Longitudinal syndromal and sub-syndromal symptoms after severe depression: 10-year follow-up study

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Background Few follow-up studies of depression have evaluated depressive symptomatology over time at both threshold and sub-threshold levels.

Aims To evaluate long-term longitudinal symptomatic course after an episode of severe depression.

Method A total of 61 participants from a previous study cohort underwent a detailed interview covering the longitudinal course of depression and pharmacological treatment over 8–11 years of follow-up.

Results Of the follow-up months, 52% were spent at an asymptomatic level, 15% at minor symptom level, 20% at residual symptom level and 13% at full depression level. Also, 30% of follow-up months were spent in an episode of depression, and 18% of patients never achieved asymptomatic status during follow-up. The percentage of patients at each symptom level remained relatively stable after the first 2 years, but levels in individuals fluctuated, with a mean of two changes in symptom levels per follow-up year.

Conclusions After severe episodes, sub-syndromal levels of depression are common and persistent, with considerable fluctuation suggesting a continuum between sub-syndromal subtypes and full depression.

Declaration of interest None. Funding detailed in Acknowledgements.

Unipolar depression in the past has been considered as an episodic illness, usually following a relapsing–remitting course, but in a minority of cases becoming a chronic refractory illness. However, more recent studies have identified lower-grade depressive subtypes such as dysthymic disorder (Akiskal, 1983), recurrent brief depression (Angst *et al*, 1990), minor depressive disorder (Skodol *et al*, 1994) and sub-syndromal symptomatic depression (Judd *et al*, 1994). Rather than being entirely separate disorders these may be part of the same spectrum of illness as full depression, in a continuum in which sufferers fluctuate between related subtypes at different times in the course of the illness (Judd *et al*, 1997). With few exceptions, published long-term follow-up studies of depression to date have concentrated on recovery and recurrence rates and state at outcome assessment, rather than evaluating inter-episodic depressive symptoms, sub-syndromal depression or symptom change over time. We followed up a cohort of people with severe depression, originally recruited in the early 1990s (Paykel *et al*, 1995; Ramana *et al*, 1995), using a longitudinal interview that allowed measurement of minor or sub-threshold forms of illness in addition to symptom change and inter-episodic symptomatology. Previously we have reported recurrence rates (Kennedy *et al*, 2003). In this paper we report symptom levels below major disorder, and time spent at various symptom levels.

METHOD

Subjects and tracing

The sample, tracing and interview methods have been reported in detail previously (Kennedy *et al*, 2003). Seventy consecutive subjects, predominantly psychiatric in-patients with severe depression who satisfied the Research Diagnostic Criteria (Spitzer *et al*, 1978) for definite primary unipolar major depression, were recruited from treatment facilities between 1990 and 1992 (Ramana *et al*, 1995). Subjects with a concurrent major psychiatric or physical illness were excluded. Subjects originally underwent 3-monthly interviews until remission and for up to 15 months thereafter to ascertain relapse, residual symptoms and impact of life events, social support, marital relationships and expressed emotion on outcome (Paykel *et al*, 1995, 1996; Ramana *et al*, 1995; Hayhurst *et al*, 1997). Both the original and present studies were approved by local Research Ethical Committees. For the current follow-up subjects were traced, through local records and by the local health authority or the National Health Service Register at the Office for National Statistics, to current general practitioners or psychiatrists, and approached through them for interview.

Interviews and information obtained

Participants were interviewed 8–11 years after initial recruitment, by an experienced psychiatrist (N.K.) masked to original study data, after written permission had been obtained. Prior to interview, psychiatric and/or general practice case notes were examined over the full follow-up period to obtain as much information as possible regarding number, length and treatment of depressive episodes in addition to any depressive symptoms recorded.

Data were collected at one or two semi-structured interviews, lasting 3–5 h each, which evaluated longitudinal clinical and treatment information over the entire follow-up period.

Longitudinal clinical and treatment information

Longitudinal symptom and treatment information over the follow-up period was obtained using an adaptation of the Longitudinal Interview Follow-up Evaluation (LIFE; Keller *et al*, 1987), originally developed for the National Institute of Mental Health Collaborative Depression Study (NIMH CDS). The LIFE was originally designed for shorter follow-up periods, to describe psychopathology in a continuous way and to record accurately subcriteria symptoms between illness episodes. This interview was used retrospectively over the entire follow-up period in this study. It is operationally linked to the Research Diagnostic Criteria and has been adapted

to satisfy DSM–IV (American Psychiatric Association, 1994) criteria. Using time-anchoring cues specific for each subject, each year of follow-up in turn was examined in detail for evidence of depressive symptoms. Onset and offset of symptoms of depression were dated to within a month, and charts, each covering a period of 1 year, were completed. Monthly psychiatric status ratings (PSRs), based on DSM–IV symptoms of depression, were recorded to identify change over time in depressive symptoms and total time spent at various symptom levels for each subject. Criteria are shown in Table 1. An additional point above full criteria for depression was added compared with the original LIFE to allow fuller evaluation of severity within major depression, so that in this study PSRs were rated 1–7 rather than the original 1–6. To aid recall, use was made of psychiatric and/or general practice notes to identify episodes of depression and treatment prior to longitudinal interview. Family members or partners, where available, were interviewed to obtain further information. Final assignment of monthly PSRs was made after further assessment of all available information during that follow-up month.

For analysis of time spent at each symptom level during follow-up, PSRs were further subdivided into four symptom severity levels adapted from the LIFE (Keller *et al* 1987, 1992). The PSRs 7–5 fulfilled criteria for major depressive disorder, PSRs 4 and 3 for residual symptoms of depression, PSR 2 for minor symptoms and PSR 1 for no symptoms. The LIFE definition of recovery of at least two consecutive months at PSR 2 or 1 was used in this study.

Antidepressant treatment prescribed for each month of follow-up was obtained from interview, case notes and general practice records. The highest dose prescribed for at least two consecutive weeks during each month was recorded. Monthly doses of individual drugs were converted into 'dose equivalents' of a standard drug of that class and grouped based on published guidelines into five levels: too low; borderline; moderate; moderately high; high (Anderson *et al*, 2000; British Medical Association and Royal Pharmaceutical Society of Great Britain, 2001). For selective serotonin reuptake inhibitors (SSRIs, fluoxetine equivalents) these were: <10 mg daily; 10–19 mg; 20–39 mg; 40–59 mg; >60 mg. For tricyclics (imipramine equivalents) they were: <100 mg; 100–149 mg; 150–199 mg; 200–249 mg; >250 mg. For monoamine oxidase inhibitors (MAOIs, phenelzine equivalents) thresholds were: <45 mg; 45–59 mg; 60–74 mg; 75–89 mg; >90 mg. For lithium they were: <400 mg; 400–599 mg; 600–799 mg; 800–1199 mg; >1200 mg. Composite antidepressant scores were thus recorded for each follow-up month, ranging from 0 (no antidepressant prescribed) to 5 (high-dose antidepressant). For each subject the mean composite antidepressant score per prescribed month was then calculated by summing the composite antidepressant scores for each prescribed month and dividing by the number of prescribed months.

Statistical methods

Statistical analyses were carried out using the Statistical Package for the Social Sciences, version 10.0 for Windows (SPSS, 1999). Validity of using the adapted LIFE over the longer follow-up period of this study was evaluated using the methods of Bland & Altman (1986). First, χ^2 tests compared grouped Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) scores at 3-monthly intervals with grouped LIFE scores at overlapping time points. The HRSD scores were grouped into asymptomatic (<7), residual symptoms (8–16) and major depression ($\geqslant17$), and LIFE PSRs were similarly grouped into asymptomatic (1–2), residual symptoms (3–4) and major depression (5–7). Raw LIFE scores were then compared with raw HRSD and Clinical Interview for Depression (CID; Paykel, 1985) scores at overlapping time points using scatterplots and the Pearson correlation coefficient (r).

Primary analysis variables were percentages of follow-up time spent at the four levels of symptom severity and changes in symptom severity levels per patient per year. Subjects in their first lifetime episode at initial presentation and subjects with previous episodes of DSM–III–R (American

Table 1 Monthly psychiatric status ratings (PSRs) for major depression

Code[1]	Term	Definition
7	Definite criteria, severe	Meets Research Diagnostic Criteria for major depression with either prominent psychotic symptoms or extreme impairment in functioning
6	Definite criteria, moderate	Meets definite Research Diagnostic Criteria with additional symptoms but no prominent psychotic symptoms and no extreme impairment in functioning
5	Definite criteria	Meets Research Diagnostic Criteria with little additional symptomatology and no prominent psychotic symptoms or extreme impairment in functioning
4	Sub-threshold	Does not meet Research Diagnostic Criteria but has major symptoms of impairment from this disorder (e.g. a person who has only 4 associated symptoms but is still unable to work)
3	Partial remission	Considerably less psychopathological impairment than full criteria, with no more than moderate impairment in functioning but evidence of disorder still obvious (e.g. depressive episode with only 2–3 symptoms in moderate degree or 1–2 symptoms in severe degree)
2	Mildly symptomatic	Either patient claims not to be totally symptom-free or rater notes the presence of symptoms of this disorder in no more than mild degree (e.g. depressive disorder with only persistence of mild insomnia from original depressive episode)
1	Asymptomatic	Patient is asymptomatic, without any residual symptoms of the disorder, but may or may not have significant symptoms from some other condition or disorder

1. PSRs 7–5 are considered as major depressive disorder, PSRs 4–3 are considered as residual depression and PSR 2 as minor symptoms.

Psychiatric Association, 1987) depression were compared using χ^2 or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables or the Mann–Whitney *U*-test where distribution was non-normal. Bivariate and multivariate logistic regression models were used to assess which index variables predicted a longer time spent at sub-threshold and full depression during follow-up. All 61 subjects interviewed using the adapted LIFE had full data-sets.

RESULTS

Tracing and sample characteristics

Full details of tracing and sample characteristics are given elsewhere (Kennedy *et al*, 2003). A total of 61 (92%) of the 66 living members of the original study cohort underwent full longitudinal interview and case-note review. Four subjects died early in follow-up, two from suicide and two from natural causes. In five cases the subjects or their general practitioner/psychiatrist refused a follow-up interview. The follow-up period covered a mean of 113 months (s.d.=8, range 97–128) during which full monthly clinical and treatment ratings were assessed.

The majority of subjects were female (67%) and married or in a stable cohabitation (75%). Mean age at intake was 40 years (s.d.=12, range 20–63) and mean age of first depression was 33 years (s.d.=14, range 9–57). At intake, diagnoses were mainly DSM–III–R recurrent depression (67%) and DSM–III–R moderate or severe depression (75%). Almost one-fifth (16%) had a history of DSM–III–R dysthymia in addition to major depression, with 7% having a chronic episode of at least 2 years' duration at index interview. Subjects whose index episode was their first showed no differences in index variables from those with previous episodes, except for older mean age of first depression: mean 38 (s.d.=10) years *v*. mean 29 (s.d.=12) years; $t=2.5$, d.f.=59, $P<0.05$.

Validity of adapted LIFE interview

Adapted LIFE was validated in this longer-term follow-up study by comparing LIFE scores at overlapping time points with HRSD and CID scores rated prospectively at approximately 3-monthly intervals for the first 18 months of the shorter-term follow-up study (Ramana *et al*, 1995). The interviewer in the current study (N.K.) was masked to HRSD and CID scores from the original shorter-term study until full analysis was complete. When grouped HRSD and LIFE PSRs were compared by cross-tabulation, relationships between the grouped scores were highly significant ($P<0.001$ by χ^2 test) at each overlapping time point. Scatterplots of raw scores showed a linear association between the variables at each time point, and strong correlations between raw LIFE scores and both HRSD ($r=0.75$–0.90) and CID scores ($r=0.78$–0.88) at overlapping time points were found, suggesting that the adapted LIFE scale had good validity over the most distal period and that of most rapid symptomatic change.

Depressive symptom severity and change over follow-up

During a total of 6907 patient-months rated over follow-up, subjects spent 52.0% of follow-up months at an asymptomatic level (PSR 1), 15.2% at minor symptom level (PSR 2), 19.6% at residual symptom level (PSR 3–4) and 13.2% at full depression level (PSR 5–7) (Table 2). Subjects spent 30% of follow-up months in an episode of depression using the LIFE definition of recovery (two consecutive months at PSR 1–2). Subjects with no prior episode of depression spent significantly less time in a major depressive state over follow-up and showed a trend towards having a higher percentage of asymptomatic months.

Figure 1 shows the percentage of subjects at different symptom levels for each month of follow-up to 12 months and Figure 2 shows the percentage at 6-monthly intervals to 102 follow-up months. The percentage with full depression fell dramatically over the first year of follow-up and the residual symptom percentage increased, followed by an increase in percentages at other symptom levels. Over the rest of the follow-up the percentage of subjects at various symptom levels remained stable, with more subjects having a rating of residual depression rather than major depression.

During the first year of follow-up the subjects spent 25% of follow-up months at an asymptomatic level, 15% at minor symptom level, 30% at residual symptom level and 30% at full depression level. During the second year, asymptomatic months had risen to 50% and minor symptom months to 17%, whereas months at residual symptom level had decreased to 19% and months at full depression to 14%. For each year of follow-up after the second year, symptom levels showed little change: 52–61% of follow-up months were rated at an asymptomatic level, 14–19% at a minor symptom level, 16–22% at a residual symptom level and 8–13% with full depression. A total of 58 (95%) of 61 subjects recovered (two consecutive months at PSR 1–2) from the index episode during follow-up. However, 11 subjects (18%)

Table 2 Percentage months spent at different depressive symptom severity levels during follow-up

Percentage follow-up months spent at different severity levels	Total (n=61) (6907 follow-up patient-months)	First episode (n=20) (2251 follow-up patient-months)	One or more prior episodes (n=41) (4656 follow-up patient-months)	First v. ⩾1 prior episodes P
Asymptomatic months (%)				
Mean (s.d.)	52.0 (34.6)	61.9 (38.0)	47.1 (32.2)	0.135[1]
Median (1st and 3rd quartile)	64.5 (6.7, 76.2)	79.5 (6.7, 89.2)	49.2 (3.9, 73.7)	
Minor symptom months (%)				
Mean (s.d.)	15.2 (15.9)	10.7 (11.5)	17.4 (17.3)	0.122[2]
Median (1st and 3rd quartile)	10.9 (3.6, 19.5)	6.3 (2.7, 11.2)	12.1 (4.8, 22.2)	
Residual depression months (%)				
Mean (s.d.)	19.6 (19.1)	17.2 (22.7)	20.8 (17.2)	0.070[2]
Median (1st and 3rd quartile)	13.8 (5.6, 25.7)	6.5 (2.7, 17.4)	15.7 (8.7, 29.2)	
Major depression months (%)				
Mean (s.d.)	13.2 (17.1)	10.3 (18.6)	14.7 (16.3)	0.022[2]
Median (1st and 3rd quartile)	7.4 (2.5, 14.2)	3.0 (1.8, 8.9)	9.8 (4.1, 17.0)	

1. Student's *t*-test.
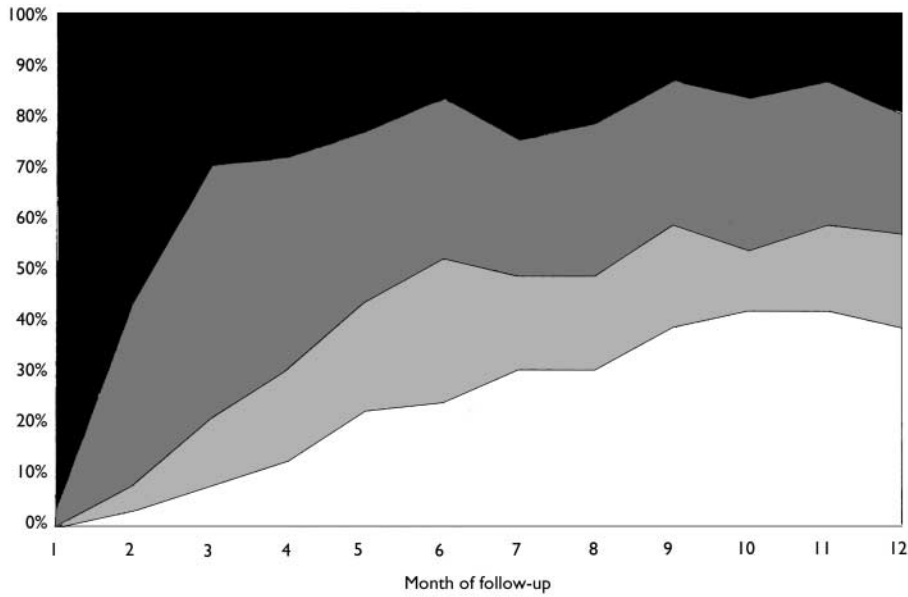2. Mann–Whitney *U*-test where non-normal distribution.

Fig. 1 Percentage of subjects at various symptom levels (monthly) over the first year of follow-up: ■, definite criteria; ▨, residual symptoms; ▨, minor symptoms; □, asymptomatic.
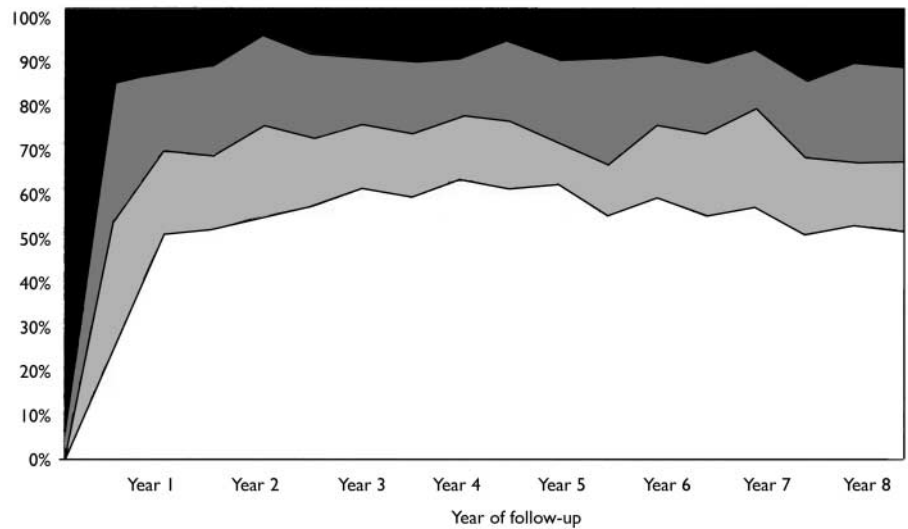

Fig. 2 Percentage of subjects at various symptom levels (6-monthly) over 8 years of follow-up: ■, definite criteria; ▨, residual symptoms; ▨, minor symptoms; □, asymptomatic.

Table 3 Change in depressive symptom severity levels during follow-up

Change in severity during follow-up	Total (n=61)	First episode (n=20)	One or more prior episodes (n=41)	First v. ⩾1 prior episodes P[1]
Overall number of symptom severity levels (n (%))				
All four levels	44 (72.1)	14 (70.0)	30 (73.2)	
Three levels during follow-up	14 (23.0)	6 (30.0)	8 (19.5)	
Two levels during follow-up	3 (4.9)	0	3 (7.3)	
One level only during follow-up	0	0	0	
Changes in symptom severity levels per year				
Mean (s.d.)	1.9 (1.3)	1.4 (1.4)	2.1 (1.2)	0.068
Range (median)	0–9 (1.4)	0–9 (1.0)	0–9 (1.8)	

1. Student's t-test.

never achieved full asymptomatic status (PSR 1) for even a month during follow-up.

Change in depressive symptom severity levels

Table 3 shows the extent to which subjects changed symptom levels during follow-up. Over 70% of the subjects spent time at each of the four levels of symptom severity, with the majority of the rest spending months at three levels. There was a mean of almost two changes in symptom levels per subject every year. Subjects in the first episode subgroup showed a trend towards fewer changes per year than those with previous episodes.

Antidepressant treatment during follow-up

Antidepressants were prescribed for a mean of 59.2% (s.d.=36.9) of follow-up months. For the whole sample, the composite antidepressant score per prescribed month, which is a measure of the adequacy of the antidepressant dose prescribed, was relatively high: mean 2.9 (s.d.=0.9). The first-episode subgroup was prescribed antidepressants for significantly fewer percentage months during follow-up: mean 45% (s.d.=41%) $v.$ mean 66% (s.d.=33%); $t=2.2$, d.f.=59, $P<0.05$. However, the mean composite antidepressant score per prescribed month was similar in the two groups: mean 2.7 (s.d.=1.0) $v.$ mean 2.1 (s.d.=1.3); $t=1.3$, d.f.=59, $P=0.21$. Women were prescribed antidepressants during significantly more percentage follow-up months than men: mean 65 (s.d.=36) $v.$ mean 46 (s.d.=37); d.f.=59, $P<0.05$. However, there was no significant difference by gender in the mean composite antidepressant score per prescribed month.

Predictors of time spent at full and residual depression over follow-up

Two dependent variables were used in separate logistic regression predictive analyses: percentage follow-up time spent at full criteria for depression (PSR 7–5) and percentage follow-up spent at residual symptom level (PSR 4–3) during follow-up, split at median length. A limited number of dichotomised predictive variables were examined covering age at index interview and at first depression (both split at mean), socio-demographic variables, family history of affective disorder,

personal history, DSM–III–R premorbid personality disorder, illness history, diagnostic subtypes and initial symptom severity.

As shown in Table 4, significant predictors of longer time at full depression after bivariate logistic regression were female gender, greater index severity, greater index anxiety and DSM–III–R episodes of depression prior to index episode. The only significant predictor of a longer time spent at residual symptom level was female gender.

Significant or near-significant variables after bivariate analysis were entered into multivariate logistic regressions with age at index episode (continuous), occupational category at index and index marital status using the same dependent variables. Only gender (odds ratio=4.63, $P<0.05$) remained significant using time spent at full depression, and none of the variables remained significant using time spent at residual symptom level as the dependent variable.

DISCUSSION

Older long-term studies of severe depression have described clinical outcome in terms of recovery, recurrence, chronicity and mortality. However, longitudinal interviewing allowed a more detailed description of the time spent at full and sub-threshold levels of depression and changing episode status. To our knowledge, the NIMH CDS has been the only study to describe systematically the longitudinal symptomatology of severe depression at threshold and sub-threshold levels in the long term (Judd et al, 1998). The current study therefore described, for the first time in a British sample, longitudinal depressive symptomatology after an episode of severe long-term depression, and evaluated whether high sustained levels of symptoms

described in the NIMH CDS were also observed in this sample.

Many patients in this sample continued to suffer from depressive symptoms, particularly at sub-syndromal levels. After a decrease in the first 2 years the percentage experiencing these symptoms did not attenuate further over the next 8 years. Individual symptom levels changed frequently and the majority of patients spent time at each different symptom level over the follow-up period. Female gender predicted the chronicity of symptoms and a longer time spent at full criteria for depression, despite receiving antidepressants during significantly more follow-up months. Index severity and previous episodes weakly predicted a longer time at full depression.

Methodological strengths and weaknesses

The strengths of the study included the high follow-up rate, interviews being conducted by one psychiatrist to aid reliability, independently collected index predictor data, extensive use of collateral information and longitudinal interviewing.

Limitations included the length of follow-up time covered by the longitudinal interview. The LIFE was originally designed to be used repeatedly over shorter periods but has been adapted for longer-term studies (Surtees & Barkley, 1994). However, the validity of using the LIFE over the entire follow-up period could still be questioned. With this in mind, full use was made of case notes and general practitioner records to aid in the identification of depressive episodes prior to interview. Additionally, LIFE ratings correlated well with prospective HRSD and CID scores collected independently for the shorter-term study over the period of greatest symptom change and the period most distal from follow-up interview, when unreliability might be expected to be highest, helping

to validate the adapted LIFE. Nevertheless, distinction between sub-syndromal symptoms, such as residual and minor symptoms of depression, particularly early in follow-up, could still have been subject to recall bias.

The participants also were at different stages in the course of illness, leading to difficulty in interpreting outcomes for individuals at a specific point in their illness. However, this sample had similar entry characteristics to previous long-term outcome studies, allowing valid comparison, and being a clinical sample it bore considerable similarity to patients seen in general psychiatric practice. Additionally, the sample followed up was relatively small, limiting the power to detect weaker predictors of chronicity.

Time spent at different symptom levels and symptom change

Participants had depressive symptoms during almost half of the follow-up months and spent 30% of follow-up time in an episode of depression despite receiving relatively high levels of antidepressant treatment; 20% of follow-up months were spent at a residual symptom level, in contrast to only 13% of follow-up months at full criteria for depression. Almost one in five never reached full asymptomatic status during follow-up. Judd et al (1998) in the NIMH CDS reported similar findings over almost 9 years, with subjects receiving similar levels of antidepressant treatment over follow-up, but they were asymptomatic for only 40% of follow-up weeks, in contrast to 50% of follow-up months in this study, possibly because a much higher percentage of patients with a history of dysthymia were included.

Previous long-term studies of depression have shown high rates of chronicity and recurrence (Lee & Murray, 1988; Surtees & Barkley, 1994). This study, with

Table 4 Significant and near-significant predictors in bivariate logistic regression of longer time spent at full depression and residual depression during follow-up (n=61)

Predictors	Longer follow-up time at full depression			Longer follow-up time at residual depression		
	Adjusted odds ratio	95% CI	P	Adjusted odds ratio	95% CI	P
Female gender	5.45	1.73–17.16	0.004	3.51	1.17–10.54	0.026
Index severity (HRSD ⩾20)	5.70	1.90–17.14	0.002	2.74	0.97–7.71	0.057
Index anxiety (CID Anxiety Scale ⩾11)	3.64	1.26–10.46	0.017	2.38	0.85–6.89	0.099
DSM–III–R episode prior to index	3.50	1.11–11.02	0.032	2.27	0.75–6.89	0.148

HRSD, Hamilton Rating Scale for Depression; CID, Clinical Interview for Depression.

others (Angst & Merikangas, 1997; Judd *et al*, 1998), adds an element of lower-grade symptomatology that persists over time. Importantly, after initial improvement from index depression, the proportion of patients with symptoms at each level did not attenuate even after 10 follow-up years. The sustained levels of sub-syndromal symptoms in the sample are in keeping with reports from the NIMH cohort (Keller *et al*, 1992) that many patients eventually develop chronic lower-grade symptoms more like dysthymia.

Sub-threshold and residual depressive symptoms after an episode of depression are important clinically because they have been associated with severe impairment of social functioning in most domains, and a gradient in degree of impairment is found when comparing asymptomatic individuals with those having sub-threshold and major depression (Judd *et al*, 2000*a*). Sub-threshold symptoms after an episode of depression have also been shown to lead to early recurrence (Paykel *et al*, 1995) and impaired long-term functioning (Judd *et al*, 2000*b*).

Are depressive subtypes linked on a continuum?

Milder subtypes of depression have been described, including minor depressive disorder (Skodol *et al*, 1994), dysthymic disorder (Akiskal, 1983) and sub-syndromal symptomatic depression (Judd *et al*, 1994), raising the question as to whether these forms are separate entities or whether different clinical symptoms and subtypes of depression are seen in individuals over time. High rates of symptom change per subject were seen in this study. Overall percentage at each level remained stable over time, but individual levels of symptom stability were low. High rates of symptom change were also reported in the NIMH CDS (Judd *et al*, 1998) and the NIMH Epidemiologic Catchment Area study when patients were re-interviewed after 1 year (Judd *et al*, 1997). Other studies using polysomnographic and family history data (Akiskal *et al*, 1997), clinical characteristics (Kessler *et al*, 1997) and social impairment (Judd *et al*, 2000*a*) have shown resemblances between sub-threshold forms of depression and major depression. This study adds to a growing body of research that various depressive subtypes are linked on a continuum and that many patients will

fulfil criteria for a number of these subtypes during the course of their illness.

Predictors of chronicity

Female gender predicted more time spent at full depressive criteria and greater chronicity of sub-threshold symptoms over time. In a long-term follow-up of the NIMH CDS cohort, female gender was strongly associated with recurrence (Mueller *et al*, 1999). Female gender has also been associated with chronicity (Scott, 1988) and poor prognosis (Kornstein *et al*, 2000), although not in all studies (Simpson *et al*, 1997).

Subjects without a previous history of depression at entry had a later age of onset of depression, spent less time at full criteria for depression and received less antidepressant treatment during follow-up than those with previous episodes. Judd *et al* (1998) reported similar findings. Previous episodes of depression have consistently predicted early relapse (Keller *et al*, 1982), in addition to recurrence or poor

outcome in long-term follow-up studies (Lee & Murray, 1988; Mueller *et al*, 1999).

This follow-up study showed that symptoms at sub-syndromal levels were common and persisted for many years after an episode of severe depression, even with reasonable levels of antidepressant treatment. Previous long-term studies of depression, which have concentrated on recurrence and chronicity at full criteria, may have underestimated the impact of milder symptoms on long-term outcome. Future treatment and outcome studies of depression also need to focus closely on sub-syndromal disorder.

ACKNOWLEDGEMENTS

CLINICAL IMPLICATIONS

■ Sub-syndromal levels of depression are common and persistent after an episode of severe depression.

■ Depressive subtypes may be linked on a continuum and many patients may fulfil criteria for various subtypes of depression during the course of their illness.

■ Female gender appears to be associated with chronicity of depressive symptoms.

LIMITATIONS

■ Assessment was retrospective, but longitudinal interview showed good validity when compared with independent prospective depression scores.

■ Sample size was relatively small, reducing the power to detect significant associations.

■ The severe, recurrent nature of depression in this sample may not be representative of depressive illness in the general population.

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