. These findings demonstrate a high variability on the frequency of depression depending on the set of diagnostic criteria used. Similar findings were reported by Teng et al, [47] as the frequency of depression ranged from 14% when using DSM-IV criteria, to 30% when using cut-off scores on the CSDD, and 44% when using NIMH-dAD provisional criteria. Starkstein et al [24] found that 38% of 971 AD patients met the NIMH-dAD criteria for depression, as compared to 27% when using DSM-IV criteria.

Assessing depression in nursing homes is complicated, given that most patients are in the middle or late stages of AD. Bruhl et al [50] found that depression in this setting is only recognized by psychiatrists in 44% of the cases, by social workers in 37% and by nursing home physicians in only 14%. Using the NIMH-dAD criteria, Verkaik et al [51] reported a point prevalence of depression of 19% among patients in psychogeriatric nursing home wards, and the most frequent symptoms of depression were depressed mood, irritability, and fatigue/loss of energy.

4.2. Validity of depressive symptoms in AD

The question also arises as to the validity of syndromes such as major and minor depression, and dysthymia when applied to individuals with AD. These subtypes of depression have been rarely examined in AD, and their validity has not been properly established.

Several studies demonstrated that AD patients meeting DSM-IV criteria for major depression have an earlier onset of depression, usually before the onset of cognitive decline [52], have poor awareness of intellectual deficits [52], show cerebral perfusion deficits in specific brain areas [53], and depressive symptoms have a significantly longer duration than in patients with dysthymia [54]. On the other hand, dysthymia most often begins after the onset of dementia [52], has a higher prevalence in the early stages of the illness [52], and is related to preservation of awareness of cognitive impairment [52]. Some depressions in AD may also be a recurrence of early and midlife depressive disorders [55].

Several studies examined the validity and specificity of depressive symptoms in AD.

Chemerinski et al [13] assessed a large series of AD patients using the HAM-D. Presence of sad mood was defined based on a score of two or more on the HAM-D item of depressed mood, and the main finding was that AD patients with sad mood had higher scores than AD patients with no sad mood for the HAM-D items of guilt, suicidal ideation, insomnia, loss of interest, psychomotor retardation and agitation, worry, anxiety, loss of energy and loss of weight. When AD patients with no depression were compared with age-comparable healthy controls, there were no significant differences on any HAM-D item. On the other hand, non-depressed individuals with AD had no more depressive symptoms than age-comparable healthy controls. Based on the finding that symptoms of depression are genuinely related to the presence of sad mood, Chemerinski et al (2001) suggested all these symptoms should be included into the syndrome of depression in AD.

Starkstein et al [44] assessed 670 AD patients with the SCID, and found that 26% met DSM-IV criteria for major depression, 26% met criteria for minor depression, and 48% were not depressed. In the stages of mild, moderate and severe dementia, major depression was significantly associated with sad mood, but the association between sad mood and minor depression in severe dementia was significantly weaker. Guilty ideation, suicidal ideation, loss of energy, insomnia, weight loss, psychomotor retardation/agitation, poor concentration, and loss of interest were the depressive symptoms that most strongly discriminated between AD patients with and without sad mood. The finding that loss of interest was significantly

more frequent among AD patients with either minor or major depression as compared to patients without depression does not agree with the NIMH-dAD criteria, which excluded loss of interest. In a longitudinal study that included 65 AD patients who remitted from a depressive episode Starkstein et al [46] found a significant improvement in sadness, guilt, suicidal ideation, insomnia, loss of interest and energy, social withdrawal, psychomotor changes, changes in appetite/weight, and anxiety. These findings suggest that all symptoms included in the DSM-IV criteria are valid for major depression in AD. Another finding from Starkstein's et al study [44] was that emotional lability was significantly associated with major depression. Another study found that more than 80% of AD patients with emotional lability had a comorbid minor or major depression, suggesting that emotional lability should be considered an indicator of depression in AD [56].

A recent study by Starkstein et al [24] examined the symptom pattern of depression in AD using LCA. The study included 971 AD patients assessed with the SCID, and three classes were identified. The first class ("major depression") included 21% of the patients, and showed a high frequency of all nine criteria for major depression. Ninety-seven percent of patients in this class met unmodified DSM-IV diagnostic criteria for major depression. A second cluster ("minor depression") included 39% of the patients and showed an intermediate frequency of depressive symptoms. Sixty-two percent of the patients in this class met DSM-IV criteria for minor depression, and others had apathy without depression. A third class ("no depression") included 40% of the patients, and showed a low frequency of all symptoms of depression and anxiety. Whereas apathy and anxiety were significant predictors of depression, irritability was not. Patients with minor depression had a significantly higher frequency of apathy, suggesting that minor depression in AD may be related to apathy in the absence of sad mood.

In a study using the HAM-D suicidality item, Harwood and Sultzer [57] found that 10% of their AD group had thoughts that "life is not worth living". Higher scores on this item were significantly associated with other symptoms of depression and with greater awareness of cognitive and functional deficits. Of note, suicidal ideation and attempts are not common in

AD [1, 58], but presence and severity of depression are strong predictors of suicidal ideation over time [59, 60].

To summarize, the validation of depressive symptoms in AD is far from completed. This is related to both the complexity of validation processes and the syndromic heterogeneity of psychiatric symptoms in dementia. As stressed by Andreasen [61] diagnostic schemes should be based upon systematic studies rather than a priori constructs and follow the 'gold standard' for establishing diagnostic validity, such as phenomenological description, biomarkers, longitudinal studies, and genetic studies. The question also arises as to whether antidepressant treatment may help to illuminate the validity of depression in AD. Several major randomized controlled trials (RCT) [62, 63] of antidepressants in AD were unable to demonstrate significant benefit of active medication over placebo, suggesting that the criteria for depression used in those studies (the NIMH-dAD and a cut-off score on the CSDD, respectively) may lack predictive validity. However, it may also be argued that response to antidepressant treatment is not a useful strategy to determine validity, given that the response rate to antidepressants in the major AD RCT is similar to the response rate for the non-AD population with depression [64]. The finding that roughly one third of individuals with depression respond to antidepressants [64], did not lead to changes to the diagnostic criteria for major depression in the DSM-5. Importantly, what the RCT in AD did show is that most symptoms of depression in AD are potentially reversible, which indicates that they are not mere artefacts of the cognitive decline. As suggested by Kendell [65], using response to treatment to test for validity has the limitation of studying outcomes under biased conditions, and the fact that no treatment is invariably effective in treating a psychiatric condition. Future studies should examine which symptoms show the greatest remission upon antidepressant treatment, identify sub-groups that may be the most sensitive to treatment, and examine the phenomenology of depression in this subgroup.

In conclusion, until specific criteria are properly validated, the diagnosis of depression in dementia should be based on a systematic mental status examination leading to a

psychiatric diagnosis based on the presence of a symptom cluster using the inclusive approach.

5. Psychiatric syndromes associated with depression in AD

Horning et al [66] suggested that depression in AD may be an emotional disturbance “reactive” to the knowledge of having dementia in the context of specific personality traits like neuroticism and external locus of control. The literature on whether depression in AD is related to having insight into the illness is conflicting, with most studies showing no significant association between insight into having AD and risk of depression [63, 64]. Migliorelli et al [67] found a significant association between anosognosia and dysthymia, but not with major depression [23]. Starkstein et al [68] reported a valid diagnostic formulation for anosognosia in AD. The frequency of anosognosia ranged from 10% in the stage of very mild dementia to 57% in the stage of severe dementia. A stepwise regression analysis showed significant correlations between anosognosia and more severe disinhibition, lower MMSE scores, and older age. On the other hand, no significant association was found between anosognosia and depression scores.

Apathy and anxiety are the most frequent comorbid conditions of depression in AD [69-73]. The prevalence of apathy among AD patients in the Cache County study was 27%, and about 40% of apathetic patients had depression [69]. Of note, 56% of AD patients with depression had comorbid apathy. The differential diagnosis between apathy and depression may be difficult given that loss of interest and motivation are critical criteria for both conditions. Somatic symptoms such as psychomotor retardation, loss of energy and hypersomnia were reported to be common in both apathy and depression [71]. A careful clinical evaluation may differentiate both syndromes based on additional symptoms such as sad mood, guilty feelings, low self-esteem and hopelessness, all of them more frequent in depression than apathy [74]. Starkstein et al [75] examined the frequency of apathy in a series of 319 AD patients and a group of age-comparable healthy individuals. Apathy in the absence of depression was diagnosed in 13% of the AD group and in none of the healthy

controls. Depression and apathy were present in 24% of the sample, whereas 22% had depression and no apathy. The finding that AD patients with apathy only and patients with neither apathy nor depression showed similar depression scores suggests that apathy may not artificially increase depression scores in AD.

Anxiety in AD was reported to range from 8% to 54%, and is a frequent comorbid condition of depression [69, 76]. In a sample of 62 AD patients Tagariello et al. [71] found a strong association between depression, as measured by a 5-point change in the HAM-D, and anxiety. The frequency of Generalized Anxiety Disorder (GAD) was 5%, and 75% of these patients also met the DSM-III criteria for major depression. Using DSM-IV criteria, Porter et al. [77] found that 63% of AD patients with anxiety also had depression. Starkstein et al. [76] validated the construct of GAD in AD in a study that assessed 552 patients with probable AD. Restlessness, irritability, muscle tension, fears, and respiratory symptoms were significantly associated with anxiety and worry. On the other hand, the symptoms of difficulty concentrating, fatigue, and sleep disturbance were not associated with excessive worry and anxiety, suggesting that the DSM-IV criteria for GAD should be modified for use in AD. GAD was diagnosed based on DSM-IV criteria in 15% of this sample and in 9% using ICD-10 criteria. About 80% of patients with GAD were also depressed, suggesting that GAD in AD is a frequent epiphenomenon of an underlying depressive syndrome.

6. Conclusions

Few studies have examined the validity of depressive symptoms in AD. A workgroup convened by NIMH proposed provisional criteria to diagnose depression in AD. They recommended using the DSM-IV criteria for major depression while making adaptations to suit individuals with dementia. Studies that compared the NIMH-dAD criteria to DSM-IV and ICD-10 diagnostic criteria showed wide discrepancies, which may be related to intrinsic differences in these nosologies. Recent studies showed that the DSM-IV symptoms of major depression are all valid for use in AD. The syndrome of depression in AD may be broadened, as apathy, anxiety and loss of insight were all found to be significantly related to

major depression in AD. Further studies are needed to validate diagnostic criteria for different syndromes of depression in AD and other dementias. Nevertheless, provisional recommendations include the assessment of depression in AD using structured psychiatric interviews and the diagnosis of depression using standardised diagnostic criteria such as the NIMH-dAD or unmodified DSM-5 criteria for major depression.

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Table 1

Diagnostic criteria for AD-associated neuropsychiatric disturbance (adapted from Lyketsos et al [41])

- A. Meeting NINCDS/ADRDA criteria for probable AD.
 - 1. A prominent disturbance of affect, disruptive to the patient or the care environment and representing a change from the patient's baseline, as evidence by the presence of one or more of the following symptoms: (1) depression; (2) irritability; (3) anxiety; (4) euphoria
 - 2. 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.
- B. Symptoms from B and C co-occur most days, and the disturbance has a duration of at least 2 weeks.
- C. The disturbance has its first onset within two years or after the onset of dementia.
- D. The disturbance cannot be explained in its entirety by another cause (e.g. a general medical condition, medications, life stressors).

Table 2

Provisional diagnostic criteria for depression of AD (adapted from Olin et al [39])

- 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 due to the direct physiological effects of a substance.
- F. The symptoms are not better accounted for by other psychiatric conditions.

Table 3

Criteria for Major Depressive Episode (Adapted from DSM-5 [78])

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 (1) depressed mood or (2) loss of interest or pleasure.

- (1) Depressed mood most of the day, nearly every day.
- (2) Markedly diminished interest or pleasure in most activities.
- (3) Significant weight loss or gain, or decrease or increase in appetite.
- (4) Early insomnia or hypersomnia nearly every day.
- (5) Psychomotor agitation or retardation nearly every day.
- (6) Fatigue or loss of energy nearly every day.
- (7) Feelings of worthlessness or excessive or inappropriate guilt.
- (8) Diminished ability to think or concentrate, or indecisiveness.
- (9) Recurrent thoughts of death, recurrent suicidal ideation.