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Apathy and Depressive Mood in Nursing Home Patients With Early-Onset Dementia

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The study explored whether apathy and depressive mood symptoms (DMS) are related to cognitive and functional features of dementia in 63 nursing home (NH) residents with early-onset dementia (EOD). All EOD residents from one NH (n = 41) and a random sample from another NH were assessed for depressive symptoms (Montgomery Asberg Depression Rating Scale [MADRS]), apathy (Neuropsychiatric Inventory [NPI]), global cognitive functions (Mini-Mental State Examination [MMSE]), activities of daily living (ADL, Minimum Data Set–Resident Assessment Instrument [MDS-RAI]), and overall dementia severity (Global Deterioration Scale [GDS]). DMS were not associated with apathy and dementia severity. Regression analyses adjusted for age, gender, the type of dementia, and DMS revealed that dementia severity measures accounted, respectively, for 14% (ADL), 13% (GDS), and 9% (MMSE) of the variance in apathy. In line with previous research in older patients, the higher apathy scores were associated with more cognitive and functional problems in EOD.

Keywords: early-onset dementia; apathy; depressive mood; depressive symptoms

Introduction

Noncognitive neuropsychiatric disturbances, such as depression and apathy, which occur in up to 90% of patients with dementia[1-3] can be seen as central components of dementia, regardless of cause or stage.[4] These provide clues to the underlying pathophysiological processes of dementia, are key determinants of differential diagnosis and prognosis,[2] and are of great importance in patient care. In this regard, acquiring insight into noncognitive disturbances is especially important for dealing with patients with early-onset dementia (EOD, onset before 65 years of age). Early-onset dementia shows a wider differential diagnosis in comparison to late-onset dementia[5] (LOD), noncognitive psychiatric disturbances are highly frequent in EOD,[6,7] and these disturbances may interfere with or delay EOD diagnosis.[8,9]

Apathy is the most common noncognitive disturbance in dementia[1,3,10]; it is badly tolerated and experienced dramatically by caregivers—even worse than cognitive deterioration.[11] Apathy in dementia is defined as the absence or lack of motivation, feelings, emotion, interest or concern not due to mood disorder, altered level of consciousness, or cognitive impairment.[12] Loss of interest or motivation can be a conspicuous symptom of depression.[13] In this regard, patients with a high level of apathy are likely to meet criteria for the diagnosis of depression even when dysphoric symptoms are absent.[14] Nevertheless, apathy should not be considered a mere symptom of depression because various studies show apathy to be a discrete syndrome in dementia.[15-17] A recent large longitudinal study by Starkstein et al[17] among 247 patients with Alzheimer's disease (AD) demonstrated that apathy at baseline was a predictor of depression 1 to 2 years later but that depression was neither necessary nor sufficient to produce apathy. The distinction between apathy and depression is

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important in clinical practice because the treatment of depression can worsen apathy (selective serotonin reuptake inhibitors[14,18]) and treatment of apathy does not necessarily ameliorate depressive symptoms.[19]

One of the major findings of Starkstein et al[17] was that apathy but not depression has been associated with a faster cognitive and functional decline. Several studies with patients having LOD demonstrated that apathy, but not (or to a lesser degree) depression, has been correlated with global disease severity and functional deficits,[14,20] cognitive impairment,[14-16,20] and poor awareness of behavioral and cognitive changes.[15] Comparing apathy and depression in relation to dementia severity may be biased, as measuring instruments may contain overlapping items and there are phenomenological commonalities between depression and apathy.[14] In this regard, it is interesting that depressive mood symptoms (DMS; such as sad mood, feelings of guilt, low self-esteem etc) in patients with LOD showed no correlation with apathy, and that mood symptoms were not associated with cognitive and functional dementia aspects.[21,22] By contrast, motivational symptoms of depression (loss of motivation and interest, energy depletion, problems with concentrations etc) have been associated with cognitive and functional aspects.[22]

The aim of this study was to investigate the association of apathy and DMS in EOD and to investigate their relation with the dementia severity. We hypothesize that apathy is unrelated to DMS; and in contrast to DMS, apathy is positively related to cognitive and functional features of dementia in EOD. To avoid a contamination of the results when examining symptoms that may be common to both apathy and depression, we focused only on DMS in our study. To the best of our knowledge, previous studies on apathy and depression in dementia have only been conducted in patients with LOD or mixed samples of patients. Little is known about depression and apathy in EOD and whether the results obtained in LOD can be simply generalized to younger patients. Clinical guidelines broadly accept the concept that EOD differs from LOD in clinical and behavioral manifestations.[23] There may be some distinctions between EOD and LOD regarding clinical aspects of psychiatric symptoms,[24-26] cognitive functions,[25] and depressive features[27] and apathy[25] in particular. The psychosocial complications that can contribute to depression[28] are enormous for patients with EOD,[8,29] thus demonstrating a need for more attention to be paid to depressive symptoms in EOD. Considering that the impact of dementia on mortality is high especially in young patients,[30] it is also important to pay attention to apathy in EOD as apathy may be related to a faster disease progression.[17]

Methods

Patients

As part of an ongoing national epidemiological EOD study in the Netherlands, 63 participants were recruited from 2 nursing homes (NHs) with specialized care for younger people with dementia. The following inclusion criteria were used based on the medical file and confirmed by a medical practitioner: diagnosis of dementia according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision; *DSM-IV-TR*) criteria[13] and diagnosis of dementia had to be established before the age of 65 by a neurologist, psychiatrist, or geriatrician. From one ward, all EOD residents (n = 41) present were included and from a second ward, a random sample (n = 22) has been drawn by investigators from a numbered list. There were no exclusions based on cognitive capacity. This study was approved by the local ethics committee (Commissie Mensgebonden Onderzoek, Arnhem-Nijmegen) and the legal representatives of all patients provided informed consent. When communication was possible, patients received a short explanation before they were interviewed. The patients had an opportunity to decline their participation. The study was undertaken in accordance with the World Medical Association Declaration of Helsinki and the Guidelines on Good Clinical Practice.

Measures

Depressive mood symptoms. The following 5 items of the Montgomery Asberg Depression Rating Scale[31] (MADRS) were used to assess mood symptoms: apparent sadness, reported sadness, inner tension, pessimistic thought, and suicidal thought. A principal component analysis with the present data (eigenvalues greater than 1.0, obligue rotation procedure) may support this distinction. All mood symptoms achieved loading higher than 0.75 except for suicide thought (loading 0.55) on the first component, which explained 33% of the variance. Concentration problems, lassitude, and inability to feel achieved loading higher than 0.57 on the second "motivational" component (17% of the variance), and reduced appetite (0.71) and a reversed MADRS item for sleep problems (0.66) loaded high on the third component (13% of the variance). The MADRS

is found to be a useful instrument for predicting depression diagnosis in our sample (area under the curve [AUC] = 0.87).[32] Each item can be scored in 7 intensity grades (0 to 6). A higher sum of the scores on the 5 mentioned items means more (severe) DMS.

Apathy. The apathy subscale of the Neuropsychiatric Inventory (Nursing Home),[33] (NPI) is one of the most frequently used instruments in research on apathy in dementia.[19] The original NPI is an informant-based rating scale developed to assess neuropsychiatric symptoms in patients with dementia. The validity and reliability of the Dutch version used in this study is established.[34] The apathy subscale contains items such as showing loss of interest, lacking motivation, less spontaneous behavior, and lacking emotions. The total subscale score was obtained by multiplying severity (1-3) by frequency (1-4) of observed apathy. A higher score means more prevalent and more severe apathy.

Dementia severity. The cognitive and functional status of patients was evaluated with 3 measures: (1) The Global Deterioration Scale[35] (GDS, range 0-7) was used to characterize dementia stage globally, where a higher score indicates more dementia severity and lower overall functioning; (2) the Mini-Mental State Examination[36] (MMSE, range 0-30) was used to assess severity of cognitive impairment, where a higher score indicates better cognitive functioning; (3) the 4 subscales of ADL (personal hygiene, toileting, locomotion, and eating) from section-G of the Resident Assessment Instrument[37] (RAI) were used to account for functional status of the patients. The data were converted into an ADL score using interRAI ADL hierarchy scale.[38] The ADL score ranges from "0" (total independence in all 4 ADLs) to "6" (total dependence in all 4 ADLs).

Procedure

All scales were interview-administered. The structured interviews with the professional caregivers (in this order: ADL, GDS, NPI, MADRS) and with patients (MMSE) were conducted by 2 graduate psychologists under the supervision of a medical practitioner and a professional psychologist. They were in their final year of the MSc and they had been trained in administering the scales. Patients were assigned randomly.

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS; v 11.5.0). Standardized Cronbach α for internal consistency of the scales and descriptive statistics were assessed. Males and females were compared (Student t test) on the main variables' scores (apathy and mood symptoms) and dementia severity measures (ADL, MMSE, GDS). Spearman correlations were determined for age, apathy, mood symptoms, and dementia severity. For exploratory purposes, patients with different types of dementia (AD, vascular dementia, frontotemporal dementia, alcohol-related dementia, and other types) were compared on the main variables' scores using analysis of variance (ANOVA). Dummy variables indicated a presence (value "1") or an absence (value "0") of different types of dementia: AD, vascular dementia, frontotemporal dementia, alcohol-related dementia. Patients from the group with "other types of dementia" received "0" values on all 4 dummy variables. To control for confounding factors, we constructed a series of hierarchical linear ("enter") regression models for both main variables. Age, gender, and dummy variables were used as predictors of a main variable in model 1. Model 2 adjusted model 1 with the second main variable (apathy for mood symptoms and vice versa), and model 3 adjusted model 2 with, respectively, MMSE, ADL, and GDS. This hierarchy of models quantifies the contribution of, respectively, cognitive impairment, functional disability, and an overall dementia severity to, respectively, apathy and mood symptoms, corrected for potentially confounding influence of the second main variable (mood symptoms for apathy and vice versa) and for influence of age, gender, and the types of dementia.

Results

There were 30 men and 33 women with an EOD diagnosis in this study. The youngest patient was 40 years old and the oldest was 71 years old (M = 59; SD = 6.4). The following types of dementia were present (first diagnosis mentioned only): 17 patients (27%) had AD, 6 patients (9.5%) had frontotemporal lobar degeneration, 12 (19%) had vascular dementia, and 13 (20.6%) had alcohol-related dementia. A total of 15 patients (23.8%) had other types of dementia, among which were dementia due to Huntington disease (n = 3), head trauma (n = 2), Parkinson disease (n = 1), postinfectious dementia (n = 3), dementia with Lewy bodies (n = 1), and dementia due to several other general medical conditions (n = 5).

Table 1. Demographical and Clinical Characteristics and Correlations Between Variables

				Spearman rho, N = 3 (Unless Other N is Noted)						
	N	M (SD)	Range	Apathy	Mood	ADL	MMSE-1	MMSE-2	GDS	Motiv.s.
Age	63	58.7 (6.4)	40-71	0.26[a]	–0.01	0.32[a]	–0.14 (44)	–0.35[b] (59)	0.48[b]	0.49[b]
Apathy	63	6.2 (4.7)	0-12	–	0.16	0.48[c]	–0.15 (44)	–0.39[d] (59)	0.52[c]	0.70[c]
Mood	63	5.1 (5.5)	0-19		–	0.10	–0.15 (44)	–0.10 (59)	0.14	0.27[c]
ADL	63	3.1 (1.9)	0-6			–	–0.34[c] (44)	–0.51[c] (59)	0.66[c]	0.54[c]
MMSE-1	44	15.1 (6.6)	2-28				–	–	–0.60[c] (44)	–0.19 (44)
MMSE-2	59	11.8 (8.1)	2-28				–	–	–0.79[c] (59)	–0.48[c] (59)
GDS	63	5.7 (0.9)	4-7						–	0.67[c]
Motiv.s.	63	8.6 (4.8)	0-18							–

Abbreviations: ADL, Activities of Daily Living score with RAI ADL hierarchy scale[38]; apathy, apathy subscale of the Neuropsychiatric Inventory (Nursing Home)[33]; GDS, Global Deterioration Scale[35]; MMSE-1, Mini-Mental State Examination[36] score excluding patients without a score; MMSE-2, MMSE score including patients without a score (filled up with a lowest score); mood, total score on 5 "mood" symptoms of the Montgomery Asberg Depression Rating Scale[31]; Motiv.s., total score on 3 "motivational" symptoms of the Montgomery Asberg Depression Rating Scale.[31]

[a]$P < .05$, 2-tailed.
[b]$P < .005$, 2-tailed.
[c]$P < .001$, 1-tailed.
[d]$P < .005$, 1-tailed.
[e]$P < .05$, 1-tailed.

The standardized Cronbach α was .79 for MADRS mood symptoms. The standardized Cronbach α for MMSE was .86 in 44 patients. Two patients refused to answer the questions and another 2 patients died shortly before examination on MMSE. Another 15 patients—all in the GDS stage 7 (the most severe dementia)—could not answer any MMSE question correctly. The missing MMSE scores for these 15 patients were conservatively filled with the lowest score acquired (score 2) in this study.[39]

Men and women did not differ in age (men: M = 59.1, SD = 6.8; women: M = 58.4, SD = 6.0; $t_{61} = 0.46$, $P = .650$) and they did not differ in total scores on the ADL (men: M = 3.0, SD = 2.0; women: M = 3.1, SD = 1.9; $t_{61} = -0.05$, $P = .961$), the MMSE (men: M = 12.3, SD = 8.2; women: M = 11.4, SD = 8.2; $t_{57} = 0.43$, $P = .668$), the GDS (men: M = 5.7, SD = 1.0; women: M = 5.6, SD = 0.9; $t_{61} = 0.13$, $P = .899$), MADRS mood symptoms (men: M = 5.5, SD = 5.9; women: M = 4.7; SD = 5.2; $t_{61} = 0.60$, $P = .552$), and MADRS motivational symptoms (men: M = 9.5, SD = 4.3; women: M = 7.7, SD = 5.1; $t_{61} = 1.53$, $P = .130$). Men had higher apathy scores (M = 7.5, SD = 4.0) than women (M = 5.1, SD = 5.1; $t_{61} = 2.05$, $P = .045$). Table 1 represents the demographic and clinical characteristics of the patients. Global Deterioration Scale is the only scale with a small range. That can be explained by the nature of the sample: patients with GDS stages 1 to 3 do not usually stay in NHs.

Apathy

One fifth of all patients (N = 13; 20.6%) had a zero score ("no apathy") on the apathy subscale. More than a half (53.8%) of the patients had a score "8" (N = 16) or a maximum score of "12" (N = 18). There was no difference on apathy score between patients with various types of dementia ($F_{4,58} = 1.19$, $P = .324$). Apathy correlated moderately and positively with the ADL disability ($r_s = .48$, n = 63, $P < .001$) and with the GDS score (overall dementia severity; $r_s = .52$, n = 63, $P < .001$). Apathy correlated also moderately and negatively with the MMSE score ($r_s = -.39$, n = 59, $P < .005$). The correlation with cognitive impairment was nevertheless not significant when excluding patients giving no correct answer on the MMSE ($r_s = -.15$, n = 44, $P = .318$). Age was positively associated with the apathy score ($r_s = .26$, n = 63, $P < .05$).

In the analysis using age, gender, and types of dementia as predictors of apathy, the general linear model 1 yielded adjusted R^2 of .22 ($\Delta F_{6,56} = 2.6$, $P = .028$) indicating that 22% of the variance in apathy was accounted by the independent variables (significance for age, $\beta = .28$, $t = 2.08$, $P = .047$, and gender, $\beta = -.25$, $t = -2.04$, $P = .042$). Model 2 adjusting for mood symptoms as predictor of apathy did not yield a significant R^2 change ($\Delta R^2 = .03$; $\Delta F_{1,55} = 2.2$, $P = .145$). Adjusting for the variables of dementia severity in model 3 yielded significant ΔR^2 indicating that the ADL score ($\Delta F_{1,54} = 12.2$; $\beta = .41$, $t = 3.50$, $P < .001$), the GDS stadium

($\Delta F_{1,54} = 11.1$; $\beta = .51$, $t = 3.33$, $P = .002$), and the MMSE score ($\Delta F_{1,54} = 7.0$; $\beta = -.43$, $t = -2.64$, $P = .011$) have been independently accounting, respectively, for 14% (ADL), 13% (GDS), and 9% (MMSE) of the variance in apathy after controlling for confounding factors of age, gender, types of dementia, and mood symptoms.

Mood Symptoms

External validation was examined by conducting Spearman rho correlation between NPI subscale "depression/dysphoria" and mood symptoms. The correlation is strong and positive ($r_s = .82$, n = 63, $P < .001$). About a half of the patients (N = 32, 49.2%) had a zero score (score "0," n = 16) or scores "1" through "3" (n = 16) on the mood symptoms of the MADRS. The highest score obtained within this study was "19" (maximum scale score is "30"). The 5 groups of patients with different types of dementia did not differ in mood symptoms ($F_{4,58} = 1.93$, $P = .117$). Table 1 indicates that mood symptoms did not correlate with age, ADL, MMSE, and GDS. No significant models were found with predictors age, gender, and types of dementia (model 1, $R^2 = .15$; $\Delta F_{6,56} = 1.6$, $P = .162$) and when adjusted for apathy (model 2, $\Delta R^2 = .03$; $\Delta F_{1,55} = 2.2$, $P = .145$) and when adjusted for dementia severity (model 3). ADL score ($\Delta R^2 = .000$; $\Delta F_{1,54} = 0.02$; $\beta = .02$, $t = 0.14$, $P = .889$), the GDS stadium ($\Delta R^2 = .002$; $\Delta F_{1,54} = 0.15$; $\beta = .08$, $t = 0.39$, $P = .696$), and the MMSE score ($\Delta R^2 = .013$; $\Delta F_{1,54} = 0.01$; $\beta = -.17$, $t = 0.87$, $P = .386$) did not associate with mood symptoms when controlled for confounding variables.

Apathy and Depressive Symptoms

The correlation between apathy and mood symptoms was weak and not significant ($r_s = .16$, n = 63, $P = .217$). A regression model with apathy as predictor of mood symptoms was not significant ($\beta = .20$, $t = 1.48$, $P = .145$) and the same was true for mood symptoms as predictor of apathy ($\beta = .19$, $t = 1.48$, $P = .145$) when controlled for age, gender, and types of dementia (model 2). For exploratory purposes, we also conducted correlation analysis for 2 additional variables representing the "motivational" and "eating and sleeping" MADRS dimensions. Motivational symptoms, in contrast to mood symptoms and "eating and sleeping," did correlate with apathy ($r_s = .70$, n = 63, $P < .001$) and showed the same pattern of correlations found for apathy, with regard to ADL ($r_s = .54$, n = 63, $P < .001$), MMSE ($r_s = -.48$, n = 59, $P < .001$), and GDS ($r_s = .67$, n = 63, $P < .001$).

Discussion

The first aim of this study was to investigate whether apathy is related to DMS in EOD. A relationship between apathy and DMS was not demonstrated in our sample. A regression analysis adjusted for age, gender, and the type of dementia did not reveal any significant model in which apathy and mood symptoms were related to each other. In contrast to mood symptoms, a correlation between apathy and the MADRS total score including both motivational and mood symptoms was found in a previous research.[32] The additional analysis in our study showed that motivational symptoms did correlate strongly and significantly with apathy suggesting an overlap in symptoms (see also Ref 14). Motivational symptoms correlated significantly with dementia severity measures. That implies that a distinction between motivational and mood depressive symptoms may be important when assessing depression in dementia.

The second aim of our study was to investigate whether apathy and mood symptoms are related to dementia severity in EOD. In line with previous research on LOD, mostly performed in patients with AD, we found positive relations between apathy on one hand and cognitive impairment, functional disability, and overall dementia severity on the other. Depressive mood symptoms were, by contrast, not associated with the measures of the dementia severity in our study. This may suggest that mood symptoms may be unrelated to the organic alterations in (EOD) dementia and represent a subjective well-being of patients.[22] Regression analyses confirmed the main findings: apathy was positively associated with the measures of dementia severity after controlling for age, gender, the type of dementia, and mood symptoms. Mood symptoms were not associated with the measures of dementia severity after controlling for age, gender, the type of dementia, and apathy.

Apathy

Men had higher apathy scores than women in our study. A review of the literature showed that apathy may be equally common in men and women but there were also some inconsistent gender differences.[1,14] Older age in our study was associated with more prevalent and severe apathy and this is in line with other studies in patients with LOD.[15,17] There

were no differences in apathy scores between various types of dementia in our study. However, our sample may be too limited to find this relationship. Other research showed some differences in apathy scores between patients with various types of dementia. When compared with AD, higher apathy scores have been found by Levy et al[21] for patients with progressive supranuclear palsy and frontotemporal dementia, and lower scores have been found in Parkinson disease.

Mood Symptoms

Mood symptoms were not influenced by gender or age. Using a variance analysis, we did not find different scores on mood symptoms in patients with diverse types of dementia. Previous literature on depression in LOD points to some higher prevalence of depression in vascular dementia than in AD[28]; however, this dementia type dependency of depression is not always consistent.[4] It is interesting that we did not find a gender difference on mood symptoms, although women may have a higher score on dysphoric symptoms than men in LOD.[14] Mood symptoms or depression may be more prevalent in women according to geriatric literature,[28] but some authors[1] report no gender difference in dementia. More research is needed to investigate gender differences in depression in EOD and mood symptoms in particular.

Motivational Symptoms

Considering that the additional analysis showed a correlation between motivational symptoms on one hand and dementia severity measures and apathy on the other hand, the "depressive nature" of motivational symptoms in patients with dementia may be questioned. Our previous analyses with the same sample revealed that the items "concentration" and "inability to feel" were scored higher in depressed patients with EOD than in nondepressed patients with EOD.[32] However, the 2 groups of patients did not differ on the third motivational item "lassitude" that may imply that this item may be characteristic for dementia and not for depression. More research is however needed on this matter.

There are several aspects of this study that should be considered when interpreting the results. First, the generalizability of our study is limited because our sample consists of patients with EOD from 2 Dutch NHs only. Second, we did not limit our sample to 1 dementia type as is usually (but not always) done in the most LOD studies on apathy and depression. Restricting the sample to patients with AD only would ignore the diversity in patients with EOD, which is an important characteristic in EOD clinical long-term care. Considering research in mixed LOD samples (eg, Levy et al[21]), the association between apathy and depressive symptoms (with mood symptoms and motivational symptoms as separate categories) on one hand and dementia severity measures on the other may have the similar patterns in more types of dementia besides the widely examined AD. The type of dementia has been taken into account in our analysis and we did not find that it significantly affected the results. However, because of a pilot character of our study, more research is welcome in larger groups of patients with EOD accounting for different possible confounders, such as type of dementia, sociodemographic factors, and medication.

A third aspect to be considered concerns the severity of the disease. Patients with less severe dementia (GDS stages 1 through 3) were not present in our study. A total of 15 of our patients (24%) could not give any correct answer on the MMSE. This indicates that it was a right choice to use other instruments based on interviews with caregivers. However, it may be questionable whether caregivers interpret depressive symptoms of patients with dementia correctly. Caregivers may have some problems with interpreting pessimistic and suicidal thoughts in patients with severe dementia[32] and that may explain the low scores on DMS in our sample. However, Snow et al[40] found that informants and clinicians overreported the severity of total depressive symptoms in both depressive demented NH patients and depressive nondemented patients when compared to patient-rated scores. Chemerinski et al[41] also reported that caregivers overreported the severity of total depressive symptoms in patients with mild dementia, but patients with dementia did not differ from caregivers in indicating depressive mood state. The latter may be relevant to the current study, where mood symptoms were analyzed separately from other depressive symptoms. It is, however, not clear whether the findings of Chemerinski et al may also relate to more severely impaired patients in NHs.

The last aspect to be considered when interpreting the results of our study concerns using the MMSE. The use of MMSE for measuring cognitive problems accompanying frontal brain lesions has been questioned.[14] Apathy in dementia is associated with frontal deteriorations[42] and apathy may differ from depressive symptoms on the affected cognitive

domains.[43] It is important to consider this in future research when choosing a proper instrument for conducting a comparison between apathy and depressive symptoms.

Conclusion

The results of our study with patients with EOD showed that higher scores on apathy were associated with more cognitive impairments, more functional dysfunctions, and a greater overall dementia severity. By contrast, mood symptoms were not associated with the dementia severity measures. This is in line with previous studies in patients with LOD. Our study showed that it may be important to distinguish mood symptoms from motivational symptoms when assessing depression in patients with dementia. More research on apathy and depressive symptoms with larger samples of patients with EOD having various types of dementia is highly recommended. Both depression[1,10] and apathy[17,19] can take a chronic course and it is important to distinguish between these disturbances because they require different clinical approaches.

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