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Psychiatry Research 96 (2000) 211–220

PSYCHIATRY RESEARCH

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Course and outcome of depressive episodes: comparison between bipolar, unipolar and subthreshold depression

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Received 28 March 2000; received in revised form 1 July 2000; accepted 16 August 2000

Abstract

It is pragmatically important to know the comparative prognoses of bipolar, unipolar and subthreshold depressions after they present to clinical attention. Previous studies focusing on bipolar and/or unipolar depressions have questionable generalizability because of overrepresentation of inpatients and/or refractory patients, and no study has yet focused on the length of subthreshold depression. The Group for Longitudinal Affective Disorders Study (GLADS) in Japan is conducting a prospective, serial follow-up study of broadly defined mood disorder patients, who had not received treatment for their index episode before study entry. The median time to recovery for bipolar depression was 2.0 months (95%CI: 0.9–3.1), that for unipolar depression 3.0 (2.5–3.6), and that for subthreshold depression 3.2 (0–12.3). Survival analyses revealed no statistically significant difference among the three. Neither was the total time unwell significantly different among the three: on average, these patients were symptomatic with two or more significant affective symptoms for 9.5 (8.0–10.9) months out of the initial 24 months of follow-up. The bipolar depressed patients tended to present with graver functional impairment at intake, but thereafter there was no statistically significant difference in the global functioning of these three diagnostic subgroups. In our sample, patients with depressive disorder not otherwise specified appeared to suffer both symptomatologically and functionally as much as patients with major mood disorders.

Keywords: Depressive disorder; Bipolar disorder; Prognosis; Follow-up studies; Remission; Social adjustment; Survival analysis

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0165-1781/00/$ - see front matter
PII: S0165-1781(00)00212-2

1. Introduction

At present unipolar major depression is estimated to constitute the fourth largest threat to mankind's quality of life, and bipolar disorder the twenty-second (Murray and Lopez, 1997). In the year 2020, the former will likely be the second largest source and the latter the 18th source of human morbidity (Prescott and Kendler, 1999). Furthermore, convincing evidence exists to show that subthreshold depression, i.e. not meeting the full diagnostic criteria for major depression, is not only prevalent but is causing considerable functional impairment (Wells et al., 1989; Broadhead et al., 1990; Johnson et al., 1992).

For clinicians, it is then vitally important to know the comparative prognoses of these clinical entities when they present as depression. How long will it take for them to recover? Once recovered, how likely are they to remain so? How functional will they be in 3 months, 6 months and so on? Previous studies indicate that unipolar depressive episodes tend to last longer than bipolar ones, that bipolar patients have more episodes than unipolar patients but that total time spent in illness may be similar between these two (Winokur et al., 1993; Angst and Preisig, 1995). However, generalizability of these findings is undermined because most cohorts were recruited as inpatients [100% in one study (Angst and Preisig, 1995) and 77% in another (Winokur et al., 1993)], and because over 80% of the patients had been receiving some treatment before being referred to the tertiary care center where the patient enrollment took place (Winokur et al., 1993). We are unaware of any study focusing on the length of episodes of subthreshold depression or depressive disorder not otherwise specified (DSM-IV) presenting to medical attention.

The Group for Longitudinal Affective Disorders Study (GLADS) has been conducting a prospective, serial follow-up study of broadly defined mood disorder patients, who had not received treatment for their index episode before study entry. The present article examines the differential prognoses of unipolar, bipolar and subthreshold depressive episodes up to 2 years of their prospective follow-up.

2. Methods

The study procedures and the patients enrolled in the Intensive Prospective Study (IPS) by the GLADS are described in detail elsewhere (Furukawa et al., 2000a). Briefly, the IPS aims at detailed prospective serial assessments of a limited number of patients with broadly defined affective disorders under naturalistic conditions. The 23 collaborating centers included psychiatric departments of 13 university hospitals, those of six general hospitals, three mental hospitals and one community mental health center from all over Japan.

Participating psychiatrists at each center administered a semi-structured interview called the Psychiatric Initial Screening for Affective disorders (PISA) (Kitamura, 1992) to a representative subset of its first-visit patients in order to ascertain the patients' eligibility. The eligibility criteria for the IPS were: (1) depressive state defined as presenting with mood or anhedonia lasting longer than 4 days, or manic state defined as presenting with elated, expansive or irritable mood lasting longer than 4 days; (2) having received no antidepressant or antipsychotic medication in the preceding 3 months; (3) aged 18 or older; and (4) absence of conditions such as mental retardation, dementia or hearing disability that would render detailed psychopathological and psychosocial assessments difficult. Comorbidity of psychotic, anxiety, substance use or other axis I disorders or of personality disorders was not excluded. Each participating center was expected to enter one patient who satisfied the inclusion criteria either every month or every 2 months, depending on the availability of human and logistic resources at each center, in order to avoid seasonal imbalance. Written informed consent was obtained from all participants after full disclosure of the purposes and procedures of the study.

The patients eligible for and consenting to the study were then interviewed within one week

of entry by a psychiatrist using a semi-structured interview called the Comprehensive Assessment List for Affective disorders (COALA) entry version (Furukawa, 1992). The COALA consists of a series of semi-structured interviews which enable serial assessment of the cohort; these include the entry version, monthly follow-up version, and 6-monthly follow-up version. Its reliability has been reported to be good to excellent (Furukawa et al., 1995). The COALA entry version provides data concerning the symptomatology of the present episode and global functioning among others. Based on computer algorithms, the COALA can derive polydiagnostic assessments of the index episode according to 29 modern operational as well as classical diagnostic systems for broadly defined affective disorders (Furukawa et al., 1999).

The cohort was followed up monthly until treatment termination and at 6-month intervals thereafter up to 2 years. The monthly assessments included for the COALA monthly follow-up version administered by the treating psychiatrists, which provided data concerning the symptomatology for the past month and global functioning as assessed by the Global Assessment Scale (GAS) (Spitzer et al., 1978). The course chart for the first 24 months of the cohort was constructed based on all the available data.

We used the statistical package SPSS for Windows 8.0 (SPSS Inc., 1997) to perform statistical analyses. All the tests of significance were two-tailed.

3. Results

3.1. Baseline characteristics of the cohort

During the period between December 1992 and December 1995, 1968 patients were screened at the 23 participating centers. Out of these, 126 patients, selected according to pre-specified rules to avoid seasonal imbalance and giving their written informed consent, were formally entered into the study and are now being followed up at the collaborating centers. The 126 patients are representative of a larger pool of 1042 patients who satisfied the eligibility criteria in terms of age ($t = -0.59$, d.f. $= 1014$, $P = 0.56$) or sex ($\chi^2 = 0.58$, d.f. $= 1$, $P = 0.81$).

The baseline main axis I diagnoses of our cohort

Table 1
Demographic and clinical characteristics of patients diagnosed with depressive episodes due to bipolar disorder, unipolar major depressive disorder and depressive disorder not otherwise specified (NOS) at baseline

	Bipolar disorder ($n = 6$)	Major depressive disorder ($n = 95$)	Depressive disorder NOS ($n = 15$)
Sex (No. and % of females)	1 (17%)	56 (59%)	5 (33%)
Age (mean ± S.D. in years)	48.7 ± 14.3	44.3 ± 15.2	40.3 ± 16.4
Education (mean ± S.D. in years)	10.7 ± 3.4	11.6 ± 2.9	12.7 ± 3.5
HRSD-17[a] during the worst week of the index episode (mean ± S.D.)	25.3 ± 9.6	28.4 ± 7.4	15.1 ± 7.1
HRSD-17 at intake (mean ± S.D.)	17.8 ± 13.8	19.9 ± 8.6	12.3 ± 5.1
Melancholic features (No. and %)	2 (33%)	44 (46%)	0
Axis I or II comorbidity (No. and %)	0 (0%)	17 (18%)	2 (13%)

[a] HRSD-17, 17-item Hamilton Rating Scale for Depression.

according to DSM-IV were major depressive disorder, single episode ($n = 67$); major depressive disorder, recurrent ($n = 28$); depressive disorder not otherwise specified (NOS) ($n = 15$); bipolar I disorder ($n = 7$: 4 depressed and 3 manic); bipolar II disorder ($n = 3$: 2 depressed and 1 hypomanic); adjustment disorder with depressed mood ($n = 1$); bereavement ($n = 3$); substance-induced mood disorder ($n = 1$); and schizoaffective disorder ($n = 1$). In the following we will focus on those who presented with depressive episodes which were due to bipolar I or II disorders ($n = 6$), major depressive disorder ($n = 95$) or depressive disorder NOS ($n = 15$). Twelve of those diagnosed as depressive disorder NOS would be diagnosed as suffering from minor depressive disorder according to the criteria provided for further study in DSM-IV. Two of these had concurrent axis I disorders of social phobia and simple phobia, respectively. For the remaining three, the episode was too short to be diagnosed as major depression. The baseline demographic as well as clinical characteristics of the three subgroups are presented in Table 1.

3.2. Follow-up and change in diagnoses

At least some data were available for up to 24 months of follow-up for 104 (90%) of 126 patients in the original cohort. One patient with major depressive disorder committed suicide at 6 months, and one patient with depressive disorder NOS died of malignancy at 12 months. Thus the number of patients who dropped out of the follow-up prematurely by 2 years was 10 (8%): seven in the major depressive disorder subgroup and three in the depressive disorder NOS subgroup.

Of the 95 patients originally diagnosed with unipolar major depression, five patients later presented with manic or hypomanic episodes, and their diagnoses were changed to bipolar I or II disorders accordingly. Of the 15 patients originally diagnosed with depressive disorder NOS, nine (60%) developed a major depressive episode within 2 years after study entry; they were then rediagnosed as unipolar major depression.

In the following we will compare the three subgroups according to the baseline diagnoses as well as according to the definitive diagnoses made

Table 2
Demographic and clinical characteristics of patients diagnosed with depressive episodes due to bipolar disorder, unipolar major depressive disorder and depressive disorder NOS at the end of 2-year follow-up

	Bipolar disorder ($n = 11$)	Major depressive disorder ($n = 97$)	Depressive disorder NOS ($n = 8$)
Sex (No. and % of females)	5 (46%)	56 (58%)	1 (13%)
Age (mean ± S.D. in years)	45.0 ± 11.5	44.9 ± 15.6	32.9 ± 13.4
Education (mean ± S.D. in years)	11.7 ± 3.2	11.6 ± 3.1	12.5 ± 3.2
HRSD-17[a] during the worst week of the index episode (mean ± S.D.)	27.3 ± 7.8	24.3 ± 7.9	16.5 ± 8.7
HRSD-17 at intake (mean ± S.D.)	20.6 ± 11.7	19.2 ± 8.5	11.8 ± 5.1
Melancholic features (No. and %)	5 (46%)	41 (43%)	1 (13%)
Axis I or II comorbidity (No. and %)	1 (9%)	16 (17%)	2 (25%)

[a] HRSD-17, 17-item Hamilton Rating Scale for Depression.

after 2 years of follow-up. The former analyses will serve to illuminate what clinicians and patients can expect from their baseline characteristics at the beginning of treatment. The latter analyses will show what, if any, differences exist between subgroups with supposedly more homogeneous etiologies. Table 2 shows the demographic and clinical characteristics of the three subgroups according to their definitive diagnoses: none was significantly different from figures for the original subgroups as presented in Table 1.

3.3. Treatment received by the cohort

The GLADS project is a naturalistic follow-up study of broadly defined affective disorder patients, and there was no control over the treatment in its protocol. A previous analysis of the cohort showed, however, that over two-thirds of the major depressant patients did not receive adequate antidepressive therapy, defined as 125 mg/day or more of imipramine or equivalent (Furukawa et al., 2000b). Only two out of the six patients diagnosed with bipolar depression at baseline were receiving lithium (400–1200 mg/day) at 1 or 6 months after study entry. Based on these findings, it may be assumed that the observed course was similar, but not identical, to the natural history.

3.4. Time to recovery and length of episode

We defined recovery of a major depressive episode in accordance with the NIMH definition (Frank et al., 1991) as 2 consecutive months with no more than one or two mild depressive symptoms. The duration of an episode was calculated excluding these last 2 months in remission.

Fig. 1 presents the time to recovery after commencement of therapy for the three original subgroups. The three survival curves were not statistically significantly different among themselves

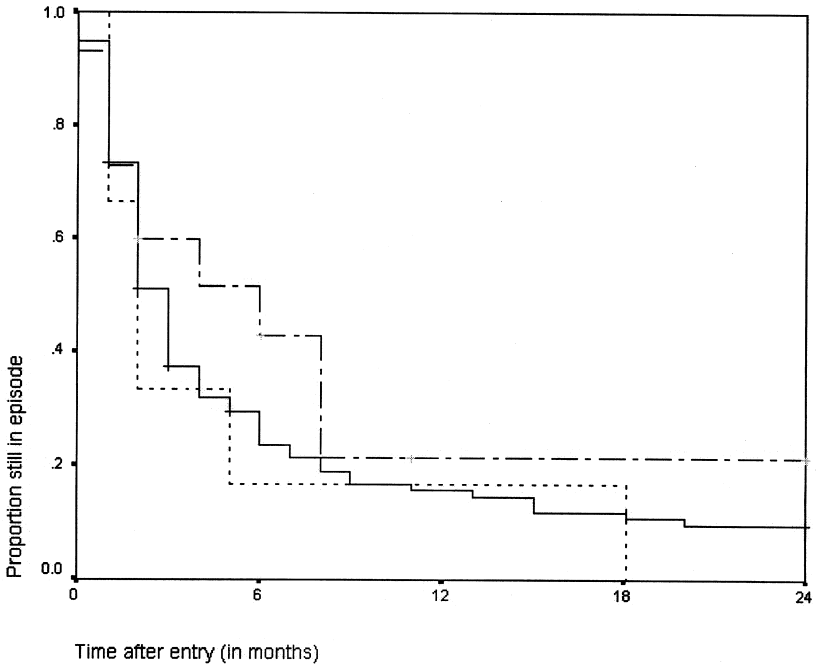

Fig. 1. Time to recovery after treatment commencement for the three diagnostic subgroups determined at baseline. --------: 6 patients diagnosed with bipolar I or II disorder, depressed, at baseline. ————: 95 patients diagnosed with unipolar major depressive disorder at baseline. - —-— -: 15 patients diagnosed with depressive disorder NOS at baseline (Kaplan–Meier log rank = 1.45, d.f. = 2, $P = 0.48$ among the three subgroups).

(log rank = 1.45, d.f. = 2, $P = 0.48$). The median time to recovery for bipolar depressed patients was 2.0 months (95%CI: 0.9–3.1), that for unipolar depressed patients was 3.0 months (2.5–3.6), and that for subthreshold depression was 3.2 (0–12.3). The percentage of patients still in the index episode at 3 months was 33% for bipolar depression, 38% for unipolar depression and 60% for subthreshold depression; that at 6 months was 17, 24, and 43%, respectively; that at 12 months was 0, 15, and 21%; and that at 24 months was 0, 9, and 21%. If we compared the time to recovery after study enrollment for the subgroups according to the definitive diagnoses, the overall survival curves were very similar to the ones presented in Fig. 1 and the three curves did not show statistically significant difference among themselves (log rank = 0.79, d.f. = 2, $P = 0.67$).

Fig. 2 presents the total time in episode for the three diagnostic subgroups by the definitive diagnoses made at 2 years. There was a trend difference in the three survival curves (log rank = 5.76, d.f. = 2, $P = 0.056$), which was mainly due to the difference between the bipolar depressive episodes and unipolar depressive episodes (log rank = 5.09, d.f. = 1, $P = 0.02$). The median length of the total episode was 4.0 (2.4–5.6) for bipolar depression, 7.0 (5.2–8.8) for unipolar depression and 10.0 (0–24.0) for subthreshold depression.

3.5. Total time unwell

The fact that at least half of the patients presenting with a major depressive episode, either bipolar or unipolar, attain recovery by 2–3 months may suggest a benign course of these disorders. However, three (50%) out of the six bipolar depressed patients who recovered relapsed into a major depressive or manic episode within 24 months of follow-up: 18 (34%) out of 53 unipolar depressed patients did so as well. Taking account of subsyndromal states, only one person among

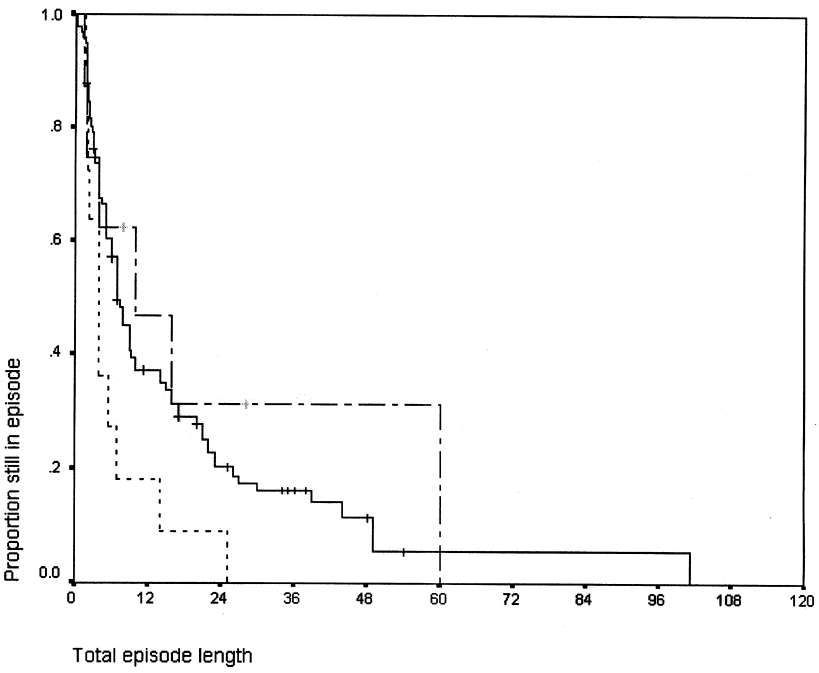

Fig. 2. Total time in episode for the three subgroups according to definitive diagnoses at 2 years of follow-up. --------: 11 patients diagnosed with bipolar I or II disorder, depressed. ————: 97 patients diagnosed with unipolar major depressive disorder. - — -; 8 patients diagnosed with depressive disorder NOS (Kaplan–Meier log rank = 5.76, d.f. = 2, $P = 0.056$ among the three subgroups).

Table 3
Total time unwell by baseline diagnostic subgroups (95% CI)[a]

	Bipolar disorder ($n = 6$)	Major depressive disorder ($n = 95$)	Depressive disorder NOS ($n = 15$)
Months unwell	15.0 (7.7–22.3)	9.0 (7.4–10.5)	10.4 (4.8–16.0)

[a]One-way analysis of variance $F = 1.74$, d.f. = 2, $P = 0.18$.

the six bipolar depressives who attained recovery could sustain that asymptomatic state up to 24 months of follow-up. Among the 83 unipolar depressives who recovered, 44 (53%) saw some return of mood syndromes. Only 4 out of the 15 patients originally diagnosed with depressive disorder NOS recovered from the minor depression without developing into a major depressive episode and remained well.

We therefore compared the total time unwell between the three subgroups (Tables 3 and 4). We assumed the worst case scenario, whereby those who dropped out of the follow-up were assumed to be symptomatic for the remaining months. Neither the original diagnostic subgroups nor the definitive diagnostic subgroups showed a statistically significant difference in the total time unwell. On average, these patients were symptomatic with two or more significant affective symptoms for 9.5 (95% CI: 8.0–10.9) months out of the 24 months of follow-up.

3.6. Functioning at 6, 12, 18 and 24 months

The GAS ratings at 6, 12, 18 and 24 months of follow-up are tabulated in Table 5 according to baseline diagnoses and in Table 6 according to follow-up diagnoses. The bipolar depressed patients tended to present with graver functional impairment at intake, but thereafter there was no statistically significant difference in the global functioning of these three diagnostic subgroups.

4. Discussion

The strengths of the present study are as follows: Firstly, our cohort was representative of various psychiatric settings. Although the 23 participating centers of the IPS arm of the GLADS project were not a random selection from all the psychiatric institutions in Japan, they consist of various types of institutions from all over Japan, and within each facility the selected sample was representative of the eligible first visit patients during the study period. The cohort was not restricted to inpatients either. Secondly, our cohort was an inception cohort of patients with depression who received antidepressant therapy for the first time during their index episode. Thirdly, the follow-up rate was satisfactory. The rate of premature dropouts by 2 years was 8%.

Possible weaknesses of the present study include the following. Firstly, our cohort was restricted to psychiatric patients. In Japan we do

Table 4
Total time unwell by definitive diagnostic subgroups (95% CI)[a]

	Bipolar disorder ($n = 11$)	Major depressive disorder ($n = 97$)	Depressive disorder NOS ($n = 8$)
Months unwell	11.8 (7.4–16.2)	9.2 (7.6–10.8)	9.1 (0.4–17.9)

[a]One-way analysis of variance, $F = 0.521$, d.f. = 2, $P = 0.60$.

Table 5
GAS scores at 6, 12, 18 and 24 months by baseline diagnostic subgroups (95% CI)[a]

	Bipolar disorder ($n = 6$)	Major depressive disorder ($n = 95$)	Depressive disorder NOS ($n = 15$)	One-way analysis of variance
GAS at intake	41.3 (20.8–61.8)	52.5 (50.1–54.9)	59.1 (53.5–64.6)	$F = 4.83$, d.f. = 2, $P = 0.01$
GAS at 6 months	62.8 (46.8–78.8)	74.4 (71.3–77.6)	68.7 (61.5–75.9)	$F = 2.29$, d.f. = 2, $P = 0.11$
GAS at 12 months	64.8 (50.6–79.1)	76.1 (72.8–79.4)	70.8 (53.9–87.6)	$F = 1.95$, d.f. = 2, $P = 0.15$
GAS at 18 months	64.0 (45.2–82.8)	74.7 (71.0–78.5)	73.3 (55.2–91.3)	$F = 1.09$, d.f. = 2, $P = 0.34$
GAS at 24 months	71.3 (45.5–97.1)	74.4 (70.8–78.1)	72.0 (66.2–77.8)	$F = 0.19$, d.f. = 2, $P = 0.82$

[a] Post hoc Scheffé comparisons revealed significant differences between bipolar disorder vs. NOS depressive disorder ($P = 0.01$) at intake.

not have the family doctor system and psychiatrists are often the first-line consultees for people who realize that their problems are mental rather than physical. However, we should be prudent in generalizing our findings beyond psychiatric/clinical samples because it is known that only a limited proportion of people who suffer from major depression present themselves to medical attention (Hirschfeld et al., 1997). A community study would be required to address the issue of the course of all persons with depression. Secondly, the sample size may appear modest, especially for the bipolar depressives and the subthreshold depressives. Some of the statistically non-significant findings reported herein could therefore be type II errors. Thirdly, the ratio of the subjects enrolled in the study over those screened and found eligible was small (126/1042). This was due to the enormous time and human efforts required for the follow-up. In designing the present follow-up study, we placed more emphasis on selecting a representative subset of all the eligible patients visiting our collaborating centers; we administered the less time-requiring PISA first and made sure that the subjects actually entered were representative of the larger pool of patients screened and found eligible.

Within these constraints, we noted no statistically significant difference in the time to recovery, defined as two consecutive months of no or minimal symptomatology, among bipolar, unipolar or subthreshold depressive episodes. After treatment began, 67% of bipolar depression, 62% of unipolar depression and 40% of subthreshold depression recovered by 3 months; the respective figures were 83, 76 and 57% by 6 months. The total time spent in episode of illness was also similar between the three subtypes.

When combined with the pre-treatment period, the total length of episode was significantly longer for unipolar depression than for bipolar depression. The median length of the total episode was 4.0 months (95%CI: 2.4–5.6) for bipolar depression and 7.0 months (5.2–8.8) for unipolar depression. These findings are in line with the previous literature (Winokur et al., 1993; Angst and Preisig, 1995).

The global functioning of the three subgroups

Table 6
GAS scores at 6, 12, 18 and 24 months by definitive diagnostic subgroups (95% CI)

	Bipolar disorder ($n = 11$)	Major depressive disorder ($n = 97$)	Depressive disorder NOS ($n = 8$)	One-way analysis of variance
GAS at intake	46.2 (35.8–56.6)	53.1 (50.6–55.5)	58.5 (51.7–65.3)	$F = 2.51$, d.f. = 2, $P = 0.09$
GAS at 6 months	70.8 (58.1–83.5)	73.9 (70.9–77.0)	67.3 (53.5–81.2)	$F = 0.79$, d.f. = 2, $P = 0.46$
GAS at 12 months	73.5 (62.7–84.4)	75.1 (71.7–78.6)	72.8 (52.2–93.3)	$F = 0.09$, d.f. = 2, $P = 0.91$
GAS at 18 months	71.7 (58.6–84.7)	74.0 (70.0–78.0)	76.5 (54.2–98.8)	$F = 0.14$, d.f. = 2, $P = 0.87$
GAS at 24 months	77.2 (62.9–91.5)	73.6 (70.0–77.2)	73.1 (64.7–81.6)	$F = 0.24$, d.f. = 2, $P = 0.79$

did not differ to a statistically significant extent between bipolar, unipolar or subthreshold depression groups except for the baseline. To the best of our knowledge, there have been three studies to date that compared social adjustment of unipolar and bipolar patients. None of them found a statistically significant difference by polarity (Dunner et al., 1978; Bauwens et al., 1991; Coryell et al., 1993). Neither did we note any difference between the three diagnostic groups of bipolar, unipolar and subthreshold depression. On average, all three groups attained satisfactory though not optimal functioning status in the 1970s according to the GAS by 2 years.

Of the 15 patients originally diagnosed with depressive disorder NOS (DSM-IV), nine (60%) developed a major depressive episode within 2 years. Among patients presenting with subthreshold depression in primary care, 16–20% develop major depression within 1 year (Maier et al., 1997; Sullivan et al., 1998). Our figure appears considerably higher, but this may be due to differences in the patient population and/or to the small sample size for depressive disorder NOS in our study. In our sample, patients with depressive disorder NOS appeared to suffer both symptomatologically and functionally as much as patients with major mood disorders.

Acknowledgements

This report was prepared on behalf of the Group for Longitudinal Affective Disorders Study (GLADS). The study was supported by Research Grants 3A-6, 6A-4, 8B-2 and 10A-5 for Nervous and Mental Disorders from the Ministry of Health and Welfare, Japan.

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