Long-Term Outcome of Major Depressive Disorder in Psychiatric Patients Is Variable

K. Mikael Holma, M.D.; Irina A. K. Holma, M.D.; Tarja K. Melartin, M.D., Ph.D.; Heikki J. Rytsälä, M.D., Ph.D.; and Erkki T. Isometsä, M.D., Ph.D.

Objective: The prevailing view of outcome of major depressive disorder (MDD), based on mostly inpatient cohorts sampled from tertiary centers, emphasizes chronicity and frequent recurrences. We investigated the long-term outcome of a regionally representative psychiatric MDD cohort comprising mainly outpatients.

Method: The Vantaa Depression Study included 163 patients with DSM-IV MDD (71.5% of those eligible) diagnosed using structured and semistructured interviews and followed up at 6 months, 18 months, and 5 years with a life chart between February 1, 1997, and April 30, 2004. The effects of comorbid disorders and other predictors on outcome were comprehensively investigated.

Results: Over the 5-year follow-up, 98.8% of patients achieved a symptom state below major depressive episode (MDE) criteria, and 88.4% reached full remission, with the median time to full remission being 11.0 months. Nearly one third (29.3%) had no recurrences, whereas 30.0% experienced 1, 12.9% experienced 2, and 27.9% experienced 3 or more recurrences. Preceding dysthymic disorder (p = .028), cluster C personality disorder (p = .041), and longer MDE duration prior to entry (p = .011) were the most significant predictors of longer time in achieving full remission. Severity of MDD and comorbidity, especially social phobia, predicted probability of, shorter time to, and number of recurrences.

Conclusion: Previous literature on mostly inpatient MDD may have, by generalizing from patients with the most severe psychopathology, overemphasized chronicity of MDD. The long-term outcome of MDD in psychiatric care is variable, with about one tenth of patients having poor, one third having intermediate, and one half having favorable outcomes. In addition to known predictors, cluster C personality disorders and social phobia warrant further attention as predictors of MDD outcome among outpatients.

(J Clin Psychiatry 2008;69:196–205)

Received Nov. 20, 2006; accepted June 11, 2007. From the Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki (all authors); the Department of Psychiatry, Helsinki University Central Hospital (HUCH), Helsinki (Drs. K. Holma, I. Holma, and Isometsä); and HUCH, Peijas Hospital, Healthcare District of Helsinki and Uusimaa, Vantaa (Drs. Melartin and Rytsälä), Finland.

This study was supported by grants from the Academy of Finland, the Healthcare District of Helsinki and Uusimaa, and the Medical Society of Finland.

The authors report no additional financial or other relationships relevant to the subject of this article.

Corresponding author and reprints: Erkki T. Isometsä, M.D., Ph.D., Institute of Clinical Medicine, Department of Psychiatry, Välskärinkatu 12 A, P.O. Box 22, 00014, University of Helsinki, Finland (e-mail: erkki.isometsa@hus.fi).

Major depressive disorder (MDD) is a long-term illness causing considerable worldwide burden.[1] Although the outcome of MDD has been extensively investigated in short- and medium-term studies, only a limited number of major studies have explored the long-term (5 years or more) course of the illness.[2–13] While many of these studies represented landmark research at the time when they were conducted, most are undeniably from a past era of treatment.[2,4,5,7–9,12,13] The different diagnostic criteria, availability of only tricyclic antidepressants, and lack of recommendations for widespread continuation and maintenance phase treatments are all major changes that undermine the generalizability of earlier findings to current practice. Only a few studies have studied long-term outcome among outpatients.[6,10] The majority are inpatient or tertiary-care studies from major universities, which renders the epidemiologic generalizability of these findings uncertain at best.[2–12] In addition, some studies have not used life-chart methods[4,5,7,9,11,12] or structured or semistructured interviews.[4,8] Furthermore, despite comorbid MDD being common[14,15] and rates of relapse and recurrence among comorbid patients being greater than among those with depression alone,[16] the effect of comorbidity on long-term outcome of MDD has been studied surprisingly little. When investigated, the reported prevalences of comorbid disorders appear too low to be credible from the current perspective.[2,6] Overall, an obvious need exists for comprehensive long-term follow-up of representative samples of psychiatric patients with MDD from the current treatment era.

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Based on these earlier, mostly inpatient, studies, MDD appears to be a uniformly chronic illness with a high risk of recurrence and incomplete lifetime recovery.[17] The long-term rates of achieving full remission have been found to vary between 80% and 92%,[2,3,6,12,13] and the long-term risk of recurrence varies between 58% and 95%.[3,6–9,18] However, even after lengthy periods of illness, a significant proportion of patients have been observed to approach remission,[5,19] and the risk of recurrence seems to increase with each successive recurrence and to decrease with longer duration of recovery.[2] Severity of major depressive episode (MDE), longer duration of index episode, preceding dysthymic disorder, and Axis I comorbid disorders have been associated with longer time to remission or nonrecovery,[2,19,20] and the probability of relapse or recurrence has been associated with the number of prior MDEs, longer duration of MDE, comorbid anxiety syndromes, and Axis II disorders.[8,9,11,18,20] Severity of depression has either predicted relapse or recurrence,[3,16] or not,[21] and has been considered a risk factor for partial remission, which causes further exposure to relapse.[6,22] Individual studies have identified some additional risk factors for poor outcome, including female gender,[23] younger[13] or older age,[8] endogenous or melancholic depression,[24] psychotic symptoms,[7] psychosocial impairment,[25] and lack of self-confidence.[26] Overall, whether the prevailing view of long-term outcome is true also of community psychiatric samples warrants investigation. It is also unclear whether the most powerful predictors are the same for short-, medium-, and long-term outcome, and whether the predictors differ depending on the clinical endpoint in question.

In this naturalistic study, we prospectively assessed the outcome of *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) MDD in a sample of 269 secondary-care patients, effectively representing psychiatric patients in a Finnish city. They were patients seeking treatment, being referred to, or already receiving care and currently showing signs of a deteriorating clinical state. We were able to overcome some limitations of previous studies by evaluating a large cohort of psychiatric outpatients and inpatients with MDD, using semistructured interviews to obtain diagnoses on all Axis I and II disorders, along with information on somatic comorbidity and psychosocial factors, and employing the life-chart methodology. The 18-month follow-up outcome findings have been reported earlier.[14] In the present 5-year follow-up study, we investigated long-term outcome and its predictors, expecting these in our representative cohort to be more variable than in preceding studies. We hypothesized that both features of MDD itself (severity of depression, duration of MDE before entry, and number of prior MDEs) and current comorbidity (Axis I, II, and III disorders) would be of importance.

METHOD

The Vantaa Depression Study (VDS) is a collaborative depression research project between 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, Vantaa, Finland. The background and methodology of the VDS have been described previously.[14,16,27]

Screening and Baseline Evaluation

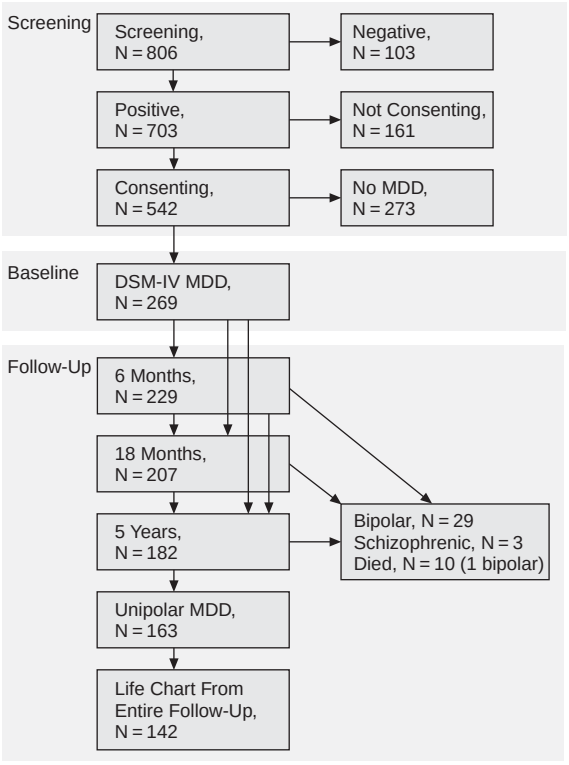
In the first phase of the study, 806 psychiatric subjects were screened for the presence of depressive symptoms during an 18-month period starting February 1, 1997. The study continued until April 30, 2004. Of the 703 eligible subjects, 542 (77%) agreed to participate and gave their written informed consent.[27] The pertinent ethics committee of the Healthcare District of Helsinki and Uusimaa approved the study.

In the second phase, a researcher using the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry (SCAN) 2.0[28] interviewed the 542 consenting patients, 269 of whom were diagnosed as having DSM-IV MDD and were included in the study. Diagnostic reliability was investigated using 20 videotaped diagnostic interviews; the κ coefficient for MDD was 0.86 (95% CI = 0.58 to 1.0), with 95% observed agreement rate. The Structured Clinical Interview for DSM-III-R personality disorders (SCID-II)[29] was used to assess diagnoses on Axis II. The baseline measurements included the 17-item Hamilton Rating Scale for Depression (HAM-D),[30] 21-item Beck Depression Inventory (BDI),[31] Beck Anxiety Inventory (BAI),[32] Beck Hopelessness Scale,[33] Scale for Suicide Ideation,[34] Social and Occupational Functioning Assessment Scale of DSM-IV (SOFAS),[35] Social Adjustment Scale Self-Report,[36] Interview for Recent Life Events,[37] Interview Measure of Social Relationships,[38] Perceived Social Support Scale-Revised,[39] and Eysenck Personality Inventory.[40]

At baseline, the majority of the patients in the MDD cohort were female (73%) and outpatients (83%), half (50%) were married or cohabited, and 60% were currently employed. Most of the patients (79%) had at least 1 comorbid disorder, and the majority (54%) had 2 or more. Over half (57%) had an anxiety disorder, a quarter (25%) had alcohol abuse or dependence, and nearly half (44%) had at least 1 personality disorder diagnosis. At baseline, most patients (88%) received antidepressants, and, for the majority (78%), the dosage was adequate for the acute phase. More than half (57%) received selective serotonin reuptake inhibitors (SSRIs) alone at baseline, about one fifth (18%) received newer antidepressants (tetracyclic, serotonin-norepinephrine reuptake inhibitor, reversible inhibitor of monoamine oxidase), only 8% received tricyclic antidepressants (TCAs), and 6% received

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Figure 1. Flowchart of the Vantaa Depression Study



Abbreviations: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; MDD = major depressive disorder.

combination treatment, usually an SSRI and a TCA. Nearly all patients (98%) received psychotherapeutic support in the early acute phase, but only a few (16%) had weekly psychotherapy.[14,41]

6-Month and 18-Month Follow-Up

After baseline, subjects were investigated at 6 and 18 months with a life-chart methodology and the scales mentioned above. Of the total of 269 subjects with current MDD initially included in the study, 198 unipolar subjects participated in the 18-month follow-up.

5-Year Follow-Up

Of the original cohort, 182 subjects participated in the 5-year follow-up interviews (Figure 1). After complete disclosure of the study to the subjects, written informed consent was obtained. The 5-year follow-up interviews were performed individually by 2 interviewers (K.M.H. and I.A.K.H.); all available medical and psychiatric records were used to complement the information. The average duration of an interview was 2–3 hours and took place in psychiatric outpatient units. The median timing of the 5-year interviews was 65.2 months (SD = 3.7 months) from baseline. By 18 months, 13 subjects' diagnoses had switched to bipolar disorder; at the 5-year follow-up, 16 subjects were diagnosed as having bipolar disorder, 1 was diagnosed with schizophrenia, and 2 were diagnosed with schizoaffective disorders (N = 32). Ten subjects had died, one of whom was bipolar. Thus, after 5 years, 163 unipolar subjects (71.5% of those eligible [N = 228]) remained for the analyses, and 65 subjects dropped out. Life-chart information on 142 of the 163 patients was available from the entire follow-up period.

The baseline sociodemographic and clinical characteristics (N = 163) were as follows: 78% (N = 127) were women; median age was 42.3 years; 88% (N = 143) were outpatients; 57% (N = 93) were married or cohabiting; 64% (N = 105) were employed; 34% (N = 56) were experiencing their first lifetime MDE; 31% (N = 51) were melancholic; 4% (N = 7) had psychotic MDD; 77% (N = 125) had comorbid Axis I or II or both diagnoses; 64% (N = 104) had an Axis I diagnosis; 10% (N = 17) had preceding dysthymic disorder; 55% (N = 89) had an anxiety disorder; 18% (N = 29) had an alcohol use disorder; 40% (N = 66) had a personality disorder; 36% (N = 58) had an Axis III diagnosis; the median 17-item HAM-D score was 18.6; the median 21-item BDI score was 27.0; and the median SOFAS score was 55.0.

The causes for dropping out (N = 65) from the study were as follows: withdrawal of consent (63.1%, N = 41), subjects unreachable despite several efforts (33.8%, N = 22), and subjects living too far away (3.1%, N = 2). The dropouts were younger (median age = 35.3 vs. 42.3 years, Z = –2.20, p = .028), were more likely to be male (36.9% vs. 22.1%, $\chi^2 = 5.28$, df = 1, p = .022), were more likely to be inpatients (24.6% vs. 12.3%, $\chi^2 = 5.33$, df = 1, p = .021), had greater percentages of alcohol dependence (26.2% vs. 6.7%, $\chi^2 = 16.2$, df = 1, p < .001) and psychotic depression (13.8% vs. 4.3%, $\chi^2 = 6.50$, df = 1, p = .011), were more likely to be not married or cohabiting (60.0% vs. 42.9%, $\chi^2 = 5.42$, df = 1, p = .020), and had a slightly lower level of functioning (median SOFAS score = 50 vs. 55, Z = –2.69, p = .007) than subjects included in the 5-year cohort. Despite these differences, the dropouts did not differ from the 5-year cohort in terms of index episode duration, time to full remission, or number of relapses or recurrences during the time they participated in the study.

Outcome Measures

After the baseline assessments, the subjects were prospectively followed up with a life chart, and BDI was rated monthly until 6 months; the outcome of MDD and comorbid disorders was then investigated at 6 and 18 months by repeated SCAN 2.0 and SCID-II interviews. In the 5-year follow-up interviews, we used SCID-I[42] instead of SCAN 2.0 (both generate DSM-IV diagnoses). All observer and self-report scales were included at follow-up assessments.

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

The exact duration of the index episode and the timing of possible relapses/recurrences were examined by gathering all available data, a best estimate of which was then integrated into a graphic of a life chart. This was created after reviewing with the subject all information from the follow-up period. Beside symptom ratings and visits to attending personnel, we also inquired about change points in the psychopathological states using probes related to important life events in order to improve the accuracy of the assessment. Our life-chart method was similar, but not identical, to the Longitudinal Interval Follow-up Evaluation (LIFE) methodology used in the National Institute of Mental Health Collaborative Depression Study (CDS), developed by Keller et al.[43] Unlike LIFE, we classified the patients' follow-up time into 3 periods: (1) full remission (none of the 9 MDE criteria symptoms), (2) partial remission (1–4 of the 9 symptoms), or (3) MDE (5 or more 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 during which the criteria for MDE were not met. Relapse was defined as a return of symptoms fulfilling the DSM-IV criteria for MDE, after a period with symptoms below the MDE threshold of less than 2 months (but more than 2 weeks). Recurrence was defined as in the DSM-IV definition for 296.3x MDD, Recurrent, as return of symptoms sufficiently severe to satisfy criteria for MDE after at least 2 consecutive months of partial or full remission.

In our 5-year follow-up analyses, we concentrated on 4 outcome measures: (1) time to full remission (time to the first onset of state of full remission lasting at least 2 consecutive months), (2) time to first recurrence after baseline, (3) probability of experiencing a recurrence, and (4) number of recurrences.

Statistical Methods

We used Kaplan-Meier survival curves to estimate the probability of remaining ill during the 5-year follow-up. Cox proportional hazards models were used for univariate and multivariate analyses to predict time to full remission or first recurrence. Univariate and multivariate logistic regression models were used for analysis of the probability of recurrence, and the linear regression model was used for analysis of the number of recurrences. In these analyses, censored data included (1) subjects who had not met the criteria for the endpoint event of analysis, either by the end of the follow-up period, or by the time they left the study and (2) subjects whose diagnoses changed before the endpoint event from unipolar to bipolar disorder or schizophrenia. All available information on the subjects was used for analyses, and all analyses were controlled for age and gender; regression analyses were also controlled for the time at risk. Subjects who had experienced a recurrence were compared with those who had not using the χ^2 statistic with Yates continuity correction or Fisher exact test when the expected cell count was less than 5 in the 2×2 table. In comparisons of continuous variables, the 2-sample t test was used for normal distribution, and the Mann-Whitney and Kruskal-Wallis tests were used for nonnormal distribution. The distribution of some continuous variables was found to be somewhat problematic, and, thus, information was dichotomized or reclassified, and graphical methods were used to control the results. The baseline predictors represented different domains of risk factors, e.g., sociodemographic features, outpatient status, clinical features of MDD, symptom and functional ability scales, Axis I and II comorbid disorders, number of Axis III disorders, MDD subtype features, and various psychosocial and personality factors. After detailed univariate analyses, we chose predictors for our final models by considering their clinical and statistical validity, significance, and relevance. The Statistical Package for Social Sciences software (SPSS), version 13.0 (SPSS Inc., Chicago, Ill.), was used.

RESULTS

At 5 years, half of the followed-up subjects (49.7%, 81/163) were in full remission, i.e., without any significant depressive symptoms, and one fourth (23.9%, 39/163) were currently in the midst of an MDE. Median scores were 8.0 (SD = 8.3) for the 17-item HAM-D, 7.0 (SD = 10.2) for the 21-item BDI, 9.0 (SD = 10.8) for the BAI, and 70.0 (SD = 15.0) for the SOFAS. The median 17-item HAM-D score was 23.0 for those currently in an MDE. At 5 years, 49.7% (N = 81) of the subjects did not receive any treatment. One fourth (24.5%, N = 40) were currently receiving psychosocial treatment, 15.3% (N = 25) were receiving psychotherapeutic support, and 9.2% (N = 15) were receiving weekly psychotherapy. Nearly half (44.8%, N = 73) were currently using an antidepressant. One sixth (14.7%, N = 24) had been hospitalized between the 18-month and 5-year follow-ups (median number of psychiatric hospitalizations = 1.0, SD = 1.2).

Within 5 years, 98.8% of the cohort achieved a symptom state below MDE criteria, with 1.2% (2 subjects) remaining in the index MDE. Seven percent of subjects (10/142) suffered from MDE continuously for 2 years or more. The subjects on average spent over half of the follow-up period in full remission (median time = 37.4 months, SD = 21.6), one fifth of the time in an MDE state (median time = 7.5 months, SD = 14.6), and one third of the time in partial remission (median time = 17.2 months, SD = 16.8) (Figure 2).

For descriptive purposes, the cohort was divided into 3 groups on the basis of time spent in various symptom states (Figure 2). About half (54.9%) of the subjects had a quite good outcome, i.e., spent most of the time after the index episode in full remission; one tenth (10.6%) suffered for most of the time from MDEs; and one third

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Figure 2. Time Spent in a Major Depressive Episode (MDE), in Partial Remission, and in Full Remission in the Vantaa Depression Study Over a 5-Year Follow-Up

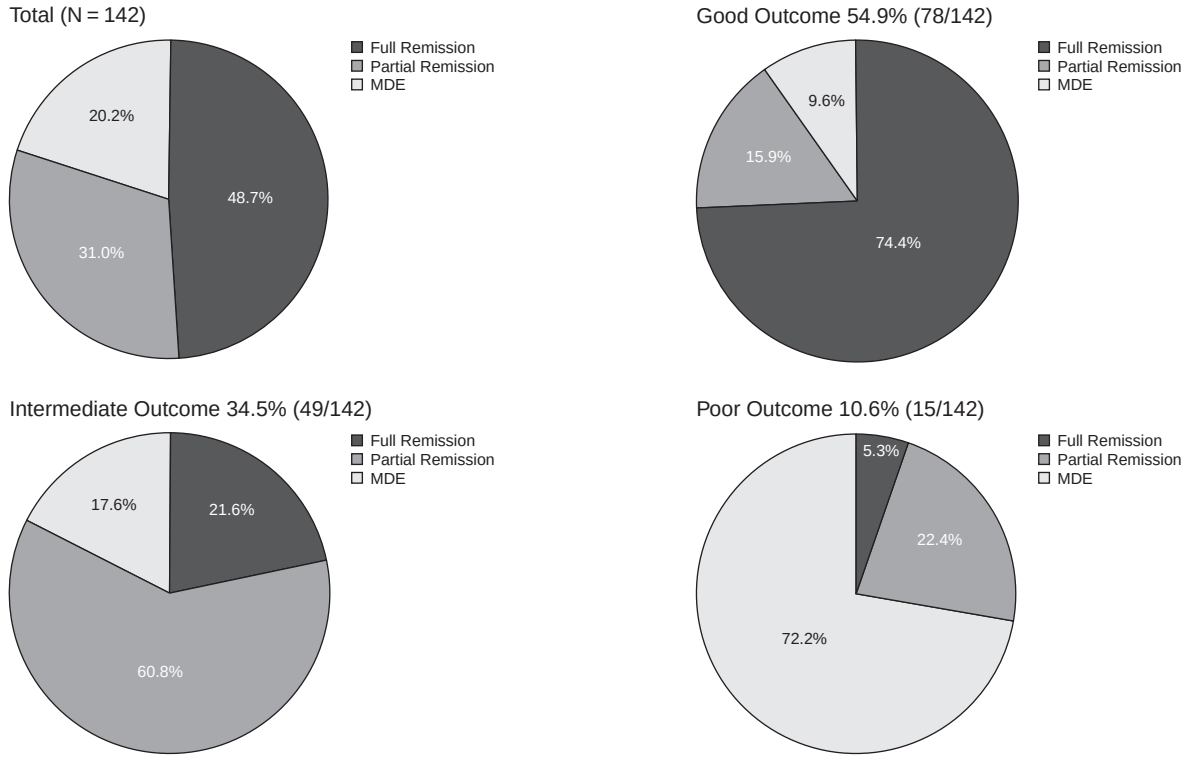
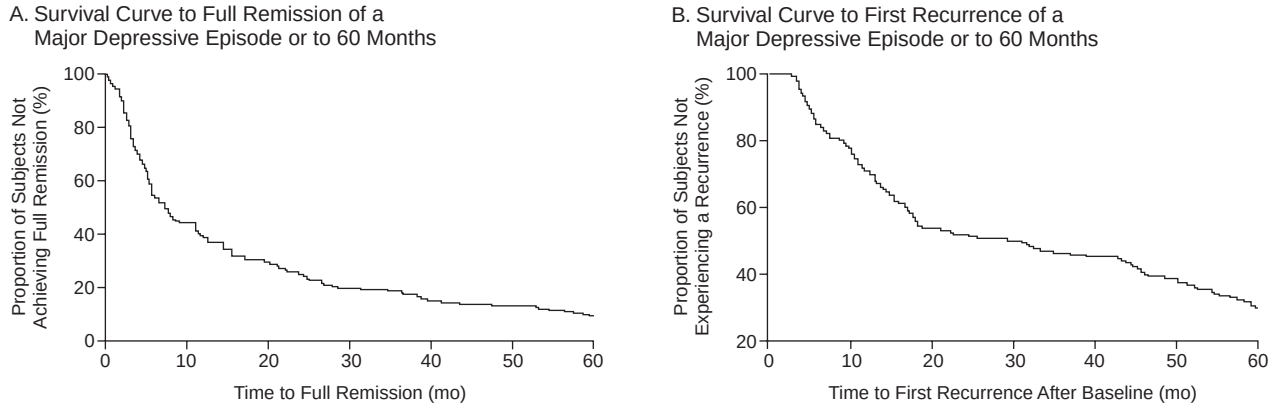


Figure 3. Survival Curves



(34.5%) had an intermediate outcome, i.e., suffered from some symptoms (partial remission) for most of the time.

Time to Full Remission

By 5 years, 88.4% of the subjects (130/147) had reached full remission lasting at least 2 months. The median time to first full remission was 11.0 months (95% CI = 7.4 to 14.6) (Figure 3A). The median index episode duration was 1.6 months from baseline and 5.5 months altogether (time with full criteria).

In univariate analyses, several individual factors predicted the time to full remission (Table 1). However, after removing all nonsignificant findings, in multivariate Cox proportional hazards analyses, preceding dysthymic disorder, cluster C personality disorder, and longer MDE preceding entry prolonged the time to full remission

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Table 1. Univariate Analyses of All Possible Predictors of Time to Full Remission, Recurrence, and Time to First Recurrence of Major Depressive Disorder (MDD) in the Vantaa Depression Study Over a 5-Year Follow-Up

	Time to Full Remission[a]			Recurrence[b]			Time to First Recurrence[a]		
Predictor at Entry	HR	95% CI	p	OR	95% CI	p	HR	95% CI	p
Age, y	1.02	1.00 to 1.03	.011	0.97	0.94 to 1.00	.070	1.00	0.98 to 1.01	.512
Gender (male)	0.94	0.66 to 1.32	.701	0.91	0.40 to 2.08	.822	1.06	0.70 to 1.58	.794
Outpatient status	1.09	0.70 to 1.70	.710	0.27	0.06 to 1.25	.094	1.68	1.04 to 2.71	.034
Clinical features of MDD									
Age at onset, y	1.00	0.99 to 1.02	.838	0.96	0.92 to 1.00	.069	1.02	1.00 to 1.04	.031
Longer MDE prior to entry	1.30	1.08 to 1.57	.006	0.96	0.91 to 1.02	.206	0.98	0.95 to 1.02	.320
No. of previous episodes	1.00	0.93 to 1.08	.902	1.34	1.01 to 1.77	.038	0.91	0.86 to 0.96	.001
Symptoms and functional ability									
17-item HAM-D	1.02	1.00 to 1.05	.094	1.12	1.04 to 1.20	.002	0.95	0.92 to 0.98	.001
21-item BDI	1.02	1.00 to 1.04	.057	1.07	1.02 to 1.13	.008	0.97	0.95 to 0.99	.002
Beck Anxiety Inventory	1.02	1.00 to 1.03	.052	1.03	1.00 to 1.07	.084	0.98	0.96 to 1.00	.019
Beck Hopelessness Scale	1.03	1.00 to 1.07	.039	1.07	0.99 to 1.16	.098	0.96	0.92 to 1.00	.039
Scale for Suicide Ideation	1.18	0.99 to 1.40	.061	1.07	1.01 to 1.13	.018	0.97	0.95 to 0.99	.005
SOFAS	0.99	0.97 to 1.01	.215	0.96	0.92 to 1.00	.073	1.02	1.00 to 1.04	.036
Axis I comorbidity									
Dysthymic disorder	1.96	1.07 to 3.57	.029	0.72	0.24 to 2.20	.567	0.99	0.52 to 1.89	.983
Anxiety disorders	0.97	0.72 to 1.31	.840	1.06	0.51 to 2.21	.878	0.84	0.58 to 1.21	.344
Phobic/nonphobic	0.99	0.73 to 1.34	.037	1.54	0.70 to 3.38	.282	0.70	0.49 to 1.01	.056
Panic disorder									
With agoraphobia	0.79	0.38 to 1.62	.516	1.25	0.13 to 12.1	.846	0.83	0.30 to 2.30	.713
Without agoraphobia	0.95	0.56 to 1.58	.833	0.53	0.17 to 1.67	.281	0.84	0.42 to 1.65	.606
Agoraphobia without panic	0.97	0.59 to 1.57	.890	1.04	0.31 to 3.51	.952	1.03	0.59 to 1.81	.919
Specific phobia	1.12	0.79 to 1.59	.529	1.04	0.45 to 2.44	.926	0.86	0.57 to 1.28	.451
Social phobia	0.76	0.51 to 1.14	.191	8.93	1.14 to 71.4	.037	0.42	0.26 to 0.68	< .001
Obsessive-compulsive disorder	0.80	0.39 to 1.65	.552	1.39	0.27 to 7.24	.698	0.80	0.37 to 1.72	.570
Generalized anxiety disorder	1.08	0.68 to 1.71	.743	1.00	0.35 to 2.84	.996	0.97	0.56 to 1.68	.914
Alcohol use disorders	0.71	0.48 to 1.05	.085	1.31	0.47 to 3.66	.608	0.72	0.46 to 1.14	.159
Dependence	0.69	0.41 to 1.18	.180	1.50	0.29 to 7.63	.625	0.55	0.31 to 0.98	.041
Abuse	0.77	0.47 to 1.28	.316	1.15	0.34 to 3.92	.820	1.00	0.54 to 1.83	.989
Axis II comorbidity									
Personality disorders	1.21	0.89 to 1.64	.225	1.21	0.56 to 2.58	.627	0.81	0.56 to 1.17	.258
Cluster A	0.82	0.54 to 1.24	.342	2.14	0.67 to 6.76	.197	0.67	0.43 to 1.04	.073
Cluster B	1.00	0.65 to 1.55	.999	1.38	0.41 to 4.59	.601	0.75	0.45 to 1.26	.275
Cluster C	1.42	1.01 to 2.00	.041	2.00	0.82 to 4.83	.126	0.74	0.50 to 1.10	.136
No. of psychiatric disorders	1.03	0.94 to 1.13	.488	1.22	0.95 to 1.55	.116	0.86	0.77 to 0.96	.005
No. of current somatic disorders	1.06	0.93 to 1.20	.946	1.05	0.41 to 2.13	.735	1.01	0.86 to 1.18	.942
No. of all Axis I–III disorders	1.04	0.97 to 1.11	.307	1.10	0.92 to 1.31	.308	0.92	0.85 to 1.00	.040
MDD subtype features									
Melancholic	0.72	0.53 to 0.98	.039	1.68	0.75 to 3.76	.212	0.86	0.59 to 1.25	.418
Atypical	0.76	0.46 to 1.25	.280	0.79	0.22 to 2.76	.706	0.83	0.46 to 1.52	.549
Psychotic	1.71	0.95 to 3.08	.178	0.61	0.13 to 2.79	.522	1.23	0.54 to 2.82	.629
Psychosocial and personality factors									
Size of social network	0.97	0.93 to 1.01	.123	0.95	0.86 to 1.04	.269	0.99	0.94 to 1.04	.603
PSSS-R	0.99	0.97 to 1.00	.015	0.99	0.96 to 1.02	.377	1.01	0.99 to 1.02	.447
Negative life events[c]	0.97	0.94 to 1.01	.108	0.98	0.90 to 1.07	.631	1.00	0.96 to 1.04	.848
Neuroticism[d]	1.03	0.99 to 1.07	.178	1.09	0.99 to 1.20	.071	0.95	0.90 to 1.00	.044
Extroversion[d]	0.97	0.93 to 1.00	.044	0.96	0.89 to 1.04	.350	1.02	0.97 to 1.06	.464
Married or cohabiting	1.13	0.84 to 1.53	.412	1.24	0.59 to 2.58	.573	0.85	0.59 to 1.22	.377
Income	0.94	0.67 to 1.30	.701	0.85	0.39 to 1.86	.679	0.95	0.64 to 1.39	.779
Employed	0.86	0.62 to 1.18	.351	1.56	0.72 to 3.37	.255	0.82	0.55 to 1.21	.316
Professional education	1.35	0.98 to 1.84	.063	1.38	0.63 to 3.01	.422	0.89	0.62 to 1.29	.533
Residential area (East Vantaa)	1.62	1.19 to 2.21	.002	1.33	0.63 to 2.81	.457	0.97	0.66 to 1.42	.887

[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 and gender, and time at risk.
[c]Interview for Recent Life Events: objective measure of negative impact of adverse life events.
[d]Eysenck Personality Inventory: for dimensions of neuroticism and extroversion.
Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, MDE = major depressive episode, PSSS-R = Perceived Social Support Scale-Revised, SOFAS = Social and Occupational Functioning Assessment Scale.

significantly (Table 2). Furthermore, within cluster C personality disorders, avoidant personality was the strongest predictor (hazard ratio [HR] = 0.67, 95% CI = 0.46 to 0.98, p = .040). Severity of MDD predicted longer time to full remission as a trend (HR = 0.98, 95% CI = 0.95 to 1.00, p = .096). Median time to full remission was longer for those who suffered from preceding dysthymic disorder (14.2 vs. 6.5 months), cluster C personality disorder (11.5 vs. 6.1 months), or MDE longer prior to entry (15.2 vs. 5.5 months).

Recurrence

During the 5-year follow-up, 70.7% (99/140) of subjects had a recurrence (Figure 3B). The median duration

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Table 2. Baseline Predictors of Time to Full Remission, Recurrence, and Time to First Recurrence of Major Depressive Disorder (MDD) in the Vantaa Depression Study Over a 5-Year Follow-Up

Predictor	HR	95% CI	p
Time to full remission[a]			
Longer MDE prior to entry	1.28	1.06 to 1.54	.011
Preceding dysthymic disorder	1.96	1.07 to 3.58	.028
Cluster C personality disorder	1.43	1.02 to 2.01	.041
Time to first recurrence[a]			
Severity of MDD (HAM-D)	0.94	0.92 to 0.98	.001
Social phobia	0.41	0.25 to 0.66	< .001
	OR		
Recurrence[b]			
Age	0.96	0.92 to 0.99	.018
Severity of MDD (HAM-D)	1.11	1.04 to 1.20	.003
Social phobia	8.26	1.04 to 66.7	.045

[a]Multivariate Cox proportional hazards models, adjusted for sex and age.
[b]Multivariate logistic regression models, adjusted for sex, age, and duration of follow-up.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MDE = major depressive episode.

Table 3. Number of Recurrences and Baseline Severity of Major Depressive Disorder (MDD) in the Vantaa Depression Study Over a 5-Year Follow-Up[a]

	Baseline Severity of MDD					
	Mild or Moderate		Severe or Psychotic		Total	
No. of Recurrences	N	%	N	%	N	%
0	33	38.8	8	14.5	41	29.3
1	25	29.4	17	30.9	42	30.0
2	10	11.8	8	14.5	18	12.9
3	10	11.8	10	18.2	20	14.3
4	2	2.4	6	10.9	8	5.7
5	3	3.5	2	3.6	5	3.6
6	2	2.4	4	7.3	6	4.3
Total	85	60.7	55	39.3	140	100
	No. of Recurrences		No. of Recurrences		No. of Recurrences	
Median	1.0		2.0		1.0	
Mean	1.29		2.20		1.63	
SD	1.51		1.74		1.65	

[a]Difference in number of recurrences between mild or moderate and severe or psychotic MDD, Mann-Whitney U test, Z = –3.40, p = .001.

of recurrent episodes was 2.9 months (SD = 1.4), i.e., shorter than index episodes.

Recurrence was predicted by several baseline factors (Table 1). However, after removing nonsignificant variables, younger age, severity of depression, and social phobia remained significant in multivariate logistic regression analyses (Table 2). There was a nonsignificant trend for number of previous episodes to predict recurrence (OR = 1.31, 95% CI = 0.99 to 1.74, p = .062). Recurrence was experienced by 56% (5/9) of subjects with mild, 66% (55/84) of subjects with moderate, and 88% (59/67) of subjects with severe or psychotic depression (χ^2 = 11.75, df = 2, p = .003). There was also a nonsignificant tendency for younger subjects (baseline age under 30 years) experiencing recurrence more often than other age groups, 82% (22/27) vs. 68% (77/113), respectively (χ^2 = 1.87, df = 1, not significant). A majority of subjects with social phobia, 94% (16/17), had a recurrence; for subjects without social phobia, the corresponding figure was 68% (83/123) (χ^2 = 6.55, df = 1, p = .017).

Time to First Recurrence

The mean time to first recurrence was 39.7 months (95% CI = 35.1 to 44.2) from baseline and 37.5 months (95% CI = 32.8 to 42.2) from the end of the index episode when calculated excluding time with full MDE criteria (Figure 3). The median duration of the first recurrent period was 2.3 months (SD = 8.0).

Time to first recurrence after baseline was predicted in univariate analyses by many baseline factors (Table 1), but after multivariate analyses, severity of MDD and number of comorbid disorders remained significant in the Cox model. When different comorbid disorders were added to the model simultaneously, social phobia was found to be by far the most significant disorder (Table 2). The mean time to first recurrence was 50.9 months (95% CI = 35.4 to 66.4) for subjects with mild, 42.9 months (95% CI = 36.6 to 49.2) for subjects with moderate, and 26.8 months (95% CI = 20.2 to 33.3) for subjects with severe or psychotic depression (log-rank χ^2 = 14.6, df = 2, p = .001). Subjects with social phobia experienced a recurrence over twice as fast as did those without social phobia, i.e., after a mean time of 17.9 months versus 40.1 months (95% CI = 9.4 to 26.3 vs. 35.1 to 45.2) (log-rank χ^2 = 12.0, df = 1, p = .001).

Number of Recurrences

During the 5-year follow-up, the subjects experienced a median number of 1.0 recurrences (SD = 1.66). One fourth of the subjects (27.9%, 39/140) experienced 3 or more recurrences (Table 3).

In univariate analyses, the number of recurrences was predicted by a number of baseline variables, including age at onset, severity of MDE, severity of anxiety, suicidal ideation, social phobia, and alcohol dependence. After multivariate linear regression analyses, severity of depression (HAM-D), social phobia, and younger age at onset as a trend remained significant (β = .04, 95% CI = 0.02 to 0.06, p = .001; β = .60, 95% CI = 0.21 to 0.99, p = .003; and β = –.01, 95% CI = –0.02 to 0.002, p = .084, respectively).

DISCUSSION

The long-term outcome of MDD in psychiatric (community-care) patients seems to be less uniform than

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

in earlier, mostly inpatient studies. One tenth of our secondary-care MDD patients had a poor outcome, while one half had a favorable outcome. Almost all patients recovered over time from their index episode, with 88% reaching full remission at some point. Nevertheless, nearly three fourths experienced at least 1 recurrence within 5 years, but most of these recurrences were briefer than the index episode. The finding that severity of MDD had a marked impact on the number of recurrences and time spent ill is, in our view, of fundamental importance when generalizations are made regarding outcome of depression. The predictors for outcome may, to some extent, also be different among outpatient samples than among the severely ill inpatients previously investigated.

Our study has some major strengths. It comprises a cohort of patients representing psychiatric outpatients and inpatients with MDD in a large Finnish city; two thirds of all depressed subjects in the city of Vantaa are estimated to be treated in the Peijas Medical Care District.[27] The study is from the modern era in terms of the use of DSM-IV diagnoses and definitions, modern antidepressants, and maintenance treatment recommendations. To our knowledge, no previous study has investigated the impact of both Axis I and II comorbidity on the long-term outcome of depression. The effect of psychosocial factors was also examined; structured and semistructured measures, both objective and subjective, were used. Furthermore, we used a life chart. However, some limitations also need to be noted. The attrition rate was 28.5% of those living and not having switched to bipolar disorder. Although the dropouts had characteristics often associated with poor outcome, it appears unlikely that they would have biased our findings regarding likelihood of recurrence, as they did not differ from those included in terms of index episode duration, time to full remission, or number of relapses or recurrences during the period they participated in the study. Because of the naturalistic nature of our study, the treatment received was not controlled for. When comparisons are made with other studies, it should be noted that our definition for full remission was strict.[16] Lastly, although we had full access to patient records, a long follow-up period, 3.5 years between the last 2 interviews, may have affected the accuracy of information regarding longitudinal outcome. As seen from the shape of the curve in Figure 3B, we probably slightly underestimated (approximately by 10% overall) the recurrence rate during the time most remote from the 5-year interview after 18 months.

We expected the long-term outcome of our mainly outpatient cohort to be more variable than in earlier studies, and this indeed proved to be the case. Studies with mostly inpatients have generally reported larger proportions of incapacitation over time[3,7,8,12] and smaller proportions of subjects having a good outcome.[7,8,44] Moreover, many studies have found chronicity to be a major problem. By contrast, our proportion of subjects never achieving even partial remission was small (1.2%), and the rate for chronic, uninterrupted MDE for 2 years or more (7%) was lower than in other studies.[2–4] Also, in contrast to previous studies, the median index episode duration (1.6 months from baseline, 5.5 months altogether) was much shorter,[8,18,45] but the median time to full remission was longer (11 months vs. 3–7 months).[2,3,18,45] Thus, the problem of partial remission after index episode was evident, although the proportion of time spent in partial remission during the 5 years was still lower than reported in the CDS and the Cambridge cohorts.[22,23] The overall more variable outcome in our study is likely to be due to the less selected nature of our cohort compared with previous predominantly inpatient cohorts from a preceding treatment era. We suggest that the prevailing psychiatric view of MDD as a uniformly chronic disorder needs to be revised. Recently, estimates of lifetime suicide mortality related to depression have undergone a similar revision, as the earlier high estimates of 15% of depressed patients dying by suicide were based on biased generalizations from inpatient populations.[46]

The probability of recurrence (71%) in our study was somewhat lower than in previous studies,[2,4,8] but, as already noted, this figure may be underestimated. However, unlike in inpatient studies, the pattern of recurrence resembled that of community samples, i.e., the recurrent episodes were shorter than the index episode.[47,48] The low rate of hospitalizations (15% after 18 months) also likely reflects milder recurrences during follow-up. Time to first recurrence and median number of recurrences corresponded to the results of previous studies.[49] However, the more heterogeneous baseline severity of depression in our cohort allowed us to verify the marked impact of severity on probability of recurrence. The findings that baseline severity of MDD predicts probability of recurrence, shorter time to first recurrence, and number of recurrences not only confirm results of our 18-month follow-up[16] over the long term, but also have implications for generalizations about risk of recurrence and potentially also for indications for maintenance treatment. Within the range of clinical severity common among outpatients, risk of recurrence is highly dependent on it.

Previous studies have largely either excluded comorbid patients or ignored the role of psychiatric comorbidity in the long-term outcome of MDD. We deliberately included comorbid cases and took into account the effect of these disorders, together with known predictors, and found comorbidity to play a major role in outcome. STAR*D,[50] a large outpatient clinical trial, has now taken into account the role of comorbid Axis I disorders on the outcome of MDD. Unfortunately, STAR*D has not studied the effect of Axis II disorders at all, and the long-term outcome has not yet been investigated. In our study, cluster C personality disorders, especially avoidant

 © Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

personality and preceding dysthymic disorder, significantly delayed time to full remission. Preceding dysthymic disorder reducing chances of recovery is a replication of the finding by Keller et al.[2] In some short- and medium-term studies, comorbid cluster C personality disorders have been found to be associated with slower recovery and longer time to response or nonresponse in different phases of MDD treatment.[51,52] In our long-term study, time to full remission was twice as long for subjects with preceding dysthymic disorder or cluster C personality disorder as for those without these diagnoses. We also found social phobia to be associated with overall risk of recurrence, shorter time to first recurrence, and number of recurrences. Earlier community studies have indicated associations between anxiety disorders or social phobia and the development of first MDE or relapse.[20,53,54] However, to our knowledge, studies have not specifically investigated the association of social phobia with MDE recurrences. Temperamental predispositions, tendency for social isolation due to avoidance, or a more cyclic course might explain why comorbid social phobia appears to increase the vulnerability to recurrence. Overall, the predictors for outcome of depression may, to some extent, be different among outpatient samples than among the severely ill inpatients mostly investigated to date. The plausibility of social phobia as a putative predictor of recurrence warrants further investigation.

In conclusion, the long-term outcome of MDD appears to be more variable when outcome is investigated among modern, community-treated, secondary-care outpatients than among inpatients. Major depressive disorder is highly recurrent also in these settings, but the recurrences seem briefer, and the outcome is unlikely to be uniformly chronic. The finding that severity of MDD had a marked impact on the number of recurrences and time spent ill is, in our view, of fundamental importance when generalizations are made regarding the outcome of depression. In addition to known predictors, such as episode duration and preceding dysthymic disorder, comorbid cluster C personality disorders and social phobia warrant further research as potential predictors of outcome.

REFERENCES

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349: 1436–1442
2. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: a 5-year prospective follow-up of 431 subjects. Arch Gen Psychiatry 1992;49:809–816
3. 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
4. Angst J, Kupfer DJ, Rosenbaum JF. Recovery from depression: risk or reality? Acta Psychiatr Scand 1996;93:413–419
5. 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
6. Kanai T, Takeuchi H, Furukawa TA, et al. Time to recurrence after recovery from major depressive episodes and its predictors. Psychol Med 2003;33:839–845
7. Lee AS, Murray RM. The long-term outcome of Maudsley depressives. Br J Psychiatry 1988;153:741–751
8. Surtees PG, Barkley C. Future imperfect: the long-term outcome of depression. Br J Psychiatry 1994;164:327–341
9. 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
10. Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. Am J Psychiatry 2006;163:872–880
11. 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
12. 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
13. 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
14. 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
15. Zimmerman M, Chelminski I, McDermut W. Major depressive disorder and Axis I diagnostic comorbidity. J Clin Psychiatry 2002;63:187–193
16. Melartin TK, Rytsälä HJ, Leskelä US, et al. Severity and comorbidity predict episode duration and recurrence of DSM-IV major depressive disorder. J Clin Psychiatry 2004;65:810–819
17. Judd LL. The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry 1997;54:989–991
18. 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
19. Mueller TI, Keller MB, Leon AC, et al. Recovery after 5 years of unremitting major depressive disorder. Arch Gen Psychiatry 1996;53: 794–799
20. 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
21. Keller MB, Lavori PW, Lewis CE, et al. Predictors of relapse in major depressive disorder. JAMA 1983;250:3299–3304
22. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;50:97–108
23. Kennedy N, Abbott R, Paykel ES. Longitudinal syndromal and subsyndromal symptoms after severe depression: 10-year follow-up study. Br J Psychiatry 2004;184:330–336
24. Kiloh LG, Andrews G, Neilson M. The long-term outcome of depressive illness. Br J Psychiatry 1988;153:752–757
25. Solomon DA, Leon AC, Endicott J, et al. Psychosocial impairment and recurrence of major depression. Compr Psychiatry 2004;45:423–430
26. Surtees PG, Wainwright NW. Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. Br J Psychiatry 1996;169:338–347
27. Rytsälä HJ, Melartin TK, Leskelä US, et al. A record-based analysis of 803 patients treated for depression in psychiatric care. J Clin Psychiatry 2001;62:701–706
28. Wing JK, Babor T, Brugha T, et al. SCAN: Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990;47:589–593
29. Spitzer RL, Williams JBW, Gibbon M. Instruction Manual for the Structured Clinical Interview for DSM-III-R (SCID). New York, NY: Biometrics Research Department; 1989
30. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
31. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
32. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin

© Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.

Psychol 1988;56:893–897
33. Beck AT, Weissman A, Lester D, et al. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol 1974;42:861–865
34. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 1979;47:343–352
35. 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
36. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111–1115
37. Paykel ES. Methodological aspects of life events research. J Psychosom Res 1983;27:341–352
38. 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
39. Blumenthal JA, Burg MM, Barefoot J, et al. Social support, type A behavior, and coronary artery disease. Psychosom Med 1987;49:331–340
40. Eysenck HJ, Eysenck ES. Manual of Eysenck Personality Inventory. London, England: University of London Press LTD; 1964
41. Melartin TK, Rytsälä HJ, Leskelä US, et al. Continuity is the main challenge in treating major depressive disorder in psychiatric care. J Clin Psychiatry 2005;66:220–227
42. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen. New York, NY: Biometrics Research, New York State Psychiatric Institute; 2002
43. Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44:540–548
44. Andrews G, Neilson M, Hunt C, et al. Diagnosis, personality and the long-term outcome of depression. Br J Psychiatry 1990;157:13–18
45. Furukawa TA, Kitamura T, Takahashi K. Time to recovery of an inception cohort with hitherto untreated unipolar major depressive episodes. Br J Psychiatry 2000;177:331–335
46. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry 2000;157:1925–1932
47. Melartin T, Leskelä U, Rytsälä H, et al. Comorbidity and stability of melancholic features in DSM-IV major depressive disorder. Psychol Med 2004;34:1443–1452
48. Spijker J, De Graaf R, Bijl 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
49. Solomon DA, Keller MB, Leon AC, et al. Multiple recurrences of major depressive disorder. Am J Psychiatry 2000;157:229–233
50. 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
51. Viinamaki 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
52. Morse JQ, Pilkonis PA, Houck PR, et al. Impact of cluster C personality disorders on outcomes of acute and maintenance treatment in late-life depression. Am J Geriatr Psychiatry 2005;13:808–814
53. Bittner A, Goodwin RD, Wittchen HU, et al. What characteristics of primary anxiety disorders predict subsequent major depressive disorder? J Clin Psychiatry 2004;65:618–626; quiz 730
54. Kessler RC, Stang P, Wittchen HU, et al. Lifetime comorbidities between social phobia and mood disorders in the US National Comorbidity Survey. Psychol Med 1999;29:555–567

 © Copyright 2008 Physicians Postgraduate Press, Inc. © Copyright 2008 Physicians Postgraduate Press, Inc.