A New Empirical Definition of Major Depressive Episode Recovery and Its Positive Impact on Future Course of Illness

Lewis L. Judd, MD[a],[*]; Pamela J. Schettler, PhD[a]; A. John Rush, MD[b];
William H. Coryell, MD[c]; Jess G. Fiedorowicz, MD, PhD[c],[d]; and David A. Solomon, MD[e]

ABSTRACT

Objective: To provide the first head-to-head test of the predictive validity of 2 resolution levels included in the current consensus definition of major depressive episode (MDE) recovery and provide an empirically based, clinically useful definition of the end of an MDE.

Method: 322 participants entering the National Institute of Mental Health Collaborative Depression Study with MDE (diagnosed by Research Diagnostic Criteria) in 1978–1981, and followed thereafter for up to 31 years, were divided into those with 8 consecutive weeks of asymptomatic MDE recovery or residual subsyndromal depressive symptom (SSD) resolution of their index MDE. These 2 levels of recovery were defined based on weekly symptom status on all depressive conditions, assessed by Longitudinal Interval Follow-Up Evaluation (LIFE) interviews conducted every 6 months. Primary measures of validity of these 2 alternative definitions were first well interval duration and long-term depressive illness burden. Groups were also compared on clinical variables, antidepressant treatment, and psychosocial function.

Results: 61.2% of subjects recovered asymptomatically from their index MDE. By survival analysis, they remained free of a depressive episode relapse or recurrence 4.2 times longer than those with SSD resolution (median = 135 vs 32 weeks; χ^2 = 70.65; $P < .0001$). This was not attributable to a difference in intensity of antidepressant medication. Compared to asymptomatic recovery, SSD resolution was associated with significantly longer and more severe index MDEs, with more miscellaneous psychopathology as well as increased long-term psychosocial dysfunction and a greater depressive illness burden during the ensuing 10 or 20 years. Asymptomatic MDE resolution was a stronger predictor of time well than any of 18 other predictors, singly or combined. Eight consecutive weeks of asymptomatic recovery had 93% overlap with a 4-week definition and conferred little benefit over 4 weeks.

Conclusions: Four consecutive weeks of asymptomatic recovery defines the end of an MDE and the beginning of a stable well state with improved psychosocial function. Residual symptom resolution is a continuation of an active state of the episode, not the end of an MDE.

[a]Department of Psychiatry, University of California, San Diego, La Jolla
[b]Duke-National University of Singapore
[c]Departments of Psychiatry and Internal Medicine, Carver College of Medicine, Iowa City, Iowa
[d]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City
[e]Department of Psychiatry and Human Behavior, Alpert Medical School, Brown University, Providence, Rhode Island; and UpToDate, Waltham, Massachusetts
*Corresponding author: Lewis L. Judd, MD, Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093 (ljudd@ucsd.edu).

The current clinical consensus is that 8 consecutive weeks with no more than "minimal" residual symptoms defines the end of a major depressive episode (MDE).[1],[2] *DSM-5* is consistent with this position, defining MDE recovery, labeled "full remission," as a period of at least 2 months without significant symptoms of an MDE.[3] MDE recovery has been operationalized in clinical trials as ≤ 7 on the 17-item Hamilton Depression Rating Scale or the equivalent on another depression scale by the end of treatment, usually without a duration requirement.[4] All of these definitions combine asymptomatic recovery and mild residual depressive symptoms. We have previously demonstrated the importance of distinguishing between these 2 levels in understanding MDE recovery, chronicity, and psychosocial function.[5–13] In this article, we present the first head-to-head comparison that we are aware of, testing the validity of these 2 levels of MDE resolution based on first well interval duration and long-term depressive illness burden (primary outcomes) as well as level of psychosocial function (secondary outcome). In addition, we address the number of weeks needed to define stable MDE recovery.

In our previous articles,[14],[15] we defined asymptomatic recovery as being symptom-free for at least 80% of the first well interval—a definition not easily applied by practicing clinicians. We now compare the stability of MDE recovery based on 8 consecutive weeks completely free of all symptoms of the preceding MDE (asymptomatic recovery) versus 8 consecutive weeks of mild residual subsyndromal depressive symptoms (SSD resolution). The sample was expanded to be more representative of major depressive disorder (MDD) by including 67 previously excluded subjects with "double depression" (chronic minor depression escalating to MDE). We have now also expanded the characteristics and outcomes associated with asymptomatic versus subsyndromal resolution and evaluated a wide range of other potentially important clinical predictors of depressive episode relapse.

METHOD

Subjects

Participants were drawn from the National Institute of Mental Health Collaborative Depression Study (CDS)[16],[17] of 955 patients seeking treatment for a major affective episode at 5 US academic centers between 1978 and 1981. Intake diagnoses were made by Research Diagnostic Criteria (RDC)[18] based on Schedule for Affective Disorders and Schizophrenia (SADS)[19] interviews. The CDS was a naturalistic, prospective, longitudinal study of course in

which participants were periodically and systematically followed for up to 31 years. Treatment was recorded, not controlled. The CDS database includes detailed information on psychiatric history, index episode characteristics, and follow-up data on weekly clinical status, somatic treatment, and psychosocial functioning gathered from self-reports, family informants, medical and research records, and ratings by trained clinical interviewers. CDS patients were required to be white (to test genetic hypotheses), speak English, have an IQ ≥ 70, and have no organic brain syndrome or terminal medical illness. Written informed consent was obtained at each site.

Four hundred eighty-seven patients entered the CDS in an active MDE, defined in RDC as ≥ 2 consecutive weeks with ≥ 5 depressive symptoms including intense sadness or dysphoria. We excluded 74 patients with bipolar disorder, schizoaffective disorder, or schizophrenia prior to intake or during follow-up. Another 91 were omitted for missing or unreliable weekly depressive symptom status data before resolution of their intake MDE, leaving 322 MDD participants in the analysis sample.

Follow-Up

Trained professional raters conducted semistructured interviews every 6 months for the first 5 years and yearly thereafter, using 4 variations of the Longitudinal Interval Follow-up Evaluation (LIFE).[20] Chronological memory prompts (eg, holidays) were used for changes in weekly symptom severity for all RDC disorders. Interview information was supplemented by available medical and research records and integrated into weekly psychiatric status ratings (PSRs), with scale values anchored to RDC diagnostic thresholds. CDS raters were rigorously trained, resulting in intraclass correlation coefficients of 0.92 for reliability of psychiatric symptom change points, 0.95 for recovery from affective episodes, and 0.88 for subsequent appearance of affective symptoms.[20] PSRs for depressive conditions were combined for each week during follow-up and classified into 1 of 4 mutually exclusive categories: the diagnostic threshold for MDE, the diagnostic threshold minor depression, SSD below either diagnostic threshold, and the asymptomatic status (no symptoms of the episode, return to usual self) (see Supplementary eTable1 at PSYCHIATRIST.COM).

Definition of MDE Recovery Level

The CDS applied an early operational definition of MDE recovery as a period of 8 consecutive weeks when the individual either has no residual RDC symptoms of the episode (1 on the MDE PSR scale, "return to usual self") or retains 1 or more symptoms of the episode in a "mild" degree (2 on the MDE PSR scale, "residual symptoms of the episode").[21]

For this analysis, we separated these 2 levels of recovery as follows: We first identified 322 participants who met the RDC definition of recovery by having 8 consecutive weeks with no more than minimal (SSD) symptoms of the index MDE. From that group, we identified 197 participants with

Clinical Points

- The current consensus definition of major depressive episode (MDE) recovery is 8 consecutive weeks with no more than minimal residual symptoms of the episode; in this article, we provide a head-to-head comparison of the 2 levels of MDE resolution contained within this definition.
- Analysis of 322 patients with MDE showed that only complete (asymptomatic) resolution of all symptoms of the episode initiates a stable period of recovery; the presence of residual symptoms indicates that the episode is still active, the patient has significant psychosocial impairment, and continued treatment is needed to prevent relapse to a syndromal level.
- Eight weeks of asymptomatic status conferred little benefit over 4 weeks; therefore, a 4-week period free of all symptoms of the episode is recommended as the new definition of MDE recovery.

asymptomatic recovery, defined as PSR 1 on MDE and any other depressive condition for 8 consecutive weeks. The start of their intake recovery was the first of these 8 asymptomatic weeks; any prior weeks with SSD were counted as part of the index MDE. The remaining 125 participants (those without an 8-week asymptomatic period) were classified as having SSD resolution of their index MDE, beginning the first of 8 weeks meeting RDC recovery criteria; this could include 1 or more weeks asymptomatic, but not 8 in a row. The end of the first well interval by either recovery definition was the first of 2 consecutive weeks with depressive symptoms at the syndromal level of MDE (5 or 6 on the MDD PSR scale) or minor depression (3 on the minor depression PSR scale).

Statistical Analyses

Comparisons of recovery groups were performed using t tests for normally distributed continuous variables, Wilcoxon rank sum tests for ordinal and nonnormally distributed continuous variables, and χ^2 or Fisher exact tests for categorical variables.

Comparison of time well following the start of asymptomatic recovery versus SSD resolution of the index MDE was made using life table methods.[22] The Kaplan-Meier product limit estimate[23,24] was used to accommodate data censored prior to the end of the first well interval due to the end of follow-up data for a given participant, a period of missing PSR data, or a period when weekly PSR ratings were judged to be of poor accuracy. Cox proportional hazards over all weeks of follow-up were computed for asymptomatic recovery versus SSD resolution and compared to 18 other potential predictors of depressive episode relapse or recurrence. The impact of recovery level was assessed by covarying for each other predictor individually, as well as for multiple covariates determined by forward stepping, allowing all significant independent predictors to enter the model.

Finally, definitions of MDE recovery based on 4 versus 8 consecutive weeks asymptomatic were examined in terms of degree of overlap and time to first depressive relapse or recurrence.

Table 1. Demographic, Clinical, and Index Episode Characteristics for CDS Participants With Asymptomatic Recovery Versus Residual Subsyndromal Depressive Symptom (SSD) Resolution of Index MDE
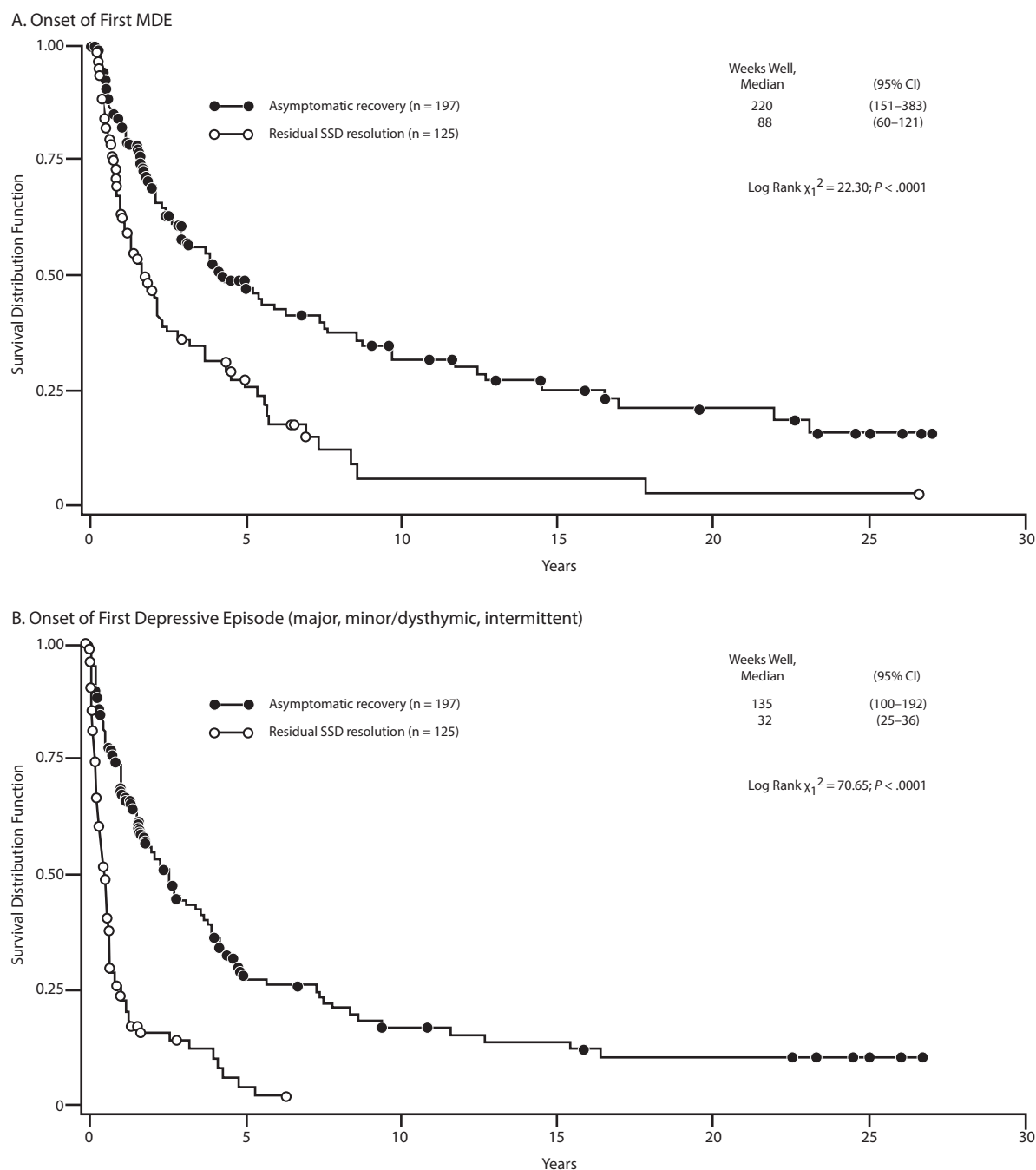
Variable	Asymptomatic Recovery (n = 197)	Residual SSD Resolution (n = 125)[a]	Statistic	P Value[b]
Demographics at intake to CDS				
Age (range, 17–76), mean (SD), y	39.8 (14.8)	38.9 (14.9)	$t_{320} = 0.53$	.598
Female, n (%)	111 (56.4)	82 (65.6)	$\chi^2_1 = 2.73$	.099
Education—some college, n (%)	105 (53.8)	57 (45.6)	$\chi^2_1 = 2.07$	.150
Marital status, n (%)				
Married/living together	110 (56.4)	59 (47.2)	$\chi^2_2 = 2.97$	.226
Separated/widowed/divorced	37 (19.0)	32 (25.6)		
Never married	48 (24.6)	34 (27.2)		
Clinical history				
Age at onset of first affective episode, mean (SD), y	30.3 (14.4)	27.9 (13.7)	$t_{320} = 1.49$	.136
Onset before age 21 y, n (%)	57 (28.9)	48 (38.4)	$\chi^2_1 = 3.12$	.077
No. of lifetime affective episodes (including index MDE), n (%)				
1 (first episode)	67 (34.0)	33 (26.4)	Wilcoxon rank sum test[c]	.124
2 or 3	88 (44.7)	51 (40.8)		
≥ 4	42 (21.3)	41 (32.8)		
Severity of index episode				
Inpatient status, n (%)	136 (69.0)	99 (79.2)	$\chi^2_1 = 4.01$	**.045**
Psychotic features, n (%)	23 (11.7)	14 (11.2)	$\chi^2_1 = 0.02$	.896
Double depression (MDE plus dysthymia), n (%)	35 (17.8)	32 (25.6)	$\chi^2_1 = 2.85$	.092
Global Assessment Scale score, mean (SD)[d]	39.7 (11.0)	37.1 (10.5)	$t_{320} = 2.11$	**.036**
Extracted Hamilton Depression score, mean (SD)[e]	24.8 (7.3)	28.1 (6.5)	$t_{320} = -4.15$	**< .0001**
Depressive mood and ideation score, mean (SD)[f]	20.6 (4.4)	21.7 (3.6)	$t_{299.0} = -2.48$[g]	**.014**
Depressive associated features score, mean (SD)[h]	44.9 (7.4)	47.6 (7.4)	$t_{320} = -3.18$	**.002**
Impairment in functioning score, mean (SD)[i]	3.44 (1.2)	3.81 (1.1)	$t_{320} = -2.78$	**.006**
Suicidal ideation and behavior score, mean (SD)[j]	5.71 (5.3)	6.54 (5.4)	$t_{320} = -1.36$	.176
Miscellaneous psychopathology score, mean (SD)[k]	23.1 (5.4)	25.9 (6.0)	$t_{320} = -4.34$	**< .0001**
Length of index episode (weeks from onset to recovery)				
Mean (SD)	164.3 (248.1)	226.2 (256.3)	$t_{320} = -2.16$	**.032**
Median (range)	63.0 (7–1,194)	116.0 (14–1,219)		
< 6 mo, n (%)	51 (25.9)	9 (7.2)	$\chi^2_1 = 17.62$	**< .0001**
6 mo to < 2 y, n (%)	76 (38.6)	47 (37.6)	$\chi^2_1 = 0.03$	.860
≥ 2 y, n (%)	70 (35.5)	69 (55.2)	$\chi^2_1 = 12.05$	**.0005**
Length of index episode after intake to CDS, wk				
Mean (SD)	29.7 (57.1)	54.3 (61.9)	$t_{320} = -3.64$	**.0003**
Median (range)	10.0 (1–468)	37.0 (1–299)		
Length of CDS follow-up, y				
Mean (SD)	16.7 (10.2)	15.7 (10.4)	$t_{320} = 0.84$	.404
Median (range)	17.0 (0.5–31.0)	16.2 (0.4–30.0)		
< 10, n (%)	63 (32.0)	49 (39.2)	$\chi^2_2 = 2.33$	.312
10 to < 20, n (%)	42 (21.3)	20 (16.0)		
20–31, n (%)	92 (46.7)	56 (44.8)		
Comorbidity during index MDE, n (%)				
Substance use disorder	40 (20.3)	28 (22.4)	$\chi^2_1 = 0.21$	.654
Any anxiety disorder[l]	20 (10.2)	16 (12.8)	$\chi^2_1 = 0.54$	.462
Other psychiatric disorders[m]	43 (21.8)	46 (36.8)	$\chi^2_1 = 8.57$	**.0034**
Comorbidity during first well interval, n (%)[n]				
Substance use disorder	26 (13.0)	17 (13.6)	$\chi^2_1 = 0.01$	.918
Any anxiety disorder[l]	34 (17.3)	17 (13.6)	$\chi^2_1 = 0.77$	.381
Other psychiatric disorders[m]	46 (23.4)	38 (30.4)	$\chi^2_1 = 1.97$	.160

[a]Depressive symptoms below the diagnostic threshold for a probable or definite MDE or minor depressive or dysthymic episode. [b]P values statistically significant at $P < .05$ are indicated in bold. [c]Wilcoxon rank sum test was run on actual number of affective episodes. [d]Global Assessment Scale score measures severity of a mixture of symptoms and impairment at the worst week in the index episode, prior to intake. Scores range from 1 (most severe and impaired) to 100 (superior functioning with no symptoms or impairment). A mean of 38 represents major impairment in several areas, or some impairment in reality testing or communication, or at least 1 suicide attempt. [e]Extracted Hamilton score, with possible range of 0–63, is an approximation of the 17-item Hamilton Depression Rating Scale score, based on 17 corresponding SADS items during the worst week in the index episode. [f]Depressive mood and ideation score, with possible range of 5–31, is the sum of 5 SADS[19] items measuring depressed mood, brooding, self-reproach, negative self-evaluation, and discouragement during the worst week in the index episode. [g]After Satterthwaite adjustment to degrees of freedom, for unequal group variances. [h]Depressive associated features score, with possible range of 14–88, is the sum of 17 SADS items measuring sleep and appetite disturbance, suicidal tendencies, indecisiveness, difficulty concentrating, pervasive loss of interest, depressed appearance, agitation, and psychomotor retardation during the worst week in the index episode. [i]SADS item 465, rating of impairment in functioning due to psychopathology at the worst point in the index episode (prior to intake). On 1–6 rating scale, 3 represents "significant effect on life." [j]Suicidal ideation and behavior score, with possible range of 1–28, is the sum of SADS items assessing suicidal tendencies, attempts, seriousness of intent, and medical threat to life during the index episode. [k]Miscellaneous psychopathology score, with possible range of 13–71, is the sum of 14 SADS items assessing obsessions-compulsions, somatic preoccupation, depersonalization, subjective anger, overt anger, worse mood in evening, antisocial behavior, suspiciousness, nondelusional ideas of reference, thought insertion, thought withdrawal, delusions of jealousy, self-pity, and demandingness. [l]Comorbid panic disorder, generalized anxiety disorder, phobic disorder, or obsessive-compulsive disorder. [m]Other psychiatric disorders includes other Research Diagnostic Criteria (RDC) diagnoses (labile personality disorder, antisocial personality disorder, Briquet's syndrome/somatization disorder, or unspecified functional psychosis) as well as unspecified disorders not included in RDC (eg, anorexia nervosa), and suspected RDC disorders for which the symptoms are too minimal to meet the probable or definite threshold (as long as those symptoms were associated with seeking or being referred for help, taking medication, or having impaired functioning). [n]The first well interval is the period from the first of 8 consecutive weeks of asymptomatic or SSD resolution to the first of 2 consecutive weeks again meeting the diagnostic threshold for major or minor depression.
Abbreviations: CDS = Collaborative Depression Study, MDE = major depressive episode, SADS = Schedule of Affective Disorders and Schizophrenia.

Figure 1. Survival Analysis of Time From Asymptomatic Recovery Versus Residual Subsyndromal Depressive Symptom (SSD) Resolution of Index Major Depressive Episode (MDE) to Onset of First MDE or Depressive Episode (major, minor/dysthymic, or intermittent) Relapse or Recurrence[a]

A. Onset of First MDE

	Weeks Well, Median	(95% CI)
Asymptomatic recovery (n = 197)	220	(151–383)
Residual SSD resolution (n = 125)	88	(60–121)

Log Rank $\chi_1^2 = 22.30$; $P < .0001$

B. Onset of First Depressive Episode (major, minor/dysthymic, intermittent)

	Weeks Well, Median	(95% CI)
Asymptomatic recovery (n = 197)	135	(100–192)
Residual SSD resolution (n = 125)	32	(25–36)

Log Rank $\chi_1^2 = 70.65$; $P < .0001$

[a]Open and closed circles indicate censored data.

RESULTS

Overall Sample

The mean age of the analysis sample was 39.4 years, and 59.9% were women. The mean age at onset of MDD was 29.4 years; for 32.6%, this occurred before age 21 years. Thirty-one percent were in their first lifetime MDE, 43.2% in their second or third episode, and 25.8% in their fourth or later episode. The mean Global Assessment Scale (GAS)[25] severity score for the index episode was 38.7, reflecting major psychopathology or impairment in several functional areas. Most (73.0%) were inpatients (as was customary for most severely depressed patients at the time). CDS follow-up ranged from 0.5 to 31 years, with a median of 17 years; 34.8% were followed for less than 10 years, 19.2% for 10 to < 20 years, and 46.0% for 20 to 31 years.

Table 2. Weeks to Relapse or Recurrence of First Follow-Up MDE or Depressive Episode of Any Type After Start of Asymptomatic Recovery Versus Residual Subsyndromal Depressive Symptom (SSD) Resolution of Index MDE

Variable	Asymptomatic Recovery (n = 197; 61.2%)	Residual SSD Resolution[a] (n = 125; 38.8%)
Time to first MDE relapse or recurrence, wk (95% CI)		
25%	84 (59–107)	38 (23–48)
Median	220 (151–383)	88 (60–121)
75%	856 (504–)[b]	281 (166–383)
Relapse, probability		
By 6 mo	0.116	0.185
By 1 y	0.176	0.375
By 2 y	0.312	0.547
By 5 y	0.524	0.742
By 10 y	0.681	0.950
Statistic[c]	Log rank χ^2 = 22.30, P < .0001	
Time to first depressive episode relapse or recurrence of any type, wk (95% CI)[d]		
25%	51 (32–62)	17 (14–21)
Median	135 (100–192)	32 (25–36)
75%	383 (227–607)	55 (43–90)
Relapse, probability		
By 6 mo	0.160	0.438
By 1 y	0.261	0.739
By 2 y	0.437	0.844
By 5 y	0.715	0.962
By 10 y	0.834	…
Statistic[c]	Log rank χ^2 = 70.65, P < .0001	

[a]Depressive symptoms below the diagnostic threshold for a probable or definite major or minor depressive or dysthymic episode.
[b]Upper limit of confidence interval cannot be computed.
[c]Log rank χ^2 reflects difference in rank order of relapse over all weeks of follow-up. Wilcoxon χ^2, which is more heavily weighted by early relapse or recurrence, had a somewhat lower value but was also significant at P < .0001.
[d]First of 2 consecutive weeks at syndromal level for major depressive episode or acute or chronic minor depressive episode.
Abbreviation: MDE = major depressive episode.

Asymptomatic Recovery Rates and Timing

The majority of the sample (61.2%) recovered asymptomatically from their index MDE. Of this group, 22.8% spent no weeks at the SSD level, 79.2% became asymptomatic within 3 months of SSD resolution, 91.4% within 6 months, and 96.4% within 1 year. The remaining 3.6% retained SSD for 12 to 17 months before achieving asymptomatic recovery.

Clinical Characteristics by Recovery Level

Compared to SSD resolution, asymptomatic recovery was associated with significantly shorter and less severe index MDEs, with less miscellaneous psychopathology (Table 1).

Duration of First Well Interval

Asymptomatic recovery was associated with a significantly longer time to first relapse or recurrence of MDE or any type of depressive episode (P < .0001) (Figure 1). The median time to the next MDE relapse or recurrence was 2.5 times longer for the asymptomatic than the SSD group (220 vs 88 weeks, respectively) and it was less than half as likely to occur during the first year (probability = 0.176 vs 0.375) (Table 2). The median time to the next major or minor depressive episode was 4.2 times longer for the asymptomatic than the SSD group (135 vs 32 weeks). Risk of depressive relapse was only about one-third as likely for the asymptomatic as for the SSD group during the first year (probability = 0.261 vs 0.739), as well as across all weeks of follow-up (hazard ratio = 0.326).

Long-Term Depressive Illness Burden

Participants spent significantly more time asymptomatic and significantly less time at every level of depressive symptom severity during 10 years following the start of asymptomatic versus SSD resolution of the index MDE (Table 3). Except for time at the MDE level, similar significant differences also occurred during 15 or 20 years of follow-up, in smaller subsamples (data not shown).

Antidepressant Medication Treatment

Composite antidepressant (CAD) medication treatment in the CDS was converted into equivalents of imipramine and coded into 5 categories: 0 = none, 1 = 1–99 mg/d, 2 = 100–199 mg/d (minimum therapeutic level), 3 = 200–299 mg/d, and 4 = 300 mg/d or more of imipramine or equivalent. During the index MDE, the 2 recovery groups did not differ on mean CAD scores or the percentage of weeks with a therapeutic level or *any* antidepressant (Table 4). During the first well interval, those with SSD resolution received a significantly more intensive mean level of antidepressant treatment than those with asymptomatic recovery (1.24 vs 0.94, respectively), although the mean level for both groups was subtherapeutic. This indicates that the shorter well interval associated with SSD resolution was not attributable to receiving less intensive antidepressant treatment. Results are consistent with earlier CDS reports[24] showing antidepressant treatment commonly below the therapeutic level, even during the index MDE.

Psychosocial Functioning

Subsyndromal depressive symptom resolution was associated with significantly poorer adolescent friendship patterns and greater impairment during the 5 years prior to intake as well as during all of long-term follow-up on work and household functioning, relationships with children and friends, involvement in recreation/hobbies, subjective life satisfaction, and clinical rating of overall social adjustment (Supplementary eTable 2). Mean personality scores measuring neuroticism—namely, emotional stability,[26] objectivity,[26] and ego resiliency[27]—reflected more dysfunction at a statistically significant level (P < .05) for the SSD resolution group (data not shown).

Recovery Level Versus Other Predictors

Risk of relapse over all follow-up weeks was significantly higher for subjects defined by level of recovery (P < .0001) and by 7 other binary variables each evaluated alone: 4 or more lifetime episodes (P < .0001), onset before age 21 years (P = .0008), total duration of index episode ≥ 2

Table 3. Percentage of Weeks at Different Levels of Depressive Severity During 10 Years After the Start of Asymptomatic Versus Residual Subsyndromal Depressive Symptom (SSD) Resolution of Index Major Depressive Episode[a]

	Percentage of Weeks in 10-Year Period After Start of First Well Interval		Significance		
Depressive Illness Level	Asymptomatic Recovery (n = 128)[a]	Residual SSD Resolution (n = 74)[a,b]	t[c]	df	P[d]
Asymptomatic					
Mean (SD)	71.5 (28.4)	30.3 (29.2)	10.10	200	**<.0001**
Range	1.7–100.0	0.0–94.8			
Level of depressive symptom severity					
Subsyndromal depressive symptoms					
Mean (SD)	9.0 (14.9)	33.4 (25.4)	−9.14	124.1[e]	**<.0001**
Range	0.0–75.0	2.7–100.0			
Minor depressive episode threshold					
Mean (SD)	12.9 (17.2)	24.7 (21.4)	−4.84	200	**<.0001**
Range	0.0–94.5	0.0–89.0			
Major depressive episode threshold					
Mean (SD)	6.6 (9.6)	11.6 (14.6)	−2.75	127.9[e]	**.007**
Range	0.0–55.8	0.0–60.5			
Minor or major syndromal threshold					
Mean (SD)	19.6 (22.5)	36.3 (27.6)	−5.01	200	**<.0001**
Range	0.0–95.5	0.0–97.3			
Depressive symptoms at any level of severity					
Mean (SD)	28.5 (28.4)	69.7 (29.2)	−10.10	200	**<.0001**
Range	0.0–98.3	5.2–100.0			

[a]Depressive illness burden is described during a period that starts with the first of 8 consecutive weeks asymptomatic or 8 consecutive weeks SSD resolution of the index major depressive episode and extends for another 519 weeks (for a total of 10 years). Some subjects had missing or unreliable data for 1 or more follow-up periods during this 10-year interval, but these subjects must have had at least 2 years (104 weeks) of data present and reliable to be included in the table. The mean number of weeks of data on which the analyses are based is 486 (SD = 45.6; range, 312–520) for asymptomatic recovery and 482.7 (SD = 57.3; range, 152–520) for SSD resolution.
[b]Depressive symptoms below the diagnostic threshold for a probable or definite major or minor depressive or dysthymic episode.
[c]A *t* test comparison was performed on arcsine transformation of percentages to normalize the distribution.
[d]*P* values statistically significant at *P* < .05 are indicated in bold.
[e]After Satterthwaite adjustment to degrees of freedom, for unequal group variances.

years (*P* = .008), absence of comorbid substance abuse at index (*P* = .022), female sex (*P* = .036), impaired premorbid friendships (*P* = .048), and being satisfied with major life role only some or none of the time (*P* = .049). After index MDE level of recovery was included as a covariate, only early onset, ≥ 4 lifetime depressive episodes, and absence of comorbid substance abuse at index remained significant (*P* = .001, .003, and .008, respectively). The other 11 binary variables examined were not significantly associated with risk for depressive relapse: comorbid anxiety disorder during the index episode (*P* = .052) or first well interval (*P* = .148), absence of comorbid substance abuse during the first well interval (*P* = .091), miscellaneous psychiatric conditions during the index episode (*P* = .121) or first well interval (*P* = .746), severe GAS score (*P* = .449), and several variables representing premorbid psychosocial functioning (impaired work [*P* = .052], household duties [*P* = .088], and overall psychosocial function [*P* = .059], low involvement in recreation/hobbies [*P* = .203], and low life satisfaction [*P* = .476]). After each of the 18 other variables were included individually as covariates, and after a combination of covariates were also entered into the forward-stepping model, SSD resolution remained a highly significant predictor of rapid relapse/recurrence at *P* < .0001.

Four-group survival analysis based on combinations of recovery level and each of the above variables (Supplementary

eTable 3) revealed that most other relapse predictors made a notable difference only within the asymptomatic recovery group; time to relapse was much faster in the SSD group for both categories of each binary variable.

Within-Subject Asymptomatic Versus SSD Resolution

Of the 125 participants with SSD resolution of their index MDE, 68 (54.4%) experienced a period of 8 consecutive weeks asymptomatic after a subsequent MDE. Median time well was 3.1 times longer than after the same subjects' intake SSD resolution (102 vs 33 weeks); their probability of relapse/recurrence decreased to 0.105 from 0.401 within the first 6 months, and to 0.329 from 0.751 within the first year. After these subjects' asymptomatic recovery from a later MDE, they had a significantly less chronic illness (*P* < .001) and better overall psychosocial function (*P* < .001) than after their index SSD resolution (Supplementary eTable 4).

4-Week Versus 8-Week Asymptomatic Recovery Definition

Eight consecutive weeks of asymptomatic recovery conveyed little benefit when compared to 4 weeks of asymptomatic recovery. Subjects who experienced 4 weeks of asymptomatic status following their index MDE had 0.93 probability of remaining asymptomatic for another 4 weeks,

Table 4. Antidepressant Treatment During Index Episode and First Well Interval Interval for CDS Participants With Asymptomatic Recovery Versus Residual Subsyndromal Depressive Symptom (SSD) Resolution of Index Major Depressive Episode

Time Period and Antidepressant Treatment	Asymptomatic Recovery	Residual SSD Resolution[a]	Significance		
			t	df	P[b]
During index episode[c]	(n = 195)	(n = 125)			
Per person CAD[d] level across all weeks, mean (SD)	1.65 (1.12)	1.63 (1.10)	0.19	318	.846
Weeks with any antidepressant, mean (SD), %[e]	69.94 (39.47)	65.13 (37.45)	1.33	318	.184
Weeks with therapeutic level of antidepressant, mean (SD), %[e,f]	28.71 (35.72)	31.18 (34.15)	−0.78	318	.435
During first well interval[g]	(n = 197)	(n = 125)			
Per person CAD[d] level across all weeks, mean (SD)	0.94 (1.12)	1.24 (1.32)	−2.12	231.5[h]	**.035**
Weeks with any antidepressant, mean (SD), %[e]	40.70 (43.72)	50.83 (45.43)	−1.78	320	.076
Weeks with therapeutic level of antidepressant, mean (SD), %[e,f]	14.41 (29.10)	21.49 (38.14)	−1.83	320	.068

[a]Depressive symptoms below the diagnostic threshold for a probable or definite major or minor depressive or dysthymic episode.
[b]P values statistically significant at P < .05 are indicated in bold.
[c]From intake through the week prior to the start of asymptomatic or SSD recovery.
[d]Antidepressant medication was combined into a 5-point weekly CAD score with the following values: 0 = none, 1 = 1–99 mg/d of imipramine or equivalent, 2 = 100–199 mg/d imipramine or equivalent, 3 = 200–299 mg/d imipramine or equivalent, and 4 = 300 mg/d or more of imipramine or equivalent. The value based on medication alone was increased to reflect electroconvulsive therapy received in a given week.
[e]A t test was performed on arcsine transformed percentages to normalize the distribution.
[f]A therapeutic dose of antidepressant is defined as a CAD value of 3 or 4 representing at least 200 mg/d of imipramine or equivalent.
[g]From first week of asymptomatic or SSD recovery to the start of subsequent depressive episode (or censoring of data).
[h]After Satterthwaite adjustment to degrees of freedom, for unequal group variances.
Abbreviations: CAD = composite antidepressant, CDS = Collaborative Depression Study.

thus meeting the 8-week definition of MDE recovery. Median time well after 4 weeks asymptomatic status was nearly as long as that obtained with the 8-week definition (124 vs 135 weeks); probability of relapse within 1 year was 0.302 versus 0.261.

DISCUSSION

A definition of MDE recovery needs to specify both level and duration of the target symptom status. The primary test of the validity of a definition of recovery is whether it marks the beginning of a stable state of wellness.[1,2] In this article, we have provided a head-to-head comparison of the 2 levels of episode resolution contained within the current consensus definition of MDE recovery—namely, 8 consecutive weeks with no symptoms versus 8 weeks with mild residual symptoms of the MDE. We found that 8 weeks of asymptomatic recovery marked the start of a 4.2 times longer well interval as well as a less chronic future depressive illness course and improved psychosocial function compared to 8 weeks with residual symptoms of the index episode. We then found that 8 consecutive weeks of asymptomatic status after the index episode conferred little clinical benefit over asymptomatic status obtained at 4 weeks. Thus, findings reported here provide definitive evidence that MDE resolution with minimal depressive symptoms should not be considered MDE "recovery" for clinical practice or research. The presence of residual depressive symptoms indicates that the episode is still active, psychosocial function remains impaired, and the patient is in need of ongoing treatment to prevent return to a syndromal level of illness.

Examination of how specific patterns of medication continuation or withdrawal could affect depressive relapse[28] was beyond the scope of this article. We did find, however, that the shorter well interval associated with SSD resolution was not attributable to receiving less intensive antidepressant medication treatment, suggesting that the 2 recovery groups may differ in the quality of their depressive illness. Participants with SSD resolution of their index MDE had significantly longer and more severe index MDEs, with more irritability and miscellaneous psychopathology. They also had significantly greater psychosocial dysfunction, both premorbidly and during long-term follow-up, suggesting that psychosocial factors need to be addressed during treatment in order to optimize the chance for asymptomatic recovery and a stable, episode-free state. None of the clinical or psychosocial differences between asymptomatic and SSD recovery groups, whether assessed individually or in combination, provided as strong a prediction of time to relapse or recurrence as level of index MDE resolution.

Recent studies[28–30] have documented the risk for relapse associated with residual depressive symptoms. Individual symptoms may be persistent symptoms of the episode or may emerge with treatment; either way, they should be monitored and treated as needed.[31,32] Specific residual symptoms may require antidepressants affecting relevant neurotransmitter systems.[33–37] It is now clear that resolution of residual depressive symptoms is necessary not only for sustained MDE recovery but also for restoration of premorbid psychosocial function.[38–41] Our finding that neuroticism-related personality measures and long-term psychosocial dysfunction are associated with intake MDE resolution to the SSD level is consistent with recent literature[42–44] indicating that some MDEs may be intertwined with long-standing maladaptive personality traits and psychosocial patterns. Combined somatic and cognitive-behavioral therapy approaches may frequently be needed to establish long-term recovery.[29,39,45]

Without differentiating asymptomatic from residual symptom status, researchers have suggested that a 4-month

period may be better than 8 weeks for defining stable MDE recovery.[1,2] We have now found that a 4-week asymptomatic period has 93% overlap with and initiates nearly as stable a well interval as the 8-week definition; however, research is needed to identify characteristics of subjects for whom a longer or shorter asymptomatic period may be needed to define stable recovery, as well as whether noncriterion symptoms should be considered.[2]

Caveats

Subjects entering the CDS between 1978 and 1981 may not reflect the full range of severity and quality of MDE patients currently presenting for treatment at primary practice and specialty settings. We feel, however, that with its greater stability, asymptomatic recovery is a broadly applicable definition of true MDE recovery.

Future research by our group will address the predictive value of specific residual symptoms as well as discreet, clinically meaningful aspects of neuroticism as predictors of time to relapse.

CONCLUSIONS

Future treatment guidelines should follow the recommendation of a 1993 Depression Guideline Panel[46] and specify that the goals of MDE treatment are, in order of priority, "(1) to reduce and ultimately to remove *all* signs and symptoms of the depressive syndrome, (2) to restore occupational and psychosocial function to the *asymptomatic* state, and (3) to reduce the likelihood of relapse and recurrence."[46(p1)] Only asymptomatic recovery provides a foundation for all of these treatment goals and should be considered "true" MDE recovery. The presence of ongoing residual depressive symptoms is the strongest available indicator that further treatment is needed because the MDE is still active, with the patient continuing to have significant psychosocial dysfunction and high risk for rapid relapse or recurrence. In our study, 4 consecutive weeks of asymptomatic status initiated nearly as stable a well period as 8 weeks, indicating that 4 weeks free of all symptoms of the episode should be the new definition of MDE recovery.

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Supplementary Material

List of Supplementary Material for the article

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Supplementary eTable 1
Classification of Depressive Symptom Severity Levels
Based on Weekly Psychiatric Status Ratings (PSRs) across All Depressive Conditions[a,b]

Depressive Symptom Severity Level	Major Depression (6-Point PSR Scale)[c]	Minor Depression (3-Point PSR Scale)[d]	DSM-III Depressive Conditions[a] (3-Point PSR Scale)[d]
1. **Asymptomatic** – No depressive symptoms of the episode; return to usual self	1	1	1
2. **Subsyndromal (SSD) level** - Depressive symptoms below the MinD/Dysthymia level	1 1 2	1 2 1 or 2	2 or 3 (Any)[e] (Any) (Any)
3. Depressive symptoms at the **MinD/Dysthymia level**	1 2 3 4	3 3 (Any) (Any)	(Any) (Any) (Any) (Any)
4. Depressive symptoms at the **MDE level**	5 6	(Any) (Any)	(Any) (Any)

Footnotes for Supplementary eTable 1:

a. Weekly symptom severity level is assigned based on each week's ratings on all depressive conditions, regardless of whether the patient was in a Research Diagnostic Criteria (RDC) episode at that time. Rated affective conditions include RDC major depressive episode (MDE); RDC minor or intermittent depressive episode, long-term (dysthymic) or short-term (MinD); and DSM-III Atypical Depression (code 296.82) and Adjustment Disorder with Depressed Mood (code 309.00). Weekly depressive symptom severity levels 1-4 are mutually exclusive.

b. Read across the table for combinations of PSR values that result in classifying a particular week at a given symptom depressive severity level. For example, a patient would be classified at the minor depression/dysthymia level for a given week if they were rated as PSR 3 or 4 on the 6-point major depression scale, or PSR 3 on the 3-point minor depression/ dysthymia scale with a PSR 1 or 2 on the 6-point major depression scale.

c. 6-Point Weekly Psychiatric Status Rating Scale values: 1 = asymptomatic, returned to usual self; 2 = residual/mild affective symptoms of the episode; 3 = partial remission, moderate symptoms or impairment; 4 = marked/major symptoms or impairment; 5 = meets definite criteria without prominent psychotic symptoms or extreme impairment; 6 = meets definite criteria with prominent psychotic symptoms or extreme impairment.

d. 3-Point weekly Psychiatric Status Rating Scale values: 1 = asymptomatic, returned to usual self; 2 = meets probable criteria (mild symptoms, below those for meeting definite criteria); 3 = meets definite criteria.

e. "(Any)" indicates any PSR value of this affective condition qualifies for the given symptom severity level, in conjunction with the values shown for other depressive conditions. For example, a given week is classified at the MDE level based on a PSR value of 5 or 6 for MDE, regardless of PSR values on any other depressive condition.

Supplementary eTable 2
Psychosocial Functioning/Impairment Associated with
Asymptomatic Recovery vs. Residual Subsyndromal (SSD) Depressive Symptom Resolution of Index MDE

Psychosocial Functioning/Impairment Variables[a]	Asymptomatic Recovery (N=197)		Residual Symptom (SSD) Resolution (N=125)		Significance		
	Mean (sd)	N	Mean (sd)	N	t	df	P
Adolescent Friendship Patterns[a]	2.90 (0.87)	197	3.20 (0.91)	124	-2.94	319	**0.004**
Worst Level of Overall Functional Impairment in Intake Episode (due to Psychopathology)[b]	3.44 (1.20)	197	3.81 (1.08)	125	-2.78	320	**0.006**
Best Level in 5 Years Prior to Intake:[c]							
Work[d]	1.58 (0.88)	175	2.04 (1.24)	103	-3.27	276	**0.001**
Household Duties[d]	1.67 (0.75)	180	1.90 (0.80)	120	-2.57	298	**0.011**
Relationship with Spouse/Partner[e]	1.96 (1.02)	139	2.12 (1.04)	80	-1.12	217	0.264
Relationship with Children[e]	1.72 (0.74)	119	2.04 (0.87)	74	-2.72	191	**0.007**
Relationship with Friends[e]	1.91 (0.85)	196	2.15 (0.94)	125	-2.40	319	**0.017**
Enjoyment of Recreation/Hobbies[e]	1.84 (0.87)	196	2.07 (0.91)	125	-2.28	319	**0.023**
Subjective Satisfaction/Contentment[e]	1.99 (0.89)	196	2.26 (0.88)	125	-2.62	319	**0.009**
Overall Rating of Social Adjustment[d]	2.16 (0.91)	196	2.52 (0.87)	125	-3.55	319	**<0.001**
Mean Level during Long-Term Follow-Up, after Start of First Well Interval:[f]							
Work[d]	1.96 (0.86)	161	2.82 (1.33)	96	-5.69	142.98*	**<0.001**
Household Duties[d]	2.08 (0.57)	173	2.33 (0.58)	105	-3.60	276	**<0.001**
Relationship with Spouse/Partner[e]	2.06 (0.84)	127	2.20 (0.83)	65	-1.10	190	0.272
Relationship with Children[e]	1.89 (0.65)	127	2.27 (0.85)	75	-3.31	125.5*	**0.001**
Relationship with Friends[e]	2.24 (0.83)	176	2.68 (0.83)	107	-4.38	281	**<0.001**
Involvement in Recreation/Hobbies[e]	2.12 (0.75)	176	2.64 (0.75)	107	-5.64	281	**<0.001**
Subjective Satisfaction/Contentment[e]	2.31 (0.71)	175	2.89 (0.69)	107	-6.70	281	**<0.001**
Overall Rating of Social Adjustment[d]	2.34 (0.78)	176	2.94 (0.77)	107	-6.30	281	**<0.001**
Mean Level during Long-Term Follow-Up[g]	N (%)		N (%)		x^2	df	P
Very Good or Good	114 (64.8)		33 (30.8)				
Fair	49 (27.8)		49 (45.8)		33.60	2	**<0.001**
Poor or Very Poor	13 (7.4)		25 (23.4)				

Footnotes for Supplementary eTable 2:

a. From Schedule of Affective Disorders and Schizophrenia (SADS) item 539 at intake, with rating values 1='superior'; 2='very good'; 3='good'; 4='fair'; 5='poor'; 6='grossly inadequate'.

b. From SADS item 465 at intake, with rating values 1='none'; 2='minor'; 3='significant effects'; 4='important modifications'; 5='major modifications'; 6='major disruption'.

c. From LIFE Base interviews, with ratings as indicated per item.

d. Rating values 1='no impairment – high level of function'; 2='no impairment – satisfactory level of function'; 3='mild impairment – mild difficulty in carrying out these activities'; 4='moderate impairment – considerable difficulty in carrying out these activities'; 5='severe impairment – virtually unable to carry out these activities' (or not doing so at all due to psychopathology).

e. Rating values = 'very good'; 2='good'; 3='fair'; 4='poor'; 5='very poor'.

f. Psychosocial assessments of worst level of function were made for each month during follow-up years 3-5, and for the last month (only) of follow-up years 6 to 31, using variants of the original LIFE interviews. Mean per-subject level of impairment was calculated based on monthly ratings after the start of asymptomatic recovery or SSD resolution of the index MDE.

g. Based on mean per-person rating across rated months during long-term follow-up, where mean $\leq$2.50='very good or good'; mean >2.50 and $\leq$3.50='fair'; and mean >3.50='poor or very poor'.

Supplementary eTable 3 (Page 1 of 3)
Median Time (Weeks) to First Depressive Relapse/Recurrence
Based on Each of 18 Clinical Variables, within Groups Defined by
Asymptomatic Recovery vs. Residual Subsyndromal (SSD) Depressive Symptom Resolution
from Index MDE[a]

Clinical Variable		Asymptomatic Recovery (N=197)		Residual Symptom(SSD) Resolution (N=125)	
1. Sex	Group [N] Mdn Wks. Well (95% CI) Signif.	Male [86] 192 (107-243)	Female [111] 108 (83-150) P=0.161	Male [43] 30 (20-42)	Female [82] 32 (24-8) P=0.962
2. Early Onset (Before Age 21)	Group [N] Mdn Wks. Well (95% CI) Signif.	Not Early [140] 149 (102-214)	Early [57] 108 (62-192) P=0.082	Not Early [77] **35** (29-43)	Early [48] **24** (18-32) **P=0.004**
3. Lifetime Number of Affective Episodes (Including Index MDE)	Group [N] Mdn Wks. Well (95% CI) Signif.	1-3 [155] **150** (111-227)	4 or More [42] **62** (36-107) **P<0.0001**	1-3 [84] 34 (25-42)	4 or More [41] 28 (19-36) P=0.422
4. Chronicity of Index Episode (Total Duration >2 Years)	Group [N] Mdn Wks. Well (95% CI) Signif.	Not Chronic [127] 197 (131-269)	Chronic [70] 108 (59-209) P=0.244	Not Chronic [56] 34 (23-43)	Chronic [69] 30 (23-42) P=0.474
5. Severity of Index Episode (Global Assessment of Severity Score <40 for Worst Period in Episode, Prior to Intake)	Group [N] Mdn Wks. Well (95% CI) Signif.	Not Severe [81] 131 (84-208)	Severe [116] 135 (93-219) P=0.987	Not Severe [44] 38 (25-46)	Severe [81] 30 (22-36) P=0.393
6. Comorbid Anxiety Disorder at Intake (Genralized Anxiety, Phobic, Panic, or Obsessive/ Compulsive Disorder)	Group [N] Mdn Wks. Well (95% CI) Signif.	No [177] **149** (108-208)	Yes [20] **69** (32-111) **P=0.031**	No [109] 33 (25-38)	Yes [16] 30 (14-65) P=0.869
7. Comorbid Anxiety Disorder during First Well Interval	Group [N] Mdn Wks. Well (95% CI) Signif.	No [163] 124 (92-197)	Yes [34] 149 (81-220) P=0.489	No [108] 32 (24-36)	Yes [17] 34 (16-68) P=0.341

Clinical Variable		Asymptomatic Recovery (N=197)		Residual Symptom(SSD) Resolution (N=125)	
8. Any Substance Abuse (Alcohol or Drug Use) Disorder at Intake	Group [N] Mdn Wks. Well (95% CI) Signif.	No [157] **124** (84-184)I	Yes [40] **201** (93-664) **P=0.025**	No [97] 33 (23-38)	Yes [28] 32 (22-68) P=0.293
9. Any Substance Abuse (Alcohol or Drug Use) Disorder during First Well Interval	Group [N] Mdn Wks. Well (95% CI) Signif.	No [171] 124 (92-184)	Yes [26] 220 (84-607) P=0.185	No [108] 31 (23-36)	Yes [17] 41 (19-227) P=0.266
10. Any Comorbid Miscellaneous Disorder at Intake (Representing Miscellaneous Psychopatholog)	Group [N] Mdn Wks. Well (95% CI) Signif.	No [154] 131 (92-208)	Yes [43] 138 (62-259) P=0.996	No [79] 38 (30-43)	Yes [46] 23 (18-30) P=0.190
11. Any Comorbid Miscellaneous Disorder during First Well Interval	Group [N] Mdn Wks. Well (95% CI) Signif.	No [151] 131 (88-214)	Yes [46] 135 (91-201) P=0.787	No [87] 34 (25-39)	Yes [38] 28 (19-43) P=0.596
12. Very Good Work Role Function (No Impairment, High Level of Function) in Best Period during 5 Years Prior to Intake (from LIFE Base)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [103] 150 (107-214)	No [72] 92 (66-197) P=0.275	Yes [41] 34 (23-43)	No [62] 32 (22-38) P=0.902
13. Very Good Household Function (No Imp., High Level Function) in Best Period during 5 Years Prior to Intake (from LIFE Base)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [83] 135 (102-227)	No [97] 111 (83-201) P=0.699	Yes [36] 35 (23-43)	No [84] 30 (23-36) P=0.382
14. Very Good Social Relationships in Best Period during 5 Years Prior to Intake (fromSADS Item 1242)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [81] 151 (107-214)	No [115] 111 (81-197) P=0.587	Yes [32] 34 (21-50)	No [93] 32 (23-36) P=0.401
15. Very Good Involvement in Recreation/ Hobbies in Best Period during 5 Years Prior to Intake (from LIFE Base)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [82] 151 (107-243)	No [114] 108 (83-167) P=0.447	Yes [38] 26 (18-36)	No [87] 34 (25-41) P=0.665

Clinical Variable		Asymptomatic Recovery (N=197)		Residual Symptom(SSD) Resolution (N=125)	
16. Very Good Subjective Contentment/Satisfaction with Life in Best Period during 5 Years Prior to Intake (from LIFE Base)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [69] 149 (93-209)	No [127] 111 (84-201) P=0.977	Yes [25] 30 (20-36)	No [100] 34 (25-42) P=0.270
17. Very Good or Good Overall Social Adjustment in Best Period during 5 Years Prior to Intake (from LIFE Base)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [127] 143 (100-209)	No [69] 111 (71-192) P=0.051	Yes [64] 36 (26-43)	No [61] 26 (21-34) P=0.299
18. Satisfied with Major Life Role Most of the Time Prior to Intake (from Personal Resources Inventory Item 255)	Group [N] Mdn Wks. Well (95% CI) Signif.	Yes [97] 149 (92-227)	No [97] 124 (81-192) P=0.156	Yes [48] 34 (22-38)	No [75] 31 (23-42) P=0.852

Footnote for Supplementary eTable 3:

a. Survival analysis was run on the number of weeks from the start of asymptomatic or SSD resolution of the index MDE to the start week of the next depressive episode relapse/recurrence of any type (MDE or minor depression). Significance (P-value) for comparison *within* the asymptomatic or SSD recovery group is based on the Log Rank x^2 statistic, comparing overall survival distributions of the 2 comparison groups across all of follow-up until censoring of data due to end of follow-up or a period of missing or "unreliable" weekly Psychiatric Status Rating (PSR) data.

Supplementary eTable 4
Within-Subject Outcomes for 68 CDS Participants
after Residual Subsyndromal (SSD) Depressive Symptom Resolution of Their Index MDE
vs. after Asymptomatic Recovery Later during Follow-Up

		Weeks to Next Depressive Episode Relapse/Recurrence		
		Post-SSD Index MDE Resolution	Post-Asymptomatic Later Recovery	Significance
Survival Analysis of Time to First Depressive Episode (Major, Minor, or Dysthymic) Relapse/Recurrence (N=68)	25% (95%CI) 50% (95%CI) 75% (95%CI)	17.5 (14-230) 33 (25-39) 55 (42-142)	42 (30-56) 102 (59-155) 241 (166-310)	P<0.001
		Probability of Relapse/Recurrence by This Time		
	6 Mos. 1 Year 2 Years 5 Years	0.401 0.751 0.851 1.000	0.105 0.329 0.512 0.780	P<0.001
Severity of Depressive Illness Illness during the Interval (N=68)		Percentage of Weeks with Each of Four Levels of Depressive Illness Severity		
		Post-SSD Index MDE Resolution	Post-Asymptomatic Later Recovery	Significance
Asymptomatic (Returned to Usual Self)	Mean (sd)	2.3 (9.3)	62.6 (30.3)	P<0.001
Subsyndromal (SSD) Depressive Symptoms	Mean (sd)	68.1 (24.3)	10.7 (15.2)	P<0.001
Minor Depressive Episode (MinD) Threshold Symptoms	Mean (sd)	22.4 (18.1)	16.9 (19.5)	N.S.
Major Depressive Episode (MDE) Threshold Symptoms	Mean (sd)	7.2 (11.0)	9.9 (14.7)	N.S.
Global Rating of Psychosocial Impairment (N=38)[a]		Level of Psychosocial Impairment		
		Post-SSD Index MDE Resolution	Post-Asymptomatic Later Recovery	Significance
	Mean (sd)	2.98 (0.65)	2.60 (0.70)	P<0.001

Footnote for Supplementary eTable 4:

a. 38 participants experienced both levels of recovery after 2 years of follow-up, when the wording for this rating was changed on versions of the LIFE interview used thereafter during follow-up. The rating is a summary judgment by the clinical rater of overall psychosocial functioning, on a scale where 1=very good; 2=good; 3=fair; 4=poor; 5=very poor.