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How many well vs. unwell days can you expect over 10 years, once you become depressed?

Furukawa TA, Yoshimura R, Harai H, Imaizumi T, Takeuchi H, Kitamura T, Takahashi K. How many well vs. unwell days can you expect over 10 years, once you become depressed?

Objective: Prognostic studies of major depression have mainly focused on episode remission and relapse, and only a limited number of studies have examined long-term course of depressive symptomatology at threshold and subthreshold levels.
Method: The Group for Longitudinal Affective Disorders Study has conducted prospective serial assessments of a cohort of heretofore untreated major depressive episodes for 10 years under naturalistic conditions.
Results: Of the 94 patients in the cohort, the follow-up rate was 70% of the 11 280 person-months. Around 77% of the follow-up months were spent in euthymia, 16% in subthreshold depression and 7% in major depression. Duration of the index episode before reaching recovery was the only significant predictor of the ensuing well time.
Conclusion: On average, patients with major depression starting treatment today may expect to spend three quarters of the next decade in euthymia but the remaining one quarter in subthrehold or threshold depression.

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Key words: depressive disorder; course; prognosis; suicide

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Significant outcomes

- This is the first systematic study to examine the 10-year course of a representative inception cohort of unipolar major depressive episodes, recruited at the time of their treatment commencement and followed up prospectively and serially with a semi-structured interview.
- Of the 10 years after starting treatment of their major depression, patients can, on average, expect to spend 77% in euthymia, 16% in subthreshold depression and 7% in major depression.

Limitations

- More than two-thirds of the patients received no or inadequate antidepressant continuation/maintenance treatment.
- Depending on the fate of the drop-outs, the overall figures may change.

Introduction

Major depression used to be considered an episodic, remitting and relapsing disorder with essentially asymptomatic intervals. It is no longer so. Recent studies have not only identified frequent existence of low grade depression between episodes (1, 2) but also revealed that residual inter-episode

subthreshold depression is associated with functional impairment (3, 4) and with very rapid relapse into a full depressive episode (5, 6).

However, up until recently, published long-term follow-up studies of depression have focused on recovery and recurrence rather than evaluating inter-episodic mood symptoms including subsyndromal depression (7–11). To the best of our knowledge, there are only two long-term studies of the course of major depression that examined the inter-episode symptoms.

Judd and his colleagues followed up 431 patients with major depression who sought treatment at five academic centers in USA for 12 years and found that, on average, these patients spent 15% of their time in major depression, 27% in minor depression, 17% in with depressive symptoms below the threshold for minor depression and 42% at an asymptomatic level (NIMH Collaborative Depression Study: 1). Kennedy and his colleagues reviewed 8–11 years' longitudinal course of patients with severe depression and found that, of the follow-up months, 13% were spent at full depression level, 20% at residual depression level, 15% at subthreshold symptom level and 52% at an asymptomatic level (2).

Unfortunately, however, both these studies are biased towards the severer end of depression spectrum and therefore suffer from a common weakness in the generalizability of their findings. For example, in the American study, the participants were recruited at five renowned tertiary-care academic centers, 77% of the participants were in-patients, 63% were suffering from recurrent depression and the index episode had lasted more than a year in 29% at time of study intake (12). In the British study, 76% were in-patients and 68% were suffering from their second or later depressive episode at intake (13).

The Group for Longitudinal Affective Disorders Study (GLADS) has been conducting a mutlti-center collaborative naturalistic cohort study of patients with heretofore untreated mood episodes who had presented to various psychiatric facilities all over Japan. We now have detailed prospective serial assessment data of this cohort for 10 years under naturalistic conditions (14).

Aims of the study

This report focuses on the overall longitudinal syndromal and subsyndromal status of the cohort and tries to answer the question about how many well days, on average, these patients can expect once they start treatment for their major depressive episode.

Material and methods

The subjects and procedures of the GLADS project have been described in detail elsewhere (9, 10) and are briefly summarized here.

The 23 collaborating centers included psychiatric departments of 13 university hospitals and 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) (15) to a representative subset of its first-visit patients to ascertain the patients' eligibility. The details of the predetermined rules on how to select a subset of first-visit patients were left to individual centers, depending on their human and logistic resources: some centers administered PISA to all their first-visit patients, other did so with those on a certain day of the week, and still others did so with those seen by one or two collaborating psychiatrists only.

The eligibility criteria were: i) depressive state or manic state, ii) having received no antidepressant or antipsychotic medication in the preceding 3 months, iii) aged 18 years or older and iv) absence of conditions that would render detailed psychopathological assessment difficult, such as hearing difficulties and difficulty in communication in the Japanese language. A total of 1843 patients were screened at the 23 participating centers between December 1992 and December 1995 (some centers did not participate throughout these 3 years). A total of 466 patients suffered from broadly defined mood disorders but either failed to meet the other entry criteria or declined consent and 126 entered the study.

The study protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan, as well as those of the participating centers. 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 1 week of entry by a psychiatrist using the entry version of the comprehensive assessment list for affective disorders (COALA) (16) The COALA consists of a series of semi-structured interviews that enable serial assessment of the cohort; these include the entry, monthly follow-up, 6-monthly follow-up and yearly follow-up versions. The reliability of the PISA and COALA has been reported to be good to excellent (17). The cohort was followed up

monthly until treatment termination, 6-monthly thereafter up to 2 years, and then annually up to 10 years. The semi-annual and annual follow-ups were conducted either in person or by telephone, using the semi-structured interview guide that elicited information regarding symptomatic and functional status at the time of the follow-up and occurrence of major depressive and (hypo)manic episodes for the past year. After completing this first part of the follow-up interview, the interviewer rated each month of the survey period in five grades as: 5, above diagnostic threshold for major depressive episodel; 4, between 5 and 3; 3, asymptomatic or minimally symptomatic with at most two out of nine diagnostic criteria symptoms of at most mild degree; 2, between 3 and 1; 1, above diagnostic threshold for manic episode, with supplementary information from case notes where available.

This paper focuses on the course and outcome of the subset of the cohort who were diagnosed with major depressive disorder according to DSM-IV (18). The cohort received 85.2 (SD 73.2) mg of imipramine or equivalent at the peak of the acute phase treatment (19), and about 56% were prescribed inadequate doses, i.e. less than 75 mg/day (20, 21). The respective figures were 45.1 (SD 64.7) mg of imipramine or equivalent per day and about 74% during continuation phase, and 42.0 (SD 74.7) mg/day and 83% at maintenance phase immediately before relapse (22). None of the study subjects received systematic psychotherapy specific to major depression such as cognitive-behavioural therapy or interpersonal psychotherapy.

Statistical analyses

After excluding missing patients because of drop-outs, natural deaths or suicides, we calculated the proportions of months spent in each depressive state defined above and their 95% confidence intervals. We next sought for predictors of well time by entering the following variables into stepwise multiple regression, with *P* to enter (0.05) and *P* to leave (0.10): sex, age, education, treatment setting (out-patient vs. in-patient), type of hospital (university hospitals, other general hospitals, mental hospitals), single episode vs. recurrent major depression, length of index episode before treatment commencement, the Hamilton Rating Scale for Depression (HRSD) scores at peak of index episode and at treatment commencement, and time required to reach recovery. Two-tailed alpha level below 0.05 was considered statistically significant.

Table 1. Clinical characteristics of the cohort

Variable	Major depressive disorder, single episode (*n* = 66)	Major depressive disorder, recurrent (*n* = 28)
Age (years), mean (SD)	44.1 (15.1)	44.3 (15.6)
Gender, *n* (%) female	36 (55)	19 (68)
Marital status		
Single, *n* (%)	19 (29)	8 (29)
Married, *n* (%)	47 (71)	20 (71)
Treatment settings		
University hospital, *n* (%)	46 (70)	11 (39)
General hospital, *n* (%)	14 (21)	11 (39)
Mental hospital, *n* (%)	6 (9)	6 (21)
Axis I comorbidity		
Dysthymia (double depression), *n*	4	2
Panic disorder, *n*	3	0
Generalized anxiety disorder, *n*	2	0
Social phobia, *n*	0	1
Anorexia nervosa, *n*	0	1
Vascular dementia, *n*	0	1
In-patient at entry, *n* (%)	12 (18)	2 (7)
Length of episode before entry (months), median (range)	3.5 (0.47–48)	1.5 (0.47–100)
Number of episodes before entry, median (range)	0	2 (1–10)

Results

Characteristics of the cohort and the rates of follow-up

Of the 126 patients who entered the study, 94 met the DSM-IV criteria for major depressive disorder, either single episode ($n = 66$) or recurrent ($n = 28$). One patient diagnosed with major depression at baseline was rediagnosed as having suffered from Alzheimer's disease from the beginning at 2-year follow-up and is therefore excluded from this study of the 10-year course. Thirty-five per cent of the annual follow-up interviews were conducted in person and the remaining 65% by telephone. Table 1 summarizes the clinical characteristics of the single episode as well as recurrent subjects.

Among the cohort with single episode major depression, we were able to ascertain five deaths by natural cause and two completed suicides over the course of the 10-year follow-up. Among the cohort with recurrent major depression, one died as natural death and two committed suicide. In addition, of the 7920 person-months of the 10-year follow-up for the cohort diagnosed with major depression, single episode upon presentation, data were missing for 2289 person-months (29%). The missing was similar for the cohort with recurrent major depression: of the 3480 person-months of follow-up, we did not have any data for 1065 person-months (31%).

Because these results were very similar for single episode vs. recurrent major depression, Table 2

Table 2. Yearly changes in rates of person-months missing due to drop-outs, natural deaths and suicides

Missing as a result of:	1st year (%)	2nd year (%)	3rd year (%)	4th year (%)	5th year (%)	6th year (%)	7th year (%)	8th year (%)	9th year (%)	10th year (%)
Drop-outs	4	6	25	28	29	34	43	40	44	41
Natural deaths	0	0	0	0	0	1	3	5	5	6
Suicides	1	1	2	2	2	2	2	3	3	4

summarizes the yearly changes of the percentages of person-months with missing data because of drop-outs, natural deaths and suicides for the entire cohort.

Those who contributed less than 70% of the follow-up months ($n = 44$) were not different from the others ($n = 50$) in terms of sex, age, education, treatment setting, type of hospital, single episode vs. recurrent major depression, length of index episode before treatment commencement or depression severity as measured with the HRSD scores at peak of index episode and at treatment commencement.

Average well vs. unwell time

Of the 66 patients with major depression, single episode upon presentation, Fig. 1 depicts the person-months spent in five distinct mood states as defined in the Methods section, with annual censorship of the missing data over the course of 10-year follow-up since treatment commencement. On average, 75% (95% CI 74–76) of the follow-up months were spent in euthymia, 19% (95% CI 18–20) in subthreshold depression and 6% (95% CI 6–7) in depression; 0.04% were spent in mania and 0.2% in hypomania.

Figure 2 represents the same for major depression, recurrent. On average, 81% (95% CI 79–82) were spent in euthymia, 11% (95% CI 9–12) in subdepression, 8% (95% CI 7–10) in depression; 0.1% were spent in mania and 0.2% in hypomania.

These proportions were statistically significantly different between the two subtypes of major depression ($\chi^2 = 83.4$, df = 4, $P < 0.001$).

Individual variation

The average numbers and figures should not obfuscate the great variability observed among individual patients in our cohorts.

Among the 66 patients who started treatment for their first major depressive episode, 12 recovered and remained well for 10 years (18%, 95% CI 11–29), 10 recovered but later experienced a subthreshold recurrence, and 20 recovered but later experienced a full episode recurrence (45% for some kind of recurrence, 95% CI 34–58). Three dropped out without ever attaining recovery, and further 17 recovered but then dropped out before the termination of their follow-up. Three showed a hypomanic, and one showed a manic episode; one committed suicide without ever attaining recovery; one after attaining recovery.

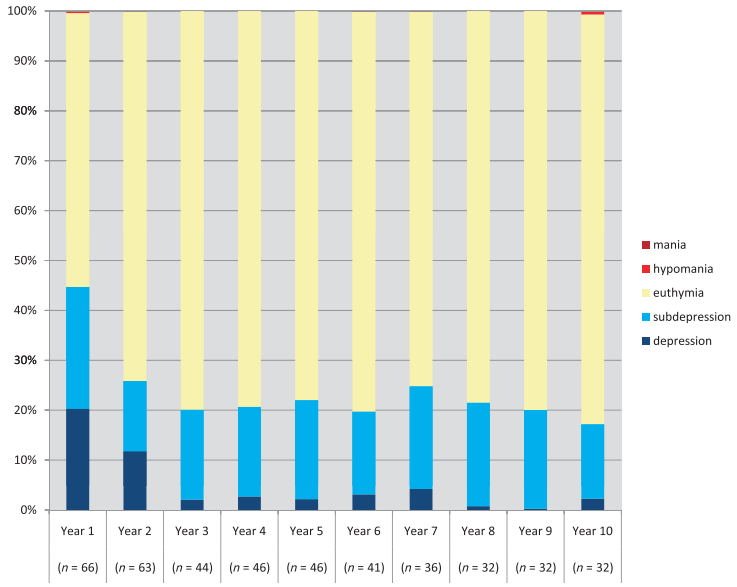

Fig. 1. Time spent in mood states over the 10 years after treatment commencement for major depression, single episode.

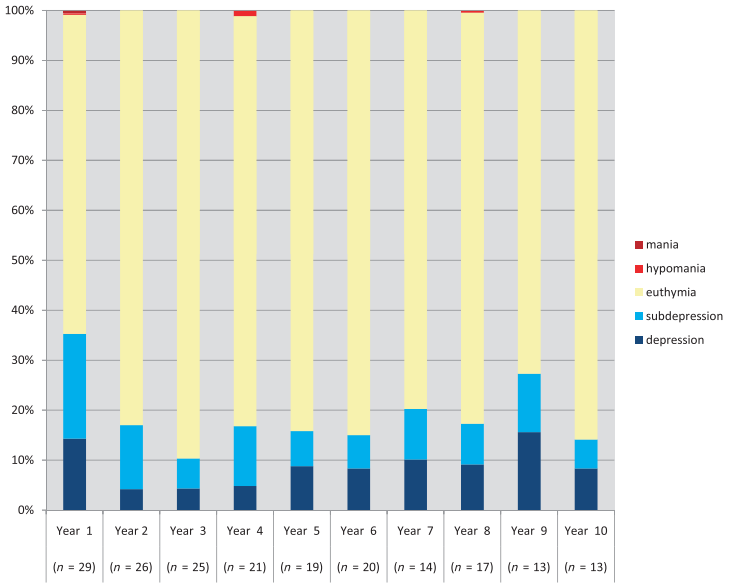

Fig. 2. Time spent in mood states over the 10-year follow-up after treatment commencement for major depression, recurrent.

Table 3. Proportion of months spent in euthymia

Proportion euthymic (%)	Major depressive disorder, single episode (n = 66)	Major depressive disorder, recurrent (n = 28)	Total (n = 94)
≥90	26 (39%)	10 (36%)	36 (38%)
89–70	20 (30%)	12 (43%)	32 (34%)
69–50	5 (8%)	2 (7%)	7 (7%)
49–30	5 (8%)	2 (7%)	7 (7%)
≤29	10 (15%)	2 (7%)	12 (13%)

Likewise, among the 28 patients who started treatment for their recurrent episode, only one recovered and remained well for 10 years (4%, 95% CI 1–18). Three recovered but later experienced a subthreshold recurrence and 11 recovered but later experienced a full episode recurrence (50% for some kind of recurrence, 95% CI 32–68). Two dropped out without every attaining recovery and four recovered but dropped out before the end of their 10-year follow-up. Three showed a hypomanic episode and one a manic episode. Of those who remitted but relapsed, two committed suicide and one never recovered.

Table 3 shows the number of patients who remained euthymic for more than 90%, 89–70%, 69–50%, 49–30% and less than 30% of their documented prospective months of follow-up.

Predictors of well time

Of all the demographic and clinical variables entered, only duration of index episode before reaching recovery was significantly predictive of the proportion of time spent in euthymia over the 10 years of follow-up ($r = -0.63$, 95% CI −0.49 to −0.74, $P < 0.001$).

Discussion

This is the first study to examine the overall 10-year course of a representative inception cohort of unipolar major depressive episodes, systematically recruited at the time of their treatment commencement at multiple treatment facilities and followed up prospectively and serially with a semi-structured interview. Although the proportions of well time were statistically significantly different between patients with single episode vs. recurrent major depression, the differences were not substantive, and this diagnostic subtype was not able to predict the ensuing well time. In the following, we therefore summarize the results for both single episode and recurrent major depression. Overall, our results suggest that newly treated patients seem to be able to expect better prognosis than previous suggested by the literature.

First, of the 94 patients in the cohort, we documented six deaths by natural cause, four suicides, two developing a hypomanic episode and two a manic episode. This suicide rate is concordant with recent studies (23, 24); the number of patients experiencing manic or hypomanic switch might be lower than expected from the literature (25, 26) but the small sample size of our cohort unfortunately precludes further examination. Second, we found out that, on average, around 75–80% of the follow-up months were spent in euthymia whereas around 20% were spent in subdepression or depression. There was, however, great individual variation such that, while 70–80% of the patients could expect to spend at least 70% of their ensuing 10 years in euthymia, a substantial minority could anticipate less than half

of their ensuing decade to be euthymic. Third, with regard to predictors of well time during the follow-up, we were able to identify only one variable, namely the duration of the index episode. The NIMH Collaborative Depression Study (CDS) found that patients with double depression and recurrent depression had more chronic symptoms than patients with their first lifetime major depressive episode (1); the Cambridge study found only the female gender to be predictive of time spent at full depression and none of the variables remained significantly predictive of time spent at subthreshold depression (2).

Table 4 summarizes the three prospective studies of between-episode symptomatology in major depressive disorder. As expected, the GLADS cohort fared best among the three, because they were inception cohort patients starting treatment for their episode and only a minority were in-patients at time of entry into the study. However, it is remarkable that, despite this difference, the three studies are more similar than dissimilar from each other (1, 2), and that, even in the GLADS cohort, as much as 16% of the follow-up months were spent in subthreshold depression in addition to 7% in major depression.

Recently, a 5-year naturalistic follow-up study of a regionally representative cohort of psychiatric patients with major depression (n = 163) was published from Finland (27). The results of this study are not directly comparable with the three studies in Table 4, because their follow-up period was only 5 years. They found that the proportions of time spent in remission, in subthreshold depression and in major depression were 49%, 31% and 20% respectively. The study authors also concluded that previous literature on mostly in-patient major depression may have, by generalizing from patients with the most severe psychopathology, overemphasized chronicity of depression.

There are several weaknesses to this study. First, the drop-out rates of 30%, although realistically unavoidable over the course of 10 years and comparing favorably with 27% drop-out in the 12-year follow-up from the NIMH CDS (1) but less favorably with 18% of the Cambridge cohort (2), are still substantive and, depending on the fate of those who dropped-out, the overall figures may change somewhat. The missing was minimal up to 2 years of follow-up but gradually increased especially after 5 years. It is to note, however, that those who contributed less than 70% follow-up person-months were not statistically significantly different from those with more complete follow-up at baseline, and that the overall picture remained fairly constant after the third year of follow-up. Second, our annual follow-up interviews did not use the LIFE interview (28) used in the NIMH CDS and Cambridge studies. This may or may not have led to underreporting of symptomatology in our cohort. However, we believe that our follow-up, being annual and serial with additional questions regarding symptomatic and functional status, supplemented with case notes, were detailed enough. Third, we need to remember that the treatments that the GLADS cohort received were grossly inadequate (22). The same was true with the NIMH CDS cohort (29) and with the Cambridge cohort (30) but to a lesser degree. To this extent, we may regard the observed course and outcome as naturalistic and a more aggressive acute phase and continued treatment may be able to ameliorate the prognosis of these patients (31). However, this possibility needs to be pragmatically demonstrated and, until that time, the 70–80% euthymic days may appear like a half-empty or half-full glass for the patients starting treatment for their major depressive episode.

Table 4. Between-episode symptomatology in three prospective studies of unipolar major depression

	GLADS (n = 94)	NIMH (n = 431)	Cambridge (n = 70)
Remitted	77%	58%	67%
Subthreshold depression	16%	27%	20%
Major depression	7%	15%	13%

There has recently been increased research interest in subsyndromal depression among patients with bipolar disorder as well (32–34). Clinically, we need to pay closer attention to lingering depression in mood disorders and make the best use of the available randomized evidence (31, 35, 36). There is growing awareness that we also need some non-pharmacological approaches to this problem such as cognitive-behavioural therapy (37, 38) and its combination with pharmacotherapy (39). In terms of research, the most pressing question is perhaps to examine if this evidence available in research settings concerning optimum pharmacotherapy and psychotherapy can be implemented in the real world and the course and outcome of the suffering patients can actually improve.

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Declaration of interests

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