Research paper

Relationship of comorbid personality disorders to prospective outcome in bipolar disorder

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ABSTRACT

Introduction There is a high incidence of Axis II personality disorders (PDs) in patients with bipolar illness, but their influence on the prospectively measured course of bipolar disorder has been less well explicated.

Methods 392 outpatients with bipolar disorder gave informed consent, completed the PDQ4 99 item personality disorder rating, and where clinically rated during at least one year of prospective naturalistic treatment. They were classified as Well on admission ($N = 64$) or Responders ($N = 146$) or Non-responders ($N = 182$) to treatment for at least six months.

Results Patients who were positive for PDs were very infrequently represented in the category of Well on admission. In addition, patients with borderline, depressive, and schizoid PDs were significantly more likely to be Non-responders compared to Responders upon prospective naturalistic treatment in the network.

Conclusions Patients with bipolar disorder and comorbid PDs were in general less likely to be Well from treatment in the community at network entry or to be a Responder to prospective treatment in the network. Therapeutic approaches to patients with PDs deserve specific study in an attempt to achieve a better long-term course of bipolar disorder.

1. Introduction

Personality disorders (PD) are among the most frequent disorders treated by psychiatrists, and their evaluation is important as they are typically associated with a more adverse course of most Axis I disorders (Zimmerman et al., 2005). This is also true for PD occurring in patients with bipolar disorder where their presence is associated with an earlier age at onset, longer episodes, and less time euthymic, and increased rates of substance abuse, suicidality, and aggression (Latalova et al., 2013).

There is a higher incidence of what used to be called Axis II personality disorders in DSM-IV (Zimmerman, 2012) in patients with bipolar illness based on self ratings on the Personality Diagnostic Questionnaire-4 (PDQ4+) performed when patients are depressed compared to euthymic (Post et al., 2018a). We also found that the total burden of scores on the PDQ4 was related to an increased incidence of 5 of 6 poor prognosis factors that are associated with a poor long term outcome, including: adversity in childhood; early age of onset; more anxiety comorbidity; and more episodes and rapid cycling (Post et al., 2018b) Each of the separate PDs was more prevalent in patients from 4 sites in the US (Los Angeles, Dallas, Cincinnati, and Bethesda) than those from the 3 sites in Europe (Utrecht, the Netherlands and Freiburg and Munich, Germany) (Post et al., 2018c). Several of these PDs including depressive, histrionic, negativistic, obsessive compulsive, and

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schizoid remained significantly greater in the US patients than the Europeans even when Inventory of Depressive Symptomology-clinician version (IDS-C) scores, age, gender, and the 6 poor prognosis factors were included in a logistic regression.

In the current manuscript we wanted to directly examine the effect of the individual comorbid personality disorders on the long term outcome of bipolar illness assessed prospectively during naturalistic treatment in our international Network (Post et al., 2010a), Patients were rated on a daily basis on the National Institute of Mental Health-Life Chart Method (NIMH-LCM). Ratings of mania and depression (none, mild, moderate, severe) were printed out graphically so they could be readily visualized and given a Clinical Global Impression-Bipolar Scale (CGI-BP) rating for a long-term outcome of 6 months of prospective treatment. We classified patients into three groups. One was those who were "Well" (N = 96; 18.3%) on admission to the Network. For this designation, they had to present as minimally or not ill at entry and then maintain this status so for at least 6 further months of follow up. 196 (37.1%) patients were called "Responders" if they were symptomatic on Network entry, but then went on to have an excellent to good long-term response for at least 6 months. These Responders included those who were rated as very much ("A" responders) or much improved ("B" responders) on CGI-BP ratings of the graphs of the daily Life Chart Method (LCM) ratings (Post et al., 2010a). 234 patients (49.6%) were classed as "Non-Responders" if they were only minimally improved (C) or not changed or worse (D) on their CGI-BP ratings over any 6-month period of their prospective treatment and follow up.

We hypothesized that compared to patients with few PDs, those with considerable PD comorbidity would fare more poorly and would have a lesser likelihood of being "Well" at Network entry or becoming a good long term "Responder" during prospective naturalistic treatment after initially being symptomatic.

2. Methods

As previously reported in more detail (Post et al., 2017, 2014, 2018a; Post et al., 2018c), outpatients average age 40 gave informed consent to be evaluated, rated, and followed in the Network, usually with weekly to monthly visits depending on their illness severity. They were diagnosed by SCID interview, and rated on each visit on the Inventory of Depressive Symptomology-Clinician version (IDS-C) (Rush et al., 1996) and the Young Mania Rating Scale (YMRS), as well as the CGI-BP (Spearing et al., 1997). They were also rated continuously for at least 1 year by a trained clinician on the NIMH-LCM for the degree of depression and mania they showed on a daily basis between each visit (Post et al., 2010a, 2010b). The ratings of depression and mania (none, mild, moderate, severe based on their degree of functional incapacity in the patients' usual family, social, educational, or occupational roles) were then printed out graphically. In this way, the long-term course of illness and response to prospective naturalistic treatment in the Network could be readily visualized and rated on the CGI-BP for the degree of overall Improvement lasting a minimal of 6 months.

CGI-BP ratings of overall improvement (Spearing et al., 1997) were performed on the 392 patients who had been rated by a clinician on the NIMH-LCM (Leverich and Post., 1996; Leverich and Post, 1998) for a minimum of 1 year so that the entire prospective course of treatment in the network could be readily visualized. Five categories of CGI-BP response for 6 months were assessed by RMP with consensus of GSL. 96 patients (18.3%) who were not ill on network entry and sustained that improvement for at least another 6 months of follow up were classified as "Well" on admission (Post et al., 2010a).

196 patients (37.1%) who had been ill on admission were rated as "Responders" if they were "very much" (A) or "much" (B) improved on the CGI-BP for at least six months during their prospective treatment (Post et al., 2010a; Post and Leverich, 2008, 2010b). A-Responders essentially achieved remission, displaying only mild depression or mania for short periods of time. B-Responders continued to show much improvement over their baseline, but still showed transient periods of residual mania or depression during their prospective course in the Network.

However, an even larger group of 234 patients (49.6%) were classified as Non-Responders as they never received a sustained CGI improvement rating over a 6-month period of more than "minimally improved" (C), or "no change" (D) or "worse". These patients may have had transient periods of moderate or marked improvement, but not on a sustained basis for a minimum of 6 months and they typically remained moderately to severely symptomatic. Both Responders and Non-Responders were treated naturalistically with an average of 2.2 medications at any one time, but the Non-Responders were exposed to many more clinical trials than the Responders experienced in an effort to find more optimal treatment responses (Post et al., 2010a).

At Network entry, patients completed a detailed questionnaire regarding a variety of demographic and course of illness variables, as previously described (Leverich et al., 2003; ; Post et al., 2010a, b) were also asked to complete the PDQ4+ (Hyler et al., 1990, 1992 2002).If patients completed the PDQ4+ (PDQ) while in a depressive state, the severity of depression IDS-C ratings acquired within 2 weeks of filling out the PDQ was used to assess the severity of their concurrent depression. We found that the total PDQ score was significantly related to 5 of 6 poor prognosis factors reported in the literature, including a history of abuse in childhood, an early age of onset of bipolar disorder, an anxiety comorbidity, and a history of 20 or more prior episodes, and rapid cycling. The relationships remained significant when they were corrected for the IDS severity of depression rating, US versus European site, gender and age at Network entry, indicating that the potential confound of depression severity at the time of PDQ assessment was not accounting for these findings.

The PDQ evaluates 1 2 separate personality disorders, each of which includes five to nine statements, scored as true or false as to whether it would "describe the kind of person you are… Think about how you have tended to feel, think, act, over the past several years" (Hyler et al., 1990; Hyler et al., 2002). The separate personality disorders are grouped in three clusters. Cluster A is described as Odd/Eccentric and includes paranoid, schizoid, and schizotypical personality disorder. Cluster B is described as Dramatic/Emotional and includes histrionic, narcissistic, borderline and antisocial personality disorder. Cluster C is described as Anxious/Fearful and includes avoidant, dependent, and obsessive-compulsive disorder.

We then examined the effect of each PD on the distribution of Well, AB Responders, and CD Non-responders by Chi square. Since the statistical significances of the analysis of the three groups appeared highly dependent on the low percentages of PDs in the Well category, we re-ran the Chi squareanalysis using only those who presented ill on admission and then considered either AB Responders or CD Non-Responders so that we could better ascertain the effect of PDs on whether these patients were able to go on or not to experience a good long term response (for at least 6 months) to prospective naturalistic treatment.

3. Results

Patients who were positive for any of the specific personality disorders (PDs) assessed had less good outcomes. That is, there were fewer of them in the Well and AB Responder categories, and more in the CD Non-responder group than those who were negative for each PD. The Chi square for the distribution of PDs among the 3 response groups was highly significant ($p < 0.01$ to 0.0001) for 7 of the 12 PDs assessed, as illustrated in Table I (columns 4 and 5). These included avoidant, borderline, dependent, negativistic, depressive, paranoid, and schizoid. The distributions were not significant for antisocial, histrionic, narcissistic, obsessive compulsive, and schizotypal PDs.

These results appeared highly dependent of the distribution in the

Table I
The effect of the presence of a comorbid personality disorder on the long-term outcome in 392 patients with bipolar disorder.

	Well n = 64	AB n = 146	CD n = 182	With Well Chi S	With Well p value	AB vs. CD Chi S	AB vs. CD P value
Antisocial	4.70%	6.80%	7.10%	0.48	0.79	0.01	0.92
Avoidant	28.10%	50.70%	53.80%	13	**< 0.005**	0.33	0.57
Borderline	10.90%	31.50%	43.40%	22.8	**< 0.0001**	**4.86**	**< 0.05**
Dependent	0.00%	14.40%	12.60%	9.9	**< 0.01**	0.21	0.64
Depressive	9.40%	41.10%	61.50%	53.7	**< 0.0001**	**13.57**	**< 0.0005**
Histronic	10.90%	14.40%	13.20%	0.46	0.8	0.1	0.75
Narcisstic	3.10%	11.60%	9.30%	3.9	0.14	0.46	0.5
Negativistic	27.80%	28.10%	31.90%	6.2	<**0.05**	0.55	0.46
Obsessive Compulsive	29.70%	45.20%	45.60%	5.4	0.067	0.01	0.94
Paranoid	7.80%	26.00%	25.30%	9.7	**< 0.001**	0.02	0.88
Schizotypal	4.70%	13.00%	15.90%	5.3	0.07	0.55	0.46
Schizoid	4.70%	13.70%	26.40%	18.1	**0.0001**	**7.92**	**< 0.005**

The first 3 rows reflect the percentage of patients with a given personality disorder who were either Well (at network entry), or Responders (AB) or Non-responders (CD) to prospective naturalistic treatment (for at least 6 months). The next 2 rows indicate the Chi Squares and p values when all 3 groups were compared. The last 2 rows in indicate the Chi Squares and p values when only the Responders (AB) are compared to the Non-responders (CD) in the 328 outpatients with bipolar disorder who were ill upon Network entry in order to more specifically assess the relationship of PDs to prospective response in the network.

"Well" category as very few patients with a PD achieved this Well status, which largely reflected how well they had done in treatment in the community prior to joining the Network (although they then would have continued to maintain that good outcome for another 6 months of prospective evaluation to considered in this Well category). In fact, fewer than 11% of the patients in the Well category had any of the PD, with the exception of somewhat higher percentages (25–30%) in avoidant, negativistic, and obsessive compulsive PDs.

In order to more directly assess how patients who had been symptomatic on admission and then went on to respond or not to prospective treatment in the Network, we directly compared only the AB Responders to the CD Non-responders (Table I, last two columns on the right). In this more direct comparison of responsiveness to prospective treatment, three of the PDs continued to show a significant effect where lower percentages of PDs were associated with the AB Responders and higher percentages with the CD Non-Responders. These 3 PDs associated with a poor response to prospective naturalistic treatment included those with: borderline PD; depressive PD; and schizoid PD. These 3 PDs were present in 25%–62% of the Non-Responsive patients.

4. Discussion

Patients with personality disorders (PDs) had poorer outcomes than those without PDs. Those without many PDs, were much more likely to be "Well" on Network entry which was largely a reflection of how they had done with prior treatment in the community, although this had to be extended for another 6 months of prospective treatment and follow up for them to meet this Well designation. There were similar trends for those with few PDs to more often be good AB Responders to prospective naturalistic treatment in the Network. However, when only the Responders and Non-Responders were compared directly, three PDs (borderline, depressive, and schizoid) occurred significantly more frequently in the Non-Responders compared to the Responders.

This indicated that among the group of patients who were ill on admission, that these three PD were most closely associated with those who would not go on to have a good long term response to prospective naturalistic treatment for 6 months. This would be the case despite multiple attempts and even more clinical drug trials than in the Responders to try to find effective long term treatment strategies (Post et al., 2010a).

Our data are consistent with a substantial literature in both unipolar (Glilo et al., 2010) and bipolar disorders (Latalova et al., 2013) that the presence of a comorbid PD is a risk factor for a poor outcome (Carpenter et al., 1995; Crawford et al., 2008; Kay et al., 1999, 2002; Kutcher et al., 1990). However, our study is novel in that the assessment of long-term treatment response was based on prospectively

assessed longitudinal clinician ratings during naturalistic treatment and not based on retrospective data or on one or more cross-sectional rating instruments. The choice of a long term treatment outcome that had to be evident for at least 6 months also places this study in a novel perspective as it represents a highly conservative measure of persistent clinical Response and not one acutely assessed by a usual measure such as transient improvement or lack of relapse for 2 months.

Moreover, since the NIMH-LCM measures of severity of depression and mania are based on clinicians' assessment of the degree of associated incapacity in the patients' usual roles, this measure of Response directly reflects not just symptomatic improvement, but also good functioning, which is increasingly considered a most important outcome measure. Thus, our main outcome measure for clinical response reflects not only fewer and less severe mood symptoms and episodes, but good functioning as well.

The three PDs (borderline, depressive, and schizoid) that most robustly were associated with a lack of a good response (i.e. CD Non-Responders) are of some interest. Borderline is one of the most frequent PDs in patients with bipolar disorder, and consists of multiple characteristics which could make treatment more difficult, including difficulty with maintaining interpersonal relationships (which could extend to the treating physician), mood lability and dysregulation, anger dyscontrol, and proneness to substance abuse (Afifi et al., 2011; Barnett et al., 2011; Carpenter et al., 1995; Goodwin and Jamison, 2007). Which of these or other components of the borderline PD profile are most closely associated with a more difficult outcome in bipolar disorder remains to be better delineated.

Borderline PD has some features, such as affective instability, impulsivity, and self-mutilation/suicidality that overlap with rapid cycling bipolar disorder and have been found to be correlated with the frequency of episodes occurring over 1 year of prospective treatment (Riemann et al., 2017). However, 6 of the other 9 core features of borderline PD, such as avoiding abandonment, interpersonal instability, identity disturbance, chronic emptiness, intense anger, and paranoid/dissociation are not related to the frequency of mood episodes occurring in bipolar disorder. Since borderline PD and rapid cycling bipolar disorder are sometime difficult to distinguish, these later 6 characteristics thus become a way of differentiating the two disorders even though affective instability, impulsivity, and self-mutilation/suicidality are the features most closely related to episode frequency (Riemann et al., 2017).

Our findings of depressive PD being associated with more long term treatment Non-Response would not be unexpected, as dysthymic baselines and PDs have been associated with increased risk for depressive recurrences in bipolar and unipolar disorder (Glilo et al., 2010). The persisting effect of higher percentages of schizoid PD

relating to long term Non-Response in our bipolar patients treated in the Network would be consistent with multiple perspectives. These might include that schizoid PD is associated with lesser amounts of the personality traits such as outgoingness and social connectedness that can have a positive effect on outcome in bipolar disorder (Quilty et al., 2009). Schizoid PD is also associated with a limited range of emotional expression, the preference for doing things alone, and social withdrawal which could impair treatment response. These later features suggest some shared features with schizophrenia or schizoaffective disorder, which also often have a difficult outcome.

These findings relating PDs to a poor outcome measured prospectively by clinicians dovetail well with our previous findings that PDs are associated with many patient-rated factors that have been related to difficult course of illness, including childhood adversity, early age of onset of bipolar disorder, anxiety comorbidity, more episodes and rapid cycling (Post et al., 2018b). This convergence of prospective and retrospective findings indicates the clinically and statistically significant role of baseline measures of PDs relating to an adverse course and outcome of bipolar disorder.

However, there are several caveats and limitations to the interpretation of these data. Notably, the personality disorder diagnoses used here were based on self-ratings on the PDQ4 which tend to inflate the incidence of personality disorders compared to those based on structured interviews (Dowson, 1992; Hunt and Andrews, 1992; Hurt et al., 1984; Hyler et al., 1990; Zimmerman and Coryell, 1990). However, even if the self-ratings are somewhat inflated compared to diagnoses obtained from direct interviews, the relatively poor outcomes of those with higher compared to lower PDQ scores would still be clinically informative.

Despite repeated reminders on each page of the PDQ4 form to rate each of the 99 true and false questions from a long term perspective (i.e. to reflect persisting personality characteristics rather than state dependent traits related episodes of illness), ratings of essentially all of the PDs were higher when patients completed the forms while depressed compared to euthymic (Post et al., 2018a). Thus, the degree of depression at the time of completing the PDQ4 forms likely colored and confounded the perspective that these personality characteristics should have been present prior to illness onset and/or persist between episodes if depression. Yet when we corrected and co-varied for the severity of depression at the time of the PDQ4 ratings, most of the relationships to poor outcome characteristics were maintained (Post et al., 2018b). Nonetheless our results should be viewed tentatively until they are replicated using clinician acquired PD diagnoses.

In this manuscript, we have used the DSM-IV approach which refers to specific Axis II PD and not the multiaxial ones suggested in DSM-5 (Zimmertman, 2012). Also, how the relationships we have examined would persist or not in countries where English was not a mainstream language is not known.

In addition, we also did not re-assess the PDs at the end of the Well or Response periods so we cannot definitively say whether the PDs improved or remained stable with recovery. However, we did see that the PDQ4 ratings were significantly correlated with severity of depression and repeat rating when patients were euthymic were correlated with those at baseline (Post et al., 2018a).

Another major limitation is that we did not have data on what psychotherapeutic strategies were utilized along with the pharmacological approaches. Also, we could not assess to what extent targeted therapies were utilized in those with more versus less PDs. However, clinicians were essentially "blind" to the quantitative aspects of the PDQ-4 during treatment unless they made their own clinical assessments of this aspect of the patients' condition. This was because the PDQ-4 rating were collated and analyzed after patients had left the network. Moreover, the literature is sparse as to what more optimal treatments might be for those with greater amounts of PD so it is unlikely that there were systematic differences in how these patients were treated.

One might also question the choice of 6 months as the duration of time in order to be considered as a Good Responder on CGI-BP ratings of the NIMH-LCM life chart graphs (Post et al., 2010a). This was an arbitrary choice which we thought would most likely represent a real long-term pharmacological response and not just a transient within course of illness variation. That is, 6 months would in high percentage of cases represent a duration of time exceeding patient's usual well-intervals and thus likely reflect real long-term improvement.

The ambiguity of which components of the spectrum of PDs lead to a poor outcome also extends to the conundrum of whether the PDs are a separate and additive syndromes to bipolar disorder or ones that has overlapping symptoms and vulnerability factors (de la Rosa et al., 2017). For example there is a high incidence of adversities in childhood in those with borderline PDs, which have been thought to be of etiological significance (Afifi et al., 2011). At the same time adversities in childhood are also associated with earlier onsets of bipolar disorder and a more pernicious course of bipolar disorder (Post et al., 2017, 2013), such that the comparative contributions of PDs themselves and their correlates with early onset and abuse in childhood become difficult to disentangle.

It is also possible that patients with a high burden of PD could be less adherent to pharmacotherapy (although we have no data to support this possibility). However, given the strong association of PD to the poor prognosis factors of early onset and history of adversity in childhood (Post et al. 2018b), efforts more specifically directed at these targets may be fruitful. Psychotherapy is more effective than pharmacotherapy in those with a history of childhood adversity in unipolar depression (Nemeroff et al., 2003). Moreover, it is possible that some pharmacotherapies may emerge as more effective in those with childhood adversity since such a history is associated with a greater lowering of acetyl-L-carnitine (LAC) in the blood of depressed patients, and treatment with LAC has shown promise as an antidepressant (Nasca et al., 2018; Post, 2018). Such a possibility as this and other targeted psychotherapeutic and pharmacotherapeutic strategies remain important areas for future clinical study.

Goldstein et al. (2015) found that dialectical behavior therapy (DBT) which was developed for patients with borderline personality disorder was more effective than treatment as usual (TAU) in adolescents with bipolar disorder. DBT was associated with greater treatment engagement and adherence and less severe depressive symptoms. Emotional dysregulation, suicidality, and functioning also improved nonsignificantly. Many of these symptom areas overlap with PD, histories of child adversity, and early age of onset of bipolar, so further study of the effectiveness of DBT in targeting these common features of bipolar disorder is clearly indicated.

Despite the limitations and cautions noted, it would appear that our data remain clinically informative, and suggest the utility of further assessment of PDs in relationship to clinical outcome in patients with bipolar disorder. In particular the findings emphasize the need for further study of what might be the most appropriate treatment strategies for those with a high burden of comorbid PDs in an attempt to achieve more favorable outcomes.

Declaration of Competing Interest

Dr. Post has spoken for Sunovion, Tekada, and will speak for Jannsen. Others' COI off their most recent submission

Author statement

All of the coauthors were involved in the design, conduct, assessment, and interpretation of these data

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