

A Prospective 12-Year Study of Subsyndromal and Syndromal Depressive Symptoms in Unipolar Major Depressive Disorders

Lewis L. Judd, MD; Hagop S. Akiskal, MD; Jack D. Maser, PhD; Pamela J. Zeller, PhD; Jean Endicott, PhD; William Coryell, MD; Martin P. Paulus, MD; Jelena L. Kunovac, MD; Andrew C. Leon, PhD; Timothy I. Mueller, MD; John A. Rice, PhD; Martin B. Keller, MD

Background: Investigations of unipolar major depressive disorder (MDD) have focused primarily on major depressive episode remission/recovery and relapse/recurrence. This is the first prospective, naturalistic, long-term study of the weekly symptomatic course of MDD.

Methods: The weekly depressive symptoms of 431 patients with MDD seeking treatment at 5 academic centers were divided into 4 levels of severity: (1) depressive symptoms at the threshold for MDD; (2) depressive symptoms at the threshold for minor depressive or dysthymic disorder (MinD); (3) subsyndromal or subthreshold depressive symptoms (SSDs), below the thresholds for MinD and MDD; and (4) no depressive symptoms. The percentage of weeks at each level, number of changes in symptom level, and medication status were analyzed overall and for 3 subgroups defined by mood disorder history.

Results: Patients were symptomatically ill in 59% of weeks. Symptom levels changed frequently (1.8/y), and

9 of 10 patients spent weeks at 3 or 4 different levels during follow-up. The MinD (27%) and SSD (17%) symptom levels were more common than the MDD (15%) symptom level. Patients with double depression and recurrent depression had more chronic symptoms than patients with their first lifetime major depressive episode (72% and 65%, respectively, vs 46% of follow-up weeks).

Conclusion: The long-term weekly course of unipolar MDD is dominated by prolonged symptomatic chronicity. Combined MinD and SSD level symptoms were about 3 times more common (43%) than MDD level symptoms (15%). The symptomatic course is dynamic and changeable, and MDD, MinD, and SSD symptom levels commonly alternate over time in the same patients as a symptomatic continuum of illness activity of a single clinical disease.

Arch Gen Psychiatry. 1998;55:694-700

LONGITUDINAL STUDIES of unipolar major depressive disorder (MDD) by Angst et al^{1,2} and Keller et al³⁻⁵ have described relapse and chronicity of major depressive episode (MDE) during the course of MDD. Detailed characterization of the disease between MDEs has rarely been the focus of systematic investigation. Some information on clinical course has been gleaned indirectly from cross-sectional studies of MDD in which alternative depressive subtypes have been described, eg, dysthymic disorder,⁶ minor depressive disorder (MinD),⁷ double depression,⁸ recurrent brief depression,⁹ and subsyndromal or subthreshold depressive symptoms (SSDs).¹⁰⁻¹⁶

Study of depressive subtypes suggests that the clinical course of MDD may be more pleomorphic and varied than previously thought. This has stimulated debate about whether MDD is a single clinical

disease characterized by a continuum of different subtypes or levels of symptoms vs the alternative proposition that unipolar disorders are a cluster of distinct clinical entities, each with different clinical characteristics and biological substrates.

After a lifetime investigating mood disorders, Winokur¹⁶ proposed that unipolar depression is clinically homogeneous but etiologically heterogeneous. Support for this position has been provided recently by various research groups.¹⁷⁻²¹ For example, we found a high rate of change in depressive subtype diagnoses for epidemiologic catchment area respondents with one diagnosis at wave 1 and another symptom level or depressive subtype 1 year later at wave 2, suggesting a dynamic, changeable clinical course of MDD even during short follow-up.¹⁷

To provide a clear test of the single clinical illness hypothesis of unipolar depression, we conducted weekly analyses

See the acknowledgments at the end of this article for the affiliations of the authors and for a list of additional contributors.

SUBJECTS AND METHODS

SUBJECTS

The analysis sample consisted of all 431 patients with unipolar MDD who entered the CDS^{22,23} during an MDE at 1 of 5 tertiary care centers from 1978 to 1981. Patients were diagnosed using Research Diagnostic Criteria²⁴ based on the Schedule for Affective Disorders and Schizophrenia.²⁵ No patient had evidence of bipolar disorder (mania, hypomania, cyclothymic personality), schizoaffective disorder, or schizophrenia prior to intake or during follow-up. Subjects were white, spoke English, had an IQ score of at least 70, and had no evidence of organic mental disorder or terminal medical illness. Informed consent was obtained.

To evaluate the influence of mood disorder history on the course of illness, the MDD cohort was divided into 3 mutually exclusive groups: (1) patients in their first lifetime MDE in the absence of ongoing dysthymia ($n = 122$, 28% of the sample), (2) patients with 1 or more prior MDEs in the absence of ongoing dysthymia ($n = 205$, 47% of the sample), and (3) patients with double depression (MDE superimposed on ongoing dysthymic disorder) ($n = 104$, 24% of the sample). The demographic and clinical characteristics of the total MDD sample and the 3 subgroups are summarized in **Table 1**.

FOLLOW-UP PROCEDURES

Trained raters interviewed patients every 6 months for the first 5 years and yearly thereafter using the Longitudinal Interval Follow-up Evaluation (LIFE).²⁶ Patient interviews were the primary information source for the LIFE, with chronological memory prompts used to obtain accurate information on changes in weekly symptom severity for all mood or other mental disorders. Interviews were supplemented through the first 5 years by detailed review of clinical, medical, and research records. Weekly depressive symptoms were rated using the LIFE Psychiatric Status Rating (PSR) scales,²⁶ as shown in **Table 2**. All CDS raters undergo rigorous training, resulting in very high intraclass correlation coefficients (ICCs) for rating changes in depressive symptoms ($ICC = 0.92$), recovery from an episode ($ICC = 0.95$), and subsequent appearance of depressive symptoms ($ICC = 0.88$).²⁶

Raters also estimated, on a 5-point scale, information reliability (accuracy) for each LIFE form.²⁶ Of the 5776 LIFE forms available (containing 195 825 weekly PSR ratings), 79.8% were rated "very good" or "good" and 18.2% "fair". Individual LIFE forms with "poor" or "very poor" ratings (2%) were omitted from the analyses. No patients were excluded from the analyses due to missing or unreliable data. Only 36 (8.4%) of 431 of patients with MDD had any missing or unreliable data before the end of their follow-up; for most, this represented 6-month or 1-year blocks of time. Because of the frequent changes in weekly PSR status, we felt it was not appropriate to impute these missing data and they were omitted from the analyses.

Follow-up for the 431 patients with MDD averaged 454.4 weeks (SD, 216.1 weeks), or 8.7 years (median, 572.0 weeks; range, 2-624 weeks). The distribution is skewed, since 195 (45.2%) of 431 patients had the full 12 years (624 weeks) of weekly PSR data, 272 patients (63.1%) had 10 years or more, 339 (78.7%) had 5 years or more, and only 46 (10.7%) had less than 2 years.

DEPRESSIVE SYMPTOM SEVERITY LEVELS

Weekly depressive symptoms were first rated using the PSR-MDD, PSR-MinD, and *DSM-III* scales (Table 2).²⁷ Next, follow-up weeks were assigned to 1 of 4 mutually exclusive depressive symptom severity levels (**Table 3**), independent of whether the patient was in an RDC episode. The 4 depressive symptom levels represent states of illness activity anchored to the diagnostic threshold for commonly observed depressive subtypes or asymptomatic status and constitute a continuum of severity: level 4 (most severe), at the threshold for MDD; level 3 (moderately severe), at the threshold for MinD; level 2 (mildly severe), SSDs (≥ 1 symptom below the diagnostic threshold for MDD or MinD); and level 1 (least severe), asymptomatic (complete absence of depressive symptoms and return to usual self).

ANTIDEPRESSANT TREATMENT

Composite antidepressant treatment scores were calculated for the first 8 weeks of intake MDD episodes (Table 1) and for each week of follow-up.⁵ Mean percentages of weeks patients received any antidepressant medication (composite antidepressant score ≥ 1) were compared for each level of depressive symptom severity.

STATISTICAL ANALYSIS

Total weeks at the 4 depressive symptom severity levels were summed and expressed as a percentage of the total number of weeks of available data for each patient. Primary analysis variables were percentages of follow-up time spent at the 4 depressive symptom severity levels. Percentages were also collapsed into binary categories and analyzed in terms of none vs any time at each level and at all possible combinations of the 4 levels. The number of symptom level changes per year and total changes during follow-up were also analyzed.

A 2-way analysis of variance was conducted to evaluate time at the 4 symptom levels and changes in symptom levels as a function of intake mood disorder history, site, and the interaction of these variables. Tukey-Kramer²⁷ post hoc *t* tests were used to compare group means, controlling for the type I error rate for pairs of subgroups. Arcsine transformation was performed to create uniform units of measurement and consistent variance over the entire range of values, and χ^2 tests or analyses of variance were used to analyze group or site differences in demographic and clinical descriptors. Analyses were performed using the SAS statistical analysis software package.²⁸ Two-tailed $\alpha = .05$ was used for all significance tests.

of depressive symptom severity in a large cohort of patients with MDD evaluated prospectively for up to 12 years in the National Institute of Mental Health Collaborative Depression Study (CDS).^{22,23} We anticipated that if the

hypothesis was correct, patients with MDD would present over time with multiple levels of depressive symptoms, and symptom levels would change relatively often.

Table 1. Demographic and Clinical Characteristics of Patients With Unipolar MDD*

Characteristic	Total (N = 431)	History of Mood Disorders at Intake			Overall Significance and Group Comparisons			
		A. First Episode (n = 122)	B. ≥1 Prior MDD Episodes (n = 205)	C. Double Depression (MDD + Dysthymia) (n = 104)	χ ²	F	df	P
Demographic Characteristics								
Sex, No. (%)								
M	170 (39.4)	58 (47.5)	70 (34.2)	42 (40.4)	5.80	NA	2	.06
F	261 (60.6)	64 (52.5)	135 (65.8)	62 (59.6)				
Age at intake, y†‡	40.3 (15.0) [17-79]	38.9 (14.6) [18-74]	41.5 (15.8) [17-79]	39.7 (13.5) [18-71]	NA	1.27	2, 428	.28
Educational status, No. (%)‡§					1.35	NA	2	.51
High school or less	207 (48.3)	53 (43.8)	103 (50.2)	51 (49.5)				
College or more	222 (51.7)	68 (56.2)	102 (49.8)	52 (50.5)				
Marital status at intake, No. (%)‡§					5.79	NA	4	.22
Married/living together	223 (52.0)	70 (57.8)	108 (52.7)	45 (43.7)				
Separated/divorced/widowed	87 (20.3)	18 (14.9)	43 (21.0)	26 (25.2)				
Never married	119 (27.7)	33 (27.3)	54 (26.3)	32 (31.1)				
Clinical History								
Age at onset of first affective episode, y	29.4 (14.3)	35.7 (15.4)	28.7 (13.8)	23.6 (11.3)	NA	22.42	2	<.001¶
Onset of first affective episode before age 21 y, No. (%)	146 (33.9)	21 (17.2)	70 (34.2)	55 (52.9)	31.90	NA	2	<.001#
Total No. of lifetime affective episodes, No. (%)								
1 (intake)	122 (28.3)	99 (81.2)	0 (0.0)	23 (22.1)				NA
2 or 3	190 (44.1)	17 (13.9)	124 (60.5)	49 (47.1)				
4 or 5	61 (14.2)	2 (1.6)	44 (21.5)	15 (14.4)				
>5	58 (13.5)	4 (3.3)	37 (18.0)	17 (16.4)				
Median No.	2	1	3	3				
Characteristics of Intake MDD Episode								
Hospitalization status, No. (%)‡					5.81	NA	2	.06
Inpatient	326 (75.6)	84 (68.8)	165 (80.5)	77 (74.0)				
Outpatient	105 (24.4)	38 (31.2)	40 (19.5)	27 (26.0)				
Worst GAS score during intake episode‡	38.4 (10.5)	40.3 (10.2)	37.6 (10.1)	37.8 (11.3)	NA	2.77	2, 428	.06
Weekly composite antidepressant score for first 8 wk of intake episode **	1.8 (1.1)	1.7 (1.2)	1.9 (1.1)	1.6 (1.1)	NA	1.22	2, 428	.27
No. of follow-up weeks with acceptable reliability ††	454.4 (216.1)	441.3 (222.7)	444.2 (218.1)	489.7 (202.0)	NA	1.85	2, 428	.16

*MDD indicates major depressive disorder; NA, not applicable; and GAS, Global Assessment of Severity.

†Values are mean (SD) [range].

‡There were significant differences across study sites for this variable.

§Information was missing for 2 patients for this variable.

||Values are mean (SD)

¶A > B > C.

#A < B < C.

**Dosage equivalents of 5 antidepressant drug classes and electroconvulsive therapy (number of treatments per week) are summed and combined into a 5-point score for each week: 0, none; 1, imipramine, 1 to 99 mg/d, or equivalent; 2, imipramine, 100 to 199 mg/d, or equivalent; 3, imipramine, 200 to 299 mg/d, or equivalent; and 4, imipramine, ≥300 mg/d, or equivalent.

††There were significant differences across study sites for this variable; however, no 2 sites were significantly different from each other based on Tukey-Kramer post hoc comparisons.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT INTAKE

As summarized in Table 1, 61% of patients in the overall CDS MDD cohort were women, 52% were married, the mean intake age was 40.3 years, the mean age at first depressive episode was 29.4 years, 71.7% had experienced at least 1 prior depressive episode, the median number of lifetime depressive episodes was 2, and 33.5% had experienced episode onset before age 21 years. Among the groups divided by mood disorder history at intake, the double depression subgroup had significantly ear-

lier onset and had the most patients (52.9%) with onset before age 21 years.

DEPRESSIVE SYMPTOM SEVERITY DURING FOLLOW-UP

As shown in **Table 4**, patients with MDD spent 41.5% of follow-up weeks asymptomatic, 26.7% of weeks with MinD symptoms, 16.5% of weeks with SSDs, and 15.3% of weeks with symptoms at the MDD level. Patients with their first lifetime MDE were symptom-free in 53.8% of weeks, significantly more often than the other 2 mood disorder history subgroups. There were no significant differences in the percentage of weeks spent at

Table 2. Psychiatric Status Rating (PSR) Scales*

Score	Status	Definition
6-Point Weekly PSR Scale for RDC Major Depressive Disorder (PSR-MDD)		
1	Asymptomatic/returned to usual self†	Return to "usual self" without any residual symptoms of MDD, although significant symptoms associated with underlying conditions may continue
2	Residual/mild depressive symptoms†	Subject claims not to be completely back to "usual self," or rater notes presence of ≥1 mild symptoms of MDD
3	Partial remission (moderate symptoms or impairment)	Considerably less psychopathology than full RDC, with no more than moderate impairment in functioning, but still with obvious evidence of MDD
4	Marked/major symptoms or impairment	Major symptoms or impairment but does not meet definite RDC criteria for MDD
5	Definite criteria without prominent psychotic symptoms or extreme impairment ‡	Meets RDC for definite MDD episode but has no prominent psychotic symptoms and no extreme impairment in functioning
6	Definite criteria with prominent psychotic symptoms or extreme impairment ‡	Meets RDC for definite MDD episode and has either prominent psychotic symptoms or extreme impairment in functioning (incapacitation)
3-Point Weekly PSR Scale for RDC Minor or Intermittent Depressive or Dysthymic Disorder (PSR-MinD)§ and for DSM-III Atypical Depression (296.82) or Adjustment Disorder With Depressed Mood (309.00) at Intake		
1	Asymptomatic†	Previously met RDC for the disorder, but currently shows no evidence of it
2	Probable criteria/mild symptoms	Previously met RDC and now has some minor manifestations of the disorder but does not meet full RDC; for the 2 DSM-III disorders, the subject does not have to meet definite criteria first
3	Definite criteria/severe symptoms	Definitely meets RDC for the disorder

*RDC indicates Research Diagnostic Criteria. Fluctuations in PSR scale ratings may be recorded without limitation during an RDC episode. Once the patient has recovered, there are prohibitions against increasing PSR scale scores until the criteria for an episode of MDD or MinD are met. Increases in symptoms that do not meet the criteria for an MDD episode may be recorded on the PSR-MinD scale if the patient definitely meets the RDC for MinD. Minimal increases in depressive symptoms that do not meet the criteria for MDD or MinD may be recorded as an "other psychiatric condition" using the PSR-MinD scale under 1 of 2 DSM-III codes: Atypical Depression (296.82) or Adjustment Disorder With Depressed Mood (309.00).

†If the patient had a score of 1 or 2 on the PSR-MDD for 8 consecutive weeks, the episode was considered to be over.

‡If a patient had a score of 5 or 6 on the PSR-MDD for 2 consecutive weeks, an episode was considered to have started.

§Short-term or long-term.

||If a patient had a score of 3 on the PSR-MinD for 2 consecutive weeks, an episode was considered to have started.

Table 3. Definition of 4 Mutually Exclusive Depressive Symptom Severity Levels Based on Weekly Psychiatric Status Rating (PSR) Scale Scores*

Depressive Symptom Severity	PSR Scale Score		
	MDD (PSR-MDD)	MinD (PSR-MinD)	DSM-III Atypical Depression (296.82) or Adjustment Disorder With Depressed Mood (309.00) (PSR-MinD)
1. No depressive symptoms/return to usual self	1	1	1
2. Subsyndromal depressive symptoms†	1	1	2 or 3
	1	2	1, 2, or 3
	2	1 or 2	1, 2, or 3
3. Depressive symptoms at the MinD level‡	1	3	1, 2, or 3
	2	3	1, 2, or 3
	3	1, 2, or 3	1, 2, or 3
	4	1, 2, or 3	1, 2, or 3
4. Depressive symptoms at the MDD level‡	5	1, 2, or 3	1, 2, or 3
	6	1, 2, or 3	1, 2, or 3

*MDD indicates major depressive disorder; MinD, minor or intermittent depressive or dysthymic disorder; and RDC, Research Diagnostic Criteria. PSR scale scores were recorded weekly independent of whether the patient was in an RDC episode (2 consecutive weeks of symptoms for an episode of minor depressive disorder, 2 years for dysthymic disorder).

†Symptoms below the diagnostic threshold for MDD or MinD.

‡As defined by RDC.

the SSD or MDD symptom levels. Patients in the double depression subgroup spent significantly more time with MinD symptoms (34.6%) than patients in the other 2

subgroups. The age of onset was significantly different between the groups but did not account for differences in time at the 4 symptom levels.

Table 4. Percentages of Follow-up Weeks Spent at Four Depressive Symptom Severity Levels for Patients With Unipolar MDD During Follow-up (≤ 12 y)*

Depressive Symptom Severity	Total (N = 431) [195 829 Total Follow-up Weeks]	History of Mood Disorders at Intake			Overall Significance and Group Comparisons†		
		A. First Episode (n = 122) [53 839 Total Follow-up Weeks]	B. ≥ 1 Prior MDD Episodes (n = 205) [91 061 Total Follow-up Weeks]	C. Double Depression (MDD + Dysthymia) (n = 104) [50 929 Total Follow-up Weeks]	F	df	P
No depressive symptoms/return to usual self, % of follow-up weeks							
Mean (SD)	41.5 (35.9)	53.8 (36.8)	38.6 (36.1)	32.7 (30.6)	9.28	2, 428	<.001‡
Median	39	62	33	30			
Subsyndromal depressive symptoms, % of follow-up weeks							
Mean (SD)	16.5 (20.2)	13.5 (17.5)	18.0 (22.5)	16.8 (17.9)	1.48	2, 428	.23
Median	8	6	9	10			
Depressive symptoms at the MinD level, % of follow-up weeks							
Mean (SD)	26.7 (24.6)	20.9 (24.2)	26.2 (24.4)	34.6 (23.5)	8.17	2, 428	<.001§
Median	20	11	19	29			
Depressive symptoms at the MDD level, % of follow-up weeks							
Mean (SD)	15.3 (21.2)	11.7 (17.8)	17.2 (23.3)	15.8 (20.3)	1.21	2, 428	.30
Median	7	5	8	8			

*MDD indicates major depressive disorder; MinD, minor or intermittent depressive or dysthymic disorder.

†Following an arcsine transformation of the percentage of weeks at each depressive symptom severity level, overall significance was determined by 2-way analysis of variance conducted to evaluate time at each symptom level as a function of history of mood disorders at intake, site, or the interaction of these 2 variables. If the overall F value was significant at $P \leq .05$ ($df = 2, 428$), then Tukey-Kramer post hoc comparisons were made for each pair of groups. Two-way analysis of variance showed no significant group-by-site interactions.

‡A > B, A > C.

§C > A, C > B.

CHRONICITY OF DEPRESSIVE SYMPTOMS

Patients with unipolar MDD manifested symptoms during 59% of follow-up weeks, and 27% never had an asymptomatic week during follow-up. To allow sufficient recovery time from the intake MDE, additional analyses were conducted on 385 patients with at least 2 years of follow-up. **Table 5** shows that 22.6% of these patients were never free of depressive symptoms at any time, with rates higher for the prior episode (26.4%) and the double depression (25.3%) subgroups than for the first episode subgroup (14.3%).

CHANGES IN DEPRESSIVE SYMPTOM SEVERITY LEVELS

Table 5 shows that 59.0% of patients with MDD with at least 2 years of follow-up spent weeks at each of the 4 levels of depressive symptom severity, 28.8% at 3 levels, and 11.2% at 2 levels; only 4 patients (1.0%) spent their entire follow-up at 1 symptom level. Patients changed symptom levels an average of 1.8 (SD, 1.4) times per year, a total of 17.1 (SD, 15) changes during follow-up. Patients in the first episode subgroup had significantly fewer total changes (13.1 [SD, 12.3]) than patients in the prior episode (18.8 [SD, 16]) or double depression (18.4 [SD, 15]) subgroups.

ANTIDEPRESSANT TREATMENT

During 25 989 person-weeks at the MDD level, patients received any antidepressant treatment (composite antidepressant score ≥ 1) in 60.8% of weeks. During 49 388 person-

weeks at the MinD level, antidepressants were administered in 54.4% of weeks, and during the 32 108 person-weeks at the SSD level, antidepressants were administered in 51.3% of weeks. During 88 266 person-weeks asymptomatic, antidepressants were administered in 27.8% of weeks.

COMMENT

The National Institute of Mental Health CDS is a 5-site, prospective, naturalistic longitudinal study of patients with affective illness that began during 1978 to 1981 and is ongoing. There were site differences in some demographic and clinical characteristics as a result of the CDS sampling strategy to obtain a diverse unipolar MDD cohort; however, site differences did not account for differences in symptomatic course. For purposes of reference, symptom levels can be associated with symptomatic thresholds of common depressive subtypes or comparable *DSM-IV* categories and asymptomatic status. Although interrater agreement was high ($ICC \geq 0.88$), there may have been some degree of error in assigning PSR levels. One would expect any such error to attenuate systematic group differences, which proved to be quite robust, providing support for the reliability of symptom severity rating. In addition, since patients entered the CDS during an MDE, the amount of follow-up time available for each patient is positively correlated with the percentage of time asymptomatic ($r = +0.21$) and negatively correlated with time at the MinD and MDD symptom levels ($r = -0.13$ and -0.20 , respectively). Although statistically significant, this accounts for no more than 4.4% of the variance of the percentage of time at the 4 depres-

Table 5. Depressive Symptom Severity Levels in Patients With Unipolar MDD During 2 to 12 Years of Follow-up*

	Total (N = 385)	History of Mood Disorders at Intake		
		A. First Episode (n = 122)	B. ≥1 Prior MDD Episodes (n = 178)	C. Double Depression (MDD + Dysthymia) (n = 95)
No asymptomatic weeks, No. (%)	87 (22.6)	16 (14.3)	47 (26.4)	24 (25.3)
Overall No. of symptom severity levels, No. (%)				
All 4	227 (59.0)	68 (60.7)	103 (57.9)	56 (58.9)
3	111 (28.8)	29 (25.9)	48 (27.0)	34 (35.8)
SSD, MinD, and MDD	59 (15.3)	11 (9.8)	27 (15.2)	21 (22.1)
Other combinations	52 (13.5)	18 (16.1)	21 (11.9)	13 (13.7)
Only 2	43 (11.2)	12 (10.7)	26 (14.6)	5 (5.3)
MinD and MDD	23 (6.0)	4 (3.6)	16 (9.0)	3 (3.2)
Other combinations	20 (5.2)	8 (7.1)	10 (5.6)	2 (2.1)
Only 1	4 (1.0)	3 (2.7)	1 (0.6)	0 (0.0)
Changes in symptom severity levels				
Per year†				
Mean (SD)	1.8 (1.4)	1.5 (1.2)	2.0 (1.5)	1.9 (1.5)
Range [median]	0-9 [1.4]	0-7 [1.2]	0-8 [1.6]	0-9 [1.4]
Total‡				
Mean (SD)	17.1 (15.0)	13.1 (12.3)	18.8 (16.0)	18.4 (15.0)
Range [median]	1-88 [11.8]	1-80 [8.8]	2-88 [13.2]	2-88 [12.8]

*MDD indicates major depressive disorder; SSD, subsyndromal depressive symptoms; and MinD, minor or intermittent depressive or dysthymic disorder.

†Overall group comparison: $F = 3.74$; $df = 2, 382$; $P = .03$; $A < B$. Two-way analysis of variance showed no significant group-by-site interaction.

‡Overall group comparison: $F = 5.66$; $df = 2, 382$; $P = .004$; $A < B$. Two-way analysis of variance showed no significant group-by-site interaction.

sive symptom severity levels and has relatively little explanatory power for our findings. The interpretability of CDS treatment data is limited, since treatment was not controlled in this study. The treatment data reflect standards of care in the regions surrounding the 5 academic centers beginning in 1978; these standards have changed over time as new antidepressants (etc) and psychotherapeutic techniques have been introduced into clinical practice.

Weekly analyses of unipolar MDD revealed prolonged chronic symptoms in the course of illness, with only 41.5% of weeks asymptomatic during an average of 8.7 years. Twenty-three percent of patients with at least 2 years of follow-up were never free of depressive symptoms for even 1 week. These new findings add the dimension of prolonged lifetime symptomatic chronicity to the grim prognosis of frequent MDE relapse/recurrence that characterizes unipolar MDD.^{1-5,29,30} It appears that the disease model of unipolar MDD is more analogous in terms of lifetime chronicity to hypertension than to lobar pneumonia or other acute episodic diseases.

Patients in their first lifetime MDE had significantly more benign courses of illness, experiencing their first depressive episodes later; fewer had onset of their first episode before age 21 years, and they were asymptomatic during more than half of the follow-up weeks. Patients with a history of MDEs, in contrast, had a significantly earlier onset of illness and had more chronic symptoms during follow-up. Patients with double depression had the most chronic symptomatic courses and earliest age of first episode onset; more than 50% had onset of their first episode before age 21 years. Once chronic episodes of dysthymia appeared during the course of MDD, they persisted and recurred. These group differences were consistent across all CDS sites and were not accounted for by differences in age of onset, affirming the strength of these findings.

In the total cohort, symptoms at the MinD level accounted for 26.7% of follow-up weeks, compared with 16.7% at the SSD level and 15.3% at the MDD level. Although the percentage of weeks at the MDD level was the lowest, it is striking that more than 15% of follow-up weeks were spent at the most severe level of depressive symptoms. Unipolar MDD has classically been defined by episodes of major depression; however, symptomatic analyses indicate that the weekly course of unipolar MDD primarily involves MinD and SSD symptoms (43.2% of follow-up weeks); these symptoms were approximately 3 times more common during the course of illness than MDD symptoms.

In this unipolar MDD cohort, SSDs were residual to MDEs and were as common as MDD symptoms during the longitudinal course of unipolar depression. Compared with no symptoms, SSDs are associated with small but significant decreases in psychosocial function^{10-15,17,31}; thus, we conclude that residual SSDs constitute an active state of illness in unipolar MDD, indicating that patients have not recovered completely from their prior MDEs. There is a need for systematic investigation of the clinical significance and treatment responses of MinD and SSDs, which combined are the most common clinically active states in unipolar major depressive disorders.

The vast majority of patients (88%) spent some follow-up weeks at 3 or 4 different levels of depressive symptom severity, and they changed symptom levels almost twice a year. This is consistent with data we¹⁷ and others¹⁹⁻²¹ have reported indicating that different levels of depressive symptom severity are very commonly observed in the same patients during their course of illness. Weekly symptomatic analysis of patients with unipolar MDD during up to 12 years of follow-up supports the proposal of Kendler and Gardner,³² based on twin studies, that unipolar depression manifests as a continuum of depressive symptoms that vary in sever-

ity and duration. We believe a growing confluence of scientific evidence^{16,17,19-21,32} supports the hypothesis that unipolar MDD is a clinically homogeneous illness in which major, minor, and subsyndromal depressive symptoms commonly alternate as different manifestations and levels of illness activity.

Clinicians evaluating patients with MDD should extend their thresholds for detecting clinically relevant illness to include all symptomatically active clinical states of unipolar depression. Researchers and public health experts should recognize that, although MDD is the most severe state of illness, the traditional, relatively exclusive focus on the MDD level of symptoms represents only the tip of the iceberg in this common, chronic, and disabling disease.

Accepted for publication March 24, 1998.

From the Department of Psychiatry, University of California, San Diego (Drs Judd, Akiskal, Zeller, Paulus, and Kunovac); the Psychiatry Service, San Diego Veterans Affairs Medical Center (Drs Akiskal and Paulus); and the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression, Clinical Studies, conducted with the participation of the following investigators: Dr Akiskal (San Diego), Dr Maser (Behavioral and Integrative Neuroscience Research Program, National Institute of Mental Health, Washington, DC), Drs Endicott (Department of Research Assessment and Training, Columbia University, New York, NY), Dr Leon (Department of Psychiatry, Cornell University, New York, NY), Dr Coryell (Department of Psychiatry, University of Iowa, Iowa City), Drs Mueller and Keller (chairperson) (Department of Psychiatry, Brown University, Providence, RI), and Dr Rice (Department of Psychiatry, Washington University, St Louis, Mo).

Funds for this study were provided in part by the Mental Health Clinical Research Grants PHSMH30914 and PHSMH49671 from the National Institute of Mental Health, Rockville, Md, and by the Roehr Fund of the University of California, San Diego.

This manuscript has been reviewed by the Publications Committee of the Collaborative Depression Study and has its endorsement.

Additional contributors to this study include: Philip W. Lavori, PhD, M. Tracie Shea, PhD, Jan Fawcett, MD, William A. Scheftner, MD, James Haley, Jo Ellen Loth, MSW, Theodore Reich, MD, Nancy C. Andreasen, MD, PhD, Paula J. Clayton, MD, Jack Croughan, MD, Gerald L. Klerman, MD (deceased), Robert M. A. Hirschfeld, MD, Martin M. Katz, PhD, Timothy Mueller, MD, Eli Robins, MD, Robert W. Shapiro, MD, Robert L. Spitzer, MD, George Winokur, MD (deceased), and Michael A. Young, PhD.

Reprints: Lewis L. Judd, MD, Department of Psychiatry, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0603.

REFERENCES

1. Angst J, Bastrup P, Grof H, Hippus W, Poldinger W, Weiss P. The course of monopolar depression and bipolar psychoses. *Psychiatry Neurol Neurochir (Amsterdam)*. 1973;76:489-500.
2. Angst J. The course of affective disorders. *Psychopathology*. 1986;19(suppl 2):47-52.
3. Keller M, Shapiro RW, Lavori PW, Wolfe N. Relapse in major depressive disorder: analysis with the life table. *Arch Gen Psychiatry*. 1982;39:911-915.
4. Keller MB, Lerman GL, Lavori PW, Coryell W, Endicott J, Taylor J. Long-term outcome of episodes of major depression: clinical and public health significance. *JAMA*. 1984;252:788-792.
5. Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RMA, Shay T. 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.
6. Akiskal HS. Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. *Am J Psychiatry*. 1983;140:11-20.
7. Skodol AE, Schwartz S, Dorenwend BP, Levav I, Shrout PE. Minor depressions in a cohort of young adults in Israel. *Arch Gen Psychiatry*. 1994;51:532-551.
8. Keller MB, Lavori PW, Endicott J, Coryell W, Klerman GL. "Double depression": 2-year follow-up. *Am J Psychiatry*. 1983;140:689-694.
9. Angst J, Merikangas K, Scheidegger P, Wicki W. Recurrent brief depression: a new subtype of affective disorder. *J Affect Disord*. 1990;19:87-98.
10. Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA*. 1989;262:914-919.
11. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA*. 1990;264:2524-2528.
12. Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA*. 1992;267:1478-1483.
13. Howarth E, Johnson J, Klerman GL, Weissman MM. Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch Gen Psychiatry*. 1992;49:817-823.
14. Sherbourne CD, Wells KB, Hays RD, Rogers W, Burnam MA, Judd LL. Subthreshold depression and depressive disorder: clinical characteristics of general medical and mental health specialty outpatients. *Am J Psychiatry*. 1994;151:1777-1784.
15. Judd LL, Rapaport MH, Paulus MP, Brown JL. Subsyndromal symptomatic depression: a new mood disorder? *J Clin Psychiatry*. 1994;55(suppl):18-28.
16. Winokur G. All roads lead to depression: clinically homogeneous etiologically heterogeneous. *J Affect Disord*. 1997;45:97-108.
17. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *J Affect Disord*. 1997;45:5-17.
18. Kessler RC, Zhao SY, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord*. 1997;45:19-30.
19. Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. *J Affect Disord*. 1997;45:31-39.
20. Akiskal HS, Judd LL, Gillin JC, Lemmi H. Subthreshold depressions: clinical and polysomnographic validation of dysthymic, residual and masked forms. *J Affect Disord*. 1997;45:53-63.
21. Judd LL. Pleomorphic expressions of unipolar depressive disease: summary of the 1996 CINP President's Workshop. *J Affect Disord*. 1997;45:109-116.
22. Katz MM, Klerman GL. Introduction: overview of the Clinical Studies Program. *Am J Psychiatry*. 1979;136:49-51.
23. Katz MM, Secunda SK, Hirschfeld RMA, Koslow SH. NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression. *Arch Gen Psychiatry*. 1979;36:765-771.
24. Spitzer RL, Endicott J, Robins E. *Research Diagnostic Criteria for a Selected Group of Functional Disorders*. 3rd ed. New York, NY: Biometrics Research Division, New York State Psychiatric Institute; 1977.
25. Spitzer RL, Endicott J. *Schedule for Affective Disorders and Schizophrenia (SADS)*. 3rd ed. New York, NY: Biometrics Research Division, New York State Psychiatric Institute; 1979.
26. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry*. 1987;44:540-548.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association; 1980.
28. *SAS User's Guide: Statistics, Version 6 Edition*. Cary, NC: SAS Institute Inc; 1992.
29. Coryell W, Endicott J, Keller M. Outcome of patients with chronic affective disorder: a 5-year follow-up. *Am J Psychiatry*. 1990;147:1627-1633.
30. Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL. The enduring psychosocial consequences of mania and depression. *Am J Psychiatry*. 1993;150:720-727.
31. Judd LL, Paulus MP, Wells KB, Rapaport MH. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *Am J Psychiatry*. 1996;153:1411-1417.
32. Kendler KS, Gardner CO Jr. Boundaries of major depression: evaluation of DSM-IV criteria. *Am J Psychiatry*. 1998;155:172-177.