BIPOLAR DISORDER: THE IMPORTANCE OF CLINICAL ASSESSMENT IN IDENTIFYING PROGNOSTIC FACTORS - AN AUDIT.

Part 3: A comparison between Italian and English mental health services and a survey of bipolar disorder

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SUMMARY

Background: Most of the prognostic factors of bipolar disorder, which determine disease course and outcome, could be detected from simple but often-unrecorded questions asked during the psychiatric clinic assessments. In previous parts of this research, we analysed various prognostic factors and focused on mixed states and rapid cycling subsets. We now compare our sample in England with a small sample from Italy to demonstrate the utility of focused prognostic questioning and of international comparison.

Methods: We collected data from the clinical notes of 70 English bipolar and 8 Italian 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%) English outpatients and 7 bipolar I (87.5%) and 1 bipolar II (12.5%) Italian outpatients. Differences between the groups are seen mainly in terms of age of onset, duration of both depressive and hypomanic episodes, presence of psychiatric family history, incidence of mixed state features and rapid cycling, presence of elated mood in response to past antidepressant treatment, and misuse of illicit drugs and alcohol.

Conclusions: In order to promote improved mental health primary care, mental health systems in all countries should develop standardized epidemiological tools that are shared between countries. We recommend the use of a questionnaire that reminds clinicians of potentially prognostic information and suggest that this might identify important components of a potential standardized diagnostic and prognostic tool.

Key words: *bipolar affective disorder – prognostic factors – comorbidity - mixed affective states - rapid cycling*

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INTRODUCTION

In the two previous parts of our research (Verdolini et al. 2014a, 2014b), we focused on the need for a prognostic staging for bipolar disorder (BD), and the implications the development of a prognostic staging system might have for treatment strategies. We identified potential prognostic factors for outcomes in bipolar disorder and analysed them in the context of our sample of patients with bipolar disorder to discern the possible clinical and management implications.

Although, prognostic staging remains one of the most important challenges in psychiatry (Kapczinski et al. 2013), is it not currently possible to evaluate which prognostic factors are the most predictive or to determine the weight that these factors have on disease severity and progression. In our opinion, more research is needed; clinicians' ability to prognosticate consistently and accurately about bipolar disorder with the knowledge of the most relevant factors' comparative weights would be a tremendous benefit to both clinicians and patients.

In the previous parts of our research, we recommended the use of a questionnaire that reminds clinicians of potentially prognostic information to ensure accurate recording of these data in the clinical notes. Using a questionnaire, it would possible to amalgamate these data from many different psychiatrists for use in further analysis – with particular focus on determining the significance of prognostic factors. It is for this reason that we compare our study's English bipolar disorder population of with an Italian bipolar disorder population

to compare and contrast bipolar prognostic factors in different countries. The Italian sample is small, but this paper functions as a pilot study for further research and as a proof-of-concept of the value of a questionnaire that would enable expanded study.

METHODS

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 consultant (M.A.) in his ASPA clinic (Assessment and Single Point of Access, or initial psychiatric assessment) in the Community Mental Health Team of Bedford (South Essex Partnership University Foundation Trust, Bedfordshire Centre for Mental Health Research) and 8 treatment-seeking adults with bipolar disorder (7 bipolar I, 87.5% and 1 bipolar II, 12.5%) at any mood state, assessed from January 2014 to July 2014 by a senior consultant (G.M.) as first outpatient examination in the Mental Health Service of Bastia Umbra, Italy. In all cases, data was anonymised and patient confidentiality was ensured.

Patients were aged between 18 and 65 years old in the English sample and between 18 to 75 years old in the Italian sample, and all patients were assessed according to the ICD-10 criteria and DSM IV-TR criteria.

Procedures

Data was anonymously drawn from the archival ASPA dataset and from the clinical notes of the Italian Mental Health Team. Information drawn was socio-demographic (gender, age, ethnicity) 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, and current and previous alcohol or illicit drug use.

Data for the English sample were collated and reported in the two previous parts of this research (Verdolini et al. 2014a, 2014b); we recapitulate this sample's sociodemographic and clinical data here to facilitate comparison with our Italian sample.

Statistical analyses were performed with the statistical software package SPSS (version 21).

RESULTS

Sociodemographic profile

English sample

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%).

Italian sample

The sample comprised 2 males (25%) and 6 females (75%), with ages between 22 and 75 years old (mean 48, s.d. 18.578). 1 patient (12.5%) was unemployed and 4 patients (50%) were employed. Of those 4 patients, 1 (12.5%) was a laborer and 4 (10%) were skilled employees. 2 patients (25%) were retired and 1 patient (12.5%) was a housewife.

All patients were Caucasian (8, 100%).

Clinical profile

Age at onset in the English sample

Using the patients' 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.

Age at onset in the Italian sample

Using the patients' clinical notes, we were able to determine the patients' ages at first depressive episode, treated and untreated, in all 8 patients. The average age of first depressive episode was 24.38 (s.d. 6.844) years old, with a range from 14 to 35 years old. The difference between the average ages of first depressive episode in the two samples is 8.52 years.

The average age of first hypomanic episode was 27.25 years (s.d. 7.833), with a range from 15 to 35 years old. The difference between the average ages of first depressive episode in the two samples is 8.12 years.

The average time period between the age at onset of the first depressive episode and the age of first hypomanic episode was 2.87 years.

Table 1. Clinical profiles of the English and Italian BD populations

	English BD sample n: 70		Italian BD sample n: 8	
Bipolar I	16	22.9%	7	87.5%
Bipolar II	54	77.1%	1	12.5%
Positive psychiatric family history	47	74.6%*	2	25%
Comfort in eating	30	47.6%*	1	12.5%
Increased sleep during the day	39	60%*	7	87.5%
Lack of concentration	51	96.2%*	7	87.5%
Anhedonia	59	92.2%*	8	100%
Suicidal ideation	54	81.8%*	8	100%
Severe retardation, paranoid thoughts, or hallucinations	24	38.1%*	4	50%
Antidepressant-related elation	7	77%*	5	62.5%
Mixed state features	33	71.7%*	8	100%
Rapid cycling	32	72.7%*	6	75%
Current alcohol misuse	27	39.7%*	2	25%
Previous alcohol misuse	41	60.3%*	2	25%
Current illicit drug misuse	14	22.6%*	1	12.5%
Previous illicit drug misuse	34	56.7%*	1	12.5%

* Percentages reported are of the sample for which the data was available

Duration of depressive and hypomanic episodes in the English sample

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 English sample is 44.12 days.

Duration of depressive and hypomanic episodes in the Italian sample

The average duration of a depressive episode was 75 (s.d. 32.071) days, with a range from 60 to 150 days.

The average duration of a hypomanic episode was 26.13 (s.d. 23.823) days, with a range from 1 to 60 days.

The mean difference between the average durations of the depression and the hypomanic episodes in our Italian sample was 48.87 days.

Psychiatric family history in both samples

74.6% of the English sample (47 patients) reported a positive family history of bipolar disorder, depression, suicide, or psychosis; information was not available for 7 patients (10%). Only 2 patients (25%) of the Italian sample reported a positive family history of bipolar disorder, depression, suicide, or psychosis.

Psychiatric and physical comorbidities in both samples

A psychiatric comorbidity was recorded in 26 patients of the English 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%).

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%).

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

In the Italian sample, only 1 patient (12.5%) reported a psychiatric comorbidity. That patient was diagnosed with a personality disorder comorbidity, narcissistic personality disorder. Furthermore, 3 patients (37.5%) reported at least one anxiety symptom and 2 patients (25%) at least one obsessive-compulsive symptom. Although these patients did not meet the full criteria for a diagnosis of borderline personality disorder, 3 patients (37.5) are recorded to have borderline personality traits.

Physical comorbidities were recorded in 33 patients (47.1%) of the English sample. Individuals with a single recorded comorbidity are reported to have comorbidities that were neurological (7, 21.2%) and endocrine (4, 12.1%) 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%), 3 (50%) reported hypothyroidism, 2 (33.3%) were noted to have hyperthyroidism, and 1 (16.7%) was recorded to have unspecified thyroid dysfunction. 2 patients (2.9%) reported irritable bowel syndrome or colitis (information not available for 2 patients, 2.9%).

In the Italian sample, only 2 patients (25%) reported a physical comorbidity. Both were endocrine comorbidities: one patient suffered with diabetes and the other with hyperthyroidism.

None of the patients in the Italian sample suffered with migraine, but 2 patients (25%) are noted to have irritable bowel syndrome or colitis.

Depressive episode features in the English sample

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. Information was not recorded for 7 patients (10%).

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

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

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

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

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

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%).

Depressive episode features in the Italian population

We were able to extract features of the depressive episodes from the clinical notes in the 100% of the sample (8 patients); of those, almost all patients had recurrent depressive episodes in the past (7 patients, 87.1%).

Eating: during depressive episodes, a surprising 7 patients (87.5%) declared that they did not find eating comforting.

Sleep: 7 patients (87.5%) reported that they slept more during the day during a depressive episode.

Concentration: 7 patients (87.5%) stated that they could not concentrate during a depressive episode

Anhedonia: all eight patients reported anhedonia.

Suicidal ideation: all eight patients reported suicidal thoughts during a depressive episode.

4 patients (50%) reported severe retardation, paranoid thoughts, or hallucinations during a depressive episode.

5 patients (62.5%) reported that antidepressants caused an increase in their mood at some point during their life.

Mixed state features and rapid cycling in both samples

71.7% (33 patients) of the English sample was noted to have mixed state features and 32 patients (72.7%) reported rapid cycling features with more than 4 changes in mood in a year.

In the Italian sample, all patients (8, 100%) reported mixed state features and 6 patients (75%) report features of rapid cycling bipolar disorder.

Current and previous alcohol and drug use in both samples

Alcohol: 27 patients of the English sample (39.7%) 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) used alcohol in the past (information not available for 3 patients, 4.3%).

Only 2 patients (25%) of the Italian sample reported current alcohol use in the present and the same two patients reported using alcohol in the past.

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

In the Italian sample, only one patient (12.5%) was noted to currently use illicit drug and the same patient was the only one to have a history of doing so.

DISCUSSION

Even though the Italian sample is too small to be significant, we can still develop some interesting links between our samples.

We have, for example, identified significant differences between the two populations. This might be due to two factors. First, the Italian sample is comprised of a greater percentages of bipolar I patients (87.5%) than the English population is (22.9%). Secondly, the Italian population considered in the research had an average age (mean 48, s.d. 18.578) greater than the English sample (mean 35 years, s.d. 12.305) with a maximum age of 75 years old instead of 65 years old.

These factors may influence both the sociodemographic composition of the samples and the clinical manifestation of the disorder, which might account for some of the main differences seen between these samples.

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The average age of onset of depressive episodes is notably higher in the Italian sample, as is the average age of first hypomanic presentation. This does not seem to be related to the differences in the demographic composition of the sample as mentioned above, but instead may be a genuinely delayed presentation of the disease. This is echoed in the difference between the absolute minimum known age at onset of depressive disorder in the English sample (5 years) and the Italian sample (14 years) as well as of hypomania, which we identified as 8 years in the English sample and 15 years in the Italian sample.

This could be related to an important factor identified in previous research (Elisei et al. 2013); the community mental health team in Bedford functions in the city in the context of a relatively industrial Bedfordshire, which differs from the rural locale of the mental health services in Umbria and this seems to be a protective factor with respect to the onset of mental disorders.

Additionally, the English sample reported a much higher percentage of psychiatric family history (74.6%) compared to the Italian sample (25%), and this agrees with research that suggests that a positive family history of psychiatric disease is not only important as prognostic factor in existing bipolar disorder but also as a risk factor for the development of disease in the first place (Post et al. 2014).

If we consider that the average durations of both depressive and hypomanic episodes are longer in our Italian sample (75 days depressive, s.d. 32.071, 26.13 days hypomanic, s.d. 23.823) than in our English sample (59.23 days depressive, s.d. 73.971, 15.11 days hypomanic, s.d. 16.613), we could hypothesize that there might be some socioenvironmental or biological differences between the two countries or between the psychiatric care available in each of the samples.

One of the main discernable contrasts is the closer link the general population has with general practitioners and primary care in England compared to in Italy, and this could easily have implications in terms of a delay in reaching psychiatric service.

As for psychiatric and physical comorbidities, the Italian sample reported very small associations with other psychiatric and physical disorders but this can easily be a result of the small sample size.

It is important to underline the similarities in the two samples in terms of depressive features. Both samples reported the presence of anhedonia, suicidal ideation, diminished concentration, severe retardation, paranoid thoughts, and hallucinations during a depressive episode. These common aspects are likely due to the established pathobiological manifestation of depressive disorder on which socioenvironmental differences have relatively little influence.

Some key differences seen are in the features of an atypical depressive episode. Although, both samples presented the same propensity toward sleeping more during the day during depressive episodes, the Italian sample showed little increase in comfort eating compared to the English sample. This might be due to social differences in conventional eating behaviours in each of the two countries.

It seems particularly salient is that all patients in the Italian sample are noted to have mixed state features and 75% of those were recorded to be rapid cycling; in comparison, just 71.7% of the English sample was reported to have mixed state features and 72.7% were noted to be rapid cycling. This is especially relevant if we consider that the 62.5% of the Italian population reported elation in response to past antidepressant treatment; this, analysed in context of the suppositions put forward in Part 2 of this research, seems to again suggest that rapid cycling and mixed state features seem to be strongly related or worsened by antidepressant treatment.

Little is known about the biological origins of differences between mixed state and rapid cycling difference in the two countries. More research is required to examine potential causes for the contrast in ages of presentation.

We also identified a difference in the strong association bipolar disorder with of substance misuse in our English sample but not in our Italian sample. This is likely related to different substance misuse habits in the general population in England and Italy and likely represents a difference in the accessibility and availability of illicit substances.

RECOMMENDATIONS, LIMITATIONS, AND CONCLUSIONS

There were limitations to our study. The small sample size of both populations (in particular of the Italian sample) and consequently reduced statistical power of the study are limitations. All of the patients in this study were either outpatients at an ASPA clinic, seen by one of the senior psychiatrists (M.A.) and discussed with another senior psychiatrist (R.Z.), or outpatients of the Mental Health Service in Bastia, seen by only one of the senior psychiatrists (G.M.) there; that only one psychiatrist per country 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 in two different countries and to represent a proof-of-concept of the value of a questionnaire that would enable expanded study.

In conclusion, we would like to make some preliminary recommendations

1) We recommend the use of a questionnaire that reminds clinicians of potentially prognostic information. In particular, specific characteristics of the

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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.

2) Mental health systems of all countries should develop standardized epidemiological tools that are shared between the countries to promote consistent and improved care, and should supervise mental health services in data collection for mental health services, day-hospitals, psychiatric wards in general hospitals, and out-patient units (Mateus et al. 2008).

3) It could be particularly useful to develop a shared vision, maybe in Europe, of dealing with bipolar disorder prognostic factors in order to reach a European Mental Health System that can state guidelines for bipolar disorders.

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