Severity and Comorbidity Predict Episode Duration and Recurrence of DSM-IV Major Depressive Disorder

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Background: Information on the naturalistic outcome of major depressive disorder (MDD) is important in developing rational clinical practices. The aim of this study was to determine the outcome of MDD in a modern secondary-level psychiatric setting and the influence of comorbidity plus psychosocial factors on the outcome of MDD.

Method: The Vantaa Depression Study is a prospective, naturalistic cohort study of 269 secondary-level care psychiatric outpatients and inpatients diagnosed with a new episode of DSM-IV MDD. Patients were initially interviewed to determine the presence of MDD using the World Health Organization Schedule for Clinical Assessment in Neuropsychiatry and to assess Axis II diagnoses using the Structured Clinical Interview for DSM-III-R personality disorders between February 1, 1997, and May 31, 1998, and were interviewed again at 6 months and 18 months. The exact duration of the index episode and the timing of relapses/recurrences were examined using a life chart.

Results: The median length of time that patients met full criteria for a major depressive episode was 1.5 (95% CL = 1.3 to 1.7) months, and the median time to full remission was 8.1 (95% CL = 5.2 to 11.0) months after entry. During the follow-up, 38% of patients had a recurrence. Although numerous factors predict outcome of MDD to some extent, severity of depression and current comorbidity were the 2 most important predictors of longer episode duration and recurrence.

Conclusion: The course of MDD in modern psychiatric settings remains unfavorable. Any estimates of duration of depressive episodes and rates of recurrence are likely to be dependent on the severity of depression and level of comorbidity. At least among a population of mostly outpatients with MDD in medium-term follow-up, severity of depression and comorbidity appear to be more useful predictors of recurrence than does the number of prior episodes. These factors should influence clinical decision-making regarding the need for maintenance therapy.

(J Clin Psychiatry 2004;65:810–819)

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This article was supported by a grant from The Academy of Finland, Helsinki.

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On the basis of available studies of its outcome, major depressive disorder (MDD) appears to be a chronic illness with a high risk of recurrence over lifetime. Prospective long-term[1–10] and shorter-term outcome studies,[11–17] as well as retrospective long-term outcome studies,[18–23] have documented high recurrence and chronicity of major depressive episodes (MDEs). However, several short-term[24–29] and a few long-term[30–33] outcome studies suggest that the prognosis of depression is better in community and primary health care settings than in psychiatric care. The tendency for patients in tertiary-level treatment centers to have undergone many prior treatments may produce bias toward more chronic, severe, and recurrent illnesses compared with more unselected cohorts of MDD patients.[29,34,35] Thus, the length of depressive episode and rate of recurrence can be expected to vary by the level of treatment setting and inpatient or outpatient status. Moreover, the most influential outcome studies were undertaken during the past era of tricyclic antidepressants and before the recommendation of continuation and maintenance treatments, so this too somewhat undermines the ability to generalize those findings to present-day psychiatric settings.

Preventing chronicity and recurrence of depressive episodes is the central aim of treatment, and information on risk factors for chronicity and recurrences is important for identifying patients at particularly high risk. Severity of the MDE, comorbid dysthymia (double depression), and longer duration of index episode before entry have been consistently associated with nonrecovery or longer

time to remission.* Severity of depression either predicts relapse[13] or not[16,38] and is a risk factor for partial remission, which causes further exposure to relapse.[4,27] The number of prior MDEs and longer duration of the MDE prior to entry have also predicted relapse/recurrence.[8,12,22,27,30,38,39] The information on age and gender as risk factors for both chronicity and recurrence is inconsistent.†

Rates of nonrecovery, recurrence, and relapse among patients with MDD and comorbid disorders are likely to be greater than among patients with depression alone. Depressed patients with panic disorder or with higher symptom ratings of anxiety have shown a longer time to recovery.[15,45–47] The U.S. National Institute of Mental Health (NIMH) Collaborative Depression Study (CDS)[48] is the only study to have investigated the effects of current comorbid alcoholism among patients with MDD, finding those with current alcoholism to be only half as likely to recover from their MDE. However, there is surprisingly little information on current Axis I comorbidity and risk of relapse/recurrence in clinical cohorts of depressive patients. The CDS found some anxiety syndromes, but not current alcoholism, to be associated with higher risk of relapse.[46,48]

In a few naturalistic outcome studies in which semistructured interviews for both MDD and Axis II disorders were used, personality disorders predicted longer time to remission[49–52] and relapse.[51,53] Convergently, high neuroticism[54] and low self-esteem[16,54,55] have also been related to longer duration of MDE.

Overall, the available evidence on the effects of current comorbidity on the outcome of MDD in clinical cohorts is somewhat difficult to interpret because of several methodological limitations. These include not using semistructured/structured interviews for both MDD and comorbid disorders, not controlling for the effects of additional comorbid disorders, or not using life-chart methodology (and thus reporting only cross-sectional findings). Although the great majority of patients with MDD in psychiatric care suffer from several Axis I and II disorders,[56] the effect of overall comorbidity on the length of MDE or risk of recurrence has not been systematically investigated. Furthermore, the overall prevalence of comorbid cases has been quite low in previous studies[8,38] as compared with the prevalences reported in more recent clinical investigations.[56,57]

Another somewhat neglected area of research is the role of psychosocial factors in the outcome of depression in psychiatric settings. Adverse life events and lack of social support are associated with worse outcome of depression in community and some clinical studies,[44,58] although in most prospective studies of severe and recurrent depression, little effect on time to remission or subsequent relapse has been found.[16,55,59]

In the present naturalistic study, we prospectively assessed the outcome of DSM-IV MDD by life chart in a sample of 269 secondary-level care patients effectively representing psychiatric patients of a Finnish city. We were able to overcome some major limitations of previous studies by evaluating a large cohort of psychiatric outpatients and inpatients with MDD using semistructured interviews to obtain diagnoses of all Axis I and II disorders along with information on somatic comorbidity and psychosocial factors and employing the life chart methodology. We hypothesized that features of MDD itself (severity of depression, duration of MDE before entry, and number of prior MDEs), current comorbidity (Axis I, II, and III disorders), and psychosocial factors (lack of social support and negative life events) would all effectively predict duration of the index episode and recurrences. We also expected duration of depression to be shorter in our representative secondary-level cohort than in the earlier, mostly tertiary-level studies.

METHOD

The Vantaa Depression Study (VDS) is a collaborative depression research project run by the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, Finland, and the Department of Psychiatry of the Peijas Medical Care District (PMCD), Vantaa, Finland. A more detailed description of the baseline methodology is presented in our earlier report.[56]

The catchment area of the VDS comprises the city of Vantaa (population 169,000 in 1997), bordering Helsinki, Finland. The PMCD Department of Psychiatry offers secondary-care psychiatric services to all Vantaa citizens. These include a psychiatric inpatient unit, a general hospital outpatient clinic, 6 community mental health care centers—each covering a specified catchment area—and 2 day hospitals. The VDS was accepted by the ethical committee of the PMCD in December 1996.

Screening and Baseline Evaluation

The first phase of patient sampling for the VDS MDD Cohort Study involved screening all patients in the PMCD with a possible new episode of DSM-IV MDD between February 1, 1997, and May 31, 1998. Every patient (N = 806) aged 20 to 59 years (1) seeking treatment at, (2) being referred to, or (3) already receiving care and now showing signs of deteriorating clinical state in the PMCD Department of Psychiatry, but without a clinical diagnosis of ICD-10 schizophrenia or bipolar I disorder,

*References 3, 8, 11, 13, 15, 17, 25, 36, 37.
†References 3, 8, 9, 17, 22, 25, 30, 39–44.

was screened for the presence of depressive symptoms by their attending mental health professional. The screening instrument included the 5 screening questions for depression from the World Health Organization (WHO) Schedule for Clinical Assessment in Neuropsychiatry (SCAN), version 2.0.[60] The Scale for Suicide Ideation (SSI)[61] was also completed to identify cases with moderate to severe suicidal ideation or plans. After either a positive response to any of the SCAN screening questions or a score of 6 or more on the SSI, irrespective of the presence of depressive symptoms, the patient was fully informed about the study project, and written informed consent was requested. Of the 703 eligible patients, 161 (22.9%) refused to participate, but 542 (77.1%) agreed and gave written informed consent. The patients who refused did not differ significantly ($p > .05$) in age or gender from those who consented.

In the second phase of sampling, the 542 participating patients were interviewed face-to-face by one of the researchers (U.S.L., P.S.L.-M., T.K.M., H.J.R., or T.P.S.) using the SCAN, version 2.0.[60] The interviewers had all received relevant training by a WHO-certified training center. They examined whether or not the current mood episode fulfilled the criteria for DSM-IV MDD. All psychiatric and medical records in the PMCD, including results from a standardized set of laboratory tests, were also available. The patients who were currently abusing alcohol or other substances were interviewed after 2 to 3 weeks of abstinence in order to exclude those with substance-induced mood disorder. On these bases, 269 of the 542 patients were diagnosed with DSM-IV MDD. Diagnostic reliability was investigated using 20 videotaped diagnostic interviews; the kappa coefficient for MDD was 0.86 (CL = 0.58, 1.0), with 95% observed agreement rate.

After the decision to include a patient in the study cohort (N = 269), the entire SCAN interview[60] was conducted to achieve a full picture of Axis I comorbid disorders. The Structured Clinical Interview for DSM-III-R personality disorders (SCID-II)[62] was used to assess diagnoses on Axis II. Current Axis III diseases were assessed via a self-report checklist with 44 items (corresponding to ICD-10 diagnoses). Only diseases diagnosed by a physician and currently under treatment were included. The 17-item Hamilton Rating Scale for Depression (HAM-D)[63] and the 21-item Beck Depression Inventory (BDI)[64] were used to assess severity of depression; the SSI,[61] suicidal behavior; the Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS),[65] functional level; the Interview for Recent Life Events (IRLE),[66] life events; and the Interview Measure of Social Relationships (IMSR)[67] and Perceived Social Support Scale-Revised (PSSS-R),[68] social support. Self-report scales, in addition to the BDI, included the Beck Anxiety Inventory (BAI),[69] the Beck Hopelessness Scale (HS),[70] the Social Adjustment Scale–Self-Report (SAS-SR),[71] and the Eysenck Personality Inventory (EPI).[72] Overall, the interviews lasted 4 to 5 hours and usually involved at least 2 separate sessions.

Follow-Up

Of the total of 269 subjects with current MDD initially included in the study, 40 subjects were missing (N = 229) at 6 months. Some of these were traced again for the 18-month follow-up (N = 207), so only 13% (35/269) dropped out from both follow-up interviews. The patients whose diagnosis switched to bipolar disorder during the 18-month follow-up (13/269 [5%]) were censored from the analyses.

Patients who dropped out from both follow-up interviews were significantly younger (median age = 31.2 vs. 42.3 years, $z = –3.32$, $p = .001$), were more often living alone (24/35 [69%] vs. 101/221 [45%], $\chi^2 = 6.33$, $df = 1$, $p = .012$), had a higher score on the EPI-neuroticism scale (median = 20.0 vs. 18.0, $z = –2.17$, $p = .030$), and more often had a comorbid dysthymia (8/35 [23%] vs. 23/221 [10%], Fisher exact test, $p = .049$).

The median times to follow-up interviews were 6.5 and 18.8 months for 6- and 18-month interviews, respectively. Most (174/198 [88%]) of the patients followed for 18 months received antidepressants at baseline, and for the majority (154/198 [78%]) this was at an adequate dosage level in the acute phase. The adequacy of psychopharmacologic and psychosocial treatments during the follow-up will be reported and discussed in detail in a subsequent paper (in preparation).

Baseline characteristics of the 198 MDD patients (the 9 patients whose diagnoses switched to bipolar were not included) who completed the 18-month follow-up are shown in Table 1.

Outcome Measures

After the baseline assessments, patients were prospectively followed up with a life chart. The BDI[64] was administered to patients monthly for 6 months. The outcome of MDD and the presence of comorbid disorders were investigated at 6 and 18 months by repeated SCAN 2.0[60] and SCID-II interviews.[62] In addition, all observer- and self-report scales were included at both follow-up assessments. All medical and psychiatric records were also available.

The exact duration of the index episode and the timing of possible relapses/recurrences were examined by gathering all available data, which were then integrated into the form of a graphic life chart. This was created after reviewing with the patient all the information from the follow-up period at the 6- and 18-month interviews, which typically lasted 2 to 3 hours. Besides symptom ratings and visits to attending personnel, we also inquired about change points in the psychopathologic states using probes related to important life events in order to improve the accuracy of the assessment. The life chart was based

Table 1. Sociodemographic and Clinical Baseline Characteristics of the 198 Patients With Major Depressive Disorder Followed for 18 Months in the Vantaa Depression Study

Characteristic	N	%
Women	143	72
Men	55	28
Outpatients	168	85
Inpatients	30	15
Married or cohabiting	107	54
Unmarried/divorced/widowed	91	46
Residential area[a]		
East	126	64
West	71	36
Currently employed[b]	125	65
Total no. of lifetime MDEs[c]		
1 (intake)	66	34
2	64	33
≥ 3	67	34
Axis I diagnosis		
Dysthymia	20	10
Any anxiety disorder	108	55
Any alcohol use disorder	44	22
Axis II diagnosis		
Any personality disorder	85	43
Cluster A	37	19
Cluster B	28	14
Cluster C	62	31
Axis III diagnosis	65	33
No psychiatric or somatopsychiatric comorbid disorder	32	16
Melancholic features	74	37
Psychotic features	13	7
	Mean	SD
Age, y	41.0	11.1
17-item HAM-D score	19.1	6.1
21-item BDI score	27.4	8.1

[a]One case (0.5%) had no permanent residence.
[b]Information missing or conflicting in 5 cases (3%).
[c]Information missing in 1 case (0.5%).
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, MDE = major depressive episode.

on DSM-IV criteria and definitions. Time after the first baseline interview was divided into 3 periods: (1) state of full remission (none of the 9 MDE criteria symptoms), (2) state of partial remission (1–4 of the 9 symptoms), or (3) state of MDE (5+ of the 9 symptoms). As a categorical variable, remission (further specified as full or partial) was defined, as in the DSM-IV, as at least 2 consecutive months in which criteria were not met for a MDE. Relapse was defined as a return of symptoms fulfilling the DSM-IV criteria for MDE after a period of less than 2 months (but more than 2 weeks) with symptoms below the MDE threshold. Recurrence was defined, as in the DSM-IV definition for 296.3x MDD, recurrent, as a return of symptoms sufficiently severe to satisfy criteria for an MDE after at least 2 consecutive months of partial or full remission.

We used 2 alternative definitions for duration of the index episode after the first baseline interview: (1) the uninterrupted duration of the episode in the state of MDE (time with full MDE criteria) and (2) time to the first onset of state of full remission that lasted at least 2 consecutive months (time to full remission).

Statistical Methods

We used the Kaplan-Meier[73] survival curves to estimate the probability of remaining ill during the 18-month follow-up. The results were reported in probabilities of achieving a symptom state below the MDE criteria and of achieving full remission. Cox proportional hazards models[74] were used in the univariate and multivariate analyses for predicting time to symptom state below MDE criteria or to full remission. In these analyses, censored data included the subjects who (1) had not achieved a symptom state below the MDE criteria or (2) had not met the criteria of full remission by the end of the follow-up period or by the time they left the study or their diagnosis switched to bipolar disorder. Patients who had a relapse/recurrence were compared with those without a relapse/recurrence using the χ^2 statistic with Yates' continuity correction or Fisher exact test when expected cell count was less than 5 in the 2×2 table. Only those who completed the whole 18-month follow-up could be included in analyses of the risk of recurrences.

In comparisons of continuous variables, the 2-sample t test was used if they were normally distributed, and the Mann-Whitney and Kruskal-Wallis tests were used if not. Backward stepwise multivariate logistic regression models were used for the analyses of predictors of relapses and recurrences. We chose predictors for our final models on the basis of our primary hypothesis but also considered their clinical and statistical validity and relevance (e.g., state vs. trait) before inclusion. Therefore, we did not enter some self-reported scale scores (e.g., PSSS-R, HS, and SSI) into our final multivariate analyses seeking independent predictors (even though they might have been significant in univariate analyses). SPSS software, version 11.0,[75] was used.

RESULTS

Duration of the Index Episode

The median time with full MDE criteria after entry was only 1.5 (95% CL = 1.3 to 1.7) months. Altogether, 78% of the cohort achieved a symptom state below MDE criteria within 3 months; 86%, within 6 months; and 95%, within 18 months (Figure 1). The median time to full remission (lasting at least 2 consecutive months) was 8.1 (95% CL = 5.2 to 11.0) months; 22% of patients reached full remission within 3 months; 42%, within 6 months; and altogether only 63%, within the 18-month follow-up (Figure 2). The median duration of MDE before the baseline interview was 3.5 (95% CL = 2.9 to 4.1) months; including the prodromal phase, the duration was 6.6 (95% CL = 6.1 to 7.1) months.

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Figure 1. Survival Curve to a Symptom State Below Criteria for a Major Depressive Episode (MDE) in the Vantaa Depression Study

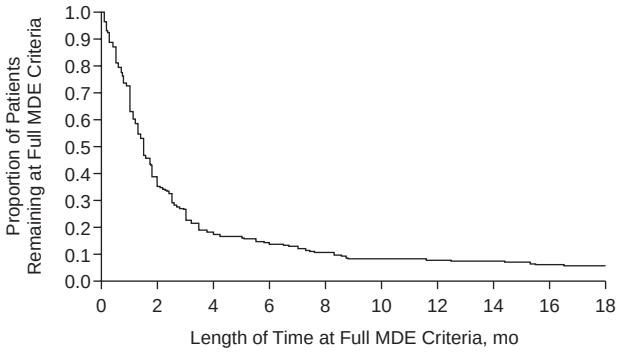
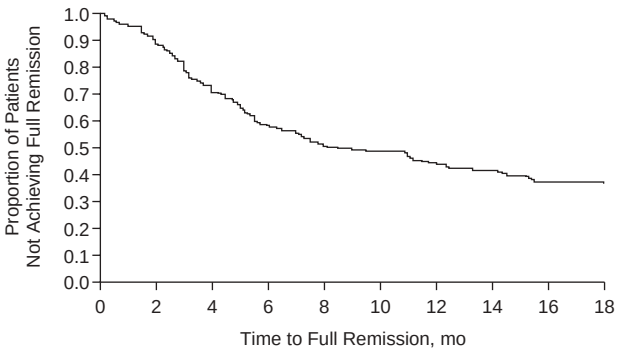


Figure 2. Survival Curve to Full Remission of a Major Depressive Episode or to 18 Months in the Vantaa Depression Study



Predictors of Duration of the Index Episode After Entry

Significant predictors of time with full MDE criteria and of time to full remission were very similar in the univariate analyses (Table 2). Achieving full remission took twice as long for those with a comorbid personality disorder (median time = 12.50 vs. 7.20 months), more severe MDD (median time = 11.00 vs. 4.20 months), or more severe anxiety symptoms (median time = 13.30 vs. 5.50 months) than the patients without personality disorder, with less severe depression, or with less severe anxiety, respectively. Outpatients and inpatients were similar regarding time to full remission (median time = 8.50 vs. 8.10 months).

After the univariate analysis was performed, all theoretically and clinically relevant predictors (age, gender, duration of MDE before entry, number of prior MDEs and somatic disorders, melancholic and psychotic subtypes of depression, personality and alcohol use disorders, mean BAI [anxiety symptoms] and HAM-D scores [severity of depression], and size of social network) were entered simultaneously into the Cox proportional hazards models. After all nonsignificant findings were removed, severity of MDD, longer duration of MDE prior to entry, and personality disorder predicted time with full MDE criteria most significantly, while time to full remission was most effectively predicted by severity of MDD and anxiety symptoms (Table 3).

Relapses

Only 20 (10%) of the 198 patients who completed 18-month interviews had an immediate relapse (return of symptoms fulfilling the DSM-IV criteria for MDE after a period with symptoms below the MDE threshold exceeding 2 weeks but less than 2 months). Those with previous MDEs (18/131 [14%] vs. 2/67 [3%], $\chi^2 = 5.65$, df = 1, p = .02) and aged ≥ 40 years (16/113 [14%] vs. 4/85 [5%], $\chi^2 = 4.77$, df = 1, p = .03) more often had relapses. When these predictors and gender were entered into the logistic regression models simultaneously, the significance of the presence of previous MDEs (OR = 5.15; 95% CL = 1.14 to 23.24, p = .03), and older age (OR = 3.19; 95% CL = 1.01 to 10.11, p < .05) remained. The median length of relapse during the follow-up was 2.20 months.

Recurrences

During the 18-month follow-up, 76 (38%) of the 198 patients had a recurrence (return of symptoms sufficiently severe to satisfy criteria for an MDE after at least 2 consecutive months of partial or full remission). Chronic cases (those fulfilling citeria for an MDE during the entire follow-up period) were excluded from these analyses. The median time to the first relapse or recurrence was 4.3 months (95% CL = 2.93 to 5.67, calculated without time with full MDE criteria after baseline); the median length of recurrence was 1.5 months. The median score on the BDI during the relapses or recurrences was 19.00 (combined due to low number; only those with BDI scores available [N = 56] included). The BDI scores during the relapses /recurrences were significantly lower than the respective patients' scores at baseline (t = 5.502, df = 55, p < .001).

Partial remission from the index episode was significantly associated with risk of recurrence during follow-up (OR = 2.14; 95% CL = 1.06 to 4.31, p = .03). However, when partial remission was added as a predictor in the multivariate models, it did not remain significant after adjusting for the other predictors. It was not included in the final multivariate models.

In univariate logistic regression analyses, several baseline factors predicted recurrence either significantly or as a trend (Table 2). However, severity of MDD and a higher number of comorbid psychiatric disorders were the 2 most significant predictors. Twenty-seven percent (3/11) of the patients with mild, 31% (31/99) with moderate, and

Table 2. Univariate Analyses of All Possible Predictors of Time With Full Criteria for a Major Depressive Episode (MDE), Time to Full Remission, and Recurrences in the Vantaa Depression Study

	Time With Full MDE Criteria[a]			Time to Full Remission[a]			Recurrences[b]		
Predictor at Entry	OR	95% CL	p Value	OR	95% CL	p Value	OR	95% CL	p Value
Age, y	1.01	1.00 to 1.02	…	1.01	1.00 to 1.03	.073	1.00	0.98 to 1.03	…
Gender, male	0.97	0.71 to 1.33	…	0.83	0.56 to 1.24	…	0.92	0.47 to 1.78	…
Outpatient status	0.90	0.62 to 1.29	…	1.05	0.65 to 1.70	…	0.78	0.34 to 1.76	…
Clinical features of MDD									
Age at onset, y	1.01	0.99 to 1.02	…	1.01	0.99 to 1.03	…	0.98	0.95 to 1.02	…
Longer MDE prior to entry	1.30	0.98 to 1.72	.069	1.30	0.91 to 1.84	…	1.78	0.97 to 3.26	.061
No. of previous episodes	1.02	0.97 to 1.08	…	1.03	0.96 to 1.10	…	1.12	0.98 to 1.28	.083
Symptoms and functional ability									
17-item HAM-D score	1.03	1.01 to 1.06	.011	1.04	1.01 to 1.07	.013	1.07	1.01 to 1.03	.018
21-item BDI score	1.03	1.01 to 1.05	.001	1.03	0.01 to 1.06	.006	1.05	1.01 to 1.09	.014
Beck Anxiety Inventory score	1.02	1.00 to 1.03	.015	1.03	1.01 to 1.04	.004	1.02	0.99 to 1.05	…
Beck Hopelessness Scale score	1.05	1.02 to 1.08	.003	1.05	1.01 to 1.09	.018	1.10	1.03 to 1.18	.006
Scale for Suicide Ideation score	1.01	1.00 to 1.03	…	1.03	1.01 to 1.06	.010	1.06	1.02 to 1.11	.004
SOFAS score[c]	1.02	1.00 to 1.03	.019	1.02	0.97 to 1.00	.076	1.01	0.98 to 1.04	…
Axis I comorbidity									
Dysthymia	0.89	0.56 to 1.42	…	1.52	0.79 to 2.91	…	1.89	0.70 to 5.09	…
Anxiety disorders	0.81	0.62 to 1.07	…	0.87	0.62 to 1.23	…	1.59	0.87 to 2.90	…
Panic disorder with agoraphobia	0.72	0.39 to 1.33	…	0.67	0.32 to 1.38	…	0.85	0.19 to 3.69	…
Without agoraphobia	0.80	0.51 to 1.28	…	0.65	0.38 to 1.11	…	1.10	0.39 to 3.09	…
Agoraphobia without panic	0.92	0.60 to 1.42	…	1.11	0.63 to 1.93	…	0.68	0.23 to 1.80	…
Specific phobia	1.02	0.75 to 1.40	…	1.15	0.77 to 1.71	…	1.26	0.64 to 2.48	…
Social phobia	1.05	0.74 to 1.50	…	0.93	0.59 to 1.45	…	1.91	0.88 to 4.18	…
Generalized anxiety disorder	0.89	0.59 to 1.34	…	1.12	0.66 to 1.89	…	1.50	0.63 to 3.52	…
Alcohol use disorders	1.01	0.72 to 1.43	…	1.15	0.75 to 1.75	…	1.35	0.65 to 2.79	…
Dependence	1.03	0.67 to 1.59	…	0.95	0.56 to 1.61	…	1.70	0.67 to 4.29	…
Abuse	0.99	0.62 to 1.58	…	0.82	0.47 to 1.45	…	0.96	0.37 to 2.51	…
Axis II comorbidity									
Personality disorders	1.46	1.10 to 1.93	.008	1.44	1.01 to 2.05	.043	1.84	1.00 to 3.38	.049
Cluster A	1.47	1.01 to 2.15	.044	1.28	0.80 to 2.04	…	1.99	0.90 to 4.38	.089
Cluster B	1.24	0.83 to 1.85	…	1.12	0.68 to 1.85	…	2.27	0.94 to 5.48	.069
Cluster C	1.54	1.13 to 2.09	.006	1.79	1.20 to 2.68	.005	1.41	0.74 to 2.71	…
No. of psychiatric disorders	1.04	0.97 to 1.13	…	1.06	0.96 to 1.18	…	1.27	1.06 to 1.53	.009
Axis III comorbidity									
No. of current somatic diseases	1.11	0.98 to 1.26	…	1.18	0.99 to 1.40	.071	1.05	0.82 to 1.36	…
No. of all Axis I–III disorders	1.06	0.99 to 1.14	.071	1.09	1.00 to 1.18	.051	1.19	1.03 to 1.38	.020
MDD subtype features									
Melancholic MDD	1.03	0.78 to 1.37	…	0.94	0.66 to 1.34	…	0.91	0.49 to 1.69	…
Psychotic MDD	1.00	0.59 to 1.69	…	0.71	0.39 to 1.33	…	0.68	0.20 to 2.36	…
Psychosocial and personality factors									
Size of social network[c]	1.03	0.99 to 1.06	…	1.04	0.99 to 1.09	.093	0.98	0.90 to 1.07	…
PSSS-R score[c]	1.02	1.01 to 1.03	< .001	1.02	1.00 to 1.03	.038	1.02	0.99 to 1.04	…
Negative life events score[d]	1.00	0.97 to 1.03	…	1.02	0.98 to 1.06	…	1.02	0.95 to 1.09	…
Neuroticism score[e]	1.05	1.01 to 1.08	.016	1.05	1.01 to 1.10	.022	1.11	1.02 to 1.21	.020

[a]Cox proportional hazards models; all analyses controlled for age and gender, risk reported for increasing time.
[b]Logistic regression models; all analyses controlled for age, gender, and time at risk for recurrence.
[c]Scales reversed in order to improve comparability.
[d]Interview for Recent Life Events: objectively measure negative impact of adverse life events.
[e]The Eysenck Personality Inventory: dimension of neuroticism.
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder, PSSS-R = Perceived Social Support Scale-Revised, SOFAS = Social and Occupational Functioning Assessment Scale for DSM-IV.
Symbol: … = NS.

58% (42/73) with severe depression had a recurrence ($\chi^2 = 12.88$, df = 2, p = .002), while the corresponding percentages were 31% (13/42), 38% (31/82), and 54% (32/59) for those with no, 1 to 2, or 3 or more comorbid disorders, respectively ($\chi^2 = 6.33$, df = 2, p = .04). In the backward stepwise multivariate logistic regression models, age, gender, duration of MDE before entry, number of prior MDEs, somatic disorders, comorbid psychiatric disorders, melancholic and psychotic subtypes of depression, mean score on the HAM-D, size of social network, and time at risk for recurrence (total time spent in partial or full remission during follow-up) were first entered as predictors. After removing nonsignificant variables, more severe depression and a higher number of comorbid psychiatric disorders remained the 2 significant predictors (OR = 1.06; 95% CL = 1.00 to 1.11, p = .04 and OR = 1.25; 95% CL = 1.03 to 1.51, p = .02, respectively).

DISCUSSION

We found duration of depressive episode to be no shorter in our secondary-level cohort than in previous,

Table 3. Predictors at Entry to Study of Longer Time With Full MDE Criteria and Time to Full Remission[a]

Predictor	OR	95% CL	p Value
Time with full MDE criteria			
Severity of MDD (HAM-D score)	1.04	1.01 to 1.07	.004
Longer MDE before entry (months)	1.36	1.02 to 1.81	.04
Personality disorder	1.36	1.02 to 1.81	.04
Time to full remission			
Severity of MDD (HAM-D score)	1.03	1.00 to 1.07	.04
Anxiety symptoms (BAI score)	1.02	1.00 to 1.04	.01

[a]Analyses by stepwise backward multivariate Cox proportional hazards models.
Abbreviations: BAI = Beck Anxiety Inventory, HAM-D = Hamilton Rating Scale for Depression, MDD = major depressive disorder, MDE = major depressive episode.

mostly tertiary-level inpatient studies. Although patients typically responded early to the treatment (most in 4 to 8 weeks), the major problems were the long period with only partial remission and the high rate of recurrence. Numerous factors predicted outcome of MDD to some extent, but severity of depression and presence of current comorbidity were the 2 most robust predictors. At least in medium-term follow-up, severity of depression and presence of comorbidity appear to be more useful predictors of recurrence than does number of prior episodes.

The present study has some major strengths. It involved a relatively large (N = 269) cohort of both outpatients and inpatients with MDD, effectively representing psychiatric patients with a new episode of MDD in a Finnish city. On the basis of an epidemiologic survey, we have estimated that two thirds of all depressed subjects in the general population of the city of Vantaa seeking treatment from psychiatrists are treated in the PMCD.[76] The patients were carefully diagnosed using structured interviews with excellent reliability (kappa = 0.86) for the diagnosis of MDD[56] plus information on all comorbid Axis I and II disorders at baseline and later interviews. However, the reliability of comorbid disorder diagnoses[56] and outcome variables is unknown.

Furthermore, somatic comorbidity, functional status, personality features, adverse life events, social support, and treatment received were also investigated besides ordinary symptom ratings. Thus, predictors from several potentially relevant domains were included. Diagnoses of Axis III disorders were based on self-report, but only diseases diagnosed by a physician were included as disorders.

The rate of dropout was low, as 87% of the cases could be interviewed at least once after baseline. As the factors associating with dropping out included both positive (younger age) and negative (living alone, neuroticism, dysthymia) outcome predictors, the small percentage of dropouts is unlikely to have biased our findings.

The study took place during the era of current antidepressants (1997–1999) in a modern community psychiatric setting; 88% of the patients received antidepressants at baseline, and for the majority (78%) these were at adequate levels in the acute phase in compliance with the American Psychiatric Association Practice Guideline.[77] However, our study was naturalistic, so the treatment was not under the control of the investigators. We also employed multivariate statistical methods to find those predictors of outcome that were independent of other associations.

However, some methodological choices need to be clarified. We investigated the outcome of depression by using a graphic life chart, which is similar, but not identical, to the Longitudinal Interval Follow-Up Evaluation (LIFE) methodology[78] used in the NIMH CDS. As with the LIFE, we inquired about change points in the psychopathologic state using probes related to important events; we also had all patient records and monthly BDI ratings (for the first 6 months) available. Unlike with the LIFE, we classified the patients' follow-up time into periods of DSM-IV MDE or partial (1–4 criteria symptoms) or full (no symptoms) remission.

While the advantage of this classification is immediate compatibility with the DSM-IV criteria, comparison of findings with studies using the LIFE can be undertaken only with some caution. For example, it appears to us that our criteria for full remission were more stringent than those used for recovery in the CDS (Psychiatric Status Ratings, 1–2; no symptoms or 1 to 2 symptoms to a mild degree). The mean ± SD HAM-D scores at the 18-month interview were 2.7 ± 2.8 for those in full remission, 8.3 ± 4.3 for those in partial remission, and 18.5 ± 4.8 for those with an MDE.

In practice, if those with only 1 or 2 symptoms were also included in the full remission grouping, we would have 76% of patients with recovery (instead of 63%); this percentage is comparable with the number of patients fully recovered in the CDS within 2 years (81%).[3] We believe that our findings can be generalized to other psychiatric settings, given the similarity of baseline depression symptom ratings and patterns of comorbidity with the available cross-sectional U.S. studies.[57,79]

Finally, our life chart and all definitions are based on the DSM-IV criteria, which are part of everyday clinical practice and known by any clinician. The major advantage is counting episodes and defining recurrences precisely as any clinician does when using the DSM-IV.

Unfortunately, there is currently no universally accepted definition of remission[80] despite significant efforts.[81] Nevertheless, in most longitudinal studies, recurrence follows a period of recovery, which is relatively consistently defined as the presence of only 1 or 2 minimal symptoms of major depression to a mild degree or a complete absence of symptoms for at least 2 months.[80] So, having used the same criteria for duration for remission, we think that our findings are comparable to other studies (e.g., the CDS,[3,7,8,36–38,40,48] the Cambridge cohort[13,14,82]).

We expected the duration of depression to be shorter in our representative secondary-level cohort comprising predominantly (85%) outpatients, compared with the studies from more selected tertiary-level academic centers and inpatients. However, this did not appear to be the case. Despite more extensive (88%) and more adequate use of the new antidepressants in the acute phase, the duration of the index episode was no shorter than in the previous studies. This finding is in contrast with the results from a Japanese sample[34] but is convergent with a more recent tertiary-level long-term outcome study.[82]

Moreover, and somewhat surprisingly, we found no differences between outpatients and inpatients regarding the length of the MDE or rates of recurrence. Our rates of remission from the index episode were comparable with the rates reported in older studies. Within 3 months, 22% of the patients in our cohort reached full remission versus 41%,[3] 30%,[17] and 33%[13] in other studies; within 6 months, 42% of the patients in our cohort reached full remission versus 54%,[3] 50%,[13] and 43%[82] in other studies. However, only two thirds (63%) of the subjects in our study reached strictly defined full remission, which also took a relatively long median time of 8 months. Although patients typically responded early to treatment, the major problem was the long period with only partial remission, which is in part explained by our strict definition of full remission. Unlike the other studies,[13,17] we also deliberately included all patients with MDD without excluding any comorbid disorders. When all the subjects with a concurrent major psychiatric or physical illness were excluded from our data, the median time to full remission somewhat decreased (from 8.1 to 7.2 months). Thus, a representative psychiatric cohort of MDD patients who typically have multiple current comorbid disorders[56] may also include subjects with many known risk factors for poor outcome of MDD.

The first of our main outcomes was the duration of depression. As in earlier prospective studies,* we found more severe depression and longer duration of the MDE before entry to predict longer episode. However, it was somewhat unexpected to find that severe MDD was such a robust predictor among all other theoretically relevant risk factors simultaneously entered into the models.

In accordance with earlier studies investigating the effects of either comorbid anxiety[45–47] or personality disorders,[49–52] anxiety symptoms and personality disorders were associated with longer duration of depression in our cohort of patients with multiple current comorbid psychiatric disorders.[56] As in 2 earlier published reports from small cross-sectional cohorts,[41,83] we found that a higher number of psychiatric and comorbid somatopsychiatric disorders were associated with a longer episode duration.

In accordance with some earlier studies,[55,59] we also found social support, as objectively measured by the size of the social network at entry, or negative impact of preceding adverse life events to have little or no effect on time to remission. In contrast, social support, as subjectively perceived, was strongly related to the duration of depression. Subjectively perceived social support and neuroticism were strongly correlated with the level of depressive symptoms or presence of comorbid personality disorders and were therefore not included in the final multivariate models.

No association between adequacy of pharmacotherapy in the acute phase and episode duration was found, probably due to homogeneity in the amount and adequacy of the treatment received.

The recurrent nature of depression is one of its fundamental features and has major treatment implications. During the follow-up, about 40% of patients in our cohort suffered a recurrence, which is consistent with the rates reported in specialty settings.[4,8,13,38,82] However, it seems that although the rate of recurrence in our study was similar to older studies, the episodes during the follow-up were milder and shorter than in earlier studies.[9] In this respect, our findings support the findings from a Japanese sample[34] in which the index episode length was calculated to be 25% to 50% shorter than in older literature. Our findings that number of prior MDEs, older age, longer duration of MDE before entry, personality disorders or neuroticism, hopelessness, and achieving only partial remission from the index episode are associated with the risk of relapse/recurrence are convergent with previous studies.† However, a higher number of comorbid psychiatric disorders and severity of depression were the most consistent predictors of relapse/recurrence.

Partial remission as a predictor in the multivariate models did not remain significant, which supports our basic interpretation of partial remission as an intermediate symptom state that is effectively predicted by more important predictors of outcome. The rate of recurrence ranged from 27% among those with a mild index episode to 58% among those with a severe one and from 31% among those with no comorbid disorder to 54% among those with 3 or more current comorbid psychiatric disorders. Thus, severe depression and high number of comorbid disorders are the major factors influencing the medium-term risk of recurrence.

Our finding that severity of MDD is one of the most important factors associated with the risk of recurrence in medium-term follow-up has major practice implications. Severity of depression has either predicted recurrences[13] or not.[16,38] In earlier studies[16,38] that found no association between severity of depression and recurrences, most of the patients were inpatients with severe and recurrent endogenous depression. The proportions

*References 3, 8, 11, 13, 15, 17, 25, 36, 37.
†References 4, 8, 12, 13, 22, 27, 30, 38, 39, 51, 53, 56.

of patients with 2 or more depressive episodes prior to entry (42%,[13,38] 80%[16]) and with endogenous/melancholic MDD (63%,[13] 85%,[38] 89%[16]), as well as patients' mean ± SD HAM-D scores (25 ± 7.5[38] and 20.5 ± 5.6[13]), have all been higher in earlier reports compared with the respective rates of 34%, 37%, and 19.5 ± 5.9 in our study.[56]

However, our finding that severity of depression predicted recurrence is consistent with the study[13] in which the clinical severity of MDD also varied from mild to severe, and the proportion of patients with melancholic features in our study was lower (37%) compared with other earlier studies. So, it appears to us that at least in the cohorts of less melancholic MDD outpatients with less severe depression in medium-term follow-up, the severity of depression might be a more useful predictor of recurrence than the number of prior MDEs. This information is particularly important regarding patients who are having their lifetime first or second episodes, when maintenance therapy is not usually recommended. We suggest that not only number of previous episodes, but also severity of depression should be considered for inclusion in future practice guidelines[77] as a factor influencing initiation of antidepressant maintenance therapy.

Overall, the course of MDD remains unfavorable in modern psychiatric settings. Any estimates of duration of depressive episode and rates of recurrence are highly dependent on the severity of depression and level of comorbidity in the population in question. At least among a population of mostly outpatients with MDD in medium-term follow-up, severity of depression and comorbidity appear to be more useful predictors of recurrence than does number of prior episodes. These factors should influence clinical decision making regarding the need for maintenance therapy.

REFERENCES

1. Angst J. The course of affective disorders. Psychopathology 1986;19: 47–52
2. Angst J, Kupfer DJ, Rosenbaum JF. Recovery from depression: risk or reality? Acta Psychiatr Scand 1996;93:413–419
3. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression. Arch Gen Psychiatry 1992;49:809–816
4. Keller MB, Boland RJ. Implications of failing to achieve successful long-term maintenance treatment of recurrent unipolar major depression. Biol Psychiatry 1998;44:348–360
5. Angst J, Preisig M. Course of a clinical cohort of unipolar, bipolar and schizoaffective patients: results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 1995;146:5–16
6. Angst J, Preisig M. Outcome of a clinical cohort of unipolar, bipolar and schizoaffective patients: results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 1995;146:17–23
7. Mueller TI, Keller MB, Leon AC, et al. Recovery after 5 years of unremitting major depressive disorder. Arch Gen Psychiatry 1996;53:794–799
8. Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999;156:1000–1006
9. Solomon DA, Keller MB, Leon AC, et al. Recovery from major depression: a 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 1997;54:1001–1006
10. Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry 2000;157:229–233
11. Wells KB, Burnam MA, Rogers W, et al. The course of depression in adult outpatients: results from the Medical Outcomes Study. Arch Gen Psychiatry 1992;49:788–794
12. Maj M, Veltro F, Pirozzi R, et al. Pattern of recurrence of illness after recovery from an episode of major depression: a prospective study. Am J Psychiatry 1992;149:795–800
13. Ramana R, Paykel ES, Cooper Z, et al. Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med 1995;25:1161–1170
14. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25:1171–1180
15. Parker G, Wilhelm K, Mitchell P, et al. Predictors of 1-year outcome in depression. Aust N Z J Psychiatry 2000;34:56–64
16. Sherrington JM, Hawton K, Fagg J, et al. Outcome of women admitted to hospital for depressive illness: factors in the prognosis of severe depression. Psychol Med 2001;31:115–125
17. Myers BS, Sirey JA, Bruce M, et al. Predictors of early recovery from major depression among patients admitted to community-based clinics: an observational study. Arch Gen Psychiatry 2002;59:729–735
18. Lee AS, Murray RM. The long-term outcome of Maudsley depressives. Br J Psychiatry 1988;153:741–751
19. Kiloh LG, Andrews G, Neilson M. The long-term outcome of depressive illness. Br J Psychiatry 1988;153:752–757
20. Andrews G, Neilson M, Hunt C, et al. Diagnosis, personality and the long-term outcome of depression. Br J Psychiatry 1990;157:13–18
21. Thornicroft G, Sartorius N. The course and outcome of depression in different cultures: 10-year follow-up of the WHO Collaborative Study on the assessment of depressive disorders. Psychol Med 1993; 23:1023–1032
22. Surtees PG, Barkley C. Future imperfect: the long-term outcome of depression. Br J Psychiatry 1994;164:327–341
23. Brodaty H, Luscombe G, Peisah C, et al. A 25-year longitudinal, comparison study of the outcome of depression. Psychol Med 2001;31:1347–1359
24. Kessler LG, Cleary PD, Burke JD. Psychiatric disorders in primary care. Arch Gen Psychiatry 1985;42:583–587
25. Sargeant JK, Bruce ML, Florio LP, et al. Factors associated with 1-year outcome of major depression in the community. Arch Gen Psychiatry 1990;47:519–526
26. Ormel J, Oldehinkel T, Brilman E, et al. Outcome of depression and anxiety in primary care: a three-wave $3^1/_2$-year study of psychopathology and disability. Arch Gen Psychiatry 1993;50:759–766
27. Lin EHB, Katon WJ, VonKorff M, et al. Relapse of depression in primary care: rate and clinical predictors. Arch Fam Med 1998;7:443–449
28. Simon GE. Long-term prognosis of depression in primary care. Bull World Health Organ 2000;78:439–445
29. Spijker J, de Graaf R, Bilj RV, et al. Duration of major depressive episodes in the general population: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry 2002;181:208–213
30. Coryell W, Endicott J, Keller MB. Predictors of relapse into major depressive disorder in a nonclinical population. Am J Psychiatry 1991;148:1353–1358
31. Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord 1997;45:31–40
32. van Weel-Baumgarten E, van den Bosch W, van den Hoogen H, et al. Ten year follow-up of depression after diagnosis in general practice. Br J Gen Pract 1998;48:1643–1646
33. Eaton WW, Anthony JC, Gallo J, et al. Natural history of Diagnostic Interview Schedule/DSM-IV major depression: the Baltimore epidemiologic catchment area follow-up. Arch Gen Psychiatry 1997;54:993–999
34. Furukawa TA, Kitamura T, Takahashi K. Time to recovery of an inception cohort with hitherto untreated unipolar major depressive disorder. Br J Psychiatry 2000;177:331–335
35. Roy-Byrne PP, Stang P, Wittchen H-U, et al. Lifetime panic–depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course and help-seeking. Br J Psychiatry

2000;176:229–235
36. Keller MB, Shapiro RW, Lavori PW, et al. Recovery in major depressive disorder. Arch Gen Psychiatry 1982;39:905–910
37. Keller MB, Klerman GL, Lavori PW, et al. Long-term outcome of episodes of major depression: clinical and public health significance. JAMA 1984;252:788–792
38. Keller MB, Lavori PW, Lewis CE, et al. Predictors of relapse in major depressive disorder. JAMA 1983;250:3299–3304
39. Keller MB, Shapiro RW, Lavori PW, et al. Relapse in major depressive disorder: analysis with the Life Table. Arch Gen Psychiatry 1982;39: 911–915
40. Keller MB, Lavori PW, Rice J, et al. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. Am J Psychiatry 1986;143:24–28
41. Keitner GI, Ryan CF, Miller IW, et al. Recovery and major depression: factors associated with twelve-month outcome. Am J Psychiatry 1992; 149:93–99
42. Huges DC, DeMallie D, Blazer DG. Does age make a difference in the effects of physical health and social support on the outcome of a major depressive episode? Am J Psychiatry 1993;150:728–733
43. Simpson HB, Nee JC, Endicott J. First-episode major depression: few sex differences in course. Arch Gen Psychiatry 1997;54:633–639
44. Zlotnick C, Shea MT, Pilikonis PA, et al. Gender, type of treatment, dysfunctional attitudes, social support, life events, and depressive symptoms over naturalistic follow-up. Am J Psychiatry 1996;153: 1021–1027
45. Coryell W, Endicott J, Andreasen NC, et al. Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. Am J Psychiatry 1988;145:293–300
46. Coryell W, Endicott J, Winokur G. Anxiety syndromes as epiphenomena of primary major depression: outcome and familial psychopathology. Am J Psychiatry 1992;149:100–107
47. Clayton PJ, Grove WM, Coryell W, et al. Follow-up and family study of anxious depression. Am J Psychiatry 1991;148:1512–1517
48. Mueller TI, Lavori PW, Keller MB, et al. Prognostic effect of the variable course of alcoholism on the 10-year course of depression. Am J Psychiatry 1994;151:701–706
49. Sato T, Sakado K, Sato S. Is there any specific personality disorder or personality disorder cluster that worsens the short-term treatment outcome of major depression? Acta Psychiatr Scand 1993;88:342–349
50. Greenberg MD, Craighead WE, Evans DD, et al. An investigation of the effects of comorbid axis II pathology on outcome of inpatient treatment for unipolar depression. J Psychopathol Behav Assess 1995;17:305–321
51. Ilardi SS, Craighead WE, Evans DD. Modeling relapse in unipolar depression: the effects of dysfunctional cognitions and personality disorders. J Consult Clin Psychol 1997;65:381–391
52. Viinamäki H, Hintikka J, Honkalampi K, et al. Cluster C personality disorder impedes alleviation of symptoms in major depression. J Affect Disord 2002;71:35–41
53. Alnaes R, Torgersen S. Personality and personality disorders predict development and relapses of major depression. Acta Psychiatr Scand 1997;95:336–342
54. Surtees PG, Wainwright NW. Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. Br J Psychiatry 1996;169:338–347
55. Andrew B, Hawton K, Fagg J, et al. Do psychosocial factors influence outcome in severely depressed female psychiatric in-patients? Br J Psychiatry 1993;163:747–754
56. Melartin TK, Rytsälä HJ, Leskelä US, et al. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. J Clin Psychiatry 2002;63:126–134
57. Zimmerman M, McDermut W, Mattia JI. Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. Am J Psychiatry 2000;157:1337–1340
58. Paykel ES. Life events, social support and depression. Acta Psychiatr Scand 1994;337:50–58
59. Paykel ES, Cooper Z, Ramana R, et al. Life events, social support and marital relationships in the outcome of severe depression. Psychosoc Med 1996;26:121–133
60. Wing JK, Babor T, Brugha T, et al. SCAN: Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990;47:589–593
61. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 1979;47:343–352
62. Spitzer RL, Williams JBW, Gibbon M, et al. Instruction Manual for the Structured Clinical Interview for DSM-III-R (SCID, 5/1/89 Revision). New York, NY: Biometrics Research Department; 1989
63. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
64. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
65. Goldman HH, Skodol AE, Lave TR. Revising Axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149:1148–1156
66. Paykel ES. Methodological aspects of life event research. J Psychosom Res 1983;27:123–128
67. Brugha TS, Sturt E, MacCarthy B, et al. The Interview Measure of Social Relationships: the description and evaluation of a survey instrument for assessing personal social resources. Soc Psychiatry 1987;22:123–128
68. Blumenthal JA, Burg MM, Barefoot J, et al. Social support, type A behavior, and coronary artery disease. Psychosom Med 1987;49:331–340
69. Beck AT, Brown G, Epstein N, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893–897
70. Beck AT, Weissman A, Lester D, et al. The measure of pessimism: the hopelessness scale. J Consult Clin Psychol 1974;42:861–865
71. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111–1115
72. Eysenck HJ, Eysenck SBG. Manual of the Eysenck Personality Inventory. London, England: University of London Press LTD; 1964
73. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. JAMA 1958;53:457–481
74. Cox DR. Regression models and life-tables (with discussion). J R Stat Soc B 1972;34:541–554
75. Statistical Package for the Social Sciences for Windows. Release 11.0.1. Chicago, Ill: SPSS Inc.; 1989–2001
76. Rytsälä HJ, Melartin TK, Leskelä US, et al. A record-based analysis of 803 patients treated for depression on psychiatric care. J Clin Psychiatry 2001;62:701–706
77. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder (Revision). Am J Psychiatry 2000;157(suppl 4):1–45
78. Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-up Evaluation. Arch Gen Psychiatry 1987;44:540–548
79. Tedlow J, Smith M, Neault N, et al. Melancholia and Axis II comorbidity. Compr Psychiatry 2002;43:331–335
80. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA 2003;289:3152–3160
81. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–855
82. Kennedy N, Abbott R, Paykel ES. Remission and recurrence of depression in the maintenance era: long-term outcome in a Cambridge cohort. Psychol Med 2003;33:827–838
83. Keitner GI, Ryan CE, Miller IW, et al. 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). Am J Psychiatry 1991;148:345–350