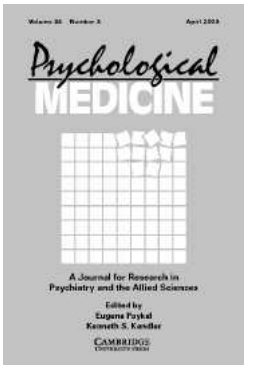

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Time to recurrence after recovery from major depressive episodes and its predictors

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ABSTRACT

Background. Depression is a remitting but recurring disease. However, there is a paucity of prospectively recorded data on the course of depression after recovery.

Method. A multi-centre prospective serial follow-up study of an inception cohort of hitherto untreated unipolar major depression ($N=95$) for 6 years. We report the time to recurrence after recovery from the index depressive episode and their predictors.

Results. The cumulative probability of remaining well without subthreshold symptoms was 57% (95% CI, 46 to 68%) at 1 year, 47% (95% CI, 36 to 58%) at 2 years and 35% (95% CI, 23 to 47%) at 5 years. The same without full relapse was 79% (95% CI, 70 to 88%) at 1 year, 70% (95% CI, 60 to 80%) at 2 years and 58% (95% CI, 46 to 70%) at 5 years. The median duration of well-interval from the end of the index episode to the beginning of the subthreshold episode was 19·0 months (95% CI, 2·4 to 35·7), and that to the end of the full episode was over 6 years. Residual symptoms at time of recovery predicted earlier recurrence.

Conclusions. The median length of the well-interval was much longer than previously reported in studies employing similar definitions but dealing with a more severe spectrum of patients. However, the sobering fact remains that less than half of the patients can expect to remain virtually symptom-free for 2 years or more after recovery from the depressive episode.

INTRODUCTION

Since Kraepelin's first demarcation between manic-depressive illness and dementia praecox, affective disorder has been considered to be a remitting but recurring disease. Recurrences after recovery from major depression and their predictors therefore represent important problems for clinicians and patients alike. However, there are still rather few long-term, well-designed studies especially with regard to the wide spectrum of unipolar depression.

The National Institute of Mental Health Collaborative Depression Study (NIMH CDS) is a prospective naturalistic study of a large cohort of people with affective disorders at five leading university medical centres in the USA. Recovery was considered to begin within the first 8 weeks of no or minimal symptoms, and recurrence was defined as the first appearance of full criteria major depression. With follow-up data up to 15 years, the median length of the well interval for unipolar depression was estimated to be 31 months and the Kaplan–Meier estimate of the cumulative proportion of recurrence was about 63% at 5 years, 80% at 10 years and 85% at 15 years (Mueller *et al*. 1999). There are only a number of baseline variables that have been

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repeatedly shown to predict a recurrence; the number of prior episodes (Solomon *et al.* 2000), the length of the index episode (Lavori *et al.* 1994), and persistence of subsyndromal symptoms (Judd *et al.* 1998*a*) are among these few.

Adopting similar definitions of recovery and relapse, all patients who recovered from an episode of major depression at the University of Naples were followed for up to 8 years. The median duration of the well interval was 30 months, and the cumulative probability of recurrence by the first year was 37% and that by the fifth year was 75% (Maj *et al.* 1992). The number of previous episodes was the only consistent predictor of recurrence.

As far as we are aware, these are the only two studies that employed prospectively serial (i.e. repeated at shorter intervals) assessments of a defined cohort of patients with depression in order to ascertain recovery and relapse/recurrence over a number of years. Two other studies estimated time to relapse after recovery, based on retrospective recollection of the course over 10 years, in a cohort of patients with depression initially assembled for the purpose of shorter follow-up study (Surtees & Barkley, 1994; Kennedy *et al.* 2003). They were both conducted in UK and reported very similar relapse rates, namely about 25% at 1 year, 35% at 2 years and >50% at 5 years.

Unfortunately, all of these studies suffer from some methodological weaknesses. In the first place, all of these studies dealt with patients towards the severe, recurrent and chronic end of depression spectrum, likely to be seen as tertiary referrals but less so in primary care. In the NIMH and the two British studies, nearly four-fifths of the cohort were in-patients at time of entry (Keller *et al.* 1982*a*; Surtees & Barkley, 1994; Kennedy *et al.* 2003). In all of these studies, >60% of the patients were suffering from recurrent depression; in the Italian sample, this proportion was >90%. Secondly, the American and Italian studies may be subject to referral filter bias because the patients were recruited in nationally renowned tertiary care academic centres in USA and Italy. Thirdly, estimation of survival curves retrospectively after more than 10 years interval in the two UK studies is likely to be less precise and an underestimate than that based on prospectively serial data collection (Surtees & Barkley, 1994).

The Group for Longitudinal Affective Disorders Study (GLADS) in Japan is a multicentre collaborative, naturalistic study of patients with heretofore untreated major depressive episodes who had presented to various psychiatric facilities all over Japan. We have been following this cohort prospectively semi-annually for 2 years and yearly thereafter for up to 6 years. We previously reported on the time to recovery of this cohort (Furukawa *et al.* 2000) and the present report focuses on their course after recovery from major depressive episode. We will present: a survival curve for well interval from the end of index episode to the beginning of first prospective 'subthreshold' depressive episode; a survival curve for well interval from the end of the index episode to the beginning of the first prospective depressive episode; and exploratory analyses of predictor variables for the course, measured at the commencement of treatment and after recovery from the index episode.

METHOD

The subjects and procedures of the GLADS project have been detailed elsewhere (Furukawa *et al.* 2000) and are briefly outlined here. The 23 collaborating centres for the GLADS project includes psychiatric departments of 13 university hospitals and six general hospitals, three mental hospitals and one community mental health centre from all over Japan.

Participating psychiatrists at each centre 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 patient' eligibility. The details of predetermined rules on how to select a subset of first-visit patients were left to individual centres, depending on their human and logistic resources. 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. Written informed consent was obtained from all participants after full disclosure of the purposes and procedures of the study. Each participating centre was expected to enter the first patient who satisfied the inclusion

criteria every 1 or 2 months in order to avoid seasonal imbalance.

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) (Furukawa, 1992). The COALA consists of a series of semi-structured interviews that enable serial assessment of the cohort; these include the entry version, monthly follow-up version, and yearly follow-up version. It provides depression severity scores according to the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1986). The reliability of the PISA and COALA has been reported to be good to excellent (Furukawa *et al.* 1995). The cohort was followed up monthly until treatment termination, 6-monthly thereafter up to 2 years, and annually up to at least 6 years until now. At each assessment the course of the illness was recorded for each month of the surveyed period.

The present paper focuses on the relapse of the subset of the cohort who were diagnosed as suffering from unipolar major depressive disorder according to DSM-IV (American Psychiatric Association, 1994). We defined recovery from a major depressive episode in accordance with the NIMH CDS definition (Keller *et al.* 1982*b*) as 2 consecutive months with no more than one or two mild depressive symptoms. After recovery, patients were considered to have relapsed into an affective disorder when they met the DSM-IV criteria for major depressive episode, manic episode, hypomanic episode. In addition, if they did not yet meet the criteria for major depressive episode but had more than two symptoms, or had only one or two symptoms that were graver than mild degree, for a month, they were considered to have relapsed into a 'subthreshold' depressive episode. The duration of the well interval was counted from the beginning of the 2-month period required for judging recovery.

We used the statistical package SPSS for Windows 11.0 (SPSS Inc., 2001) to perform Kaplan–Meier analyses to depict survival curves of the state of recovery from major depressive episodes and Cox regression analyses for exploratory analysis of their predictors. A two-tailed alpha of 0·05 was considered statistically significant. In the initial phase of univariate exploratory analysis of the predictors, we did not adjust for multiple comparisons because we were looking for possible predictors. Once the candidate predictors emerged, we entered them together in multivariate analyses in order to adjust for confounding.

RESULTS

A total of 1843 patients were screened at the 23 participating centres between December 1992 and December 1995 (some centres 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. Of these, 95 met the DSM-IV criteria for major depressive disorder, either single episode ($N=67$) or recurrent ($N=28$). Fifty-six subjects (59%) were females and the mean age was 44·3 (S.D. = 15·2; range = 18 to 86). Fifty-eight (61%) were recruited in university hospitals, 25 (26%) in general hospitals and 12 (13%) in mental hospitals. The mean score for the 17-item HRSD upon study entry was 19·9 (S.D. = 8·6) and only 14 (15%) were in-patients upon study entry. The median length of the depressive episode before entry was 3 months (range = 2 weeks to 100 months). The major depressive disorder was superimposed on pre-existing dysthymia in five (5%).

We recorded recovery from major depression in 82 (86%) of our cohort. Five subjects never satisfied the recovery criteria for the 72 months of follow-up, one switched into mania and two into hypomania without any euthymic interval, one committed suicide at 7 months without ever attaining recovery, and four were lost to follow-up before recovery was ascertained. Of the 82 who had recovered by the 72 months of follow-up, 50 experienced a subthreshold relapse as defined above, 12 never experienced a subthreshold relapse, and 20 were lost to follow-up without ever reporting a subthreshold relapse: 31 experienced a full relapse as defined above; 19 never presented with a full relapse; and 32 were lost to follow-up without ever recording a full relapse.

Fig. 1 shows the cumulative probability of remaining well from the end of the index episode to the beginning of the prospective subthreshold depressive episode for those who attained

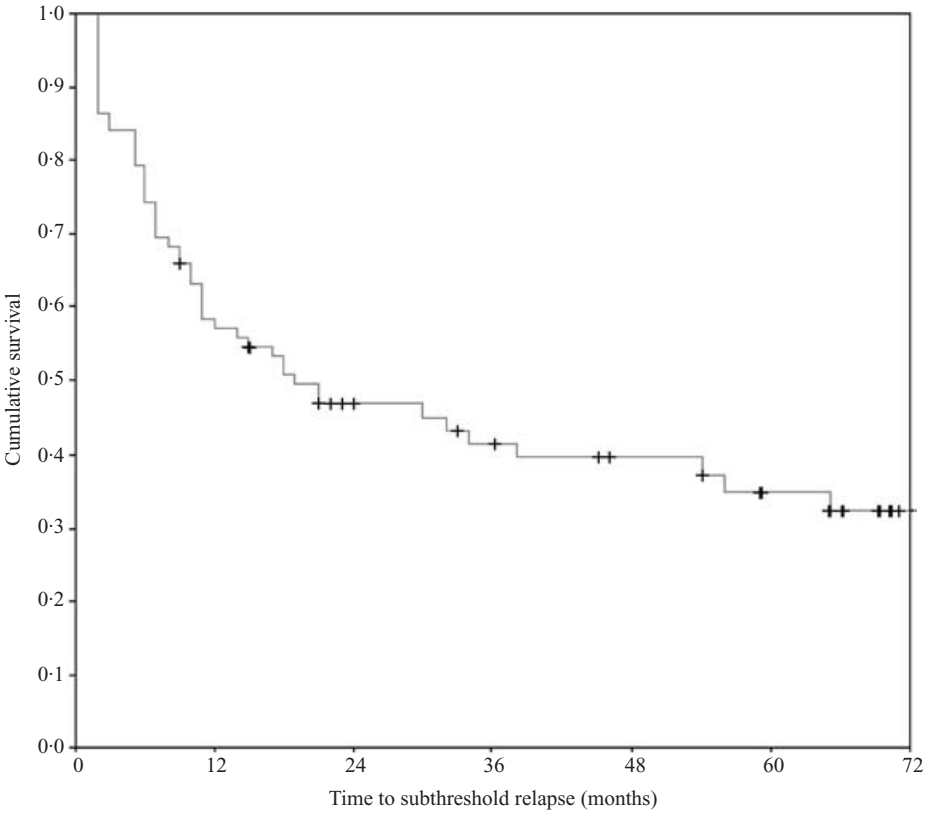

FIG. 1. Cumulative probability of remaining well from the end of the index episode to the beginning of the prospective subthreshold depressive episode.

recovery during follow-up ($N=82$): 74% (95% CI, 65 to 84%) remained completely well at 6 months; 57% (46 to 68%) at 1 year; 47% (36 to 58%) at 2 years; and 35% (23 to 47%) at 5 years. Thirty-two per cent (20 to 44%) were remaining without any subthreshold recurrence at 72 months of follow-up. The median duration of well-interval from the end of the index episode to the beginning of the subthreshold depressive episode was 19·0 months (95% CI, 2·4 to 35·7 months). The mean duration with upper limit of 72 months was 34·3 months (27·6 to 41·0 months).

Fig. 2 depicts the survival curve of remaining well from the end of the index episode to the beginning of the prospective major depressive episode ($N=82$): 94% (89 to 99%) remained without full relapse/recurrence up to 6 months; 79% (70 to 88%) up to 12 months; 70% (60 to 80%) up to 24 months; and 58% (46 to 70%) up to 60 months. Only 45% (32 to 58%) had relapsed by 72 months of follow-up. Therefore, the median duration of well interval from the end of the index episode to the beginning of the prospective major depressive episode was not ascertained, but it is likely to be $\geqslant 6$ years. The mean duration with upper limit of 72 months was 49·7 months (43·4 to 55·9 months).

We next performed exploratory analyses of predictor variables, measured at treatment commencement and after recovery from index episode, of the time to subthreshold relapse and full relapse. Baseline variables entered into univariate Cox regression analyses included age, gender, education, marital status, treatment setting, in-patient status, length of the index episode before treatment, single episode or recurrent, HRSD scores during the worst week of the index episode and during the week preceding the intake interview, endogenicity as defined by

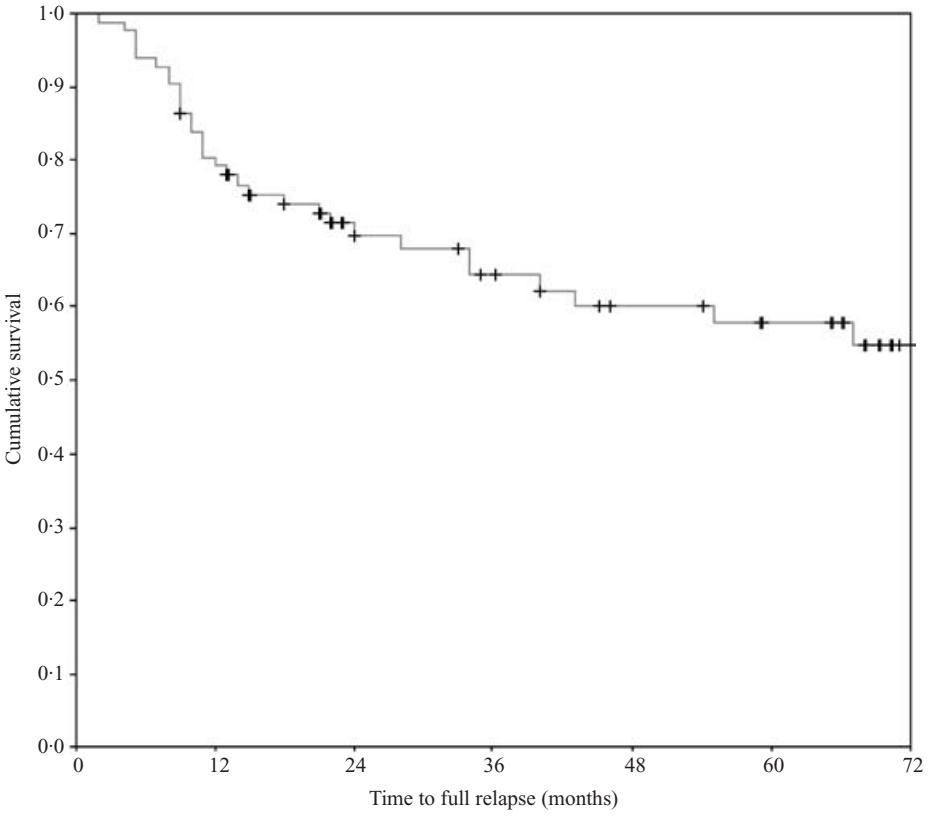

FIG. 2. The survival curve of remaining well from the end of the index episode to the beginning of the prospective major depressive episode.

DSM-IV, Axis I co-morbidity and family history of major depression, and employment for the preceding past 3 years; variables measured after recovery from index episode included the HRSD score at recovery, and the treatment received at recovery (in imipramine equivalents) and the treatment received at relapse, either subthreshold or full.

With regard to subthreshold relapse, three variables emerged as predictors that were statistically significant at P level of 0·05: (*i*) treatment setting (those seen at mental hospitals were more likely to relapse than those visiting general hospitals: OR = 3·0, $P = 0{\cdot}003$); (*ii*) HRSD score at recovery from index episode (those scoring $\geqslant 2$ were more likely to relapse than those scoring 0 or 1: OR = 2·7, $P = 0{\cdot}008$); and (*iii*) amount of antidepressants being prescribed at subthreshold relapse (for every 25 mg increase in imipramine or equivalent prescribed, OR = 1·3, $P = 0{\cdot}011$; actually patients were receiving, on average, 27 mg/day of imipramine equivalents, when they relapsed). After entering these three variables at the same time into Cox regression, only the HRSD score at recovery remained statistically significant: OR for treatment-setting became 1·4 (95% CI, 0·38 to 5·0, $P = 0{\cdot}63$); that for HRSD score became 2·6 (1·1 to 6·3, $P = 0{\cdot}03$); and that for antidepressant became 1·3 (1·0 to 1·7, $P = 0{\cdot}10$). With regard to full relapse, no predictor variable emerged.

DISCUSSION

The relapse of major depression appears to be more infrequent and distant than previously reported. By adopting essentially identical criteria, previous studies reported the time to relapse to be around 30 months (Maj *et al.* 1992;

Mueller *et al*. 1999; Kennedy *et al*. 2003). We found that, among our cohort who were less chronic and less recurrent, the median of the well interval from the end of the major depressive episode to the beginning of next prospective episode was likely to be >72 months. Once remitted, only 21% of the cohort relapsed by 12 months, 30% by 2 years and 42% by 5 years. Our initial suspicion that the foregoing studies were biased towards sicker people was borne out.

Such a rosy picture, however, fails to capture the full consequences of major depression. Examining the full weekly course over 12 years of the NIMH Collaborative Depression Study, Judd and his colleagues pointed out that subthreshold depressive states, i.e. with some depressive symptoms but not meeting the full episode threshold, were more common than the full syndromal states (Judd *et al*. 1998*b*), and these subsyndromal states are associated with substantial functional impairments (Wells *et al*. 1989; Furukawa *et al*. 2001). In this sense the time to subthreshold relapse after recovery would perhaps be closer to what clinicians and patients would understand with the term 'well interval'. The survival curve of subthreshold relapse after recovery was quite different from that of full relapse and subthreshold relapse was ascertained considerably earlier than full relapse.

Only a few prognostic factors emerged in our *post hoc* exploratory analyses. Our finding that the residual symptoms at time of remission predicted subsequent relapse is in line with some previous studies (Judd *et al*. 1998*a*). On the other hand, we could not replicate the predictive value of previous episodes.

Possible weaknesses of the present study are as follows. First and foremost, sample size of our study may be too small to detect some important but infrequent predictive factors. Secondly, the transportability of these Japanese findings to other medical systems may not be straightforward. However, the current cohort appears to be comparable to those seen in primary care settings in many countries, because we recruited first-visit patients with untreated depressive episodes and because Japan does not have the family doctor system and psychiatrists are often the first-line doctors that people consult when they realize that their problems are mental rather than physical. Thirdly, the effect of the treatment on the course of the disease could not be determined in the present study as this was a naturalistic study without any control over the treatment provided. Whether adequate antidepressant treatment after recovery could ameliorate the prognosis of patients with this severity of depression is an empirical question and a recent comprehensive meta-analysis shows that the answer is likely to be positive (Geddes *et al*. 2003).

On the other hand, the greatest strength of our study was perhaps the wide spectrum of clinical settings represented in our cohort. Although the 23 participating centres 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 in-patients. The study is, therefore, subject less to referral filter bias than, for example, studies conducted on in-patients at one or a few academic institutions. Secondly, we performed prospective, serial assessments repeated at least every 6 to 12 months with reliable semi-structured interviews and applied predefined operational criteria to determine recovery, relapse and subthreshold relapse. Our study was therefore able to minimize detection biases due to inaccurate recall or inconsistent application of decision criteria. Finally, the follow-up rate was satisfactory.

In conclusion, the time to relapse among patients who recovered from a major depressive episode may be much longer than previously estimated, when we look at wider spectrums of clinical populations. However, even among this cohort, the cumulative percentage of syndromal relapse nears 50% and that of subthreshold relapse is 65% by the 5th year. Only half of the patients can expect to remain virtually symptom-free for >19 months after recovery from the depressive episode.

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