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Research report

Major depressive disorder: A prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse

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Abstract

Background: The study tested whether level of recovery from major depressive episodes (MDEs) predicts duration of recovery in unipolar major depressive disorder (MDD) patients. *Methods:* MDD patients seeking treatment at five academic centers were followed naturalistically for 10 years or longer. Patients were divided on the basis of intake MDE recovery into residual depressive symptoms (SSD; $N = 82$) and asymptomatic ($N = 155$) recovery groups. They were compared on time to first episode relapse/recurrence, antidepressant medication, and comorbid mental disorders. Recovery level was also compared to prior history of recurrent MDEs (> 4 lifetime episodes) as a predictor of relapse/recurrence. *Results:* Residual SSD compared to asymptomatic recovery patients relapsed to their next MDE > 3 times faster (median = 68 vs. 23 weeks) and to any depressive episode > 5 times faster (median = 33 vs. 184 weeks). Residual SSD recovery status was significantly associated with early episode relapse (OR = 3.65) and was stronger than history of recurrent MDEs (OR = 1.64). Rapid relapse in the SSD group could not be attributed to higher comorbidity or lower antidepressant treatment. *Limitations:* Although inter-rater agreement on weekly depressive symptom ratings was very high (ICC > 0.88), some error may exist in assigning recovery levels. Antidepressant treatments were recorded, but were not controlled. *Conclusions:* MDE recovery is a powerful predictor of time to episode relapse/recurrence. Residual SSD recovery is associated with very rapid episode relapse which supports the idea that SSD is an active state of illness. Asymptomatic recovery is associated with prolonged delay in episode recurrence. These findings of this present study have important implications for the goals of treatment of MDD and for defining true MDE recovery. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: MDE recovery; Residual symptoms; Rapid episode relapse

1. Introduction

Studies in community samples report high prevalence and increased psychosocial impairment associated with threshold depressive symptoms (SSD) (Wells et al., 1989; Broadhead et al., 1990; Johnson et al., 1992; Judd et al., 1994, 1996, 1997), which have been defined as minimal depressive symptoms

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beneath the diagnostic threshold for minor, dysthymic or major depressive disorders (Judd et al., 1994, 1996, 1997). We have reported that SSD are very commonly observed in patients with unipolar major depressive disorder and are an integral component of the symptomatic course of illness (Judd et al., 1996, 1998).

In addition, a relationship has been described between SSD and major depressive episodes (MDEs), since some investigators have observed SSD to be associated with significantly increased prevalence of future and past MDEs (Broadhead et al., 1990; Howarth et al., 1992; Sherbourne et al., 1994; Judd et al., 1997).Other researchers have also found residual subthreshold depressive symptoms following major depressive episode (MDE) recovery are associated with increased rates of episode relapse (Faravelli et al., 1988; Simmons and Thase, 1992; Thase et al., 1992; Fava et al., 1994a,b; Paykel et al., 1995).

To determine more definitively the clinical significance of residual SSD, we investigated the course of illness of a large cohort of patients with unipolar MDD, followed prospectively for 10 years by the NIMH Collaborative Depression Study (CDS) (Katz and Klerman, 1979; Katz et al., 1979). Patients who recovered from intake MDEs with residual SSD vs. asymptomatic recovery were compared on a wide spectrum of clinical and course variables. More specifically, the study was designed to determine if completeness or level of MDE recovery (residual SSD vs. asymptomatic recovery) predicted duration of recovery. Further, since earlier CDS studies have reported history of antecedent MDEs (1–3 vs. >4) to be the strongest predictor of early relapse (Keller et al., 1982, 1983), this relapse risk factor was also compared to residual SSD recovery of MDEs.

2. Methods

2.1. The NIMH Collaborative Depression Study (CDS) clinical studies program

2.1.1. Subjects

Subjects were nonbipolar MDD patients seeking treatment at one of five academic centers during 1978 to 1981 (Katz and Klerman, 1979; Katz et al., 1979), who were followed to at least 10 years and who had a well-defined first well interval (as defined below) during follow-up. Intake diagnoses were obtained by Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) based on using Schedule for Affective Disorders and Schizophrenia (SADS) interviews (Spitzer and Endicott, 1979). Patients entered the CDS during an MDE in the absence of ongoing dysthymia; patients with evidence, at intake or follow-up, of bipolar disorders (mania, hypomania, cyclothymic personality), schizoaffective disorder or schizophrenia were excluded from the MDD cohort of 327 patients. All CDS patients were white, English-speaking, with no organic mental disorder nor terminal illness and intelligent quotients >70. Each site obtained informed consent for study participation. Ninety MDD patients were excluded in advance of the analyses because they did not experience relapse/recurrence during follow-up ($N=44$), had missing or unreliable data ($N=10$) or did not meet the criteria for residual SSD or asymptomatic recovery defined below ($N=36$).

2.2. Follow-up procedures

Trained raters interviewed patients every 6 months for the first 5 years, and yearly thereafter, using variations of the Longitudinal Follow-up Evaluation (LIFE) (Keller et al., 1987). Patients are the primary source of information for the LIFE; chronological memory prompts are used to obtain accurate information on weekly symptom severity for all mood or other mental disorders. Interviews through 5 years were supplemented by detailed review of clinical, medical and research records. Weekly depressive symptomatology was rated using the LIFE Psychiatric Status Rating (PSR) Scales (Keller et al., 1987) shown in Table 1. CDS interviewers undergo rigorous training, resulting in very high intra-class correlation coefficients (ICC) for rating weekly symptom change points (ICC = 0.92) episode recovery (ICC = 0.95) and point of subsequent depressive symptom appearance (ICC = 0.88).

2.3. First well interval variables

As described in Table 1, RDC defines MDE recovery as >8 consecutive weeks at PSR-MDD ‘1’

Table 1
Psychiatric status rating scales

Six-point weekly psychiatric status rating scale for RDC major depressive disorder (PSR-MDD)[e]		
Code	Status	Definition
1.	Asymptomatic/returned to usual self[a]	Subject is returned to 'usual self' without any residual symptoms of the MDD disorder, although significant symptomatology from underlying conditions may continue.
2.	Residual/mild depressive symptoms[a]	Subject claims not to be completely back to 'usual self' or rather notes presence of one or more symptoms of the MDD disorder in no more than mild degree.
3.	Partial remission (moderate symptoms or impairment)	Considerable less psychopathology than full criteria, with no more than moderate impairment in functioning, but still with obvious evidence of the disorder.
4.	Marked/major symptoms or impairment	Has major symptoms or impairment but does not meet definite RDC criteria for MDD.
5.	Definite criteria without prominent psychotic symptoms or extreme impairment[b]	Meets RDC criteria 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[b]	Meets RDC criteria for definite MDD episode, and has either prominent psychotic symptoms or extreme impairment in functioning (incapacitation).

Three-point weekly psychiatric status rating scale for RDC minor depressive or dysthymic disorders (PSR-MinD) (short-term or long-term) and for DSM-III atypical depression (296.82) or DSM-III adjustment disorder with depressed mood (309.00) at intake[e]		
Code	Status	Definition
1.	Asymptomatic[c]	Previously met RDC criteria for the disorder, but currently shows no evidence of it.
2.	Probable criteria/mild symptoms	Previously met RDC criteria and now has some minor manifestations of the disorder but does not meet full RDC criteria. For the two DSM-III disorders, the subject does not have to meet definite criteria first.
3.	Definite criteria/severe symptoms[d]	Meet definite RDC criteria for the disorder.

[a] Eight consecutive weeks of PSR-MDD '1' or '2' defines the end of RDC MDD episode.
[b] Two consecutive weeks of PSR-MDD '5' or '6' defines the start of an RDC MDD episode.
[c] Eight consecutive weeks at PSR-MDD '1' or '2' defines the end of an RDC episode of Minor Depressive or Dysthymic Disorder.
[d] Two consecutive weeks at PSR-MinD '3' defines onset of an RDC episodes of Minor Depressive or Dysthymic Disorder.
[e] Fluctuations in PSR ratings may be recorded without limitation during the time patients are in an RDC depressive episode; once recovered there are coding prohibitions against increasing PSR scores until criteria for an episode of MDD or MinD are met. Increases in symptomatology that do not meet criteria for an MDD episode may be recorded on the PSR-MinD scale if the patients meets 'definite' RDC criteria for MinD. Minimal increases in depressive symptomatology not meeting MinD or MDD criteria can be recorded as an 'Other Psychiatric Condition' under one of two DSM-III codes: *Atypical Depression* (DSM-III code 296.82) or *Adjustment Disorder with Depressed Mood* (DSM-III code 309.00) using the three-point PSR-MinD scale.

or '2'; RDC definition of episode relapse/recurrence is defined by >2 consecutive weeks at PSR-MDD '5' or '6' MDE or >2 weeks at PSR-MinD '3', which is where all new episodes of minor depressive or dysthymic disorder (MinD) are coded. *Start* of the first well interval was identified as the first week of intake MDE recovery; *end* of the first well interval was defined as the last week before onset of the first prospective episode relapse/recurrence. (see above)

2.4. Definition of the two recovery groups

All weeks of the first well interval, during 10 years of follow-up were classified into two categories: weeks when patients were rated asymptomatic as PSR-MDD '1' and/or PSR-MinD '1'; and weeks patients were rated with residual substhreshold depressive symptoms (SSD) or PSR-MDD '2' and PSR-MinD '2'. Following these two

recovery groups were created: (1) *the residual SSD recovery group* – 82 patients with all of their well interval weeks rated PSR-MDD or PSR-MinD '2'; and (2) *the asymptomatic recovery group* – 155 patients with at least 80% of well interval weeks rated PSR-MDD and PSR-MinD '1.' The 36 patients eliminated from the analysis sample did not meet apriori definitions of residual SSD or asymptomatic MDE recovery and were extremely varied in percentage of weeks asymptomatic (median weeks at PSR '1' = 41.4%; range 2–79%). It was felt that this group was too heterogeneous in their recovery status to be included in the analysis sample for this first investigation of the recovery status risk factor.

2.5. Antidepressant medication treatment during the first well interval

Antidepressant medication dosage was combined into a five-point weekly composite antidepressant (CAD) score: '0' = none; '1' = 1–99 mg/qd of imipramine or equivalent; '2' = 100–199 mg/qd imipramine or equivalent; '3' = 200–299 mg/qd of imipramine or equivalent; '4' = 300 mg/qd and above of imipramine or equivalent (Keller et al., 1992). Recovery groups were compared on mean weekly CAD scores for the intake MDE and the first well interval. Percentage of weeks during the well interval with 'any' (CAD $>$ '1') and 'adequate' (CAD $>$ '3') antidepressant medication treatment were also compared.

2.6. Relationship of comorbid mental or substance use disorders to intake MDD episode recovery status

Prevalence of comorbid mental or substance use disorders during the intake MDE and first well interval were compared for the two recovery groups.

2.7. Statistics

Statistical comparisons of the two recovery groups were made for continuous variables using *t*-tests; comparisons across categories of nominal variables were made with Chi-square or Fisher's Exact tests (two-tailed alpha level of $P = 0.05$). The non-parametric Wilcoxon Rank Sum Test was used to test the relationship between recovery status and ordinal variables.

Comparison of the recovery period were made using life-table methods to model the cumulative probability of depressive episode relapse as a function of successive numbers of weeks remaining 'well' (Cox and Oakes, 1984). The Kaplan–Meier product limit estimate (Kaplan and Meier, 1958) was used to accommodate data censored prior to end of the first well interval. The relative importance of history of recurrent MDEs and the recovery status risk factors were evaluated three ways. First, the predictive value of each risk factor was tested separately using the generalized Wilcoxon test to compare relapse curves for number of lifetime depressive episodes or for recovery status in the first well interval (Kalbfleisch and Prentice, 1980). Second, survival analysis was repeated for four groups defined by combinations of these two dichotomous variables to explore the possible interactive effects between the two predictors of depressive episode relapse. Third, the Cox Proportional Hazards model was used to examine the strength of each variable while controlling for the other (Cox and Oakes, 1984).

Previous CDS reports on UD have focused primarily on relapse to MDEs (Keller et al., 1982, 1983, 1992). For this paper, the survival analyses were performed two ways-predicting time to first episode of any depressive condition (major, minor depressive or dysthymic disorders) and predicting time to first MDE relapse.

3. Results

3.1. Demographic and clinical characteristics

Significantly more asymptomatic recovery patients had intake MDEs of <6 months. Almost twice the percentage of residual SSD recovery patients had intake MDEs >2 years, and there were non-significant trends for residual SSD patients to have higher GAS scores and higher rates of in-patient treatment (Table 2).

Table 2
Demographic and clinical characteristics: A comparison of patients with unipolar major depressive disorder who recover from the intake MDD episode to subsyndromal residual depressive symptoms vs. the asymptomatic status

		Residual symptom recovery group ($N = 82$)	Asymptomatic group ($N = 155$)	Significance
Age:[a]	Mean (S.D.)	39.7 (15.4)	40.0 (15.5)	0.15; df = 235; $P = 0.883$ (NS)
Age group:[a]				
17 to 30	*N* (%)	23(28.0)	64 (41.3)	$X^2 = 4.84$;
31 to 50	*N* (%)	36 (43.9)	49(31.6)	df = 2;
Over 50	*N* (%)	23 (28.0)	42 (27.1)	$P = 0.089$ (NS)
Female:	*N* (%)	55(67.1)	93 (60.0)	$X^2 = 1.14$; df = 1; $P = 0.285$ (NS)
Education:				
High school or less	*N* (%)	46 (56.1)	67 (43.2)	$X^2 = 3.56$;
College or more	*N* (%)	36 (43.9)	88 (56.8)	df = 1; $P = 0.059$ (NS)
Marital status:[a]				
Married/living together	*N* (%)	40 (48.8)	91(58.7)	$X^2 = 3.85$;
Separated, divorced, or widowed	*N* (%)	21(25.6)	24 (15.5)	df = 2 $P = 0.146$ (NS)
Never married	*N* (%)	21(25.6)	40 (25.8)	
Age at onset of first affective episode	Mean (S.D.)	29.6 (14.1)	33.0 (14.7)	$t = 1.20$; df = 235; $P = 0.232$ (NS)
Age at onset of first MDD episode	Mean (S.D.)	30.3 (14.0)	33.0 (14.7)	$t = 1.34$; df = 235; $P = 0.182$ (NS)
Number of lifetime affective episodes (including intake)				$X^2 = 2.10$;
1 to 3	*N* (%)	57 (69.5)	121 (78.1)	df = 1;
4 or more	*N* (%)	25 (30.5)	34 (21.9)	$P = 0.147$ (NS)
In-patient status at intake[a]	*N* (%)	65 (79.3)	107 (69.0)	$X^2 = 2.82$; df = 1 $P = 0.O93$ (NS)
Global assessment scale (GAS) score: Worst week of intake episode[a]	Mean (S.D.)	37.6 (10.0)	40.0 (10.9)	$t = 1.65$; df = 235; $P = 0.100$ (NS)
Total duration of intake MOD episode (weeks)[a,b]				
0 to 6 months	*N* (%)	5 (6.1)	44 (28.4)	2 = 4.5;
6 months to 1 year	*N* (%)	15 (18.3)	34 (21.9)	$P = 0.0008$[c]
1 to 2 years	*N* (%)	26 (31.7)	41(26.4)	
Over 2 years	*N* (%)	36 (43.9)	36 (23.2)	
Mean weekly composite antidepressant (CAD) score [a,d,e]	Mean (S.D.)	1.68 (1.07)	1.70(1.11)	$t = 0.16$; df = 233; $P = 0.87$ (NS)

[a] Significant differences across study sites occurred for this variable.
[b] From onset to recovery.
[c] Wilcoxon 2 Sample Rank Sum Test, by SAS NPAR1 WAY procedure on original values (not recorded).
[d] Dosage equivalents of five antidepressant drug classes and ECT are summed and combined into a five-point score for each week as follows: (0) none; (1) 1–99 mg/qd of imipramine or equivalent; (2) 100–199 mg/qd imipramine or equivalent; (3) 200–299 mg/qd of imipramine or equivalent; (4) 300 mg/qd and above imipramine or equivalent.
[e] Two cases missing data.

Table 3
Comparison of patients with unipolar major depressive disorder who recover from the intake MDD episode to subsyndromal residual depressive symptoms vs. the asymptomatic status: nature of first prospective episode relapse during 10 years of follow-up

		Residual symptoms recovery group ($N = 82$)	Asymptomatic recovery group ($N = 55$)	Significance
Overall three category comparison:				
Remained well (no relapse)	*N* (%)	11(13.4)	53(34.2)	
Relapsed first to minor/intermittent depressive episode	*N* (%)	45 (54.9)	43 (27.7)	$X^2 = 19.81$; df = 2
Relapsed first to MDD episode	*N* (%)	26(31.7)	59(38.1)	$P < 0.001$
Remained well vs. relapsed:				
Remained well	*N* (%)	11(13.4)	53 (34.2)	$X^2 = 11.66$;
Relapsed (any depressive Dx)	*N* (%)	71(86.6)	102 (65.8)	df = 1; $P < 0.001$
Within relapse groups only:				
Relapsed first to minor/intermittent depressive episode	*N* (%)	45(63.4)	43(42.1)	$X^2 = 6.75$; df = 1;
Relapsed first to MDD episode	*N* (%)	26 (36.6)	59 (57.9)	$P < 0.01$
Within relapse groups only				
First to minor/intermittent depression:				
Minor/intermittent only (no MDD)	*N* (%)	17 (37.8)	16 (37.2)	$X^2 = 0.45$
Minor/intermittent episode merges with MDD episode	*N* (%)	13 (28.9)	15 (34.9)	df = 2; $P = 0.80$(NS)
Minor/intermittent episode followed by separate MDD episode later	*N* (%)	15 (33.3)	12 (27.9)	

3.2. Diagnosis of first prospective relapse episode

As shown in Table 3, significantly more asymptomatic recovery patients had no episode recurrence throughout 10 years of follow-up than residual SSD recovery patients (34.2 vs. 13.4%, respectively). Nearly two-thirds (63.4%) of SSD recoverers who relapsed, did so first to episodes of MinD; the majority of asymptomatic recovers (57.9%) relapsed to MDEs.

3.3. Survival analysis of the first well interval comparing residual SSD and asymptomatic recovery patients

In Fig. 1 it is shown that MDE relapse was more than three times faster for residual SSD than asymptomatic recovery (median = 68 vs. 231 weeks; $P < 0.0001$). The second survival analysis (Fig. 2), shows that SSD recovery patients relapsed to *any* depressive episode (MinD or MDD) 5.5 times faster than asymptomatic recoverers (median = 33 vs. 184 weeks; $P < 0.0001$).

In Fig. 3 two risk factors associated with early relapse are combined: recovery status (SSD vs. asymptomatic); and history of recurrent depressive episodes (1–3 vs. >4 prior episodes, including the intake episode) (Keller et al., 1982, 1987). The history of >4 depressive episodes was significantly associated with early relapse *only* within asymptomatic recovery patients (median = 79 vs. 224 weeks, respectively; $P < 0.0001$). The recurrent MDEs risk factor had little effect on weeks to relapse among residual SSD recovery patients; in fact, the two survival curves are virtually superimposed (median = 28 vs. 34 weeks, respectively; $P = 0.283$; NS). The two variables were compared in Cox Proportional Hazards models. After controlling for the effect of recurrent MDEs history, unipolar MDD patients with residual SSD recovery were 368% more likely to relapse during any given interval following recovery than asymptomatic recovery patients (OR = 3.68; 95% CI = 2.64–5.12). In contrast, the >4 recurrent antecedent MDE history risk factor, after controlling for MDE recovery, increased the likelihood of relapse by only 64% over the probability for patients with one to three prior episodes (OR = 1.64; 95% CI = 1.17–2.29).

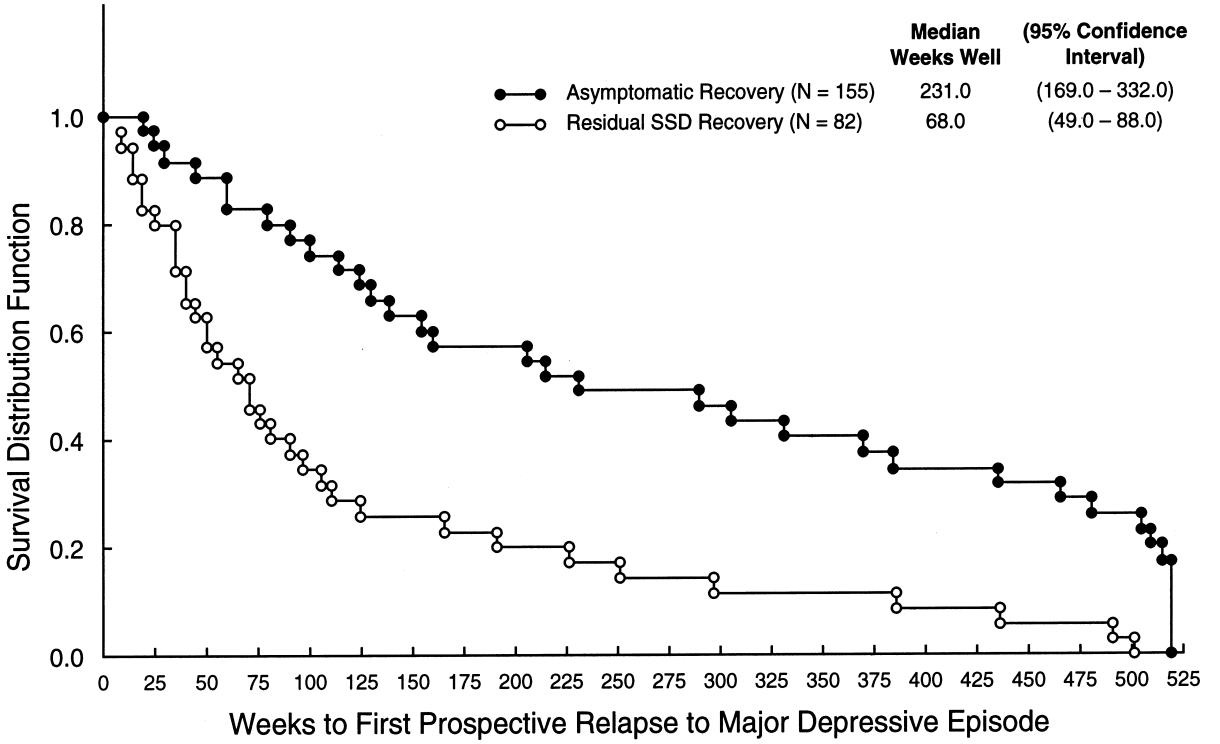

Fig. 1. Survival analysis of weeks to *major depressive episode* relapse (MDE): comparing patients with unipolar major depressive disorder who recovered from intake MDE with residual subsyndromal depressive symptoms vs. asymptomatic status. Wilcoxon Chi Square Test of Difference = 47.96; $P < 0.0001$.

3.4. Relationship of antidepressant medication treatment to recovery status and duration of the first well interval

Mean weekly CAD scores during the intake MDE were not significantly different between residual SSD and asymptomatic recovery patients (Table 2). Mean weekly CAD scores during the first well interval were significantly higher for SSD recovery at 1.3 (sd = 1.3), compared to 0.9 (sd = 1.1) for asymptomatic recovery (CAD of '1' = 1–99 mg of imipramine or equivalent qd) ($t = 2.48$; df = 235; $P = 0.014$). SSD recovery patients received any antidepressant medication for an average of 50.9% (sd = 44.9%) of weeks during the well interval, compared to 38.4% (sd = 42.8%) of weeks for the asymptomatic recoverers ($t = 2.10$; df = 235; $P = 0.037$). Percent of first well interval weeks at therapeutically adequate doses of antidepressant medication (defined as CAD > '3', or at least 200 mg of imipramine or equivalent qd) for SSD recovery was 22.4% (sd = 38.4%) – nearly double the 12.6% (sd = 26.5%) for asymptomatic recovery patients ($t = 2.09$; df = 235; $P = 0.039$).

3.5. Comorbid mental or substance use disorders

The overall prevalence of comorbid mental or substance use disorders at intake was significantly higher for the SSD than the asymptomatic recovery group (39.0 vs. 26.4%; Chi-square = 3.98; df = 1; $P = 0.046$). The only specific diagnosis on which the groups differed was the 'Other Psychiatric Disorders' category (24.4 vs. 12.3% Chi-square = 5.74, df = 1; $P = 0.017$), a catch-all RDC category that includes personality disorders and miscellaneous other diagnoses. However, during the first well interval, the two recovery groups did not differ significantly in their rates of overall or individual comorbid mental or substance use disorders.

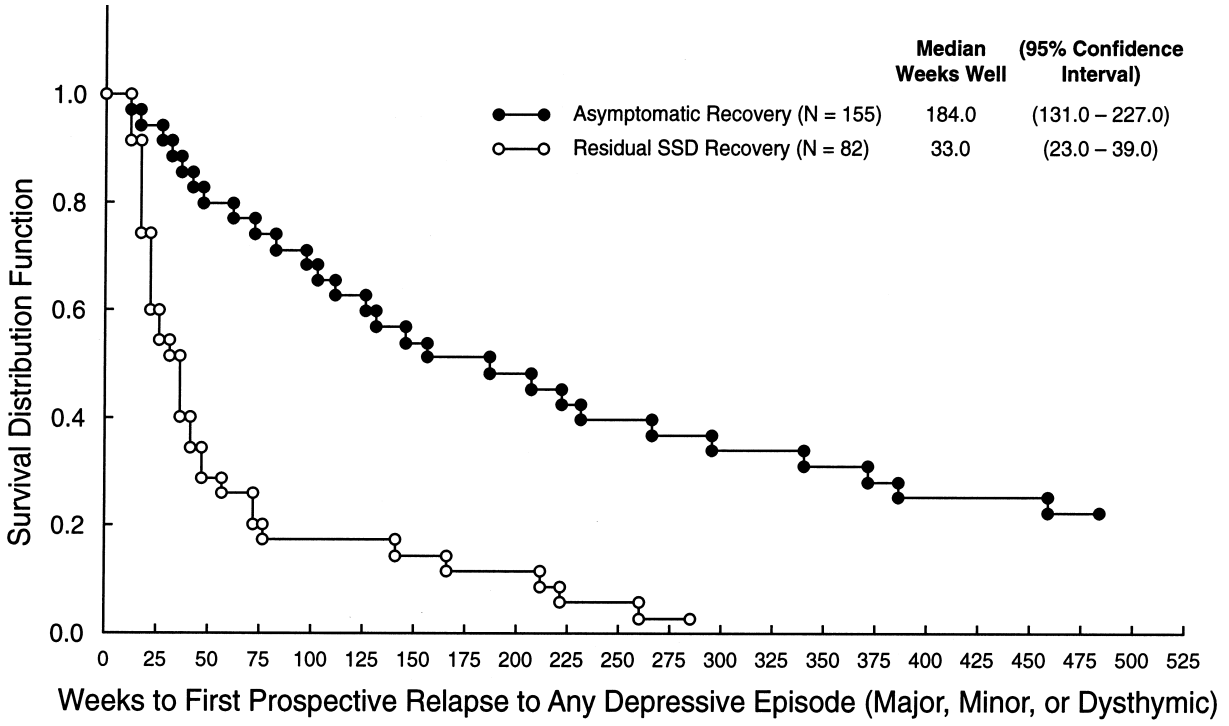

Fig. 2. Survival analysis of weeks to *any* depressive episode relapse: comparing patients with unipolar major depressive disorder who recovered from the intake MDD episode with residual subsyndromal depressive symptoms vs. asymptomatic status. Wilcoxon Chi Square Test of Difference = 80.29; $P < 0.0001$.

4. Discussion

The main finding is that patients with asymptomatic recovery remained well for a median of 231 weeks (4.4 years) before MDE recurrence, which indicates true or full MDE recovery, compared to 68 weeks for residual SSD recovery, indicating the MDE was incompletely or only partially remitted (DMS-IV, APA, 1994). We conclude that residual SSD recovery from depressive episodes is a robust and important clinical marker, strongly associated with very rapid episode relapse in unipolar MDD.

Our findings are similar to the observations of Paykel et al. (1995) who reported on a smaller MDD sample ($N = 60$) followed-up more briefly (15 months). Both studies found that about one-third (34 and 32%, respectively) of UD patients recover from MDEs with residual SSD. Paykel et al. (1995) found residual SSD recovery to be associated with significantly elevated rates of relapse, while our present analyses of the prospectively studied MDD-CDS cohort showed it to be a predictor of very rapid episode relapse, the results of these two studies were not explained by lower antidepressant medication treatment. In the aggregate there is a strong confluence of scientific evidence that residual SSD recovery is an important predictor of very rapid and frequent episode relapse (Faravelli et al., 1988; Simmons and Thase, 1992; Thase et al., 1992; Fava et al., 1994a,b; Paykel et al., 1995).

Keller et al. (1982), (1987) reported that history of recurrent MDEs (> 4) was the strongest predictor of early MDE relapse in MDD patients in the 5 year CDS follow-up data (Keller et al., 1982, 1983). These analyses of the CDS 10 year data confirms their prior observations. However, residual SSD recovery has a significantly stronger association with early depressive episode relapse than the recurrent MDE risk factor (OR = 3.68) vs. 1.64, respectively). In fact, the effect on relapse time of antecedent

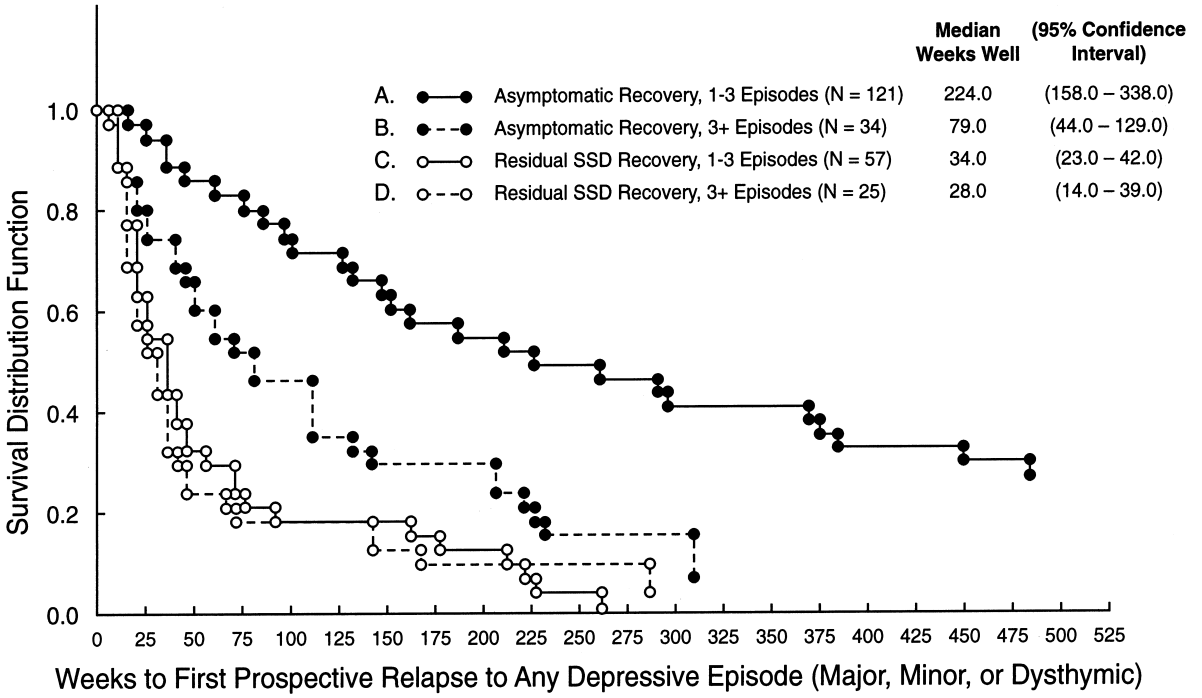

Fig. 3. Survival analysis of weeks to *any* depressive episode relapse, combining two relapse risk factors in patients with unipolar major depressive disorder: History of recurrent major depressive episodes (1–3 vs. >4 episodes) and recovery status (SSD vs. asymptomatic recovery). Wilcoxon Chi Square Test of Difference: A (224.0 weeks) vs. B (79.0 weeks) Chi Square = 20.66; $P < 0.0001$; A (224.0 weeks) vs. C (34.0 weeks) Chi Square = 77.03; $P < 0.0001$; A (224.0 weeks) vs. D (25.0 weeks) Chi Square = 67.81; $P < 0.0001$; B (79.0 weeks) vs. C (34.0 weeks) Chi Square = 6.18; $P = 0.013$; B (79.0 weeks) vs. D (28.0 weeks) Chi Square = 7.40; $P = 0.004$; C (34.0 weeks) vs. D (28.0 weeks) Chi Square = 1.14; $P = 0.283$ (NS).

recurrent MDEs is significant *only* among asymptomatic recovery patients. Thus, risk for early relapse associated with residual SSD recovery is so strong that it appears to override the effect of the history of recurrent MDEs.

We found no evidence that rapid episode relapse is attributable to less intense antidepressant treatment during the intake MDE or the first well interval. In fact, SSD recovery patients received significantly more antidepressant medication and adequate medication for more well interval weeks than asymptomatic recoverers. Our findings also support other studies which have correlated residual depressive symptoms with poor treatment response rather than inadequate antidepressant treatment (Mindham et al., 1973; Prien and Kupfer, 1986; Georgotas and McCue, 1989; Maj et al., 1992).

This suggests that residual SSD may require higher doses, different classes or combinations of antidepressant medication, or augmentation with mood stabilizers. Other investigators have reported that subsyndromal and minor depressive symptomatology respond to depression-specific brief psychotherapies (Miranda and Munoz, 1994; Fava et al., 1994a,b) or have delayed episode relapse (Frank et al., 1991a,b; Fava et al., 1994a,b). It will be important to determine in large prospective controlled treatment studies, whether all MDD patients can be treated to the asymptomatic status and which therapeutic strategies are most successful in achieving this important and necessary therapeutic goal.

Full symptom free recovery from MDEs is strongly associated with significantly prolonged delays in episode recurrence or no episode recurrence altogether. Resolution of MDEs to residual SSD, although defined by RDC (PSR '1' or '2') as 'recovery' is, in fact, not recovery. It is partial or incomplete MDE remission (DSM-IV, APA, 1994),

indicating the MDE is still active and the treatment response is incomplete. These data combined with other reports that SSD is associated with psychosocial impairment and increased health service use (Wells et al., 1989; Broadhead et al., 1990; Johnson et al., 1992 Judd et al., 1994, 1996, 1997) add further confirmation that SSD is a clinically relevant state of illness activity in unipolar MDD.

Some methodological limitations are inherent in this study. The CDS is a five site prospective naturalistic study of mood disorder patients initiated during 1978 to 1981 continuing to the present. Site differences were present in some demographic and clinical characteristics as a result of the CDS sampling strategy to obtain a diverse MDD cohort, but the impact of recovery status on time to relapse was consistent across all five sites. Although inter-rater agreement is high (ICC $>$ 0.88) there may be 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 further evidence of symptom rating reliability. Relatively few (13.4%) of SSD recoverers had the end of their first well interval extending beyond 10 years of follow-up (i.e., censored relapse data). The rate was higher (34.2%) in asymptomatic recoverers, but nearly half the censored cases in this group (49%) still had $>$ 5 years of well interval data. We felt this was ample information for valid and stable assignment of recovery status. Thirty-six of 273 MDD patients (13.2%) not meeting one of the two a priori recovery definitions were omitted from the analyses; these patients were very heterogeneous in their recovery status (median weeks PSR '1' = 41.4%; range 2–79%). In this initial investigation of the SSD recovery risk factor, we chose to develop two relatively homogeneous recovery groups for contrast, and define recovery status based upon all weeks of the first well interval, rather than on a specific period of recovery (e.g., first 8 weeks well interval, etc.) to highlight the effect of recovery status on duration of the first well interval. In addition, the CDS recorded, but did not control treatment, which limits conclusions from treatment data. Also, because of censored data, mean CAD treatment scores may have been calculated from different time intervals across subjects; treatment data should be interpreted with this in mind.

Only a few clues emerge from this study about clinical differences between residual SSD and asymptomatic recoverers. Residual SSD recoverers had non-significant trends toward greater illness severity at intake (GAS scores and inpatient status) and their intake MDE episodes lasted significantly longer than those of the asymptomatic recovery group. During the intake MDE but not the first well interval, residual SSD recovery group had a significantly higher overall rate of comorbid mental disorder diagnoses, particularly the category that includes personality disorders and miscellaneous psychopathology. Whether certain temperamental traits or personality disorder predispose MDD patients to incomplete MDE recovery is the subject of a current study.

In 1991, respected mood disorder researchers reviewed the scientific literature and proposed terms for the course of unipolar MDD, inviting the field to test empirically their preliminary definitions (Frank et al., 1991a,b). Our data do not support the proposed definition, that MDE full remission or recovery is achieved when the patient no longer meets '... syndromal criteria for the disorder and *has no more than minimal symptoms*' or that 'asymptomatic' status is defined by $<$ 2 depressive symptoms (SADS) or Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) scores of $<$ 7. These definitions of full remission or recovery are in error since they allow for residual SSD to be present and do not require the complete absence of depressive symptoms. In aggregate, our and other investigations (Faravelli et al., 1988; Simmons and Thase, 1992; Thase et al., 1992; Fava et al., 1994a,b; Paykel et al., 1995; Fava, 1996) indicate that an essential requirement for defining of full MDE remission or MDE recovery is the achievement of a completely depressive symptom free status. Indeed, previous research has shown that in MDD patients with residual symptomatic chronicity the illness continues to be clinically and neurophysiologically active (Akiskal, 1982). Widespread acceptance of treatment goals primarily emphasizing resolution of symptomatology below syndromal criteria for the episode (e.g., HDRS of '7'), but not requiring complete resolution of residual SSD, could inadvertently contribute to further chronicity of MDD patients. Failure to treat MDE's to the asymptomatic status may have resulted

in MDD patients being treated only to residual SSD, resulting in heightened risk for early relapse in a cycle repeating itself throughout the course of illness.

In conclusion, further prospective controlled study is needed to determine if achieving the goal of asymptomatic recovery for MDEs can consistently prevent or delay episode relapse or recurrence and improve social and vocational functioning throughout the unipolar MDD patient's lifetime.

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