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Prevalence of depressive disorders and change over time in late-stage ALS

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Abstract

Objective—To determine the prevalence of depressive disorders and symptoms in patients with late-stage ALS, to identify possible risk and protective factors associated with depression, and to determine whether depression increases as death approaches.

Methods—Semistructured interviews were conducted monthly with hospice-eligible patients with ALS and caregivers until the study endpoints of death or tracheostomy. Standardized measures were administered to assess depressive disorders and symptoms, hopelessness, spiritual beliefs, attitudes toward hastened death, quality of life, and related constructs.

Results—Sixty-three percent of eligible patients were enrolled. Of the 80 participants, 17 were seen only once; the number of monthly assessments for the others ranged from 2 to 18. For the 53 patients who died, median interval between last assessment and death was 30 days. At study baseline, 81% had no depressive disorder, 10% had minor depression, and 9% had symptoms consistent with major depression. Diagnoses of depression were made on 16% of 369 monthly assessments. Fifty-seven percent of patients never had a depression diagnosis at any visit, and 8% were depressed at all visits. There was no trend toward increasing depression as death approached. Presumed protective factors including spiritual beliefs, spouse as care partner, financial situation, depression in caregiver, and hospice participation did not distinguish between those who were depressed and those who were not.

Conclusions—Results of multiple measures of depression and distress converged to indicate that major depression in people with late-stage ALS is rare, although transient depressive symptoms may occur, and depression does not generally increase as death approaches.

To many people, professional and lay, it seems self-evident that depression is a “normal” response to the diagnosis of progressive and lethal disease, as AIDS was in the 1980s and ALS is today. The corollary assumption is that depressive symptoms increase as physical disability worsens and death approaches. However, there is little evidence for seriously medically ill patients in general and ALS patients in particular. Published findings are inconsistent.^{1,2} It is not known whether depressive symptoms worsen or diminish as death approaches. Accurate identification of depressive disorders can lead to effective therapeutic interventions to improve the quality of life of both the patient and the caregiver, while at the same time reducing prescription of antidepressant medication based solely on the assumption that it is only natural for ALS patients to be depressed as their physical symptoms worsen.

Five years ago, we reported prevalence rates of depression in ambulatory ALS patients and noted the paucity and inconsistency of evidence.³ This is still true. To our knowledge, only two studies have used standardized methods to generate psychiatric diagnoses. In one investigation,⁴ clinical depression was assessed using the Diagnostic Interview Schedule; 11%

of 100 ALS patients were found to have current major depression. We³ evaluated 56 ambulatory patients with ALS using the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (4th ed.; DSM-IV) to generate psychiatric diagnoses. Eighty-eight percent of the patients had no diagnosis, 2% major depression, and 10% minor depression. After an average of 5.5 months, 20 patients were reassessed. Despite progressive decline in physical function, depressive symptoms did not increase.

Among cross-sectional studies using self-report symptom measures, substantially higher rates of depressive symptoms in ALS have been reported;^{5–7} rates of “moderate depression” or “significantly elevated rates of depression” have ranged from 22%⁸ to 75%⁹ in advanced ALS. Other studies have found lower prevalence of depression in patients with ALS.^{10–12} Serial studies also gave mixed findings.^{13,14}

Overall, evidence for widespread depression among ALS patients is limited; available studies are inconsistent with regard to sample composition, methods, measures, and findings. Accordingly, this study was designed to 1) determine the prevalence of syndromal depressive disorders (meeting DSM-IV criteria) in ALS patients expected to live <6 months, 2) identify possible risk and protective factors associated with depression or more transient distress, and 3) determine whether depressive disorders and depressive symptoms (that are not severe enough to meet DSM-IV criteria) increase or diminish as death approaches.

Methods

Sample

Although our intent was to recruit potential participants from multiple sites, 94% were enrolled in the Eleanor and Lou Gehrig MDA/ALS Research Center at Columbia University (New York). The clinic coordinator identified potential participants whose forced vital capacity was <50%, a value related to risk of hospice admission and death or need for mechanical ventilation within 6 months.¹⁵ Eligible patients were nondemented, spoke English, had a nonpaid caregiver who agreed to participate, were not using mechanical ventilation at baseline, could communicate at least “yes” and “no,” and lived within a 3-hour drive from our medical center. The study was initiated in January 2000 and terminated in June 2004.

Measures

Patient Health Questionnaire—Because many patients with late-stage ALS can no longer speak, interactive queries and follow-up probes needed for the Structured Clinical Interview for DSM-IV, the gold standard diagnostic evaluation in psychiatry, are often limited or not feasible. We therefore used the Patient Health Questionnaire (PHQ),¹⁶ a questionnaire developed for use with medically ill patients; it assesses the nine DSM-IV criteria for major and minor depressive disorder. Even patients who communicate only with eye movements are able to respond. Each item is scored as follows: 0 = did not occur at all, 1 = several days, 2 = more than half the days, 3 = nearly every day (in last 2 weeks). The PHQ generates a numerical score (the sum of item scores) and a diagnostic impression based on number of items endorsed.

For a diagnosis consistent with major depression, at least five items, including depressed mood or loss of interest, must be endorsed as occurring more than half the days or nearly every day. For minor depression, three or four items must be endorsed, again including depressed mood or loss of interest. We departed from the standard scoring on three items that were sometimes directly caused by ALS: sleep problems, poor appetite, and psychomotor retardation. When inappropriate, these were not scored. Instead, we prorated the remaining items to generate a total score. The resulting “diagnoses” are not true diagnoses because other psychiatric conditions that might modify them (e.g., mania) were not assessed, and detailed probes could

not be performed. However, this method is suitable for patients with extremely restricted or absent verbal and writing capacities, and we consider it the best available strategy for appraising depression in the context of late-stage ALS.

Beck Depression Inventory–Revised—The Beck Depression Inventory–Revised¹⁷ (BDI-II) is self-report scale that assesses severity of depressive symptoms, if present. Total scores can range from 0 to 63. Scores under 10 signify absence of depression, 10 to 16 mild symptoms, 17 to 29 moderate symptoms, and 30+ severe symptoms.

Mini-Mental State Examination—The Mini-Mental State Examination¹⁸ (MMSE), a widely used brief, standardized assessment of mental status, was administered at baseline. Subsequently, a shorter five-item version was used to assess cognitive status if indicated.

Memorial Delirium Assessment Scale—Interviewers were instructed to use the Memorial Delirium Assessment Scale¹⁹ to rate delirium when they noted symptoms or a marked change in the patient's mental status.

Beck Hopelessness Scale—We used a 10-item short form of the Beck Hopelessness Scale²⁰ (BHS) to assess outlook about the future, for example, "I look forward to the future with hope and enthusiasm." It is usually used as a measure of psychopathology, but in the context of ALS, it may serve rather to assess realism vs denial.

Holland Systems of Beliefs Inventory—The Holland Systems of Beliefs Inventory²¹ is a 15-item self-report trait measure with a 4-point response format, with higher scores indicating greater endorsement of the sustaining role of religion and spirituality. A sample item is, "Prayer or meditation has helped me cope during times of serious illness."

Schedule of Attitudes Toward Hastened Death—The Schedule of Attitudes Toward Hastened Death²² (SAHD) is a 20-item true/false scale, including items designed to assess the wish to live, for example, "Because my illness cannot be cured, I would prefer to die sooner rather than later." The total score is the sum of items, reversed as needed, from 0 to 20.

Quality-of-Life Enjoyment and Satisfaction Questionnaire—The Quality-of-Life Enjoyment and Satisfaction Questionnaire²³ (QOL) is a 15-item short form inquiring about satisfaction with various domains of daily experience. Scores are summed to produce a total score. We also examined two items separately: overall well-being and life satisfaction.

Bradburn Affect Balance Scale—The Bradburn Affect Balance Scale²⁴ is a brief 15-item scale yielding scores on two dimensions: positive affect and negative affect. The total score is the sum of item scores on each dimension.

ALS Functional Rating Scale—In the ALS Functional Rating Scale–Revised²⁵ (ALSFRRS-R), the 12 items assess disease severity in the domains of fine motor, gross motor, bulbar, and respiratory function. Lower scores signify greater disability.

Visual Analog Scales—On the Visual Analog Scales, we included 13 items covering major domains from the foregoing scales for use when patients were no longer able to respond to the more lengthy scales. Each item was read, and the respondent was asked to rate degree of agreement on a 10-point scale ranging from "absent or not at all" to "always or nearly always." Both positive and negative states were queried.

Procedures

After the clinic coordinator identified potential participants, she called to describe the study and obtain preconsent for the research team to make contact. The principal investigator then called for further explanation and gave the patient's name to interviewers. Interviews were scheduled at the patient's convenience and almost always in his or her home. Monthly interviews were conducted until patients met a study endpoint of tracheostomy or death.

Statistical analysis

Categorical data were analyzed using χ^2 , and t tests were used for comparison of continuous variables. Pearson correlations were used to analyze relationships between measures of distress and resilience. Because many correlations were performed, only those significant at $p = 0.01$ are noted (see table 2). In the analyses of protective and predisposing factors for depression at study baseline, Bonferroni corrections were planned if preliminary results indicated significance at the $p = 0.05$ level, uncorrected. All tests were two tailed. Except as noted, $p = 0.05$.

Results

One hundred forty-four patients were identified as potentially eligible. Forty-seven refused to participate, and 17 died before the first interview. Table 1 compares study participants and "refusers." We found no differences between groups on any measure, including rate on hospice initially or cumulatively, or those eventually choosing tracheostomy. Eighty patients and 77 caregivers were interviewed at least once.

Of the 80 patients, 19 completed only the baseline assessment, including 8 who died before their second interview. Thirty-five patients were seen on ≥ 3 occasions, and five patients were assessed ≥ 15 times. During the period of observation, 53 patients died, 11 had an elective tracheostomy, 6 dropped out, and 10 were alive when the study ended.

Age ranged from 27 to 85, 20% were under age 50, and one-third were over 70. Eighty-six percent were white; the others were black, Hispanic, or Asian. Only 8% had less than high school education, and 23% had a graduate degree. Catholicism was the most common religion.

At study entry, 50% had significantly impaired or absent speech; 45% had excessive saliva, including 15% with constant drooling; 33% used enteral feeding; 40% were unable to write; and half were totally dependent for self-care. Whereas only three patients at study entry required 24-h/day use of noninvasive positive pressure ventilation, 53% required at least intermittent use. Mean baseline ALSFRS-R score was 23.3 (SD = 7.8, range = 7 to 41). At the last study visit, of those seen more than once ($n = 61$), mean ALSFRS score was 17.1 (SD = 6.7), and 69% were totally dependent for self-care.

At baseline, nearly two-thirds lived with spouses, and three-fourths received help from a paid home attendant (mean of 40 h/week, range = 7 to 168 h/week, median 20 hours). For 60% of patients, the spouse was the identified caregiver study participant.

Question 1: Prevalence of depression at study baseline

Data were available for 78 of the 80 patients seen at study baseline. Based on the self-rated PHQ, 81% ($n = 63$) had no depression diagnosis at baseline, 10% ($n = 8$) had minor depression, and 9% ($n = 7$) had symptoms consistent with major depression.

Numerical scores on the PHQ represent severity of depressive symptoms, if present. At study baseline, 66% ($n = 50$) had PHQ scores under 10 (normal to mild symptoms), 18% ($n = 14$) in

the 10 to 14.9 range (moderate), 14% ($n = 11$) in the 15 to 19.9 range (moderately severe), and 1 patient had a score of 20+ (severe depressive symptoms). PHQ numerical scores suggest slightly higher rates of depression than the diagnostic classification but have less specificity because the essential criteria of depressed mood or loss of interest are not necessarily present.

On the 21-item self-rated BDI, a measure of severity of depressive symptoms, we had baseline data for 66 patients. Mean score was 13 ($SD = 7.7$, range = 1 to 32). Thirty-eight percent (25/66) of patients had scores in the “not depressed” range. Another 38% had mild symptoms, 18% ($n = 12$) had moderate symptoms, and 6% ($n = 4$) had severe symptoms; scores of the latter two groups together (24%) are consistent with the presence of a depressive disorder. This prevalence is very close to the 23% identified on the PHQ as having minor or major depression. For patients whose PHQ scores were in the normal range, the mean BDI score was 8.8 ($SD = 5.4$). In contrast, for patients whose PHQ scores were 15 to 20, mean BDI score was 20.7 ($SD = 7.4$).

Sixty patients completed the BHS at study baseline. The BHS queries concern expectations for the future. Mean score was 3.6 ($SD = 2.8$) which, when doubled (because we only used half the items), falls in the “moderately hopeless” range. Sixty-five percent ($n = 39/60$) had scores in the absent to mild range; 13% in the “moderately hopeless” range, and 22% in the “severe” range of hopelessness; the latter respondents did not see much of a future and expected things to get worse rather than better. Given their diagnosis and prognosis, this response may not signify pathology, however.

The SAHD was administered to 48 patients. The mean score of 4.9 ($SD = 4.0$) is similar to that found in a sample of 47 AIDS patients admitted to a care facility for the terminally ill.²²

Correlations between measures of distress and resiliency at baseline are shown in Table 2. The upper panel of correlations (under Distress) suggests reasonable construct validity for the measures. Virtually all the different indicators of distress and well-being are correlated at high levels ($r > 0.40$) and in expected directions.

More severe depressive symptoms (BDI and PHQ), greater hopelessness (BHS), and the desire to hasten death were significantly correlated with higher scores on measures of suffering, anger, perceived caregiver burden, weariness, and negative affect. The distress measures were inversely correlated with resiliency indicators. By contrast, pain, importance of religion, and spiritual beliefs were unrelated to depressive symptoms or level of hope. ALS severity (ALSFRS-R) was not significantly correlated with any indicator of distress or resiliency.

Question 2: Role of protective and predisposing factors at study baseline

We next examined personal, situational, and attitudinal factors associated with the presence or absence of depression.

History of depression and depression treatment—Thirty-eight percent (31/79) of patients reported treatment (not otherwise specified) for depression at some time in their lives. Treatment was initiated before the onset of ALS for 16 patients (20%) and after diagnosis for the remaining 15. During the study, 14 patients (70% of those treated) received antidepressant medication intended to treat depression, and 6 saw a counselor or therapist. Fourteen of them were no longer clinically depressed ($PHQ < 10$), whereas 6 patients continued to be symptomatic, including the patient with the highest PHQ score (over 20).

Spiritual beliefs and religious faith—Religion and spirituality are often considered to play a protective role for people who are facing difficult situations. The Holland Systems of Beliefs Inventory was administered to 53 patients. Eleven patients (20%) obtained the highest

possible score. As shown in table 2, the total score was not significantly correlated with self-reported depression (BDI) or with hopelessness (BHS). Scores on the Religious Belief Sub-scale showed an inverse relationship with attitudes toward hastened death ($r = -0.23, p = 0.07$), such that stronger spiritual beliefs were associated with less reported interest in hastening death.

Relationship to caregiver—We found no difference between the presence or absence of depression among those whose caregiver was a spouse ($n = 43$) vs other person ($n = 32$). Five patients had no designated caregiver at study entry ($\chi^2 = 1.08, 1 \text{ df}, p = 0.30$).

Income and insurance—Better financial and insurance resources may also serve as a protective factor. To investigate this possibility, we dichotomized the sample at the median household income of \$60,000/year. The prevalence of depression did not differ between the income groups ($\chi^2 = 0.01, 1 \text{ df}, p = 0.95$). We also dichotomized the sample according to whether or not families had out-of-pocket caregiving expenses. Patients in the two groups did not differ in the prevalence of depression ($\chi^2 = 0.01, 1 \text{ df}, p = 0.21$). Finally, we compared the presence or absence of depression for those who had paid help <20 h/week vs those who had more hours; again, there was no difference in depression rate ($\chi^2 = 1.28, 1 \text{ df}, p = 0.26$).

Caregiver mood—An association between depression in caregivers and depression in patients has been elsewhere reported. However, no association was found within patient-caregiver dyads. In 45 dyads, neither was depressed; in four, both were depressed. In the other 26 dyads, one but not the other had a baseline diagnosis of minor or major depression ($\chi^2 = 0.01, 1 \text{ df}, p = 0.92$).

Hospice—Finally, we expected that hospice would play a protective role and that patients on hospice would be less likely to be depressed. At baseline, 35% of study participants were on hospice. We compared PHQ diagnoses at the baseline visit for those on hospice vs those not on hospice. Contrary to our expectations, those on hospice were more likely to have a depressive diagnosis at study baseline ($\chi^2 = 7.84, 1 \text{ df}, p < 0.005$).

Question 3: Longitudinal pattern of mood status

Of the 80 patients seen at least once, 53 died during the period of observation, and 11 chose long-term mechanical ventilation. We examined patterns of distress over time to assess the relationship between distress and progression of disease, that is, time to death or elective tracheostomy.

Mood status over time—The 61 patients seen more than once had a total of 369 assessments, ranging from 2 to 18 for each subject. Diagnoses of depression were made on 16% of these occasions. Fifty-seven percent (35/61) of patients never had a depression diagnosis at any visit, and 8% ($n = 5$) were depressed in all visits. Table 3 shows no overall trend toward increasing depression over time.

Among medically ill patients, depressive symptoms or diagnostic impression at a single monthly visit is not necessarily clinically significant if the distress does not persist. Only 15% ($n = 9$) of the 61 patients seen at least twice were depressed at two or more consecutive visits. In contrast, 28% ($n = 17$) experienced intermittent symptoms that were not sustained and that are perhaps better characterized as distress rather than syndromal depression.

Mood status in last 3 months before death—For those who died, median interval between last assessment and death was 30 days, and the mean was 40 days ($SD = 38$ days). Seventeen patients were evaluated only once before their deaths, of whom 35% ($n = 6$) were depressed, including 2 with major and 4 with minor depression. Among the 36 seen more than

once before death, 31% (n = 11) had symptoms of depression defined by the PHQ at the last visit before death, including 19% (n = 7) who had been depressed the preceding visit as well. An additional 19% (n = 7) were depressed at the second or third to last assessment but were not depressed at the final assessment (counting back from death). Finally, 50% (n = 18) were never depressed in the three visits before death.

Discussion

In this longitudinal study of 80 patients with late-stage ALS, 9% had symptoms consistent with major depression, and another 10% had symptoms consistent with minor depression. The prevalence of major depression is comparable with that reported previously by other investigators⁴ (but minor depression was not assessed in that study) and somewhat higher than the rate reported by our group for patients with earlier-stage ALS.³ The prevalence of depression in patients with ALS is clearly higher than that reported for the total population, which for a 12-month period is estimated as 4 to 5%,²⁶ but lower than that reported in many groups of medically ill patients.^{2,27,28} This is the more surprising given the relatively high rate of depression treatment (20%) in this sample before the diagnosis of ALS. We conclude that patients with late-stage ALS are more likely to be depressed than medically healthy adults but that depression affects only a small subset of patients with an anticipated life expectancy of ≤ 6 months.

To examine which patients are most at risk for depression, we identified factors that might reduce or increase risk, identified as such in other studies. However, spiritual beliefs, spouse as care partner, financial status, depression in caregiver, and hospice participation did not distinguish patients who experienced depression and those who did not.

Longitudinal assessments failed to detect increasing rates of depression, either in terms of patterns over time for all patients or in the 3 months prior to death for those who died during the study. Moreover, we noted great variability in whether patients met criteria for depression over monthly assessments (see table 3). Thus, the absence of clear associations between protective factors and risk of depression may be related to the transient state of depressive symptoms in people approaching death.

It is conceivable but unlikely that depression was underreported because of cognitive impairment, which has been identified in some ALS patients on the basis of neuropsychological tests such as verbal fluency, consistent with a diagnosis of frontotemporal lobar dementia.^{29, 30} In our study, all but two subjects scored in the normal range of the MMSE at study baseline and those two died within the month. On subsequent visits, only five got scores $>10\%$ below the maximum score, and they too died within the month. Although we recognize the difficulty of comprehensive neuropsychological assessment in our patients with limited or absent speech and movement, there are no indications of widespread dementia in our sample, nor would its presence necessarily influence elicitation of depression, if present.

These findings should be interpreted in light of several study limitations. Perhaps the major issue concerns sample bias. Nearly all participants were patients at a single major ALS center. Such centers are likely to have a more positive approach about ALS and to offer more support and practical assistance than other sites of care, which itself may be beneficial. Patients with nonpaid caregivers may be less likely to be depressed than those with none. More depressed patients may be less willing to participate in a project described as “studying how people cope with serious illness.” In view of these considerations, our findings may represent a “best case” scenario of psychological adjustment to ALS.

Another limitation is that nearly all patients were white, middle class, and educated. Also, one-third of those approached for study participation declined. These “refusers” did not differ in

demographic features or characteristics of care that we were able to assess (see table 1). It is also possible that the monthly study visits themselves may have been perceived as supportive, promoting well-being and interest in survival, as seen in the 14% rate of tracheostomy. However, this rate is roughly equivalent to the 12% observed in the “refuser” group of patients in the same clinic. Finally, our psychiatric evaluations were necessarily restricted, given the substantial impairments in ability to communicate in this late-stage patient group.

By contrast, a number of the features of this research suggest confidence in these findings. We used multiple measures of depression whose findings converged. The sample was relatively large, interviews were conducted monthly, and voluntary attrition was low. We conclude that major depression in people with late-stage ALS is rare (<10%), although transient depressive symptoms may occur, and that risk of depression does not necessarily increase with the approach of death. The overall pictures derived from multiple measures of various aspects of depression and distress converge to provide an integrated picture of resiliency rather than despair.

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Table 1
Features of study participants and patients declining participation

Feature	Participants, n = 80	Patients declining participation, n = 47
Male, %	56	46
Ethnicity, % white	86	82
Live with caregiver, %	81	86
Spouse caregiver, %	60	89
Patient in nursing home at baseline, %	4	3
On hospice at baseline, no. (%)	28/80(35)	19/47(40)
On hospice over follow-up, no. (%)	47/80(59)	27/47(57)
Tracheostomy over follow-up, %	14	12

No comparison reached significance at 0.05 or better.

Table 2

Correlates of distress and resilience

	BDI	PHQ	BHS	SAHD	Well-being	Life satisfaction
Distress						
BDI	—	0.58*	0.65*	0.45*	−0.54*	−0.47*
BHS	0.65*	0.48*	—	0.67*	−0.66*	−0.44*
SAHD	0.45*	0.48*	0.67*	—	−0.44*	−0.32*
PHQ	0.58*	—	0.48*	0.48*	−0.30	−0.25
Visual Analog Scale						
Pain	−0.14	−0.15	−0.17	0.14	0.17	0.08
Suffering	0.44*	0.24	0.35*	0.42*	−0.27	−0.26
Anger	0.43*	0.20	0.40*	0.32	−0.22	−0.09
Caregiver burden	0.35*	0.16	0.24*	0.35	−0.31	−0.12
Weariness	0.40*	0.52*	0.41*	0.58*	−0.27	−0.18
Bradburn negative items	0.75*	0.49*	0.55*	0.33*	−0.63*	−0.66*
Resiliency						
Holland beliefs	−0.12	−0.03	−0.14	−0.23	−0.06	−0.05
Endicott QOL	−0.71*	−0.45*	−0.54*	−0.52*	0.78*	0.69*
Visual Analog Scale						
Perceived control over ALS	−0.33*	−0.24	−0.31*	−0.23	0.35*	0.27*
Optimism	−0.58*	−0.42*	−0.52*	−0.42*	0.45*	0.34*
Desire to live	−0.25	−0.48*	−0.46*	−0.47*	0.21	0.36*
Energy	−0.38*	−0.38*	−0.41*	−0.28*	0.37*	0.38*
Importance of religion	−0.01	0.16	−0.06	−0.08	0.04	0.21
Spiritual beliefs	−0.03	0.04	−0.13	−0.17	0.14	0.37*
Bradburn positive items	−0.56*	−0.41*	−0.47*	−0.26	0.31	0.51*
Disease severity						
ALSFRS-R	−0.11	−0.06	−0.05	−0.02	0.08	0.13

* $p \leq 0.01$.

BDI = Beck Depression Inventory; PHQ = Patient Health Questionnaire; BHS = Beck Hopelessness Scale; SAHD = Schedule of Attitudes Toward Hastened Death; QOL = Quality-of-Life Enjoyment and Satisfaction Questionnaire; ALSFRS-R = ALS Functional Rating Scale–Revised.

Table 3

Patterns of depression diagnoses over time

Pattern	n	%
Consistently absent	35	57
Increasing depression over time	6	10
Decreasing depression over time	5	8
Consistently present	5	8
Inconsistent patterns		
Absent–present–absent	9	15
Present–absent–present	1	2

Total number of assessments = 369 in n = 61 patients.