The impact of affective temperaments on clinical and functional outcome of Bipolar I patients that initiated or changed pharmacological treatment for mania

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ABSTRACT

Background: Affective temperaments have been shown to impact on the clinical manifestations and the course of bipolar disorder. We investigated their influence on clinical features and functional outcome of manic episode. **Method:** In a naturalistic, multicenter, national study, a sample of 194 BD I patients that initated or changed pharmacological treatment for DSM-IV-TR manic episode underwent a comprehensive evaluation including briefTEMPS-M, CTQ, YMRS, MADRS, FAST, and CGI-BP. Factorial, correlation and comparative analyses were conducted on different temperamental subtypes. **Results:** Depressive, cyclothymic, irritable and anxious temperaments resulted significantly correlated with each other. On the contrary, hyperthymic temperament scores were not correlated with the other temperamental dimensions. The factorial analysis of the briefTEMPS-M sub-scales total scores allowed the extraction of two factors: the Cyclothymic-Depressive-Anxious (Cyclo-Dep-Anx) and the Hyperthymic. At final evaluation Dominant Cyclo-Dep-Anx patients reported higer scores in MADRS and in CTQ emotional neglect and abuse subscale scores than Dominant Hyperthymic patients. The latter showed a greater functional outcome than Cyclo-Dep-Anx patients. **Conclusions:** Affective temperaments seem to influence the course of mania. Childhood emotional abuse and neglect were related to the cyclothymic disposition. Cyclothymic subjects showed more residual depressive symptoms and Hyperthymic temperament is associated with a better short-term functional outcome.

Keywords: bipolar disorder, affective temperaments, mania.

1. INTRODUCTION

In clinical setting, the course of bipolar disorder (BD) (El-Mallakh et al., 2008) is characterized by a high number of relapses with frequent chronicity and consequent impairment in psychosocial functioning and health-related quality of life (Rosa et al., 2008; Sylvia et al., 2014; Tohen et al., 2009). As a consequence, the definition of remission in BD comprises both symptomatic and functional recovery. Symptomatic remission means the resolution of the symptoms of the disorder, which disappear or at least decrease to a minimal level. Functional recovery means the ability to return to an adequate level of functioning, including occupational status, familial and social adjustment and personal weel-being (Harvey, 2006; Martinez-Aran et al., 2007; Tohen et al., 2003).

Acute mania seems to present a favorable prognosis, although incomplete symptomatic remission and persisting impairment of psychosocial functioning are not uncommon. In fact, most patients achieve symptomatic remission but less than half reach a functional recovery within 24 months after a manic/mixed episode (Haro et al., 2011; Strejilevich et al., 2013; Swann et al., 2002; Tohen et al., 2003; van der Voort et al., 2015). For this reason, there is a growing interest in the factors related to outcome and remission of BD episodes (Haro et al., 2011; Kora et al., 2008; Treuer and Tohen, 2010).

Several studies explored the role of socio-demographic and clinical features in predicting remission of mania (Haro et al., 2011; Kora et al., 2008; Sylvia et al., 2014; Treuer and Tohen, 2010). Affective temperaments seem to impact on the clinical features and the course of BD (Akiskal, 2000; Hantouche et al., 1998; Iasevoli et al., 2013; Perugi et al., 2012; Pompili et al., 2014). In particular, temperaments might play

a predisposing or pathoplastic role in the state symptomatology and in several co-morbid syndromes (Perugi and Akiskal, 2002). An Italian study on a national sample of BD I patients in different phase of the illness prospectively explored the influence of affective temperaments and psychopathological traits, such as separation anxiety and interpersonal sensitivity, on the clinical features of BD (Perugi et al., 2012). Interestingly, the cyclothymic-sensitive patients reported a higher number of suicide attempts and a prevalently depressive course of the illness, while hyperthymic patients showed higher number of severe manic episodes requiring hospitalization. Finally, the two temperamental subtypes showed a different profile in term of lifetime comorbidity. Cyclothymic patients presented more frequently Panic Disorder/Agoraphobia, Social Anxiety Disorder and Borderline Personality Disorder in comparison with hyperthymics. On the contrary, Antisocial Personality Disorder was more represented among hyperthymic than cyclothymic patients (Perugi et al., 2012).

More recently, a relationship between temperamental subtype and neurocognition has been reported. In particular, high ratings of cyclothymia and irritability in BD patients have been associated with better processing speed, working memory, reasoning and problem-solving (Russo et al., 2014). On the other hand, BD patients with hyperthymic temperament showed greater cognitive deficits in set shifting and verbal working memory than BD patients with non-predominant temperaments (Xu et al., 2014). The role of affective temperaments in the prediction of the illness severity and global functioning has been prospectively explored in inpatients with major depressive disorder and BD (Pompili et al., 2013), suggesting a long-term predictive power of the hyperthymic temperament with respect to better health and social functioning.

Previous studies on the influence of affective temperaments on the clinical features and the course of BD have been conducted mainly in patients evaluated during depression. The aim of the present study is to investigate the influence of affective temperaments on the clinical and functional outcome of manic episodes.

2. MATERIALS AND METHODS

2.1. Study design and sample

This was a multicentric, prospective, longitudinal, non-interventional study conducted in in 34 recruiting Italian sites representative of the entire national territory. The study population included in- or out-patients aged ≥ 18 years with manic episode in the context of a BD I, diagnosed according to DSM-IV-TR criteria (American Psychiatric Association, 2000), and requiring the initiation or a change (but not a dose change) of treatment for mania with an oral antipsychotic and/or mood stabilizer. The assignment of the patients to a particular therapeutic strategy was independent of the decision to include the patient in the study. Therapeutic choices were made, in a naturalistic setting, by the treating psychiatrist according to his/her clinical experience and guidelines. Patients not able to read or understand the informed consent, pregnant or breast-feeding women, subjects participating in a separate study that had an interventional design and the members of the site personnel or their immediate family members were not eligible for participation.

The study duration was 3 months for each patient (5 visits): screening for inclusion in the study and baseline assessment were concomitants; follow-up visits at week 1, 3, 8 and 12 (± 1 week). Participating psychiatrists recorded observational data on a regular basis. However, these observations had to occur only during visits that where part of the standard course of care. Although patient consent had to be achieved as required by local laws and regulations, data collection did not require any patient intervention beyond usual practice and did not alter the care provided.

Patients meeting all inclusion criteria were assessed by the Young Mania Rating Scale (YMRS) and the Montgomery and Asberg Depression Rating Scale (MADRS) for the evaluation of the severity of affective symptomatology

(Montgomery and Asberg, 1979; Young et al., 1978). The global severity of manic episode was evaluated by the Clinical Global Impression Scale-Bipolar Illness (CGI-BP), which allowed determining the degree of change from the immediately preceding phase and from the worst phase of illness (Spearing et al., 1997). The Functioning Assessment Short Test (FAST) scale was used to assess the social, occupational, psychological and cognitive functioning (Rosa et al., 2007). At each visit after baseline (week 1, 3, 8 and 12, ± 1 week), psychiatrist used the same psychopathological tools to assess symptoms evolution over time. At week 12, patients were administered the Childhood Trauma Questionnaire (CTQ) to assess the occurrence of childhood trauma (Bernstein et al., 2003). The Temperament Evaluation of Memphis, Pisa, Paris and San Diego brief-version (briefTEMPS-M) was also administered at week 12 to investigate temperamental characteristics (depressive, cyclothymic, hyperthymic, irritable, anxious) (Erfurth et al., 2005a).

2.2. Ethics

All patients gave their written informed consent prior to any study-related procedure was started. The study protocol was approved by the reference Ethic Committee of each study site.

2.3. Diagnostic assessment

The diagnosis of manic episode in BD I patients was made by the treating psychiatrist according to the DSM-IV-TR criteria (American Psychiatric Association, 2000). Manic symptoms were quantitatively and qualitatively assessed through the YMRS (Young et al., 1978), an 11-items scale that carefully investigates the key symptoms of mania, i.e. those that are generally present during all the course of mania. The investigated areas pertained to mood, motor activity, thought disorders, judgment ability, aggressiveness, libido, sleep and general behaviour. The YMRS was

specifically created for the evaluation of manic symptoms and their evolution during treatment.

Depressive symptomatology was investigated by the MADRS (Montgomery and Asberg, 1979), which was expressly created to be sensitive to the evolution of depressive symptoms over time. The assessment of depressive symptoms is thought to be relevant also during manic phases, since the possible occurrence of dysphoria and switching towards a mixed state. Its 10 items explore depressed mood, inner tension, sleep and appetite disturbances, concentration difficulties, asthenia, inability to feel, pessimistic and suicidal thoughts.

The global psychopathology was evaluated by the CGI-BP (Spearing et al., 1997), a version of CGI that preserves the fundamental assets of the original global rating instrument focusing on the specific components of BD. It allows determining a global evaluation in three areas: the severity of the illness, the global improvement and the efficacy index (comparison of the patient's baseline condition to a ratio of current therapeutic benefit and severity of side effects).

Impairment in different areas of functioning (e.g. cognitive and social functioning) could be present in BD patients (Depp et al., 2010; Iverson et al., 2011). In addiction to symptoms, the evaluation of various areas of psychosocial functioning is relevant for understanding the clinical outcome and the recovery process. The psychosocial functioning was investigated through the administration of the FAST (Rosa et al., 2007). The FAST is organized in 6 clusters (autonomy, occupational functioning, cognitive functioning, financial management, social functioning and leisure time) whose items are evaluated from absence of difficulty to high difficulty. The FAST shows strong psychometric properties and it is sensitive to different mood states.

The assessment of temperamental characteristics was performed by the briefTEMPS-M version (Erfurth et al., 2005a). The briefTEMPS-M allows investigating 5 temperamental sub-scales: depressive, cyclothymic, hyperthymic, irritable and anxious. All of the briefTEMPS-M temperaments correlate quite well (Pearson r 0.49 - 0.72) with the original version of the longer TEMPS-M.

The validated brief version (28 items) of the CTQ (Bernstein et al., 2003) was used to retrospectively assess the reported childhood abuse experiences among adolescents and adults (from 12 years old up). The CTQ items are based on a review of the child abuse literature and assess five types of negative childhood experiences: emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. These five types of experiences are each assessed by five items; three additional items assess tendencies of respondents to minimize or deny abuse experiences. Respondents rate the truth of each statement on a 1-5 scale, from Never true when they were growing up to Very often true when they were growing up.

In order to minimize the influence of the acute manic-mixed symptomatology, briefTEMPS-M and CTQ were collected at week 12.

2.4. Statistical analyses

A factorial analysis on the briefTEMPS-M item scores was performed in order to detect the underline affective temperamental dimensions. The initial factors were extracted by means of principal component analysis (type 2) and then rotated according to varimax criteria in order to achieve a simple structure. This simplification is equivalent to maximizing the variance of the squared loading in each column. The criterion used to select the number of factors was an eigenvalue greater than 1. This

procedure made it possible to minimize the correlations between the factors, allowing their optimization as classificatory tools for each subject.

In order to explore possible relationships among different temperamental dimension, we utilized Pearson's correlation coefficients. Subsequently, with the aim of evaluating the way different temperamental dimensions were associated, another factorial analysis was performed on the briefTEMPS-M sub-scales (depressive, cyclothymic, hyperthymic, anxious and irritable) in order to detect possible composite dimensions. The criterion used to select the number of factors was an eigenvalue greater than 1.

Subsequently, in order to analyze the relationships among different temperamental subtypes of BD and other clinical characteristics, we used the following procedure: the factorial scores were standardized as z-scores to facilitate the comparisons of scores among the factorial measures. All the subjects were then grouped into different subtypes on the basis of the highest z-scores obtained for each factor (dominant factor). This procedure gives the opportunity to classify groups of subjects on the basis of the most statistically abnormal temperamental cluster. In this way, it is possible to resolve the problem of identifying a cut-off for including patients into the different identified clusters. In order to verify how distinct the subtypes are, how much overlap exists between them and how many cases fell close to multiple category, we analyzed the mean z-scores across the factors for each dominant group. By doing so, it is possible to give meaningful interpretations of the differential associations between different dominant subgroups and other variables.

Finally, we used t-test and Chi square respectively for comparison of continuous or parametric variables (Mann–Whitney and Fisher exact test when appropriated). In consideration of the exploratory nature of the study, we considered

levels of significance of $p<0.05$, without operating any correction for multiple comparisons. We utilized the statistical routines of the SPSS.20 for Mac.

3. Results

Overall, 245 patients were screened in 34 recruiting sites and 243 of them were included in the study. Two patients were excluded from the evaluable population due to not switching therapy for BD I. One-hundred ninety-seven patients completed the 12-week follow-up. Our analyses were performed on the 194 patients who completed the brief TEMPS-M scale.

Affective temperamental dimensions: correlations and distribution

The principal component factorial analysis of the briefTEMPS-M item scores yelded five main factors explaining the 61.45% of the variance (Table 1). The first factor (13.23% of the variance) consisted of the items from 22 to 27 eploring irritable temperament, the second factor (13.00% of the variance) comprised the depressive temperament items from 1 to 7 and items 33 and 35 included in the anxious temperament scale, the third factor (12.75% of the variance) the cyclothymic temperament items from 8 to 14, the fourth (12.06% of the variance) the hyperthymic items from 15 to 21 and the fifth (10.40% of the variance) anxious temperament items fom 29 to 35.

The Pearson's correlations among the briefTEMPS-M temperamental sub-scales and CTQ total score, depressive, cyclothymic, irritable and anxious temperaments, as well as with CTQ total score resulted significantly correlated (Table 2). On the contrary, hyperthymic temperament scores were not correlated with CTQ

total score as well as the other temperamental dimensions, with the exception of irritable temperament.

In line with this finding, the factorial analysis of the mean scores of the briefTEMPS-M sub-scales showed 2 main factors explaining 72.32% of the variance (Table 3). The first factor (49.65% of the variance) consisted of cyclothymic, depressive, irritable and anxious temperaments; the second factor (22.67% of the variance) was represented by the hyperthymic and irritable temperaments as only positive component, and by depressive and cyclothymic temperaments as negative component.

Comparisons between temperamental subtypes

The comparisons of demographic, familial and clinical variables between dominant Cyclothymic-depressive-anxious (Cyclo-Dep-Anx) patients (n=93) and dominant Hyperthymic patients (n=101) are reported in Table 4. The two temperamental subtypes were similar for gender, marital status, education, occupational level and work absences due to BD. Furthermore, the two groups did not show a statistically significant difference in the age at the date of informed consent, in the age at first diagnosis of BD I and in the age at first episode. Dominant Hyperthymic patients reported a higher family history for BD in comparison to dominant Cyclo-Dep-Anx patients. The two groups showed similar rates of lifetime comorbidity with anxiety disorders, eating disorders, borderline personality disorder and substance use disorder. No differences between the two temperamental subtypes were observed in clinical features such as inpatients status, rapid cycling before baseline, dominant polarity and number of previous depressive, manic, mixed and hypomanic episodes. In addition, dominant Cyclo-Dep-Anx patients and dominant

Hyperthymic patients were similar for history and number of suicide attempts, history of psychotic symptoms, number of hospitalization and forced treatments.

The comparisons between the two temperamental subtypes in YMRS, MADRS, FAST and CTQ scores are reported in Table 5. We found no differences between the two groups in YMRS total score at baseline and at final evaluation. Regarding MADRS, the two temperamental subtypes showed similar total scores at baseline, while dominant Cyclo-Dep-Anx patients reported a significantly higher total score at final evaluation. Similarly, no differences between the two groups were observed at baseline in all FAST sub-scales and total scores, while dominant Cyclo-Dep-Anx patients reported significantly higher mean scores in all FAST sub-scales than dominant Hyperthymic patients at final evaluation. Finally, we found statistically significant differences between the two temperamental subtypes in CTQ total score and in two CTQ sub-scales. In particular, dominant Cyclo-Dep-Anx patients showed higher mean scores in childhood "emotional abuse" and "neglect experiences" scales when compared with dominant Hyperthymic patients.

4. DISCUSSION

In our manic population, correlation analyses indicated that depressive, cyclothymic, irritable and anxious temperaments are strongly related each other and inversely related with hyperthymic temperament. This finding is consistent with previous observations in Italian (Perugi et al., 2012), German (Brieger et al., 2003) and Hungarian (Gonda et al., 2009) clinical samples, selected in different phases of the illness, as well as in Lebanese general population (Karam et al., 2007). Considering a psychometric perspective, the affective temperamental dispositions measured by

TEMPS-M are actually two: the first mainly characterized by emotional instability and the second by emotional intensity. Temperamental irritability resulted to be associated with both cyclothymic and hyperthymic subtypes, suggesting that irritability may be interpreted as a mixed component in our manic patients, belonging to both hypertymic and cyclothymic temperamental dimensions (Akiskal et al., 1998; Perugi et al., 2001; Perugi et al., 2014).

In the present sample, there were no significant differences in the two temperamental subtypes regarding gender distribution, marital status, education, occupational level and work absences due to BD. These results are in line with a study conducted in a sample of lithium-treated manic patients, in which similar TEMPS-A scores for the five temperaments were reported in males and females (Rybakowski et al., 2013). On the contrary, in BD I patients prospectively selected on the basis of different index episodes, the comparison between dominant cyclothymic and dominant hyperthymic patients revealed an overrepresentation of the female gender among cyclothymics. This observation is consistent with previous reports in general (Signoretta et al., 2005) and clinical (Akiskal et al., 1998; Erfurth et al., 2005b; Perugi et al., 1990) populations. In fact, in a meta-analysis of six studies performed on healthy populations, males attained significantly higher scores for hyperthymic temperament than females, while the opposite happened for cyclothymic, depressive and anxious temperaments (Vazquez et al., 2008). A research on Polish college students showed a similar profile (Borkowska et al., 2010).

In our sample, the two temperamental subtypes did not differ in age, age at first episode and age at first diagnosis of BD I. Cyclo-Dep-Anx and hyperthymic patients also showed similar rates of lifetime comorbidity with anxiety, eating, borderline personality disorder and substance use disorders. There were no differences between

the two groups in clinical characteristics such as rapid cycling, dominant polarity and number of previous depressive, manic, mixed and hypomanic episodes. In addition, dominant Cyclo-Dep-Anx patients and dominant hyperthymic patients were similar for history and number of suicide attempts, presence of psychotic symptoms, number of hospitalization and number of forced treatments. In previous reports on patients selected on the basis of an index depressive episode (Akiskal et al., 2003; Maina et al., 2010; Nilsson et al., 2012; Perugi et al., 2012), cyclothymic patients reported a prevalently depressive course, while hyperthymic patients showed more severe manic episodes requiring hospitalization. Suicide attempts were more frequent in cyclothymic than in hyperthymic patients, probably reflecting at least in part the higher incidence of depressive episodes (Pompili et al., 2012). These discrepancies with our results could be accounted by the different index episode of the selected samples. In our manic patients, dominant hyperthymics reported more frequently a positive first-degree family history for BD in comparison to dominant Cyclo-Dep-Anx patients. On the contrary, a study on BD I patients selected in different phases of the illness reported higher rates of first-degree family history for mood disorders in cyclothymic than in hyperthymic patients (Perugi et al., 2012).

At baseline evaluation, the severity of manic and depressive symptomatology was similar in the two temperamental subtypes. Conversely, Cyclo-Dep-Anx patients showed higher severity of depressive symptoms at the final evaluation in comparison to hyperthymic patients. These observations seem to confirm a patoplastic role of affective temperament on state symptoms of BD (Perugi and Akiskal, 2002). Studies conducted on BD I patients indicated that mixed episodes are more frequent in subjects with inverse temperaments (Akiskal and Benazzi, 2003; Akiskal et al., 1998; Rottig et al., 2007): patients with depressive temperament tend to present mixed mania

and patients with hyperthymic temperament develop more frequently mixed depression. The greater severity of depressive symptoms in our manic patients with Cyclo-Dep-Anx temperaments in comparison with hyperthimic patients is consistent with this hypothesis.

Few studies investigated the influence of affective temperaments on treatment response and outcome (Goto et al., 2011; Rybakowski et al., 2013). In particular, Ribakowski and colleagues (2013) explored the temperamental correlates of lithium response, using a scale that retrospectively assessed the efficacy of the prophylactic therapy (Grof et al., 2002). The Authors showed a significant correlation between favourable long-term lithium response and hyperthymic temperament and concluded that this temperament should be added to the clinical features associated with positive lithium response. They also hypothesized that this finding may be related to the greater lithium efficacy in acute euphoric mania in comparison to dysphoric manic episode (Vieta, 2005). In the same study, lithium response was negatively associated with cyclothymic, depressive and anxious temperaments, suggesting that these subtypes are distinct from hyperthymic temperament (Vellante et al., 2011).

Interestingly, in our sample the two temperamental subtypes did not show differences in terms of functional impairment at baseline evaluation, probably due to the severity of the manic symptoms. On the contrary, at final evaluation dominant Cyclo-Dep-Anx patients showed a greater impairment in social, occupational, psychological and cognitive functioning in comparison with dominant hyperthymic patients. The presence of residual depressive symptoms might be associated with a worst functional outcome. However, the better functional recovery of hyperthimic patients might be related to other clinical or biological variables. In a genome wide association study, three SNP's on chromosomes 12 and 22 were found significantly

associated with hyperthymic temperament. They were located near the MDM1 and FBLN1 genes and one of them (fibulin 1 gene) is associated with neurotrophic activities (Greenwood et al., 2012). This finding suggests the possible existence of different neurotrophic activities in different temperamental subtypes.

Finally, in our sample, childhood traumatic experiences such as emotional abuse and neglect experiences were related to the cyclothymic disposition, indicating a possible temperamental matrix. According to previous reports, a history of childhood abuse seems to act as a disease course modifier in patients with BD (Brown et al., 2005; Perna et al., 2014) and it has been associated to early-onset of the illness (Post and Leverich, 2006) and suicidality (Carballo et al., 2008; Leverich et al., 2002). Recent studies pointed out how childhood trauma affects differently the BD patients and the general population, both from a clinical (Janiri et al., 2015) and a neurobiological (Janiri et al., 2017) point of view. In this perspective, our results seem to support the view that childhood history of emotional and fisical neglect is related to the presence of temperamental mood instability rather than temperamental intensity or mood disorder in itself. A possible interpretation is that an underlying temperamental mood instability could be the substrate for trauma hypersensitivity in patients with BD (Perugi et al., 2011).

Several methodological issues should be taken into account in interpreting our results. Limitations of our study include the small sample size and the fact that the participating centers were not randomly selected, which may led to a bias through the inclusion of psychiatrists with a particular interest in BD. Because this study was conducted in routine clinical services, clinicians who evaluated these patients could not be held entirely blind to the various measures administered. On the other hand, investigators were psychiatrists who were sophisticated in clinical evaluation—rather

than mere raters of psychopathology—thereby ensuring clinically valid data collection; moreover, the use of systematic semi-structured instruments minimize the unintended biases due to lack of blindness. Finally, the temperamental inventory, though standard in the field from a reliability standpoint, taps constructs with uncertain validity. For this reason, it is possible that several of the shared features between affective states, on one side, and affective temperaments, on the other, may at least in part overlap. Temperamental evaluation was conducted at the end of the osevational period when the influence of the state symptomatology is minimized.

In conclusion, in our sample of BD I patients selected on the basis of an index manic episode, dominant Cyclo-Dep-Anx and hyperthymic subjects reported important differences in terms of residual depressive symptoms and functional outcome. In fact, Cyclo-Dep-Anx patients showed more severe depressive symptoms than hyperthymic patients. On the other side, dominant hyperthymic group reported a less impairment in social, occupational, psychological and cognitive functioning. Finally, a history of childhood emotional abuse and neglect resulted related to the cyclothymic disposition, suggesting a possible temperamental matrix.

Our results support the view that different affective temperaments may influence the clinical presentation and the outcome of the manic and depressive episodes. In clinical practice, the pathoplastic effect on the acute symptomatology and the influence on the course of the illness of different temperamental dispositions should be considered for the choice of the treatment and the prognostic evaluation. Further research in patients treated with different drugs is necessary in order to investigate possible therapeutic implications of temperamental subtypes in short- and long-term outcome of different BD episodes.

CONFLICT OF INTEREST

G. Perugi has acted as consultant of Eli Lilly, Lundbeck, Angelini; received grant/research support from Eli Lilly and Lundbeck; he was on the speaker/advisory board of Sanofi Aventis, Eli Lilly, Jannsen-Cilag, Lundbeck, Angelini.

A. De Bartolomeis has acted as consultant for Lundbeck, Otsuka and Roche, has been involved in unrestricted educational activity sponsored by Janssen, Lundbeck, Chiesi, Roche and Otsuka, and has been recipient of preclinical research grant from Otsuka and Lundbeck.

A. Fagiolini is /has been a consultant and/or a speaker and/or has received research grants from Angelini, Astra Zeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Eli Lilly, Janssen, Lundbeck, Novartis, Otsuka, Roche

G. Maina has acted as consultant of Otsuka, Lundbeck; received grant/research support from Eli Lilly and Lundbeck; was on the speaker/advisory board of Otsuka, Asta Zeneca, Jannsen-Cilag, Lundbeck, Pfizer.

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REFERENCES

Akiskal, H.S., 2000. Temperament and mood disorders. Harv Ment Health Lett 16 (8), 5-6.

Akiskal, H.S., Benazzi, F., 2003. Family history validation of the bipolar nature of depressive mixed states. J Affect Disord 73 (1-2), 113-122.

Akiskal, H.S., Hantouche, E.G., Allilaire, J.F., 2003. Bipolar II with and without cyclothymic temperament: "dark" and "sunny" expressions of soft bipolarity. J Affect Disord 73 (1-2), 49-57.

Akiskal, H.S., Hantouche, E.G., Bourgeois, M.L., Azorin, J.M., Sechter, D., Allilaire, J.F., Lancrenon, S., Fraud, J.P., Chatenet-Duchene, L., 1998. Gender, temperament, and the clinical picture in dysphoric mixed mania: findings from a French national study (EPIMAN). J Affect Disord 50 (2-3), 175-186.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders, fourth ed., text rev. Washington, DC: Author.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 27 (2), 169-190.

Borkowska, A., Rybakowski, J.K., Drozdz, W., Bielinski, M., Kosmowska, M., Rajewska-Rager, A., Bucinski, A., Akiskal, K.K., Akiskal, H.S., 2010. Polish validation of the TEMPS-A: the profile of affective temperaments in a college student population. J Affect Disord 123 (1-3), 36-41.

Brieger, P., Roettig, S., Ehrt, U., Wenzel, A., Bloink, R., Marneros, A., 2003. TEMPS-a scale in 'mixed' and 'pure' manic episodes: new data and methodological considerations on the relevance of joint anxious-depressive temperament traits. J Affect Disord 73 (1-2), 99-104.

Brown, G.R., McBride, L., Bauer, M.S., Williford, W.O., Cooperative Studies Program 430 Study, T., 2005. Impact of childhood abuse on the course of bipolar disorder: a replication study in U.S. veterans. J Affect Disord 89 (1-3), 57-67.

Carballo, J.J., Harkavy-Friedman, J., Burke, A.K., Sher, L., Baca-Garcia, E., Sullivan, G.M., Grunebaum, M.F., Parsey, R.V., Mann, J.J., Oquendo, M.A., 2008. Family history of suicidal behavior and early traumatic experiences: additive effect on suicidality and course of bipolar illness? J Affect Disord 109 (1-2), 57-63.

Depp, C.A., Mausbach, B.T., Harvey, P.D., Bowie, C.R., Wolyniec, P.S., Thornquist, M.H., Luke, J.R., McGrath, J.A., Pulver, A.E., Patterson, T.L., 2010. Social competence and observer-rated social functioning in bipolar disorder. Bipolar Disord 12 (8), 843-850.

El-Mallakh, R.S., Ghaemi, S.N., Sagduyu, K., Thase, M.E., Wisniewski, S.R., Nierenberg, A.A., Zhang, H.W., Pardo, T.A., Sachs, G., Investigators, S.-B., 2008. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. J Affect Disord 111 (2-3), 372-377.

Erfurth, A., Gerlach, A.L., Hellweg, I., Boenigk, I., Michael, N., Akiskal, H.S., 2005a. Studies on a German (Munster) version of the temperament auto-questionnaire TEMPS-A: construction and validation of the briefTEMPS-M. J Affect Disord 85 (1-2), 53-69.

Erfurth, A., Gerlach, A.L., Michael, N., Boenigk, I., Hellweg, I., Signoretta, S., Akiskal, K., Akiskal, H.S., 2005b. Distribution and gender effects of the subscales of a German version of the temperament autoquestionnaire briefTEMPS-M in a university student population. J Affect Disord 85 (1-2), 71-76.

Gonda, X., Fountoulakis, K.N., Rihmer, Z., Lazary, J., Laszik, A., Akiskal, K.K., Akiskal, H.S., Bagdy, G., 2009. Towards a genetically validated new affective temperament scale: a delineation of the temperament phenotype of 5-HTTLPR using the TEMPS-A. J Affect Disord 112 (1-3), 19-29.

Goto, S., Terao, T., Hoaki, N., Wang, Y., 2011. Cyclothymic and hyperthymic temperaments may predict bipolarity in major depressive disorder: a supportive evidence for bipolar II1/2 and IV. J Affect Disord 129 (1-3), 34-38.

Greenwood, T.A., Akiskal, H.S., Akiskal, K.K., Bipolar Genome, S., Kelsoe, J.R., 2012. Genome-wide association study of temperament in bipolar disorder reveals significant associations with three novel Loci. Biol Psychiatry 72 (4), 303-310.

Grof, P., Duffy, A., Cavazzoni, P., Grof, E., Garnham, J., MacDougall, M., O'Donovan, C., Alda, M., 2002. Is response to prophylactic lithium a familial trait? J Clin Psychiatry 63 (10), 942-947.

Hantouche, E.G., Akiskal, H.S., Lancrenon, S., Allilaire, J.F., Sechter, D., Azorin, J.M., Bourgeois, M., Fraud, J.P., Chatenet-Duchene, L., 1998. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). J Affect Disord 50 (2-3), 163-173.

Haro, J.M., Reed, C., Gonzalez-Pinto, A., Novick, D., Bertsch, J., Vieta, E., Board, E.A., 2011. 2-Year course of bipolar disorder type I patients in outpatient care: factors associated with remission and functional recovery. Eur Neuropsychopharmacol 21 (4), 287-293.

Harvey, P.D., 2006. Defining and achieving recovery from bipolar disorder. J Clin Psychiatry 67 Suppl 9, 14-18; discussion 36-42.

Iasevoli, F., Valchera, A., Di Giovambattista, E., Marconi, M., Rapagnani, M.P., De Berardis, D., Martinotti, G., Fornaro, M., Mazza, M., Tomasetti, C., Buonaguro, E.F., Di Giannantonio, M., Perugi, G., de Bartolomeis, A., 2013. Affective temperaments are associated with specific clusters of symptoms and psychopathology: a cross-sectional study on bipolar disorder inpatients in acute manic, mixed, or depressive relapse. J Affect Disord 151 (2), 540-550.

Iverson, G.L., Brooks, B.L., Langenecker, S.A., Young, A.H., 2011. Identifying a cognitive impairment subgroup in adults with mood disorders. J Affect Disord 132 (3), 360-367.

Janiri, D., Sani, G., Danese, E., Simonetti, A., Ambrosi, E., Angeletti, G., Erbuto, D., Caltagirone, C., Girardi, P., Spalletta, G., 2015. Childhood traumatic experiences of patients with bipolar disorder type I and type II. J Affect Disord 175, 92-7.

Janiri, D., Sani, G., Rossi, P., Piras, F., Iorio, M., Banaj, N., Giuseppin, G., Spinazzola, E., Maggiora, M., Ambrosi, E., Simonetti, A., Spalletta, G., 2017. Amygdala and hippocampus volumes are differently affected by childhood trauma in patients with bipolar disorders and healthy controls. Bipolar Disord 19 (5), 353-362.

Karam, E.G., Mneimneh, Z.N., Salamoun, M.M., Akiskal, H.S., Akiskal, K.K., 2007. Suitability of the TEMPS-A for population-based studies: ease of administration and stability of affective temperaments in its Lebanese version. J Affect Disord 98 (1-2), 45-53.

Kora, K., Saylan, M., Akkaya, C., Karamustafalioglu, N., Tomruk, N., Yasan, A., Oral, T., 2008. Predictive factors for time to remission and recurrence in patients treated for acute mania: health outcomes of manic episodes (HOME) study. Prim Care Companion J Clin Psychiatry 10 (2), 114-119.

Leverich, G.S., McElroy, S.L., Suppes, T., Keck, P.E. Jr, Denicoff, K.D., Nolen, W.A., Altshuler, L.L., Rush, A.J., Kupka, R., Frye, M.A., Autio, K.A., Post, R.M., 2002. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol Psychiatry 51 (4), 288-97.

Maina, G., Salvi, V., Rosso, G., Bogetto, F., 2010. Cyclothymic temperament and major depressive disorder: a study on Italian patients. J Affect Disord 121 (3), 199-203.

Martinez-Aran, A., Vieta, E., Torrent, C., Sanchez-Moreno, J., Goikolea, J.M., Salamero, M., Malhi, G.S., Gonzalez-Pinto, A., Daban, C., Alvarez-Grandi, S., Fountoulakis, K., Kaprinis, G., Tabares-Seisdedos, R., Ayuso-Mateos, J.L., 2007. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disord 9 (1-2), 103-113.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry 134, 382-389.

Nilsson, K.K., Straarup, K.N., Jorgensen, C.R., Licht, R.W., 2012. Affective temperaments' relation to functional impairment and affective recurrences in bipolar disorder patients. J Affect Disord 138 (3), 332-336.

Perna, G., Vanni, G., Di Chiaro, N.V., Cavedini, P., Caldirola, D., 2014. Childhood trauma, temperament, and character in subjects with major depressive disorder and bipolar disorder. J Nerv Ment Dis 202 (9), 695-698.

Perugi, G., Akiskal, H.S., 2002. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. Psychiatr Clin North Am 25 (4), 713-737.

Perugi, G., Fornaro, M., Akiskal, H.S., 2011. Are atypical depression, borderline personality disorder and bipolar II disorder overlapping manifestations of a common cyclothymic diathesis? World Psychiatry 10 (1), 45-51.

Perugi, G., Maremmani, I., Toni, C., Madaro, D., Mata, B., Akiskal, H.S., 2001. The contrasting influence of depressive and hyperthymic temperaments on psychometrically derived manic subtypes. Psychiatry Res 101 (3), 249-258.

Perugi, G., Medda, P., Swann, A.C., Reis, J., Rizzato, S., Mauri, M., 2014. Phenomenological subtypes of severe bipolar mixed states: a factor analytic study. Compr Psychiatry 55 (4), 799-806.

Perugi, G., Musetti, L., Simonini, E., Piagentini, F., Cassano, G.B., Akiskal, H.S., 1990. Gender-mediated clinical features of depressive illness. The importance of temperamental differences. Br J Psychiatry 157, 835-841.

Perugi, G., Toni, C., Maremmani, I., Tusini, G., Ramacciotti, S., Madia, A., Fornaro, M., Akiskal, H.S., 2012. The influence of affective temperaments and psychopathological traits on the definition of bipolar disorder subtypes: a study on bipolar I Italian national sample. J Affect Disord 136 (1-2), e41-e49.

Pompili, M., Innamorati, M., Gonda, X., Erbuto, D., Forte, A., Ricci, F., Lester, D., Akiskal, H.S., Vazquez, G.H., Rihmer, Z., Amore, M., Girardi, P., 2014. Characterization of patients with mood disorders for their prevalent temperament and level of hopelessness. J Affect Disord 166, 285-291.

Pompili, M., Innamorati, M., Gonda, X., Serafini, G., Sarno, S., Erbuto, D., Palermo, M., Elena Seretti, M., Stefani, H., Lester, D., Perugi, G., Akiskal, H., Siracusano, A., Rihmer, Z., Tatarelli, R., Amore, M., Girardi, P., 2013. Affective temperaments and hopelessness as predictors of health and social functioning in mood disorder patients: a prospective follow-up study. J Affect Disord 150 (2), 216-222.

Pompili, M., Innamorati, M., Rihmer, Z., Gonda, X., Serafini, G., Akiskal, H., Amore, M., Niolu, C., Sher, L., Tatarelli, R., Perugi, G., Girardi, P., 2012. Cyclothymic-depressive-anxious temperament pattern is related to suicide risk in 346 patients with major mood disorders. J Affect Disord 136 (3), 405-411.

Post, R.M., Leverich, G.S., 2006. The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. Dev Psychopathol 18 (4), 1181-1211.

Rosa, A.R., Franco, C., Martinez-Aran, A., Sanchez-Moreno, J., Reinares, M., Salamero, M., Arango, C., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2008. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom 77 (6), 390-392.

Rosa, A.R., Sanchez-Moreno, J., Martinez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health 3, 5.

Rottig, D., Rottig, S., Brieger, P., Marneros, A., 2007. Temperament and personality in bipolar I patients with and without mixed episodes. J Affect Disord 104 (1-3), 97-102.

Russo, M., Mahon, K., Shanahan, M., Ramjas, E., Solon, C., Braga, R.J., Burdick, K.E., 2014. Affective temperaments and neurocognitive functioning in bipolar disorder. J Affect Disord 169, 51-56.

Rybakowski, J.K., Dembinska, D., Kliwicki, S., Akiskal, K.K., Akiskal, H.H., 2013. TEMPS-A and long-term lithium response: positive correlation with hyperthymic temperament. J Affect Disord 145 (2), 187-189.

Signoretta, S., Maremmani, I., Liguori, A., Perugi, G., Akiskal, H.S., 2005. Affective temperament traits measured by TEMPS-I and emotional-behavioral problems in clinically-well children, adolescents, and young adults. J Affect Disord 85 (1-2), 169-180.

Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res 73 (3), 159-171.

Strejilevich, S.A., Martino, D.J., Murru, A., Teitelbaum, J., Fassi, G., Marengo, E., Igoa, A., Colom, F., 2013. Mood instability and functional recovery in bipolar disorders. Acta Psychiatr Scand 128 (3), 194-202.

Swann, A.C., Bowden, C.L., Calabrese, J.R., Dilsaver, S.C., Morris, D.D., 2002. Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania. Neuropsychopharmacology 26 (4), 530-536.

Sylvia, L.G., Rabideau, D.J., Nierenberg, A.A., Bowden, C.L., Friedman, E.S., Iosifescu, D.V., Thase, M.E., Ketter, T., Greiter, E.A., Calabrese, J.R., Leon, A.C., Ostacher, M.J., Reilly-Harrington, N., 2014. The effect of personalized guideline-concordant treatment on quality of life and functional impairment in bipolar disorder. J Affect Disord 169, 144-148.

Tohen, M., Frank, E., Bowden, C.L., Colom, F., Ghaemi, S.N., Yatham, L.N., Malhi, G.S., Calabrese, J.R., Nolen, W.A., Vieta, E., Kapczinski, F., Goodwin, G.M., Suppes, T., Sachs, G.S., Chengappa, K.R., Grunze, H., Mitchell, P.B., Kanba, S., Berk, M., 2009. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 11 (5), 453-473.

Tohen, M., Zarate, C.A., Jr., Hennen, J., Khalsa, H.M., Strakowski, S.M., Gebre-Medhin, P., Salvatore, P., Baldessarini, R.J., 2003. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 160 (12), 2099-2107.

Treuer, T., Tohen, M., 2010. Predicting the course and outcome of bipolar disorder: a review. Eur Psychiatry 25 (6), 328-333.

van der Voort, T.Y., Seldenrijk, A., van Meijel, B., Goossens, P.J., Beekman, A.T., Penninx, B.W., Kupka, R.W., 2015. Functional versus syndromal recovery in patients with major depressive disorder and bipolar disorder. J Clin Psychiatry 76 (6), e809-814.

Vazquez, G.H., Kahn, C., Schiavo, C.E., Goldchluk, A., Herbst, L., Piccione, M., Saidman, N., Ruggeri, H., Silva, A., Leal, J., Bonetto, G.G., Zaratiegui, R., Padilla, E., Vilaprino, J.J., Calvo, M., Guerrero, G., Strejilevich, S.A., Cetkovich-Bakmas, M.G., Akiskal, K.K., Akiskal, H.S., 2008. Bipolar disorders and affective temperaments: a

national family study testing the "endophenotype" and "subaffective" theses using the TEMPS-A Buenos Aires. J Affect Disord 108 (1-2), 25-32.

Vellante, M., Zucca, G., Preti, A., Sisti, D., Rocchi, M.B., Akiskal, K.K., Akiskal, H.S., 2011. Creativity and affective temperaments in non-clinical professional artists: an empirical psychometric investigation. J Affect Disord 135 (1-3), 28-36.

Vieta, E., 2005. Bipolar mixed states and their treatment. Expert Rev Neurother 5 (1), 63-68.

Xu, G., Lu, W., Ouyang, H., Dang, Y., Guo, Y., Miao, G., Bessonov, D., Akiskal, K.K., Akiskal, H.S., Lin, K., 2014. Association of affective temperaments measured by TEMPS-a with cognitive deficits in patients with bipolar disorder. J Affect Disord 161, 109-115.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133, 429-435.

Table 1 - Factorial analysis (PCA extraction, Varimax solution) of briefTEMPS-M in 194 BD I patients experiencing a manic episode.

	Components				
	Irritable	**Depressive**	**Ciclothymic**	**Hyperthymic**	**Anxious**
1. People tell me I am unable to see the lighter side of things	0.34	**0.40**	0.20	-0.11	0.22
2. I think things often turn out for the worst	0.18	**0.70**	0.24	-0.15	0.07
3. I have always blamed myself for what others might consider no big deal	0.19	**0.75**	0.13	-0.05	0.08
4. I'm the kind of person who doubts everything	0.14	**0.68**	0.19	-0.21	0.04
5. I am told that I often get pessimistic about things, and forget previous happy times	0.26	**0.72**	0.18	-0.08	0.26
6. I have been a worrier for as long as I can remember	0.08	**0.77**	0.19	0.03	0.17
7. Many people have told me not to worry so much	-0.05	**0.70**	0.20	-0.02	0.11
8. I get sudden shifts in mood and energy	0.30	0.22	**0.71**	-0.04	0.09
9. I often start things and then lose interest before finishing them	0.34	0.17	**0.61**	-0.12	0.20
10. My mood often changes for no reason	0.28	0.20	**0.76**	-0.03	0.18
11. I constantly switch between being lively and sluggish	0.23	0.19	**0.78**	-0.17	0.16
12. I go back and forth between feeling overconfident and feeling unsure of myself	0.10	0.31	**0.75**	-0.10	0.22
13. The way I see things is sometimes vivid, but at other times lifeless	0.16	0.29	**0.74**	-0.08	0.09
14. I am the kind of person who can be	0.17	0.07	**0.68**	0.06	-0.03

sad and happy at the same time					
15. I have great confidence in myself	-0.10	-0.19	-0.01	**0.70**	-0.15
16. I often get many great ideas	0.08	-0.11	-0.02	**0.82**	0.05
17. I can accomplish many tasks without even getting tired	0.18	-0.07	-0.19	**0.69**	0.10
18. I have a gift for speech, convincing and inspiring to others	0.02	-0.05	0.05	**0.78**	0.05
19. I love to tackle new projects, even if risky	0.20	-0.05	-0.01	**0.71**	-0.05
20. Once I decide to accomplish something, nothing can stop me	0.16	0.13	0.04	**0.79**	-0.02
21. I have abilities and expertise in many areas	-0.03	-0.01	-0.20	**0.71**	-0.01
22. When I disagree with someone, I can get into a heated argument	**0.63**	0.10	0.04	0.36	0.12
23. I am a grouchy (irritable) person	**0.74**	0.18	0.22	0.00	0.15
24. When crossed, I could get into a fight	**0.78**	0.21	0.12	0.11	0.13
25. When angry, I snap at people	**0.81**	0.20	0.19	0.14	0.09
26. My biting humor has gotten me into trouble	**0.75**	0.10	0.24	0.04	0.08
27. I can get so furious I could hurt someone	**0.7**	0.10	0.26	0.09	0.08
28. I am known to swear a lot	**0.67**	0.10	0.27	0.03	0.14
29. I often have an upset stomach	0.22	0.15	0.27	-0.03	**0.72**
30. When I'm nervous, I may have diarrhea	0.11	0.07	0.02	-0.01	**0.86**
31. When I'm nervous, I often feel nauseous	0.15	0.21	0.02	-0.01	**0.81**

32. When I'm nervous, I have to go to the bathroom more often	0.10	0.24	0.14	0.04	**0.82**
33. When someone is late coming home, I fear they may have had an accident	0.18	**0.49**	0.03	0.06	0.25
34. I easily get headaches when stressed	0.09	0.28	0.32	-0.01	**0.60**
35. Sudden noises startle me easily	0.11	**0.50**	0.16	0.05	**0.42**
Eingenvalue	4.63	4.55	4.46	4.22	3.64
% of Variance	13.23	13.00	12.75	12.06	10.40

Table 2 - Correlations among temperamental (briefTEMPS-M Depressive, Cyclothymic, Hyperthymic, Irritable and Anxious sub-scale scores) subtypes and CTQ total score in 194 BD patients experiencing a manic episode.

	Temperament				
	Depressive	Cyclothymic	Hyperthymic	Irritable	Anxious
Depressive	1	**0.52***	-0.14	**0.43***	**0.56***
Cyclothymic	**0.52***	1	-0.16	**0.50***	**0.46***
Hyperthymic	-0.14	-0.16	1	**0.21***	-0.01
Irritable	**0.43***	**0.50***	**0.21***	1	**0.42***
Anxious	**0.56***	**0.46***	-0.01	**0.42***	1
CTQ total score	**0.30***	**0.22***	0.16	**0.36***	**0.26***

*$p < 0.01$

Table 3 - Factorial analysis (PCA extraction, Varimax solution) of briefTEMPS-M Depressive, Cyclothymic, Hyperthymic, Irritable and Anxious sub-scale scores in 194 BD I patients experiencing a manic episode.

	Components	
	Cyclo-Dep-Anx	Hyperthymic
Depressive	**0.82**	-0.18
Cyclothymic	**0.82**	-0.09
Hyperthymic	-0.08	**0.95**
Irritable	**0.73**	**0.43**
Anxious	**0.78**	0.02
Eingenvalue	2.48	1.13
% of Variance	49.65	22.67

Table 4 - Comparison of demographic, clinical and familial variables between dominant cyclothymic-depressive-anxious and hyperthymic temperamental subtypes in 194 BD I patients experiencing a manic episode.

	Hyperthymic (n=101)	Cyclo-Dep-Anx (n=93)	t or chi-square	p
Gender (males) n (%)	46 (45.5)	39 (41.9)	0.26	0.61
Education (<8 years) n (%)	9 (8.9)	9 (9.7)	0.37	0.70
Marital status (married) n (%)	44 (43.6)	32 (34.4)	1.22	0.21
Work: unemployed n (%)	24 (23.8)	20 (21.5)	0.20	0.51
Patients with work absences due to BD n (%)	19 (18.8)	15 (16.1)	0.24	0.62
Inpatients n (%)	60 (59.4)	46 (49.5)	1.93	0.17
Family history for BD n (%)	49 (48.5)	30 (32.3)	5.30	**0.02**
Anxiety disorders n (%)	33 (32.7)	28 (30.1)	0.27	0.62
Borderline personality disorder n (%)	4 (4.0)	3 (3.2)	0.34	0.49
Eating disorders n (%)	7 (6.9)	7 (7.5)	0.12	0.81
Cannabis n (%)	15 (14.9)	16 (17.2)	0.29	0.64
Opiates n (%)	2 (2.0)	5 (5.4)	1.61	0.21
Cocaine n (%)	5 (5.0)	6 (6.5)	0.12	0.81
Alcohol n (%)	24 (23.8)	20 (21.5)	0.31	0.71
Other substance use n (%)	9 (8.9)	3 (3.2)	2.85	0.13
Rapid cycling before baseline n (%)	2 (2.0)	7 (7.5)	3.37	0.07
History of psychotic symptoms n (%)	61 (60.4)	60 (64.5)	0.35	0.55

History of suicide attempts n (%)	17 (16.8)	10 (10.8)	1.49	0.22
Dominant polarity of previous disease n (%): Depressive Manic None Not known	 15 (14.9) 56 (55.4) 25 (24.8) 5 (5.0)	 20 (21.5) 44 (47.3) 28 (30.1) 1 (1.1)	4.67	0.20
Age at the date of informed consent, mean	48.90 (14.37)	47.52 (12.85)	0.71	0.48
Age at first diagnosis of BD I, mean	35.84 (13.88)	33.60 (13.23)	1.15	0.25
Age at first episode, mean	33.97 (13.65)	32.66 (11.99)	0.71	0.48
Total number of depressive episodes mean	3.19 (5.32)	3.33 (4.37)	-0.21	0.84
Total number of manic episodes (current excluded), mean	3.98 (5.40)	3.67 (3.75)	0.47	0.64
Total number of mixed episodes, mean	0.97 (2.62)	1.30 (2.60)	-0.88	0.38
Total number of hypomanic episodes mean	3.09 (11.29)	1.86 (3.43)	1.01	0.32
Number of suicide attempts, mean	1.59 (0.80)	1.60 (0.70)	-0.04	0.97
Number of hospitalizations over the last 12 months, mean	1.06 (0.81)	1.16 (0.93)	-0.50	0.62
Number of forced treatments over the last 12 months, mean	0.67 (0.49)	1.00 (0.82)	-1.12	0.28

Table 5 - Comparison of MADRS, YMRS, FAST and CTQ scores between dominant cyclothymic-depressive-anxious and hyperthymic temperamental subtypes in 194 BD I patients experiencing a manic episode.

	Mean		t	*p*
	Hyperthymic (n=101)	Cycl-Dep-Anx (n=93)		
MADRS Total Score				
Baseline	12.91 (5.86)	12.87 (7.11)	1.44	0.97
Final	5.58 (6.26)	7.76 (7.78)	0.45	**0.03**
YMRS Total score				
Baseline	28.97 (9.78)	26.99 (9.34)	1.44	0.15
Final	5.12 (6.24)	4.75 (4.92)	0.45	0.65
FAST Baseline				
Total score	38.64 (17.13)	40.02 (15.40)	-0.59	0.56
Autonomy	6.20 (3.71)	6.49 (3.39)	-0.57	0.57
Occupation	8.97 (5.14)	9.44 (4.62)	-0.64	0.52
Cognitive	7.94 (4.36)	8.21 (3.83)	-0.45	0.65
Financial	3.67 (1.89)	3.49 (1.95)	0.67	0.51
Social	9.62 (4.85)	9.82 (4.52)	-0.30	0.76
Leisure	3.15 (1.94)	3.41 (2.08)	-0.88	0.38
FAST Final				
Total score	17.38 (13.96)	25.34 (15.92)	-3.70	**0.00**
Autonomy	2.47 (2.84)	3.76 (3.23)	-2.93	**0.00**
Occupation	5.11 (4.55)	7.41 (4.95)	-3.19	**0.00**
Cognitive	2.92 (3.32)	4.57 (3.58)	-3.33	**0.00**
Financial	1.27 (1.54)	1.83 (1.95)	-2.21	**0.03**
Social	4.07 (3.68)	6.10 (4.09)	-3.57	**0.00**
Leisure	1.79 (1.62)	2.57 (1.85)	-3.1	**0.00**
CTQ				
Total score	44.80 (10.74)	48.73 (13.33)	-2.25	**0.03**
Emotional abuse	8.25 (3.69)	9.73 (4.44)	-2.53	**0.01**
Physical abuse	6.61 (2.93)	7.41 (3.95)	-1.60	0.11
Sexual abuse	6.09 (2.59)	6.41 (3.04)	-0.79	0.43
Emotional neglect	12.00 (4.17)	13.26 (4.82)	-1.94	**0.05**
Physical neglect	11.85 (2.07)	12.02 (2.37)	-0.54	0.59