The Effect of Moderate and Excessive Alcohol Use on the Course and Outcome of Patients With Bipolar Disorders: A Prospective Cohort Study

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Objective: Comorbid alcohol use disorders (AUDs) are frequently associated with negative effects on course and outcome of bipolar disorder. This prospective cohort study assessed the effect of actual alcohol use (no, moderate, and excessive) on the course and outcome of patients with bipolar disorders.

Method: Between June 2003 and November 2005, 137 outpatients (aged 23–68 years) with *DSM-IV*–diagnosed bipolar I (66%) or II (34%) disorder rated their mood and the number of alcohol units consumed daily for a period up to 52 weeks with the National Institute of Mental Health Self-Rating Prospective Life-Chart Method (LCM). At baseline, the Structured Clinical Interview for *DSM-IV* was administrated, and demographic, social, and clinical characteristics were obtained. At monthly visits, the Clinical Global Impressions Scale-Bipolar Version (CGI-BP), the Global Assessment of Functioning (GAF) scale, and the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36) were rated. Based on the alcohol use in the first 4 weeks of follow-up, patients were assigned to 1 of 3 groups: no/incidental, moderate, or excessive alcohol use.

Results: None of the sociodemographic and clinical characteristics at baseline were significantly different between the 3 drinking groups, with the exception of—and as a consequence of the group assignment—the prevalence of lifetime and current diagnosis of AUD. Also, no differences between the 3 drinking groups were found on any of the clinical outcome variables, ie, number of days ill (depressed, hypomanic/manic, and total); severity of depression, mania, and overall bipolar illness (LCM); GAF score; CGI-BP (depression, mania, and overall); and all the subscales of the MOS-SF-36. Also, the number of episodes according to *DSM-IV* and the Leapfrog method showed no significant differences between the drinking groups.

Conclusions: In this sample of patients and with the sensitive measurement of mood and drinking status over a full year, we could not confirm the findings of other studies indicating a negative effect of excessive alcohol use on the course of bipolar illness. This study found that neither moderate nor excessive use of alcohol has a negative effect on the course and outcome of bipolar illness. Possible explanations for these findings are discussed.

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Many patients with bipolar disorders (BDs) use alcohol on a regular basis. About 50% of patients with bipolar disorders meet lifetime criteria for comorbid substance use disorders (SUDs).[1–6] The negative effects of comorbid SUDs (including alcohol use disorders [AUDs]) on course and outcome of bipolar disorder are well documented.[5,7] Previous studies found that bipolar disorder with comorbid SUD is associated with an earlier age at onset[8–11] but, in other studies, also with a later age at onset,[12–14] a higher number of episodes,[15] longer episodes,[16] more symptoms during interepisode intervals,[17,18] a higher probability to experience syndromal recurrence,[13,19] more mixed episodes,[20] a higher number of total mood-related symptoms and manic symptoms at presentation,[21] more hospitalizations,[3,22] more suicidality,[23] decreased treatment adherence,[17,18] and poorer response to treatment[16,24] compared to bipolar disorder without comorbid SUD.

In contrast, the effects of actual alcohol consumption, including moderate use, in bipolar disorder are less well known. Therefore, we did a search of EMBASE: Psychiatry (1997–2nd quarter 2008), MEDLINE (1950–present), and PsycINFO (1958–May 2008) with the following search words: *mania, manic depressive illness, bipolar disorder, moderate alcohol use, alcohol consumption, alcoholism, alcohol abuse, alcohol dependence, drinking behavior,* and *social drinking.* In addition, cross-references from the obtained articles were also used to find other articles on this subject. This search resulted in 10 published studies that addressed the effects of alcohol use on the course and outcome of bipolar disorder: 5 retrospective studies and 5 prospective follow-up studies. The 5 prospective studies[19,24–27] and 1 of the retrospective studies[28] mainly looked at previous and/or current AUD without further specification of the actual amount of alcohol intake. The main findings of these 5 prospective studies were that AUD in BD patients was associated with syndrome recurrence in adolescents,[19] poor residential status and occupational outcome,[25] and shorter

time in remission.[25,26] In addition, first-episode patients for whom AUD predated BD were older and were more likely to recover than patients with BD only and patients for whom BD predated AUD, while patients for whom AUD developed after the onset of BD spent more time in affective episode and had more AUD symptoms.[24,27]

The other 4 studies[21,22,29,30] also looked at the actual amount of alcohol intake. The frequency and volume of alcohol consumption in these studies, all with a retrospective design, was assessed in different ways. Reich et al[22] measured alcohol consumption (excessive-moderate and chronic-episodic) by using prior records of patients. Salloum et al[21] assessed alcohol use with a 4-point scale (absent-mild-moderate-severe misuse, rated by a clinical investigator) based on the report of patients about their alcohol use during the period of 2 weeks before their participation in the study. McKowen et al[29] used the timeline follow-back method.[31] With this method, patients retrospectively charted the amount of alcohol and number of drinking days in a calendar-like fashion over a 30-day episode before entering the study. Goldstein et al[30] preformed the only study that addressed the association of moderate alcohol use and illness severity in bipolar disorders using the Khavari Alcohol Test to assess the frequency and volume of overall alcohol consumption, as well as consumption of beer, wine, and spirits.[32] The most important findings of these 4 studies were that moderate or excessive alcohol use was found to be associated with (1) being hospitalized versus never been hospitalized[22]; (2) more frequently having a rapid cycling course and a recent diagnosis[29]; (3) more mood lability, more manic symptoms, more other drug use, and more impairment in overall functioning[21]; and (4) more lifetime manic episodes and emergency department visits in men and more lifetime depressive and hypomanic episodes in women.[30]

All 10 studies have considerable limitations. In the 5 retrospective studies, recall bias may have influenced the reliability and validity of the data, whereas in the 5 prospective studies, only a very spaced follow-up was performed with periods between the various assessments ranging between 4 and 192 weeks. In addition, only use/abuse of alcohol in general was assessed and almost never the actual amount of alcohol intake. As a consequence, almost no data are available about the effect of moderate alcohol consumption on the course and outcome of bipolar disorder. In addition, it is difficult to compare the results of the studies due to variations in patient populations (eg, hospitalized versus nonhospitalized), in diagnostic assessments and criteria, and in definitions of episodes and thresholds. Finally, most of the studies did not specify whether patients also used illegal drugs, which is relevant as there is a strong correlation of AUD with drug abuse and dependence.[33]

In conclusion, to our knowledge, there is no well-designed prospective follow-up study that compared the effect of actual amounts of alcohol use on the course and outcome of patients with bipolar disorders. Therefore, we conducted a prospective cohort study in which patients with a bipolar disorder were asked to register their mood symptoms and their actual alcohol use every day for a period of 12 months. We hypothesized a priori that the course and outcome of bipolar patients with moderate use of alcohol would not differ from patients who did not or only occasionally use alcohol. We also hypothesized that patients with excessive use of alcohol would have a significantly worse course and outcome compared to patients with no or occasional as well as patients with moderate use of alcohol.

METHOD

Subjects and Recruitment

Patients had to meet the following inclusion criteria: (1) aged 18–75 years; (2) meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria[34] for bipolar I disorder or bipolar II disorder; (3) not having a serious physical illness that might influence the diagnosis or course of bipolar disorder, according to the clinical judgment of the treating physician; (4) able and willing to participate in the study for 1 year; and (5) with adequate command of the Dutch language. The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht (The Netherlands). All patients gave written informed consent after full explanation of the study.

Between June 2003 and November 2005, a total of 180 outpatients were approached: 128 patients from 13 mental hospitals, including 2 academic medical centers; 4 patients from 1 addiction treatment center; and 48 patients through the Dutch Association for Manic-Depressive Patients and Relatives. Of these, 158 patients (88%) entered baseline assessment. The other 22 patients were excluded because they did not give informed consent (n = 18), had no adequate command of the Dutch language (n = 1), had too severe alcoholism (n = 1), suffered from a substance-induced mood disorder (n = 1), or had a schizoaffective disorder (n = 1).

From the 158 patients who completed the baseline assessment, 137 subjects (87%) participated in the study for at least 2 months, 125 patients (79%) participated for at least 6 months, and 104 patients (66%) completed the whole year. Analyses were based on the 137 patients with follow-up data during at least 2 months. Reasons for the 33 noncompleters beyond 2 months were aversion to the daily registrations (n = 16), developing a depressive (n = 2) or manic episode (n = 2), worsening of their alcohol dependence (n = 2), noncompliance (n = 2), death by a natural cause (n = 1) or liver coma due to alcoholism (n = 1), and other reasons (n = 7).

Assessment

At entry, the Structured Clinical Interview for *DSM-IV* (SCID-I)[35] was administrated by trained mental health care

professionals. In order to compare the results of our study with other studies, data were also obtained by means of the Network Enrollment Questionnaire of the former Stanley Foundation Bipolar Network.[36,37] These data included demographic and social characteristics, such as marital status, educational background, past and current level of occupational functioning and household income, and clinical characteristics, such as family history of psychiatric illness, estimated prior course of illness variables (number of prior episodes, number of hospitalizations, history of rapid cycling, history of alcohol-induced depression, hypomania, mania, and cycle acceleration), treatment adherence, and number of past suicide attempts. Self-report data about substance use were obtained with a questionnaire about the present and past use of substances (quantity, frequency, and age at onset), including information on caffeine, nicotine, alcohol, cannabis, ecstasy, amphetamines, lysergic acid diethylamide (LSD), cocaine, heroine, and other drugs.

During the full year of the study, patients rated their mood with the National Institute of Mental Health (NIMH) Self-Rating Prospective Life-Chart Method (LCM) every day. The LCM is a reliable method for the measurement of severity of mood symptoms (mania or depression) and related level of dysfunction on a 5-point scale (0 = no, 2.5 = mild, 5 = low moderate, 7.5 = high moderate, and 10 = severe dysfunction), which also allows to assess hypomanic, manic, and depressive episodes in patients with bipolar disorders.[38–45] Using the LCM, patients were also asked to report daily on their use of medication and their intake of alcohol (number of alcohol units), for which patients got written and verbal instructions about the standard units of alcohol in beer, wine, and spirits. One unit was defined as 12 mL pure alcohol (equals about 10 g of alcohol) equaling 100 mL of wine (12% alcohol), 250 mL of beer (5% alcohol), or 35 mL of liquor (35% alcohol).[46]

At baseline and at every monthly visit during follow-up, the LCM registrations were checked and approved by the research assistants who then also completed the Clinical Global Impressions Scale-Bipolar Version (CGI-BP),[47] the Global Assessment of Functioning (GAF) scale,[48] the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36),[49] and a questionnaire concerning the direct and indirect medical care utilization of the prior month.

Outcome Measures

Based on the LCM registrations (up to 1 year), the following clinical outcome measures were calculated per first 4 weeks and per year: (1) the number of manic days (LCM score at least low moderate mania), the number of hypomanic days (LCM score mild mania), the number of depressed days (LCM score at least low moderate depression), and the total number of days ill; (2) the mean severity of mania, depression, and overall bipolar illness over the observation period (mean LCM score for each pole [manic or depressed] separately or the maximum of both poles [overall]; days on which patients switched mood states at least once were assigned to the most severe depression score and the most severe mania score); and (3) the number of episodes based on *DSM-IV* criteria and on the so-called NIMH Leapfrog method as previously described by Denicoff et al.[41] In addition, monthly assessment questionnaire outcomes were obtained: (4) GAF scores, (5) CGI-BP scores, and (6) MOS-SF-36 scores.

Based on *DSM-IV*, manic episodes were counted if they included a minimum score on the LCM of 7 days of at least low moderate mania (or hospitalization), hypomanic episodes were counted if they included a minimum of 4 days of an LCM score of mild mania, and depressive episodes were counted if they included a minimum of at least 14 days with an LCM score of low moderate depression (or hospitalization).

According to the Leapfrog method, a manic episode required a minimum of 1 day of moderate or severe mania, a hypomanic episode required a minimum of 2 days of mild mania, and a depressive episode required 2 days of moderate depression or 1 day of severe depression. In addition, an episode was considered ended with a switch in mood polarity (from mania to depression or vice versa), after at least 2 weeks of complete euthymia, or when the euthymic interval between 2 successive hypomanic, manic, or depressive episodes was at least 1 day greater than the longest duration of the adjacent episode of the same polarity.[41,50]

Outcome Predictors

In order to distinguish different types of drinking patterns at baseline, subjects were assigned to 3 different groups (no or incidental use, moderate use, or excessive use), based on the average number of units of alcohol per week that patients used in the first 4 weeks of the study. We chose the Dutch standard of about 10 g of pure alcohol per standard drink (unit) and the following a priori defined drinking levels: level I (no or incidental use) as 0–2 units of alcohol/wk (n = 44); level II (moderate use) for males as 3–21 units/wk and for females as 3–14 units/wk (n = 49); and level III (excessive use) for males as 22 or more units/wk and for females as 15 or more units/wk (n = 44).[46] Males were considered to have a heavy drinking day if they consumed 5 or more units per day, and females were considered if they consumed 4 or more units per day.[51]

Weekly alcohol intake (no, moderate, and excessive) and the number of heavy drinking days during the first 28 days and of the follow-up period were used as the main predictors of outcome. In addition, lifetime or current AUDs and SUDs (alcohol excluded) were used as predictors of outcome.

To gain insight into the validity and stability of the operationalization of alcohol level, the number of switches between alcohol levels during the observation period was studied. A switch from one level to another between 2

consecutive weeks was indicated according to the definition of alcohol level, accompanied by the demand that a difference of at least 5 drinks between 2 weeks should be present. Application of this definition to the alcohol levels found at baseline (first 4 weeks) showed that most switches occurred between the moderate and excessive drinking levels (mean ± SD number of switches per year: level I, 1.7 ± 3.5; level II, 6.9 ± 6.0; level III, 5.2 ± 6.3; $F = 10.8$; $P < .01$).

In the total sample of N = 137, 44 subjects (32%) did not change their alcohol level at any time during the observation period. The majority (n = 28) of these 44 nonswitchers remained in the first, no-drinking level I. From the other 93 subjects who switched levels at least 1 time, 38 subjects (28%) switched alcohol level more than 5 times during follow-up. The majority of changes occurred between level II and III. Spearman rank correlation test between alcohol level in the first 4 weeks and during follow-up was .81 ($P < .01$), indicating good correspondence between initial and follow-up levels, and, as such, the 2 measurement periods were usable for further analysis.

Confounders

A positive family history of SUDs, more than 10 prior manic or depressive episodes, a history of prior rapid cycling, and poor occupational functioning at study entry, which have been found to predict outcome of bipolar disorder in general, were considered as potential confounders for the relation between alcohol-use levels and 12-month clinical course and outcome.[50]

Statistical Analysis

All analyses were performed with the data of the 137 patients who completed at least 2 months of registration after baseline. No significant differences ($P < .10$) were found in the sociodemographic and baseline variables on mood symptoms, alcohol use, and other drug use between the 104 patients who completed the full study and the 33 patients with at least 2-month, but less than 12-month, follow-up data.

We used the 3 initial levels of alcohol use (no or incidental, moderate, and excessive use during the first 4 weeks of registration) as the main predictors for outcome variables.

Explorative analysis of the homogeneity of variance showed that some of the dependent variables scored significantly on the Levene statistic, indicating differences in variance (possibly due to outliers) in these variables for the 3 distinct alcohol levels. After log transformation of these variables, these differences in variance disappeared. Thus, the transformed scores for these variables were entered into the analyses.

Variables based on life-chart data with less than 365 days of observations were corrected with the use of the length of the actual observation period (values were multiplied by 365 and divided by number of observations).

Means and standard deviations on outcome variables were generated, and χ^2 tests or F tests of means were used to assess differences between the 3 alcohol levels on outcome variables using a significance level of $\alpha = .01$.

RESULTS

Sample Characteristics at Baseline

The 137 patients returned 44,808 days with LCM data (mean ± SD = 327 ± 76 per patient; range, 62–365 days per patient). The mean ± SD of recorded LCM days for alcohol use per group level I, II, and III were respectively 339 ± 66, 327 ± 80, and 317 ± 80 and did not differ significantly ($F_{136} = .99$, $P > .10$). Thirty-seven patients (84%) of level I completed 90% or more of the 365 days of life-chart registration, versus 38 patients (78%) in level II and 33 patients (75%) in level III. There was no significant difference in number of recorded life-chart days between the 3 group levels ($P > .5$).

Sociodemographic data at baseline are shown in Table 1. Patients in the 3 drinking groups were comparable with respect to all sociodemographic variables: mean age, 46 years; males, about 50%; with partner, about 50%; high school education, about 50%; and not able to work, about 50%.

The clinical characteristics at baseline, as presented in Table 2, show that 90 of the patients (66%) had a bipolar I disorder (46 male, 44 female) and 47 (34%) had a bipolar II disorder (25 male, 22 female). The gender distribution within the bipolar I and II groups did not differ significantly, $\chi^2_1 = .01$, $P = .53$ (results not presented). Of the 137 patients, 52% had a BD only; in 21% of the patients, BD predated AUD by 1 year or more; and in 27% of the patients, AUD predated BD with a year or more.

None of the clinical characteristics were significantly different between the 3 drinking groups, with the exception of—and as a consequence of the assignment—the prevalence of lifetime and current diagnosis of AUD: 66% of the level III patients had a lifetime AUD, and 50% had a current AUD; 26% and 8% of the level II patients had a lifetime or current AUD; and 41% and 2% of the level I patients had a lifetime or current AUD. The only patient of the level I group with current AUD at baseline stopped his alcohol intake at the start of the LCM registration. Current abstainers can either be lifetime abstainers or abstinent former alcoholics. Therefore, baseline comparisons were also performed without those level I patients with a lifetime diagnosis of AUD. Again, there were no significant differences except the differences in AUD diagnosis. Since neither of the baseline characteristics and the a priori confounders (positive family history of SUDs, more than 10 prior manic or depressive episodes, a history of prior rapid cycling, and poor occupational functioning at study entry) were significantly different for the 3 drinking groups, prediction of outcome by drinking level was not corrected for baseline variables.

Table 1. Sociodemographic Characteristics at Baseline of Participants With No or Incidental Alcohol Use (Level I), Moderate Alcohol Use (Level II), or Excessive Alcohol Use (Level III)[a]

Characteristic	Level I (n = 44)	Level II (n = 49)	Level III (n = 44)	Total (n = 137)	Statistic	*P* Value
Age, mean (SD), y	46.7 (9.4)	44.4 (10.9)	46.8 (10.2)	45.9 (10.2)	$F_2 = 0.85$	.43
Gender, male	22 (50)	26 (53)	24 (55)	72 (53)		
					$\chi^2_2 = 0.19$	.91
Marital status						
With partner	18 (41)	24 (49)	25 (57)	67 (49)		
Without partner	25 (57)	25 (51)	19 (43)	69 (50)		
Unknown, n	1 (2)			1 (1)		
					$\chi^2_2 = 1.95$	.38
Annual income, €						
< 20,000	30 (68)	28 (57)	24 (55)	82 (60)		
≥ 20,000	14 (32)	18 (37)	18 (41)	50 (36)		
Unknown, n		3 (6)	2 (5)	5 (4)		
					$\chi^2_2 = 1.16$	.56
Educational level						
≤ High school	22 (50)	20 (41)	23 (52)	65 (47)		
> High school	21 (48)	29 (59)	21 (48)	71 (52)		
Unknown, n	1 (2)			1 (1)		
					$\chi^2_2 = 1.51$	.47
Job matches qualification						
Yes	3 (7)	6 (12)	6 (14)	15 (11)		
No	41 (93)	43 (88)	38 (86)	122 (89)		
					$\chi^2_2 = 1.18$	.55
Unable to work						
Yes	24 (55)	22 (45)	20 (45)	66 (48)		
No	20 (45)	27 (55)	24 (55)	71 (52)		
					$\chi^2_2 = 1.06$	.59

[a]Baseline characteristics are presented as n (%) unless noted otherwise.

Table 2. Clinical Characteristics at Baseline of Participants With No or Incidental Alcohol Use (Level I), Moderate Alcohol Use (Level II), or Excessive Alcohol Use (Level III)

Characteristic	Level I n = 44 (32%)	Level II n = 49 (36%)	Level III n = 44 (32%)	Statistic	*P* Value[a]
Diagnosis, n (%)					
Bipolar I disorder	29 (66)	31 (63)	30 (68)		
Bipolar II disorder	15 (34)	18 (37)	14 (32)		
				$\chi^2_2 = 0.25$	.88
Lifetime diagnosis, n (%)					
Alcohol use disorder (abuse and dependence)	18 (41)	13 (27)	29 (66)	$\chi^2_2 = 14.8$	**.001**
Drug abuse and dependence	11 (25)	7 (14)	11 (25)	$\chi^2_2 = 2.16$	.34
Anxiety disorder	18 (41)	16 (33)	13 (30)	$\chi^2_2 = 1.35$	.51
Current diagnosis, n (%)					
Alcohol use disorder (abuse and dependence)	1 (2)	4 (8)	22 (50)	$\chi^2_2 = 43.8$	**< .001**
Drug abuse and dependence	2 (5)	4 (8)	2 (5)	$\chi^2_2 = 0.75$	.69
Anxiety disorder	6 (14)	7 (14)	6 (14)	$\chi^2_2 = 0.01$	.99
Parental history, n (%)					
Depression	29 (66)	29 (59)	23 (52)	$\chi^2_2 = 1.69$	.43
Bipolar disorder	11 (25)	24 (49)	20 (45)	$\chi^2_2 = 6.3$	.04
Alcoholism	9 (20)	15 (31)	13 (30)	$\chi^2_2 = 1.42$	.49
Drug abuse and dependence	2 (5)	1 (2)	4 (9)	$\chi^2_2 = 2.42$	.30
Age at onset of bipolar disorder, mean (SD), y	23.8 (9.6)	24.3 (9.7)	24.3 (10.6)	$F_2 = 0.05$	.96
Duration of bipolar disorder, mean (SD), y	23 (10.1)	19.8 (11.9)	22.6 (12.4)	$F_2 = 1$	.36
No. of episodes, mean (SD)					
Depression	17.1 (30.8)	13.7 (20.3)	14.8 (17.8)	$F_2 = 0.23$	.80
Mania or hypomania	12.7 (19.9)	14.7 (24.6)	14.0 (19.7)	$F_2 = 0.1$	.91
No. of hospitalizations, mean (SD)					
Depression	0.85 (1.5)	0.7 (1.2)	1.1 (3.2)	$F_2 = 0.47$	.62
Mania or hypomania	1.2 (1.6)	1.2 (2.1)	1.7 (3.0)	$F_2 = 0.66$	.52
Age at onset of alcohol use disorder (abuse and dependence), mean (SD), y	22.7 (7.8)	25.3 (12.3)	26.2 (9.5)	$F_2 = 0.65$	.53
Rapid cycling, n (%)	16 (36)	15 (31)	12 (27)	$\chi^2_2 = 0.87$	.65
History, n (%)					
Alcohol-induced depression	4 (9)	4 (8)	3 (7)	$\chi^2 = 0.31$	.86
Alcohol-induced mania or hypomania	3 (7)	3 (6)	4 (9)	$\chi^2 = 0.17$	.91
Cycle acceleration	2 (5)	1 (2)	4 (9)	$\chi^2 = 2.0$	.36
No. of serious suicide attempts, n (%)					
1 or more	9 (20)	12 (24)	9 (20)	$\chi^2 = 0.20$	.91

[a]Bolded *P* values denote significance.

Table 3. Outcome in Patients With No or Incidental Alcohol Use (Level I), Moderate Alcohol Use (Level II), or Excessive Alcohol Use (Level III)

	Level I (n = 44)		Level II (n = 49)		Level III (n = 44)		Statistic					
							First 4 Weeks			Year		
Variable	First 4 Weeks, Mean (SD)	Follow-Up Year,[a] Mean (SD)	First 4 Weeks, Mean (SD)	Follow-Up Year,[a] Mean (SD)	First 4 Weeks, Mean (SD)	Follow-Up Year,[a] Mean (SD)	*F*	*df*	*P*[b]	*F*	*df*	*P*[b]
No. of heavy drinking days[c]	0.02 (0.15)	0.35 (1.4)	2.1 (2.6)	2.1 (2.6)	17.2 (6.9)	13.5 (7.4)	223	2	**<.001**	110	2	**<.001**
No. of drinks/day	0.06 (0.09)	0.18 (0.4)	1.3 (0.7)	1.3 (0.9)	5.3 (2.1)	4.5 (2.4)	197	2	**<.001**	103	2	**<.001**
No. of days ill per 4 weeks												
No. of depressed days[d]	5.2 (8.4)	5.0 (6.8)	4.2 (7.7)	4.2 (6.5)	5.4 (8.6)	5.0 (7.0)	0.29	2	.75	0.23	2	.80
No. of hypomanic days[e]	3.8 (6.8)	3.3 (4.6)	2.8 (4.8)	3.1 (4.5)	3.9 (6.3)	2.3 (3.1)	0.56	2	.57	0.79	2	.45
No. of manic days[d]	1.5 (5.8)	0.96 (2.6)	0.69 (2.7)	0.73 (1.65)	0.27 (1.1)	0.34 (0.7)	1.6	2	.21	1.4	2	.24
Total no. of days ill	10.5 (12)	9.2 (8.3)	7.7 (10.7)	8.0 (8.3)	9.5 (9.8)	7.6 (7.9)	0.76	2	.47	0.4	2	.65
Mean severity (LCM)												
Depression[f]	1.4 (1.7)	1.4 (1.5)	0.91 (1.4)	1.1 (1.3)	1.5 (1.7)	1.4 (1.5)	2.0	2	.14	0.94	2	.40
Mania[g]	0.63 (1.3)	0.49 (0.76)	0.39 (0.77)	0.44 (0.62)	0.40 (0.63)	0.27 (0.37)	1.0	2	.37	1.7	2	.18
Overall	2.2 (2.0)	2.2 (1.6)	1.4 (1.6)	1.6 (1.3)	2.0 (1.8)	1.8 (1.6)	2.3	2	.10	0.71	2	.49
GAF score (1–100)	68 (13)	68 (9.7)	73 (9.0)	72 (9.9)	70 (11)	68 (10.5)	2.1	2	.13	2.2	2	.11
CGI-BP score (1–7)												
Depression	2.2 (1.2)	2.3 (0.99)	1.8 (1.0)	2.1 (0.86)	2 (1.1)	2.3 (1.0)	1.7	2	.19	0.77	2	.46
Mania	1.5 (0.90)	1.5 (0.62)	1.4 (0.80)	1.4 (0.43)	1.6 (0.90)	1.5 (0.58)	0.51	2	.60	0.04	2	.96
Overall	2.5 (1.3)	2.4 (1.1)	1.9 (1.2)	2.2 (0.90)	2.5 (1.1)	2.3 (0.93)	3.1	2	.05	0.91	2	.41
MOS-SF-36 score[h]												
Physical functioning	85 (20)	85 (18)	84 (21)	87 (14)	84 (18)	85 (15)	0.06	2	.94	0.23	2	.80
Social functioning	67 (24)	65 (17)	65 (22)	66 (17)	63 (28)	62 (19)	0.21	2	.81	0.91	2	.41
Physical problems	65 (44)	64 (29)	56 (43)	68 (28)	67 (39)	64 (27)	0.86	2	.43	0.25	2	.77
Emotional problems	58 (45)	56 (32)	57 (40)	57 (28)	54 (42)	56 (30)	0.10	2	.90	0.00	2	.99
Mental health	65 (19)	64 (15)	63 (18)	65 (13)	61 (18)	61 (13)	0.54	2	.58	0.81	2	.45
Vitality	55 (19)	53 (14)	53 (20)	57 (14)	53 (21)	54 (14)	0.18	2	.83	0.84	2	.44
Pain	83 (20)	73 (19)	73 (23)	73 (14)	80 (23)	69 (18)	0.26	2	.08	0.55	2	.58
General health	61 (19)	60 (19)	60 (24)	61 (17)	54 (22)	56 (15)	0.17	2	.20	0.95	2	.40
No. of episodes (*DSM-IV*) per year												
Depressive		1.1 (1.9)		0.62 (1.3)		0.91 (1.5)				1.1	2	.33
Hypomanic		3.3 (5.0)		2.9 (3.4)		2.1 (2.6)				1.2	2	.29
Manic		0.33 (1.1)		0.40 (1.1)		0.12 (0.39)				1.2	2	.30
No. of episodes (Leapfrog method) per year[i]												
Depressive		2.7 (4.5)		2.3 (2.9)		2.4 (2.6)				0.14	2	.87
Hypomanic		5.1 (7.9)		4.6 (5.8)		3.2 (4.3)				1.1	2	.33
Manic		2.1 (5.3)		1.5 (3.3)		0.98 (2.0)				1.0	2	.37

[a]Follow-up year per 4 weeks of LCM registration.
[b]Bolded *P* values denote significance.
[c]Heavy drinking defined as ≥ 5 units/d (males) and ≥ 4 units/d (females).
[d]See text for explanation.
[e]See text for explanation.
[f]Range from 0 to –10. See text for explanation.
[g]Range from 0 to +10. See text for explanation.
[h]Scores on the MOS-SF-36 range from 1–100. Higher score correlates with better functioning, better health, and fewer problems.
[i]See text for explanation.
Abbreviations: CGI-BP = Clinical Global Impressions Scale-Bipolar Version, *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, GAF = Global Assessment of Functioning scale, LCM = National Institute of Mental Health (NIMH) Self-Rating Prospective Life-Chart Method, MOS-SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.

Outcome and Outcome Prediction

Table 3 shows that there were large and significant differences between the 3 groups in the number of heavy drinking days and drinks per drinking day during the first 4 weeks and during further follow-up. Surprisingly, no differences between the 3 drinking groups were found in any of the clinical outcome variables, ie, not in terms of the number of days ill (depressed, hypomanic/manic, and total), severity of depression, mania and overall bipolar illness, GAF score, CGI-BP score (depression, mania, and overall), and all the subscales of the MOS-SF-36. Also, the number of episodes according to the *DSM-IV* and the Leapfrog method showed no significant difference between the drinking groups. Because the number of drinks per week of level III has no upper limit, the same outcome analyses were made with the top 10% of heavy drinking day patients and the 22 patients (50%) of level III patients with a current AUD at baseline. Again, no significant differences were found in outcomes between the groups. To exclude a possible negative effect on outcome of the level I patients with a lifetime diagnosis of AUD, additional follow-up comparisons were performed without those level I patients. Once more, there were no significant differences in outcome between the groups. In order to check for potential confounding of the relationship

between drinking levels and outcome by the presence of a lifetime AUD diagnosis at baseline, we repeated the analyses for those subjects with no lifetime AUD (n = 77). Again, no significant differences were found between the 3 alcohol group levels with respect to mood severity scores, number of episodes, and number of ill days.

DISCUSSION

The main result of our study is that we found no differences in clinical baseline characteristics or in the 1-year course and outcome between bipolar patients with no or incidental alcohol use, moderate alcohol use, and excessive alcohol use as assessed during the first 4 weeks of the study.

These findings confirm the first part of our hypothesis—that the prospective course and outcome of bipolar patients with moderate use of alcohol would not differ from patients who did not or only occasionally use alcohol. This is in contrast with the findings of Goldstein and colleagues,[30] who found that even small amounts of alcohol had a negative effect on several clinical characteristics. It is difficult to compare the results of our study with those of Goldstein and colleagues because, in the latter study, only bipolar patients without any lifetime or current SUD (inclusive alcohol) and who exceeded the weekly maximum intake for their gender were included. In our sample, 27% of the patients with moderate alcohol use had, at baseline, a lifetime diagnosis of AUD, 8% had a current AUD, 14% had a lifetime drug use disorder, and 8% had a current drug use disorder. However, these differences between the studies do not explain why no effect of moderate alcohol compared to no or incidental use on outcome was found in the current study.

To our surprise, the second part of our hypothesis—that patients with excessive use of alcohol would have a significantly worse 12-month course and outcome compared to both bipolar patients with no or occasional drinking and those with moderate drinking—was not confirmed. Thus, our data are not in line with the findings from the literature showing that excessive use of alcohol or the presence of an AUD predicts a negative course and outcome of patients with a bipolar disorder in terms of the severity of the illness and social functioning. Moreover, we did not find any association between excessive alcohol use and gender, suicidality, or family history of AUD, as other studies did.

What are the possible explanations for these unexpected findings regarding the patients with excessive alcohol use? First, our patients with excessive alcohol use may have been less ill than the patients in previous studies. Despite the fact that they used alcohol in excessive amounts and had many heavy drinking days at baseline (17.2 per first 4 weeks) and during the follow-up (13.5 per 4 weeks), "only" 50% of them met *DSM-IV* criteria for a current AUD diagnosis and 66% for a lifetime AUD, while in all previous studies (except the Goldstein et al study[30]), comparisons were made between bipolar patients with or without AUD, alcohol misuse, or alcoholism. However, a post hoc analysis of the current study among the participants with a higher drinking threshold for excessive use and current AUD at baseline also did not reveal that this subgroup was associated with a worse outcome. Second, our patients with excessive alcohol use may have had lower rates of abuse and dependence of other drugs. In the current study, "only" 25% had a lifetime drug use disorder and only 5% had a current drug use disorder. The percentage of patients in the previous studies who, next to alcohol, also used other drugs/substances, were, if mentioned, higher (35%).[21] In these studies, however, no correction for comorbid drug use was reported in the analyses. This means that part of the observed effect of heavy alcohol use on the course of bipolar disorders in other studies may have been the result of comorbid drug abuse or dependence. Third, the negative effect of excessive alcohol use on the outcome of BD may have an effect only in the early years of the disorder, whereas its effect levels out with longer illness duration and a higher number of previous episodes. This is supported by a previous study[52] in the Danish case register with 22 years of registration that found that concurrent alcoholism increased the risk of recurrence of episodes during the initial course of unipolar and bipolar disorder but that it had no effect on recurrences later in the course of the illness. In our sample, the mean illness duration was about 22 years and the mean number of episodes was more than 20. Indeed, the age of the patients in the 4 referred studies[22,23,29,30] was 4–12 years younger than in our study. In line with this explanation are the findings of a 7-year follow-up study[53] showing that younger patients (aged 17–26 years) may have a greater likelihood that alcohol use and bipolar symptoms increase and decrease in unison. Fourth, the differences between the findings in our study and those in the literature may reflect a difference between Europe and the United States, where 9 of the 10 previous studies were conducted. Indeed, there are indications that bipolar disorder in Europe starts at a later age and has a more benign course than in the United States.[54] In the (former Stanley Foundation) Collaborative Bipolar Network, US patients reported a higher frequency of comorbid substance misuse than European patients (47% versus 27%).[54] In our sample, 29 of the 137 patients (21%) had a lifetime diagnosis of drug abuse or dependence, which is comparable to the above European data and, indeed, lower than the 35% as found in the US study by Salloum et al.[21] Similar differences may exist in the effects of excessive alcohol use on the course of the disorder, although no simple explanation for such a difference is currently available. Fifth, all participants (including the patients with excessive use) in our study reported to be very adherent to their prescribed medication, both at baseline and during follow-up, ie, to have taken their medication on more than 90% of the recorded days, according to their LCM registration. It should be noted that self-reported adherence has a specificity of 90%, and that patients may overestimate their actual adherence with 17%.[55,56] Generally, nonadherence is very common

(20%–70%) among BD patients and has a negative effect on the course and outcome of bipolar disorder.[57,58] Moreover, current SUD, but not past SUD, is associated with treatment nonadherence.[59] Adherence (medical and behavioral) with treatment grows with time, which could be an explanation that patients in their early course (0–10 year) of bipolar illness suffer more from the effects of excessive use of alcohol. The high rate of adherence in our sample could be an important protective factor for the effect of excessive alcohol use on clinical outcome. Sixth, the close monitoring with monthly assessments of the patients may have had a positive effect on outcome, and a possible reason why the negative effects on outcome of excessive drinking were nullified. Seventh, it cannot be excluded that excessively drinking patients were significantly different from occasionally and moderately drinking patients in aspects that were not measured in the current study and that these aspects had a positive effect on outcome, thus compensating for the negative effect of excessive alcohol use. A final possibility is that patients sensitive to the negative effects of alcohol were not present in the current study due to the rather serious requirements for participation, including the daily registration of mood and alcohol and substance use. They may, for instance, be over represented among the 18 of the 180 patients (10%) who were approached and who refused to participate. However, it seems unlikely that this relatively small group would have changed the results completely.

Our study has both strengths and limitations. The major strengths include the prospective design with 12 months of daily follow-up assessments, the broad spectrum of confounders that were considered, and the broad range of outcome parameters that were included. A major limitation is selection and its effect on the external validity of our findings. Thirty-eight of the 137 patients (28%) were members of the Dutch Association for Manic Depressives and Relatives, and they should be considered as very motivated patients and adherent to the therapy. Finally, 1 year of detailed follow-up may not be long enough to catch the negative effects of excessive use of alcohol on the course of BD.

In conclusion, despite the methodological strengths of our study, we could not confirm the findings of previous studies that excessive use of alcohol has a negative effect on the course and outcome of bipolar illness. We also did not find that moderate use of alcohol has a negative effect. Previous studies showing such negative effects had different designs and partly included other types of patients, such as patients in an earlier phase of their illness and/or with more comorbid drug abuse and poorer medication compliance. Our findings suggest that recommendations to patients with BD to refrain from alcohol completely[30] are not applicable to all patients with BD. Based on the results of the other studies, recommendations as such should be given, especially to BD patients in the early course of their illness.

Nevertheless, we support recommendations from others[28,56,58,60] that both BD patients with and without alcohol use or a comorbid AUD should be stimulated and controlled for their regular use of medication and that patients with a comorbid AUD should receive integrated treatment for their BD and AUD.[61]

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