Historical Perspectives and Natural History of Bipolar Disorder

Jules Angst and Robert Sellaro

A review of two centuries' literature on the natural history of bipolar disorder, including modern naturalistic studies and new data from a lifelong follow-up study of 220 bipolar patients, reaches the following conclusions: the findings of modern follow-up studies are closely compatible with those of studies conducted before the introduction of modern antidepressant and mood-stabilizing treatments. Bipolar disorder has always been highly recurrent and considered to have a poor prognosis.

Bipolar patients who have been hospitalized spend about 20% of their lifetime from the onset of their disorder in episodes. Fifty percent of bipolar episodes last between 2 and 7 months (median 3 months). The intervals between the first few episodes tend to shorten; later the episodes return at an irregular rhythm of about 0.4 episodes per year with high interindividual variability. Switches from mania into mild depression and from depression into hypomania were frequently reported in the 19th century and the first half of the 20th.

Antidepressant and antimanic drugs have to be given as long as the natural episode lasts. Given the poor outcome of bipolar disorders found in naturalistic follow-up studies and our lifelong investigation, intensive antidepressant, antimanic, and mood-stabilizing treatments are required in most cases. Despite modern treatments the outcome into old age is still poor, full recovery without further episodes rare, recurrence of episodes with incomplete remission the rule, and the development of chronicity and suicide still frequent. Biol Psychiatry 2000;48:445–457 © *2000 Society of Biological Psychiatry*

Key Words: Bipolar disorder, natural history, course, recurrence, outcome

Introduction

This article briefly reviews the natural history of bipolar disorder, giving special weight to historical studies before the era of antidepressants; integrates the results of modern naturalistic follow-up studies; and from our own findings 1) reanalyzes data from an early multicenter study (Angst et al 1968b, 1973) and 2) includes some new data from our lifelong Zurich follow-up study (Angst and Preisig 1995a, 1995b). The article focuses mainly on episodes and recurrence and, to a lesser extent, outcome; it does not deal with rapid cycling and seasonal depression. Recent reviews of the course of bipolar disorder have been published by Lavori et al (1984), Keller (1987), Goodwin and Jamison (1990), Coryell and Winokur (1992), Verdoux and Bourgeois (1995), Kessing et al (1998), Goldberg and Harrow (1999), Marneros (1999), and Bourgeois and Marneros (in press).

The Concept of Bipolar Disorder

We owe the categorization of bipolar disorder as an illness to Falret, who in 1851 and 1854 on the basis of longitudinal observations developed the entity of "folie circulaire" (circular madness), defined by manic and melancholic episodes separated by symptom-free intervals. In 1854 Baillarger used the term *folie à double forme* to describe cyclic (manic–melancholic) episodes (Pichot 1995; Ritti 1879). Kraepelin called such cyclic episodes "double attacks." In both French diagnoses the prognosis was considered to be "desperate, terrible and incurable" (Bourgeois and Marneros, in press). Circular illness was described by most authors as a recurrent condition; it became the prototype of the larger group of periodic psychoses embracing periodic mania, periodic melancholia, and periodic cyclic disorders (Ballet 1903; Mendel 1881; Pilcz 1901; Ziehen 1902, 1907).

The Concept of Mixed States

The history of the concept of mixed states has been extensively studied by Marneros (in press): what we today call "mixed states" were probably already known at the beginning of the 19th century and named "mixtures" (*Mischungen*) by Heinroth in 1818 and "middle forms" (*Mittelformen*) by Griesinger (1845). Guislain (1852) gave clear descriptions of different syndromes of mixed states. The history of bipolar disorder by Haustgen (1995) traces the term *mixed states* to J.P. Falret's son Jules Falret (1861).

Very influential in this field was Weygandt (1899), who worked with Kraepelin and whose monograph distinguished three forms of mixed states: manic stupor, agitated

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melancholia (depression with flight of ideas and agitation), and unproductive mania (elated mood, increased motor activity, and inhibition of thinking). Kraepelin's (1899) textbook descriptions of mixed states were founded on Weygandt's monograph. Further progress was made by Rehm's monograph (1919, 113), which classified mixed states systematically on the basis of the permutations of the three elements that had been defined by Kraepelin: thought disorder, mood, and psychomotor activity (identified as a, b, and c for mania and as A, B, and C for depression).

Kraepelin's Manic–Depressive Insanity

At the turn of the 19th century Kraepelin's unifying approach to the classification of mood disorders (1899) resulted in bipolar disorders being subsumed within manic–depressive insanity (MDI), a broad group that included single-episode and recurrent depression. Kraepelin (1913, 1183) was later himself to raise the possibility of the heterogeneity of MDI. Unlike the French concepts, Kraepelin's MDI had a good prognosis and did not develop into severe dementia, although Kraepelin conceded the existence of mild residual states after recovery from the episodes themselves (*Schwächezustände;* Kraepelin 1913, 1349) and of mild fluctuations between episodes. Kraepelin considered periodicity to be unimportant for the diagnosis (Pilcz 1901). As a consequence of Kraepelin's unification of affective disorders, research on their course frequently failed to distinguish between depression, mania, and bipolar disorder (Bratfos and Haug 1968; Fuller 1935; Paskind 1930; Pollock 1931a, 1931b, 1931c; Poort 1945; Rennie 1942; Tomasson 1947).

Notable contemporary authors nevertheless disagreed with Kraepelin's unitarian approach, and their studies of the natural history of affective disorders maintained the distinction between mania, depression, and bipolar disorder (Ballet 1903; Pilcz 1901; Ziehen 1902, 1907). This data on the course of bipolar disorder collected in the 19th century and the first half of the 20th, before the introduction of modern antidepressants and mood stabilizers, is of special value in that it represents the disorder's untreated natural history.

Onset of Bipolar Disorder

The dating of the age of onset is to a certain extent unreliable because it is usually retrospective and dependent on insecure recall. Bipolar disorder begins about 10 years earlier than recurrent depression, as shown by a review of the literature (Angst 1988). Earlier studies indicated a mean age of 28 to 33 years; epidemiologic and newer clinical studies show that bipolar symptoms start frequently in adolescence (Weissman et al 1988) and that manic episodes manifest usually in the early 20s (Fogarty et al 1994).

Periodic Mania and Switches of Polarity

There is considerable interest today in data on the course of single and multiple episodes, which can answer questions about the psychopathology, duration, and frequency of episodes; the syndromal stability over lifetime; and the frequency with which initial major depression develops into bipolar disorder. Today the switch of an episode from depression to hypomania is often assumed to be drug induced, but the phenomenon was already very common as "reactive hyperthymia" before the introduction of antidepressants.

A century ago the concept of periodic mania was well known and the diagnosis much more frequent, quite simply because it was applied to cases that today would be considered bipolar disorders. For instance, an initial depressive syndrome cycling into a manic episode, although frequently observed, was not considered an indication of bipolarity (Mendel 1881; Ziehen 1902). Similarly, "postmelancholic reactive hyperthymia" with clear hypomanic symptoms was compatible with the diagnosis of pure periodic melancholia (Ziehen 1907, 26).

Mania switching into depression was likewise very commonly reported as "reactive depression" (Ziehen 1902, 546, 554; Wernicke 1906, 355). Postmanic depression lasted a few days or a few weeks according to Wernicke (1906, 355). Mild depression was observed preceding or terminating manic attacks in most of the 128 manic patients studied by MacDonald (1918).

Modern naturalistic and treatment studies have also found that mania frequently cycles into depression: the rates of cycling observed in follow-up studies over 8 weeks vary from 17% (Tohen et al 1990) to 30% (Keller et al 1986a). Our earlier retrospective record study of 300 manic patients (admitted between 1920 and 1970) found that 21% of manic episodes cycled into depression, a rate that did not change significantly during the intervening decades (Angst 1987).

In a retrospective record study, depression switching into hypomania was found in 29% of bipolar patients hospitalised between 1920 and 1959 (Angst 1987).

Diagnostic Change from Depression to Bipolar Illness

The syndromal course over lifetime has been little investigated. It was frequently assumed that mania was predominant in earlier years and depression in the second half of life. Kinkelin (1954) followed-up 146 hospital first admis-

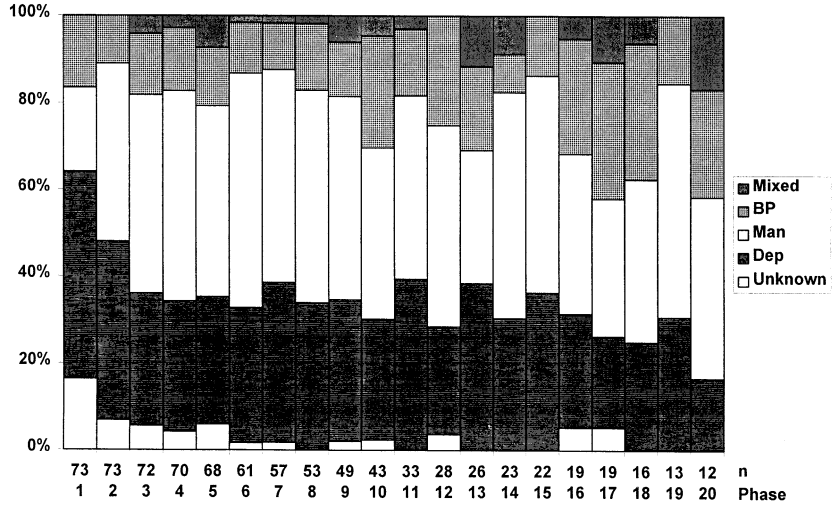

Figure 1. Proportion of syndromes across 20 episodes in male subjects. BP, bipolar; Man, mania; Dep, depression.

sions suffering from MDI (1929–1947) until 1948 in a study covering an average of 21.8 years of the total course of the disorder. Of the 146 cases, 125 began with depression and 21 with mania. During the follow-up period 36 (28.8%) of the 125 depressive patients developed manic episodes, a figure that would correspond to a diagnostic change from depression to bipolar illness of 1.3% per year of observation. Marneros et al (1991b) reported that the initial diagnosis of depression remained stable in 79% of cases over 27 years. In our preponderantly prospective study we found a rate of diagnostic change from depression to hypomania/mania of about 1% per year (Angst and Preisig 1995a). Coryell and colleagues' (1995a) intensive prospective follow-up study of 381 depressive subjects over 10 years found that 10.2% developed into mania (5.2%) and hypomania (5.0%), which also corresponds to a 1% change per year of observation.

In their monograph, Marneros et al (1991a) found that mania frequently developed into schizomania or mixed states.

Syndromal Stability of the Course

New data from our Zurich follow-up study confirmed a major gender difference in the psychopathology of bipolar patients over the first 20 episodes (Angst 1978): female subjects manifested significantly more depressed episodes and male subjects more cyclic episodes (mania and depression), whereas pure manic and mixed episodes were equally frequent in both genders (Figures 1 and 2). The syndromal proportions were found to remain remarkably stable over 20 episodes (Angst and Weis 1967), which also means, for instance, that aging brings no increase in the depressive component of bipolar illness.

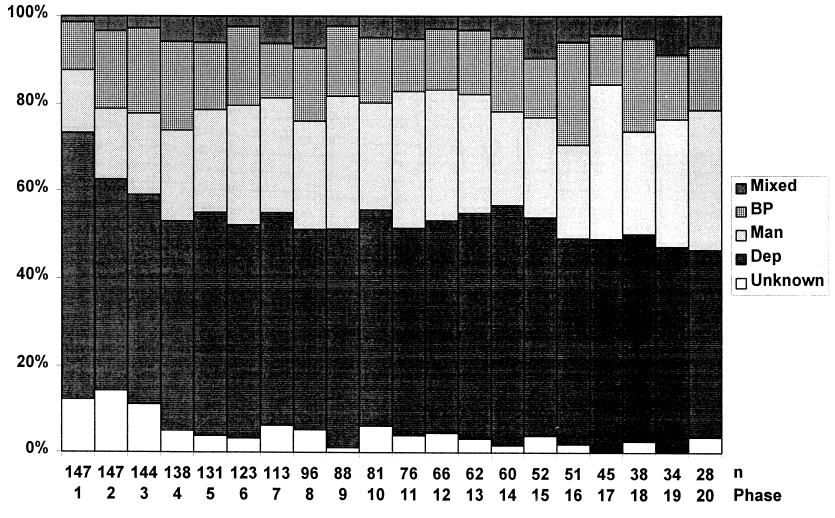

Figure 2. Proportion of syndromes across 20 episodes in female subjects. BP, bipolar; Man, mania; Dep, depression.

Table 1. Length of Episodes (Months) of Patient Samples

	Mean	Median	Q_1	Q_3
Mendel (1881)		5–6	3–4	6–7
Kraepelin (1913)	6–8			
Panse (1924)	7			
Wertham (1929)		4–6	2–4	8–10
Rennie (1942)	3.5[a]–5.8[b]			
Kinkelin (1954)	3.5–8.4			
Angst and Preisig (1995a)	4.3[c]	3[d]	2	5

[a]First episode.
[b]Third episode.
[c]Mean after logarithmic transformation.
[d]Median of Table 2.

Natural Length of Episodes

Valuable data on the natural length of episodes were published before the introduction of effective treatments (Table 1).

Mendel (1881, 155) reported data on the length of manic episodes ($N = 43$), from which a median duration of 5–6 months ($Q_1 = 3–4$ months, $Q_3 = 6–7$ months) can be computed; Mendel found only one episode which lasted 10–12 months and one over 1 year. Kraepelin (1913) stressed the great variability in episode length but estimated that most episodes lasted between 6 and 8 months.

Panse's follow-up study (1924) of 205 hospitalized bipolar patients found an identical mean length of 7 months for manic and depressive episodes.

Wertham (1929) provided the most conclusive data on episode length with his investigation of 1000 male and 1000 female first admissions for mania. From his published histograms we can today estimate the length of episodes as lognormally distributed, with a mode between 2–4 months and a median duration of 4–6 months ($Q_1 = 2–4$ months, $Q_3 = 8–10$ months). There was no follow-up; most of these manic cases may therefore have been bipolars.

Rennie (1942) found that there was a lengthening of repeated manic episodes, with the first episode lasting 3.5 months, the second 5.2 months, the third 5.8 months, and the fourth and fifth even longer. Rennie ascribed this to a prolonging effect of aging, since before the age of 45 episode length remained constant.

Unlike Rennie, Kinkelin (1954), in a longitudinal study, found no systematic change in episode length between the first and seventh episodes. Among 347 bipolar patients the mean length of depressive episodes varied impressively from 3.5 to 8.4 months, and of manic episodes from 4 to 11.6 months. Kinkelin, too, concluded that later episodes tended to be longer.

In the NIMH Collaborative Study on the Psychobiology of Depression Clinical Studies (Keller et al 1986a) survival analysis demonstrated that mixed or cycling episodes were slower to recover than pure depressed or pure manic episodes. Perugi et al (1997) also reported that episodes involving mixed states lasted significantly longer (mean 13.4 months) than manic episodes (8.8 months).

The computation of the length of episodes has to take into account their lognormal distribution (Angst and Weis 1967) and to control for the individual number of episodes (Slater 1938). In patients experiencing multiple cyclic (bipolar) episodes, the episodes tend to be slightly shorter, whereas in general the latest episode tends to be longer because of the development of chronicity in some cases, as found in our multicenter study on the course of mood disorders (Angst et al 1973).

In the Baltimore Epidemiologic Catchment Area Follow-Up Eaton et al (1997) found a median length of episodes of approximately 8 to 12 weeks; this is shorter than that reported in treated populations, but similar to the median episode length of 8 weeks reported in a community study of adolescents in Oregon (Lewinsohn et al 1994).

The most recent data from the Zurich follow-up study (Angst and Preisig 1995a) showed a mean episode length of 4.3 months ($s = 5.44$) calculated on the basis of intraindividual means. The median length of episodes is not obviously dependent on the total number of episodes—see Table 2, where subgroups with two to 10 episodes are computed separately (following Slater's [1938] suggestion). On the whole, the median length of episodes in bipolar illness (on the basis of individual medians) was 3 months ($Q_1 = 2$ months, $Q_3 = 5$ months). There is a difference in length dependent on psychopathology. Pure manic and pure depressive episodes lasted 3 months ($Q_1 = 2$, $Q_3 = 5$), as did mixed episodes ($M = 3$; $Q_1 = 2$, $Q_3 = 7$); in contrast, cyclic episodes lasted almost 50% longer ($M = 4.19$; $Q_1 = 2.5$, $Q_3 = 7.75$). These figures are based on intraindividual medians. We found no gender differences in median episode length.

The shorter episode length reported by modern studies may be a result of their including milder cases or, what is more probable, a consequence of antidepressant therapy: medication has usually to be maintained for a further 6 months after recovery to avoid relapse into the still persistent latent episode, which represents the natural history.

Recurrence of Bipolar Disorder

The total number of episodes experienced by patients is amply reported. Findings regarding the occurrence of single episode cases vary widely, ranging from 0% to 55%

Table 2. Total Number of Episodes and Length (Zurich Study)

Episodes	Patients	Median length of episodes (months)									
2	4	1.5	5.8								
3	8	6.0	2.8	9.0							
4	9	3.0	5.0	6.0	9.0						
5	15	5.5	4.5	4.6	4.0	5.8					
6	14	2.5	5.5	5.0	3.8	2.8	2.9				
7	21	3.0	5.0	4.0	4.3	3.5	3.0	4.0			
8	12	2.9	3.0	2.0	3.0	2.4	2.5	4.0	4.0		
9	13	3.5	4.5	4.0	4.0	3.0	2.5	2.5	2.0	1.0	
10	15	4.5	3.5	3.0	3.5	4.5	3.0	3.0	3.0	3.0	6.0
Episodes		1	2	3	4	5	6	7	8	9	10

(Goodwin and Jamison 1990), with five of 11 studies reporting rates between 0% and 8%. It is clear that any loss of information will inflate nonrecurrence rates; furthermore, the length of follow-up and development into chronicity have to be taken into account in assessing findings.

The earlier literature assumed that periodic mania had a better prognosis with fewer episodes and better outcome than periodic melancholia or circular disorder, the latter having the worst outcome (Rehm 1919, 107); however, Rehm also found twice as many manic cases (53%) than circular cases (26%) with short free intervals between episodes (up to 1 year), reflecting a higher periodicity of mania (it is unclear whether the length of observation in these cases was the same).

Certain methodological advances contributed to the investigation of the question of recurrence. One was the introduction of a more precise terminology and clear definitions of remission, recovery, relapse, and recurrence (Frank et al 1991). Another was the introduction of life table analyses into psychiatry, a method first used for length of hospitalization (Kramer 1969) and for follow-up data after recovery from depression (Klerman et al 1974) and soon also applied in longitudinal studies of bipolar disorder (Dunner et al 1976, 1979; Fleiss et al 1976, 1978). Lavori et al (1984) applied life table methods to reanalyze 40 earlier studies on the relapse/recurrence of affective disorders; the results varied considerably between the studies, and the authors formulated the hypothesis of the heterogeneity of patients' courses in terms of low or high hazard with a low or high risk of relapse. More recently, survival analysis was applied to prospective data on recurrence after remission (Fleiss et al 1978; Gitlin et al 1995; Keller et al 1993; Lavori et al 1984).

In a 2-year placebo-controlled lithium study Fleiss et al (1978) found that under placebo 80% of bipolar I patients experienced recurrences within about 70 weeks. (Admittedly a treatment study of this type dealt with a selected sample of patients, who, for instance, had had a mean number of two episodes in the previous 2 years.) The 4-year follow-up of a naturalistic study of mania showed recurrence in 72% of patients, with a mere 28% remaining in remission (Tohen et al 1990). Patients who were symptomatic at the 6-month follow-up had a 45% greater chance of a recurrence within the next 3.5 years.

Course of Subtypes of Bipolar Disorder

Important findings from a naturalistic study, the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression, Clinical Studies (Keller et al 1993), showed a high rate of recurrence for pure mania (48% by 1 year and 81% by 5 years) and even higher rates for the mixed cycling group (57% by 1 year and 91% by 5 years). Over 7 years the rate of recurrence was 81%. The length of sustained recovery was associated with a lower risk for recurrence over the subsequent 4 years, but over a period of 10 years this predictive power decreased considerably (Coryell et al 1995b); the authors showed that even under sustained lithium prophylaxis recurrences were present in more than 70% of cases within 5 years of recovery. This finding is consistent with the outpatient study of Gitlin et al (1995), in which 73% of 82 bipolar patients had relapses/recurrences over an average of 4.3 years despite maintenance pharmacotherapy (two thirds of patients who relapsed experienced multiple relapses). Among the 26 patients who suffered no relapse 46% continued to show significant symptoms of mania or depression.

The NIMH Collaborative Program on the Psychobiology of Depression, Clinical Studies (Coryell et al 1989) provided no evidence that the course of bipolar II disorder differed from that of bipolar I, which confirms our own findings (Angst 1986).

A recent study comparing patients suffering from bipolar II disorder with major depressive subjects under fluoxetine showed similar relapse/recurrence rates of 36% versus 35% after 50 weeks and 44% versus 49% after 62

weeks (Amsterdam et al 1998). This study provides no indication of a deterioration in the course of bipolar II disorder due to antidepressant medication; on the contrary, the disorder had a better course than under placebos.

Marneros et al (1991a) reported that bipolar disorder and schizo-bipolar disorder had very similar course characteristics.

Is Recurrence of Bipolar Illness Progressive?

Describing the intervals between episodes, Kraepelin (1913, 1365) found a progressive shortening of the first three intervals (first interval of male/female subjects 4.6/4.3 years, second interval 2.8/2.0 years, third interval 1.2/1.4 years). His data, like that of some other authors, are not controlled for the total number of episodes: clearly the intervals between episodes in patients having few episodes over a lifetime will be longer than in patients who experience many. We owe this particular methodological breakthrough to Eliot Slater (1938), who, in his paper on the periodicity of manic–depressive insanity, investigated 116 patients of the Forschungsanstalt für Psychiatrie in Munich who had been personally diagnosed by Kraepelin. Studying the length of intervals between episodes, Slater made his major methodological contribution by controlling for the total number of episodes and analyzing separately the subgroups with 1, 2, 3, . . . , *n* intervals. He showed that there was indeed a shortening of the intervals, but only between the first few manifestations of the illness. Investigating the individual periodicity, he concluded that every patient had his or her own rhythm.

In 1968 Bratfos and Haug applied Slater's method to the follow-up data on 215 cases of manic–depressive disorder (including depression) in an analysis of the length of the intervals between episodes. Correcting for the number of episodes, the authors found that the first interval length was 2.1 years, the second was 4.8 years, and the third was 2.2 years; thus no clear tendency emerged from these data.

Again following Slater's method of correcting for the number of episodes, Angst et al (1973) published the results of a multinational retrospective and partially prospective hospital record study on the course of 393 bipolar and 634 unipolar depressive patients. Analyzing cycle lengths, they indirectly confirmed Slater's finding that the intervals shortened as the number of recurrences increased; however, the median cycle lengths gave clear evidence only for continuous shortening of the first three cycles; the pattern of later recurrences seemed to be unpredictable. On the other hand, nonparametric tests between successive cycle lengths showed a significant shortening from cycle one to cycle 11 (Angst et al 1973, 499). Marneros et al (1991a) confirmed the shortening of cycles on the basis of the Cologne naturalistic follow-up study of 30 bipolar and 56 schizo-bipolar patients. Zis et al (1980) and Zis and Goodwin (1979) arrived at similar conclusions. This seemed to confirm earlier findings that had suggested decreasing cycle length (e.g., those of Kraepelin [1913, 1325] or Kinkelin [1954], although not controlled for number of cycles—see Figure 6-3 in Goodwin and Jamison [1990]). All these results, together with the finding that precipitation rates decrease (Angst 1966, 41) with increasing recurrence, led Roy-Byrne et al (1985) to speak of sensitization and Post et al (Post 1992; Post et al 1984, 1986) to develop the theory that vulnerability grows with the number of episodes and the theory of conditioning, sensitization, and kindling (by analogy with electrophysiologic kindling).

National data on hospital admissions and readmissions can also provide a rough estimate of the natural history of severe cases. Kessing et al (1998a, 1998b) recently described the course of Danish hospital admissions on the basis of a nationwide register of ICD-8 diagnoses. Rehospitalizations were taken as a measure of recurrence. The authors found, on the basis of 2903 bipolar cases, a progressive shortening of the interval between discharge from hospital and the next rehospitalization and, therefore, a deteriorating course. Selection bias did not completely explain the shortening intervals between hospital admissions, and control for gender and age did not alter the conclusions. So far, then, it would seem to have been established that the course of bipolar disorder is recurrent and progressive, but this aspect is still surrounded by considerable controversy, which may partially be due to the possibility "that recent studies deal with different, more broadly diagnosed populations than the seminal, earlier studies" (Grof et al 1995).

The Lithium Controversy: Does Recurrence Improve Spontaneously?

One controversy about the natural history of bipolar disorder dates back to 1968 and the criticism by two reputed British authors, Blackwell and Shepherd of lithium trials. They assumed not only the inefficacy of lithium but also that bipolar disorder had a good prognosis, making long-term prophylaxis unnecessary. This view was supported theoretically by Lader (1968) and empirically by Saran (1969), who found no evidence for high recurrence in his follow-up data and who concluded that past recurrence was not predictive for recurrence in the future. Saran's findings were of critical importance because the early work on lithium had been based statistically on the assumption that high recurrence in a patient's previous history should be expected to repeat itself in the future. Saran concluded that his findings on the spontaneous

course corresponded to the course as observed under lithium treatment by Baastrup and Schou (1968). Saran's findings have not been confirmed by other studies: a methodological investigation by Isaaksson et al (1969) demonstrated the persistence of recurrence for bipolar and unipolar depression, and the same conclusion was reached by Laurell and Ottosson (1968).

Stability of Recurrence after Initial Deterioration

Another debated question is whether the course of bipolar disorder is really progressive, characterized by unlimited shortening of cycles throughout (Angst et al 1973). This model is disconfirmed by a number of new studies. The recent summary of the literature by Kessing et al (1998b) shows that Fukuda et al (1983), who investigated not the early but the later course of the illness, could find no shortening of cycles (a finding that would still be compatible with the hypothesis that shortening is a feature of the first few cycles only). This aspect of the systematic shortening of cycle length was also very seriously questioned in the reviews by Coryell and Winokur (1992) and Solomon et al (1995), which drew mainly on Winokur and colleagues' findings (1994) from the prospective naturalistic NIMH study covering 10 years (Turvey et al 1999). This study found that the second cycle was clearly shorter than the first, the third a little longer than the second, but the fourth and fifth cycles were again shorter. On the other hand, Winokur et al (1993) stressed that bipolar illness was highly recurrent, with an "inexorable continuation of episodes and hospitalisations," and could find no data suggesting that the illness burned out at a later stage.

On the basis of prospective data Coryell and Winokur (1992) found that rapid cycling, which is observed in 20% to 25% of bipolar patients, is usually a transient manifestation and not therefore a characteristic of the long-term course.

Meta-Analysis of Two Studies on the Course

Samples and Methodology

Here we reanalyze some data from our two studies, the mainly retrospective multicenter study published by Angst et al (1973) and the Zurich follow-up study described by Angst and Preisig (1995a).

1. The multicenter study (Angst et al 1968a, 1973) consisted of consecutive hospital admissions of bipolar and unipolar depressive patients from Basel (103); Berlin (104); Hamilton, Canada (69); Prague (132); Zurich (392); Glostrup, Denmark (100); and Landeck, Germany (140). For the present analysis the Zurich sample was excluded, to avoid any overlap with the Zurich follow-up study. The remaining sample consisted of 329 bipolar patients. The data collection was mainly of the retrospective type based on case histories and verbal information. The documentation of the course was carried out by means of a standardized form of protocol in which all data were entered separately for each episode and subsequent interval (Angst and Weis 1968). In retrospect the onset (date) and length (months, weeks) of previous episodes and aspects of treatment (none, ambulatory, hospital) were assessed. The degree of remission was coded as full, partial, or unknown. Psychopathology was coded with a list of 10 syndromes. The data were reanalyzed for this study.
2. The Zurich follow-up study consisted of 406 consecutive hospital admissions for severe depression or mania from 1959 to 1963. Regular follow-up investigations (by telephone, interviews, and record collection) were conducted in 1963, 1965, 1979, 1975, 1980, and 1985. In 1991 and 1997 mortality data were available from the Swiss federal office of statistics. Seventy-six percent of patients had died by the end of 1997. The sample and the methodology of assessments were described in detail by Angst and Preisig (1995a). The principal data collected were comparable to the multicenter study, but psychopathology and treatment were assessed in more detail. The 220 bipolar patients were reanalyzed for this article.

Results

Table 3 presents the data from the mainly retrospective multicenter study and demonstrates a systematic shortening of the first four cycles. The predominantly prospective data from the Zurich sample (Table 4) shows a significant shortening between cycles 1 and 2 only, with no systematic change thereafter. In both studies the conclusions were confirmed by *t* tests for dependent measures.

In a survival analysis of the Zurich follow-up data significant differences were found between cycles 1–5 but were difficult to interpret. The first cycle was longer and the second cycle shorter than all the others. Otherwise the survival curves were very similar (Figure 3). The mean cycle length was 28.7 months ($s = 30.93$) but the median length, which is much more representative, only 18 months ($Q_1 = 3$, $Q_3 = 18$); exclusion of the first longer cycle does not change this median.

In conclusion, we found a shortening of cycle length at the beginning of the disorder only; later episodes were persistently recurrent but occurred at irregular intervals without any systematic deterioration or amelioration, thus

Table 3. Total Number of Cycles and Length (Multicenter Study)

Cycles	Patients	Median length of cycles (months)								
1	18	23								
2	35	26	15							
3	38	38	20	15						
4	45	21	27	13	14					
5	39	35	18	19	13	11				
6	31	42	31	19	15	15	9			
7	26	28	18	16	12	13	15	12		
8	27	42	17	14	14	9	11	9	10	
9	17	37	20	18	9	8	12	15	15	12
Cycles		1	2	3	4	5	6	7	8	9

This table does not include Zurich data.

confirming Winokur and colleagues' (1993, 1994) findings.

Episode Frequency per Year

Periodicity can also be expressed by the episode frequency per year. In a follow-up of 140 bipolar I patients over 11.4 years Dunner et al (1979) found 0.54 episodes per year; we found 0.37 (Angst and Preisig 1995a). Marneros' group found 0.41 episodes per year (Marneros 1999; Marneros et al 1991a) for bipolar disorder and about half as many in the case of recurrent depression. These figures included the first cycle, which is considerably longer than later ones. Dunner et al (1979) found no relationship between episode frequency and age of onset (which was not consistent with our early results; Angst and Weis 1967). The question of a gender difference in episode frequency per year remained open. After the onset of their disorder, bipolar patients spent on the average about 19% of their lives in affective episodes over an observation period of 27 years (Angst and Preisig 1995a).

In the present analysis the median cycle length (on the basis of individual medians) was 18 months ($Q_1 = 12$ months, $Q_3 = 33.5$ months), a length that corresponds to a recurrence rate of 0.66 episodes per year. On the basis of an episode length of 3 months (median), bipolar patients spent about 2 months/year in episodes. We could not find any gender differences (Mann–Whitney *U* test) in episode frequency measured by cycle length. Recently Gottschalk et al (1995) found some evidence for a nonlinear deterministic structure in long-term daily mood records of six out of seven bipolar patients, something not found in normal control subjects. Further research on a chaotic course is certainly desirable.

Correlates of Recurrence

For the analysis of correlates with long-term recurrence we excluded the first two cycles and entered the median of all intraindividual medians of cycle length as the dependent variable into a multiple regression analysis. Cycle length did not correlate with gender, retrospective versus prospective data collection, or long-term administration of tricyclic antidepressants. This finding does not confirm the assumed deterioration of the course of bipolar illness under tricyclics (Arnold and Kryspin-Exner 1965; Koukopoulos et al 1980; Till and Vuckovik 1970; Tondo et al 1981). Unsurprisingly, long-term lithium and antipsy-

Table 4. Total Number of Cycles and Length (Zurich Study)

Cycles	Patients	Median length of cycles (months)								
1	4	64								
2	8	105	12							
3	9	55	21	34						
4	15	78	25	33	45					
5	14	30	22	37	19	20				
6	21	44	35	36	24	24	17			
7	12	42	23	34	16	17	30	17		
8	13	34	22	23	30	23	12	17	28	
9+	124	26	19	21	15	15	12	12	12	12
Cycles		1	2	3	4	5	6	7	8	9+

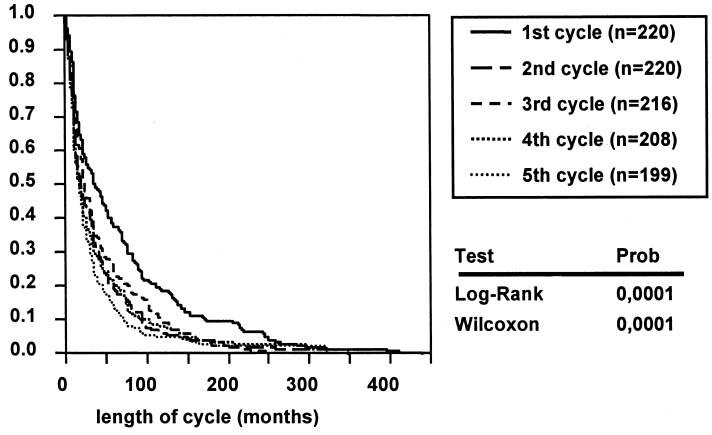

Figure 3. Survival analysis of cycle lengths (first to fifth).

chotic medication correlated with shorter cycles; this result is explicable by the selection of highly recurrent cases for prophylaxis. The syndromal characteristics of episodes had some impact on cycle length: it was significantly shorter in cases with cyclic versus pure (manic or depressive) episodes and in those with more manic than depressive episodes.

Poor Outcome of Bipolar Disorder in Early Follow-Up Studies

In the predrug era most bipolar cases were described as manifesting residual symptoms after recovery from episodes. Their state was described as "unsteady, moody, irritable, indolent, egocentric" (Pilcz 1901, 61–62), a symptom that often preceded the episodes or had even been present since childhood. Kraepelin (1913, 1185), too, although assuming a good prognosis, admitted the existence of mild residual "debility states." Ziehen (1902) estimated complete recovery in periodic mania to occur at most in 20% of cases.

In a follow-up of first admissions from 1920 to 1947 over a mean of 22 years Kinkelin (1954) found chronicity (including severe residual states) in 14.6% of depressive subjects ($N = 89$) and in 41% of circular cases ($N = 51$).

An important follow-up study of 297 bipolar and 945 unipolar patients in the Phipps Clinic (admissions from 1913 to 1940) was published by Stephens and McHugh (1991). Compared with depressive subjects, bipolar patients had an earlier age of onset on admission and were more likely to be psychotic; they also had more serious premorbid characteristics, more sudden onsets (44%), more previous admissions (62% for depression and 67% for mania), and more problems with alcohol, but more bipolar than depressed patients were discharged in a recovered state. In bipolar disorders they found a lifetime average of 3.6 hospitalizations, and in their follow-up they observed 0.19 episodes of depression and 0.29 episodes of mania per year followed up. Only 2% of all patients had manic episodes with no lifetime depressions; this small group had the best outcome. Bipolar patients ($N = 301$) had the poorest outcome: 7% were recovered, 50% improved, and 43% unimproved at the follow-up rating. The rates of recovered, improved, and unimproved patients were 19%, 56%, and 25% for pure mania ($N = 16$) and 25%, 44%, and 32% for pure depression ($N = 700$).

In a follow-up of 86 manic patients over 30 to 40 years, outcome (measured by psychiatric symptoms) was good in 43% of cases, fair in 18%, and poor in 25% (Tsuang et al 1979).

Poor Outcome in Recent Follow-Up Studies

Modern studies (e.g., a 4.5-year follow-up study by Goldberg et al [1995]) showed that only 41% of bipolar patients had a good overall outcome, the remainder being moderately impaired (37%) or showing poor functioning (22%). Gitlin et al (1995) found a poor outcome even under prophylactic medication (mainly lithium); poor outcome was more closely associated with the number of depressive episodes than the number of manic episodes. In their above-mentioned NIMH Collaborative Program on the Psychobiology of Depression with a 15-year intensive follow-up, Coryell et al (1998) found that 56.6% of 113 bipolar I patients had had no symptoms over the past 12 months, 22.1% had had symptoms for fewer than 52 weeks, and 20.4% had had symptoms in all 52 weeks, representing a poor outcome (defined as having had symptoms of major depressive disorder, mania, or schizoaffective disorder in all 52 weeks of year 15).

The short-term outcome, 12 months after discharge from hospital, was similar in patients with manic episodes or mixed episodes (Keck et al 1998), whereas in Keller and colleagues' (1986b) study after 18 months of follow-up mixed episodes also developed more frequently

Table 5. Outcome of 219 Patients in the Zurich Follow-Up Study (Median Age at Follow-Up or Death, 68 Years)

Recovered (GAS score > 60, no episodes over the past 5 years)	16.0%
Remitted (GAS score > 60) but still recurrent (<5 years since last episode)	25.5%
Incomplete remission (GAS score 1–60) over more than 5 years	7.8%
Incomplete remission, course still recurrent	27.0%
Chronic (last episode without remission, minimum length 2 years)	15.9%
Suicide	7.8%

GAS, Global Assessment Scale.

into chronicity (32%) than pure manic episodes (7%). In bipolar I patients poor outcome did not correlate clearly with early onset of the disorder or cycling per se (Coryell et al 1998), but persistence of depressive symptoms in years 1 and 2 was correlated with impairment after 15 years (household duties, recreational activities, overall satisfaction, and global social adjustment). Such early persistence of depressive symptoms predicted a poor prognosis of a bipolar subtype, whereas this was not the case for early persistence of manic symptoms.

The lifetime outcome of bipolar disorder in our Zurich follow-up study is given in Table 5 and demonstrates a poor prognosis despite modern treatments. Up to a median age of 68 years only 16% of patients had recovered; 52% still suffered from recurrent episodes and the remaining patients had become chronically ill or had committed suicide. These data underline the poor outcome into old age and the need for intensive treatment. This table shows the outcome of bipolar disorder before the occurrence of an organic brain syndrome in the elderly, which was found in 14.5% of cases. The previous number of affective episodes was not correlated with the development of an organic brain syndrome (Angst and Preisig 1995b).

Future studies on outcome should clearly distinguish between different outcome measures, since Tohen et al (2000) have shown that functional recovery can be much worse than syndromal recovery.

Conclusions

Several important conclusions regarding episodes, recurrence, and outcome have emerged from this review and data analysis of the natural history of bipolar disorder:

1. Before the introduction of modern drugs, spontaneous mild depression following a manic episode and spontaneous hypomania following a melancholic episode were very common; they were interpreted as "reactive" and had no effect on the principal diagnosis of pure mania or pure melancholia. This historical fact has to be taken into account in today's hypothesis of drug-induced hypomania or drug-induced depression; these have to be proven statistically by placebo-controlled trials.
2. Our decades-long prospective study shows that over lifetime the proportions of mania and depression in bipolar disorder remain stable into old age. Bipolar female subjects manifest more depression than bipolar male subjects.
3. Mixed states have been described since the early 19th century. Modern studies have demonstrated that they have a poorer prognosis than other bipolar conditions, with slower remissions and higher risk for chronicity.
4. The natural length of affective episodes has probably not changed over the past 120 years. Patients responding to antidepressants still require a maintenance treatment throughout the underlying episode. In clinical studies the median length of episodes is 3 to 6 months; in epidemiological studies it is 2 to 3 months.
5. The recurrence of bipolar disorder was always the rule; it now seems to be established that there is some initial shortening of intervals/cycles, followed by an irregular persistent recurrence, with a median cycling of 18 months. In contrast to earlier reports, the new studies show that there is no unlimited shortening of cycle length—not therefore supporting the kindling model. In several studies rapid cycling has been found to be relatively frequent, but usually transient.
6. Lifelong outcome has rarely been studied, and precise data on the natural outcome are scarce. Some new prospective studies demonstrate that most patients continue to suffer from residual depressive or hypomanic symptoms between episodes, and many are functionally impaired.
7. Overall research into the natural history of bipolar illness shows that it has a poor prognosis, as reflected by high recurrence, chronicity of episodes or residual symptoms, and premature death by suicide and somatic disorders; however, unlike schizophrenia, which is characterized by much higher chronicity and the predominance of negative and psychotic symptoms, chronicity in bipolar disorders is rarer (10–20%) and the more frequent residual states are limited to characteristic depressive and hypomanic symptoms.

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