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ORIGINAL PAPER

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Recurrence of bipolar disorders and major depression

A life-long perspective

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Abstract *Objective* It is not known whether the risk of recurrence declines with time in bipolar disorders and in major depression. This study describes the life-long recurrence risk of bipolar I, bipolar II and major depressive disorders. *Method* 160 bipolar-I, 60 bipolar-II and 186 depressive patients hospitalised between 1959 and 1963 were followed up every five years from 1965 to 1985. The course prior to the index hospitalisation was assessed in retrospect. The recurrence risk was computed by the multiplicative intensity model (Aalen et al. 1980). *Results* The cumulative intensity curves for the transition from states of remission to new episodes remained linear over 30 to 40 years after onset, indicating a constant risk of recurrence over the life-span up to the age of 70 or more. The recurrence risk of bipolar disorders (0.40 episodes per year) was about twice that of depression (0.20 episodes per year); BP-II disorders had only a slightly higher recurrence risk than BP-I disorders. There were no significant gender differences in the course of either bipolar or depressive disorders. *Conclusion* If long-term trials confirm its efficacy, these results support lifelong prophylactic treatment of severe types of mood disorders.

Key words bipolar disorder · depressive disorder · follow-up · recurrence

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Introduction

Currently many patients with mood disorders receive long-term medication. If the patient remains well during maintenance treatment, sooner or later the question arises whether medication should be titrated and finally stopped or whether it should be continued, and if so for how long. Or, is the natural history so poor and the treatment so effective that the medication should be given lifelong?

Controlled cessation trials have demonstrated high recurrence risks (review of Suppes et al. 1993) although they cannot distinguish between rebound effects and natural history of the disorder.

New, large, case-register studies by Kessing et al. (1999, 1999, 2001, 2001) based on the recurrence of hospitalisations nation-wide in Denmark found a progressive deterioration in the course. The merit of Kessing's analysis, using a frailty model, is that it takes the intra-individual course into account (Kessing and Andersen 2001). Turvey et al.'s (1999) 10-year prospective naturalistic study found that the second cycle of bipolar disorders was clearly shorter than the first, the third a little longer than the second, but the fourth and fifth cycles were again shorter. In a recent re-analysis of our long-term follow-up study, using less sensitive non-parametric statistics, we found in bipolar disorders a systematic shortening only between cycle 1 and 2; later there was no clear trend (Angst and Sellaro 2000).

A recent review of two centuries' literature on the natural history of bipolar disorder concluded that bipolar disorder has always been highly recurrent and considered to have a poor prognosis, and that the findings of modern follow-up studies are closely compatible with those of studies conducted before the introduction of modern antidepressant and mood-stabilising treatments (Angst and Sellaro 2000). But what is the long-term prognosis of recurrent mood disorders in general?

The main question is whether multiple past episodes are a risk factor for future recurrences and whether the

risk of recurrence remains constant, without great changes in the long term, or whether it may decrease spontaneously, especially in the elderly. The question is of practical importance for treatment decisions and is also justified because the cycle length (time from onset of one episode to the onset of the next) is known to shorten at the beginning of mood disorders; the second cycle is usually shorter than the first (Angst and Sellaro 2000). Our original assumption that this shortening would continue over many cycles and finally reach a certain limit was questioned by several studies: Fukuda et al. (1983), Coryell and Winokur (1992), Solomon et al. (1995), Kessing et al. (1998); the controversy was summarised in a review by Suppes et al. (2000) and in the very comprehensive review of Marneros and Brieger (2002)).

From a methodological point of view it is important to control for the number of episodes, because patients with a history of multiple episodes tend to have shorter cycles/intervals in the future than those with a few; therefore one should break down the total sample into cohorts stratified by the total number of episodes (Slater 1938). One can also base analyses on intra-individual logarithmic means of cycle length because both length of episodes and cycles are log-normally distributed (Angst and Weis 1967).

So far, most studies of the recurrence risk of mood disorders have been descriptive, counting the number of recurrences as a function of follow-up duration or number of episodes per year (Marneros et al. 1988). The latter authors found an annual frequency of episodes of 0.23 for bipolar and 0.12 for depressive disorders (Marneros et al. 1991). The counting method does not take into consideration the fact that the patient is only at risk of recurrence during the inter-episode period, and therefore underestimates the force of morbidity.

A further methodological progress came with the paper of Lavori et al. (1996) which introduced survival analysis for repeated events into psychiatry. In their 10-year prospective study of 173 bipolar and 555 depressive patients the authors found a persistence risk of well to ill transitions (recurrences) in both groups and estimated that the cumulative intensity was about double that in the bipolar than in the depressed group. They concluded that the transitions continued in both groups, suggesting that over ten years the two disorders neither "burn out" nor "spiral into chronicity".

The most recent methodological progress was introduced by Kessing et al. (1999, 2001), who applied frailty models (Andersen et al. 1993) taking the intra-individual course into account, and by Solomon et al. (2000), both of whom showed progressive recurrence with increasing number of episodes.

The purpose of this first of two papers is to analyse the risk of recurrence of depression and bipolar disorders over a period of decades on the basis of a life-long follow-up and to answer the question: is recurrence constant or does it increase or decrease over the life-span?

Methods

Sample and diagnoses

The sample consists of 160 bipolar-I patients, 60 bipolar-II patients and 186 unipolar depressive patients, who were admitted between 1959 and 1963 to the Zurich University Psychiatric Hospital with a diagnosis of mania, endogenous depression, endo-reactive depression, manic-depressive disorder, or affective disorder with mood-congruent or mood-incongruent psychotic features (hallucinations or delusions) including schizo-affective disorder. The diagnoses of bipolar disorder took the lifetime course into account. Of the patients 61 % met criteria for psychosis over lifetime, which underlines the fact that we are dealing with a seriously ill hospitalised group (Angst and Preisig 1995a). The distinction between mania and hypomania and between severe and mild depression was made on the basis of the need for hospitalisation, as originally suggested by Dunner, Fleiss and Fieve (1976) in their definition of bipolar II disorder. The softer, DSM criteria for BP-II disorders could not be applied in retrospect using all available sources (records, reports of doctors, relatives and the patients). Bipolarity was assumed as soon as hypomania occurred for a few days, regardless of whether it seemed to be drug-induced or not. Early onset was defined by an onset before the age of 40, late onset at the age of 40 or more. Follow-ups were carried out in 1963, 1965, 1970, 1975, 1980 and 1985; data on mortality were collected in 1991 and 1997 (Angst et al. 2002). The course was assessed in retrospect by family doctors' reports, records of in- and outpatient services and reports by patients and significant others. A detailed description of the sample, all subjects of which qualified also for modern criteria for major depression can be found in Angst and Preisig (1995a). In addition extensive descriptive data on the course of this sample were published by Angst and Preisig (1995b) and will not be summarised again in this paper, which will focus exclusively on the recurrence risk.

Measures

Length of episodes was measured in months and weeks and length of cycles in months. Biphasic episodes shifting for instance from depression to hypomania were counted as one episode. The time spent in illness was calculated by duration of illness divided by length of observation since onset. Outcome was measured at the last interview in 1985 by the Global Assessment Scale (GAS) of Endicott et al. (1976). Two ratings were made in cases of an actually running episode: a GAS rating of the actual state and one before the last episode. Residual states were defined by GAS scores and duration in years. Chronicity was defined as the last episode without recovery over at least two years.

Statistics

The recurrence risk was computed by the multiplicative intensity model (Aalen et al. 1980), a method which was introduced for this purpose into psychiatry by Andersen and Rasmussen (1986) and Lavori et al. (1996). The computer program was provided by Lavori. All computations were based on follow-up in years since the first onset of the disorders.

For Table 1 chi square statistics were used for categorical data and non-parametric analyses of variance (Kruskal-Wallis test) were applied for continuous measures.

Results

Descriptive course characteristics of the samples

The subgroups consisted of 186 unipolar major depressives, 160 bipolar I and 60 bipolar II patients; the latter group was 87 % female (Table 1).

Table 1 Characteristics of the sample

	MDD	BP-II	BP-I	Test statistic	df	P
N	186	60	160			
	%	%	%	χ^2		
Male	22.6	13.3	40.6	21.6	2	< 0.001
Early onset (< 40 years)	38.2	61.7	76.3	51.5	2	< 0.0001
Dead by 1985	43.6	41.7	41.3	4.7	4	0.32
Suicide by 1985	13.4	6.7	8.1	3.6	2	0.16
Psychotic symptoms	50.5	43.3	78.8	37.5	2	< 0.001
	Median	Median	Median	Kruskal-Wallis		
Age of onset	46.0	37.0	26.5	63.9	2	< 0.001
Age at follow-up	70.5	72.5	65.0	20.6	2	< 0.001
# episodes	4.0	10.5	10.0	119.7	2	< 0.001
# episodes per year	0.2	0.3	0.4	45.5	2	< 0.001
Length of episodes (months)	5.4	4.0	4.2	10.1	2	0.006
Length of cycles (months)	56.5	36.4	33.0	46.5	2	< 0.001
Total length of observation (months)	291.5	362.0	387.0	38.2	2	< 0.001
Duration of illness	211.5	313.5	338.5	52.3	2	< 0.001
Time spent in illness (mean %)	21.0	19.0	19.0	5.0	2	0.08
	%	%	%	χ^2		
Outcome				25.1	10	0.005
GAS ≥ 61 & ≥ 5 years	25.8	18.3	15.1			
GAS ≥ 61 & < 5 years	25.3	35.0	22.1			
GAS 1–60 & ≥ 5 years	9.1	6.7	8.2			
GAS 1–60 & < 5 years	14.5	18.3	32.7			
Chronic	11.8	15.0	13.8			
Suicide	13.4	6.7	8.2			

GAS Global Assessment Scale (Endicott et al. (1976–7997)

At the last follow-up in 1985 BP-I subjects were significantly younger, but they had an earlier age of onset than the other two groups, which also explains their long observation time and duration of the illness. BP-II patients took an intermediate position in age of onset and length of observation. A total of 40 % of patients had died; suicide occurred slightly (n. s.) more often among MDD than bipolar patients. Time spent in illness was about 20 % of lifetime after onset and did not vary between the groups.

The course variables demonstrate that the two BP subgroups took a similar course but differed clearly from MDD. The two BP groups had a much higher total number of episodes and annual episode frequencies and shorter episode and cycle lengths.

The outcome, assessed by the GAS, was best in MDD and worst in BP-I patients, whereas BP-II cases took an intermediate position.

Bipolar disorder vs. depression

Fig. 1 shows the cumulative intensity curves of the transition from states of remission to new episodes. The data can be interpreted over 40 years of follow-up; during that long period there was no substantial change in the recurrence risk indicated by the linear lines in both bipolar and unipolar depressive disorders. The cumulative intensity is much higher in bipolars, indicating a doubled recurrence risk.

Bipolar I vs. Bipolar II disorders

Fig. 2, which shows the cumulative risk with 95 % confidence intervals, demonstrates a slightly but significantly higher recurrence risk of BP II versus BP I disorders, persisting over decades.

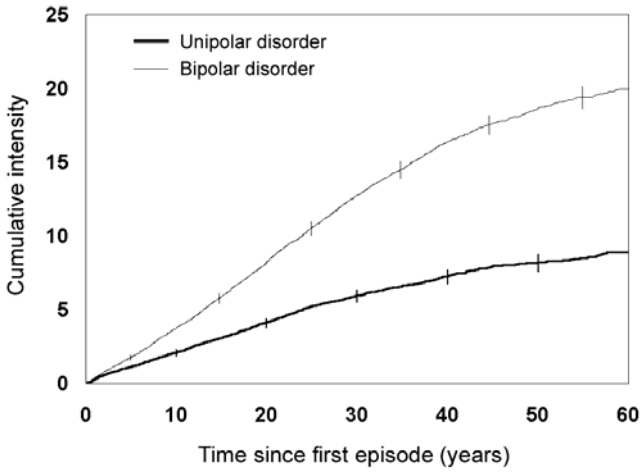

Fig. 1 Bipolar disorder vs. unipolar disorder (vertical bars indicate 95 % confidence intervals)

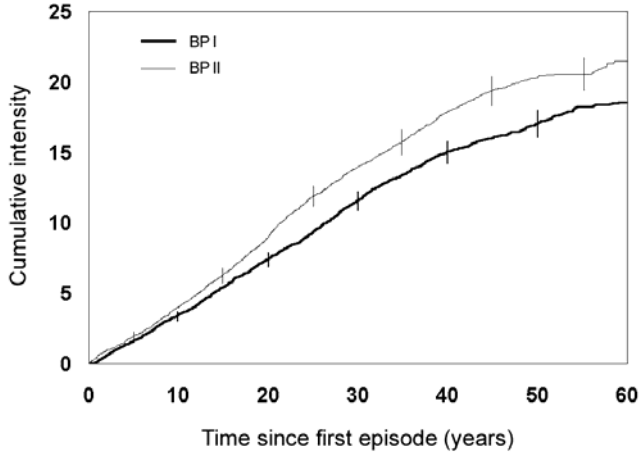

Fig. 2 Bipolar I disorder vs. bipolar II disorder (vertical bars indicate 95% confidence intervals)

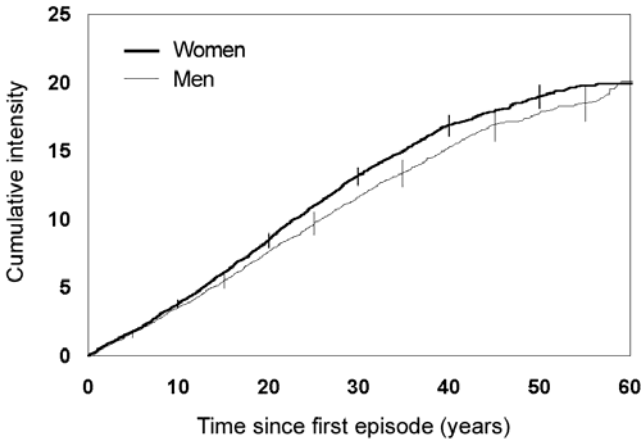

Fig. 3 Bipolar disorders divided into men and women (vertical bars indicate 95% confidence intervals)

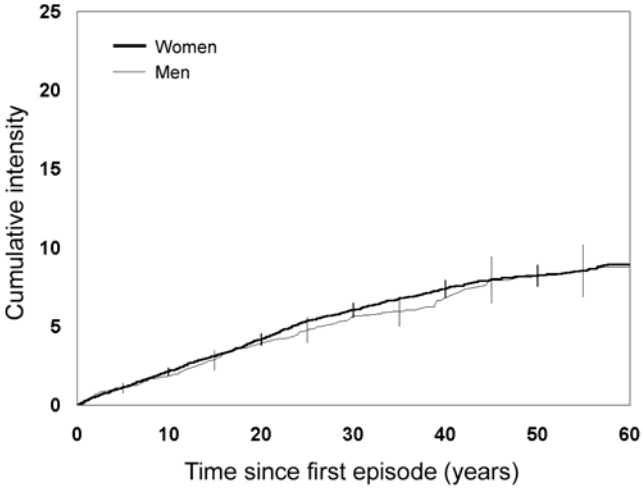

Fig. 4 Major depressive disorders

Bipolar disorder and gender

Fig. 3 shows the transitions from healthy to ill for both women and men with bipolar disorder; women tend to have a slightly higher recurrence risk than men, but the two curves do not differ significantly.

Depression and gender

Fig. 4 shows no evidence of a gender difference in the recurrence risk of severe major depressives. This remained true when the patients were in their sixties and seventies.

Age of onset and recurrence

For this analysis early onset (before the age of 40) and late onset disorders (bipolars and depressives) were considered; no significant differences in recurrence were found (results not shown).

Discussion

In practice, the decision how long to continue a maintenance medication has to be made on the basis of two questions: 1) what is the naturalistic prognosis of the specific mood disorder from which the patient is suffering? and 2) how severe were the individual previous history of the illness and its social consequences before the prophylactic medication was started? This paper can only contribute to answering the first question.

Our data confirm again that the recurrence risk of bipolar disorders is about double that of major depression. Most important is the replication of a constant recurrence risk first demonstrated convincingly by Lavori et al. (1996) over a period of ten years and our finding that this period can be extended to at least 40 years of

follow-up. It is of further interest that the recurrence risk remains constant over the life-span in both bipolar disorder and depression, although the two groups differ as regards the magnitude of that risk. We found no clear gender difference either in recurrence or between early and late onset cases.

A further important finding is the great similarity between the recurrence risk of BP-I and BP-II disorders, although the latter have a slightly poorer prognosis. The recurrence risk in BP-II disorder was markedly higher than in major depressive disorders, pointing to the paramount importance of distinguishing BP-II from unipolar MDD. There is new evidence for the assumption that BP-II disorders are very frequently misdiagnosed as MDD even by psychiatrists (Hantouche and Akiskal 1998) and that the current diagnostic criteria for hypomania may be too strict (Angst 2002).

Our findings that the risk of recurrence remains constant are in line with survival analyses of the mortality of the same patient samples, which showed that the suicide risk in mood disorders persisted over decades up to the age of about 70 (Angst et al. 2002).

This study has certain limitations in that it deals with severe, hospitalised cases of mood disorders and follow-up was only possible at five-year intervals. Between the follow-ups the course was assessed in retrospect. The strength of the study is that it is a lifelong follow-up.

In conclusion our finding of a lifelong constant recurrence risk of mood disorders together with the results of Kessing et al. (1999) and Solomon et al. (1995) indicating a progression of the disorder with increasing number of episodes suggests the continuing need for anti-recurrence prophylaxis over the entire lifespan. Whether this need for secondary prevention is met by current medications and psychosocial interventions is a question for appropriately targeted clinical trials.

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