Which factors delay treatment in bipolar disorder? A nationwide study focussed on duration of untreated illness

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Abstract

Aim: The aim of the present study was to detect factors associated with duration of untreated illness (DUI) in bipolar disorder (BD).

Method: A total of 1575 patients were selected for the purposes of the study. Correlation analyses were performed to analyse the relation between DUI and quantitative variables. The length of DUI was compared between groups defined by qualitative variables through one-way analyses of variance or Kruskal-Wallis's tests according to the distribution of the variable. Linear multivariable regressions were used to find the most parsimonious set of variables independently associated with DUI: to this aim, qualitative variables were inserted with the numeric code of their classes by assuming a proportional effect moving from one class to another.

Results: An inverse significant correlation between length of DUI and time between visits in euthymic patients was observed ($r = -.52$, $P < .001$). DUI resulted to be longer in patients with: at least one lifetime marriage/partnership ($P = .009$), a first psychiatric diagnosis of major depressive disorder or substance abuse ($P < .001$), a depressive polarity of first episode ($P < .001$), no lifetime psychotic symptoms ($P < .001$), BD type 2 ($P < .001$), more lifetime depressive/hypomanic episodes ($P < .001$), less lifetime manic episodes ($P < .001$), presence of suicide attempts ($P = .004$), depressive episodes ($P < .001$), hypomanic episodes ($P = .004$), hospitalizations ($P = .011$) in the last year.

Conclusions: Different factors resulted to increase the length of DUI in a nationwide sample of bipolar patients. In addition, the DUI was found to show a negative long-term effect in terms of more suicidal behaviour, more probability of hospitalization and depressive/hypomanic episodes.

KEYWORDS

bipolar disorder (BD), clinical features, duration of untreated illness (DUI), outcome

1 | INTRODUCTION

Bipolar disorder (BD) is a prevalent and severe psychiatric condition, often associated with prominent social dysfunction (Kjærstad et al., 2019), cognitive impairment (Buoli, Caldiroli, Caletti, Zugno, & Altamura, 2014) and disability (Grande, Berk, Birmaher, & Vieta, 2016). Different factors have been associated with poor prognosis in BD including: duration of illness (Altamura, Serati, & Buoli, 2015; Melloni et al., 2019), lifetime presence of psychotic symptoms (Ahn et al., 2017; Altamura et al., 2019), rapid-cycling (Buoli et al., 2017; 2019; Perlis et al., 2010), prevalent manic polarity (Belizario, Silva, & Lafer, 2018), concomitant substance abuse (Messer, Lammers, Müller-Siecheneder, Schmidt, & Latifi, 2017), lack of treatment compliance (Fuentes, Rizo-Méndez, & Jarne-Esparcia, 2016) and psychiatric/medical comorbidity (Forty et al., 2014; Passos et al., 2016).

Delay of proper (ie, guideline-recommended) treatment, which is alternatively indicated as duration of untreated illness (DUI), is one of the factors that have been reported to affect negatively the course of BD (Altamura et al., 2010; Hong et al., 2016). With regard to BD, DUI has been defined as the time between the onset of the first major mood episode and the initiation of an appropriate treatment (Dell'Osso et al., 2013). A correct pharmacological treatment should not only be effective toward the acute episode but also positively modify long-term course of illness and, in relation to BD, these needs are met by mood stabilizers and atypical antipsychotics, that have proven efficacy in prevention of mood recurrences (Altamura, Buoli, et al., 2015).

Some studies reported that a longer DUI was associated with negative outcomes in BD including a higher number of suicide attempts (Altamura et al., 2010; Drancourt et al., 2013) and of mood episodes (Drancourt et al., 2013; Hong et al., 2016). These results are

consistent with recent findings from a sample of psychotic bipolar subjects showing that patients with a DUI longer than 8 years resulted to have more mood episodes and hospitalizations than those with a shorter DUI (Altamura, Buoli, et al., 2015). More recently, a longer DUI was found to predict more tobacco consumption in subjects affected by BD (Medeiros, Lafer, Kapczinski, Miranda-Scippa, & Almeida, 2018). In contrast, two reports failed to find an association between DUI and, respectively, rapid cycling (Buoli et al., 2017) and number of suicide attempts (Kvitland et al., 2016).

Other studies focused on the factors that can facilitate or hamper early diagnosis and appropriate treatment in BD. In this perspective, three recent independent reports showed that the presence of psychotic symptoms—an indicator of higher severity of illness—in BD was associated with a shorter DUI, and consequently earlier recognition and administration of an appropriate treatment of this condition (Altamura et al., 2019; Kim et al., 2019; Murru et al., 2015). These results are consistent with what has been reported in a sample of pregnant bipolar women who showed a shorter DUI when having previous suicide attempts (Serati, Buoli, & Altamura, 2015). On the other side, other factors seem to hamper an early recognition and administration of proper treatment of bipolar patients including misdiagnosis due to the first presentation with a depressive mood episode (Altamura, Buoli, et al., 2015; Hong et al., 2016; Zhang et al., 2017).

Taken as a whole, available literature is still controversial about the role of DUI in modifying the course of BD and also in terms of factors that can contribute to the delay in receiving an appropriate treatment in bipolar patients. Furthermore, most of the available data in the field come from studies with relatively small sample sizes and/or using different definition of DUI, as highlighted by an updated meta-analysis (Dagani et al., 2017).

More robust data about the demographic and clinical variables associated with DUI are, therefore, necessary to implement prevention strategies and personalized treatments. In this framework, the first purpose of the present study was to identify, in the largest multicenter study of Italian bipolar patients, the factors associated with a long DUI and, consequently, with a delay in the prescription of an appropriate treatment. The second objective was to verify whether a longer DUI is related to an unfavourable course of BD, as reported by some previously mentioned reports (Altamura et al., 2010; Altamura, Buoli, et al., 2015; Drancourt et al., 2013; Medeiros et al., 2018).

2 | METHOD

A total sample of 1675 patients with BD was enrolled from different Italian psychiatric clinics in the context of RENDiBi project (National Epidemiological Research on Bipolar Disorder). The protocol was approved by the local Ethics Committees. Patients were diagnosed as affected by BD according to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders) criteria (American Psychiatric Association, 2000). Diagnoses were made by expert psychiatrists, who had regularly followed up the interviewed patients, and confirmed by the MINI International Neuropsychiatric Interview (Buoli, Cesana, Barkin, Tacchini, & Altamura, 2018; Sheehan et al., 1998). Patients consecutively attending at outpatient or inpatient services were selected for the purpose of the study. The inclusion criteria were a diagnosis of BD and an age ≥ 18. Exclusion criteria included: (a) patients who had not been screened in the last 12 months making it impossible to collect data for the last year of observation) and (b) patients whose clinical information was incomplete. Clinical

TABLE 1 Socio-demographic variables of the total sample and values of DUI/Pearson's correlation according to these variables

Variables		Total sample N = 1575	DUI (mean ± SD)	*P*
Gender	Male	669 (42.5%)	5.57 ± 9.55	.078
	Female	906 (57.5%)	6.25 ± 9.72	
Education (years) missing n = 2	<13	565 (35.9%)	6.38 ± 10.10	.366
	≥13 and <16	706 (44.9%)	5.85 ± 9.44	
	≥16	302 (19.2%)	5.44 ± 9.28	
Employed missing n = 3	Yes	1188 (75.4%)	6.16 ± 9.89	.567
	No	386 (24.6%)	5.35 ± 8.86	
Marriage or partnership	≥1	1064 (67.6%)	5.74 ± 9.59	**.009**
	Never	511 (32.4%)	6.78 ± 10.16	
Living alone missing = 2	Yes	1313 (83.4%)	6.70 ± 10.58	.284
	No	262 (16.6%)	5.81 ± 9.45	
Variables		**Total sample *N* = 1675**	**Pearson's correlation (*r*)**	***P***
Age		48.61 ± 13.43	0.17	**<.001**

Note: Statistically significant *P* values are given in bold for the following analyses: analyses of variance or Kruskal-Wallis's tests for qualitative variables and correlation analysis for age. Mean ± SD of total sample are reported for age. The percentages referred to the total sample (excluding the missing data) are reported into brackets for qualitative variables.
Abbreviation: DUI, duration of untreated illness.

TABLE 2 Lifetime clinical variables of the total sample and values of DUI/Pearson's correlation according to these variables

Variables		Total sample N = 1575	DUI (mean ± SD)	*P*
BD subtype missing: n = 75	1	963 (61.1%)	4.94 ± 8.71	**< .001**
	2	537 (38.9%)	8.41 ± 11.17	
First psychiatric diagnosis missing: n = 11	MDD	680 (43.5%)	8.30 ± 10.88	**< .001**
	BD	517 (33.1%)	2.55 ± 6.71	
	Eating disorders	180 (11.5%)	5.55 ± 5.97	
	Anxiety disorders	137 (8.8%)	5.76 ± 9.52	
	Substance abuse	30 (1.9%)	8.20 ± 9.73	
	Others	20 (1.2%)	6.61 ± 9.57	
Family history of psychiatric disorders (patients' parents and siblings)	None	251 (15.9%)	5.31 ± 8.91	.283
	MDD	374 (23.8%)	6.16 ± 10.05	
	BD	334 (21.2%)	6.71 ± 10.29	
	Others	616 (39.1%)	5.69 ± 9.32	
Polarity of first episode missing n = 3	Depressive	871 (55.4%)	7.33 ± 10.45	**<.001**
	Hypomanic/manic	567 (36.1%)	4.30 ± 8.40	
	Unidentifiable	134 (8.5%)	4.19 ± 7.74	
Lifetime presence of psychotic symptoms missing n = 1	Yes	757 (48.1%)	4.76 ± 8.62	**<.001**
	No	817 (51.9%)	7.08 ± 10.39	
Lifetime number of manic episodes missing = 18	0	577 (37.1%)	8.35 ± 11.03	**<.001**
	1–2	424 (27.2%)	4.44 ± 8.64	
	3–5	333 (21.4%)	3.87 ± 7.12	
	6–8	97 (6.2%)	4.73 ± 8.20	
	>8	126 (8.1%)	6.91 ± 10.64	
Lifetime number of hypomanic episodes missing: n = 24	0	697 (44.9%)	3.91 ± 7.61	**<.001**
	1–2	391 (25.2%)	5.42 ± 9.18	
	3–5	245 (15.8%)	8.15 ± 1.53	
	>6	218 (14.1%)	11.28 ± 12.55	
Lifetime number of depressive episodes missing: n = 8	0	132 (8.4%)	3.33 ± 7.06	**<.001**
	1–2	430 (27.4%)	3.47 ± 7.12	
	3–5	439 (28.0%)	6.39 ± 9.94	
	>6	566 (36.2%)	8.21 ± 10.99	
Presence of rapid-cycling	Yes	119 (7.6%)	6.25 ± 9.72	.845
	No	1456 (92.4%)	5.23 ± 9.65	
Lifetime presence of medical comorbidity missing: n = 41	Yes	420 (27.4%)	6.44 ± 10.33	.920
	No	1114 (72.6%)	5.72 ± 9.35	
Lifetime presence of psychiatric comorbidity missing: n = 3	Yes	753 (47.9%)	5.73 ± 9.40	.420
	No	819 (52.1%)	6.18 ± 9.88	
Lifetime presence of attempted suicide	Yes	419 (25.3%)	6.29 ± 9.91	.468
	No	1156 (74.7%)	5.84 ± 9.56	

Variables	Total sample *N* = 1675	Pearson's correlation (*r*)	*P*
Age at first diagnosis of BD	37.54 ± 13.39	.37	**<.001**
Age at first prescription of mood stabilizer/atypical antipsychotic	37.48 ± 13.37	.39	**<.001**
Duration of illness (years)	17.22 ± 12.50	.43	**<.001**
Age at onset of BD	31.35 ± 12.00	−.26	**<.001**
Age at first psychopharmacological prescription (including BZD)	3.87 ± 11.86	.05	**.036**
Age at first contact with psychiatric services	31.22 ± 12.16	.08	**.002**

(Continues)

TABLE 2 (Continued)

Variables	Total sample N = 1675	Pearson's correlation (r)	P
Age at first psychiatric diagnosis	30.61 ± 11.89	.04	.119
Time between first psychiatric diagnosis and first diagnosis of BD (years)	6.72 ± 9.27	.49	**<.001**
Time between age at first psychopharmacological treatment and age at first treatment for BD (years)	−6.72 ± 9.27	.52	**<.001**
Time between age at diagnosis of BD and age at first mood episode (years)	6.00 ± 9.70	.96	**<.001**

Note: Statistically significant *P* values are given in bold for the following analyses: analyses of variance or Kruskal-Wallis's tests for qualitative variables and correlation analysis with DUI for quantitative ones. Mean ± SD of total sample are reported for quantitative variables. The percentages referred to the total sample (excluding the missing data) are reported into brackets for qualitative variables.
Abbreviations: BD, bipolar disorder; BZD, benzodiazepines; DUI, duration of untreated illness; MDD, major depressive disorder.

information was obtained through a review of the clinical charts and clinical interviews with patients and available relatives. One hundred patients were not included in the analyses of this article for the lack of information about DUI. A detailed list of included Italian psychiatric clinics, as well as the method of calculation of sample size, has been previously reported (Buoli et al., 2019). Data were entered into an electronic central database (electronic Case Report Form: e-CRF).

Collected data included the following socio-demographic and clinical variables:

- socio-demographic variables: age, gender, education, employment, marital status, living alone;
- lifetime clinical variables: BD subtype, age at onset of BD, age at first psychopharmacological prescription (including benzodiazepines), age at first contact with psychiatric services, type of first psychiatric diagnosis, age at first psychiatric diagnosis, age at first diagnosis of BD, age at first prescription of mood stabilizer/atypical antipsychotic, polarity of first episode, duration of illness (years), DUI (years), time between first psychiatric diagnosis and first diagnosis of BD (years), time between age at first psychopharmacological treatment and age at first treatment for BD (years), time between age at diagnosis of BD and age at first mood episode (years), family history of psychiatric disorders (parents and siblings), lifetime presence of psychotic symptoms, lifetime number of manic episodes, lifetime number of hypomanic episodes, lifetime number of depressive episodes, presence of rapid-cycling, lifetime presence of medical comorbidity, lifetime presence of psychiatric comorbidity, lifetime presence of attempted suicides;
- clinical variables-last year of observation: type of current episode, presence of manic episodes, presence of depressive episodes, presence of hypomanic episodes, presence of psychotic symptoms, presence of attempted suicides, comorbidity with substance use disorders, presence and number of hospitalizations, presence of insight, attribution of symptoms to a psychiatric disorder, current pharmacological treatment, treatment adherence, number of visits, time between visits for euthymic patients (days), administration of psychoeducational interventions (according to Colom's model) (Vieta et al., 2009).

As mentioned in the introduction, DUI was considered as the time between the first major mood episode of BD and the prescription of a proper pharmacological treatment (mood stabilizer or atypical antipsychotic with stabilizing effects) (Altamura, Buoli, et al., 2015; Buoli, Serati, & Altamura, 2014). We considered as an appropriate stabilizing therapy the prescription of drugs that have a clear stabilizing effect in the long-term treatment—mood stabilizers (lithium, valproate, lamotrigine)—and atypical antipsychotics labelled by European Medical Agency (EMA) for relapse prevention (aripiprazole, olanzapine, quetiapine) (Altamura & Dragogna, 2013).

Descriptive analyses of the total sample were performed. Correlation analyses have been performed to analyse the relation between DUI and quantitative variables. The length of DUI was compared between groups defined by qualitative variables through one-way analyses of variance (ANOVAs) or Kruskal-Wallis's tests according to the distribution of the variable. Furthermore, linear multivariable regression models were used to find the most parsimonious set of variables independently associated with the length of DUI, according to a backward procedure; to this aim, qualitative variables have been inserted with the numeric code of their classes by assuming a proportional effect moving from one class to another. Specifically, three models were performed considering the statistical significance of the previous statistics and grouping the variables in clinical lifetime variables (first model: type of first psychiatric diagnosis, polarity of the first episode, lifetime presence of psychotic symptoms, lifetime number of depressive episodes, lifetime number of manic episodes, lifetime number of hypomanic episodes), socio-demographic and clinical variables of the last year (second model: marital status, presence of attempted suicide, presence of depressive episodes, presence of manic episodes, presence of hypomanic episodes, presence of hospitalization), variables related to treatment (third model: type of current episode, current pharmacological treatment, administration of psychoeducational interventions). The variables that resulted statistically significant in these three models were inserted in a further final model.

The level of statistical significance was set at a nominal value of $P \leq .05$.

Statistical analyses were performed by SAS 9.2 version.

TABLE 3 Clinical variables of the total sample and values of DUI/Pearson's correlation according to these variables (last year of observation)

Variables		Total sample N = 1575	DUI (mean ± SD)	*P*
Type of current episodea	Depressive	234 (14.9%)	8.04 ± 11.10	**.021**
	Manic	192 (12.2%)	5.30 ± 9.62	
	Hypomanic	21 (1.3%)	7.10 ± 12.24	
	Mixed manic	44 (2.8%)	7.73 ± 11.08	
	Mixed hypomanic	13 (0.8%)	4.69 ± 9.78	
	Mixed depressive	49 (3.1%)	6.18 ± 9.30	
	Mixed (undefined)	40 (2.5%)	2.63 ± 4.36	
Presence of manic episodes missing: n = 84	Yes	307 (20.6%)	4.82 ± 9.18	**.016**
	No	1184 (79.4%)	6.35 ± 9.82	
Presence of depressive episodes missing: n = 89	Yes	681 (45.8%)	7.06 ± 10.26	**<.001**
	No	805 (54.2%)	5.18 ± 9.18	
Presence of hypomanic episodes missing = 107	Yes	293 (20.0%)	6.90 ± 9.95	**.004**
	No	1175 (80.0%)	5.90 ± 9.72	
Presence of psychotic symptoms missing: n = 3	Yes	392 (24.9%)	4.99 ± 8.65	.110
	No	1180 (75.1%)	6.30 ± 9.95	
Presence of attempted suicides	Yes	419 (26.6%)	6.29 ± 9.91	**.004**
	No	1156 (73.4%)	5.84 ± 9.56	
Presence of substance misuse	Yes	193 (12.3%)	5.93 ± 9.44	.692
	No	1382 (87.7%)	5.96 ± 9.68	
Presence of hospitalization	Yes	663 (42.1%)	6.59 ± 10.04	**.011**
	No	912 (57.9%)	5.50 ± 9.33	
Presence of Insight missing: n = 2	Yes	1108 (70.4%)	5.99 ± 9.57	.773
	Partial	398 (25.3%)	5.77 ± 9.58	
	No	67 (4.3%)	6.67 ± 11.50	
Attribution of symptoms to a psychiatric disorder missing: n = 3	Yes	1015 (64.6%)	6.10 ± 9.58	.762
	Partial	442 (28.1%)	5.70 ± 9.52	
	No	115 (7.3%)	5.87 ± 10.78	
Current pharmacological treatment missing: n = 20	Mood stabilizers	1023 (65.8%)	5.99 ± 9.65	**<.001**
	Tricyclic antidepressants	27 (1.7%)	10.76 ± 12.41	
	Antidepressants (excluding tricyclics)	92 (5.9%)	8.62 ± 10.85	
	Antipsychotics	393 (25.3%)	4.79 ± 8.65	
	Benzodiazepines	20 (1.3%)	8.42 ± 11.42	
Treatment adherence missing: n = 7	Yes	1105 (70.5%)	5.92 ± 9.55	.422
	Partial	356 (22.7%)	5.77 ± 9.66	
	No	107 (6.8%)	7.13 ± 10.70	
Psychoeducation missing: n = 7	Yes	260 (16.6%)	5.03 ± 9.23	**.029**
	No	1308 (83.4%)	6.14 ± 9.74	
Variables		**Total sample N = 1675**	**Pearson's correlation (*r*)**	***P***
Number of hospitalizations		1.54 ± 1.16	−.01	.71
Number of visits		9.67 ± 9.10	.04	.12
Time between visits when patients are in euthymia (days)		46.61 ± 40.29	−.52	**<.001**

Note: Statistically significant *P* values are given in bold for the following analyses: analyses of variance or Kruskal-Wallis's tests for qualitative variables and correlation analysis with DUI for quantitative ones. Mean ± SD of total sample are reported for quantitative variables. The percentages referred to the total sample (excluding the missing data) are reported into brackets for qualitative variables.

[a]The other patients were in euthymia at the time of evaluation.

3 | RESULTS

The total sample included 1575 patients: 669 males (42.5%) and 906 females (57.5%). Mean DUI was 5.96 years ±9.65. The results of descriptive and correlation analyses as well as the values of DUI according to qualitative variables are reported in Tables 1, 2 and 3.

An inverse significant correlation was found between DUI and age at onset (r = –.26, P < .001) and time between visits of euthymic patients (r = –.52, P < .001). DUI resulted to be directly significantly correlated with: age (r = .17, P < .001), age at first psychopharmacological prescription (including benzodiazepines) (r = .05, P = .036), age at first contact with psychiatric services (r = .08, P = .002), age at first diagnosis of BD (r = .37, P < .001), age at first prescription of mood stabilizer/atypical antipsychotic (r = .39, P < .001), duration of illness (r = .43, P < .001), time between first psychiatric diagnosis and first diagnosis of BD (r = .49, P < .001), time between age at first psychopharmacological treatment and age at first treatment for BD (r = .52, P < .001), time between age at diagnosis of BD and age at first mood episode (r = .96, P < .001). In contrast, no significant correlation resulted between DUI and age at first psychiatric diagnosis (r = .04, P = .119), number of visits in the last year of observation (r = .04, P = .12) and number of hospitalizations in the last year of observation (r = –.01, P = .71).

DUI resulted to be significantly different according to: marital status (χ^2 = 6.71, P = .009), type of first psychiatric diagnosis (F = 22.84, P < .001), polarity of first episode (F = 19.35, P < .001), lifetime presence of psychotic symptoms (χ^2 = 16.47, P < .001), administration of psychoeducation in the last year (χ^2 = 4.79, P = .029), bipolar subtype (χ^2 = 41.11, P < .001), presence of suicide attempts in the last year (χ^2 = 8.27, P = .004), lifetime number of depressive episodes (F = 24.29, P < .001), lifetime number of manic episodes (F = 21.26, P < .001), lifetime number of hypomanic episodes (F = 39.65, P < .001), presence of depressive episodes in the last year (χ^2 = 21.21, P < .001), presence of manic episodes in the last year (χ^2 = 5.79, P = .016), presence of hypomanic episodes in the last year (χ^2 = 8.41, P = .004), presence of hospitalizations in the last year (χ^2 = 6.52, P = .011), current pharmacological treatment (F = 5.00, P < .001) and type of current mood episode (F = 2.50, P = .021).

Specifically, a longer DUI was found: in patients with at least one lifetime marriage/partnership; in subjects who received the first diagnosis of Major Depressive Disorder or substance abuse; in those who had a bipolar onset with a Major Depressive Episode or absence of lifetime psychotic symptoms; in patients who did not receive psychoeducation in the last year; in type 2 bipolar patients; in subjects who had suicide attempts in the last year of observation and presented more lifetime depressive or hypomanic episodes, but less manic episodes; in patients who had at least one depressive or hypomanic episode in the last year, but no manic episodes in the last years; in subjects who were hospitalized at least one time in the last year; in subjects who were currently treated with antidepressants or anxiolytics, and who had a current depressive episode.

No significant differences in DUI resulted in groups divided according to the other qualitative variables (P > .05).

The first linear multivariable regression on clinical lifetime variables showed that length of DUI was significantly associated with: the first diagnosis of Major Depressive Disorder or substance abuse (P = .048), an onset of BD with a Major Depressive Episode (P = .004), more lifetime depressive episodes (P < .001) and more lifetime number of hypomanic episodes (P < .001). In contrast, lifetime presence of psychotic symptoms (P = .086) and lifetime number of manic episodes (P = .089) remained at a borderline significance level.

The second linear multivariable regression model on sociodemographic and clinical variables of the last year showed that the length of DUI was significantly associated with: being married or in partnership (P < .001), presence of depressive episodes (P = .002), manic episodes (P = .013) or hospitalizations (P = .001) in the last year. In contrast, the presence of attempted suicides or hypomanic episodes in the last year was not statistically associated with the length of DUI in the final model (P > .05).

The third linear multivariable regression model on variables related to treatment showed that the length of DUI was significantly associated only with a current depressive episode (P = .017), but not with the type of current pharmacological treatment or the administration of psychoeducational interventions in the last year (P > .05).

The global model, including all the variables that remained as statistically significant in the previously reported three models, indicated that the variables independently associated with a longer DUI were: a depressive polarity of the first bipolar episode (P = .001) (Figure 1), a higher number of lifetime depressive episodes (P < .001), a higher number of lifetime hypomanic episodes (P < .001), being married or in partnership (P = .007) and a first diagnosis of Major Depressive

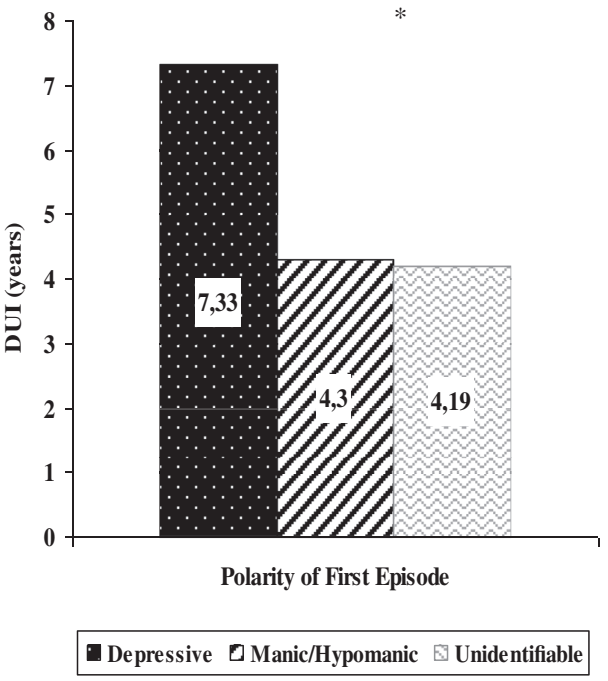

FIGURE 1 Duration of untreated illness (DUI) in bipolar patients according to the polarity of first episode. *P = .001 according to multivariable logistic regression

Disorder/substance misuse at a borderline significance level ($P = .071$). In contrast, the presence of depressive/manic episodes and hospitalizations in the last year as well as a current depressive episode did not maintain their significant association with the length of DUI in this final model ($P > .05$).

4 | DISCUSSION

The results of the present research show that different factors are associated with a longer DUI, including lifetime variables and others related to recent clinical manifestations. Among the first ones, the presence of at least one marriage/partnership, BD type 2, a first psychiatric diagnosis of Major Depressive Disorder or substance abuse, first presentation with a Major Depressive Episode, absence of lifetime psychotic symptoms, more depressive/hypomanic episodes, less manic episodes are associated with a longer DUI. Furthermore, focusing on quantitative lifetime variables, it is astonishing that bipolar patients approximately wait for 6 years to receive a correct diagnosis after the first contact with psychiatric clinics for a mood episode. Of note, a previous Italian study conducted on a sample of 320 bipolar patients reported a DUI of 6 years corresponding to the median value of this variable in the study sample (Altamura et al., 2010).

With regard to the clinical variables of the last year of observation, a longer DUI was found to be associated with recent attempted suicides, hospitalizations, depressive and hypomanic episodes, and with no recent administration of psychoeducation. Furthermore, a shorter DUI correlated with more time between visits in euthymic patients. In contrast, less recent manic episodes were associated with a longer DUI, the length of this variable being likely influenced by bipolar subtype I, as reported above. It is also necessary to take into account that patients with longer DUI can have more likelihood of suicide attempts or hospitalizations as they are inherently more severely ill.

Going into detail of the different variables significantly associated with DUI, type of marital status was reported to a have a variable impact on outcome of bipolar patients. Some studies reported that being married or in relationship was associated with less suicidal risk in BD (Schaffer et al., 2015; Shabani et al., 2013). Others, in agreement with our results, found that marriage/partnership was associated with negative outcome factors including a longer DUI especially in elderly subjects (Serafini et al., 2018), or no improvement in quality of life (Bo et al., 2019). A possible explanation is that some factors favouring marriage or partnership in bipolar patients, such as BD type 2, are in turn associated with a longer DUI (Dell'Osso et al., 2017). Similarly to our results, BD type 2 was found to be a predictor of a longer DUI in a Chinese study (Zhang et al., 2017) and this is not surprising because this bipolar subtype has a frequent onset with a Major Depressive Episode (Serafini et al., 2019) that can hamper the diagnosis of BD and consequently delay proper treatment. On the other hand, misdiagnosis of BD with other psychiatric conditions especially Major Depressive Disorder leads to a number of negative effects, including social and work impairments, alcohol or substance misuse, and suicidal behaviour (Altamura et al., 2010; Altamura, Buoli, et al., 2015; Daveney, Panagioti, Waheed, & Esmail, 2019; Nasrallah, 2015). Other factors may favour misdiagnosis and consequently a longer DUI including absence of lifetime psychotic symptoms and prevalent depressive/hypomanic episodes as found by different authors (Matza, Rajagopalan, Thompson, & de Lissovoy, 2005; Xiang et al., 2013) apart from the present study. Taken as a whole, the data presented in this article robustly show that a correct diagnosis of recent-onset BD presenting with depressive or hypomanic symptoms is crucial to reduce the overall DUI (Vöhringer & Perlis, 2016).

Considering the detrimental long-term effects of a longer DUI, as indicated by the clinical variables of last year of observation, our data seem to support that delayed treatment implies less clinical stabilization, as shown by the association with more frequent recent attempted suicides, hospitalizations, depressive/hypomanic episodes, less time between visits in euthymic patients, and no recent administration of psychoeducation. Our findings are consistent with those reported by previous articles in smaller samples, showing poor stabilization of bipolar patients with longer DUI in terms of more frequent suicidal behaviour (Altamura et al., 2010) and more mood episodes (Drancourt et al., 2013). Poor clinical stabilization of bipolar subjects with long DUI is also supported by the fact that these patients have more visits, despite being euthymic, probably as a consequence of subthreshold symptoms or for other negative-associated outcomes (eg, suicidal behaviour) that require a strict monitoring (De Dios et al., 2012). In this framework, patients with longer DUI probably receive less psychoeducation in the light of more severe symptoms that hamper the administration of this type of psychosocial treatment. Of note, a previous study remarked that psychological interventions including psychoeducation can be more effective when introduced in early stages of illness (Reinares et al., 2010). Early recognition and proper treatment of bipolar patients is, therefore, a priority to ameliorate outcome of BD. Different strategies were explored to achieve this goal including early treatment in a specialized out-patient mood disorder clinic than standard out-patient treatment (Kessing et al., 2013), the identification of more specific biomarkers for BD than Major Depressive Disorder (Shao et al., 2019), or the widespread use of specific rating scales (Van Meter et al., 2019). Another challenge is to find robust clinical and biological factors that could differentiate bipolar and unipolar depression in order to identify subjects with a high likelihood to change the diagnosis in BD after a single first Major Depressive Episode (Hirschfeld, 2014). In this sense, future research should identify convincing strategies to reduce delayed treatment in BD.

Finally, in spite of being representative of the largest multicentric study conducted in Italy so far, results of the present article should be interpreted in light of the following considerations:

1. Patients were treated in different regions in Italy that have a slightly different psychiatric organization and this can have influenced DUI and relative outcomes. However, the whole organization of mental health in Italy is regulated by law 180, which provides for a strong presence of community health services;

2. Some variables were collected retrospectively and this might have made some data less accurate than in controlled studies;
3. The study did not include a follow-up monitoring due to the cross-sectional nature of the study;
4. DUI was calculated as the time between the first major mood episode and the prescription of an appropriate treatment for BD (mood stabilizer or atypical antipsychotics with a mood stabilizing effects), however, alternative definitions have been proposed (eg, the time between onset of symptoms and diagnosis of BD) (Dagani et al., 2017);
5. Some other factors including psychiatric comorbidity can have influenced the present results.

Taken as a whole the results of the present manuscript indicate that different factors may be associated with a longer DUI in patients affected by BD especially those related to misdiagnosis (eg, a first diagnosis of Major Depressive Disorder). In turn, a longer DUI is a negative prognostic factor as shown by its association with suicide attempts and hospitalizations. Prevention strategies aimed to reduce DUI should be therefore planned to ameliorate outcome of bipolar patients.

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DATA AVAILABILITY STATEMENT

The data that support the findings were registered on eCRF and are available upon reasonable request.

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