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Outcomes of bipolar patients referred to the French Centres of Expertise network: a 2 year-follow-up observational study

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Complete List of Authors:	Henry, Chantal; AP-HP, Hôpitaux Universitaires Henri Mondor, Psychiatry; Institut Pasteur, Neurosciences, Perception and Memory Unit Godin, Ophelia; Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universités, INSERM et UPMC Univ Paris 06 (UMR_S 1136), Courtet, Philippe; Montpellier University, Azorin, Jean-Michel; Hôpital Sainte-Marguerite, Gard, Sébastien; CH Ch Perrens, Pole 3-4-7 Bellivier M.D., Frank; P&#65533;le de Psychiatrie Polosan, Mircea; Centre expert en troubles Bipolaires, Institut des Neurosciences Grenoble, équipe « Fonctions Cérébrales et Neuromodulation », INSERM/CHU Grenoble, Université Joseph Fourier, Pôle Psychiatrie et Neurologie Kahn, Jean Pierre; Centre Psychothérapique de Nancy, Psychiatry Roux, Paul; Université de Versailles Saint-Quentin-en-Yvelines, UFR des sciences de la santé Simone Veil, , Laboratoire EA4047 Handiresp; Centre Hospitalier de Versailles, Service Universitaire de psychiatrie de l'adulte Aubin, Valérie; Centre hospitalier Princesse-Grace, Psychiatry Costagliola, Dominique; INSERM and UPMC Univ Paris 06 (UMR_S 1136) Leboyer M.D., Marion; Professor, Psychiatry Etain, Bruno; Hopital Albert Chenevier, Pole de Psychiatrie
Keywords:	bipolar disorder, cognitive functioning, clinical aspects, health service, Longitudinal study

Abstract:	Objective: A new system of care for patients with bipolar disorders was established in France and has introduced an innovative care model based on clinical collaboration between centers of expertise and referring practitioners. We report the results of the outcome for the first two years of follow-up for those patients assessed within the network. Method: A total of 984 patients were included in the study. We compared several parameters (mood episodes, hospitalization) one year before inclusion and evolution during the 2-years of follow-up using the patient as its own control. Other outcomes were compared at baseline and during follow-up. We estimated the evolution of these parameters over a period of two years using mixed models for continuous parameters and a generalized linear model for categorical variables, adjusting for potential confounding factors.

	Results: Number of hospitalization days decreased by 55% when comparing one year before inclusion versus during the follow-up morevover patients displayed an improvement of functioning associated with a decrease of residual mood symptoms, less psychiatric comorbidities, improvement of sleep and a better adherence to treatment. Conclusion: This study demonstrates an overall improvement of patients followed for two years in specialized centers for bipolar disorders. We discussed the organization of our model of care compared to other specific system of care for bipolar disorders. This system by stimulating a better collaboration between health care professionals, suggesting personalized proposal for treatment based on a bio-psychosocial approach and involving actively patients and families is able to improve the outcome of BD patients.

Outcomes of bipolar patients referred to the French Centres of Expertise network: a 2 year-follow-up observational study

Running Head: Longitudinal outcomes of bipolar patients

Chantal HENRY*, MD, PhD[1,2,5,6,19], Ophelia GODIN*, PhD[3, 4,5], Philippe Courtet, MD, PhD[5,13,14], Jean-Michel Azorin, MD, PhD[5,7], Sébastien Gard, MD[5,15], Frank Bellivier, MD, PhD [5,9], Mircea Polosan, MD, PhD[5,10,11,12], Jean-Pierre Kahn, MD[5,16], Paul Roux, MD, PhD[5,17,18], Valerie Aubin, MD, PhD [5,8], the FACE-BD collaborators, Dominique Costagliola, PhD[3,4], Marion Leboyer, MD PhD[1,2,5,6], and Bruno Etain, MD, PhD[5,9]

* Equal contribution

Collaborators:

Laouamri H, PhD[5], Souyris K, PhD[5], Barteau V, BD[5] Geoffroy PA[5,9 MD], Raust A, Psych[1,2,5,6], Raoul Belzeaux, MD, PhD[5,7], Loftus Josephine, MD, PhD[5,8], Sportiche S, MD[5,9], Aouizerate B [5,15], Olié E, MD[5,13,14],, Ducasse D, MD[5,13,14], Viglianese N, Psych[5,7], Lescalier L, Psych[5,7], Cohen RF, Psych[5,16], Wajsbrot-Elgrabli O, Psych[5,16], Garçon S, Psych[5,10,11,12], Katia M'Bailara, PhD Psych[5,15], Hardy-Bayle MC, MD, PhD[5,17,18]Grevin I, Psych[5,17,18]

Affiliation

1. INSERM, U955, Equipe 15 Psychiatrie Translationnelle, 94000, Creteil, France;
2. Université Paris-Est Créteil Val de Marne, 94000, Creteil, France;
3 Sorbonne Universités, Université Pierre et Marie Curie, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP UMRS 1136), 75013, Paris, France;
4. INSERM, UMR_S 1136, F-75013 Paris, France;
5. Fondation FondaMental, Fondation de Coopération Scientifique, 94000, Créteil, France;
6. AP-HP, Hôpital H. Mondor - A. Chenevier, Pôle de Psychiatrie, 94000, Créteil, France;
7. Département de Psychiatrie, Hôpital Sainte-Marguerite, 13274 Marseille cedex 9 France;
8. Département de Psychatrie, Centre Hospitalier Princesse Grace, BP489, 98012 Monaco ;
9. Université Paris Diderot et AP-HP, GH Saint-Louis - Lariboisière - Fernand Widal, Département de Psychiatrie de de Médecine Addictologique, Paris, France ;
10. Université Joseph Fourier, Grenoble I, BP 53, 38041 Grenoble, France;
11. CHU de Grenoble, CS10217, 38043, Grenoble, France ;
12. Grenoble Institut des Neurosciences (GIN) Inserm U 836, Chemin Fortuné Ferrini, 38706 La Tronche, France ;
13.Département d'Urgence et Post Urgence Psychiatrique,, CHU Montpellier, France;
14. INSERM U1061, Université de Montpellier, Montpellier, France;

15. Centre Expert Bipolaire, Pôle de Psychiatrie Générale Universitaire, Centre Hospitalier Charles Perrens, Bordeaux, France ;
16 Université de Lorraine, CHU de Nancy et Pôle 6 de Psychiatrie et Psychologie Clinique – Centre Psychothérapique de Nancy – 1 rue du Docteur Archambault – 54520 LAXOU Cedex, France ;
17. Centre Hospitalier de Versailles – 78150 – Le Chesnay, France;
18. Université de Versailles-Saint-Quentin-en-Yvelines, EA 4047 – Versailles, France ;
19. Institut Pasteur, Unité Perception et Mémoire, F-75015 Paris, France ;

Corresponding author:

Chantal Henry, MD, PhD

Pôle de psychiatrie du CHU Créteil,

Hôpital A.Chenevier, 40 rue de Mesly, 94000 Créteil, France. Tel.: +33 1 49 81 32 31;

fax: +33 1 49 81 30 99. Email: chantal.henry@inserm.fr

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Abstract

Objective: A new system of care for patients with bipolar disorders was established in France and has introduced an innovative care model based on clinical collaboration between centers of expertise and referring practitioners. We report the results of the outcome for the first two years of follow-up for those patients assessed within the network.

Method: A total of 984 patients were included in the study. We compared several parameters (mood episodes, hospitalization) one year before inclusion and evolution during the 2-years of follow-up using the patient as its own control. Other outcomes were compared at baseline and during follow-up. We estimated the evolution of these parameters over a period of two years using mixed models for continuous parameters and a generalized linear model for categorical variables, adjusting for potential confounding factors.

Results: Number of hospitalization days decreased by 55% when comparing one year before inclusion *versus* during the follow-up morevover patients displayed an improvement of functioning associated with a decrease of residual mood symptoms, less psychiatric comorbidities, improvement of sleep and a better adherence to treatment.

Conclusion: This study demonstrates an overall improvement of patients followed for two years in specialized centers for bipolar disorders. We discussed the organization of our model of care compared to other specific system of care for bipolar disorders. This system by stimulating a better collaboration between health care professionals, suggesting personalized proposal for treatment based on a bio-psychosocial approach and involving actively patients and families is able to improve the outcome of BD patients.

Keywords: bipolar disorder, cognitive functioning, clinical aspects, health service, longitudinal study

Introduction

Bipolar Disorder (BD) is a chronic disease characterized by the recurrences of (hypo)manic and depressive episodes and severe alterations of functioning. Moreover, BD is associated with numerous psychiatric and somatic comorbidities and high suicide rates[1], leading to a heavy burden for patients and their families and a high cost to society. Direct costs are mostly linked to psychiatric hospitalizations and indirect costs to loss of productivity, functioning and quality of life.[2]

Randomized trials suggest that both pharmacotherapy and adjunctive psychosocial interventions are effective in reducing the risk of recurrences[3] but relapses are still frequent.[1] Even when the number of recurrences is reduced, a return to previous levels of functioning may be not the rule, and poor functioning is often related to chronic residual symptoms.[4] Results from controlled trials are often difficult to generalize because they exclude patients with substantial medical or psychiatric comorbidities, and generally only consider monotherapy. “Real-world” or observational studies on large cohorts, without any exclusion criteria, allowing multiple medications, can help to unravel which factors may improve outcomes in patients with BD. These factors are associated with the individuals themselves, features of the disorder, their individualized profile of the disorder course and its response to treatment, as well as the modalities of treatment and patient support. Compliance with guidelines has been shown to improve the outcome of BD patients, linked to strategies of patient management, such as in collaborative care models.[5]

In line with this last point, an initiative was launched in France, with the support of the Ministries of Research and Health to develop a network of nine BD expert centers throughout France. The goal was to introduce a new model for clinical collaboration between centers of expertise and referring clinicians (general practitioners, private and public psychiatrists). The centers offer access to all BD cases with few barriers for referral and no biases towards

treatment-refractory cases.[4,6] There is an emphasis on providing reliable, systematic, multi-disciplinary case assessments and also on sharing the results of the assessments and treatment recommendations with the referring clinicians. The recommendations follow a disease management model based on evidence-based treatment guidelines, encourage the use of psychosocial interventions such as psychoeducation, and are personalized as a function of the characteristics of the disorder, the preferences of the patient, and former responses to treatment. Taking all of these elements into consideration along with recent knowledge makes it possible to provide highly personalized proposals for treatment. We offer to monitor the patients once a year making it possible to assess patients' individual outcomes.

We analyzed two years of prospective follow-up data of patients referred to an expert center to assess the relevance of this new system of care.

Materials and methods

Design of FACE-BD

The methods are presented briefly below, and have been described in more detail elsewhere.[6] The network of expert centers dedicated to BD is an innovative health care system in France. Until recently, mental health care in France has been based essentially on catchment areas. Because of the complexity of the diagnosis of BD disorders, this network was created to provide support to clinicians for the management of BD patients and, in parallel, to generate clinically relevant data.

Site selection

Sites must be affiliated with an academic center that is actively involved in BD care and research, and motivated to integrate into the network. There are currently 9 expert centers in France. Members of the clinical teams from each center have monthly meetings to ensure inter-rater reliability, receive training in new therapeutic interventions, develop research protocols, and maintain the levels of expertise required in this tertiary care system.

Participant enrollment

Patients are referred by GPs or psychiatrists (private or public practice), who subsequently receive a detailed evaluation report that outlines recommended therapeutic interventions. Although patients are re-assessed and followed at the expert center each year, routine care and treatment are still managed by the referring physician, meaning that patients received TAU (treatment as usual) but modified by the provided recommendations.

There are no exclusion criteria for referral, and patients meet the diagnostic criteria for any BD sub-type (I, II, or NOS). The centers only treat outpatients and do not accept emergency referrals or currently hospitalized patients. The same package of evaluations is used by all

centers and the full assessment is performed by members of a specialized multidisciplinary team: a nurse, a psychologist, a neuro-psychologist, and a psychiatrist.

The assessment protocol was approved by the relevant ethical review board and requires only a letter of information for patients (CPP-Ile de France IX, January 18th, 2010). A web-based application, e-bipolar© was developed to collect data for clinical monitoring and research purposes. Access to this web-based system is carefully regulated and approval was obtained from the body overseeing the safety of computerized databases (CNIL) (DR-2011-069).

Assessments

Upon entry into the study, the patients were interviewed by a senior psychiatrist specialized in BD to clinically evaluate the diagnosis.

The Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID) was used to confirm the BD diagnosis, as well as to assess the course BD and all comorbid psychiatric disorders.[7] Current mood states were assessed using the Montgomery and Asberg Depression Rating Scale[8] (MADRS) and the Young Mania Rating Scale.[9]

We systematically record information related to the patient's education, marital status, economic status, and family history of mood disorders. Patients' history of somatic diseases and treatment for these conditions were recorded using a checklist questionnaire. Current psychotropic treatments were recorded and adherence to treatment was assessed using the French version of the Medication Adherence Rating Scale (MARS).[10] MARS is a 10-yes/no item questionnaire, a low score is correlated with a low likelihood of medication adherence and a total score ≥ 8 is associated with a higher likelihood of medication adherence.

Global social functioning was evaluated using the Global Assessment of Functioning scale (GAF) and the Functioning Assessment Short Test (FAST).[11] The GAF uses a scale from 0 to

100 to evaluate an individual's overall functioning level, where higher scores indicate greater levels of functioning. The FAST is an interview specifically developed to assess the level of disability in BD patients and includes items on autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. This scale provides a total score of functioning and also six specific domain subscores. A higher score indicates worse social functioning.

Sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI) [12,13], which is a 19-item self-completed questionnaire requiring the participant to describe patterns of sleep, such as typical bedtime and waking time, sleep latency, and actual sleep time. A higher score indicates worse sleep quality.

Statistical analysis

Among the 1311 patients followed-up in the expert Center, 984 had at least one follow-up visit after one or two years. The characteristics of drop-out patients were as followed: younger of age, Bipolar Type NOS, more depressive symptoms, lower functioning, and a higher proportion of comorbidities (tobacco, substance abuse, and sleep disturbances). They also used a higher number of psychiatric medications at baseline (data not shown).

Socio-demographics, clinical characteristics, and psychiatric co-morbidities are presented as the means and standard deviation for continuous variables and frequency distributions for categorical variables.

To assess the clinical evolution of patients over two years, we first performed two by two comparisons between the baseline visit and 12-month visit, the baseline visit and 24-month visit, and between the 12 and 24-month visits. The Wilcoxon signed rank test (for continuous parameters) and Mc Nemar test (for categorical variables) were used. To evaluate the global evolution of parameters over time, we performed linear mixed models for continuous parameters and a generalized linear model for categorical variables, adjusting for age, gender, and duration of the disease.

To assess factors associated with an improvement of functioning over the two years, we performed linear mixed model including time, gender, age, bipolar subtype, duration of the disease, depressive symptoms (MADRS score), manic symptoms (YMRS score), sleep disturbances (PSQI score), Body Mass Index, anxiety disorders, substance use disorders, adherence to medication (MARS score), and psychotropic medication (Atypical Antipsychotic, mood stabilizer, and antidepressant use).

We used the multiple imputation method and inverse-probability-of-attrition weights (IPAW) to address missing data and selection bias due to patient dropout.[14] Multiple imputation

involves the creation of multiple complete datasets by assigning plausible predicted values to otherwise missing values, followed by the separate analysis of each imputed dataset, and finally the combination of the point estimates and estimated standard errors to come up with a single, multiply-imputed set of estimates. Multiple imputed datasets were generated using the PROC-MI procedure of SAS with the fully conditional specification methods. The imputation model included all variables in the analysis. We chose to generate 10 imputed datasets based on simulation studies, demonstrating little gain in statistical power for higher numbers of imputations. For IPAW, we calculated the probability of remaining in the study at each wave, based on observed baseline covariate history using logistic regression models. Weights were calculated as the ratio of predicted probabilities from two logistic regression models: the probability obtained from a model with baseline covariates divided by the probability obtained from a second model with baseline covariates, as well as time-varying covariates. For explanatory variables, we selected important variables that potentially affect drop out: age, gender, education level, bipolar subtype, age of onset, depressive and manic symptoms, functioning, body mass index, psychiatric comorbidities (sleep disturbance, anxiety and substance use disorders), adherence to medication, and antipsychotic medication. We then used these probabilities to compute analytical weights that are inversely proportional to the probability of remaining in the study. Results without multiple imputations and IPAW were also added in annexes. The tests were two-sided and the significance level was fixed at 5%. All analyses were conducted using SAS (release 9.3; SAS Statistical Institute, Cary, NC).

Results

Table 1 shows the baseline characteristics of the 984 patients followed for two years. The mean age at baseline assessment was 42.7 years (±12.5) and there were 58.8% women and 41.2% men. Most patients (83.4%) had a high school diploma. Unemployment rate was relatively high, with 18.9% of the patients being unemployed (two-fold the national unemployment rate in France). 49.5% of the individuals suffered from type I, 40.7% from type II, and 9.9% from BD not otherwise specified. The mean age at onset was 24.7 (± 9.9 years). Regarding lifetime psychiatric comorbidities, the rate of anxiety disorders was 44.5% and substance use disorders 29.3%; 41.5% of the patients had a history of at least one suicide attempt. The mean number of medications received at baseline assessment was 2.3 (±1.2) with 42.4% of patients receiving an antidepressant. The most frequently prescribed classes of mood stabilizers were anticonvulsants (57.2%) followed by atypical antipsychotics (APA) (34.0%), and lithium (31.3%). Patients showed moderate to serious impairment of global functioning as assessed using the GAF scale at baseline (13.5% had a score < 51 and 39.9% a score < 70). Using the FAST, we obtained a mean total score of 21.0 (±14.6) corresponding to 67.5% of patients with impaired functioning (FAST total score ≥ 12).

Hospitalizations and mood episodes: comparison between one year before inclusion and evolution during the 2-years of follow-up

As a whole, the mean number of hospitalizations during the lifespan was 2.6 (sd=2.8), and the mean number of episodes during the course of BD was 6.9 (sd=5.8). In Table 2, we compared the number and duration of hospitalization as well as the number of episodes one year before inclusion to the Expert Center and the evolution during the 2 years.

The mean length of hospitalization 1 year before inclusion was 16.8 days and decreased to 14 days at one year and to 7.5 days after two years of follow up. We also observed a reduction of the mean number of mood episodes of any polarity.

In order to control potential bias, we have considered the sub-group of patients who have been hospitalized the year before inclusion (n=266): 54% of them have been rehospitalized during the 2 years follow-up and when rehospitalized, the mean duration of hospitalization also decrease over time (34.6 days (sd=5.9) year before, 37.5 days(sd= 7.3) year one, 8.2 days(sd= 8.2) year two, p=0.009).

Functioning and other outcomes from baseline to 24 months of follow-up (Table 3)

Patients globally were improved as shown by a decrease of the FAST and GAF scores. However, since the FAST score was dependent of the presence of hospitalization (higher score in occupational functioning items), we also ran the analysis excluding patients hospitalized in the year before inclusion. Here again, we showed a reduction in the FAST score from 20.7 (sd=0.7) at baseline to 17.6 (sd=0.7) one year later and 15.8 (sd=0.8) two year later (p=<0.0001).

The level of depressive and manic symptoms decreased significantly during the follow-up period, as well as the frequency of comorbidities. Substance use and anxiety disorders decreased respectively from 30.8% to 23.6% and 49.3% to 39.3%, . The score evaluating sleep disturbances also improved over time while body mass index remained stable over the two years. There was better concordance to evidence-based guidelines concerning medication, with a higher prescription of mood stabilizers and a lower use of antidepressant during follow-up even these differences were of small magnitude.

Using a multivariate model, we showed that improvement of functioning was associated with an improvement of depressive and manic residual symptoms, reduction of comorbidities (anxiety disorder and substance use disorders), lower BMI, and improved adherence to medication (Table 4).

Discussion

This observational study on patients followed during two years provides evidence that patients with BD who were monitored in a specialized center for BD displayed an improvement in several outcomes measures, in particular a 55% reduction of the length of hospitalization. The study also demonstrated an overall improved functioning and highlights several determinants of this improvement concerning lower mood residual symptoms, better quality of sleep and medication adherence.

To assess the relevance of this new system of care, we chose the hospital admission rate since it is an objective proxy measure of illness outcome and indicative of severe functional impairment or behavioral disturbances, and thus linked to syndromal relapses. Hospitalizations also have the highest direct economic cost.[15] We show a global favorable outcome in particular on hospitalization rates with a substantial decrease in the length of hospital stays (from 16.8 to 7.5 days/year), associated with a reduction in the number of full-blown episodes during the follow-up. However, we also explored two measures of functioning, which referred more to functional recovery, the ultimate goal in the management of any disease. Using these outcomes, we observed that the patients globally improved, whatever the subgroup considered (those hospitalized one year before the inclusion and those who were not). Several determinants were associated with an improved functioning, such as decreased of residual mood symptoms, improvement of sleep quality, a reduced BMI, a better adherence to medication, which is coherent with previous findings.[16–18] The lack of an effect of age or type of bipolarity in the multivariate model indicates that these benefits might be broad-based. It should be noted that even mild decrease in residual depressive symptoms (reduction of 2.6 on the MADRS score) was enough to have a significant positive impact on functioning. The improvement of sub-threshold depressive symptoms is therefore a major challenge for the overall improvement of bipolar patients.

Worldwide, various specialized programs of care for patients with BD have been developed to improve the course of the disorder. Several models have been implemented in different countries such as specialized clinics, collaborative care models or our network of Expert centers in France [5,19–23] The clinical impact and the effectiveness of the implementation of such models have not always been extensively reported in the literature although this would help their widespread and stimulate the interest of policies makers when dealing with a disorder characterized by huge direct and indirect costs.

Collaborative care models for BD have been tested and compared to standard care in randomized, controlled, effectiveness trials. The key principles of the collaborative care system are: enhancement of patient self-management skills via a structured psycho-education group, support for referring clinicians through evidence-based clinical practice guidelines in a simplified format, and enhanced access to, and continuity of, treatment through a nurse care manager. These trials reported improved clinical outcomes[24], reduction of the number of months with depressive symptoms[20], a decreased rate of readmissions to hospital[25], an improved functioning and quality of life[25,26] , an improved adherence to guidelines[5], an increase of employement rates.[22] Other models such as combining of a model of specialized care for BD and a psychosocial treatment (Enhanced Clinical Intervention (ECI))[23], early treatment in a specialized outpatient mood disorder clinic (*versus* standard care)[27] demonstrated also a positive impact on the course of BD.

Our expert center model does not fit with a collaborative care model but shares some characteristics. Patients are referred by general practitioners or psychiatrists, who afterwards receive a detailed evaluation report along with suggestions for therapeutic interventions. Although patients are assessed at the expert centers, routine care and treatment is still undertaken by the treating physician. The goal is to help clinicians improving evidence-based management of BD and to provide a more 'personalized medicine' approach. Many

clinicians in France are not familiar with existing guidelines or are reluctant to use them.[28] Our goal is to support clinicians to adopt guidelines based on accurate explanations using a bottom-up strategy based on individual refereed cases.[29,30] The ultimate goal is that clinicians can more confidently and accurately identify the best combinations of interventions suitable for a given patient, while in the long-term familiarizing them with 'personalized medicine' models.

The challenge of our model is to integrate the clinician's expertise with the patient's preferences, actively involve the family when possible, and include all involved health care professionals including the general practitioner. In France, the general practitioner acts as the primary clinical coordinator for most medical chronic conditions, but is not always included in the decision making and the follow-up of the patient with psychiatric disorders. It is necessary to reconcile psychological and pharmacological approaches to somatic and mental health in a bio-psychosocial approach in a cohesive manner, as suggested in recent guidelines.[31] Following the baseline assessment, the pluridisciplinary team of the expert center provides a detailed report to the patient and the referrals. We conclude the report with suggestions for pharmacological and psychological interventions, familial support if appropriate, and lifestyle adjustments (management of substance misuse, diet, sleep). These personalized conclusions are explained to the patient and the report is delivered to the patient and sent to all the health care professionals involved in managing the patient's care. Brief practice guidelines on pharmaceutical treatment are provided to clinicians to aid in monitoring the patient and the side effects of the treatment. A short guideline on lithium is also provided to patients when appropriate. The expert center helps clinicians to find professionals for specific psychosocial interventions such as psychoeducation for example. Psychologists of the expert center can also provide short and specific interventions (cognitive behavioral therapy,

psychoeducation for patients and caregivers, cognitive and functional remediation) when appropriate.

The main limitation of our study is that it was not a randomized trial with a comparator group (follow-up as usual for example). We undertook analyses taking each patient as its own controls for hospitalization and number of episodes (one year before the inclusion *versus* two years after) in order to provide information on individualized trajectories of change. Nevertheless, we cannot conclude that the changes are only due to the care model. In this study, we were not able to report the types of psychosocial interventions provided to patients in addition to their usual treatment and their potential impact on functioning in this study.

Among the strengths of this study, we took advantage of a large cohort with a follow up of two years for which the sampling was representative of the population, the cases clinically complex, and many patients severely impaired. A large set of variables was used to assess improvement. We evaluated two main outcomes, an objective measure (length of hospitalizations) and functional assessment using a specific tool for BD.

In conclusion, we showed that our system of care based on a better collaboration between health care professionals, involving actively patients and families and proposing personalized care developing on a bio-psychosocial approach, can improve the outcome of BD patients. We also highlighted some ingredients of the observed improvement of functioning that might be targeted during interventions, such as residual mood symptoms, sleep, BMI or medication adherence. Further studies in this cohort would have to clarify more individualized trajectories of changes in order to better target those patients who require intensive follow-up *versus* those with more favorable outcomes. Further works are also require to estimate the cost benefit derived from decreased hospitalizations rates and better functioning.

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Table 1 : Baseline characteristics of the 984 patients followed-up during two years

Socio-demographic characteristics n (%) or mean(sd)	
Women, n (%)	579 (58,8)
Mean age (sd)	42,7 (12,5)
High education level, n (%)	746 (83,4)
Occupational status n (%)	
Full time	438 (5,0)
Unemployed	166 (18,9)
Pension	42 (4,8)
Retired	77 (8,8)
Other	153 (17,5)
Referring doctors, n(%)	
Psychiatrist	725 (78,4)
General practitioner	125 (13,5)
Other	75 (8,1)
Illness caracteristics	
Bipolar subtype n (%)	
BP I	487 (49,5)
BP II	400 (40,7)
BP NOS	97 (9,9)
Age of onset, mean (SD)	24,7 (9,9)
Duration of illness, mean (SD)	17,9 (11,5)
Depressive symptoms (MADRS score), mean (SD)	9,3 (8,5)
Manic symptoms (YMRS score), mean (SD)	2,5 (3,8)
Fast score, n (%)	21,0 (14,6)
<12	634 (67,5)
≥12	306 (32,5)
Global social functioning (GAF) n (%)	
100-71	426 (46,7)
70-51	364 (39,9)
< 51	123 (13,5)
Comorbidities	
Smoking n (%)	
No	433 (45,5)
Ex	119 (12,5)
Current	401 (42,1)
Substance abuse, n (%)	269 (29,3)
Body Mass Index, mean (sd)	25,8 (4,9)
Anxiety disorders, n (%)	406 (44,5)
Sleep disturbance (PSQI score), mean (SD)	7,0 (3,7)
Suicide attempt, n (%)	397 (41,5)
Adherence to treatment (Mars score), mean (sd)	7,1 (1,9)

Number of treatment, mean (sd)	2,3 (1,2)
APA, n (%)	275 (34,0)
Lithium, n (%)	253 (31,3)
Anticonvulsants, n(%)	463 (57.2)
Antidepressant, n (%)	343 (42,4)

Table 2: Hospitalizations and mood episodes in patients with bipolar disorders: Comparison between one year before inclusion and evolution during the 2 years followed-up

	PATIENT WITH BD FOLLOWED UP 2 YEARS						
	One year before inclusion	Between baseline and visit at 12 month	Between baseline and visit at 24 month	$P^{*}_{v0\ vs\ v12}$	$P^{*}_{v0\ vs\ v24}$	$P^{*}_{v12\ vs\ v24}$	$P^{\dagger}$
Number of hospitalization, mean (se)	0.57 (0.01)	0.34 (0.01)	0.24 (0.01)	**<0.0001**	**<0.0001**	**0.0242**	**<0.0001**
Duration of hospitalization (in days), mean (se)	16.8 (0.6)	14 (0.7)	7.5 (0.7)	0.1961	**<0.0001**	**0.0016**	**0.0003**
Number of mood episodes, mean (se)	1.4 (0.05)	0.6 (0.05)	0.6 (0.06)	**<0.0001**	**<0.0001**	0.47	**<0.0001**

* Wilcoxon signed Rank Test or Mc Nemar test

† Mixed model (for continuous variables) or GEE model (for categorical variables) adjusted for gender, age and duration of the disease

Table 3: Evolution of illness characteristics, functioning, comorbidities and medications in patients with bipolar disorders followed-up 2 years

	PATIENT WITH BD FOLLOWED UP 2 YEARS						
	Visit at baseline	Visit at 12 month	Visit at 24 month	$P^{*}_{v0\ vs\ v12}$	$P^{*}_{v0\ vs\ v24}$	$P^{*}_{v12\ vs\ v24}$	$P^{\dagger}$
Functioning							
Functioning (FAST score), mean (se)	22.3 (0.2)	20.8 (0.2)	18.9 (0.4)	**0.0398**	**0.0001**	**0.0363**	**<0.0001**
Global social functioning (GAF), mean (se)	65.5 (0.2)	68.7 (0.2)	69.0 (0.4)	**<0.0001**	**<0.0001**	0.767	**<0.0001**
Illness characteristics							
Depressive symtoms (MADRS score), mean (se)	8.9 (0.05)	6.6 (0.05)	6.2 (0.08)	**<0.0001**	**<0.0001**	0.2968	**<0.0001**
Manic symptoms (YMRS score), mean (se)	2.7 (0.02)	2.2 (0.03)	2.4 (0.04)	**0.0087**	0.1729	0.4771	**0.0223**
Comorbidities							
Substance abuse, n (%)	303 (30.8)	247 (25.1)	232 (23.6)	**<0.0001**	**<0.0001**	**<0.0001**	**0.0049**
Body Mass Index, mean (se)	26.0 (0.05)	26.0 (0.05)	26.1 (0.07)	0.8417	0.6596	0.8296	0.5078
Anxiety disorders, n %	485 (49.3)	397 (40.3)	387 (39.3)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Sleep disturbance (PSQI score), mean (se)	7.1 (0.02)	6.8 (0.02)	6.5 (0.06)	**0.0523**	**0.0036**	0.2173	**0.0013**
Treatment							
Adherence to treatment (MARS score), mean (se)	7.0 (0.01)	7.5 (0.02)	7.5 (0.04)	**<0.0001**	**<0.0001**	0.6395	**<0.0001**
APA, n (%)	340 (34.5)	347 (35.3)	364 (37.0)	**<0.0001**	0.1734	**0.0223**	0.1109
Anticonvulsants, n (%)	552 (56.1)	571 (58)	693 (60.3)	**<0.0001**	**<0.0001**	**<0.0001**	0.2035
Lithium, n (%)	298 (30.3)	355 (36.1)	351 (35.7)	**<0.0001**	**<0.0001**	**0.0336**	**<0.0001**
Antidepressant, n (%)	427 (43.4)	403 (41.0)	394 (40.0)	**<0.0001**	**<0.0001**	**<0.0001**	0.1995
Number of medication, mean (se)	2.3 (0.02)	2.4 (0.01)	2.5 (0.02)	0.1191	**0.0498**	0.6105	**0.0315**

* Wilcoxon signed Rank Test or Mc Nemar test

† Mixed model (for continuous variables) or GEE model (for categorical variables) adjusted for gender, age and duration of the disease

Table 4: Global model explaining the evolution of functioning (evaluated with the FAST score) over time

	Evolution of functioning	
	FAST score estimate (se)	P value*
Time	**-0,07 (0,02)**	**0,005**
Gender (male)	-0,73 (0,66)	0,281
Age	0,02 (0,03)	0,503
Bipolar disorders 1 vs NOS	1,54 (1,05)	0,153
Bipolar disorders 2 vs NOS	0,24(1,08)	0,830
Depressive symptomes (MADRS score)	**0,88 (0,03)**	**<0,0001**
Manic symptoms (YMRS score)	**0,16 (0,07)**	**0,040**
Sleep disturbance (PSQI score)	**0,32 (0,08)**	**0,0003**
Body Mass Index	**0,41 (0,06)**	**<0,0001**
Anxiety disorders	**2,7 (0,8)**	**0,008**
Substance abuse	**3,5 (0,7)**	**0,0005**
Adherence to medication (MARS score)	**-0,40 (0,14)**	**0,012**

* linear mixed model