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Direct medical cost of bipolar disorder: insights from the FACE-BD longitudinal cohort

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Introduction

Bipolar disorder (BD) is a severe chronic psychiatric disorder affecting 0.5 to 1% of the population worldwide (Frank et al., 2015). BD is characterized by lifetime fluctuations of mood (manic and depressive episodes) and is the cause of a heavy societal burden.

Because of its high prevalence and recurrent course, there is a need to estimate the economic impact of BD to guide public health policies. The World Health Organization estimated that BD resulted in a greater burden than all forms of cancer (Jin and McCrone, 2015). Williams et al. (Williams et al., 2011) found that BD had a higher adjusted mean per member per month cost than depression, asthma, coronary artery disease or diabetes. In addition, BD represents a financial burden for the individuals and their families (Jin and McCrone, 2015).

In US claim databases, the cost of BD (including direct healthcare costs, non-healthcare costs and indirect costs) has been estimated at \$202 billion in 2015, corresponding to an average of \$81,559 per individual. The cost of BD was related to caregiving (36%), direct healthcare costs (21%) and unemployment (20%) (Cloutier et al., 2018).

In France, a limited number of studies investigated the cost of BD. Gonzalez-Pinto et al. (Gonzalez-Pinto et al., 2010) and de Zélicourt et al. (de Zélicourt et al., 2003) estimated the cost of type I bipolar disorder in France based on the data available in a single French hospital.

However, because of the heterogeneity of healthcare systems, it is difficult to compare costs across countries (Charrier et al., 2013; Jin and McCrone, 2015).

To date, the diagnosis of BD is only based on clinical assessment. However, previous studies have investigated the cost of BD in large databases with limited access to clinical evaluation. This top-down approach allowed to include a large number of patients but with uncertainty in clinical diagnosis. In addition, there is a need to understand the determinants of BD cost, which requires access to precise clinical information (such as the history of suicide attempts or the type of bipolar disorder) which are usually not reported in health insurance databases (Jin and McCrone, 2015). In addition, the vast majority of the studies published to date were retrospective and did not include a follow-up of the costs. Because BD is a chronic and cycling disorder, there is a need to understand the evolution of the cost and its determinants (Jin and McCrone, 2015).

The French Expert Centers network for BD offer an unprecedented opportunity to study the cost of BD. Individuals can be referred to the expert centers either by their psychiatrist or their general practitioner (GP). The expert centers are not providing a close follow-up. Instead, the expert centers are providing to individuals and physicians a comprehensive somatic, psychiatric and cognitive evaluation and evidence-based recommendations in terms of medications, psychological and / or social interventions. The individuals are then systematically referred back to their healthcare providers for regular follow-up and for implementation of the recommendations. All patients are eligible for a follow-up with annual visits within the network if they have a confirmed diagnosis of bipolar disorder.

This study thus aimed at (i) estimating the direct healthcare cost associated with BD and its contributing factors and (ii) studying the evolution of the cost during a two year follow-up period in French centers of expertise for individuals with BD.

Methods

Study population

BD patients included in our study were all clinically assessed within the Fondamental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) cohort in France.

The FACE-BD cohort contains data issued from the evaluations done in the French national network of expert centers, set up by a scientific cooperation foundation in France, the Fondation FondaMental to create a network strongly connected to primary and specialized care, offering a standardized and thorough assessment, providing support for routine care and aiming to spread good clinical practice to improve the outcome of bipolar disorder (Henry et al., 2017). Patients are recruited in 9 centers: in the Paris area (Versailles, Créteil, 10th district of Paris), the South East (Grenoble, Marseille), the South West (Bordeaux, Montpellier), the East (Nancy) of France and Monaco. The FondaMental network provides a standardized clinical assessment (with a e-medical file) to patients referred by their general practitioner or psychiatrist for diagnosis or therapeutic recommendations, who subsequently receive a detailed evaluation report with suggestions for therapeutic interventions.

The network provides a thorough and standardized assessment of BD patients. All outpatients, aged 16 years or above and diagnosed with BD according to *DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.)* criteria (all BD subtypes [I, II and not otherwise specified]), were assessed in expert centers. The only exclusion criteria for clinical assessment were dementia or related disorders (Alzheimer disease, fronto-temporal dementia, dementia with Lewis bodies) or mental retardation.

All centers used the same package of thorough and standardized clinical assessments, described in detail elsewhere (Godin et al., 2020; Henry et al., 2017). Patients were reassessed at 1 year and 2 years.

Data collection

A team composed of psychiatrists and psychologists, specifically trained to assess patients with BD, conducted interviews with patients using the SCID (structured interview for DSM 4 disorders) and systematically recorded the clinical features of BD, as well as current medication. In addition, a systematic and standardized clinical assessment was performed (Henry et al., 2017) and included socio-demographic characteristics (gender, age, marital status, education level, employment status), characteristics of the illness (bipolar subtype, age at onset, history of suicide attempt, evaluation of functioning with the FAST (Functional assessment staging tool, (Rosa et al., 2007)), adherence to treatment with the MARS (Medication Adherence Report Scale, (Godin et al., 2020)), somatic (mainly overweight and metabolic syndrome) and addiction (tobacco, alcohol, cannabis and other drugs).

Timeline

On the day of inclusion, patients filled a questionnaire regarding their use of healthcare services during the previous year and were interviewed by a psychiatrist. For patients who accepted a follow-up in their expert center, the same evaluation was conducted at each follow-up visit to record their use of medication and hospital admissions.

Cost calculation

We defined direct healthcare costs as the sum of costs related to the use of healthcare services (Supplementary Material 1). The details of cost computation is described elsewhere (Laidi et al., 2018).

Briefly, we estimated the cost of full-time hospitalisation (psychiatric services) based on the cumulative length of full-time hospitalisation in the year prior to the clinical evaluation.

In France, there is no single unified tariff for one day of hospitalization. We estimated the daily cost of hospitalisation based on data from the French health public insurance (Assurance maladie - AM). In 2018 (Rapport Charge et produits 2021), AM estimated the total cost of hospitalisation for psychiatric disorders to € 9 681 929 850. We divided this figure by the total number of days of hospitalisation (19.4 millions) computed by the French agency for information on hospitalisation (ATIH), leading to a daily cost of hospitalisation of € 398 per day. This calculation assumes that the per-diem cost is independent from the diagnosis. The cost of medications was estimated based on the French social insurance tariff public database (<http://base-donnees-publique.medicaments.gouv.fr/>) in 2019. For each treatment of each patient, the unit cost of each daily intake was multiplied by 365 to compute a yearly cost by patients.

We calculated the cost of consultations within the expert centers. This clinical assessment is considered as day care and typically lasts 1.5 days. We valued this cost at €218 per day (€ 327 for 1.5 day) based on public information available online (<https://www.scansante.fr/applications/cout-dunites-doeuvre>).

Factors associated with direct healthcare costs

We conducted a literature search to identify factors influencing direct healthcare costs or hospital admissions.

First, we explored demographic characteristics and found that age and gender were significantly associated with readmission in full time hospitalization (Fellinger et al., 2018; Fornaro et al., 2018; Hamilton et al., 2016; O'Hagan et al., 2017).

Second, we searched for socio-economic factors associated with increased rates of hospitalization or length of stay. Having a spouse or partner was associated with a 52% risk reduction of hospitalization (Hoblyn et al., 2009) which replicates previous findings (Goi et al., 2009; Shim et al., 2017). Employment status was also associated with length of stay (Luciano et al., 2016; Shim et al., 2017).

Last, we searched for clinical features or comorbidities associated with increased rate of hospitalization or length of stay. Based on the literature, we selected the type of bipolar disorder (i.e, type I, type II) (Carvalho et al., 2014; Fornaro et al., 2018; Gianfrancesco et al., 2007; Kupka et al., 2005), the functioning (Hamilton et al., 2016) and the adherence to treatment (Gonzalez-Pinto et al., 2010; Keck et al., 1998; Strakowski et al., 1998). In addition, four comorbidities were associated with increased hospitalization: alcohol and/or substance abuse (Brady and Sonne, 1995; Fornaro et al., 2018; Goldstein et al., 2006; Hoblyn et al., 2009), cardio-metabolic comorbidity (Correll et al., 2017), having a coexisting anxiety disorder (Chen et al., 2013) and smoking tobacco (Kupka et al., 2005).

As our data came from a multicenter survey, we included the center of inclusion as a proxy to assess a potential variability in direct health care costs that would be linked to the specificity of the geographical areas.

Based on our literature search, we included four socio-demographic features (gender, age, marital, employment status, and educational level), four clinical features of BD (type of bipolar disorder, functioning, adherence to treatment), five comorbidities (smoking status, alcohol abuse, cannabis abuse, substance abuse, comorbid anxiety disorder, and overweight (BMI > 25 kg/m²) and the center of inclusion in our univariate model.

Statistical analyses

Demographic, socioeconomic, and clinical characteristics were described using frequency for categorical variables and means, standard deviations, and medians for continuous variables.

The MARS scale measures the adherence to the treatment and has been validated in French ([Misdrahi et al. 2004](#)). A total score ≥ 8 is associated with a higher likelihood of medication adherence ([Henry et al. 2017](#)). We included the MARS scale as a categorical variable in our model. We conducted secondary analyses to study the association between the cost of BD and adherence to treatment. We conducted a univariate analysis to test the association between every item of the MARS score and the cost of BD. We conducted two multivariate analyses : in the first one, we included only the significant items of the MARS score in univariate analyses and in the second one we included the total MARS score as a continuous variable.

We computed for each patient, the yearly cost associated with direct healthcare as described in the cost calculation section. To account for the uncertainty of our measure, we estimated the 95% confidence interval of the mean, the median, the first, and the third quartile of the direct healthcare cost. To determine demographic, socioeconomic, and clinical factors associated with direct health care costs, univariable analysis were performed using non-parametric tests because of the non-normality of the direct health care cost distribution (Wilcoxon-Mann-Whitney test or Kruskal-Wallis test for categorical variables; calculation of the Spearman rank correlation coefficient for continuous variables).

Variables with p value < 0.20 in univariable analysis were included in the multivariable regression analysis. Considering that the distribution of costs was skewed, a gamma generalized linear model with log links was performed. Coefficients were exponentiated to express the effect as rate ratio estimates. To account for the uncertainty, we used a bootstrapping method to test the internal validity of the model. We performed the multivariate analysis on 1,000 samples created from the original dataset and we provided the 95% CI of each estimated parameter (rate ratio estimates associated to each included variable/modality) as well as the percentages of samples in which each variable was significantly associated with direct health care costs at a 5% and 10% levels respectively.

Evolution of direct healthcare costs during a two-year follow-up period

In a subsample of individuals followed-up during 2 years, evolution of cost during follow-up was estimated. Evolution of direct health cost was evaluated using linear mixed models adjusted for age and gender, with subject as a random effect to account for dependence among

observations for the same subject (Proc mixed procedure in SAS software [SAS Institute, Cary, NC, USA] with three measures: baseline, year 1 and year 2) and with a compound symmetry covariance structure.

Comparisons between individuals followed and those who were supposed to be followed up were performed using Chi-square tests for categorical variables and student t-tests, Wilcoxon Mann Whitney-test or Kruskal-Wallis test for continuous variables depending on the characteristics of the variable distributions.

To take into account the missing data and lost to follow-up, we used the multiple imputation method and inverse-probability-of-attrition weighting (IPAW) (See Supplementary Material 5 for a description of the procedure). Last, we conducted a last-observation carried forward analysis (LOCF), where any missing data was imputed by the last information available.

Results

Population characteristics

One thousand one hundred and sixteen patients were included at baseline. Demographic and clinical characteristics of the participants are reported in Table 1. Patients were recruited in 9 centers across France and in Monaco. The mean age of our sample was 41 years, 60% of patients were females, 46% of patients suffered from type I BD and 36% of patients had a history of suicide attempt ; the mean duration of illness was 17 years, patients had an average (standard deviation, sd) MADRS score of 10 (8) and an average (sd) YMRS score of 2 (3).

[Insert Table 1]

Direct healthcare costs

The analysis included all 1116 patients. Direct health care costs ranged from € 989 to € 102 372. The mean (95% CI, estimated by the bootstrapping method) direct healthcare cost was € 6910 (€ 6193 - € 7580) per year and per patient. The median (95% CI, estimated by the bootstrapping method) direct healthcare cost was € 1101 (€ 1016 - € 1191). Results are reported in Supplementary Material 1. As expected, hospitalizations were driving the cost of direct healthcare costs and represented 87% of total healthcare costs (Figure 1).

[Insert Figure 1]

Factors associated with direct healthcare costs: univariate analysis

Results from the univariate analysis are reported in Table 1. Three demographic characteristics were associated with direct healthcare costs at a $p < 0.05$ level. In patients with BD, age, living alone, and being unemployed were associated with higher costs. Four clinical characteristics were associated with direct healthcare costs. Type I BD, history of suicide attempt, lower functioning, and smoking tobacco were associated with higher costs. However, age of onset, adherence to treatment, substance, cannabis, or alcohol abuse were not associated with direct healthcare costs. There was a site effect suggesting variability within the different sites of inclusion with a mean cost ranging from € 4329.8 (Versailles) to € 9923.6 (Monaco). In addition, gender and substance abuse were associated with direct healthcare costs at a $p < 0.2$ level and were added to our multivariate model.

Factors associated with direct healthcare costs: multivariate analysis

Results from the multivariate analysis are reported in Table 2. Age and employment status remained significant in the multivariate model and were associated with higher direct healthcare costs. Two clinical features of BD were associated with higher cost : type I BD and history of suicide attempt. Smoking status was associated with higher direct healthcare costs. In addition, we found a strong site effect, confirming that the direct healthcare cost varied across the centers of inclusion. The type of bipolar disorder and the history of suicide attempts were two factors for which the size of the association was among the highest values. The direct healthcare cost was in average 2.1 times higher in bipolar type I patients and 1.6 times higher in patients with a history of suicide attempts.

[Insert Table 2]

Evolution of direct healthcare costs during a two-year follow-up period

Of the 1116 patients recruited at baseline, 266 (23%) completed a two year follow-up in the fundamental advanced centers of expertise. There was a significant decrease of direct healthcare costs over time $p < 0.001$, during the two-year follow-up period. On average, the direct healthcare costs dropped from € 6170 at baseline to € 1281 after 24 months of follow-up, corresponding to an average decrease above 50% (linear mixed model with gamma distribution, time : $\beta = -0.05$, standard error = 0.004 - $p < .0001$) (Figure 2, Supplementary Material 3b).

Because only one-quarter of patients at baseline were follow-up for a two-year period, we conducted additional analyses. We compared at baseline the demographic and clinical characteristics of patients with (BD-FU) and without follow-up (BD-WFU) (Supplementary Material 2). At baseline, there was no difference in global healthcare cost when comparing BD-FU and BD-WFU. However, patients with BD-FU tended to have better functioning, reduced depressive and manic symptoms, reduced consumption of tobacco, and reduced substance abuse. To study the effect of lack of follow-up for these individuals, we conducted a multiple imputation analysis (Supplementary Material 4) and a last observation carried forward analysis (Supplementary Material 5).

[Insert Figure 2]

Secondary analyses.

When considering the MARS scale as a continuous variable, we found that low adherence to treatment was associated with a lower cost of BD in our multivariate analysis contrary to what we expected (supplementary material 6). To further understand the relationship between adherence and the cost of bipolar disorder, we studied separately how every item of the MARS scale was associated with the cost of bipolar disorder in univariate analyses. These results (as well as the detailed questions of MARS scale) are reported in supplementary material 7. As expected, “forgetting medications” and “taking medication only when feeling sick” were both associated with a higher cost. However, two other items of the MARS (related to side effects and insight) were associated with the cost in the opposite direction. All other items from the MARS were not associated with the cost of bipolar disorder. Last, we tested in a multivariate analysis the relation between the significant items from the MARS in the univariate analysis and the cost of bipolar disorders. Results are reported in supplementary material 8. In this analysis, only the two items for whom adherence to treatment was associated with lower cost remained significant (“forgetting medications” and “taking medication only when feeling sick”).

Discussion

In our sample, the average direct healthcare cost per year and per patient with BD was € 6910 and the median cost was € 1101. To the best of our knowledge, this is the first estimation of the direct healthcare cost of patients with BD in France.

The French social health insurance estimated the average cost per year and per patient for mood and neurotic disorders to € 4460 in 2018 (Fiche Pathologie, Assurance Maladie 2018, www.ameli.fr). The diagnosis was based on algorithms combining ICD10 diagnosis with the use of medication analyses for patients benefiting from full public health insurance coverage with mood and neurotic disorders. Mood and neurotic disorders include a very broad and heterogeneous spectrum of psychiatric disorders, from personality to bipolar disorder. In this spectrum, bipolar disorder is the most severe disorder and is likely to be associated with higher costs. Although the definition of the disorder was different, our results are coherent with those from the French social health insurance, suggesting a good external validity of our results.

Because the organization and funding of care for psychiatric disorders can vary depending on the country, international cost comparisons are difficult (Charrier et al., 2013). In the USA, Cloutier et al. (Cloutier et al., 2018) recently reported the direct health care cost of BD to be \$17 000 dollars (€14414) per year and per patient, the authors included patients with a diagnosis of type I BD, which was associated in our sample with a cost of € 7,096. In Sweden, the average cost per patient and per year was estimated at € 28 000, with direct health care costs representing 25% (€ 7000 per year and per patient) of the total cost. Kleine-Budde et al. (Kleine-Budde et al., 2014) conducted a systematic review of cost-of-illness studies in bipolar disorder. The authors reported direct healthcare costs per capita, ranging from \$ 8 000 to \$ 14 000 purchasing power parity (PPP). In a sample of 169 patients recruited in 4 Spanish university hospitals, Hidalgo-Mazzei et al. (Hidalgo-Mazzei et al., 2015) found that the mean direct cost of a manic episode was € 4 771 euros ; 77% of this cost was related to hospitalization. Despite the difficulty to compare costs across countries, our results are coherent with those from the literature. Our results are in line with these results and suggest that the cost of hospitalization is driving direct healthcare costs. In addition to its cost, hospitalizations in psychiatry are often associated with trauma (Paksarian et al., 2014). Thus, both from the patient and the payer perspective, there is a need to prevent hospitalization (Wingård et al., 2017) in bipolar patients. As pharmacological interventions alone may have a limited impact in the reduction of hospitalization (Wingård et al., 2017), implementing center of expertise (Henry et al., 2017), innovant mobile / web-based applications to improve follow-up (Fletcher et al., 2018), or psychoeducation (Buizza et al., 2019) might be key to improve adherence to treatment (García et al., 2016), and reduce the cost of BD while improving patients well-being.

We found that the diagnosis of BD I was associated with higher cost compared to BD II and patients with BD not otherwise specified. This result was expected since patients with BD I have higher manic severity and comorbidities (Baek et al., 2011) leading to frequent hospitalizations. We found an increased direct health care cost in patients aged < 35 years compared to patients aged > 48 years. Contrary to our results, O'Hagan et al. (O'Hagan et al., 2017) found that an age range of 42-53 years was associated with an increased risk of readmission. However, Shim et al. (Shim et al., 2017) did not find any effect of age on length of hospitalization in bipolar

disorder. Although these discrepant findings are difficult to interpret, it is important to note that the French health care system offers a limited number of interventions for young adults facing mental health issues. The French mental health care system is divided in small catchment areas organized in a similar fashion and providing unspecialized care. This organization leads to a delayed diagnosis of bipolar disorder (Drancourt et al., 2013), likely to be associated with more severe symptoms and longer hospitalizations in young adults in France.

We found that being unemployed vs active was associated with a higher cost. Again, this result was expected, since patients with shorter hospitalization duration are more likely to be active than unemployed (Shim et al., 2017).

The MARS scale measures the adherence to the treatment and has been validated in French (Misdrahi et al. 2004). A total score ≥ 8 is associated with a higher likelihood of medication adherence (Henry et al. 2017), which is why we selected this cut off in our analyses. With the MARS score considered as a categorical variable, we found no association between adherence to treatment and the cost of BD. However, when considering the MARS scale as a continuous variable, a higher adherence to treatment was associated with a higher cost. This result is in line with a previous study published in the same cohort (Corr  rard et al. 2017), where an increased adherence to treatment was associated with less hospitalizations.

The MARS scale is measuring different aspects of medication adherence. The two first items of this scale are related to unintentional adherence to treatment (eg. forgetting to take medication), whereas the others are related to intentional adherence (eg. patient not taking their medication because they are feeling better) and also to the representation that the patient has from his / her condition (which might be more related to insight than to adherence). We found that two items of the MARS score were positively associated with the cost of BD and two items were negatively associated with the cost of BD.

Altogether, these results suggest that the MARS scale is difficult to interpret in the context of medico-economic studies. The insight of BD patients is not necessarily correlated to the adherence to treatment. However, in our multivariate analysis we found that patients that tend to forget to take their medication are associated with a higher cost, which is interesting from the perspective of policy makers (supplementary material 8)."

A significant effect of the site of inclusion on direct health care costs was also found. This result cannot be explained solely based on the information gathered in our database. For privacy purposes, we did not collect the address of each participant in our study and patients living in distant locations could be addressed to a single center because there are only 10 expert centers for BD across France. These differences might be related to types of referral that may differ across the different sites of inclusion, depending on the local healthcare organization. Patients recruited in the expert centers can be referred either by their psychiatrist working in the public or private sector, or by their general practitioner / family doctor.

Last, our results confirm that, independent from other factors, BD with a history of suicide attempts is associated with increased direct healthcare costs. BD is associated with one of the highest risks of suicide among psychiatric disorders (Harris and Barraclough, 1997; Pallaskorpi et al., 2017). In our sample, 36% of patients had history of suicide attempts, which is in line with rates reported in the literature (Latalova et al., 2014). Stensland et al. found that suicide attempts are associated with higher total health costs in patients with BD (Stensland et al.,

2010). Pharmacological and non-pharmacological strategies can be effective to reduce suicide attempts in bipolar patients. However, a limited number of studies specifically tested the effectiveness of specific (such as cognitive behavioral therapy, interpersonal and social rhythm therapy) or unspecific (such as psychoeducation) therapies to reduce suicide attempts in BD . Our work underlines the relevance to study cost-effectiveness (Chisholm et al., 2005) of interventions that reduces suicide risk in patients with BD (Dome et al., 2019).

A subsample of 266 BD patients (23% of our total sample) had data during a follow-up for a 2 year period. Visits to the centers of expertise for BD at one and two years after baseline were proposed in addition to a classical follow-up by the referent psychiatrist or family doctor. In France, only a few psychiatrists are specialized in bipolar disorder. The consultation within the expert centers of expertise provided recommendations to the patient and his doctor to improve management of BD (Etain et al., 2020). After each consultation, the expert centers are providing recommendations on medication and psychosocial interventions, such as psychoeducation. Our results suggest that specialized consultation for BD, in addition to a classical follow-up by a general psychiatrist can reduce the cost of bipolar disorder. However, these results must be interpreted with caution. Only 23% of patients engaged in long-term follow-up in the Expert centers. The clinical characteristics of patients accepting vs not-accepting the follow-up were significantly different. Given the risk of selection, it is impossible to draw any firm conclusion on the cost-effectiveness of the centres of expertise in the general population of BP patients. Future randomized cost-effectiveness studies could assess the cost-effectiveness of care pathways in BD.

Our study has several strengths. The cost of BD has been assessed mostly by top-down approaches in large administrative databases with limited clinical characterization, or based on the prevalence of BD (Cloutier et al., 2018). Our study provides in a large sample of BD patients recruited across France with an extensive and homogeneous clinical characterization, an estimation of the cost of BD. We were able to test a large number of potential associated factors with higher direct healthcare cost in the multivariate analysis.

A subsample of 266 patients with BD were followed up during 2 years. Despite a high attrition rate, our results suggest the benefit of specialized consultations in BD, in addition to regular consultations with a general psychiatrist or a family doctor to reduce the cost of BD and ultimately direct healthcare costs.

Several limitations must be considered before interpreting our results. Our sample is probably not representative of all patients with bipolar disorder, particularly because institutionalized, hospitalized patients or outpatients with severe symptoms were not referred to the participating expert centers. This resulted likely in an underestimate of the direct health cost estimation. Because of the high attrition rate, it is difficult to estimate the real evolution of the direct health cost, even if the sensitivity analysis were consistent with our main results. We were not able to compute societal cost in our sample because this information was not available.

To our knowledge, our study is the first to investigate the cost of BD and its evolution in a deeply phenotyped longitudinal sample and to demonstrate the feasibility of medico-economic evaluation in a national network of centres of expertise.

Ethics and Consent statement: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The follow-up protocol was approved by the institutional review board (Comité de Protection des Personnes Ile de France IX; 18 January 2010). In accordance with the French laws for non-interventional studies and according to the Ethical Committee, the study participation requires only an information letter since the clinical data were collected as part as the usual medical care system in France.

Data availability: The data that support the findings of this study are available from the corresponding author (CL), upon reasonable request.

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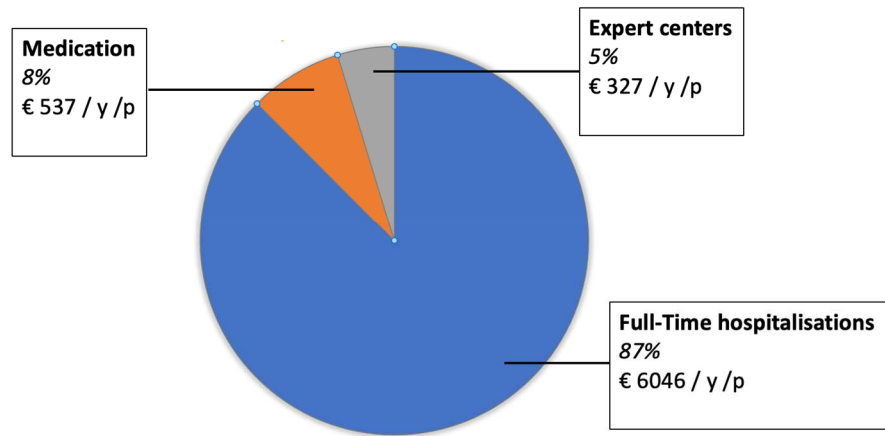
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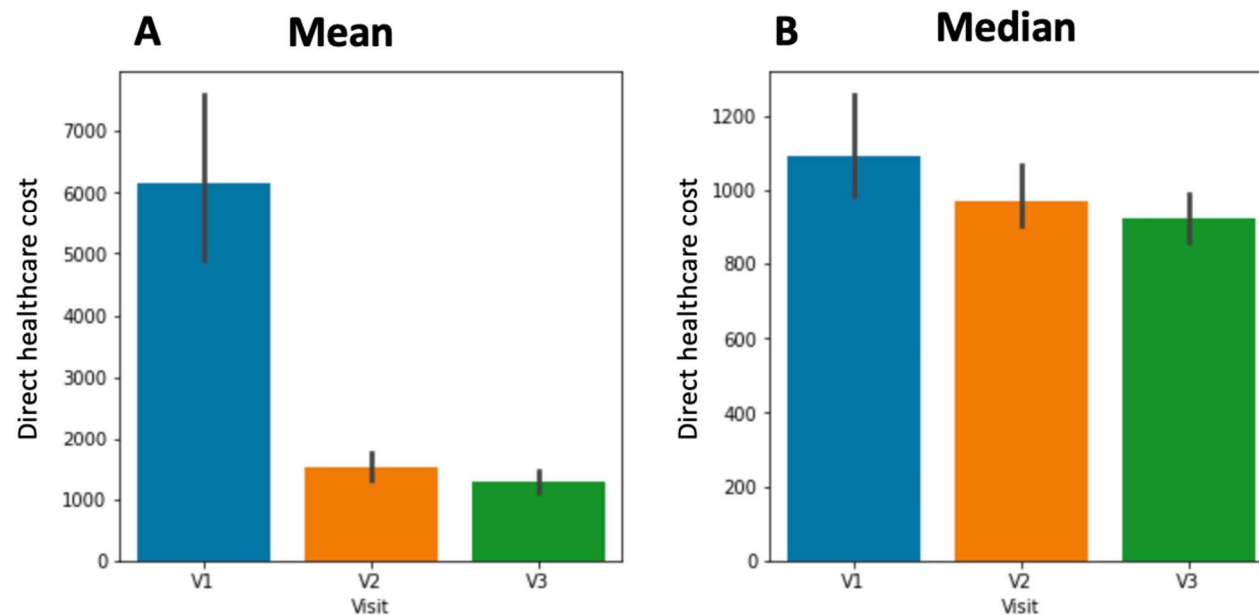
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Figure 1. Direct healthcare cost repartition



Legend
y / p: per year and per patient

Figure 2. Evolution of direct healthcare cost during a two year follow-up period



Legend: V1 = cost (euros) during the year prior the first visit in the expert centers,
V2 = cost (euros) during the year prior the second visit in the expert centers (one year after V1),
V3 = cost during the year prior the third visit in the expert centers (two years after the first visit).

Table 1. Factors associated with direct health cost: univariate analysis (n=1116)

	All sample N(%)	Cost Mean (sd)	P Mann- Whitney- Wilcoxon
Demographic characteristics			
Gender			
Female	668 (59.8)	6966.6 (11519)	0.1886
Male	448 (40.1)	6826.4 (13035)	
Age (years), mean (sd)	40.8 (12.5)		0.0467
<35	361 (32.3)	8961.2 (14453)	
35-48	397 (35.6)	6179.6 (10928)	
>48	358 (32.1)	6476.8 (11977)	
Living alone			0.0040
No (Married)	578 (51.8)	5901.6 (10388)	
Yes	538 (48.2)	7994.0 (13713)	
High education level (≥Bac)			0.6020
No	309 (29.6)	6167.2 (10776)	
Yes	802 (72.2)	7180.3 (12642)	
Employment status			<0.0001
Unemployed	563 (50.4)	8958.7 (14753)	
Active	553 (49.6)	4824.8 (8228)	
Illness characteristics			
Bipolar subtypes			<0.0001
Bipolar I	511 (45.8)	9606.2 (13710)	
Bipolar II	495 (44.4)	4645.8 (10349)	
Bipolar NOS	110 (9.8)	4576.6 (9002)	
Early onset	24.1 (9.7)		0.7482
No	583 (52.2)	6678.8 (11697)	
Yes	533 (47.8)	7163.4 (12624)	
History of suicide attempt			<0.0001
No	714 (64.0)	5807.0 (10996)	
Yes	402 (36.0)	8869.8 (13753)	
FAST, mean (sd)	20.9 (14.6)		0.0010
<12	367 (32.9)	6005.1 (11833)	
≥12	749 (67.1)	7353.8 (12278)	
MARS, mean (sd)	6.9 (1.9)		0.1797
0-7	640 (57.3)	6681.2 (12237)	
8-10	476 (42.7)	7218.4 (12027)	
Anxiety disorders			0.9995
No	598 (54.4)	7101.4 (12092)	
Yes	501 (45.6)	6627.5 (11895)	
Current smokers			0.0048
No	611 (54.7)	5589.2 (9610)	
Yes	505 (45.3)	8508.7 (14487)	
Substances abuse			

No	732 (65.6)	6439.4 (11379)	0.1321
Yes	384 (34.4)	7808.0 (13454)	
Alcohol abuse			
No	849 (76.1)	6774.0 (11988)	0.3213
Yes	267 (23.9)	7343.8 (12644)	
Cannabis abuse			
No	913 (81.8)	6578.2 (11541)	0.4126
Yes	203 (18.2)	8403.7 (14494)	
Overweight(BMI >25), mean (sd)	25.9 (5.1)		
No	549 (49.2)	6272.4 (11605)	0.0087
Yes	567 (50.8)	7528.0 (12625)	
Expert Center of Inclusion			
Bordeaux	43	7727.4 (14153)	0.0271
Colombes	22	6422.9 (8593)	
Creteil	128	6893.7 (10781)	
Grenoble	173	8048.9 (14256)	
Fernand Vidal	155	5810.3 (9885)	
Marseille	143	9194.5 (16726)	
Monaco	25	9923.6 (13578)	
Montpellier	107	7793.2 (12202)	
Nancy	119	6687.4 (10879)	
Versailles	201	4329.8 (8057.5)	

Mean MADRS: 10.4 (sd=8.8); Mean YMRS: 2.2 (sd=3.6), mean duration of illness: 16.8 (sd=11.1)

Table 2: Factors associated with direct health cost: Multivariate analysis

	Multivariable analysis (generalized linear model)		Internal validation of the model (bootstrapping method)		
	Rate Ratio 95% CI	P	95% CI	%0.05	%0.10
Gender Women Men	1(ref) 0.94 (0.82- 1.1)	0.3642	0.78 – 1.12	11.6	18.7
Bipolar subtype type 1 No Yes	1(ref) 2.1 (1.8-2.4)	<0.0001	1.75 – 2.50	100.0	100.0
Age <35 35-48 >48	1(ref) 0.8 (0.7-0.9) 0.8 (0.7-0.9)	0.0029 0.0287	0.62 – 0.95 0.64 – 1.04	67.5 40.8	78.4 53.7
Employment status Active Unemployed, retired, other inactive	0.7 (0.6-0.8) 1(ref)	<0.0001	0.57 – 0.83	98.1	99.1
Living alone No Yes	1(ref) 1.1 (0.97-1.3)	0.1277	0.94 – 1.32	21.2	31.4
Substance abuse No Yes	1(ref) 0.9 (0.8-1.1)	0.2676	0.76 – 1.13	12.4	19.6
Suicide attempt No Yes	1(ref) 1.6 (1.4-1.8)	<0.0001	1.31 – 1.95	99.9	99.9
Functioning (FAST score)	1.00 (0.99- 1.01)	0.7964	0.99 – 1.01	5.4	11.8
Overweight No	1(ref)				

Yes	1.1 (0.97-1.3)	0.1270	0.93 – 1.33	25.8	37.0
Current smoker					
No	1(ref)				
Yes	1.3 (1.1-1.5)	0.0005	1.05 – 1.53	77.2	84.2
Adherence to medication (MARS)					
0-7	0.9 (0.8-1.1)	0.2706	0.77 – 1.13	17.9	27.1
8-10	1 (ref)				
Expert Center of inclusion					
Bordeaux	1(ref)	<0.0001		96.3	98.4
Creteil	1.3 (0.9-1.8)		0.73		
Colombes	1.0 (0.6-1.8)		–		
Montpellier	1.3 (0.9-1.8)		2.23		
Grenoble	1.3 (0.9-1.9)		0.56		
Nancy	1.2 (0.8-1.7)		–		
Marseille	1.5 (1.0-2.2)		1.85		
Fernand Vidal	0.9 (0.7-1.4)		0.71		
Versailles	0.8 (0.6-1.2)		–		
Monaco	1.4 (0.8-2.4)		2.20		
			0.80		
			–		
			2.18		
			0.71		
			–		
			1.89		
			0.90		
			–		
			2.41		
			0.59		
			–		
			1.60		
			0.51		
			–		
			1.32		
			0.68		
			–		
			2.83		