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The Prognostic Significance of Subsyndromal Symptoms Emerging after Remission of Late-Life Depression

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Abstract

Background—Attainment of remission is viewed as the optimal outcome of acute antidepressant treatment. However, some patients experience subsyndromal symptoms after they achieve remission. This study examines the prognostic significance of subsyndromal symptoms occurring during the first six months after remission of late-life depression.

Methods—Older (60–89 years) inpatients and outpatients, with unipolar major depression, were followed until remission (asymptomatic or almost asymptomatic for 3 consecutive weeks). Two hundred and forty-two achieved remission after uncontrolled antidepressant treatment. This analysis focused on remitted patients who had follow-up data over a 2.5 year period (N=185).

Results—Approximately 18% of patients relapsed. Of the remainder (n=152), 42.8% had subsyndromal depressive symptoms during the 6 months following remission. Cox's Proportional Survival Analysis demonstrated that longer duration of subsyndromal symptoms (number of weeks with LIFE-Psychiatric Status Rating Scale (PSR) score of 3 or 4) in the first 6 months after remission was significantly associated with shorter time to recurrence and higher recurrence rate (Hazard Ratio:1.16; 95% CI= 1.08–1.24). Based on our analysis, patients with 0, 4, 8, and 12 weeks of subsyndromal symptoms in the first six months after remission have estimated recurrence rates of 28%, 45%, 66%, or 86%, respectively, during the ensuing two years.

Conclusions—These findings highlight the clinical importance of subsyndromal symptoms occurring after remission in late-life depression. They also argue that studies of geriatric depression may complement the definition of remission with information on subsyndromal symptoms occurring after the initial asymptomatic period.

INTRODUCTION

Depression is a relapsing and recurring illness. Beyond suffering and compromised quality of life (Charney et al. 2003; Kessler et al. 2006), prolonged depression in late life increases medical burden and mortality both in medically ill and medically healthy persons (Bruce et al. 1994; Steffens et al. 1994). Disability conferred by late-life depression increases dependency needs, care costs, family disruption and often leads to institutionalization (Alexopolous et al. 2002).

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Attainment of remission is viewed as the optimal outcome of acute antidepressant treatment (Anderson et al. 2008; Nierenberg & Wright 1999; Thase & Ninan 2002) in both young and older adults. Remission, defined as an almost asymptomatic state, is considered a stable clinical state with a low risk for relapse and recurrence (Fava et al. 2007; Frank et al. 1991; Rush et al. 2006). Patients who improve, but fail to achieve remission, have significant functional impairment, compromised quality of life, and high utilization of health care services (Miller et al. 1998; Simon et al. 2006). While remission is desirable, remission rates in mixed-age samples of patients with major depression treated with first-line antidepressant treatment are 30–35% and decline significantly with successive treatment failures (Nelson 2006). Remission may even be more difficult to achieve and sustain in depressed older patients (Mueller et al. 2004; Reynolds et al. 1996).

Several definitions of remission have been proposed. Most definitions specify two conditions. Attainment of an almost asymptomatic state over a predetermined period of time, usually 1–2 weeks (Frank et al. 1991; Rush et al. 2006). Inherent in these definitions is the assumption that once remission is achieved, patients would continue to have favorable long-term outcomes (Rush et al. 2006; Paykel et al. 1995; Thase & Simons 1992). Empirical studies support this point of view in both young adults and late-life depression since depressed patients who achieve remission have a lower relapse rate than those who improve but remain symptomatic (Rush et al. 2006; Ramana et al. 1995, Van Londen et al. 1998). However, patients who remain asymptomatic for the short period of time required to satisfy the definition of remission may still experience subsyndromal symptoms after remission.

Achievement of remission is often followed by development of subsyndromal depressive symptoms affecting up to 50% of patients (Nelson 2006; Rush 2007). In some cases, subsyndromal depressive symptoms are self-limited, but in others they may evolve into a recurrence of depression. This study focuses on the prognostic significance of subsyndromal depressive symptoms during the six months following remission of late-life depression, the period during which if a full blown depressive episode occurs it would be classified as a relapse (Nierenberg & Wright 1999; Riso et al. 1997). It is hypothesized that long duration of subsyndromal symptoms during the six months following attainment of remission is a predictor of recurrence.

METHODS

Subjects

The subjects were outpatients and inpatients of a psychiatric university hospital consecutively recruited for an uncontrolled treatment study of geriatric depression. There were no subjects recruited through advertisement. Inclusion criteria were: 1) age of 60 years or older, 2) diagnosis of unipolar Major Depressive Disorder according to DSM-IV; 3) a Longitudinal Follow-up Examination (LIFE) Psychiatric Status Rating Scale (PSR) score ≥ 5 (5=Definite Criteria for MDD/Without Prominent Psychotic Symptoms or Extreme Impairment) (Keller et al. 1987); (3) the presence of an informant who has knowledge of the patient's history and had enough contact so that he or she could observe behavioral changes within 1 week; and (4) residence at a distance within 45-minute from the psychiatric university hospital. All participants received uncontrolled treatment for depression. After complete description of the study, subjects signed written informed consent approved by the Weill-Cornell Medical College Institutional Review Board.

Exclusion criteria were: 1) a history of psychiatric illness (except personality disorder) other than unipolar depressive disorder diagnosed prior to the onset of the first depressive episode; (2) severe acute medical illness, i.e. metastatic cancer, decompensated cardiac, liver or renal failure, major surgery, and stroke or myocardial infarction 6 months prior to study entry; 3)

spinocerebellar degeneration, Huntington's chorea, Parkinson's disease, or multi-infarct dementia; 4) moderate to severe dementia as evidenced by a Mini-Mental State Examination (Folstein et al. 1975) MMSE score lower than 20; and 5) severe behavioral disability defined as complete impairment in performance of activities of daily living domain of the Philadelphia Multilevel Assessment Instrument (MAI) (Lawton et al. 1982). These criteria resulted in a group of older patients with unipolar major depression but without a major medical illness, moderate or severe dementia, or severe disability.

Systematic Assessment

At baseline, diagnostic assessment was based on the SCID-R. Depression severity was assessed with the Psychiatric Status Rating Scale (PSR) of Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al. 1987). Cognitive impairment was measured with the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) and Mattis Dementia Rating Scale (DRS) (Mattis 1989). Medical burden was quantified using the total score (except the psychiatric domain) of the Cumulative Illness Rating Scale, Modified Version for Geriatrics (CIRS-G) (Miller et al. 1992). CIRS-G information was obtained from the medical history and physical examination, as well as the available laboratory test results. Disability was assessed with the Instrumental Activities of Daily Living (IADL) subscale of the Philadelphia Multilevel Assessment Instrument (MAI); the IADL subscale provides information about the participant's ability to perform nine IADLs (Lawton et al. 1982).

After the baseline evaluation, the patients and informants (when necessary) had in-person evaluations every 6 months and telephone evaluations 3 months in between each in-person session. An extra in-person evaluation was conducted when the participant first met criteria for remission and for recurrence. If the participants were unable to come to the hospital, research assistants visited them at their homes. During follow-up evaluations, depressive symptoms were assessed with the PSR. The PSR assessed the presence and severity of depressive symptoms each week during the 6 months prior to each assessment. Memory prompts and detailed questioning are used to improve the accuracy of information. When patients are unable to offer information and when discrepancies are detected, raters interview individuals who have frequent contact with the patients and/or contact the patients' own physicians to obtain additional information. Thus the PSR utilizes an information gathering process similar to that of a clinical examination. The PSR classifies the status of depression on a scale of 1 to 6. PSR score 1 refers to an "Asymptomatic Status/Returned to Usual Self" status without any residual symptoms of the MDD disorder. PSR score 2 refers to "Residual/Mild Depressive Symptoms" with presence of one or more symptoms of no more than the mild degree. PSR score 3 refers to "Subsyndromal Symptoms/Moderate Symptoms" with no more than moderate impairment in functioning. PSR score 4 refers to "Major Symptoms" with major impairment in functioning but does not meet full criteria of MDD. PSR score 5 refers to "Definite Criteria for MDD/Without Prominent Psychotic Symptoms or Extreme Impairment". Finally, PSR score=6 refers to "Definite Criteria for MDD/With Psychotic Symptoms or Extreme Impairment" (Keller et al. 1987; Judd et al. 1998). Cognitive impairment (MMSE), medical burden (CIRS-G), and disability (IADL Domain of MAI) were assessed at two time points, at baseline, when the MDD diagnosis was made and when they first met criteria for remission.

Intensity of antidepressant drug treatment (AD) was classified with the Composite Antidepressant Score – Revised (CAD) (Alexopoulos et al. 1996). CAD orders intensity of AD treatment on a scale of 0–4 with 0=no medication; 1 corresponds to treatment with daily doses of Bupropion <100 mg, Nortriptyline <30, Setraline <25 mg, Paroxetine, Fluoxetine, or Citalopram <10 mg, Venlafaxine <50 mg, or Escitalopram < 5 mg; 2 corresponds to Bupropion 100–199 mg, Nortriptyline 30–49, Setraline 25–49 mg, Paroxetine, Fluoxetine, or Citalopram 10–19 mg, Venlafaxine 50–75 mg, or Escitalopram 5–10 mg; 3 corresponds

to Bupropion 200–300 mg, Nortriptyline 50–80 mg, Sertraline 50–100 mg, Paroxetine, Fluoxetine, or Citalopram 20–30 mg, Venlafaxine 76–150 mg, or Escitalopram 10–15 mg; and 4 corresponds to Bupropion >300 mg, Nortriptyline >80 mg, Sertraline >100 mg, Paroxetine, Fluoxetine, or Citalopram >30 mg, Venlafaxine >150 mg, or Escitalopram >15 mg. The investigators had no control over treatment with antidepressants. The antidepressants were prescribed by community-based physicians responsible for the patients' clinical care.

Definitions of Remission, Duration of Subsyndromal Symptoms, and Recurrence

In this study, *remission* was defined as a PSR score of ≤ 2 for 3 consecutive weeks, without the presence of depressed mood or lack of interest or pleasure, after an episode of MDD. This definition is consistent a) with studies of late-life depression (Alexopoulos et al. 2009; Bhalla et al. 2006; Rutherford et al. 2007; Taylor et al. 2011), in which the required duration for remission has been 1–3 consecutive weeks of a specific cut-off score; and b) with the recommendations from the ACNP Task Force on Remission and Response (Fava, Ruini & Belaise 2007). *Relapse* was defined as a PSR score ≥ 5 during the first six months after remission. *The duration of subsyndromal symptoms after remission* (“Duration Subsyndromal Symptoms”) was calculated by the number of weeks of PSR scores of 3 or 4 in the first 6 months following remission in subjects who did not meet criteria for relapse. *Recurrence* was defined as a PSR score ≥ 5 occurring between 6 months to 2½ years (last research observation since baseline) after remission.

Statistical Analysis

Bivariate analyses compared subjects who had a recurrence of depression with subjects who remained well using Chi-square and Wilcoxon-Mann-Whitney tests. Then, Cox Proportional Hazards Survival Analyses were performed to explore the association of “Duration Subsyndromal Symptoms” during the risk period for relapse (in the first six months following remission) with time to recurrence. Any participant who did not have a recurrence was considered censored. To examine whether the effect of “Duration Subsyndromal Symptoms” on time to recurrence remained significant in the presence of confounding variables, we created a final Cox Proportional Hazards regression model including variables that were associated with time to recurrence (Using Cox Proportional Hazards models and $p < 0.15$). The hazard rates of each predictor were tested for proportionality with a Cox model including the variable and its interaction with $\log(\text{time to recurrence}) - 5.69$. The constant, 5.69, is the average of the logs of the survival times. For the final Cox regression model, we used backward elimination with $p = 0.05$ as the criterion for removing an explanatory variable from the model. All analyses were performed with SAS 9.1 and S-Plus 7.0.

RESULTS

A total of 317 older outpatients (N=191) and inpatients (N=126) who met DSM-IV criteria for Major Depressive Disorder entered this study. Of these, 242 achieved remission after receiving uncontrolled antidepressant treatment, 42 did not remit and 33 were lost to follow-up or had incomplete data to determine remission. There were no significant differences between those who were lost to follow-up or had incomplete data (N=33) vs. the rest (N=284) on age, entry status (inpatient vs. outpatient), and years of education. However, patients who were lost to follow-up or had incomplete data had a significantly higher percentage of males than the rest 284 patients (Males percentage: 15.45% vs 7.22%, chi-square=5.47, df=1, $p=0.019$).

Among the subjects who achieved remission (N=242), 57 were lost to follow-up or had incomplete data in the first 6 months after remission. This report focuses on the 185 subjects

who remained in remission for 6 months and had follow-up data for up to 2.5 years thereafter. The subjects who were lost to follow-up or had incomplete data were older by an average of 4.37 years than the 185 subjects with follow-up data (Mann-Whitney: $z=3.08$, $p=0.0021$). Further, a higher percentage of inpatients were lost to follow-up or had incomplete data compared to subjects with follow-up (50.88% vs. 31.35%, chi-square=7.22, $df=1$, $p=0.0072$). There were no significant differences on gender and years of education between the two groups.

Relapse and Subsyndromal Symptoms

Despite the stringent definition of remission requiring 3 weeks of an almost asymptomatic state, 17.8% (33/185) of remitted subjects experienced a relapse during the 6 months following remission. Subjects who relapsed were older and more cognitively impaired at entry than those who remained relapse-free (Table 1).

Even among participants who remained relapse free within 6 months after remission ($N=152$), a rather high number developed clinically significant depressive symptomatology. Specifically, only 57.24% (87/152) were asymptomatic or had mild residual depressive symptoms (PSR scores of 1 and 2) during the 6-month period following remission, while 42.76% (65/152) of relapse-free subjects developed subsyndromal symptoms (PSR scores of 3 or 4). In this last group ($N=65$), 47.69% (31/65) subsyndromal symptoms lasted up to 4 weeks, 38.46% (25/65) lasted 4–8 weeks, and 13.85% (9/65) lasted longer than 8 weeks.

Recurrence

Further analysis focused on the 152 depressed elderly subjects who achieved remission and remained relapse free for 6 months. Of the 152 subjects, 108 were outpatients and 44 were inpatients. Most depressed subjects had a recurrent disorder (Table 2). Their average age at onset was in midlife. On average, their index episode was of moderate severity. They had significant medical burden, mild or no cognitive impairment, and some impairment in instrumental activities of daily living.

Of the 152 subjects who remained in remission of depression past the relapse risk period (6 months), 45 had a recurrence (a PSR score ≥ 5) during the ensuing 2 years (2.5 years since remission). After taking into consideration censored participants, the estimated recurrence rate derived from the Cox Proportional Hazards model during the 2 years of follow-up was 37.6% (95% CI: 29.2% – 47.6%). Bivariate comparisons between subjects who suffered a recurrence and those who remained well showed no significant difference in any demographic or clinical variables. The only exception was that subjects who suffered a recurrence had a longer duration of subsyndromal symptoms in the six months following remission of depression than subjects who remained well throughout the follow-up period (Table 2).

The duration of subsyndromal symptoms was significantly associated with time to recurrence (Wald Chi-square=18.28, $p<0.0001$, Hazard Ratio=1.16, 95% Hazard Ratio Confidence Interval=1.08 – 1.24); the higher the number of weekly PSR scores of 3 or 4 in the first 6 months after remission, the shorter the time to recurrence. Specifically, participants with 4, 8, and 12 weeks of PSR score of 3 or 4 in the first 6 months after remission had 45%, 66%, and 86% recurrence rates respectively (Figure 1).

Further analysis examined whether the relationship of subsyndromal symptom duration to recurrence remained significant in the presence of potential confounding variables. To this end, exploratory univariate analyses were conducted using Cox Proportional Hazards Model to identify demographic and clinical variables related to time to recurrence with a p value

equal to or lower than 0.15 (Table 3). These variables were included in a multivariate Cox Proportional Hazards Model.

The final Cox predictive model of recurrence was constructed after use of backward elimination in which variables with $p > 0.05$ were removed. The resultant model consisted of “Duration Subsyndromal Symptoms” (Wald Chi-square=18.72, $p < 0.0001$, Hazard Ratio=1.17, 95% Hazard Ratio Confidence Interval=1.09 – 1.25), Intensity of AD treatment (Wald Chi-square=0.64, $p = 0.42$, Hazard Ratio=1.12, 95% Hazard Ratio Confidence Interval=0.85 – 1.48), and Intensity of AD treatment x Time (Wald Chi-square=5.78, $p = 0.016$, Hazard Ratio=1.24, 95% Hazard Ratio Confidence Interval=1.04 – 1.49).

To further assure that our continuous measure of intensity of antidepressant treatment (CAD scores ranging from 0–4) adequately captured the role of treatment, we used a categorical definition of antidepressant treatment (adequate vs. inadequate) and repeated the above analysis. According to this definition, as “adequate” was characterized treatment with CAD intensity ≥ 3 and “inadequate” was treatment with a CAD intensity ≤ 2 . In a Cox’s proportional hazard model including Adequate Antidepressant Treatment, Duration of Subsyndromal Symptoms, and the interaction of Adequate Antidepressant Treatment x Time, the results were similar to the previous final model. Specifically, “Duration of Subsyndromal Symptoms” (Wald Chi-square=18.69, $p < 0.0001$, Hazard Ratio=1.17, 95% Hazard Ratio Confidence Interval=1.09 – 1.25), Adequacy of AD treatment (Wald Chi-square=0.51, $p = 0.47$, Hazard Ratio=1.35, 95% Hazard Ratio Confidence Interval=0.60 – 3.05), and Adequacy of AD treatment x Time (Wald Chi-square=6.01, $p = 0.014$, Hazard Ratio=2.23, 95% Hazard Ratio Confidence Interval=1.17 – 4.23).

The significant interaction of adequacy of antidepressant treatment with time indicates that the relationship of treatment to recurrence was not the same over time. Specifically, during the first 4 months of follow-up, patients with adequate antidepressant treatment were 5 times less likely to recur than patients with inadequate antidepressant treatment (Wald Chi-square=7.82, $p = 0.0052$, HR=5.37, 95% Hazard Ratio Confidence Interval =1.65–17.46). However, adequacy of antidepressant treatment after the first 4 months of follow-up was not significantly associated with reduced recurrence rates (i.e. after 10 months following remission) (Wald Chi-square=1.50, $p = 0.23$, HR=0.52; 95% Hazard Ratio Confidence Interval =0.23 – 1.40).

DISCUSSION

The principal finding of this study is that subsyndromal symptoms in the first 6 months after remission are common and predict subsequent recurrence of late-life depression; the longer the duration of subsyndromal symptoms, the shorter the time to recurrence and the higher the recurrence rates. Older patients who experience subsyndromal symptoms for 0, 4, 8, and 12 weeks during the six months after remission have an estimated recurrence rate of 28%, 45%, 66% and 86% respectively during the ensuing two years. The relationship of subsyndromal symptoms to recurrence is independent of the intensity of antidepressant drug treatment during the month preceding recurrence.

To our knowledge, this is the first study to demonstrate that increased duration of subsyndromal symptoms occurring soon (six months) after remission is associated with increased risk for recurrence of late-life depression. Nonetheless, this observation is consistent with findings from controlled and uncontrolled treatment studies suggesting that subsyndromal symptoms forecast poor long-term outcomes in elderly and in younger patients (Paykel et al. 1995; Thase & Simons 1992; Ramana et al. 1995; Judd et al. 1998; Van Londen et al. 1998; Dombrovski et al. 2007; Frank & Levenson 1990; Karp et al. 2004;

Taylor et al. 1999). With one exception (Frank & Levenson 1990), studies of adults documented that subsyndromal symptoms at the point of remission or during the continuation and maintenance treatment phases were associated with high recurrence rates during the next two years (Ramana et al. 1995; Judd et al. 1998; Karp et al. 2004). In late life, subsyndromal depressive symptoms occurring prior to or during the maintenance treatment phase predicted subsequent recurrence of major depression (Dombrovski et al. 2007; Taylor et al. 1999). Finally, recent evidence suggests that treating subsyndromal depression symptoms may prevent major depression in late life (van't Veer-Tazelaar et al. 2009).

This study's findings need to be viewed in the context of this study's limitations. These include the lack of controlled treatment and the absence of a control group. While uncontrolled treatment may be a limitation, the treatment offered to the subjects of this study was of low to medium intensity (Table 1 and 2). While a control group is desirable, the lack of a randomization reduced the subject selection bias inherent in randomized treatment studies. Another limitation may be the retrospective assessment of depressive symptoms at six-month intervals and a telephone assessment in between. While direct assessment of depressive symptoms at more frequent intervals is desirable, the LIFE and PSR employed by this study are instruments validated by the NIMH Collaborative Study of Depression (Keller et al. 1987), and have been used in studies with mixed-age (Judd et al. 1998, Keller et al. 1992) and elderly depressed patients (Hinrichsen 1992). Finally, the MMSE cut-off of 20 may have allowed inclusion of individuals with cognitive impairment or early stage dementia. A wide range of cognitive impairment coexists with depression in older adults and increases with age (Arve 1999). A more stringent MMSE cut-off score would have resulted in a sample of younger cognitively intact, and relatively healthy participants and not accurately capture important clinical aspects of an older population differentiating them from younger adults.

A number of clinical characteristics have been associated with poor outcomes of late-life depression. Overall cognitive dysfunction (Story et al. 2008), impairment in some executive functions (Alexopoulos et al. 2005; Sneed et al. 2007), and psychomotor slowing (Butters et al. 2004) each has been associated with slow and/or poor response to antidepressant treatment. Similarly, medical burden has been shown to predict poor long-term outcomes of late life depression in some studies (Cui et al. 2008). Finally, disability has a reciprocal relationship with depressive symptoms and worsens the long-term prognosis of late-life depression (Alexopoulos et al. 2002). In this study, however, cognitive impairment, medical burden, and disability assessed both at entry, when the subjects were symptomatic, and at the beginning of remission (Table 3) had weak associations with recurrence of depression that did not reach statistical significance. However, cognitive impairment and medical burden were associated with relapse in the first 6 months after remission (Table 1). Consequently, the group of the recurrence analyses was enriched with patients with low cognitive impairment and medical burden since many of those with greater cognitive impairment and medical burden had already relapsed. Nevertheless, further investigation of the association of medical comorbidity and cognitive impairment with recurrence rates is warranted.

The adequacy of antidepressant drug treatment during the first four months of follow-up predicted low recurrence rates. However, later on, adequacy of drug treatment did not significantly influence recurrence rates. Since a high number of recurrences occurred during the first 4 months of follow-up, the group with longer follow-up might have been depleted from patients at high risk for recurrence. This observation may account, at least in part, for the lack of a significant relationship between treatment adequacy after the first four months of follow-up and recurrence of depression.

The findings of this study have methodological and clinical implications. On a methodological level, long-term outcome studies of geriatric depression may include information on subsyndromal states occurring soon after the attainment of remission because of their prognostic value. In this study, focusing only on remission defined as of an almost asymptomatic state over three weeks predicted an average recurrence rate of 37.6% over two years. However, the occurrence and duration of subsyndromal depressive symptoms following remission increased the prediction of recurrence. For example, a patient without any subsyndromal symptoms after remission had a 28% chance of recurrence within two years. In contrast, the probability of recurrence of a patient with subsyndromal depressive symptoms lasting 12 weeks was 86%.

On a clinical level, while remission is a desirable outcome, it should not be viewed as a permanent state and attention shall be given to subsyndromal depressive symptoms developing after remission. Vigilant follow-up should aim to identify depressive symptoms after remission of late-life depression and treatment plans should be formed aiming to shorten their duration. While suppressing subsyndromal symptoms may reduce suffering and disability, studies are needed to establish whether it reduces recurrence rates. The possibility remains that subsyndromal symptoms are an index of a “virulent” disorder whose outcomes may change little with symptom suppression.

In conclusion, this study documents that a large percentage of depressed older patients develop subsyndromal depressive symptoms after remission of major depression. The duration of subsyndromal symptoms after remission is proportionately associated with recurrence of depression in the ensuing two years. While the mechanisms relating subsyndromal symptoms to recurrence are unclear it is prudent to remain clinically vigilant during the first few months after remission of late life depression.

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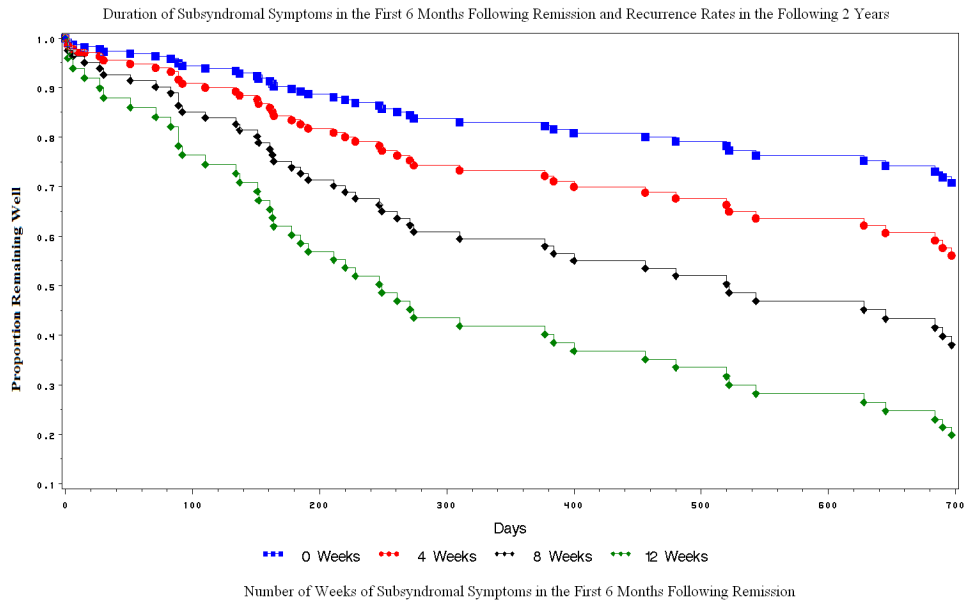


Figure 1. Duration of Subsyndromal Symptoms in the First 6 Months Following Remission and Recurrence Rates in the Ensuing 2 Years

Survival curves of time to recurrence of elderly depressed patients who experience 0, 4, 8, and 12 weeks of subsyndromal symptoms during the first 6 months following remission. The survival curves start 6 months after remission (0 days) and end 2 years later. Calculated by the Proportional Hazards Model: “Duration Subsyndromal Symptoms” associated with time to recurrence. Proportional Hazards Likelihood Ratio for the overall model: $\chi^2=13.74$, $df=1$, $p<0.0002$; for Duration Subsyndromal Symptoms: $\chi^2=18.28$, $df=1$, $p<0.0001$.

Table 1
Demographic and Clinical Characteristics on 185 Older Subjects with Major Depression Followed for 6 Months after Remission.

	Had a Relapse (N=33)				Remained Relapse-free (N=152)				Chi-square	p
	N	Perc (%)	SD	Range	N	Perc (%)	SD	Range		
Gender									0.0004	0.98
Female	21	63.64%			97	63.82%				
Entry Status at Last MDD Episode									2.29	0.13
Inpatient	14	42.42%			44	28.95%				
Outpatient	19	57.58%			108	71.05%				
									Mann-Whitney Wilcoxon	
	Mean	SD	Range	Mean	SD	Range	z	p		
Age	75.12	6.27	64-86	71.96	7	60-89	2.41	0.02		
Education (years)	13.18	3.88	5-21	14.17	3.09	7-21	-1.62	0.1		
Age at Onset	59.34	16.65	30-83	56.45	18.27	14-87	0.81	0.42		
Duration of Last Episode	53.25	42.46	3-174	66.5	74.75	3-522	-0.26	0.79		
Number MDD Episodes	2.45	1.41	1-6	2.05	1.24	1-7	1.6	0.11		
Entry (Index Episode)										
DRS Total ¹	133.74	7.11	116-144	136.47	7.23	111-144	-2.07	0.0387		
CIRS Total ²	6.23	3.13	2-3	5.51	3.24	0-19	1.08	0.28		
IADL ³	24	3.73	15-27	25.56	2.32	15-27	-1.66	0.1		
At Onset of Remission⁴										
DRS Total ¹	130.54	12.93	100-143	137.34	6.8	103-144	-1.88	0.0593		
CIRS Total ²	5.96	3.23	0-12	4.6	3.14	0-13	1.93	0.06		
IADL ³	25.2	3.29	17-27	25.77	2.28	15-27	-0.12	0.91		
Antidepressant (AD) Drug Treatment										
Intensity ⁵	2.42	1.47	0-4	2.17	1.61	0-4	0.57	0.57		

¹ Mattis Dementia Rating Scale;

- ² Cumulative Illness Rating Scale-Geriatric Version;
- ³ Philadelphia Multilevel Assessment Instrument – IADL Subscale;
- ⁴ When remission was first identified
- ⁵ Composite Antidepressant Score (CAD) in last month before relapse or in the sixth month.

Table 2

Demographic and Clinical Characteristics on 152 Older Subjects with Major Depression Who Remained in Remission Past the Risk Period for Relapse and Were Followed for Two Years.

	Had a Recurrence (N=45)			Remained Recurrence-free (N=152)			Chi-square	p
	N	Perc (%)		N	Perc (%)			
Gender							2.51	0.11
Female	33	73.33%		64	59.81%			
Entry Status at Last MDD Episode							2.49	0.12
Inpatient	9	20.00%		35	32.71%			
Outpatient	36	80.00%		72	67.29%			
							Mann-Whitney Wilcoxon	
	Mean	SD	Range	Mean	SD	Range	z	p
Age	72.27	6.73	60-89	71.83	7.14	60-89	0.31	0.76
Education (years)	14.00	3.10	8-20	14.24	3.10	7-21	-0.31	0.75
Duration of Subsyndromal Symptoms	3.64	3.82	0-14	1.33	2.66	0-14	4.00	<0.0001
Age at Onset	58.34	17.46	20-87	55.65	18.64	14-83	0.74	0.46
Duration of Last Episode	89.62	106.40	11-522	57.67	54.51	3-283	1.49	0.14
Number MDD Episodes	1.94	1.08	1-6	2.09	1.31	1-7	-0.30	0.76
At Entry (Index Episode)								
DRS Total ¹	137.60	5.52	127-144	135.98	7.85	111-144	0.66	0.51
CIRS Total ²	5.68	2.74	1-12	5.45	3.42	0-19	0.83	0.41
IADL ³	25.53	1.80	20-27	25.57	2.50	15-27	-1.24	0.21
At Onset of Remission⁴								
DRS Total ¹	138.00	5.58	119-144	137.06	7.28	103-144	0.48	0.63
CIRS Total ²	4.29	3.12	0-12	4.73	3.16	0-13	-0.73	0.46
IADL ³	26.21	1.03	23-27	25.63	2.55	15-27	-0.34	0.74
Antidepressant (AD) Medication Treatment								
Intensity of AD Treatment ⁵	2.44	1.39	0-4	2.53	1.41	0-4	-0.53	0.6

- ¹ Mattis Dementia Rating Scale;
- ² Cumulative Illness Rating Scale-Geriatric Version;
- ³ Philadelphia Multilevel Assessment Instrument – IADL;
- ⁴ When remission was first identified
- ⁵ Composite Antidepressant Score (CAD) in last month before recurrence or before last follow-up.

Table 3

Bivariate Relationships of Demographic and Clinical Variables to Time to Recurrence in 152 Older Subjects with Major Depression Who Remained in Remission Past the Risk Period for Relapse.

Variables	Cox Proportional Hazards Model		
	Hazard Ratio (95% CI)	Wald χ^2	P
Age	1.01 (0.97–1.06)	0.22	0.64
Education	0.99 (0.90–1.09)	0.04	0.83
Gender	1.60 (0.83–3.11)	1.97	0.16
Outpatient/Inpatient Status at Entry	1.41 (0.95–2.08)	2.91	0.08
Duration Subsyndromal Symptoms	1.16 (1.08–1.24)	18.28	<.0001
Duration of Index MDD Episode	1.00 (1.00–1.06)	2.85	0.09
Age at Onset of MDD	1.00 (0.99–1.02)	0.57	0.45
Number MDD Episodes	0.97 (0.94–1.29)	0.16	0.69
<u>At Entry</u>			
DRS Total ¹	1.03 (0.99–1.08)	1.80	0.18
CIRS Total ²	1.07 (0.97–1.18)	1.77	0.18
IADL ³	0.95 (0.84–1.10)	0.39	0.53
<u>At Onset of Remission</u>			
DRS Total ¹	1.02 (0.97–1.07)	0.51	0.48
CIRS Total ²	0.98 (0.88–1.09)	0.15	0.70
IADL ³	1.07 (0.89–1.29)	0.44	0.51
Intensity of AD Treatment ⁴	1.12 (0.85–1.47)	0.62	0.43
Intensity of AD Treat X Time [§]	1.23 (1.03–1.46)	5.41	0.02

[§]Time=log(time to recurrence)-5.69; The constant, 5.69, is the average of the logs of the survival times. The hazard ratio of Intensity of AD Treatment scores was not proportional over time as shown by the significant *Intensity of AD Treat x Time* interaction

¹Mattis Dementia Rating Scale

²Cumulative Illness Rating Scale-Geriatric Version

³Philadelphia Multilevel Assessment Instrument – IADL Subscale

⁴Composite Antidepressant Score (CAD) in last month before recurrence or before last follow-up.