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BIPOLAR DISORDER: THE IMPORTANCE OF CLINICAL ASSESSMENT IN IDENTIFYING PROGNOSTIC FACTORS - AN AUDIT. Part 1: An analysis of potential prognostic factors

Norma Verdolini[1], Jonathon Dean[2], Sandro Elisei[3], Roberto Quartesan[3], Rashid Zaman[3,4] & Mark Agius[4,5]

[1]School of Specialization in Psychiatry, Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy
[2]School of Clinical Medicine, University of Cambridge, Addenbrooke's Hospital Gonville and Caius College, Cambridge, UK
[3]Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, University of Perugia, Santa Maria della Misericordia Hospital, Perugia, Italy
[4]South Essex Partnership University Foundation Trust, Bedfordshire Centre for Mental Health Research in association with the University of Cambridge, Department of Psychiatry, University of Cambridge, UK
[5]Clare College Cambridge, The University of Cambridge, Cambridge, UK

SUMMARY

Background: *Prognostic factors of bipolar disorder must be identified to assist in staging and treatment, and this may be done primarily during the initial psychiatric assessment. In fact, most of the prognostic factors, which determine disease outcome, could be detected from simple but often-unrecorded questions asked during the psychiatric clinic visit.*

Methods: *We collected data from the clinical notes of 70 bipolar outpatients seen at the initial psychiatric assessment clinic about socio-demographic and clinical factors to determine whether various factors had relevance to prevalence, prognosis, or outcome.*

Results: *The sample comprised 16 bipolar I (22.9%) and 54 bipolar II (77.1%) outpatients; a psychiatric comorbidity was noted in 26 patients (37.1%). 60.9% (42 patients) reported anxiety features and 12 patients (17.6%) were noted to have obsessive-compulsive characteristics. Percentages reported in our results are of the sample for which the data was available. Anhedonia is a depressive feature that was present in most of the population where this data was available (92.2%, 59 patients) and 81.8% (54 patients) reported suicidal thoughts during a depressive episode. 74.6% (47 patients) had a family history of bipolar disorder, depression, suicide or psychosis. 27 patients (39.7%) reported current alcohol use and 14 patients (22.6%) current illicit drug use.*

A comparison between 10 prognostic factors found that only the correlations between current illicit drug use/previous illicit drug use (χ^2=11.471, P<0.001), current alcohol use/previous alcohol use (χ^2=31.510, P<0.001) and current illicit drug use/anxiety (χ^2=5.094, P=0.022) were statistically significant; the correlation between previous illicit drug use/previous alcohol use (χ^2=5.071, P=0.023) and previous alcohol use/family history (χ^2=4.309, P=0.037) were almost statistically significant. 17 patients (24.3%) of the 70 bipolar patients were assigned to a care coordinator; we have evaluated the possible differences between the patients with or without a care coordinator on the basis of the presence of 10 possible prognostic factors and found no statistically significant differences between these two groups of patients.

Conclusions: *We have identified several trends in our patients with bipolar disorder that agree with previous research. Our sample suggested that the assignation of a care coordinator is not done on a clinical basis. In our sample, some patients were found not to have information available so we suggest that a questionnaire to remind clinicians of potentially useful information would be helpful to aid in prognostication. In particular, specific features of the disease, like family history, age at onset, and features of depressive episodes may be highlighted as our sample suggests that these are often unrecorded when not known or negative.*

Key words: *bipolar affective disorder – prognostic factors*

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INTRODUCTION

Prognostic staging is increasingly considered to be one of the most important current challenges for psychiatry. A staging system is commonly used as a heuristic tool to indicate where an individual lies on an illness spectrum from 'at risk' (but asymptomatic) to 'end-stage' (poor prognosis). The use of this approach has a positive effect on patient outcomes because the clinician may be capable of facilitating access to a selection of stage-specific strategies for treatment (Kapczinski 2013). Provision of treatments in stage-specific strategies helps clinicians personalise treatment for their patients while providing consistent care, suggesting that staging is a viable and valuable addition to clinical care in bipolar disorder (Kapczinski 2013).

A staging system should be able to predict disease progression and stratify relevant outcomes in a consistent way using prognostic factors and clinical end-points. Additional study of transition periods from

'at risk' to 'subsyndromal' and then again between 'syndromal' illness and later stages of bipolar disorder is required to help validate relevant clinical end-points of a potential staging system. There is a long-standing debate over whether bipolar disorder is indeed a generally progressive illness (Goodwin 2007) for which a staging system would be functional, but a substantial proportion of patients – perhaps between 40% and 50% (Kessing 1998) – are thought to present with a progressive course, making clinical staging relevant.

Specific models of staging have been put forward (Berk 2007a, Berk 2007b, Kapczinski 2009) considering several different clinical features as proxy measures of disease progression. The most prominent (Berk 2007a, Berk 2007b, Kapczinski 2009) propose an asymptomatic period of 'stage 0' that identifies individuals who are putatively at higher-than-average risk of a disorder, but who are currently asymptomatic. The disease then progresses to subthreshold syndromes, to above-threshold syndromes, to multiple bipolar episode with relapses, and finally to an end stage of persistent and unremitting illness. These models were able to demonstrate that those patients with bipolar disorder with multiple episodes had a worse prognosis on symptom scores and functioning and quality of life (Rosa 2012). Significant clinical differences have been observed between patients with first and multiple episodes (Azorin 2011), primarily in terms of severity of depression, suicide attempts, and the number of years before receiving a correct diagnosis.

If we consider a prognosis on the basis of its proper meaning, the prediction of the probable course and outcome of a disease, we must determine the most significant prognostic factors and the effects that they have on the disease course to be able to accurately prognosticate. It is for this reason that outcomes and prognostic factors for bipolar disorder should be identified, and if possible early on during the initial psychiatric assessment to maximise the benefit gained from prognostication.

In fact, we argue that most of the prognostic factors could be detected from simple, but often-unrecorded questions asked during the psychiatric clinic assessment.

Consequently, the work in the proposed project has proceeded in four phases corresponding to specific aims:

- **Phase 1:** the authors reviewed the literature, searching for known bipolar disorder prognostic factors and the impact that comorbid disorders could have on the course and outcomes of the illness in order to develop a useful set of questions that could be utilised with patients to determine their prognosis.
- **Phase 2:** the authors have assessed, going through individual clinical notes, whether patients with bipolar disorder are asked about these prognostic features and whether their responses are recorded.
- **Phase 3:** the authors analysed the ten most relevant prognostic factors and attempted to correlate them to assess whether they might be linked to each other or to the course and prognosis of bipolar disorder. The factors assessed were patients' anhedonia, suicidal thoughts, borderline personality disorder symptoms, OCD symptoms, anxiety, family history of psychiatric disorders, current alcohol use, previous alcohol use, current illicit drug use, and previous illicit drug use.
- **Phase 4:** the authors evaluated the assignation of a care coordinator during the assessment phase of presentation to secondary care to better understand if patients were referred to these professionals in consideration of the aforementioned prognostic factors.

This article recommends that psychiatrists assess patients with bipolar disorder not only with the intent of diagnosing them, but also with the intent of determining their stage of disease and their prognostic factors to identify possible high-risk groups of patients. Later, we will argue that doing so with the use of a questionnaire and a staging system may help psychiatrists identify patients that need special treatment considerations and we will describe any correlation between prognostic factors and disease outcome.

METHODS

Participants

This study included 70 treatment-seeking adults diagnosed with bipolar disorder (16 bipolar I, 22.9%, and 54 bipolar II, 77.1%) at any mood state, assessed from 2011 to 2014 by a senior psychiatrist (M.A.) in his ASPA clinic (Assesment and Single Point of Access, or initial psychiatric assessment). Patients were aged between 18 and 65 years old and were assessed according to the ICD-10 and DSM IV-TR criteria.

Procedures

Data was anonymously drawn from the archival ASPA dataset. Information drawn was socio-demographic (gender, age, ethnicity, occupation) and clinical in nature. Clinical data points extracted from the clinical notes were psychiatric diagnosis, psychiatric comorbidities, physical comorbidities, age at first depressive and hypomanic episodes (even if subsyndromal), eating and sleeping habits during depressive episodes, concentration, anhedonia, suicidal ideation, psychotic characteristics, whether the patient had rapid cycling or mixed state features, psychiatric family history, current and previous alcohol or illicit drug use, and assignation of a care coordinator.

Statistical analysis

$\chi 2$ tests were used to evaluate associations between categorical variables. All statistical analyses were performed with the statistical software package SPSS (version 21), using a significance level of 5% (p-value ≤ 0.05).

RESULTS

Sociodemographic profile

The sample comprised 27 males (38.1%) and 43 females (61.4%), with ages between 18 and 61 years old (mean 35, s.d. 12.305). 28 patients (40%) were unemployed and 26 patients (41.4%) were employed. Of those 26 patients, 12 (17.1%) were laborers, 7 (10%) were skilled employees, and 7 (10%) were professionals. 6 patients (8.6%) were students, 8 patients (11.4%) were housewives, and 2 patients (2.9%) were retired.

The most represented ethnicity was Caucasian (66, 94.3%); other ethnicities were not significantly represented in the sample (2 Indian patients, 2.9%; 1 Caribbean patient, 1.4%; 1 Asian patient, 1.4%). Percentages reported in our results are of the sample for which the data was available.

Clinical profile

Age at onset

Using the clinical notes, we were able to determine the patients' ages at first depressive episode, treated and untreated, in 56 patients (80%). The average age of first depressive episode was 15.86 (s.d. 8.737) years old, with a range from 5 to 49 years old.

The age of onset of patients' first hypomanic episode was recorded in 40 patients (57.1%) who were able to remember when it happened; information was not recorded for 25 patients (35.7%) and 5 patients (7.2%) stated that they could not remember when it happened. The average age of first hypomanic episode was 19.13 years (s.d. 7.763), with a range from 8 to 46 years old.

The average time period between the age at onset of the first depressive episode and the age of first hypomanic episode was 3.27 years.

Duration of depressive and hypomanic episodes

The average duration of the depressive episodes was recorded for 55 patients (78.6%). The average duration of a depressive episode was 59.23 (s.d. 73.971) days, with a range from 2 to 360 days.

The average duration of a hypomanic episode was 15.11 (s.d. 16.613) days, with a range from 2 to 90 days (information available in 78.6% of the population, 55 patients).

The mean difference between the average durations of the depression and the hypomanic episodes in our sample is 44.12 days.

Psychiatric family history

74.6% of the population (47 patients) reported a positive family history of bipolar disorder, depression, suicide, or psychosis; information was not available for 7 patients (10%).

Psychiatric and physical comorbidities

A psychiatric comorbidity was recorded in 26 patients of the sample (37.1%). In those 26 patients, the comorbidities identified were anxiety disorder (14, 53.8%), personality disorder (5, 19.2%), ADHD (4, 15.4%), anxiety disorder with eating disorder (2, 7.7%), and anxiety disorder with personality disorder (1, 3.8%, see figure 1).

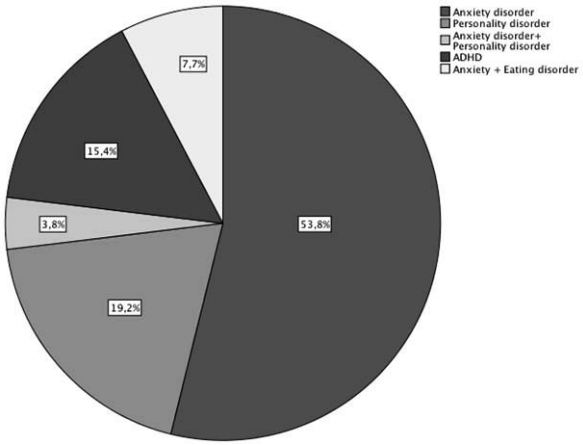

Figure 1. Psychiatric comorbidities

In the patients recorded to have anxiety disorder comorbidities (17, 24.3%), post-traumatic stress disorder was the most represented (6, 35.3%) followed by obsessive-compulsive disorder (5, 29.4%), panic attack disorder (4, 23.5%), social phobia (1, 5.9%) and generalized anxiety disorder (1, 5.9%, see figure 2).

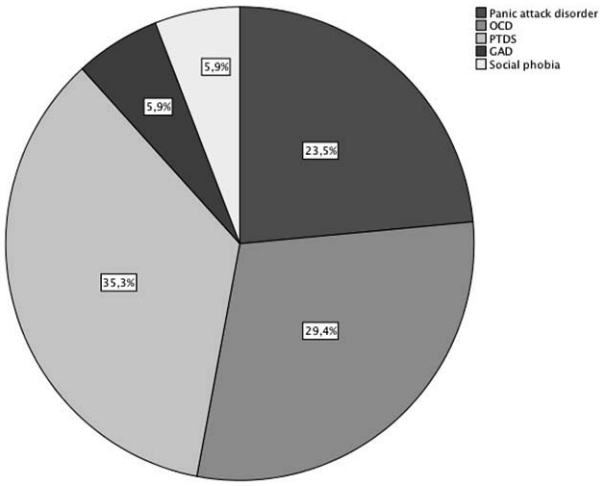

Figure 2. Anxiety disorders in comorbidity

It is worth noting that 60.9% of the sample (42 patients, see figure 3) reported at least one anxiety symptom (information not available for 1 patient, 1.4%) and 12 patients (17.6%) at least one obsessive-compulsive symptom (information not available for 2 patients, 2.9%).

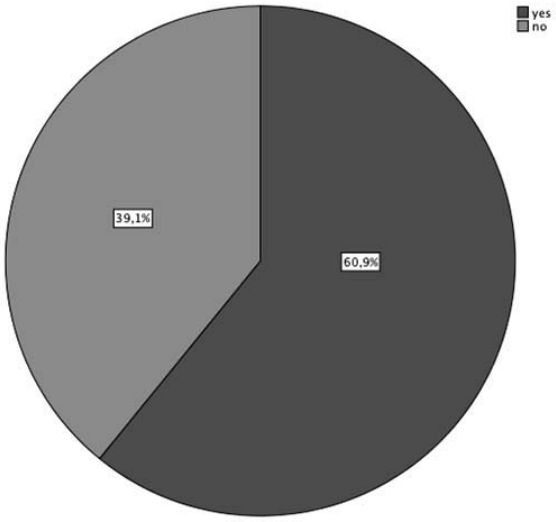

Figure 3. Anxiety symptoms

6 patients (8.6%) were diagnosed with a personality disorder comorbidity, and in all six cases the disorder was borderline personality disorder. 2 patients (2.9%) were diagnosed with an eating disorder and in both cases the disorder was bulimia nervosa.

33 patients (47.1%) of our sample were recorded to have a physical comorbidity. Individuals with a single recorded comorbidity are reported to have comorbidities that were neurological (7, 21.2%) and endocrine (4, 12.1%, see figure 4) in nature; these numbers do not include patients with multiple comorbidities.

Of those with multiple comorbidities, 13 patients (19.1%) suffered with migraine (information not available for 2 patients, 2.9%) and 2 patients (2.9%) with irritable bowel syndrome or colitis (information not available for 2 patients, 2.9%). With respect to endocrine comorbidities, 6 (9%) of the patients in our total sample are noted to have thyroid abnormalities. 4 (66.6%) reported hypothyroidism, 1 (16.7%) are noted to have hyperthyroidism, 1 (16.7%) was noted to have hyperthyroidism, and 1 (16.7%) was noted to have unspecified thyroid dysfunction.

Depressive episode features

We were able to extract features of the depressive episodes from the clinical notes in the 95.7% of the sample (67 patients); of those, almost all patients had recurrent depressive episodes in the past (65 patients, 97%).

Eating: during depressive episodes, 30 patients (47.6%) declared that they found eating comforting. 33 patients (52.4%) did not report finding comfort in eating (see figure 5). Information was not recorded for 7 patients (10%).

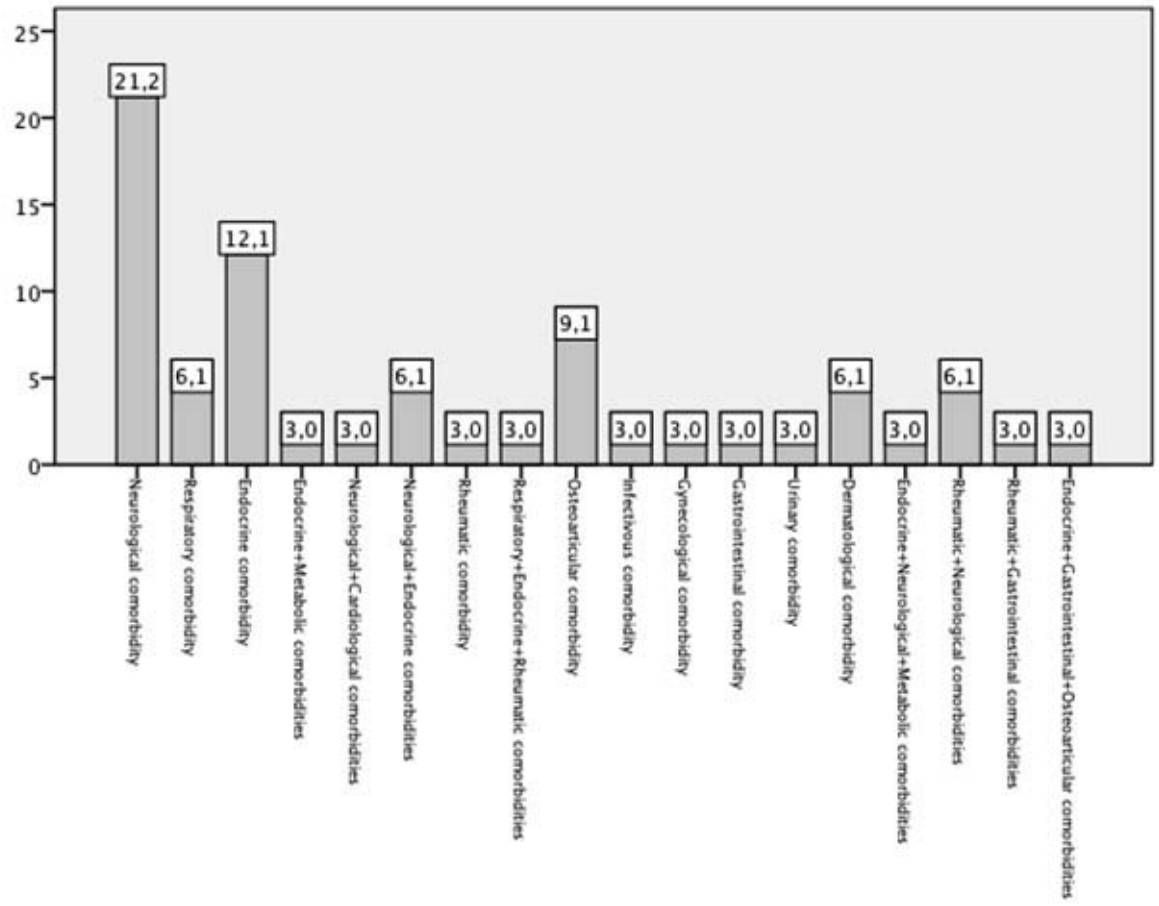

Figure 4. Physical comorbidities

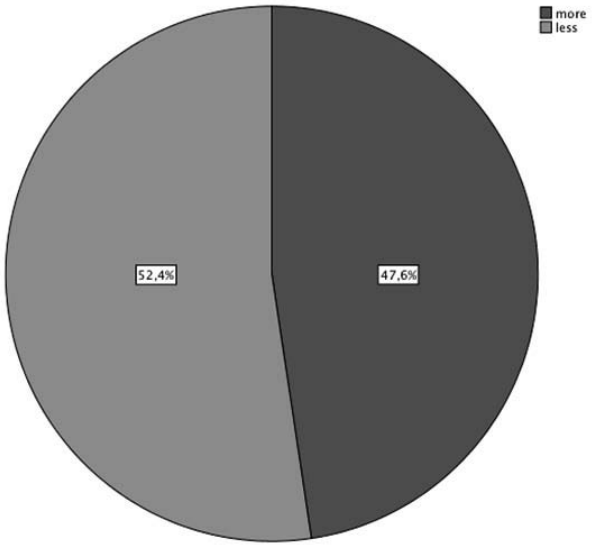

Figure 5. Eating during depressive episodes

Sleep: 39 patients (60%, see figure 6) reported that they slept more during the day during a depressive episode (information not available in 5 patients, 7.1%).

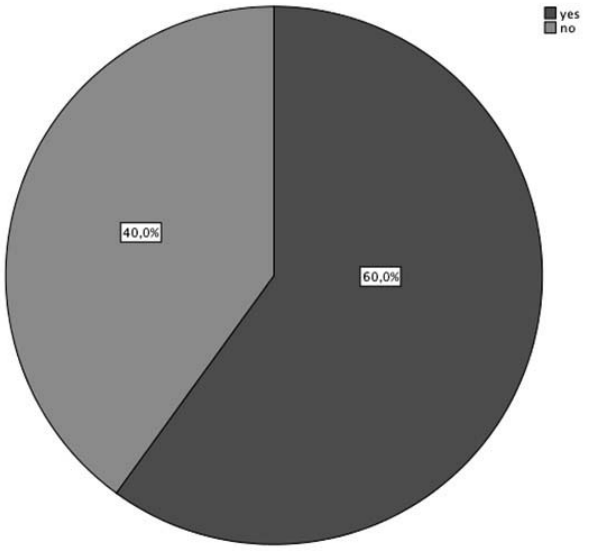

Figure 6. Sleeping during the day during depressive episodes

Concentration: 51 patients (96.2%, see figure 7) stated that they could not concentrate during a depressive episode (information not available for 17 patients, 24.3%).

Anhedonia: 59 patients (92.2%, see figure 8) reported anhedonia (information not available in 6 patients, 8.6%).

Suicidal ideation: 81.8% (54 patients, see figure 9) reported suicidal thoughts during a depressive episode (information not available for 4 patients, 5.7%).

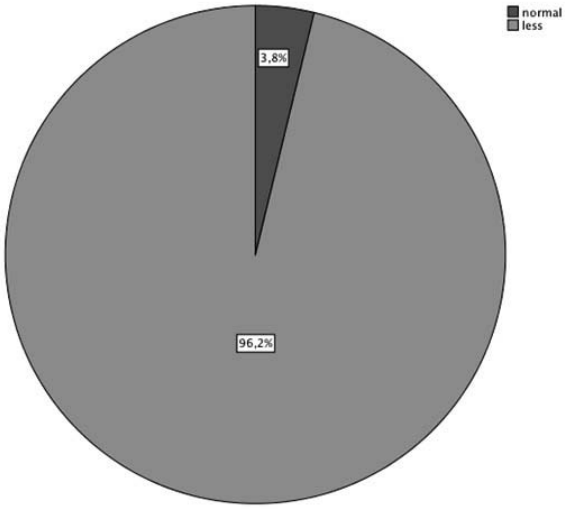

Figure 7. Concentration during depressive episodes

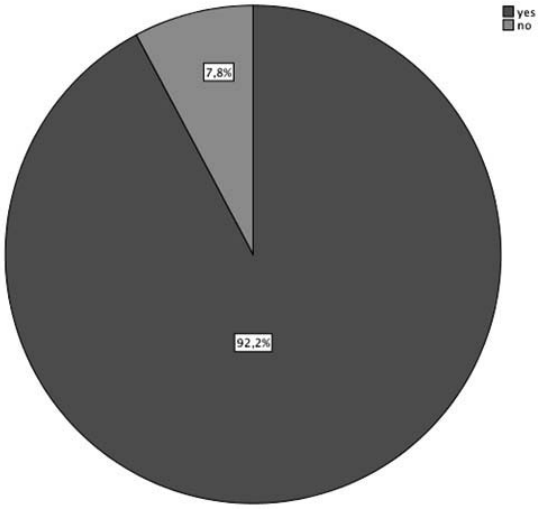

Figure 8. Anhedonia during depressive episodes

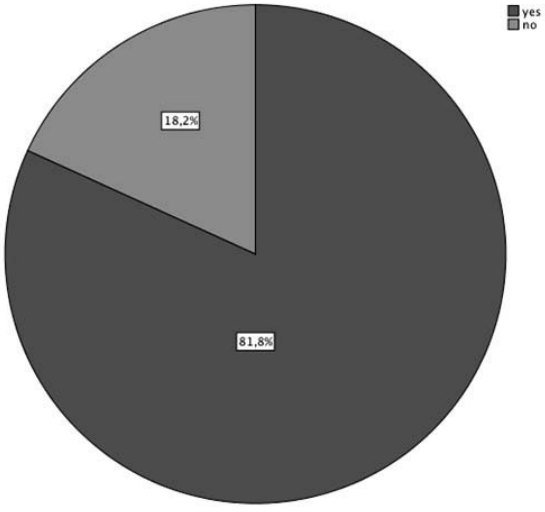

Figure 9. Suicidal ideation during depressive episodes

Furthermore, 24 patients (38.1%, see figure 10) reported severe retardation, paranoid thoughts, or hallucinations during a depressive episode (information not available for 7 patients, 10%).

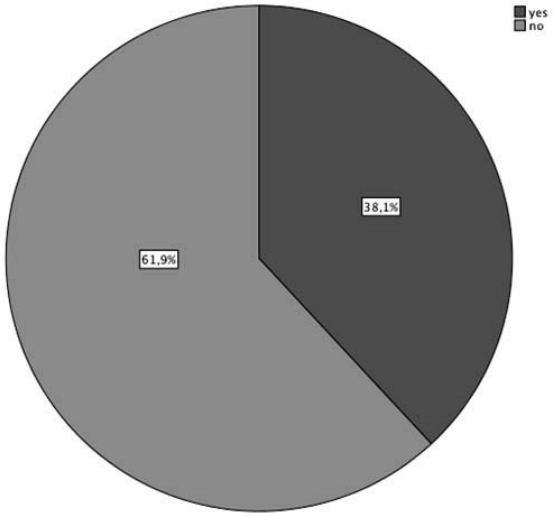

Figure 10. Severe retardation, paranoid thoughts or hallucinations during depressive episodes

7 patients (77%) reported that anti-depressants caused an increase in their mood at some point during their life but information was not available in most patients (61, 87.1%).

Current and previous alcohol and drug use

Alcohol: 27 patients (39.7%, see figure 11) reported current alcohol use and 41 patients (60.3%) reported no alcohol use (information not available for 2 patients, 2.9%); in addition, 49.3% of the sample (33 patients, see figure 12) used alcohol in the past (information not available for 3 patients, 4.3%).

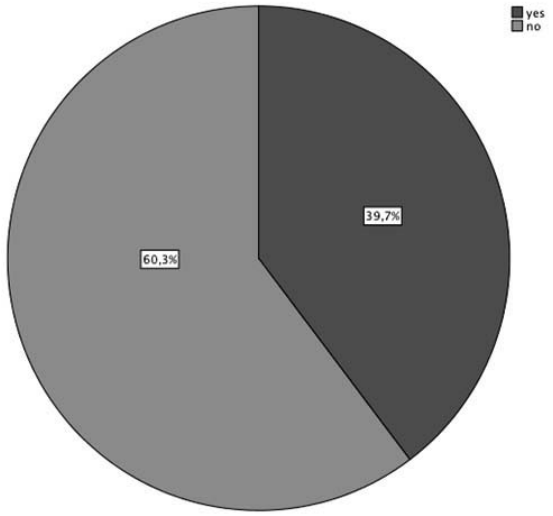

Figure 11. Current alcohol use

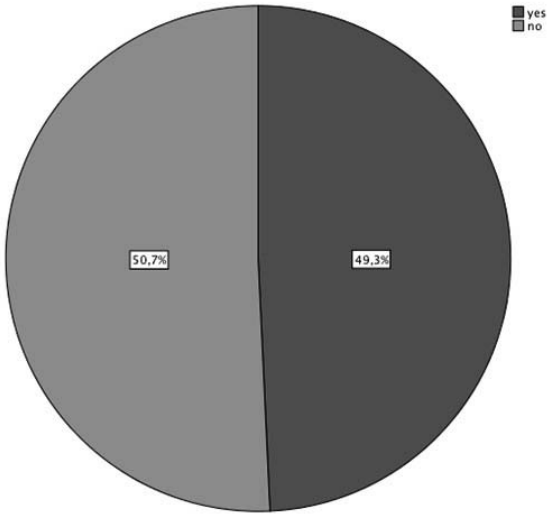

Figure 12. Previous alcohol use

Illicit drug use: 14 patients (22.6%, see figure 13) reported current illicit drug use (information not available for 8 patients, 11.4%) and 56.7% of the population (34 patients, see figure 14) reported illicit drug use in the past (information not available for 10 patients, 14.3%).

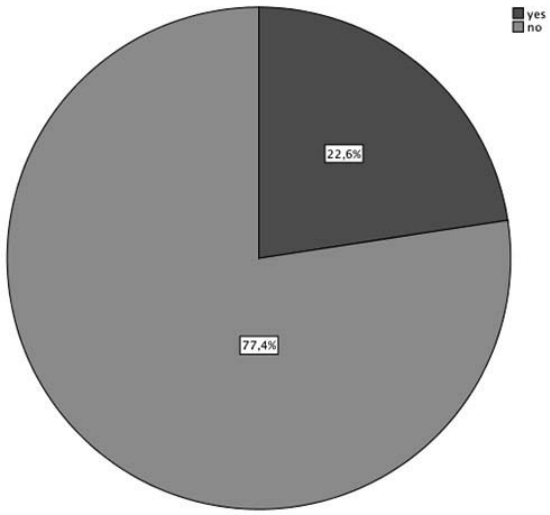

Figure 13. Current illicit drug use

Correlations between prognostic factors

A comparison between the 10 prognostic factors was done in order to assess if there were statistically significant correlations (see table 1).

Only the correlation between present illicit drug use/ previous illicit drug use (χ^2=11.471, P≤0.001), current alcohol use/previous alcohol use (χ^2=31.510, P≤0.001) and current illicit drug use/anxiety (χ^2=5.094, P=0.022) were statistically significant; the correlation between previous illicit drug use/previous alcohol use (χ^2=5.071, P=0.023) and previous alcohol use/family history (χ^2=4.309, P=0.037) were almost statistically significant.

Table 1. Correlation between prognostic factors

	Anhedonia	Suicidal ideation	Anxiety	OCD	Borderline symptoms	Family history	Current alcohol use	Previous alcohol use	Current illicit drug use	Previous illicit drug use
Anhedonia	-	χ^2=6.058 P=0.042	χ^2=0.709 P=0.374	χ^2=0.904 P=0.454	χ^2=1.702 P=0.288	χ^2=1.335 P=0.327	χ^2=0.134 P=0.550	χ^2=0.004 P=0.669	χ^2=1.367 P=0.320	χ^2=0.369 P=0.485
Suicidal ideation	χ^2=6.058 P=0.042*	-	χ^2=2.805 P=0.086	χ^2=1.003 P=0.293	χ^2=0.971 P=0.305	χ^2=0.052 P=0.545	χ^2=5.909 P=0.019*	χ^2=0.988 P=0.255	χ^2=0.592 P=0.349	χ^2=0.041 P=0.559
Anxiety	χ^2=0.709 P=0.374	χ^2=2.805 P=0.086	-	χ^2=0.247 P=0.438	χ^2=0.083 P=0.570	χ^2=0.674 P=0.297	χ^2=0.420 P=0.346	χ^2=0.719 P=0.275	χ^2=5.094 P=0.022	χ^2=0.380 P=0.362
OCD	χ^2=0.904 P=0.454	χ^2=1.003 P=0.293	χ^2=0.247 P=0.438	-	χ^2=1.066 P=0.291	χ^2=1.955 P=0.151	χ^2=3.393 P=0.061	χ^2=0.982 P=0.255	χ^2=1.134 P=0.296	χ^2=0.172 P=0.470
Borderline symptoms	χ^2=1.702 P=0.288	χ^2=0.971 P=0.305	χ^2=0.083 P=0.570	χ^2=1.066 P=0.291	-	χ^2=0.062 P=0.642	χ^2=0.157 P=0.525	χ^2=0.002 P=0.649	χ^2=2.029 P=0.187	χ^2=0.130 P=0.523
Family history	χ^2=1.335 P=0.327	χ^2=0.052 P=0.545	χ^2=0.674 P=0.297	χ^2=1.955 P=0.151	χ^2=0.062 P=0.642	-	χ^2=1.932 P=0.137	χ^2=4.309 P=0.037	χ^2=0.091 P=0.535	χ^2=3.033 P=0.076
Current alcohol use	χ^2=0.134 P=0.550	χ^2=5.909 P=0.019*	χ^2=0.420 P=0.346	χ^2=3.393 P=0.061	χ^2=0.157 P=0.525	χ^2=1.932 P=0.137	-	χ^2=31.510 P=0.000	χ^2=2.126 P=0.126	χ^2=0.554 P=0.317
Previous alcohol use	χ^2=0.004 P=0.669	χ^2=0.988 P=0.255	χ^2=0.719 P=0.275	χ^2=0.982 P=0.255	χ^2=0.002 P=0.649	χ^2=4.309 P=0.037	χ^2=31.510 P=0.000	-	χ^2=0.111 P=0.490	χ^2=5.071 P=0.023
Current illicit drug use	χ^2=1.367 P=0.320	χ^2=0.592 P=0.349	χ^2=5.094 P=0.022	χ^2=1.134 P=0.296	χ^2=2.029 P=0.187	χ^2=0.091 P=0.535	χ^2=2.126 P=0.126	χ^2=0.111 P=0.490	-	χ^2=11.471 P=0.000
Previous illicit drug use	χ^2=0.369 P=0.485	χ^2=0.041 P=0.559	χ^2=0.380 P=0.362	χ^2=0.172 P=0.470	χ^2=0.130 P=0.523	χ^2=3.033 P=0.076	χ^2=0.554 P=0.317	χ^2=5.071 P=0.023	χ^2=11.471 P=0.000	-

*not statistically significant due to small sample size

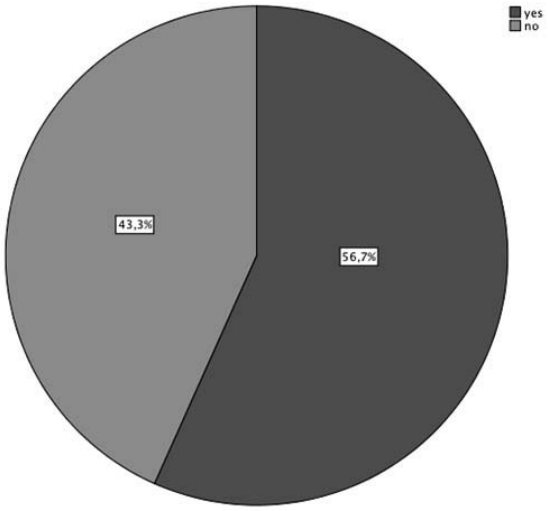

Figure 14. Previous illicit drug use

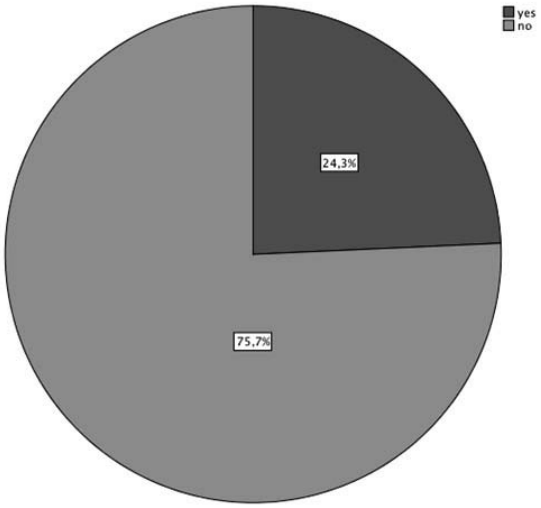

Figure 15. Care coordinators

Care coordinators

17 (24.3%, see figure 15) of the 70 bipolar patients were assigned to a care coordinator during the assessment phase of their presentation to Secondary Care.

We have evaluated if there were statistically significant differences between patients who had been assigned a care coordinator and those who had not on the basis of the presence of ten factors that we considered prognostic: anhedonia (χ^2=0.829, P=0.333), suicidal ideation (χ^2=0.005, P=0.604), borderline personality disorder symptoms (χ^2=0.324, P=0.443), OCD symptoms (χ^2=2.664, P=0.107), anxiety (χ^2=0.023, P=0.560), family history (χ^2=4.701, P=0.037*), present alcohol use (χ^2=0.001, P=0.603), previous alcohol use (χ^2=1.298, P=0.201), present illicit drug use (χ^2=0.298, P=0.454), and previous illicit drug use (χ^2=0.611, P=0.328). No statistically significant differences were found between the two groups of patients.

DISCUSSION

Our study demonstrates that it is possible to determine various prognostic factors that may aid psychiatrists in stratifying risk and in highlighting potentially

complicating factors that can worsen the long-term outcome of bipolar disorder. In our sample of patients, we identified an early average age of first depressive episode, both syndromally and subsyndromally, of 15.86 years old (s.d.: 8.737); longitudinal prospective studies have provided convergent evidence that bipolar disorder-related mood episodes typically debut as depressive episodes in adolescence (Duffy 2014).

We can provide further evidence for this with our sample, in which hypomanic symptoms appeared at an average age of 19.13 years old (s.d.: 7.763).

According to the literature, hypomania and mania remain rare observations in children, and they only appear later in adolescence and early adulthood. This is evident in our sample; we discovered that there was an average lag-time of 3.27 years during which the patient would be unable to receive an ICD-10 diagnosis of bipolar disorder, during which there would be consequential implications for psychopharmacological treatment. This seems to be in line with Post et al. (2014), who speculated that bipolar disorder might evolve in a series of reliable stages starting with non-specific non-mood disorders in childhood (e.g. anxiety), followed by minor mood and adjustment disorders in early adolescence, then major depressive episodes, and finally hypomanic or manic episodes (Duffy 2010). The evolution of the disease in this manner would suggest that the manic polarity of bipolar disorder would not manifest until adolescence or later, and our data support this.

It is also worth noting that the durations of depressive and of hypomanic episodes, both syndromally and subsyndromally, are disparate; the mean duration of a depressive episode in our study was 44.12 days longer than that of a hypomanic episode. Patients are generally more likely to complain of feeling low than of feeling high, but the difference in duration is another factor in patients' priorities and this is an issue that must be considered in the choice of targeted psychopharmacological treatment.

A positive family psychiatric history seems to be another important factor not only because it is, according to prior research, the most robust risk factor in predicting bipolar disorder in an undiagnosed patient (Gottesman 2010), but also because the family burden of psychiatric disease has strong prognostic implications and is predictive of comorbid disorders. In our sample, 74.6% of the population (47 patients) reported a positive family history of bipolar disorder, depression, suicide, or psychosis. Lapalme et al. (Lapalme 1997) reported that a bilineal positive family history of mood disorders resulted in substantially increased lifetime incidence of mood disorders in offspring; in fact, there are a large number of genes – each of individually small effect but with cumulative and potentiating consequences – contributing to the development of bipolar disorder (Craddock 2010). We know also that psychosocial stress and adverse rearing environments can of course have long-lasting impact on neurobiology and behaviour at an epigenetic level (Roth 2009), and it seems likely that families with large burdens of psychiatric disease might cause psychosocial stress in index patients.

The familial burden of psychiatric disease has recently been studied (Duffy 2014) and it was reported that high-risk offspring had an increased lifetime risk of a broad spectrum of disorders including anxiety, sleep disorders, substance misuse, and attention-deficit hyperactivity disorder-ADHD when compared with controls. In addition, according to Post et al. (Post 2014), the parental load of mood disorders is significantly associated with earlier onset of illness, an increased history of physical or sexual abuse, anxiety disorder, rapid cycling and a greater number of total poor prognostic factors.

In our sample, 42 patients (60.9%) reported at least one anxiety symptom, and an anxious comorbidity was diagnosed in 17 patients (24.3%). Other studies suggest that our percentage is lower than that of previous studies, in which about 30–60% of patients with bipolar disorder had at least one comorbid anxiety disorder (Corry 2013). In our population, these anxiety disorders were represented by post-traumatic stress disorder - PTSD (6, 35.3%), obsessive-compulsive disorder-OCD (5, 29.4%), panic attack disorder (4, 23.5%), social phobia (1, 5.9%) and generalized anxiety disorder-GAD (1, 5.9%).

Comorbid anxiety disorders represent an important prognostic factor because they are associated with decreased likelihood of remission and they negatively influence the clinical course of bipolar disorder. Specifically, the presence of OCD has a consistently negative impact on the outcome of bipolar I disorder (Kim 2014). It is for this reason that in DSM-V, the new specifier "with anxious distress", has been introduced to append to the diagnosis of patients with bipolar or depressive disorder, as a substantial body of research has underscored the importance of the presence of anxious comorbidities on patient prognosis (El-Mallakh 2008).

We can see this in numerous studies that have demonstrated that comorbid anxiety disorders and OCD are associated with greater severity, earlier age at onset, higher suicide risk, greater impulsivity, diminished acute response to pharmacological treatment, and unfavourable course of bipolar disorder (Feske 2000, Bauer 2005, Simon 2007). It is worth noting that a previous study (Gaudiano 2005) suggested that depression, not mania, mediates the relationship between comorbid anxiety and treatment outcome; in fact, the anxiety symptoms accompanying bipolar disorder have been reported to primarily affect the depressive outcomes of bipolar disorders (Goldberg 2012).

Furthermore, a recent study (Wang et al. 2014) discovered that the genes involved in metabolizing dopamine and encoding dopamine receptors, such as aldehyde dehydrogenase 2 (ALDH2) and dopamine D2 receptor (DRD2) genes, may be important to the pathogenesis of BD-II comorbid with anxiety disorders.

With regards to PTSD, the results of our sample are in line with the previous reports where patients with bipolar disorder have elevated rates of this disorder ranging from 16% to 39% (Quarantini 2010); furthermore, the authors reported that the group with comorbid PTSD had worse quality of life, more rapid cycling, higher rates of suicide attempts, and a lower likelihood of staying recovered.

Borderline personality disorder (BPD) comorbidity, however, does not seem to have significant effects on the course of bipolar disorder. Surprisingly, in our sample, we discovered a smaller comorbidity between patients with bipolar disorder and borderline personality disorder (9%, 6 patients). This was at a lower rate than the co-occurence of 15% that previous research has suggested (Gunderson 2014).

We can see from previous research that neither bipolar I nor bipolar II has statistically significant interactions with BPD, except that bipolar II delayed BPD's time to remission (Gunderson 2014). A possible explanation is that bipolar II may be a heterogeneous syndrome in which a subset has a variation of BPD on the basis of bipolar II's high prevalence of typical BPD characteristics such as rejection sensitivity, childhood trauma, and repeated suicide attempts. However, Gunderson et al. (Gunderson 2014) suggested that there is a significant interaction of co-occurring BPD and mood depressive disorder, suggesting an overlap in their psychopathology and having significant implications for prognosis and treatment.

But, if we consider that there is a relationship between atypical depression, borderline personality disorder, and bipolar II disorder that remains understudied, things become more complicated. The symptomatology of "atypical depression" includes reactive mood, a pattern of stable interpersonal sensitivity (exaggerated vulnerability to feeling hurt by criticism or rejection), and reverse vegetative symptoms such as increased appetite and hypersomnia. Perugi et al. (Perugi 2011) found that, when adopting the "narrow criteria" of the DSM-IV, 24% of atypical depressives could be classified as bipolar; when using broader criteria, 78% could be considered to belong to the "soft" bipolar spectrum.

Consequently, it is not unexpected that in our population, which presented with a very high percentage of bipolar II disorder (77.1%, 54) most patients reported features of atypical depression. In particular, 30 patients (47.6%) declared that they find eating comforting during a depressive episode and 39 patients (60%) reported that they sleep more in the day during a depressive episode.

As for substance use, our sample reported a large amount of previous (alcohol 49.3%, illicit drugs 56.7%) and current (alcohol 39.7%, illicit drugs 22.6%) substance use. Furthermore, we discovered that there were statistically significant correlations between current illicit drug use and previous illicit drug use (χ^2=11.471, P≤0.005) and between present alcohol use and previous alcohol use (χ^2=31.510, P≤0.005), with nearly statistically significant correlations between previous illicit drug use and previous alcohol use (χ^2=5.071, P=0.023) and between previous alcohol use and family history (χ^2=4.309, P=0.037).

Our findings reflect those of recent research (Nery 2014) which reported that the variables most strongly associated with a lifetime alcohol use disorder diagnosis in bipolar patients were substance use disorder (non-alcohol), substance misuse during first mood episodes, and family history of substance use disorder. Furthermore, the authors (Nery 2014) reported that an increased incidence of alcohol abuse was seen in the offspring of bipolar patients as well as both an earlier age onset of bipolar disorder and increased risk of drug abuse.

In addition, we reported that there was a statistically significant correlation between present illicit drug use and anxiety (χ^2=5.094, P=0.022); this seems to be in line with previous research (Baldessarrini 2014) in which initial episodes of subsyndromal anxiety not only preceded relatively high risks of later alcohol abuse (after depression or anxiety: 66.7%, 33.3%), generalized anxiety (63.6%, 36.4%), obsessive–compulsive disorder (50.0%, 29.2%), and panic disorder (50.0%, 20.9%), but also were associated with a substance abuse comorbidity in 30.4% of all subjects. Furthermore, previous research has described an association between bipolar disorder, alcohol use, and PTSD (Nery 2014).

Consequently, drug misuse and family history of substance use disorders may indicate that a patient with bipolar disorder would be at higher risk of developing or of already having a concomitant alcohol use disorder (Nery 2014) that would obviously be detrimental to the course of the disease; this seems to be particularly salient if we consider that recent research (Tidemalm 2014) stated that comorbid substance use disorder doubled the risk of subsequent suicidal behaviour in men with bipolar affective disorder.

Patients with bipolar disorder are, of course, at prominent risk of suicidal ideation and action. A review has estimated the risk of suicide in bipolar patients to be 20–30 times higher than that of the general population (Pompili 2013); the lifetime prevalence of attempted suicide in bipolar patients has been estimated to 34% in women and 19% in men. It has been suggested that the risk of suicide is higher in bipolar II than in bipolar I (Pompili 2013).

In addition, Tidemalm et al. (Tidemalm 2014) determined that the variable of many lifetime manic episodes did not increase the risk of attempted suicide while having many lifetime mixed episodes, an early onset of psychiatric problems, or a personality disorder were all positive predictors in women. Comorbid substance use disorder was a predictor in men; perhaps counterintuitively, family history of affective disorder did not predict suicide attempt during follow-up.

Anxiety disorders and various specific features of recent depressive episodes (the intensity of depressive

episodes, the severity of episodes, depression with atypical features, early onset, and need of psychiatric inpatient care) have previously been identified as risk factors for suicidal behaviour (Tidemalm 2014).

In our sample of bipolar patients, 81.8% reported suicidal thoughts but we did not find correlations between suicidal thoughts and other prognostic factors. This was likely due to the small number of patients, though most of our population was reported to have the risk factors for suicide attempts listed above.

We know that some physical conditions and comorbidities can be related to bipolar disorder such as migraine (Saunders 2014), epilepsy (Holland et al. 2013), and irritable bowel disease-IBD (Mykletun 2010). Saunders et al. (2014) reported that migraine was associated with more severe and frequent depression and with an earlier age of onset in women and mixed symptoms in men, and Mykletun et al. (Mykletun 2010) reported an association between IBD and mood and anxiety disorders. Despite this research, little else is conclusively known about the prognostic effects of these physical comorbidities. In our sample, only 2 patients (2.9%) are reported to suffer from irritable bowel disease but more research is required to determine the mechanism by which these comorbidities affect bipolar disease.

Finally, in our research we tried to analyse the possible association between the assignation of a care coordinator during the assessment phase of a patient presenting to secondary care and prognostic factors but we found no statistically significant correlations; procedurally, the assignation of a care coordinator in our sample did not take into consideration prognostic factors for bipolar disorder and was instead done on the basis of other considerations such as social or economic factors.

RECOMMENDATIONS, LIMITATIONS AND CONCLUSIONS

There were limitations to our study. The small sample size and consequently reduced statistical power of the study are limitations; all of the patients in this study are outpatients at the ASPA clinic seen by only one of the senior psychiatrists (M.A.) of the clinic; that only one psychiatrist is involved is a limitation as well, as this may produce a bias as a result of a single clinician's preponderance towards particular questions.

In any case, this paper would like to represent a pilot study for the analysis of prognostic factors for bipolar disorder. Consequently, although to date it has proven difficult to assess the relative weight of individual risk factors (Tidelmalm 2014), further research is required to evaluate which are the most powerful and predictive prognostic factors and the weight that they have on disease severity and progression. We stated earlier in this article that this would allow clinicians to maximise the benefit gained from prognostication. Being able to do this might also allow health services to distribute resources on a community level more effectively with the aim of targeting environmental or public health factors that most severely affect patient prognosis.

In conclusion, on the basis of our results, we would like to make some preliminary recommendations:

1) An effective clinical staging model for bipolar disorder should be generated because it would provide an important framework to guide early intervention services and prevention efforts. In fact, there is growing evidence that future morbidity in bipolar disorders may be anticipated by the nature of initial or early illness episodes or even by patient temperaments (Kim 2014). Consequently, the associations of initial clinical presentations with long-term patterns of morbidity may be of particular value in determining prognosis, providing timely interventions, anticipating treatment responses, and planning long-term clinical needs of patients.
2) Bipolar disorder often occurs in the context of familial risk and therefore a detailed family history should be taken and used to determine the possible trajectory of illness. Coupled with clinical suspicion, patients' family history provides clinicians with a focused lens through which we may view otherwise non-specific clinical presentations (Post 2014).
3) Given the clinical significance of comorbid anxiety disorders and OCD in bipolar disorder, routine and regular evaluations of comorbid anxiety disorders and OCD using formal diagnostic interviews are recommended. Furthermore, special attention and management strategies are required for patients with these comorbid disorders to achieve better treatment outcomes (Kim 2014).
4) Research has demonstrated frequent overdiagnosis of bipolar disorders in patients with borderline personality disorder and underdiagnosis of borderline personality disorder in those with bipolar disorder. Misdiagnosis of bipolar disorder in borderline patients can have destructive consequences by encouraging exaggerated hopes for pharmacologic efficacy. Correctly differentiating between borderline personality disorder and bipolar disorder is therefore a crucial element of the initial psychiatric assessment, in which bipolar II is often an uncertain diagnosis (Gunderson 2014).
5) Drug misuse and family history of substance use disorders are characteristics that are easily assessed in the clinical setting and their presence may indicate a patient with bipolar disorder is at high risk. The admission of substance use should therefore warrant increased vigilance in the treatment of patients with bipolar disorder, especially in consideration of the dramatically increased risk of suicide.

6) The funds available to the mental health system should naturally be allocated with consideration to the diseases that burden the population, and we recommend an increased focus on weighting and tackling preventable prognostic factors that we have identified in this paper. For example, public health campaigns could improve outcomes for patients with bipolar disorder by improving their mental and physical health simultaneously.
7) In our opinion, the method this trust uses for assigning care coordinators needs revision. There may be scope for potential cost savings or revised protocols for trusts regarding care coordinators if further study demonstrates no benefit in all aspects of disease outcome. Currently, care coordinators are often assigned to ASPA patients in non-clinical manner based on factors such as the quality of the description of the patient in the GP referral letter and the resulting distribution of care coordinators is nearly random at initial presentation; later, care coordinators are assigned based on assessed need, but we highlight the importance of early intervention and of continued compliance to treatment as further reason for revision.
8) In our sample, some patients' notes did not have information available that might have been prognostic. We recommend the use of a questionnaire that reminds clinicians of potentially prognostic information. In particular, specific characteristics of the disease such as family history, age at onset, and features of depressive episodes may be asked as usual in an interview, but may not be recorded if the patient answers that he or she cannot remember or that a feature is not present. A questionnaire could remind clinicians to record these data despite the response, and this would aid in prognostication and might facilitate further audit in the future. The authors of this paper will be continuing this research by utilising a questionnaire in the ASPA clinic to ensure that all patient prognostic factors have been recorded.

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Correspondence:
Norma Verdolini
School of Specialization in Psychiatry, Division of Psychiatry, Clinical Psychology and Rehabilitation
Department of Medicine, University of Perugia, Santa Maria della Misericordia Hospital
Perugia, Italy
E-mail: norma.verdolini@libero.it