ORIGINAL PAPER

Michael Bauer · Tasha Glenn · Paul Grof · Natalie L. Rasgon · Wendy Marsh · Kemal Sagduyu ·
Martin Alda · Ute Lewitzka · Johanna Sasse · Eliza Kozuch-Krolik · Peter C. Whybrow

Frequency of subsyndromal symptoms and employment status in patients with bipolar disorder

■ **Abstract** *Objective* This study investigated the frequency of episodes and subsyndromal symptoms based on employment status in patients with bipolar disorder. *Methods* Patients with bipolar disorder ($n = 281$) provided daily self-reported mood ratings for 5 months, returning 46,292 days of data. Data were analyzed using three employment status groups: disabled ($n = 75$), full-time employee or full-time student ($n = 135$), and other ($n = 71$). Demographic characteristics were compared by employment status. A univariate general linear model with employment status and other demographic variables as fixed factors and covariates was used to analyze the percent of days in episodes and percent of days with subsyndromal symptoms. *Results* While there was no significant difference in the percent of days in episodes among the employment groups, disabled patients suffered subsyndromal symptoms of depression twice as frequently as those in the full-time group. Disabled patients spent 15% more days either in episodes or with subsyndromal symptoms than those in the full-time group, equivalent to about 45 extra sick days a year. *Conclusion* Frequent subsyndromal symptoms, especially depressive, may preclude full-time responsibilities outside the home and contribute to disability in bipolar disorder. Additional treatments to reduce the frequency of subsyndromal symptoms are needed.

■ **Key words** bipolar disorder – employment – disability – subsyndromal symptoms

M. Bauer (✉) · U. Lewitzka · J. Sasse · E. Kozuch-Krolik
Dept. of Psychiatry and Psychotherapy
Universitätsklinikum Carl Gustav Carus
Technische Universität Dresden
Fetscherstraße 74
01307 Dresden, Germany
Tel.: +49-351/458-0
Fax: +49-30/450-517962
E-Mail: michael.bauer@uniklinikum-dresden.de

M. Bauer · P.C. Whybrow
Dept. of Psychiatry and Biobehavioral Sciences
Semel Institute for Neuroscience and Human Behavior
University of California Los Angeles (UCLA)
Los Angeles (CA), USA

T. Glenn
ChronoRecord Association Inc.
Fullerton (CA), USA

P. Grof
Mood Disorders Center of Ottawa
Ottawa (ON), Canada

P. Grof
Dept. of Psychiatry
University of Toronto
Toronto (ON), Canada

N.L. Rasgon
Dept. of Psychiatry and Behavioral Sciences
Stanford School of Medicine
Palo Alto (CA), USA

W. Marsh
Dept. of Psychiatry
University of Massachusetts
Worcester (MA), USA

K. Sagduyu
Dept. of Psychiatry
University of Missouri
Kansas City School of Medicine
Kansas City (MO), USA

M. Alda
Dept. of Psychiatry
Dalhousie University
Halifax (NS), Canada

Introduction

Patients with bipolar disorder experience high rates of unemployment and functional impairment [16, 26, 27, 34]. Worldwide, bipolar disorder is a leading cause of disability [40]. The symptoms experienced most frequently by patients receiving treatment for bipolar disorder do not meet the DSM-IV criteria for an episode of mania or depression [5, 6, 28, 29, 43]. These subsyndromal symptoms that occur between major episodes are primarily depressive, and have a similar pattern in both bipolar I and II disorders [6, 28, 29]. While the number of pharmacological agents available for the treatment of bipolar disorder has rapidly expanded over the last decade, efficacy for most agents was established in relation to the treatment or prevention of major episodes of mania or depression. However, subsyndromal symptoms may also be associated with significant functional disability [1, 9, 30, 36, 54] and there is only limited understanding of the relationship between the perceived daily symptoms of bipolar disorder and employment status. We investigated the frequency of both episodes and subsyndromal symptoms using daily self-reported mood ratings and employment status in a sample of patients with bipolar disorder.

Methods

Data source

Daily mood rating data were obtained from an ongoing, long-term naturalistic study of patients with bipolar disorder. Inclusion in the study required a DSM-IV diagnosis of bipolar disorder, an age of 18 years or older, current treatment with pharmacological agents, and that the patient would complete daily self-reporting of mood for 5 months using computer software in their native language. Only minimal exclusion criteria were used to reflect routine clinical practice and patient heterogeneity. The diagnosis of bipolar disorder was made by the prescribing psychiatrist in a clinical interview. All patients received treatment as usual for bipolar disorder. Patients were recruited from university hospital mood clinics by the participating physicians or by word-of-mouth and received no compensation for participation other than being allowed to use the software indefinitely. All participants were informed about the study prior to providing written informed consent. The study was approved by each local institutional review board.

Two datasets have been combined to enhance the ability to analyze data by important grouping variables. The first dataset contains data collected between 2002 through 2005. During this period, 247 patients enrolled in the study and 203 returned data, as previously published [5]. The second dataset is from patients who enrolled and returned data during the year 2006. During 2006, 158 patients enrolled in the study and 107 returned data. Data from the 203 patients in the first dataset were combined with data from the 107 patients in the second dataset for a total of 310 unique patients included in this study.

To assess if this patient sample was representative of a larger population of patients with bipolar disorder, the demographic characteristics of the 310 patients were compared with other published studies of patients with bipolar disorder as shown in Table 1. Although the patient sample in this study contains somewhat more minority patients and patients with bipolar II disorder, the demographic profile of the patients in this study was similar to that of patients in other studies of bipolar disorder.

Data for current analysis

Of the 310 unique patients, 17 patients were missing employment status and 12 were retired. These 29 patients were excluded. A total of 281 patients were included in the statistical analysis.

Data collection instrument

All mood-ratings in this analysis were self-reported by patients using ChronoRecord software which was installed on the patient's home computer. ChronoRecord self-ratings were previously validated with clinician ratings on HAMD and YMRS [4, 7], and missing mood ratings were shown to be unrelated to patient demographics or severity of illness (missing completely at random) [4]. ChronoRecord software was described in detail elsewhere [4, 7], and was based upon the ChronoSheet, an established paper-based form for self-reporting [8]. In addition to mood, the patients recorded sleep, menstrual data, psychiatric medications, and life events every day, and weight weekly. To record mood, ChronoRecord uses a 100-unit visual analogue scale between the extremes of mania and depression. During a half-hour training session, personal anchor points were set by the patient to describe the most depressed and most manic states they ever experienced. The patient's anchor point for mania, and daily self-ratings of mania or hypomania reflect activation levels for either euphoric or dysphoric mood [4].

Based upon the validation studies [4, 7], a mood entry less than 40 was considered depression, 40–60 euthymia, and greater than 60 hypomania/mania. The range of depression varied between mild symptoms (an entry of 20–39) to moderate to severe symptoms (an entry of 0–19). The range of mania varied from hypomania (an entry of 61–80) to moderate to severe symptoms of mania (an entry of 81–100). Days with mood ratings of depression or hypomania/mania that did not meet the DSM-IV length criteria for an episode were considered to be days with subsyndromal symptoms. This definition of subsyndromal, as symptoms that meet the criteria for severity but not length, was used in prior research [5, 6, 36].

Employment status

During the study enrollment process, the patient provided their initial employment status and occupation. Any changes in employment status during the study were entered into the "Life events" field in ChronoRecord. Three employment status groups were created from the employment data: disabled, full-time and other. The disabled group included patients who were receiving a government disability payment for bipolar disorder, or who were unemployed, not seeking work and in the process of applying for government disability. The full-time group included those who were meeting full-time responsibilities outside the home as either full-time employees or full-time students. All full-time employment was competitive, and patients were considered to be employed full-time, or full-time students, only if they remained such throughout the study period. The other employment status group included part-time employees, those who were unemployed and seeking work and those with home duties. Part-time employment could be competitive or sheltered, and could be discontinuous during the study.

In the US, Social Security Administration Disability Insurance defines disability as a "complete inability to work" with no recognition of partial disability [48]. Since 73% ($n = 201$) of the 281 patients resided in the US and only 27% ($n = 75$) outside the US, the other employment status group was needed to categorize patients who did not maintain full-time responsibilities outside the home but were not disabled.

Table 1 Comparison of demographic characteristics with patients in other studies of bipolar disorder

	ChronoRecord (n = 310) %	Step BD[a] (n = 1000) %	Stanley registry[b] (n = 2839) %	VA cooperative[c] (n = 306) %	Group health[d] (n = 441) %	NDMDA survey[e] (n = 600) %	Stanley network[f] (n = 261) %
Age	38 SD = 10.7	41 SD = 2.6	Median 40.1	47 SD = 10.1	44 SD = 13	[g]	43 SD = 1.3
Gender							
Male	29	41	35	91	32	34	44
Female	71	59	65	9	68	66	56
Ethnicity							
Caucasian	82	93	90				93
Minority	18[h]	7		23	12		7
Marital status							
Married	45	36	33			38	43
Separated/divorced	14	24	33	[i]	[j]	34	26
Other	41	37	33			28	31
Education							
High school	11	18		[k]			7
Some college	32	[l]					38
College graduate	57		33			55	55
Employment status							
Full-time	46	35	[m]			25	39
Disabled	26	15	[n]	28			
Other	28	50		[o]	[p]		
Age of onset	21 SD = 9.9	17 SD = 8.6	Mean 19.8	21 SD = 9.0		[q]	23 SD = 10.4
Diagnosis							
BP I	63	71		87	76		81
BP II	34	24					16
BP NOS/other	3	5					

[a] Systematic Treatment Enhancement Program for Bipolar Disorder [33]
[b] Stanley Center Bipolar Disorder Registry [34]
[c] Veteran Affairs Cooperative Study Program 430 [10]
[d] Washington State Group Health Cooperative (a managed care organization) [47]
[e] National Depression Manic Depression Association 2000 Survey [26]
[f] Stanley Foundation Bipolar Network [49]
[g] Most between age 31 and 60
[h] Minority details are: Hispanic 9%, Asian 4%, Other 3%, Black 2%
[i] 70% other than married or widowed
[j] 73% not married or widowed
[k] 6% < 12 years
[l] 82% some college plus
[m] Employed: 39% men, 34% women
[n] On disability, welfare or retired: 34% men, 30% women
[o] 54% unemployable
[p] 37% unemployable
[q] 33% under 15, 27% age 15–20, 39% over 20

Enrollment date

Several drugs received FDA approval for the treatment of bipolar disorder during the data collection period. To control for treatment changes due to these drugs, a variable was created to group each patient based on their enrollment date in the study. The first group included patients who enrolled before June 2003 (approval of lamotrigine), the second group included those who enrolled between June 2003 and January 2005 (approval of quetiapine, ziprasidone and aripiprazole in late 2004), and the third group included those who enrolled after January 2005.

Statistical analysis

Episodes of hypomania/mania and depression were determined using a published algorithm to calculate episodes from daily self-reported mood data [14]. The DSM-IV criteria were used for the minimum episode length, with 14 days for depression and 4 days for hypomania. To be considered using a medication, a patient had to take any dose of the drug for at least 50% of the days. The Pearson X^2 test was used to compare medications among the enrollment date groups, and to compare categorical demographic variables among the employment status groups. A univariate general linear model (GLM) was used to compare all continuous demographic variables with employment status as a fixed factor. Continuous demographic variables that showed a statistically significant ($P < 0.05$) difference among the employment groups were analyzed for collinearity using a correlation analysis. If continuous variables were significantly correlated, a single representative variable was chosen for inclusion in the model.

A univariate GLM with employment status as a fixed factor was used to estimate marginal means of the percent of days in episodes and the percent of days with subsyndromal symptoms. Additional categorical and continuous variables that were significantly different by employment status were included as fixed factors or covariates. The enrollment date variable was included as a fixed factor to control for treatment changes over time. For employment status to be significant in any GLM estimation, both the corrected model F-statistic and the pairwise employment status t-statistic had to be significant at the 0.05 level. The Sidak method was used to adjust significance levels for multiple comparisons of the estimated marginal means for all pairwise employment status t-statistics. SPSS 14.0 was used for all calculations.

Results

The 281 patients returned 46,292 days of data. The mean percent of missing mood ratings per patient was 7.8%, or 12 days over 5 months. Comparing the medications received by enrollment date, no significant difference was found in the use of lithium ($X^2 = 1.981$, df = 2, $P = 0.371$), valproate ($X^2 = 2.870$, df = 2, $P = 0.238$), antidepressants ($X^2 = 0.937$, df = 2, $P = 0.626$) or benzodiazepines ($X^2 = 0.698$, df = 2, $P = 0.705$). As expected, the use of lamotrigine increased from 20% before June 2003 to 34% of all patients after January 2005 ($X^2 = 12.073$, df = 2, $P = 0.002$) and the use of atypical antipsychotics increased from 32% before June 2003 to 45% of all patients after January 2005 ($X^2 = 6.061$, df = 2, $P = 0.048$). Of the 281 patients, 9 took typical antipsychotics, 8 of whom enrolled before June 2003.

The distribution of the 281 patients by employment status was 27% ($n = 75$) in the disabled group, 48% ($n = 135$) in the full-time group, and 25% ($n = 71$) in the other group. Of the 75 patients in the disabled group, 50 were receiving and 25 were applying for government disability. Of the 135 patients in the full-time group, 70% ($n = 94$) were working full-time and 30% ($n = 41$) were full-time students. The occupations of the 94 working full-time were: 44% ($n = 41$) professional, 15% ($n = 14$) clerical, 15% ($n = 14$) technical, 12% ($n = 11$) managers, 7% ($n = 7$) other, 5% ($n = 5$) arts and 2% ($n = 2$) laborers. Of the 71 patients in the other employment status group, 52% ($n = 37$) were working part-time, 23% ($n = 16$) were unemployed seeking work, and 25% ($n = 18$) had home duties.

The distribution of the demographic variables by employment status for the 281 patients is shown in Table 2. The distribution of employment status was not significantly different for those living in or outside the US. Patients in the full-time group were younger, more likely to be married, reported fewer hospitalizations, and were taking antipsychotic medications less frequently than disabled patients. Table 3 compares the distribution of any episode or subsyndromal symptom by employment group. Of the 281 patients, 36% ($n = 102$) experienced at least one episode and 60% ($n = 168$) experienced subsyndromal symptoms during the study period. There was no significant

Table 2 Patient demographics by employment status ($n = 281$)

	Disabled ($n = 75$)		Full-time ($n = 135$)		Other ($n = 71$)		Test	df	P
	n	%	n	%	n	%			
Sex							$X^2 = 2.752$	2	0.253
Male	28	37	36	27	20	28			
Female	47	63	99	73	51	72			
Diagnosis							$X^2 = 3.707$	4	0.447
BP I	53	71	79	58	45	64			
BP II	21	28	51	38	23	32			
BP NOS	1	1	5	4	3	4			
Education							$X^2 = 2.958$	4	0.565
High school	11	15	13	10	6	8			
Some college	25	34	43	32	20	28			
College graduate	38	51	78	58	45	64			
Marital status							$X^2 = 19.621$	4	0.001
Divorced	17	23	8	6	11	16			
Single	32	42	60	47	17	26			
Married	26	35	60	47	39	58			
Antidepressants							$X^2 = 0.430$	2	0.806
Yes	35	47	67	50	32	45			
No	40	53	68	50	39	55			
Antipsychotics							$X^2 = 8.157$	2	0.017
Yes	36	48	40	30	31	44			
No	39	52	95	70	40	56			
Any medication							$X^2 = 1.236$	2	0.539
Yes	70	93	125	93	63	89			
No	5	7	10	7	8	11			
Country of origin							$X^2 = 0.987$	2	0.610
US	57	76	100	74	49	69			
Outside US	18	24	35	26	22	31			
Hospitalizations	2.72 SD = 3.40		1.31 SD = 2.05		2.44 SD = 3.93		F = 6.471	2,272	0.002
Age of onset	23.61 SD = 10.59		20.37 SD = 8.56		19.23 SD = 8.73		F = 4.451	2,265	0.013
Days of data returned	176.43 SD = 46.40		153.80 SD = 56.26		139.76 SD = 49.97		F = 0.675	2,278	0.510
Age	40.72 SD = 9.05		33.96 SD = 9.82		38.93 SD = 8.76		F = 14.574	2,278	<0.001
Years of illness	16.97 SD = 10.82		14.13 SD = 10.47		19.66 SD = 10.76		F = 6.106	2,264	0.003

Table 3 Number of patients with episodes and subsyndromal symptoms by employment status ($n = 281$)

	Disabled ($n = 75$)		Full-time ($n = 135$)		Other ($n = 71$)		Test	df	P
	n	%	n	%	n	%			
With episodes							$X^2 = 2.979$	2	0.225
Yes	31	41	51	38	20	28			
No	44	59	84	62	51	72			
With depressed episodes							$X^2 = 7.939$	2	0.019
Yes	25	33	26	19	11	16			
No	50	67	109	81	60	84			
With manic episodes							$X^2 = 3.632$	2	0.163
Yes	15	20	36	27	11	16			
No	60	80	99	73	60	84			
With both depressed and manic episodes							$X^2 = 4.299$	2	0.117
Yes	9	12	11	8	2	3			
No	66	88	124	92	69	97			
With sub-syndromal symptoms							$X^2 = 0.200$	2	0.905
Yes	46	61	81	60	41	58			
No	29	39	54	40	30	42			

difference between the groups in the percentage of patients with any episode. However, a larger percentage of disabled patients experienced one or more depressed episodes with a mean of 33, 19 and 16% in the disabled, full-time and other groups, respectively ($X^2 = 7.939$, df = 2, $P = 0.019$).

There were five demographic variables that were significantly different among the employment groups: marital status, age, age of onset, years of illness and number of hospitalizations. Correlation analysis showed that age was significantly correlated with years of illness ($r = 0.592$, $P < 0.01$), age of onset ($r = 0.351$, $P < 0.01$) and number of hospitalizations ($r = 0.130$, $P < 0.05$). The model to analyze the percent of days in episodes and percent of days with subsyndromal symptoms included employment status, enrollment date and marital status as fixed factors and age as a covariate.

The results from the pairwise comparisons of the employment groups for all days are shown in Table 4. There were no significant differences between the employment groups in the mean percent of days spent in a depressed or manic episode. However, the mean percent of days with subsyndromal depression was significantly larger when comparing the disabled group with either the full-time group (29 vs. 15%, df = 201, $P < 0.001$) or the other group (29 vs. 18%, df = 140, $P < 0.023$). Furthermore, the mean percent of days in any episode plus the mean percent of days with subsyndromal symptoms was also significantly larger when comparing the disabled group with the full-time group (44 vs. 29%, df = 201, $P < 0.002$). The

Table 4 Pairwise comparison of estimated marginal mean percent of days in episodes or with subsyndromal symptoms by employment status ($n = 281$)

	Disabled ($n = 75$)		Full-time ($n = 135$)		Other ($n = 71$)		Disabled vs. full-time				Disabled vs. other			
	Mean %	SE	Mean %	SE	Mean %	SE	Mean difference	df[b]	SE	P[c]	Mean difference	df[b]	SE	P[c]
Marginal mean[a] percent of days not in any episode														
Days euthymic	63	3.1	78	2.6	73	3.2	−15	201	4.0	<0.001	−10	140	4.4	0.049
Days with subsyndromal depression	29	2.7	15	2.3	18	2.8	14	201	3.5	<0.001	11	140	3.8	0.023
Days with subsyndromal mania	9	1.6	7	1.4	9	1.7	d				d			
Days with severe subsyndromal depression	8	1.3	4	1.1	5	1.4	d				d			
Days with severe subsyndromal mania	1	0.5	1	0.4	1	0.5	d				d			
Marginal mean[a] percent of all days														
Days in any episode	14	2.5	10	2.0	11	2.6	d				d			
Days in depressed episode	9	2.0	6	1.6	6	2.0	3	201	2.5	0.407	3	140	2.8	0.548
Days in manic episode	5	1.4	4	1.2	6	1.4	d				d			
Days in episode + days with subsyndromal depression or mania	44	3.5	29	2.9	34	3.7	15	201	4.5	0.002	10	140	5.0	0.116
Days in episode + days with severe subsyndromal depression or mania	21	2.7	13	2.3	16	2.8	d				d			

[a] Marginal means at age 37.03
[b] 7 full-time and 4 other patients were missing marital status
[c] t-statistic with Sidak adjustment for multiple comparisons
[d] Corrected model significance not <0.05

Table 5 Pairwise comparison of estimated marginal mean percent of days within episodes by employment status, for patients having episodes ($n = 102$)

	Disabled ($n = 31$)		Full-time ($n = 51$)		Other ($n = 20$)		Disabled vs. full-time				Disabled vs. other			
	Mean %	SE	Mean %	SE	Mean %	SE	Mean difference	df[b]	SE	p[c]	Mean difference	df[b]	SE	p[c]
Marginal mean[a] percent of days within episodes														
Days with depression	50	6.2	33	5.4	38	7.5	17	76	8.1	0.094	12	48	9.5	0.514
Days with severe depression	21	4.2	16	3.7	16	5.1	d				d			
Days with mania	28	6.7	34	5.8	29	8.1	d				d			
Days with severe mania	5	1.8	4	1.6	5	2.2	d				d			

[a] Marginal means at age 37.95
[b] 4 full-time and 1 other patients were missing marital status
[c] t-statistic with Sidak adjustment for multiple comparisons
[d] Corrected model significance not <0.05

mean percent of days of euthymia was significantly smaller in the disabled group versus either the full-time group (63 vs. 78%, df = 201, $P < 0.001$) or the other group (63 vs. 73%, df = 140, $P < 0.049$). Considering only the days within episodes, the results of the pairwise comparisons for the 102 of the 281 patients who experienced episodes during the study are shown in Table 5. No significant differences were found between the employment groups for either the percent of days depressed or manic within an episode. Other than employment status, no factors or covariates included in the model were significant for any analysis.

Discussion

This study adds to the literature concerning the consequences of subsyndromal symptoms in patients with bipolar disorder. In this sample, there were no differences in the percent of days spent in episodes, or in the severity of symptoms within episodes between the patients who were in the disabled and full-time groups. However, disabled patients spent about twice as many days with subsyndromal symptoms of depression as those in the full-time group, and were more likely to have a depressed episode. These results are consistent with prior findings that subsyndromal depressive symptoms are associated with significant functional impairment [1, 9, 20, 27, 30, 36, 54], and that depressive symptoms may be more disabling than manic symptoms [9, 12, 30]. Similarly, in patients with unipolar disorder, minor depression has previously been associated with increased workplace absenteeism [11].

When not in an episode, patients in the full-time group spent 78% of days euthymic, while those who were disabled spent 63% of days euthymic. Compared to patients in the full-time group, disabled patients spent 15% more days either in episodes or with any subsyndromal symptoms, equivalent to 45 extra sick days a year. Although not all symptomatic days may be taken as sick days, this large number would preclude full-time employment in standard work situations. The finding that disabled patients report significantly more symptomatic days is consistent with prior observations that cumulative morbidity from bipolar disorder may be a better predictor of psychosocial functioning than the number of episodes [9, 22, 23]. Studies of work loss in patients with bipolar disorder found high levels of workplace absenteeism and disability [21, 32, 42] with large associated costs to employers and the health-care system [13, 21]. Additionally, the lack of impact of educational level on employment status is also in agreement with prior studies [9, 25], and with surveys of patients with bipolar disorder showing unemployment rates of about 60% among those with college degrees [26, 34]. Patients with part-time scheduled responsibilities outside the home also suffered more subsyndromal depression and were euthymic less often than those in the full-time group.

The interaction between depression, employment and disability is complex, and with this naturalistic approach, causality between subsyndromal symptoms and disability cannot be determined. Unemployment may contribute to the depressive symptoms experienced by the disabled group [17]. In a study of 756 people that did not consider psychiatric history, job loss triggered depression, poor health and impaired functioning [44]. The receipt of disability benefits may also be a disincentive to seek vocational training or employment [18, 48]. In the US, the medical benefits that accompany disability payments, including those for specialized mental health care, may provide another disincentive [19]. Yet, the distribution of employment status was not significantly different for patients residing in and outside the US, even though the relationship between government disability and health care benefits varied widely. Regardless of causality, more frequent subsyndromal symptoms would make it more difficult for patients with bipolar disorder to maintain full-time scheduled responsibilities outside of the home.

There are other limitations to this study. Researchers have also defined subsyndromal symptoms as minor symptoms [43], symptoms less severe than hypomania or minor depression [2, 28], and as

symptoms partially meeting the DSM-IV criteria for the required length [1]. This study does not address other issues that may contribute to both subsyndromal symptoms and employment status including substance abuse [41], medical comorbidities [24, 38], cognitive impairment [37, 45], psychosocial factors [15, 25] and socioeconomic status [51]. Other limitations include the relatively short length of the study period, the use of self-reported data, and the requirement for the patient to have access to a computer. The components of the other employment status group were too small to analyze separately. Finally, understanding the impact of subsyndromal mood symptoms is not intended to blur the critical diagnostic concept of bipolarity [3].

While disabled patients suffered subsyndromal depression about twice as often as those in the full-time group, subsyndromal depression was the most frequently experienced symptom by all patients, regardless of employment status. This predominance of subsyndromal depression is consistent with prior studies [6, 28, 29, 43], and persists in spite of the expansion in treatments available for bipolar disorder over the last decade. The focus of pharmaceutical treatments has been on managing acute episodes and preventing relapse. As the relation between subsyndromal symptoms and functional disability is better recognized, future development and evaluation of pharmacological treatments should also address the frequency and severity of symptoms that occur between major episodes. Similar to the approach used for epilepsy, the initial approval of a drug as an adjunctive agent rather than as monotherapy may be a useful approach to determine efficacy for subsyndromal symptoms, as well as for treating or preventing major episodes [31]. Moreover, the importance of the patient perspective of efficacy was noted in a recent draft FDA guidance regarding the use of patient-reported outcomes during the drug approval process [50]. As with other chronic illnesses in which there is no easily measurable marker of disease activity, increased attention to the impact of symptoms on the daily life of the patients with bipolar disorder may also help to improve control over the disease [52, 53]. Psychotherapeutic techniques offer a promising approach to assist in coping with symptoms that remain between episodes [35, 39, 46]. For some patients, these interventions may be necessary to improve social functioning despite optimal psychopharmacology, and the use of these programs should be expanded.

Conclusions

While there was no difference in the percent of time spent in episodes, disabled patients with bipolar disorder suffered subsyndromal symptoms of depression twice as often as those who were employed full-time or were full-time students. Although most patients with bipolar disorder recover from acute illness to the extent that that they no longer meet the DSM-IV criteria for an episode, the burden associated with subsyndromal symptoms may preclude full-time responsibilities outside the home and contribute to disability. The findings of this study highlight the need for treatments to minimize the frequency of subsyndromal symptoms.

References

1. Altshuler LL, Post RM, Black DO, Keck PE Jr, Nolen WA, Frye MA, Suppes T, Grunze H, Kupka RW, Leverich GS, McElroy SL, Walden J, Mintz J (2006) Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J Clin Psychiatry 67:1551–1560
2. Angst J, Merikangas K (1997) The depressive spectrum: diagnostic classification and course. J Affect Disord 45:31–39
3. Baldessarini RJ (2000) A plea for integrity of the bipolar disorder concept. Bipolar Disord 2:3–7
4. Bauer M, Grof P, Gyulai L, Rasgon N, Glenn T, Whybrow PC (2004) Using technology to improve longitudinal studies: self-reporting in bipolar disorder. Bipolar Disord 6:67–74
5. Bauer M, Grof P, Rasgon NL, Marsh W, Munoz RA, Sagduyu K, Alda M, Quiroz D, Glenn T, Baethge C, Whybrow PC (2006) Self-reported data from patients with bipolar disorder: impact on minimum episode length for hypomania. J Affect Disord 96:101–105
6. Bauer M, Glenn T, Grof P, Pfennig A, Rasgon NL, Marsh W, Munoz RA, Sagduyu K, Alda M, Quiroz D, Sasse J, Whybrow PC (2007) Self-reported data from patients with bipolar disorder: frequency of brief depression. J Affect Disord 101:227–233
7. Bauer M, Wilson T, Neuhaus K, Sasse J, Pfennig A, Lewitzka U, Grof P, Glenn T, Rasgon N, Bschor T, Whybrow PC (2008) Self-reporting software for bipolar disorder: validation of Chrono-Record by patients with mania. Psychiatry Res 159:359–366
8. Bauer MS, Crits-Christoph P, Ball WA, Dewees E, McAllister T, Alahi P, Cacciola J, Whybrow PC (1991) Independent assessment of manic and depressive symptoms by self-rating: scale characteristics and implications for the study of mania. Arch Gen Psychiatry 48:807–812
9. Bauer MS, Kirk GF, Gavin C, Williford WO (2001) Determinants of functional outcome and healthcare costs in bipolar disorder: a high-intensity follow-up study. J Affect Disord 65:231–241
10. Bauer MS, McBride L, Williford WO, Glick H, Kinosian B, Altshuler L, Beresford T, Kilbourne AM, Sajatovic M, Cooperative Studies Program 430 Study Team (2006) Collaborative care for bipolar disorder: part I: intervention and implementation in a randomized effectiveness trial. Psychiatr Serv 57:927–936
11. Broadhead WE, Blazer DG, George LK, Tse CK (1990) Depression, disability days, and days lost from work in a prospective epidemiologic survey. JAMA 264:2524–2528
12. Calabrese JR, Hirschfeld RM, Frye MA, Reed ML (2004) Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. J Clin Psychiatry 65:1499–1504
13. Dean BB, Gerner D, Gerner RH (2004) A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder. Curr Med Res Opin 20:139–154
14. Denicoff KD, Smith-Jackson EE, Disney ER, Suddath RL, Leverich GS, Post RM (1997) Preliminary evidence of the reliability and validity of the prospective life-chart methodology (LCM-p). J Psychiatr Res 31:593–603
15. Dickerson FB, Boronow JJ, Stallings CR, Origoni AE, Cole S, Yolken RH (2004) Association between cognitive functioning

and employment status of persons with bipolar disorder. Psychiatr Serv 55:54–58

16. Dion GL, Tohen M, Anthony WA, Waternaux CS (1988) Symptoms and functioning of patients with bipolar disorder 6 months after hospitalization. Hosp Community Psychiatry 39:652–657

17. Dooley D, Fielding J, Levi L (1996) Health and unemployment. Annu Rev Public Health 17:449–465

18. Drew D, Drebing CE, Van Ormer A, Losardo M, Krebs C, Penk W, Rosenheck RA (2001) Effects of disability compensation on participation in and outcomes of vocational rehabilitation. Psychiatr Serv 52:1479–1484

19. Elinson L, Houck P, Pincus HA (2007) Working, receiving disability benefits, and access to mental health care in individuals with bipolar disorder. Bipolar Disord 9:158–165

20. Fagiolini A, Kupfer DJ, Masalehdan A, Scott JA, Houck PR, Frank E (2005) Functional impairment in the remission phase of bipolar disorder. Bipolar Disord 7:281–285

21. Gardner HH, Kleinman NL, Brook RA, Rajagopalan K, Brizee TJ, Smeeding JE (2006) The economic impact of bipolar disorder in an employed population from an employer perspective. J Clin Psychiatry 67:1209–1218

22. Gitlin MJ, Swendsen J, Heller TL, Hammen C (1995) Relapse and impairment in bipolar disorder. Am J Psychiatry 152:1635–1640

23. Goldberg JF, Harrow M (2004) Consistency of remission and outcome in bipolar and unipolar mood disorders: a 10-year prospective follow-up. J Affect Disord 81:123–131

24. Guo JJ, Keck PE, Li H, Patel NC (2007) Treatment costs related to bipolar disorder and comorbid conditions among Medicaid patients with bipolar disorder. Psychiatr Serv 58:1073–1078

25. Hammen C, Gitlin M, Altshuler L (2000) Predictors of work adjustment in bipolar I patients: a naturalistic longitudinal follow-up. J Consult Clin Psychol 68:220–225

26. Hirschfeld RM, Lewis L, Vornik LA (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 64:161–174

27. Huxley N, Baldessarini RJ (2007) Disability and its treatment in bipolar disorder patients. Bipolar Disord 9:183–196

28. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB (2002) The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 59:530–537

29. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, Solomon DA, Leon AC, Keller MB (2003) A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 60:261–269

30. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB (2005) Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 62:1322–1330

31. Kaufman KR (2002) Comparative bioethics in bipolar and epilepsy research. Seizure 11:51–56

32. Kessler RC, Akiskal HS, Ames M, Birnbaum H, Greenberg P, Hirschfeld RM, Jin R, Merikangas KR, Simon GE, Wang PS (2006) Prevalence and effects of mood disorders on work performance in a nationally representative sample of US workers. Am J Psychiatry 163:1561–1568

33. Kogan JN, Otto MW, Bauer MS, Dennehy EB, Miklowitz DJ, Zhang HW, Ketter T, Rudorfer MV, Wisniewski SR, Thase ME, Calabrese J, Sachs GS, STEP-BD Investigators (2004) Demographic and diagnostic characteristics of the first 1,000 patients enrolled in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Bipolar Disord 6:460–469

34. Kupfer DJ, Frank E, Grochocinski VJ, Cluss PA, Houck PR, Stapf DA (2002) Demographic and clinical characteristics of individuals in a bipolar disorder case registry. J Clin Psychiatry 63:120–125

35. Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P (2003) A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective

disorder: outcome of the first year. Arch Gen Psychiatry 60:145–152

36. MacQueen GM, Marriott M, Begin H, Robb J, Joffe RT, Young LT (2003) Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. Bipolar Disord 5:349–355

37. Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, Malhi GS, Gonzalez-Pinto A, Daban C, Alvarez-Grandi S, Fountoulakis K, Kaprinis G, Tabares-Seisdedos R, Ayuso-Mateos JL (2007) Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disord 9:103–113

38. McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, Konarski JZ, Kennedy SH (2007) Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin Psychiatry 20:406–416

39. Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL (2003) A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 60, 904–912

40. Murray CJ, Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 349:1436–1442

41. O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE (1991) Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 159:123–129

42. Olfson M, Fireman B, Weissman MM, Leon AC, Sheehan DV, Kathol RG, Hoven C, Farber L (1997) Mental disorders and disability among patients in a primary care group practice. Am J Psychiatry 154:1734–1740

43. Paykel ES, Abbott R, Morriss R, Hayhurst H, Scott J (2006) Subsyndromal and syndromal symptoms in the longitudinal course of bipolar disorder. Br J Psychiatry 189:118–123

44. Price RH, Choi JN, Vinokur AD (2002) Links in the chain of adversity following job loss: how financial strain and loss of personal control lead to depression, impaired functioning and poor health. J Occup Health Psychol 7:302–312

45. Robinson LJ, Ferrier IN (2006) Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 8:103–116

46. Scott J, Garland A, Moorhead S (2001) A pilot study of cognitive therapy in bipolar disorders. Psychol Med 31:459–467

47. Simon GE, Ludman EJ, Bauer MS, Unützer J, Operskalski B (2006) Long-term effectiveness and cost of a systematic care program for bipolar disorder. Arch Gen Psychiatry 63:500–508

48. Social Security Advisory Board: The Social Security Definition of Disability (2003) http:\\www.ssab.gov. Accessed 15 Jan 2008

49. Suppes T, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, McElroy SL, Rush AJ, Kupka R, Frye MA, Bickel M, Post RM (2001) The Stanley Foundation Bipolar Treatment Outcome Network. II: demographics and illness characteristics of the first 261 patients. J Affect Disord 67:45–59

50. Department US, of Health, Human Services FDA Center for Drug Evaluation, Research; U.S. Department of Health, Human Services FDA Center for Biologics Evaluation, Research; U.S. Department of Health, Human Services FDA Center for Devices, Radiological Health ddd (2006) Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 4:79

51. Vaez M, Rylander G, Nygren A, Asberg M, Alexanderson K (2007) Sickness absence and disability pension in a cohort of employees initially on long-term sick leave due to psychiatric disorders in Sweden. Soc Psychiatry Psychiatr Epidemiol 42:381–388

52. Wenger NK (1988) Assessment of quality of life: a medical imperative. Cardiovasc Drugs Ther 1:553–558

53. Wiklund I (2004) Assessment of patient-reported outcomes in clinical trials: the example of health-related quality of life. Fundam Clin Pharmacol 18:351–363

54. Yatham LN, Lecrubier Y, Fieve RR, Davis KH, Harris SD, Krishnan AA (2004) Quality of life in patients with bipolar I depression: data from 920 patients. Bipolar Disord 6:379–385