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The Stanley Foundation Bipolar Network: Results of the Naturalistic Follow-Up Study after 2.5 Years of Follow-Up in the German Centres[1]

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Bipolar disorder · Course of illness · Comorbidity · Mood stabilizer · Treatment · Stanley Foundation

Abstract
The Stanley Foundation Bipolar Network (SFBN) is an international, multisite network investigating the characteristics and course of bipolar disorder. Methods (history, ratings and longitudinal follow-up) are standardized and equally applied in all 7 centres. This article describes demographics and illness characteristics of the first 152 German patients enrolled in the SFBN as well as the results of 2.5 years of follow-up. Patients in Germany were usually enrolled after hospitalisation. More than 72% of the study population suffered from bipolar I disorder and 25% from bipolar II disorder. The mean ± SD age of the study participants was 42.08 ± 13.5 years, and the mean ± SD age of onset 24.44 ± 10.9 years. More than 40% of the sample reported a rapid-cycling course in history, and even more a cycle acceleration over time. 37% attempted suicide at least once. 36% had an additional Axis I disorder, with alcohol abuse being the most common one, followed by anxiety disorders. During the follow-up period, only 27% remained stable, 56% had a recurrence, 12.8% perceived subsyndromal symptoms despite treatment and regular visits. 27% suffered from a rapid-cycling course during the follow-up period. Recurrences were significantly associated with bipolar I disorder, an additional comorbid Axis I disorder, rapid cycling in history, a higher number of mood stabilizers and the long-term use of typical antipsychotics. Rapid cycling during follow-up was only associated with a rapid-cycling course in history, a higher number of mood stabilizers and at least one suicide attempt in history.

Introduction

Bipolar disorder is a common, severe and persistent illness with a prevalence rate of 1.3–1.7% [1, 2]. According to some authors who also include bipolar spectrum disorders, the prevalence rate increases to 3–7% [3–6]. Taking this into account, bipolar illness affects at least 1 million people in Germany, about 4 million in the USA and 3.2 million people in Europe. Even though research

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efforts have been reinforced lately, many questions still remain open concerning the course, treatment and origins of this devastating illness. In 1989 and 1994, the National Institute of Mental Health organized two bipolar disorder workshops which concluded that there is still an enormous need for research on bipolar illness [7, 8]. Especially the need for controlled clinical treatment trials for bipolar depression and maintenance treatment was emphasized. Furthermore, the two workshops recommended the development of a consortium of academic centres, patient advocacy groups and the pharmaceutical industry to increase the number and representativeness of patients in controlled clinical trials and to help develop methods and assessment devices that would accurately describe the illness course [9]. As a result, the Stanley Foundation Bipolar Network (SFBN) was established with the generous support of Vada and Theodore Stanley in order to improve research for bipolar affective disorders. A detailed description of the SFBN, its rationale and the methods used is published elsewhere [10–12]. In brief, the aim of the Network is to enroll a large number of bipolar patients for longitudinal studies. Patients are seen at least once a month and psychopathology is assessed using well-known, validated rating scales and prospective life chart methodology [13]. Depending on the course of the illness, patients are offered to participate in randomized open or double-blind clinical trials. Patients not eligible or willing to participate in clinical treatment trials are followed up in the Naturalistic Follow-up Study (NFS). Treatment of these patients is not restricted, but up to the clinician's choice. The results of the NFS of the two German centres after 2.5 years of follow-up are presented in this paper.

Methodology

Until 1998, the Network had been composed of four University Hospitals in the USA (Bethesda, Los Angeles, Dallas and Cincinnati) and one in The Netherlands (Utrecht). In 1999, the Psychiatric Hospitals of the Universities of Munich and Freiburg, Germany joined the SFBN as affiliated sites. In Germany, patients recruited to the study were usually enrolled after hospitalisation or by self-referral. All patients provided written informed consent prior to entering the network. The inclusion criteria for entry were the diagnosis of bipolar disorder (I, II, NOS) or schizoaffective disorder (bipolar type) according to DSM-IV, age older than 18 years and the willingness to return for monthly follow-up visits. Comorbid psychiatric or medical illnesses were no exclusion criteria, except any substance abuse requiring acute treatment.

At entry, the diagnosis and other Axis I disorders were confirmed using the Structured Clinical Interview of DSM-IV [14]. Demographic and clinical variables were assessed using questionnaires completed by clinicians and patients [9]. Axis II disorders (Personality Disorder Questionnaire [15]), depressive [Inventory of Depressive Symptoms [16] (IDS)], manic [Young Mania Rating Scale [17] (YMRS)] and psychotic symptomatology [Positive and Negative Syndrome Scale [18] (PANSS)], overall mood [Clinical Global Impressions Scale for Bipolar Illness [19] (CGI-BP)] and global functioning [Global Assessment of Functioning Scale [20] (GAF)] were assessed as well. The course of the illness was assessed using the retrospective and prospective Life-Chart Methodology (LCM) [13].

Patients were usually followed up monthly, but when clinically indicated, also more often. At every follow-up visit, the same psychometric scales were applied again (IDS, YMRS, CGI-BP, GAF, LCM) to assess symptomatology, the course of illness and treatment.

Patients had the choice to receive their medical care entirely at the Stanley Research Clinics or to visit a psychiatrist in a private practice. Treatment in the NFS was not standardized, but was up to the treating psychiatrist's choice depending on the course of the illness.

Statistical analyses were performed using the Statistical Products for Service Solutions version 10.1. Frequencies were run on demographic and clinical variables as well as treatment characteristics. Fisher's exact test was used to test significance for categorical, Student's t test was used to evaluate continuous variables. Statistical significance was set at 0.05 (two-tailed).

Results

More than 700 patients with bipolar or schizoaffective disorders have been enrolled in the whole Network so far [9]. In Germany, 152 patients have been enrolled consecutively since 1999 and have been followed up prospectively for an average of 13.13 months (1–32 months).

Clinical and Demographic Variables of the Sample

Table 1 shows the most important demographic and clinical variables of the 152 patients enrolled in Germany. Most patients suffer from a bipolar I disorder (72.1%), followed by patients with bipolar II disorder (25.2%). Only few patients with a bipolar disorder NOS or schizoaffective disorder participated in the study (0.7 and 2%, respectively). The distribution of age and sex is comparable with other cohort studies of bipolar patients [9, 21]. Almost 60% of the patients lived on their own, either in an apartment or in sheltered housing. Only 40% lived together with their partners or families. This is also in line with other studies [22]. While in many epidemiologic studies most bipolar patients also suffer from comorbid Axis I disorders, above all substance abuse and anxiety disorders, in our sample, only 35.8% of the patients had had an additional Axis I disorder during their lifetime, of which substance abuse was the most common one (26.3%), followed by anxiety disorders (12.5%). Only few patients also suffered from an eating disorder (7.2%).

Table 1. Demographic and clinical variables

	Whole sample (n = 152)	Bipolar I (n = 108)	Bipolar II (n = 38)
Current age, years	42.08 ± 13.5 (21–80)	40.95 ± 12.62	45.89 ± 15.10
Gender, %			
Female	51.7	50.9	50.0
Male	48.3	49.1	50.0
Marital status, %			
Married/cohabitation	40.4	37.4	44.7
Widowed	2.1	1.9	7.9
Divorced/separated	15.7	14.1	21.1
Single	41.8	46.2	26.3
Current living situation, %			
With spouse/partner	40.4	36.8	47.4
Single parent	2.1	0.9	5.3
Single	46.4	49.1	44.7
With family of origin	8.2	9.4	2.6
In group home	1.4	1.9	0
Other	1.4	1.9	0
Diagnosis, %			
Bipolar I	72.1		
Bipolar II	25.2		
Bipolar NOS	0.7		
Schizoaffective disorder	2.0		
Age of onset, years	24.44 ± 10.9 (9–63)	23.97 ± 11.2 (13–63)	25.82 ± 10.5 (9–50)
Age at first treatment	29.77 ± 10.6	29.65 ± 11.5	29.94 ± 9.3
Age at first hospitalisation	31.11 ± 13.2	30.45 ± 12.2	31.57 ± 13.7
Comorbid Axis I disorders, %	35.8	35.9	37.8
Any substance abuse	26.3	25.5	28.9
Alcohol abuse	17.8	18.9	18.4
Substance abuse (without alcohol)	8.5	6.6	10.5
Any anxiety disorder	12.5	10.4	18.4
Any eating disorder	7.2	9.4	0

Table 2 shows the distribution of the socioeconomic status of the sample. Even though many patients were highly educated (28.3% finished university or a comparable education), only one third of the sample was able to work full-time in jobs which matched their qualifications. Most of the patients were unable to work (13.5%), retired (26.6%) unemployed (7.8%) or in rehabilitation programs (3.5%). The limitation of the occupational functioning is also obvious from household income. One third of the bipolar patients has to live with less than 10,000 EUR/year, more than half of the sample with less than 20,000 EUR/year.

When asked for their own judgement, more than two thirds (61.4%) of the patients feel that their occupational functioning is limited moderately to severely due to their bipolar illness even in free intervals.

Important illness characteristics are shown in table 3. Almost 41% of the patients reported a history of rapid cycling. No significant differences were found between the diagnostic groups (data not shown). Almost 14% of the sample suffered from ultradian cycling which was defined as cycling within a day. Almost half of the sample (44.7%) reported a worsening of their illness over time due to cycle acceleration, a substantial number of patients additionally reported an increase in severity. These findings are also in line with other studies [9, 22]. There is a big difference between the number of episodes and hospitalizations. While the vast majority of patients (83.4%)

Table 2. Socioeconomic status

	Whole sample (n = 152)	Bipolar I (n = 108)	Bipolar II (n = 38)
Employment status, %			
Full-time			
Equal to qualifications	29.6	26.4	34.2
In household	2.8	2.9	5.3
Below qualifications	2.8	2.9	2.6
Part-time	7.8	5.9	10.5
Unemployed	7.8	5.9	13.2
Rehabilitation program/sheltered workshop	3.5	4.9	0.0
Unable to work	13.5	17.6	2.6
Retired/disability pension	26.6	27.5	23.7
Other	6.4	5.9	7.9
Education, %			
Hauptschulabschluss (10 years)	8.1	5.7	10.5
Mittlere Reife (High school)	8.7	10.4	5.3
Abitur (13 years)	26.2	31.1	13.2
Apprenticeship	28.9	26.4	36.8
University	22.9	12.6	23.7
Graduation	5.4	3.8	10.5
Household income in DM, %			
<20,000	30.6	32.4	24.3
20,000–39,999	25.9	29.5	16.2
40,000–59,999	13.6	14.3	10.8
60,000–79,999	12.9	9.5	21.6
80,000–99,999	6.1	4.8	10.8
100,000+	9.5	7.6	16.2
Occupational functioning limited by bipolar illness (free interval), %			
Not limited	0.8	1.1	0
Mildly	37.8	36.6	38.9
Moderately	23.6	24.7	25.0
Markedly	15.0	17.2	11.1
Severely	12.6	10.8	11.1
No free interval	10.2	9.7	13.9

have suffered from at least 5 episodes in their lives, only half of the patients have been hospitalized as often as that. The difference is even clearer in patients which have suffered from more than 20 episodes. While almost 40% of the sample say they have had at least 20 episodes in their lifetime, only 9.2% have also been hospitalized as often as that. There was no statistical difference between the two major diagnostic groups (data not shown).

Results of the Follow-Up Period

During the prospective observation period, only 27% of all patients remained free of symptoms. The majority of patients (56%) suffered from at least one recurrence. 12.8% of the patients perceived subsyndromal symptoms not long or severe enough to fulfil the diagnostic criteria for a recurrence. That means a vast majority of the sample (68.8%) suffered from mood disturbances despite treatment adherence and regular visits to a professional. About a quarter of the study population suffered from a rapid-cycling course during follow-up (26.5%). The treatment of 111 patients of the sample could be analysed more precisely. Of this subsample, almost all (97.3%) were on at least 1 mood stabilizer during follow-up. Most of the patients were on just 1 mood stabilizer (60.4%), about one third of the sample (33.3%) had a combination treatment of 2 mood stabilizers, and the remaining patients were on either 3 or 4 mood stabilizers (2.7 and 0.9%, respectively). Even though there is a wide range of treatment options now, the most important mood stabilizer is still lithium. Almost one quarter of our sample (23.1%) were on lithi-

Table 3. Illness characteristics

	Whole sample (n = 141)	Bipolar I (n = 107)	Bipolar II (n = 36)
History of rapid cycling, %	40.7	39.8	41.2
No rapid cycling	59.3	60.2	58.8
Rapid cycling	16.8	14.0	20.6
Ultra-rapid cycling	9.9	11.8	5.9
Ultradian cycling	13.7	14.0	14.7
Number of episodes, %			
1–4	16.5	14.6	20.6
5–10	26.3	24.0	32.4
11–20	17.3	19.8	11.8
20+	39.8	41.7	35.3
Hospitalizations, %			
0–4	54.6	53.5	54.8
5–10	26.1	25.6	29.0
11–20	10.1	9.3	12.9
20+	9.2	11.6	3.2
Cycle acceleration, %	44.7	44.4	38.9
More severe episodes of depression	55.1	51.0	66.7
More severe episodes of hypomania	34.4	35.7	35.3
More severe episodes of mania	38.6	41.2	0
History of suicide attempts, %			
None	63.4	62.8	63.9
At least 1	36.6	37.2	36.1
More than 4	7.5	8.5	5.6
Interepisode symptoms, %			
No symptoms	42.0	42.4	42.9
Mild symptoms	38.9	37.0	42.9
Significant symptoms	4.6	4.3	2.9
Substantial symptoms	2.3	3.3	0
Cycle continuously	12.2	13.0	11.4
Feeling of stigmatization, %			
Not at all	31.7	29.2	37.1
Mild	26.8	27.0	25.7
Moderate	30.1	33.7	25.7
Severe	11.4	10.1	11.4

um alone, another 21.2% on a combination treatment of lithium and another mood stabilizer (e.g. valproate or carbamazepine). An increasing number of patients is also on a combination treatment of lithium and an atypical antipsychotic (4.6%). Valproate alone or in combination with another mood stabilizer was the treatment of choice in 30.3% of the study population. Interestingly, there is still a high proportion of patients who also get a long-term treatment with antidepressants or typical antipsychotics (for at least 6 months, 42.3 and 24.5%, respectively). During the observation period, 50 patients (33%) dropped out for various reasons.

Recurrences

About 56% of the patients suffered from at least one recurrence in the follow-up period. Patients with a bipolar I disorder significantly more often had a recurrence than patients with a bipolar II disorder ($p < 0.044$). Furthermore, patients with an additional comorbid Axis I disorder or a rapid-cycling course in history also suffered more often from a recurrence than patients without any ($p < 0.047$ and $p < 0.005$, respectively). However, there is also another significant difference: patients who had a recurrence during the follow-up period were on significantly more mood stabilizers and more often on an additional

Table 4. Recurrence during follow-up

	Recurrence	No recurrence	p value
Age[1]	43.18 ± 13.50	39.32 ± 11.43	0.081
Age of onset[1]	24.12 ± 11.66	25.85 ± 9.31	0.351
Gender: female[2]	39 (50)	33 (55)	0.608
Bipolar I[2]	62 (82)	37 (65)	0.044*
Any comorbid Axis I disorder[2]	34 (43)	15 (25)	0.047*
Substance abuse[2]	25 (32)	12 (19)	0.124
Anxiety disorder[2]	12 (15)	5 (8)	0.297
Eating disorder[2]	7 (9)	4 (6)	0.755
Rapid cycling in history[2]	37 (56)	15 (29)	0.005*
Suicide attempt in history[2]	22 (39)	14 (29)	0.309
Living situation (alone)[2]	45 (58)	31 (56)	1.0
Number of mood stabilizers[1]	1.52 ± 0.72	1.26 ± 0.49	0.033*
Use of antidepressants[2, 3]	27 (45)	17 (37)	0.433
Use of antipsychotics[2, 3]	21 (36)	5 (11)	0.006*

Figures in parentheses are percent values.
1 T test.
2 Fisher's exact test.
3 More than 6 months during follow-up.

Table 5. Rapid cycling during follow-up

	Rapid cycling	No rapid cycling	p value
Age[1]	41.79 ± 11.35	41.62 ± 13.44	0.943
Age of onset[1]	31.5 ± 13.99	26.18 ± 10.19	0.085
Female[2]	19 (49)	57 (53)	0.711
Bipolar I[2]	27 (71)	80 (76)	1.0
Comorbid axis I disorder[2]	12 (31)	39 (38)	0.558
Substance abuse[2]	11 (28)	27 (25)	1.0
Anxiety disorder[2]	7 (18)	11 (10)	1.0
Eating disorder[2]	1 (3)	9 (8)	0.291
Early age of onset (0–17)[2]	15 (38)	16 (15)	1.0
Rapid cycling in history[2]	27 (75)	27 (31)	0.000*
Suicide attempt in history[2]	17 (59)	19 (23)	0.001*
Living situation (alone)[2]	24 (62)	59 (58)	1.0
Number of mood stabilizers[1]	1.70 ± 0.64	1.26 ± 0.59	0.001*
Use of antidepressants[2, 3]	14 (42)	33 (42)	1.0
Use of antipsychotics[2, 3]	10 (31)	17 (22)	1.0

Figures in parentheses are percent values.
1 T test.
2 Fisher's exact test.
3 More than 6 months during follow-up.

typical antipsychotic than patients who remained stable ($p < 0.033$ and $p < 0.006$, respectively). There were no significant differences concerning gender, age, age of onset, living situation (alone vs. with family), suicide attempts in history and long-term antidepressant use during the follow-up period (table 4).

Rapid Cycling

More than a quarter of the sample (26.5%) had a rapid-cycling course (i.e. at least 4 episodes within 12 months) during the follow-up period. Moreover, patients who actually suffered from rapid cycling significantly more often had a rapid-cycling course in their history ($p <$

0.000) and were on more mood stabilizers than patients without rapid cycling ($p < 0.001$). If patients had more than 4 episodes during the follow-up period, they significantly more often had at least one suicide attempt in history ($p < 0.001$). There were no significant differences between patients with or without a rapid-cycling course concerning age, age of onset, gender, comorbid disorders, alcohol or substance abuse, living situation (alone or with family) and long-term antidepressant or antipsychotic use during follow-up (table 5).

Discussion

In this article, the characteristics of the first 152 German patients enrolled in the SFBN as well as some features of the follow-up period are described. As far as the demographic and clinical variables are concerned, there are not many differences between our patient sample and other clinical samples of bipolar patients [9, 21, 22]. Gender, age, martial status, education and diagnosis are comparable with those of other studies. Like the American SFBN study participants [9], the majority of our patients was highly educated, but only one third was able to work in positions which met their qualifications. More than half of the sample worked below their qualifications, in sheltered workshops or were unable to work and therefore got an invalidity pension. This limitation of functioning was reported by the patients themselves and was also reflected by the low annual household income of less than 10,000 EUR for more than 30% of the study population. Thus, the German SFBN study population confirms the results of other naturalistic studies [9, 23].

The major discrepancy to other studies, however, is the difference in comorbid psychiatric disorders. While many studies describe a proportion of up to 50% of bipolar patients with an additional substance abuse [2, 24–26] and up to a 93% frequency of lifetime anxiety disorders in bipolar I patients [27], in our study, only 35.8% had an additional Axis I disorder. Like in other studies, alcohol abuse was the most frequent one (17.8%) followed by anxiety disorders (12.5%). The reason for such a low rate is not quite sure. A selection bias may be possible. With bipolar disorder often unrecognized, many patients may seek care in a setting specialized in their comorbid disorder. Additionally, most reports on high comorbidity rates are based on US populations which may not be comparable with conditions in Germany.

More than 40% of the patients report a rapid-cycling course in history, and almost 27% had 4 or more episodes during the 2.5 years of follow-up. While other studies describe different predictors for rapid cycling such as age, age of onset, female sex, bipolar II disorder or antidepressant use [28], our study could not confirm these results. There was only an association between rapid cycling and suicide attempts, rapid cycling in history and a higher number of mood stabilizers. These associations are not surprising. It is rather obvious that a single mood stabilizer is often not enough to prevent new episodes, the more severe the disorder is.

Concerning treatment, it has to be stated that despite our elaborated setting and state-of-the-art treatment, more than half of the patients experienced a relapse during follow-up. Patients with bipolar I disorder or a comorbid Axis I disorder were on highest risk for relapse. It is an obvious conclusion that we still lack a 'golden standard' in treatment, especially in this high-risk population of bipolar patients.

This study has a number of limitations to generalize these data. First of all, the study population was usually enrolled after hospitalisation in a university hospital. That is why this sample does not represent patients in the community but rather patients who are severely ill, which is also reflected by the high percentage of patients who had more than 20 episodes. Still, the major results of this study are comparable with other studies with clinical samples. Another limitation is that patients had to be willing to complete ratings and attend regular appointments. Usually, patients willing to do so were not hospitalised for their first episode, but had already been ill for several years. On the other hand, the SFBN has a number of strengths like standardized methodology, detailed prospective ratings of mood, sleep, life events and medication and continuous longitudinal follow-up.

Nonetheless, this study again reveals the high morbidity of this illness despite multiple treatment available and therefore emphazises the need for research in this particular field.

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