Adequacy of Treatment Received by Diagnosed and Undiagnosed Patients With Bipolar I and II Disorders

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Objective: To investigate the adequacy of pharmacotherapy received by psychiatric inpatients and outpatients with a research diagnosis of bipolar I or II disorder, including patients both with and without a clinical diagnosis of bipolar disorder.

Method: In the Jorvi Bipolar Study (JoBS), 1630 psychiatric inpatients and outpatients in 3 Finnish cities were systematically screened between January 1, 2002, and February 28, 2003, for bipolar I and II disorders using the Mood Disorder Questionnaire. By using SCID-I and -II interviews, 191 patients were diagnosed with bipolar disorder (90 bipolar I and 101 bipolar II). Information was collected on clinical history, diagnosis, and treatment. The adequacy of treatment received was evaluated.

Results: Of the 162 patients with previous bipolar disorder episodes, only 34 (20.9%) of all and 30 (55.5%) of those with a clinical diagnosis of bipolar disorder were using a mood stabilizer at onset of the index episode. Only 81 (42.4%) of all 191 patients and 76 (65.0%) of those diagnosed with bipolar disorder received adequate treatment for the acute index phase. The factor most strongly independently associated with adequate treatment was clinical diagnosis of bipolar disorder (OR = 25.34). In addition, rapid cycling (OR = 2.45), polyphasic index episode (OR = 2.41), or depressive index phase (OR = 3.36) independently predicted inadequate treatment. Outpatients received adequate treatment markedly less often than inpatients.

Conclusions: Clinical diagnosis of bipolar disorder is by far the most important prerequisite for adequate treatment. Problems in treatment are associated mostly with outpatient settings, where adequacy of treatment of bipolar depression is a major concern. Lack of attention to the longitudinal course of illness is another major problem area.

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For patients with bipolar disorder, a gap exists between optimal and actual pharmacotherapy treatments. Several clinical studies[1–4] indicate that treatment recommendations of practice guidelines[5–13] and treatments received in practice differ, often markedly. For example, Simon et al.,[3] in a report on the first 1000 participants of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, stated that only for 59% did the pharmacotherapy meet the criteria for "minimally adequate" mood stabilizer use. Lim et al.[1] examined medications at discharge of 1471 patients admitted to hospital with bipolar I–associated mania or depression and found that only 1 in 3 patients with psychotic features and 1 in 6 without psychotic features were receiving medication consistent with the 2000 Expert Consensus Guidelines for bipolar disorder. Blanco et al.[2] analyzed 865 visits to a psychiatrist by patients with bipolar disorder, as recorded in the National Ambulatory Medical Care Survey database between 1992 and 1999, and found that over one third of the visits did not include a prescription for any mood stabilizer, but during almost half of the visits an antidepressant was prescribed and, in about half of these, without a prescription of a mood stabilizer. In fact, treatment practices that are rejected by virtually all guidelines, such as antidepressant monotherapy without a mood stabilizer,[1,2,4,14] appear surprisingly common.

On the other hand, some studies have found somewhat better adherence to guideline recommendations. In a sur-

vey of French psychiatrists by Verdoux et al.,[15] 82% of bipolar outpatients had at least 1 mood stabilizer, and 68% at least 1 antipsychotic. Ahmed and Anderson[16] reviewed case notes of outpatients with a clinical diagnosis of bipolar affective disorder and found that 75% had a mood stabilizer and 20% had antipsychotics alone or in 43% of patients combined with a mood stabilizer. However, the dosage of mood stabilizers was often inadequate. Lloyd et al.[17] examined the charts of subjects under the care of 4 hospitals in North East England and found that 85% had a mood stabilizer. Twenty-three percent of patients were prescribed antidepressants, combined with a mood stabilizer in all but 3 cases. Farrelly et al.[18] also reviewed the case notes of 84 consecutive patients attending the Cambridge Mental Health Service outpatient clinics and found the treatment to be consistent with the British Association for Psychopharmacology 2003 guidelines[19] in 72% of episodes. Overall, none of these studies report optimal treatment, and, in many cases, treatment appears clearly inadequate for the majority of bipolar patients.

Whether findings from a study can be generalized to the majority of bipolar patients is often uncertain. Patients have often been sampled exclusively from specialty clinics[3,16,18] and include only either inpatients[1,14] or outpatients[2,3,15–18,20] or only bipolar I patients.[1,14] In some studies, the diagnosis is made based on a patient register or on a clinical diagnosis alone,[1,2,15–18,20] leaving the validity of the diagnosis uncertain. Moreover, few studies have examined treatment in the acute phase or have not clearly defined the phase investigated.[2–4,15–17,20] Most importantly, however, virtually all of these studies have included only clinically diagnosed bipolar patients. Frye et al.[4] screened their study population with the Mood Disorder Questionnaire (MDQ), but they did not confirm the diagnosis with an interview, which renders the diagnosis uncertain. As bipolar disorder commonly remains undiagnosed even in psychiatric settings,[21] studies based solely on clinically diagnosed bipolar patients give an overly optimistic view of the true epidemiology of treatment of bipolar disorder.

The aim of this study was to investigate the adequacy of pharmacotherapy in a representative sample of patients with a research diagnosis of bipolar I or II disorder, including both those who were and those who were not yet clinically diagnosed with bipolar disorder. Patients were receiving treatment in a secondary-level psychiatric setting, representing psychiatric patients of 3 adjacent cities in Finland in 2002–2003.

METHOD

The Jorvi Bipolar Study (JoBS) is a collaborative bipolar research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, and the Department of Psychiatry, Jorvi Hospital, Helsinki University Central Hospital (HUCH), Espoo, Finland. The Department of Psychiatry of Jorvi Hospital provides secondary-care psychiatric services to all citizens of Espoo, Kauniainen, and Kirkkonummi (261,116 inhabitants in 2002). The ethics committee of HUCH approved the study protocol.

The JoBS methodology is described in detail elsewhere.[21] In brief, the first phase of patient sampling for the JoBS cohort study involved screening all inpatients and outpatients at the Department of Psychiatry, Jorvi Hospital, who possibly had a new episode of DSM-IV bipolar disorder between January 1, 2002, and February 28, 2003. Every patient aged 18 to 59 years who was (1) seeking treatment, (2) referred to treatment, or (3) already receiving care and now showing signs of deteriorating clinical state was screened with the MDQ[22] for the presence of bipolar disorder by attending mental health professionals in the department. After a positive screen or suspected bipolar disorder, the patient was fully informed about the study and written informed consent was requested. Altogether, 1630 patients were screened, 546 of whom were positive; 49 of these patients refused a face-to-face interview, and 7 could not be reached.

In the second phase of sampling, the 490 consenting patients were interviewed face-to-face by a researcher (O.M., H.V., P.A., K.S., S.L., and Marita Pippingsköld, M.D.) using the Structured Clinical Interview for DSM-IV disorders, research version with psychotic screen (SCID-I/P).[23] Altogether 201 patients were diagnosed with DSM-IV bipolar disorder and had a current episode. Ten patients refused to participate further, leaving 191 patients in the bipolar cohort study. Interrater reliability was assessed via videotaped interviews, which were blindly assessed by another rater (20 interviews; κ for bipolar disorder = 1.0, bipolar I = 1.0, bipolar II = 1.0). The Structured Clinical Interview for DSM-IV personality disorders (SCID-II)[24] was used to assess Axis II diagnoses. Bipolar II depressive mixed states were defined according to Benazzi and Akiskal[25] (depressive mixed state = 3 or more simultaneous intra-episode hypomanic symptoms present for at least 50% of the time during a major depressive episode).

In addition to SCID-I/P and SCID-II, the cohort baseline measurements included the following observer scales: Young Mania Rating Scale,[26] 17-item Hamilton Rating Scale for Depression,[27] Scale for Suicidal Ideation,[28] and Social and Occupational Functioning Assessment Scale of DSM-IV.[29] The self-report scales included the 21-item Beck Depression Inventory,[30] Beck Anxiety Inventory,[31] Beck Hopelessness Scale,[32] and Perceived Social Support Scale-Revised (PSSS-R).[33]

The JoBS cohort of 191 patients comprised 90 bipolar I (50 male, 40 female) and 101 bipolar II (40 male, 61 female) patients, with a mean age of 38 years.[21] Of these 191 patients, 117 had a clinical diagnosis of bipolar disorder before intake into the study. Specifically, 162 patients

Table 1. Proportion of Patients Treated With Mood Stabilizers[a] of the 191 Patients in Jorvi Bipolar Study

Diagnosis	Mood Stabilizer: Yes, N (%)	Mood Stabilizer: No, N (%)
Type of index phase**		
Depression (N = 106)	56 (53)	50 (47)
Hypomania (N = 21)	10 (48)	11 (52)
Mania (N = 23)	21 (91)	2 (9)
Mixed (N = 15)	9 (60)	6 (40)
Depressive mixed (N = 26)	11 (42)	15 (58)
Bipolar subtype*		
I (N = 90)	63 (70)	27 (30)
II (N = 101)	44 (44)	57 (56)
Clinical diagnosis of bipolar disorder*		
Yes (N = 117)	102 (87)	15 (13)
No (N = 74)	5 (7)	69 (93)
Total (N = 191)	107 (56)	84 (44)

[a]Lithium, valproate, carbamazepine, oxcarbazepine, lamotrigine.
*p < .001.
**p = .005.

had previous episodes of bipolar disorder, and, of these, only 54 had a clinical diagnosis of bipolar disorder before the onset of the index episode. Over their lifetime, the 191 patients in the study had had a median of 5 episodes. At intake into the cohort, 47 bipolar I and 59 bipolar II patients had depression, 5 bipolar I and 16 bipolar II patients had hypomania, 23 bipolar I patients had mania, 15 bipolar I patients had mixed state, and 26 bipolar II patients had depressive mixed state as the index phase.[21] Information about treatments received during the current episode and at the time of the interview was gathered in the interview and from psychiatric records. All regularly used medicines were included. We also investigated whether the onset of the index episode took place while patients were taking a mood stabilizer (lithium, valproate, carbamazepine, or oxcarbazepine). Rapid cycling was defined as in the DSM-IV as 4 or more distinct phases during 1 year, but depressive mixed states were also accepted as distinct phases. A polyphasic episode was defined as an episode consisting of more than 1 distinct phase (depressive, hypomanic, manic, mixed, or depressive mixed phase).[21]

Definitions of adequate acute-phase pharmacotherapy were based on published treatment guidelines.[5–9] We defined the treatments irrespective of dosage, serum concentration, or duration of treatment as follows: (1) Adequate treatment for bipolar depression included monotherapy with lithium or lamotrigine or combinations of lithium, valproate, carbamazepine, or olanzapine with an antidepressant. The combination of lamotrigine with an antidepressant was interpreted as inadequate treatment in bipolar I patients. (2) Adequate treatment for mania included monotherapy or combinations of lithium, valproate, carbamazepine, atypical antipsychotics, or haloperidol. Treatment was interpreted as inadequate if an antidepressant was used. (3) Adequate treatment for hypomania was defined the same as for mania. (4) Adequate treatment for mixed state was defined the same as for mania, except that treatment was interpreted as inadequate if a conventional antipsychotic was used. (5) Adequate treatment for depressive mixed state was defined the same as for mixed state. (6) Adequate treatment for rapid cycling included monotherapy or combinations of lithium, valproate, or carbamazepine. Treatment with lamotrigine was interpreted as adequate for bipolar II patients. Treatment was classified as inadequate if an antidepressant was used.

Statistical Methods

Student t test, Pearson χ^2 test, and the Mann-Whitney U test were used as appropriate. The Mantel-Haenszel χ^2 test and logistic regression models were used to adjust for confounding factors. SPSS software, version 11.5 (SPSS, Inc., Chicago, Ill.), was used.

RESULTS

Maintenance Treatment at Onset of Index Episode

Of the 162 patients with previous episodes of bipolar disorder, only 34 (20.9%) had a mood stabilizer at the onset of the index episode. Of these 162 patients, 54 had a clinical diagnosis of bipolar disorder before the onset of index episode, and 30 (55.5%) of these diagnosed patients had a mood stabilizer before the index episode started. Within the subgroup of clinically diagnosed patients with previous episodes, no significant difference was present between the 2 types of bipolar disorder, as 21 (55.3%) of 38 bipolar I and 6 (42.9%) of 14 bipolar II patients had a mood stabilizer.

Acute Treatment of Index Phase

Mood stabilizers. Overall, just over half of the patients received 1 or multiple mood stabilizers (Table 1). Whether patients had mood stabilizers was in univariate analyses associated with several factors. Patients with bipolar I had mood stabilizers more often than those with bipolar II disorder, men more often than women (61/90 [67.8%] vs. 46/101 [45.5%], $\chi^2 = 9.55$, df = 1, p = .002), and inpatients more often than outpatients (48/65 [73.8%] vs. 59/126 [46.8%], $\chi^2 = 12.7$, df = 1, p < .001). Patients with a clinical diagnosis of bipolar disorder mostly had a mood stabilizer, whereas patients without the diagnosis very rarely had one (Table 1). Somewhat unexpectedly, patients with rapid cycling had mood stabilizers less often than non–rapid cycling patients (27/62 [43.5%] vs. 80/129 [62.0%], $\chi^2 = 5.80$, df = 1, p = .016).

More specifically, 28 (14.7%) of the 191 patients and 28 (23.9%) of the 117 patients with a clinical diagnosis of bipolar disorder received lithium (Table 2). Bipolar I patients had lithium more often than bipolar II patients

Table 2. Medication of the 191 Patients in the Jorvi Bipolar Study According to the Index Phase and Clinical Diagnosis of Bipolar Disorder[a]

Index Phase	Lithium	Valproate	Carbamazepine or Oxcarbazepine	Lamotrigine	Antidepressant	Antipsychotic	Benzodiazepine	Hypnotic	No Psychotropic Medicine
All patients (N = 191)									
Depression (N = 106)	15 (14.2)	41 (38.7)	4 (3.8)	1 (0.9)	73 (68.9)	26 (24.5)	18 (16.9)	24 (22.6)	9 (8.5)
Hypomania (N = 21)	2 (9.5)	8 (38.1)	0 (0.0)	0 (0.0)	5 (23.8)	5 (23.8)	2 (9.5)	3 (14.3)	6 (28.6)
Mania (N = 23)	9 (39.1)	15 (65.2)	1 (4.3)	0 (0.0)	0 (0.0)	17 (74.0)	7 (30.4)	3 (13.0)	0 (0.0)
Mixed (N = 15)	1 (6.7)	9 (60.0)	0 (0.0)	0 (0.0)	3 (20.0)	2 (13.3)	2 (13.3)	1 (6.7)	4 (26.7)
Depressive mixed (N = 26)	1 (3.8)	10 (38.5)	1 (3.8)	0 (0.0)	13 (50.0)	3 (11.5)	3 (11.5)	4 (15.4)	3 (11.5)
Clinical diagnosis (N = 117)									
Depression (N = 61)	15 (24.6)	39 (63.9)	3 (4.9)	1 (1.6)	36 (59.0)	20 (32.8)	12 (19.7)	11 (18.0)	4 (6.6)
Hypomania (N = 13)	2 (15.4)	8 (61.5)	0 (0.0)	0 (0.0)	1 (7.7)	4 (30.8)	2 (15.4)	3 (23.1)	3 (23.1)
Mania (N = 23)	9 (39.1)	15 (65.2)	1 (4.3)	0 (0.0)	0 (0.0)	17 (74.0)	7 (30.4)	3 (13.0)	0 (0.0)
Mixed (N = 7)	1 (14.3)	7 (100.0)	0 (0.0)	0 (0.0)	1 (14.3)	2 (28.6)	2 (28.6)	1 (14.3)	0 (0.0)
Depressive mixed (N = 13)	1 (7.7)	10 (76.9)	1 (7.7)	0 (0.0)	5 (38.5)	1 (7.7)	1 (7.7)	2 (15.4)	0 (0.0)

[a]All values are expressed as N (%).

(21/90 [23.3%] vs. 7/101 [6.9%], $\chi^2 = 10.24$, df = 1, p = .001). Valproate was received by 83 (43.5%) of the 191 patients and 79 (67.5%) of the 117 patients with a clinical bipolar diagnosis (Table 2). Valproate was received by men more often than women (50/90 [55.6%] vs. 33/101 [32.7%], $\chi^2 = 10.14$, df = 1, p = .001), bipolar I patients more often than bipolar II patients (49/90 [54.4%] vs. 34/101 [33.7%], $\chi^2 = 8.36$, df = 1, p = .004), and inpatients more often than outpatients (38/65 [58.5%] vs. 45/126 [35.7%], $\chi^2 = 9.03$, df = 1, p = .003).

Antidepressants. Altogether 94 (49.2%) of the 191 patients had an antidepressant. Bipolar II patients had an antidepressant more often than bipolar I patients (63/101 [62.4%] vs. 31/90 [34.4%], $\chi^2 = 14.86$, df = 1, p < .001), patients without a clinical bipolar diagnosis more often than patients with the diagnosis (51/74 [68.9%] vs. 43/117 [36.8%], $\chi^2 = 18.77$, df = 1, p < .001), and patients with a polyphasic last episode more often than those with a monophasic last episode (57/98 [58.2%] vs. 37/93 [39.8%], $\chi^2 = 6.45$, df = 1, p = .032). Most of the depressive and half of the depressive mixed patients had an antidepressant (Table 2).

More than half of the 94 patients (50 [53.2%]) with an antidepressant had the antidepressant without a concurrent mood stabilizer or an atypical antipsychotic (Table 3). Of the patients receiving antidepressants, 35 (37.2%) had a concurrent mood stabilizer, 2 (2.1%) had an atypical antipsychotic, and 7 (7.4%) had a mood stabilizer plus an atypical antipsychotic (Table 3). Most of the 43 clinically diagnosed patients (39 [90.7%]) with an antidepressant had their antidepressants with a mood stabilizer, whereas nearly all of the 51 patients (48 [94.1%]) without a clinical diagnosis of bipolar disorder and an antidepressant had their antidepressants without a mood stabilizer.

Overall Adequacy of Acute-Phase Treatment

Overall, 81 (42.4%) of the 191 patients were classified as having received adequate acute-phase treatment (Table 4): men more often than women, bipolar I patients more often than bipolar II patients, and inpatients more often than outpatients. All manic patients received adequate treatment, as compared with less than one third of depressive or depressive mixed patients. Only one fourth of patients with rapid cycling and less than one third of patients with a polyphasic index episode received adequate treatment.

Inadequacy in treatment of rapid cycling was mainly due to absence of a mood stabilizer (35/47 [74.5%]) or presence of an antidepressant (34/47 [72.3%]). Inadequate treatment of patients with a polyphasic index episode was also mainly due to the absence of a mood stabilizer or atypical antipsychotic (33/69 [47.8%]) or the presence of an antidepressant during rapid cycling (25/69 [36.2%]).

Table 3. Proportions of Use of Each Class of Medications (antidepressants, mood stabilizers, atypical antipsychotics) by the 191 Patients in Jorvi Bipolar Study

	None of These Drug Classes		Antidepressant Only		Mood Stabilizer Only		Atypical Antipsychotic Only		Antidepressant Plus Mood Stabilizer		Antidepressant Plus Atypical Antipsychotic		Mood Stabilizer Plus Atypical Antipsychotic		Antidepressant Plus Mood Stabilizer Plus Atypical Antipsychotic	
Variable	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Men (N = 90)	8	8.9	17	18.9	30	33.3	3	3.3	17	18.9	1	1.1	10	11.1	4	4.4
Women (N = 101)	21	20.8	33	32.7	16	15.8	0	0.0	18	17.8	1	1.0	9	8.9	3	3.0
p Value	.020		.029		.005		.033		.849		.935		.612		.589	
Bipolar subtype																
I (N = 90)	13	14.4	10	11.1	25	27.8	3	3.3	14	15.6	1	1.1	18	20.0	6	6.7
II (N = 101)	16	15.8	40	39.6	21	20.8	0	0.0	21	20.8	1	1.0	1	1.0	1	1.0
p Value	.788		.000		.260		.033		.349		.935		.000		.030	
Index phase																
Depression (N = 106)	13	12.3	34	32.1	14	13.2	1	0.9	30	28.3	2	1.9	5	4.7	7	6.6
Hypomania (N = 21)	7	33.3	4	19.0	7	33.3	0	0.0	1	4.8	0	0.	2	9.5	0	0.0
Mania (N = 23)	0	0.0	0	0.0	9	39.1	2	8.7	0	0.0	0	0.0	12	52.2	0	0.0
Mixed (N = 15)	4	26.7	2	13.3	8	53.3	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0
Depressive mixed (N = 26)	5	19.2	10	38.5	8	30.8	0	0.0	3	11.5	0	0.0	0	0.0	0	0.0
p Value	.007		.001		.001		.202		.000		.688		.000		.076	
Treatment setting																
Outpatient (N = 126)	25	19.8	40	31.7	32	25.4	0	0.0	18	14.3	2	1.6	6	4.8	3	2.4
Inpatient (N = 65)	4	6.2	10	15.4	14	21.5	3	4.6	17	26.2	0	0.0	13	20.0	4	6.2
p Value	.008		.012		.552		.010		.049		.196		.001		.203	
Bipolar diagnosis																
Yes (N = 117)	8	6.8	4	3.4	44	37.6	3	2.6	32	27.4	0	0.0	19	16.2	7	6.0
No (N = 74)	21	28.4	46	62.2	2	2.7	0	0.0	3	4.1	2	2.7	0	0.0	0	0.0
p Value	.000		.000		.000		.085		.000		.050		.000		.008	
Rapid cycling																
Yes (N = 62)	13	21.0	21	33.9	14	22.6	0	0.0	10	16.1	1	1.6	1	1.6	2	3.2
No (N = 129)	16	12.4	29	22.5	32	24.8	3	2.3	25	19.4	1	0.8	18	14.0	5	3.9
p Value	.130		.098		.735		.123		.583		.606		.002		.821	
Monophasic (N = 93)	16	17.2	16	17.2	26	28.0	3	3.2	18	19.4	1	1.1	11	11.8	2	2.2
Polyphasic (N = 98)	13	13.3	34	34.7	20	20.4	0	0.0	17	17.3	1	1.0	8	8.2	5	5.1
p Value	.488		.006		.222		.037		.720		.970		.397		.270	

Table 4. Proportions of the 191 Patients in Jorvi Bipolar Study Receiving Adequate Treatment

	Undiagnosed				Bipolar Diagnosis				All Patients			
	Total	Adequate Treatment			Total	Adequate Treatment			Total	Adequate Treatment		
Variable	N	N	%	p	N	N	%	p	N	N	%	p
Men (N = 90)	23	2	8.7		67	45	67.2		90	47	52.2	
Women (N = 101)	51	3	5.9	.662	50	31	62.0	.563	101	34	33.7	.009
Bipolar subtype												
I (N = 90)	23	3	13.0		67	47	70.1		90	50	55.6	
II (N = 101)	51	2	3.9	.167	50	29	58.0	.174	101	31	30.7	.000
Index phase												
Depression (N = 106)	45	3	6.7		61	30	49.2		106	33	31.1	
Hypomania (N = 21)	8	0	0.0		13	9	69.2		21	9	42.9	
Mania (N = 23)	0	0	0.0		23	23	100.0		23	23	100.0	
Mixed (N = 15)	8	2	25.0		7	6	85.7		15	8	53.3	
Depressive mixed (N = 26)	13	0	0.0	.135	13	8	61.5	.000	26	8	30.8	.000
Treatment setting												
Inpatient (N = 65)	14	2	14.3		51	34	66.7		65	36	55.4	
Outpatient (N = 126)	60	3	5.0	.255	66	42	63.6	.733	126	45	35.7	.009
Rapid cycling												
Yes (N = 62)	32	2	6.3		30	13	43.3		62	15	24.2	
No (N = 129)	42	3	7.1	.879	87	63	72.4	.005	129	66	51.2	.000
Mono/polyphasic												
Monophasic (N = 93)	29	1	3.4		64	51	79.7		93	52	55.9	
Polyphasic (N = 98)	45	4	8.9	.342	53	25	47.2	.000	98	29	29.6	.000
Bipolar diagnosis												
Yes (N = 117)									117	76	65.0	
No (N = 74)									74	5	6.8	.000

Among the patients with a depressive index phase, the main reasons for inadequate treatment comprised not having a mood stabilizer or an atypical antipsychotic (34/73 [46.6%]), having an antidepressant during rapid cycling (24/73 [32.9%]), and/or having valproate monotherapy without an antidepressant (16/73 [21.9%]).

Impact of Diagnosis on Adequacy of Treatment

By far the most important cause of inadequate treatment of bipolar patients was the lack of a bipolar diagnosis. These patients rarely (5/74 [6.8%]) had a mood stabilizer and often had an antidepressant without a mood stabilizer (46/74 [62.2%]). However, even when the diagnosis had been assigned, pharmacotherapy was often (in 35.0% of cases) classified as inadequate. The main reasons for this inadequacy were lack of a mood stabilizer or an atypical antipsychotic (12/41 [29.3%]), presence of an antidepressant in rapid cycling (13/41 [31.7%]), and/or treatment of depression with valproate without an antidepressant (14/41 [34.1%]).

Independent Predictors of Adequate Treatment in Multivariate Models

In the logistic regression model (Table 5), adequate treatment was the dependent variable, and age, sex, bipolar subtype, index phase, rapid cycling, treatment setting, mono- or polyphasic index episode, any lifetime anxiety disorder, any lifetime substance use disorder, any personality disorder, and number of hospital treatments were independent variables. The factors most strongly independently associated with inadequate treatment were not having a clinical diagnosis of bipolar disorder (OR = 25.34), rapid cycling (OR = 2.45), polyphasic index episode (OR = 2.41), and depressive index phase (OR = 3.36).

DISCUSSION

The JoBS cohort is a representative sample of secondary-level community psychiatric bipolar I and II inpatients and outpatients, both those who had been clinically diagnosed and those who had been undiagnosed. The findings that just one fifth (21%) of these patients had maintenance treatment at the onset of the episode and less than one half (42%) were given adequate treatment in the acute phase are epidemiologically important. The value of correctly diagnosing bipolar disorder cannot be overemphasized. In addition to the lack of diagnosis, undertreatment appears to be related to the longitudinal course of the disorder, as only a minority of patients with rapid cycling or a polyphasic episode received appropriate treatment. Undertreatment is also related to the depressive phases as less than one third of depressed patients received adequate treatment. From an epidemiologic perspective, it is also noteworthy that the problems are mostly situated in the outpatient context, where the majority of patients are treated.

The strengths of the JoBS include a relatively large clinical cohort study from community-level psychiatric care, with a catchment area of 3 Finnish cities and systematic screening for bipolar I and II disorders using the MDQ (cut-off modified to maximize sensitivity) among

Table 5. Logistic Regression Models Predicting Inadequate Treatment for the 191 Patients in Jorvi Bipolar Study

Diagnosis	β	Wald	df	OR	95% CI for OR	p
Undiagnosed bipolar disorder	3.23	35.94	1	25.34	8.81 to 72.90	< .001
Rapid cycling	0.90	4.16	1	2.45	1.04 to 5.80	.041
Polyphasic	0.88	4.98	1	2.41	1.11 to 5.21	.026
Index phase depressive	1.21	8.98	1	3.36	1.52 to 7.41	.003

both psychiatric inpatients and outpatients.[21] The patients in the JoBS were carefully diagnosed using semi-structured interviews, completed by several informants in any case of uncertainty, with excellent reliability for diagnosing both bipolar I and II disorders. In addition, Axis I and II comorbid disorders were assessed using SCID-I/P and SCID-II. Psychopharmacologic treatment received was examined by collecting all available data from interviews and from patients' psychiatric records.

However, several methodological points need to be addressed. First, although we took patients into the cohort during the early acute phase, thus minimizing contamination of treatment by the study,[21] in some cases the study may have had an effect on clinical decisions regarding diagnosis and pharmacotherapy. Second, we could not systematically evaluate the dosage, duration of treatment, or serum levels of the medicines. If anything, these 2 factors are likely to increase the proportion of patients classified as having received adequate treatment. Third, in the acute phase we investigated only first-line treatment prescribed and cannot thus exclude the possibility that in some individual cases provision of adequate treatment was delayed and started after the investigation. Fourth, our bipolar II cases included 8 DSM-IV bipolar not-otherwise-specified patients (hypomania of 2–3 days or depressive mixed states) clinically similar to the other bipolar II patients.[21] However, excluding these cases would have had only a minimal effect on the results. Fifth, since we also included depressive mixed states, as defined by Benazzi and Akiskal,[25] which would be diagnosed as major depressive episodes in the DSM-IV, we had 26 fewer cases of depression in the index phase as compared with strict DSM-IV diagnoses. However, classifying the depressive mixed states as depressions would have had no impact on the rate of adequate treatment of depression (31.1% vs. 31.1%). Sixth, since we included depressive mixed states as a distinct phase, we also had more cases with rapid cycling (9 more) and polyphasic episodes (4 more). Seventh, the timing of patient recruitment between 2002 and 2003 may have had an influence on the medications chosen, specifically affecting lamotrigine treatment since lamotrigine became reimbursed for bipolar disorder in Finland during the study. Finally, all estimates of the frequency of adequate treatment are dependent on the definition of adequate treatment. Neither randomized controlled studies nor universally accepted practice guideline recommendations exist for all types and phases of bipolar disorder: this is particularly true for bipolar II overall and specifically for depressive mixed states. Thus, any definition of adequate pharmacotherapy is somewhat arbitrary. For example, we did not accept valproate monotherapy as adequate treatment for the depressive phase, as evidence of its efficacy is still limited.[34] Had we accepted it, 43% of depressive patients and 49% of patients overall would have received adequate treatment. While all such issues of definition influence the percentage of patients adequately treated, none of them alone markedly affects the overall picture.

One of our main findings was that no more than one fifth (21%) of patients had maintenance treatment at onset of the episode. For patients with a previous bipolar diagnosis, the proportion was only just over half (56%). Moreover, fewer than half (42%) of the bipolar patients received adequate acute-phase treatment. This result was mostly due to the lack of a bipolar diagnosis, as only a small minority (7%) of the undiagnosed patients were given adequate treatment. Although clinical diagnosis was very important as a predictor of adequate treatment, it by no means guaranteed proper treatment. Among the diagnosed, about two thirds (65%) received treatment that we defined as adequate, which is not synonymous with optimal treatment. It is noteworthy that the rate of adequate treatment varied markedly by illness phase; treatment received was adequate for mania (100%), but far from adequate for bipolar depression (31%). The reasons underlying shortcomings in treatment may at least in part be related to the working conditions of practicing psychiatrists. The clinician is faced with different kinds of often contradictory information as well as limited time, and the patient may have urgent problems that need immediate attention and action. A comprehensive diagnostic evaluation may take longer than the time available. The patient may deny having the disorder or for some other reason find the treatment unacceptable. The attending psychiatrist might also lack the necessary training and knowledge of how to treat bipolar patients adequately.[35] Still, as bipolar disorder is a life-threatening[36] and often chronic mental disorder with marked psychosocial impairment[37–44] and considerable health costs,[45,46] providing adequate treatment is an important aim.

To the best of our knowledge, no previous study has evaluated the differences in quality of treatment provided

to inpatients and outpatients. We found a clear difference in the adequacy of treatment between inpatient and outpatient settings. This finding mainly reflects the significantly greater proportion of patients with a diagnosis of bipolar disorder in hospital settings, as well as differences in the proportions of bipolar I and II patients and differences in the types of mood phases treated in different settings. Most episodes of bipolar depression are treated in outpatient settings, and we found that only a fraction of these cases received adequate treatment. That treatment of depressive phases may be problematic even among inpatients was documented by Lim et al.[1] in their study of 1471 hospitalized bipolar I patients; they found less than one third (31%) of depressive patients with psychotic features and less than one fifth (17%) of those without these features discharged without the recommended pharmacotherapy. From an epidemiologic perspective, these findings are of major importance because the course of bipolar disorder is dominated by depressive phases,[37,39,44] and these phases carry a high risk for suicide[36] and functional disability.[38]

Somewhat unexpectedly, we found that patients with rapid cycling or polyphasic episodes significantly less often received adequate treatment. The main reasons for inadequate treatment in rapid cycling were absence of a mood stabilizer and presence of an antidepressant. Although most practice guidelines recommend avoiding antidepressants in rapid cycling, we found that the proportion of patients receiving antidepressants was no lower for rapid cyclers than for non–rapid cyclers; actually the trend was the opposite (this was also true for patients who had rapid cycling and a clinical diagnosis of bipolar disorder). That rapid cycling may not reduce the proportion of patients receiving antidepressants is in line with the findings of Simon et al.[3] and Lloyd et al.[17] It thus appears that having rapid cycling does not influence whether antidepressant treatment is received. One reason for this antidepressant treatment of rapid cyclers may be that the attending psychiatrists do not pay sufficient attention to the longitudinal course of the illness. Another explanation may be that information on how to treat these patients is missing, overly complex, or contradictory. The main reasons for inadequate treatment for polyphasic episodes were absence of a mood stabilizer (or an atypical antipsychotic) and presence of an antidepressant despite rapid cycling. Another possible explanation for inadequate treatment in rapid cycling or polyphasic episodes is that the pharmacotherapy of the former phase or episode remains poorly monitored, and treatment thus does not follow transitions in the different phases or episodes. Even though rapid cycling and polyphasic episodes are partly correlated, both are significant in the regression model as independent predictors of inadequate treatment. This observation highlights the importance of the longitudinal view of illness in treatment. More systematic use of life charts and regular mood ratings would be likely beneficial in helping clinicians to grasp the longitudinal course of their patients and thus improve quality of care.

In conclusion, besides the correct diagnosis being crucial, the longitudinal course of bipolar disorder appears to pose an obstacle to providing adequate treatment for patients with the disorder. Improving the quality of treatment of bipolar depression in psychiatric outpatient settings is a central public health issue.

Drug names: carbamazepine (Equetro, Tegretol, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal).

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