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Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes?

Zorrilla I, Aguado J, Haro JM, Barbeito S, López Zurbano S, Ortiz A, López P, Gonzalez-Pinto A. Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes?

Objective: To examine whether bipolar disorder patients who stop cannabis use during a manic/mixed episode have better clinical and functional outcomes than continued use or never use.
Method: Data from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM), a 2-year prospective observational study in adults with a manic/mixed episode of bipolar disorder, was used. Three cannabis use groups were: current use (between 12-week and 24-month visits); no current but previous use (during first 12 weeks); and never use. Associations between cannabis use and outcomes were analyzed using regression models.
Results: Of 1922 patients analyzed, 6.9% were current users, 4.6% previous users, and 88.5% never users. Clinical outcomes differed between groups ($P < 0.019$): previous users had highest rates of remission (68.1%) and recovery (38.7%), and lowest rates of recurrence (42.1%) and relapse (29.8%). Logistic regression showed previous users had similar outcomes to never users (all $P > 0.05$), whereas current users had lower recovery ($P = 0.004$) and remission ($P = 0.014$), higher recurrence ($P = 0.014$), greater work impairment ($P = 0.016$), and were more likely not to be living with partner ($P = 0.006$) than never users.
Conclusion: Bipolar patients who stop using cannabis during manic/mixed episode have similar clinical and functional outcomes to never users, while continued use is associated with higher risk of recurrence and poorer functioning.

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Key words: bipolar disorder; cannabis; functioning; remission; relapse

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Significant outcomes

- Bipolar patients who stop using cannabis during a manic/mixed episode have similar clinical and functional outcomes to those who have never used cannabis, whereas patients who continue to use cannabis have a higher risk of recurrence and poorer functioning.

Limitations

- Accurately assessing cannabis use.
- Only adult patients were studied.
- Medication variables were not included as covariates in the regression models presented.

Introduction

Cannabis is the most common illicit drug used by people with bipolar disorder, with lifetime prevalence rates ranging from 26% to 46% (1–5). In a case-control study of 471 patients with bipolar disorder and 1761 controls, individuals with bipolar disorder were 6.8 times more likely

to report a lifetime history of cannabis use (6). Some authors have found current cannabis abuse rates of 22% in patients hospitalized with mixed or manic episodes of bipolar disorder (1) and of 12.5% in a naturalistic sample of bipolar patients from Spain (7).

Cannabis use in bipolar disorder has been associated with an earlier age of onset (5, 8–11), greater severity, more time in manic/mixed episodes (12), more psychotic symptoms (13), more rapid cycling (14), poorer life functioning (6), and higher rates of non-adherence (15, 16). Thus, cannabis use appears to worsen the course of illness, but no previous studies have prospectively examined the impact of stopping cannabis use on the course of bipolar disorder, compared with never use or continued use of cannabis.

The European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) was a large 2-year prospective observational study of the clinical and functional outcomes of patients receiving treatment for a manic/mixed episode of bipolar disorder (17, 18). In a report based on data collected during the first 12 months of treatment in the EMBLEM study, cannabis use had surprisingly little impact on functional outcomes, such as independent living, work impairment, relationships, and social activities (15). However, this negative result may be due to the method used to define the cannabis use group; i.e., patients who were taking cannabis at any time during the 3-months before the baseline assessment or during the 12-month treatment period (15). As this cannabis use group included 436 patients with any cannabis use, abuse or dependence over a 15-month period (15), it gave no information on the course of the illness among patients who stopped using cannabis. However, given the high rate of cannabis use in bipolar disorder, it is possible to differentiate patients who stop using cannabis from those who continue to use it, and to examine the long-term outcomes in these two groups.

Aims of the study

The aim of this *post hoc* analysis of data from the the European Mania in Bipolar Longitudinal Evaluation of Medication study was to examine the course of bipolar disorder in patients according to their cannabis use habits after controlling for potential confounding variables. We hypothesized that patients who stop using cannabis would have better functional and clinical outcomes.

Material and methods

Study design and patients

The study design and baseline characteristics of the the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study population have been described in detail elsewhere (17, 19). Briefly, this was a 2-year prospective observational study conducted by 530 investigators across 14 European countries. The study enrolled 3684 patients and consisted of two phases: (i) an acute phase lasting from baseline to 12 weeks and (ii) a maintenance phase lasting from 12 weeks up to 24 months postbaseline. There was a maximum of 10 data collection points (at baseline, at weeks 1, 2, 3, 6, and 12, and at 6, 12, 18, and 24 months postbaseline), all occurring within the normal course of patient care. Four countries (Denmark, Germany, Spain, and Switzerland) did not participate in the maintenance phase of the study.

All 3684 enrolled patients met the standard diagnostic criteria (DSM-IV, ICD-10, or clinical judgment) for a manic/mixed episode of bipolar disorder. The study was approved in all countries according to local requirements for ethical and/or regulatory approval for observational studies, and all patients gave written informed consent before study enrollment.

The primary objective of the study was to assess changes in the course of mania of patients with an index manic/mixed episode treated with olanzapine, other antipsychotics, mood stabilizers, and treatment combinations. Medications could be given as monotherapy or in combination, and could be changed at any time according to clinical need. Further objectives of the study included evaluation of symptomatic recovery, remission, and relapse, together with functional status and economic outcomes. This report focuses on clinical and functional outcomes over the 2-year follow-up period.

Assessments

At baseline, patient sociodemographic data and psychiatric history were recorded, together with their history of substance abuse (cannabis use problem ever, alcohol use problem ever, other substance use problem ever; recorded as yes or no for each).

Severity of illness was assessed at every visit using the Clinical Global Impression–Bipolar Disorder (CGI-BP) scale (20). At baseline and during the acute phase, clinicians assessed severity of mania using the Young Mania Rating Scale (YMRS) (21) and severity of depressive symptoms

using the 5-item version of the Hamilton Depression Rating Scale (HAMD-5) (22).

Information on medication was recorded at each visit. Adherence to medication was assessed by a researcher at each visit as reported previously (16).

Investigators were requested to assess current cannabis use of patients at the following visits: baseline, 12 weeks, 6, 12, 18, and 24 months. Current use covered the previous 3 months, was based on patient self-report, and the clinical experience and judgment of the investigator, and recorded as no use, use, abuse, or dependence. In the present analysis, use, abuse, and dependence were combined together as any use. Current alcohol use and substance use (including illicit drug use [excluding cannabis], non-medical use or prescription, and over-the-counter drugs) were recorded in the same way.

Definitions of cannabis, alcohol, and other substance use groups. For the analyses, we defined three cannabis use groups based on cannabis use during the maintenance phase of the study: (i) previous use, (ii) current use, and (iii) never use. Previous use was defined as any cannabis use recorded from the baseline visit to the 12-week visit (i.e., during the acute phase) but no current use recorded during any of the maintenance-phase visits. Current use was defined as any cannabis use recorded during the maintenance phase (i.e., after the 12-week visit and up to and including the 24-month visit), regardless of previous use during the acute phase. Never use was defined as no current or previous use of cannabis (i.e., no recorded cannabis use during either the acute or maintenance phases). Alcohol and other substance use groups were defined in the same way.

Outcome measures

Functional outcomes included work impairment, relationship status, and living situation; they were measured at the last available visit during the maintenance phase. For the analyses, these variable were dichotomized as some work impairment vs. no work impairment, living together vs. not living together (relationship status), and independent residence vs. dependent residence (living situation).

Clinical outcomes included remission, recovery, recurrence, and relapse. Remission was defined as having a CGI-BP overall score of <3 at two consecutive visits and no relapse or in-patient admission for an acute episode of bipolar disorder between these visits. It was defined from 6 weeks onward for four intervals (12 weeks–6, 6–12, 12–18, and 18–24 months) and summarized as a yes/no variable for the whole 6–24-month period. Recovery was defined as achieving functional remission and reporting adequate social functioning (defined as no/mild work impairment, living independently, and having four or more social activities in the past 4 weeks and/or living together with a partner). It was defined from 12 weeks for two intervals (12 weeks–6 months and 6–12 months) and summarized as a yes/no variable for the 6–24-month period. Relapse was considered to have occurred in patients who had not achieved remission if they had any of the following: an increase in CGI-BP mania score from the previous visit, with an end rating of ≥4; in-patient admission for an acute episode of bipolar disorder; and a psychiatrist report of relapse since the previous assessment. It was defined from 12 weeks for four intervals (12 weeks–6 months, 6–12, 12–18, and 18–24 months) and summarized as a yes/no variable for the 6–24-month period. Recurrence was considered to have occurred in patients who had achieved remission and then fulfilled the above criteria for relapse.

Statistical analysis

Only patients eligible for the maintenance phase were included in the analysis (n = 2416).

Baseline characteristics of the three patient groups by cannabis use habits were summarized using descriptive statistics, and the groups were compared using chi-square or Fisher's exact tests (for categorical variables) and Kruskal–Wallis tests (for continuous variables).

Kaplan–Meier survival analyses were performed to estimate the time to remission, recovery, recurrence, and relapse over 24 months for each of the cannabis use groups.

Logistic regression models were used to determine the association between cannabis habits and the clinical and functional outcomes measured. Covariates included in the final model (M1) were selected by backward elimination using $P < 0.05$. Data are presented as odds ratios (ORs), 95% Wald confidence intervals (CIs), and P values. In a second regression model (M2), alcohol and other substance use variables were included as covariates together with all the covariates considered for M1 regardless of their significance.

Cox regression models were adjusted to analyze the effect of cannabis habits on the time to remission, recovery, relapse, and recurrence and included the same covariates as for the logistic regression analysis.

All data were analyzed using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Demographic and clinical characteristics

Of the 2416 patients enrolled in the maintenance phase, 486 did not start the follow-up and 8 had no data on the use of cannabis/alcohol/substances, resulting in 1922 patients eligible for analysis. Of these 1922 patients, 132 (6.9%) were classified as current cannabis users, 89 (4.6%) as previous users, and 1701 (88.5%) as never users. The alcohol habit groups comprised 37.7% current users, 13.4% previous users, and 49.0% never users. For other substances, 3.7% were current users, 4.4% previous users, and 91.9% never users.

The demographic and baseline characteristics of patients by cannabis use group (Table 1) show significant differences between groups for many variables, including age, sex, and baseline symptom severity. The never use group was older, contained more females, and had a higher body mass index than the other two groups. The current use group had a higher number of previous manic episodes, greater dissatisfaction with life, more severe CGI-BP mania and overall bipolar symptoms, a higher proportion of rapid cyclers, and a higher frequency of past suicide attempts. Moreover, compared with the never use group, both cannabis use groups (current use and previous use) had a higher frequency of in-patients, lower proportions of individuals living with a partner, higher rates of delusions/hallucinations and psychosis symptoms, more severe CGI hallucinations, more suicide

Table 1. Baseline characteristics of patients by their cannabis use habits during 2 years of follow-up

Variable	Never use (N = 1701)	Previous use (N = 89)	Current use (N = 132)	P value*
Age, years	46.2 (12.9)	35.3 (10.1)	35.8 (9.8)	**<0.0001**
Sex, female, n (%)	981 (59.6)	27 (30.7)	42 (33.3)	**<0.0001**
Body Mass Index (kg/m^2)	26.3 (5.0)	24.9 (4.2)	24.3 (4.6)	**<0.0001**
Number of dependents	0.7 (1.0)	0.4 (0.9)	0.5 (0.9)	**0.001**
Age at onset of bipolar disorder, years	30.5 (11.1)	26.1 (7.0)	24.5 (7.3)	**<0.0001**
Age at first mania, years	32.1 (12.0)	26.7 (7.7)	26.2 (7.7)	**<0.0001**
Number of manic episodes in previous 12 months, n (%)				
1	954 (57.3)	53 (62.4)	60 (45.8)	**0.040**
2	461 (27.7)	21 (24.7)	44 (33.6)	
3 or more	169 (10.2)	9 (10.6)	23 (17.6)	
Number of depressive episodes in previous 12 months (n (%)				
0	749 (44.3)	50 (56.8)	53 (40.5)	0.215
1	581 (34.4)	23 (26.1)	45 (34.4)	
2 or more	250 (14.8)	10 (11.4)	26 (19.8)	
Type of episode, mania/mixed, n (%)	1254 (75.8)/401 (24.2)	71 (80.7)/17 (19.3)	91 (70.0)/39 (30.0)	0.177
In-patient status, n (%)	574 (33.8)	39 (43.8)	60 (45.5)	**0.005**
Number of bipolar disorder-related admissions	0.8 (1.5)	0.9 (0.9)	1.0 (1.3)	**0.008**
Rapid cycler, n (%)	241 (15.7)	12 (15.4)	30 (24.6)	**0.037**
Delusions/hallucinations, n (%)	731 (47.1)	50 (61.7)	75 (62.5)	**<0.001**
Presence of psychosis, n (%)	632 (37.3)	46 (51.7)	72 (54.5)	**<0.0001**
History of at least one suicide attempt, n (%)	116 (7.0)	9 (10.5)	17 (13.3)	**0.021**
Relationship, living together, n (%)	771 (45.4)	21 (23.6)	36 (27.3)	**<0.0001**
Housing conditions, independent residence, n (%)	1020 (60.0)	46 (51.7)	77 (58.3)	0.282
Some social activities, n (%)	1351 (79.7)	76 (85.4)	99 (75.0)	0.168
Some work impairment, n (%)	1396 (87.3)	76 (87.4)	120 (93.0)	0.163
Dissatisfaction with life, n (%)	669 (39.5)	40 (44.9)	72 (54.5)	**0.015**
CBI-BP overall in past year	4.1 (1.3)	4.0 (1.4)	4.6 (1.3)	**<0.0001**
CGI-BP overall	4.7 (1.1)	4.6 (1.1)	5.1 (1.0)	**<0.0001**
CGI-BP mania	4.8 (1.0)	4.7 (1.0)	5.1 (1.0)	**<0.001**
CGI-BP depression	1.9 (1.2)	1.7 (1.1)	2.1 (1.5)	0.153
CGI hallucination and delusions	2.8 (1.8)	3.3 (1.7)	3.6 (2.0)	**<0.0001**
YMRS total	26.0 (9.6)	26.5 (9.5)	30.0 (9.6)	**<0.0001**
HAMD-5 total	3.1 (2.9)	2.7 (2.7)	3.8 (4.1)	0.577
Adherence				
Medication not prescribed	372 (22.1)	26 (29.2)	32 (24.2)	**<0.001**
Almost always adheres	892 (53.0)	37 (41.6)	48 (36.4)	
Adheres half the time	325 (19.3)	18 (20.2)	36 (27.3)	
Almost never adheres	94 (5.6)	8 (9.0)	16 (12.1)	

Data presented as mean (SD) or n (%).

CGI-BP, Clinical global impression bipolar disorder; YMRS, Young mania rating scale; HAMD-5, 5-item version of the Hamilton Depression Rating Scale.

*Bold values indicate significance.

attempts, younger ages of bipolar onset and first manic episode, more hospital admissions, and poorer medication adherence.

Functional and clinical outcomes of bipolar disorder

Functional outcomes for the cannabis, alcohol, and other substance use groups (Fig. 1) show

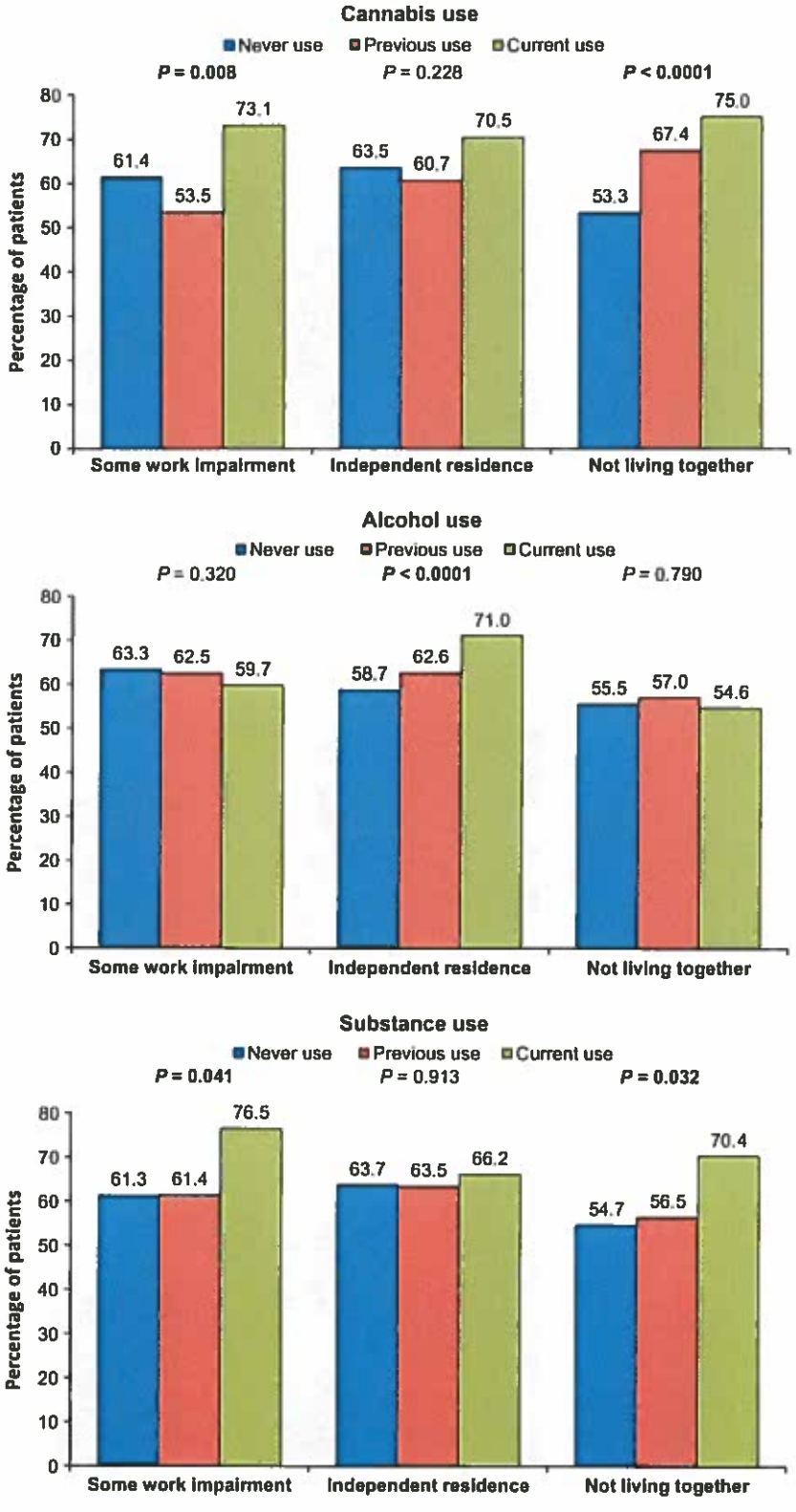

Fig. 1. Functional outcomes in the cannabis, alcohol, and other substance use groups.

significantly more work impairment and less living with a partner in the current cannabis use and current substance use groups, while significantly more of the current alcohol use group were living independently.

Figure 2 summarizes the rates of recovery, remission, recurrence, and relapse for the cannabis, alcohol, and other substance use groups. There was significantly less recovery and remission and significantly more recurrence and relapse in the

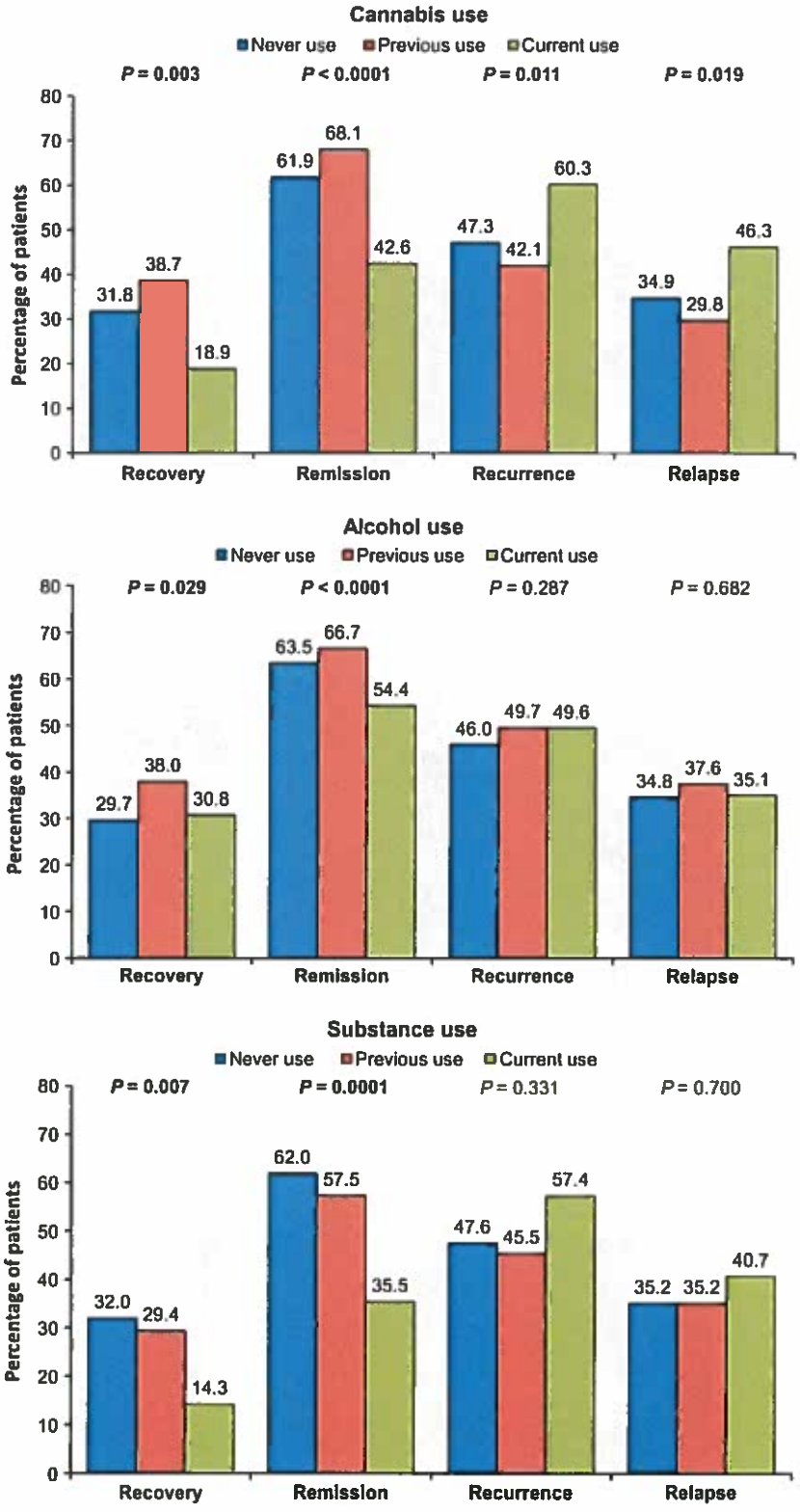

Fig. 2. Clinical outcomes in the cannabis, alcohol, and other substance use groups.

current cannabis use group than in the other two cannabis habit groups. Additionally, there was significantly less recovery and remission in the current alcohol use and current substance use groups, but no differences in the rates of recurrence and relapse.

Kaplan–Meier analysis showed significant differences between the three cannabis use groups in the survival curves for the time to remission (log-rank test: $\chi^2 = 21.78$; df = 2; $P < 0.0001$), recovery (log-rank test: $\chi^2 = 14.85$; df = 2; $P = 0.001$), relapse (log-rank test: $\chi^2 = 9.91$; df = 2; $P = 0.007$), and recurrence (log-rank test: $\chi^2 = 7.69$; df = 2; $P = 0.021$). The median time to remission was longer in the current use group (571 days, 95% CI 539–588) compared with the other two groups (never users: 236 days, 95% CI 209–345; previous users: 189 days, 95% CI 1.5–357), while the times to relapse and recurrence were shorter in current use group. Median time to recovery was shorter in the previous use group (565 days) and longer in the never use group (629 days), compared with the current use group (601 days). Confidence intervals for the median time to recovery are not reported because less than 50% of patients in any cannabis use group achieved recovery (see Fig. 1).

The proportion of patients with suicide attempts during the maintenance phase (6–24 months) was higher in the cannabis current use group (9/130, 6.9%) than in the never use (51/1701, 3.0%) and previous use (4/90, 4.4%) groups ($P = 0.046$).

Effect of cannabis use habits on clinical and functional outcomes

Logistic regression models showed that current cannabis use (vs. never use) was associated with lower rates of remission and recovery, and higher rates of recurrence, but was not associated with relapse (Table 2). When alcohol and other substance use variables were included in the model (M2 model), cannabis current use was only significantly associated with recurrence. The odds of work impairment and not living together with a partner were also significantly higher in the cannabis current use group (vs. never use). Only the association of cannabis current use with relationship status was maintained when alcohol and other substance use variables were included in the model. Notably, Table 2 shows that the ORs for the previous use group (i.e., those who stopped using cannabis vs. never use) were not significant for any of clinical and functional outcomes in either model.

Effect of cannabis use on time to recovery, remission, recurrence, and relapse

Cox regression models showed that cannabis use (vs. no use) was associated with time to recovery, relapse, and recurrence (Table 3). When alcohol and other substance use variables were included in the model, only time to recurrence remained significantly associated with cannabis use.

Table 2. Odds ratios and 95% Wald confidence limits for associations of cannabis habit with clinical and functional outcomes from logistic regression models

	M1 model			M2 model*		
	Odds ratio	95% confidence limits	*P* value*	Odds ratio	95% confidence limits	*P* value†
Recovery						
Current use‡	0.39	0.207–0.734	**0.004**	0.58	0.286–1.156	0.120
Previous use‡	1.68	0.909–3.105	0.098	1.77	0.920–3.400	0.088
Remission						
Current use‡	0.57	0.368–0.892	**0.014**	0.85	0.515–1.417	0.541
Previous use‡	1.30	0.770–2.198	0.325	1.40	0.790–2.485	0.248
Recurrence						
Current use‡	1.69	1.113–2.577	**0.014**	1.59	1.005–2.521	**0.048**
Previous use‡	1.01	0.636–1.600	0.969	0.96	0.582–1.591	0.881
Relapse						
Current use‡	1.42	0.901–2.248	0.130	1.40	0.835–2.353	0.201
Previous use‡	0.76	0.435–1.318	0.325	0.81	0.446–1.458	0.476
Work impairment (some work impairment)						
Current use‡	1.85	1.123–3.042	**0.016**	1.71	0.983–2.976	0.057
Previous use‡	0.90	0.525–1.549	0.709	0.97	0.544–1.720	0.910
Relationship status (not living together)						
Current use‡	2.91	1.369–6.172	**0.006**	3.41	1.470–7.904	**0.004**
Previous use‡	0.87	0.407–1.848	0.712	1.15	0.508–2.612	0.735
Living situation (independent residence)						
Current use‡	1.51	0.859–2.657	0.152	1.31	0.691–2.481	0.409
Previous use‡	1.44	0.778–2.667	0.246	1.27	0.647–2.480	0.490

*M2 model: alcohol and other substance use included as covariates in the model.

†Bold values indicate significance.

‡vs. cannabis never use.

Table 3. Hazard ratios of effect of cannabis use (vs. no use) on times to recovery, remission, recurrence, and relapse (Cox regression analysis)

	M1 model			M2 model*		
	Hazard ratio	95% Wald confidence limits	*P* value†	Hazard ratio	95% Wald confidence limits	*P* value†
Recovery	0.53	0.298–0.959	**0.036**	0.59	0.320–1.076	0.085
Remission	0.69	0.472–1.001	0.050	0.73	0.487–1.101	0.135
Recurrence	1.67	1.206–2.320	**0.002**	1.47	1.030–2.092	**0.034**
Relapse	1.61	1.116–2.316	**0.011**	1.43	0.966–2.121	0.079

*M2 model: alcohol and other substance use included as covariates in the model.
†Bold values indicate significance.

Discussion

These analyses of data from the the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study are the first to explore the long-term consequences of continuation or cessation of cannabis use on remission, recovery, recurrence, and relapse in patients with bipolar disorder. Our findings indicate that the negative effects of cannabis use on the course of bipolar disorder disappear when patients stop using it: We found that patients who stopped using cannabis during an acute manic/mixed episode had similar clinical and functional outcomes at 2 years as those who have never used cannabis. Our results also showed that patients who continued to use cannabis had worse outcomes than those who either stopped using cannabis or had never used it. Current cannabis use during the maintenance phase was associated with lower rates of symptomatic remission and functional recovery, and a higher risk of recurrence of bipolar disorder, independent of baseline characteristics. It was also associated with poorer functional outcomes (work impairment and not living together with a partner) compared with never use, whereas functional outcomes were similar in those who had either stopped or never used cannabis. These findings imply that stopping cannabis use is an important goal to achieve in cannabis users with bipolar disorder.

Our findings are consistent with those from a study in patients with first-episode psychosis (which included patients who met the criteria for bipolar disorder with psychotic features), where those who stopped using cannabis had better functioning over 8 years of follow-up than patients who continued using cannabis or had never used it (23). Another study in first-episode psychosis patients reported that continued cannabis use was associated with worse social outcomes during 2 years (24).

Importantly, our analysis assessed cannabis use separately from use of alcohol and other substances, and adjusted for their effects on the association between cannabis use and outcomes. Abuse substances other than cannabis (including alcohol) are known to have a negative impact on the treatment and course of bipolar disorder (2, 25–27), including poorer functioning (28). The results of this research show that some but not all the associations between outcomes and cannabis use are also observed with alcohol use. Therefore, both continued cannabis and alcohol use are considered a risk factor for poor outcome. Few studies have specifically examined the effect of cannabis use on long-term outcomes in patients with bipolar disorder. Previous reports indicate that cannabis use in bipolar patients is associated with deleterious effects, including more prolonged and severe mania symptoms, poorer adherence to treatment, poorer quality of life, a higher risk of hospitalization, and more suicidal behaviour (6, 29–31). In an earlier analysis of the EMBLEM population, cannabis use (vs. non-use) was significantly associated with greater severity of mania and psychosis symptoms during the first 12 months of follow-up examined in that analysis (15). Additionally, cannabis users were less likely to have a relationship than non-users (15). However, the use of cannabis, alcohol, and other substances can change over time, which may impact on bipolar patient outcomes. For example, alcohol/substance abuse decreased during 10 years of follow-up in a group of bipolar patients with predominantly manic symptoms, but not in those with predominantly depressive symptoms, who had a more severe course of illness (32). Thus, it would be interesting to examine whether relapses or recurrences in the current cannabis use group were more likely to be depression. However, the definition of relapse was based on the CGI-BP score and information on the mood state (e.g., via symptom-based YMRS or HAMD scales) was not collected during long-term follow-up.

Our analysis extends the previous 12-month findings from EMBLEM (15) by comparing clinical and functional outcomes over 2 years in

patients who continue to use cannabis with those who cease cannabis use or who have never used it. We found that continued cannabis use was associated with less chance of recovery and remission after an acute manic/mixed episode and a higher risk of recurrence than never use of cannabis. Continued cannabis use was also associated with a longer time to remission and a shorter time to recurrence/relapse of bipolar disorder than either stopping or never using cannabis. After controlling for alcohol and other substance use, the increased risk of recurrence and not living together with a partner was maintained in the current cannabis use group.

Strakowski et al. (14) reported better rates of recovery among patients whose cannabis use preceded bipolar disorder, although this did not remain significant when potential confounders were included in the analysis. The current analysis was not able to determine whether cannabis use occurred prior to or following bipolar onset.

In the present analysis, 6.9% of patients with bipolar disorder from the European countries participating in EMBLEM were classified as current cannabis users during the maintenance phase. This is consistent with the reported rate of co-occurring cannabis use disorders in patients with bipolar disorder (7.2%) in a recent national epidemiological survey in the United States (10). EMCDDA European Drug Report 2014 (www.emcdda.europa.eu/data/2014) gives tables of the prevalence of cannabis use for all adults (age 15–64) by country. For the countries participating in EMBLEM, the prevalence of cannabis use in the previous month ranged from 1.4% in Finland to 7% in Spain. Likewise, the prevalence of cannabis use in the last year in the countries taking part in EMBLEM ranged from 1.7% in Greece to 9.6% in Spain (33). Various factors may mediate the association between cannabis use and clinical/functional outcomes in bipolar disorder. Other analyses of EMBLEM data found that cannabis use problems during the acute treatment of mania were associated with reduced medication adherence during maintenance treatment (16). Moreover, in a previous report of 144 bipolar patients after a first hospitalization for mania (14), patients with co-occurring cannabis use (before or after bipolar onset) spent less time during follow-up being fully adherent with at least one mood stabilizer than patients without cannabis use, but the difference was not statistically significant. These observations suggest that poor adherence to treatment among bipolar patients using cannabis may contribute toward the increased risk of recurrence and relapse. In another report from EMBLEM, Cox regression models also showed an association between adherence and risk of recurrence and relapse (34). Adherence to medication has also been found to be an important mediator of the association between cannabis use and symptom outcome in patients with first-episode psychosis; individuals with continuous cannabis use had poorer symptom outcomes at 12 months than those who ceased cannabis use, despite improved adherence to medication (35). It remains unclear whether the benefit of ceasing cannabis is related to improved adherence, is a benefit *per se*, or both, but a previous report concluded that continuous cannabis use has a deleterious effect on outcome independently of being adherent to medication (35). Further studies are needed to investigate the interaction between cannabis use and adherence in patients with bipolar disorder. Notably, however, impulsivity in bipolar disorder has been associated with cannabis use and adherence (36), and with symptom severity (37), suggesting that impulsivity may be a suitable target for intervention to improve outcomes.

We observed a significantly higher rate of suicide attempts over the 2-year follow-up in the current cannabis user group compared with the other two cannabis habit groups. An association between cannabis use and suicide has been reported previously (6) and is probably mediated by other factors, such as the use of alcohol and other substances. Previous studies have shown a high prevalence of suicide attempts in bipolar disorder (38), and drug and alcohol abuse have been identified as risk factors for suicide in bipolar disorder (39). Moreover, previous data from EMBLEM have shown a strong association between suicidal behaviour and a history of alcohol/other substance abuse (40). Additionally, in a 5-year follow-up of patients with first-episode psychosis in Spain, suicidal behaviour was associated with abuse of stimulants (cocaine, amphetamines) at the baseline assessment (41).

Limitations of this study include the difficulty of accurately assessing cannabis use, which was based on patient self-report and the judgment of the researcher. It is possible that there may be under-reporting of cannabis use. Our definition of cannabis use may have differed from other studies, but was consistent with that used previously by González-Pinto (23). Also, combining use, abuse, and dependence of alcohol means that occasional and heavy drinking is in the same category, which may be a confounding factor when included as an adjusted vari-

able. Additionally, although the definitions of remission, recovery, and relapse were consistent with previous EMBLEM analyses, they differ from other studies, making comparisons difficult. Nevertheless, the definitions share some similar criteria to those used in other studies, that is, work and social impairment for functionality, and presence of symptoms for no remission.

Further limitations are that this is a *post hoc* analysis and that the study only included adult patients; therefore, the results cannot be generalized to children or adolescents with bipolar disorder, who tend to have a worse disease course and are at even higher risk of substance use disorders (42). Finally, another limitation of the present findings is that drug treatment may have influenced the disease course, but medication variables were not included as covariates in the regression models presented. However, the pattern of association between cannabis use and clinical outcomes was similar when medication variables were included in the models (data not shown).

In summary, these results from the EMBLEM study suggest that bipolar patients who stop using cannabis during a manic/mixed episode have similar clinical and functional outcomes to those who have never used cannabis, whereas patients who continue to use cannabis have a higher risk of recurrence and poorer functioning. The clinical implications of our findings are that a holistic management plan for bipolar patients should include psychoeducation and other treatments/interventions that focus on stopping use of cannabis, alcohol, and other drugs, as well as on improving adherence and preventing relapses.

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