Personality disorder among youth with first episode psychotic mania: An important target for specific treatment?

Running title: Personality disorder in first episode mania

Melissa K Hasty [a], Craig A Macneil[a], Sue M Cotton [a,b], Michael Berk [a,b,c,d,e], Linda Kader[a], Aswin Ratheesh [a,b], Julie Ramain[f]*, Andrew M. Chanen[a,b], Philippe Conus [a,f]

[a] Orygen, Melbourne, Australia

[b] Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia

[c] Deakin University, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia

[d] Department of Psychiatry, The University of Melbourne, Parkville

[e]Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville,

[f] Treatment and Early Intervention in Psychosis Program (TIPP), Service of General Psychiatry, Department of Psychiatry CHUV, Lausanne University, Switzerland

* Corresponding author: Julie Ramain. Lausanne University Hospital (CHUV), Place Chauderon 18, 1003 Lausanne, Switzerland. Email: julie.ramain@chuv.ch

ABSTRACT

Aim: Personality disorder is a common co-occurrence ('comorbidity') among patients with bipolar disorder and appears to affect outcome negatively. However, there is little knowledge about the impact of this comorbidity in the early phases of bipolar disorder. We examined the prevalence and effect of personality disorder co-occurrence on outcome in a cohort of youth with first episode mania with psychotic features.

Methods: Seventy-one first episode mania patients, aged 15 to 29, were assessed at baseline, 6, 12, and 18 months as part of a randomized controlled trial of olanzapine and chlorpromazine as add-on to lithium in first episode mania with psychotic features. The current study involved secondary analysis of trial data.

Results: A co-occurring clinical personality disorder diagnosis was present in 16.9% of patients. Antisocial and narcissistic personality disorder were the most common diagnoses. Patients with co-occurring personality disorder had higher rates of readmission to hospital, lower rates of symptomatic recovery and poorer functional levels at 6 months, but these differences disappeared after 12 and 18 months.

Conclusions: In the early phase of bipolar disorder, patients with personality disorder comorbidity display delayed symptomatic and functional recovery and increased likelihood to need hospital readmissions. These observations suggest that routine assessment for personality disorder and specific interventions are important in order to improve short-term treatment efficacy in this subgroup.

Keywords: bipolar disorder, depression, first episode, mania, personality disorder.

INTRODUCTION

Personality disorder (PD) commonly co-occurs among people with bipolar disorder (BD), with an estimated prevalence between 20% and 80% (Carpenter, Clarkin, Glick, & Wilner, 1995; Zimmerman, Balling, Chelminski, & Dalrymple, 2020; Zimmerman & Morgan, 2013). A recent systematic review (Bezerra-Filho et al., 2015) identified that 41.2% of euthymic BD patients had at least one co-occurring ('comorbid') PD. This wide variability in reported prevalence of PD among individuals with BD might be influenced by differences in the method of assessment, the measures used, and potential effects of mental state features upon the assessment of personality pathology (George, Miklowitz, Richards, Simoneau, & Taylor, 2003). Diagnosis of PD might also be difficult in people with BD because of ambiguity or similarities among diagnostic criteria for BD and PD (Blacker & Tsuang, 1992; Ghaemi & Barroilhet, 2015; Zimmerman & Morgan, 2013). Nonetheless, these data suggest that the prevalence of PD among people with BD is considerably higher than among the general population, which is estimated to be 9.6% in high-income countries (Quirk, Berk, et al., 2016; Winsper et al., 2020).

Few studies have focused upon PD co-occurrence in the early phase of BD (Yen et al., 2015). A key challenge in studying this phase of disorder is that both personality and mood-related psychopathology become clinically apparent from puberty through to young adulthood, frequently co-occur, can reinforce one another (presence of one disorder leading to the amplification of the manifestations of the other), and can be difficult to differentiate clinically due to some similarities in symptomatology such as irritability, impulsivity and mood instability for example (Chanen, Berk, & Thompson, 2016). Kutcher, Marton, and Korenblum (1990) assessed 20 euthymic bipolar teens and found that 35% met DSM-III-R criteria for at least one PD. The group with BD and PD differed significantly from the BD without PD group in terms of increased

lithium unresponsiveness and neuroleptic treatment at time of personality assessment, but not in terms of age, sex, age of illness onset, serum lithium level, rapid cycling, substance abuse history, alcohol abuse history, or number of suicide attempts.

Some data are available for older samples with first episode mania (FEM). Dunayevich et al. (1996) compared rates of comorbid PD among adult in-patients with FEM (mean age 27 years) and individuals who had experienced multiple episodes of mania (mean age 43 years). They found that the prevalence of PD in the first-episode group (33%) was half that of the multi-episode group (65%). Pica et al. (1990), examined rates of PD among 26 inpatients with recent-onset BD and schizoaffective disorder (bipolar type). Using a structured interview after affective symptoms had stabilized, they observed that 62% of their sample were diagnosed with comorbid PD, mostly belonging to DSM-III Cluster B.

PD can have adverse effects upon treatment outcomes for a wide range of mental state (formerly Axis I) disorders (Hasin et al., 2011; Skodol et al., 2011). For BD, the presence of a concurrent PD has been associated with an increased likelihood of hospitalization, longer time to symptom stabilization, more chronic impairments in social and occupational functioning, greater medical comorbidity, increased levels of suicidality, and greater utilization of psychiatric services (Bieling et al., 2003; Quirk et al., 2017; Quirk, Stuart, et al., 2016; Zimmerman et al., 2020). Co-occurring PD has also been found to be a significant predictor of mood episode severity (Post et al., 2018), medication non-adherence (Colom et al., 2000), and higher risk of relapse (Gasperini, Scherillo, Manfredonia, Franchini, & Smeraldi, 1993), although a study reported no effect on functional outcome (Kavanagh, Williams, et al., 2019).

Data on the effects of co-occurring PD in the early phase of BD are scarce. In a recent publication, Ng et al. (2017) reported that amongst individuals with BD, both the presence and the severity of PD symptoms (mainly cluster B and C) are correlated with the rate of onset of a manic/mixed episode and of conversion from less severe BD to bipolar I disorder. Dunayevich et al. (2000) reported that while all FEM patients had similar symptomatic and functional outcome 12 months following discharge from hospital, those with co-occurring PD had poorer syndromal recovery (8 contiguous weeks without a depressive, mixed, or manic syndrome).

In summary, little is known about the prevalence of PD co-occurrence among younger patients, who are closer to the usual average age of onset of a FEM. Also, the little data available suggest that PD might have a negative influence upon patients' outcomes in early phase of BD. There is a need to clarify the effect that co-ocurring PD might have on the outcomes of clinical trials (Kavanagh, Brennan-Olsen, et al., 2019). Indeed, while the early phase of non-affective psychoses has received extensive attention, research focusing on the early phase of affective psychoses is much more limited (Conus & McGorry, 2002), despites their public health significance (Conus, Macneil, & McGorry, 2014); the identification of factors that may influence outcomes is therefore important (Conus et al., 2010).

In this context, the current study had two aims: (i) to report the prevalence of co-occurring PD in adolescents and young adults who present with a first episode of psychotic mania; and (ii) to examine the effects that co-ocurring PD has on short-term treatment outcomes. We hypothesized that individuals with co-occurring PD would have poorer outcomes across the treatment period, compared with individuals without a co-occurring PD.

METHOD

Participants and Setting

The study includes 71 participants (68% males), aged between 15-29 years, who attended the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia(October 2001-February 2006). At entry, these patients met DSM-IV criteria (American Psychiatric Association, 1994) for a FEM with psychotic features and had a minimum baseline score of 20 on the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). All participants received a diagnosis of either BD I or schizoaffective disorder at 12- and 18-month follow-up.

All participants were drawn from a larger randomised controlled trial (RCT), which compared olanzapine versus chlorpromazine as an adjunct to lithium for the treatment of a first manic or mixed episode with psychotic features (Conus et al., 2015). The study was approved by the Melbourne Health Research and Ethics Committee and participants provided written informed consent.

Participants were prospectively evaluated using diagnostic, symptomatic, and functional assessments over 18 months by research assistants. They received 18 months of treatment, provided by both a clinical psychologist and a psychiatrist, which included assertive case management, regular medical reviews, and pharmacological treatment.

Exclusion criteria were as follows: (i) immediate risk of harm to self or others at commencement of the RCT; (ii) use of neuroleptic medication or mood-stabilisers in the two months preceding admission to EPPIC; (iii) presence of organic mental disease, including intellectual disability: (iv) having a history of clinically significant medical illness (liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological or metabolic disturbances), clinically relevant biochemical or haematological abnormalities; (v) being pregnant or lactating; (vi) having a history of epilepsy, a severe drug allergy or hypersensitivity; and/or (vii) having insufficient fluency in English.

Measures

The Structured Clinical Interview for DSM-IV Axis I disorders-patient version (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2007) was completed at 8 weeks, 12 and 18 months to ensure stability of diagnosis. PD diagnoses were based on a consensus process involving two senior psychologists (MH & CM), a senior psychiatrist (LK) and the clinical case manager involved in patient's treatment. Diagnoses were made using DSM-IV diagnostic criteria, and were derived from data obtained through longitudinal follow up by each participant's treating team and from information provided by family. A conservative approach was taken, whereby diagnosis of PD was made only if the patient met full criteria, outside of significant episodes of mood disturbance. Individuals who presented with sub-syndromal PD were not included in the PD group. The presence or absence of co-occurring PD was used as a dichotomous variable.

The outcomes of interest included remission of mood symptoms, occupational functioning, relapse, and medication adherence. These variables were dichotomised for analysis (e.g., remission of manic symptoms achieved/not achieved). The YMRS and the Hamilton Depression Rating Scale (HAMD-21; Hamilton, 1967) were used as measures of remission from mood symptoms. In line with usual cut-offs, YMRS score of <12, and a HAMD-21 score of <8 were considered as remission from manic and depressive syndrome respectively. The outcomes were assessed by Research Assistants who were not aware of the PD diagnostic status. The Brief Psychiatric Rating Scale was used to assess symptoms, either as a global score or as psychotic symptom scores on the sub-scales (BPRS; Overall et al., 1962).

Vocational/education status was assessed using the Modified Vocational Status Index (Tohen et al., 2000). Occupational functioning was defined as engagement in either full or part time (>30 hours/week) work or studies. We assessed functioning with the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994), and Social and Occupational Functioning Scale (SOFAS; American Psychiatric Association, 1994). Relapse was identified when there was intervention (including increase in medication, hospital admission, emergency visit, acute services involvement) for a mood or psychotic episode. Total number of mood episodes included the index episode plus any relapses and switches to a different mood episode.

Data Analysis

Descriptive statistics including means, standard deviations (*SD*s), frequencies, and percentages are presented for each PD to depict the characteristics of the patients. To assess the relationship

between the presence of comorbid PD and outcomes following a FEM, a series of logistic regression analyses were conducted with PD (present/absent) as the dependent variable, and the individual demographic and outcome variables as independent variables. From these analyses, odds ratios (*OR*) and the 95% confidence intervals (CI) of the *OR*s were derived. The Wald statistic (*z*) was used to determine significance of associations. Last observation carried forward was used for missing data at follow-up time points.

RESULTS

Prevalence of comorbid personality disorders

Data were available for 71 participants. Figure 1 shows the demographic characteristics of the two groups and the frequency for each PD. Twelve (16.9%) of the participants were diagnosed with a PD (8 males (16.7% of the males) and 4 females (17.4% of the females)), with two of these participants meeting criteria for two PDs (both males, with antisocial and narcissistic PD). The most common PD diagnoses were antisocial and narcissistic PD.

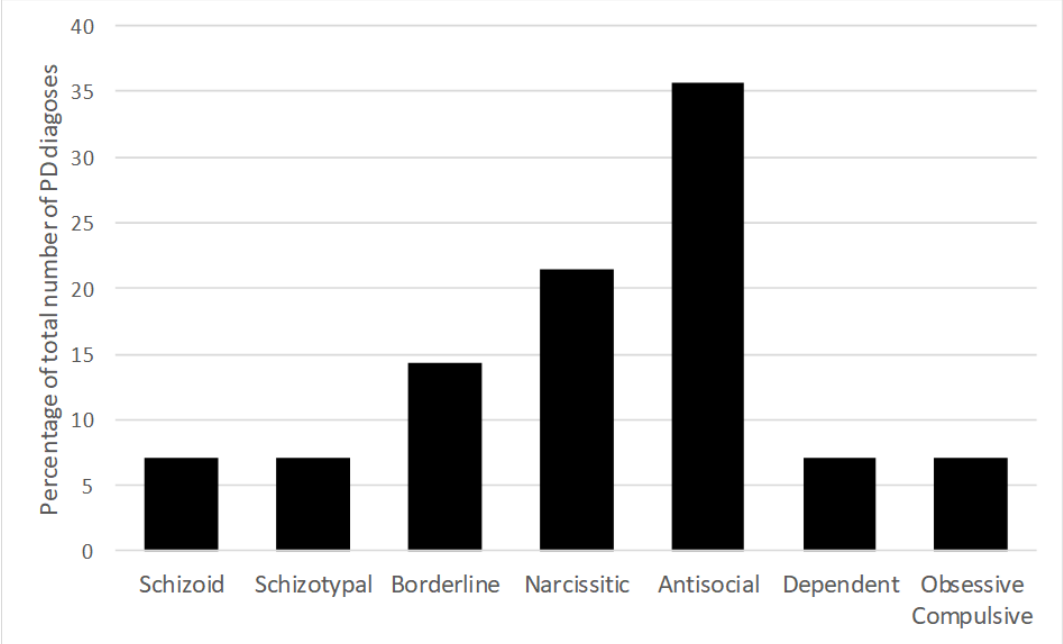

Figure 1. Types of PD based on total number of PD diagnoses (*n*=14).

Demographic and baseline characteristics

Demographic and baseline characteristics of patients with and without co-occurring PD are reported in Table 1. Bivariate logistic regression analyses indicated that there were no significant group differences in age, gender, education, unemployment, baseline symptoms or functioning, substance use disorder (SUD) at baseline, or history of trauma or suicide attempts. Symptom intensity (BPRS scores) was similar in both sub-groups at baseline regarding global symptomatology (t(69)=-0.35, p=.728), and positive psychotic symptoms (t(69)=-0.10, p=.921.)

Table 1. *Demographic and baseline characteristics of those with BD with and without comorbid PD.*

		Comorbid PD					
		Yes	No		95% CI		
	Statistic	(n=12)	(n=59)	OR	Lower	Upper	*p*-value
Age (years)	M(SD)	21.2(2.2)	21.5(3.0)	0.96	0.77	1.20	.710
Gender %Female	%(n)	33.3(4)	32.2(19)	1.05	0.28	3.94	.939
Years in school	%(n)	11.7(1.5)	11.7(1.5)	0.99	0.65	1.49	.942
Unemployed	%(n)	18.2(2)	40.7(24)	0.32	0.06	1.63	.172
YMRS	M(SD)	35.8(7.4)	35.7(7.4)	1.00	0.92	1.09	.993
HAMD-21	M(SD)	7.4(5.2)	8.4(6.6)	0.97	0.88	1.08	.625
GAF	M(SD)	30.6(9.8)	31.5(11.1)	0.99	0.93	1.05	.778
SOFAS	M(SD)	34.4(13.7)	35.5(11.7)	0.99	0.94	1.04	.782
SUD	%(n)	40.0(4)	45.2(14)	0.81	0.19	3.45	.775
Hx of trauma	%(n)	72.7(8)	67.9(36)	1.26	0.30	5.35	.755
Hx of SA	%(n)	27.3(3)	10.7(6)	3.13	0.65	15.08	.156

CI, confidence interval; *p<0.05;**p<0.01; OR, odds ratio; YMRS, Young Mania Rating Scale; HAMD-21, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning Scale; SOFAS, Social and Occupational Functioning Scale; SUD, substance use disorder; Hx, history; SA, suicide attempt.

Outcomes

Comparison of outcomes, over the 18-month follow-up between patients with and without co-occurring PD, are reported in Table 2.

At 6-month follow-up, patients with co-occurring PD were less likely to have reached remission of manic (z=7.81, p=.005) and depressive (z=5.06, p=.024) symptoms. In addition, these patients had significantly poorer functional levels at 6 months based on the SOFAS (z=4.86, p=.027) and GAF (z=6.87, p=.009). These differences however were not apparent at 12 and 18 months. Finally, these patients had more inpatient admissions overall than those who did not have a co-occurring PD (z=7.59, p=0.006).

Table 2. *6, 12, and 18 month outcomes of those with BD with and without comorbid PD*

		Comorbid PD					
		Yes	No		95% CI		
Variable of interest	Statistic	(n=12)	(n=59)	OR	Lower	Upper	*p*-value
Remission on YMRS							
6 months**	%(n)	54.5(6)	91.1(51)	0.12	0.03	0.53	.005
12 months	%(n)	88.9(8)	72.7(40)	3.00	0.35	26.06	.319
18 months[1]	%(n)	100.0(10)	77.4(41)				
Remission on HAMD-21							
6 months*	%(n)	36.4(4)	73.2(41)	0.21	0.05	0.82	.024
12 months	%(n)	55.6(5)	75.9(41)	0.40	0.09	1.70	.213
18 months	%(n)	87.5(7)	76.5(39)	2.15	0.24	19.3	.493
GAF							
6 months**	M(SD)	51.5(16.2)	64.3(12.0)	0.93	0.89	0.98	.009
12 months	M(SD)	55.7(15.1)	61.8(16.6)	0.98	0.94	1.02	.265
18 months	M(SD)	58.9(13.8)	63.4(16.3)	0.98	0.94	1.02	.416
SOFAS							
6 months*	M(SD)	55.2(17.3)	65.4(11.6)	0.94	0.89	0.99	.027
12 months	M(SD)	55.6(13.7)	62.4(16.6)	0.98	0.94	1.01	.208
18 months	M(SD)	57.4(13.6)	63.7(17.0)	0.98	0.94	1.02	.272
Employed/studying≥30 hours/week							
6 months	%(n)	18.2(2)	50.0(27)	0.22	0.04	1.13	.069
12 months	%(n)	54.5(6)	60.7(34)	0.78	0.22	2.86	.703
18 months	%(n)	50.0(5)	65.5(36)	0.52	0.14	2.05	.357
Clinical outcomes							
≥1 relapse	%(n)	41.7(5)	56.4(31)	0.55	0.16	1.96	.359
Number of mood episodes	M(SD)	2.2(0.9)	2.0(1.0)	1.17	0.62	2.2	.631
Inpatient admissions**	M(SD)	3.0(2.2)	1.5(1.1)	1.86	1.20	2.90	.006

CI, confidence interval; *p<0.05;**p<0.01; OR, odds ratio; YMRS, Young Mania Rating Scale; HAMD-21, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning Scale; SOFAS, Social and Occupational Functioning Scale.

[1]Odds ratio could not be estimated due to 100% of PD cases achieving remission

DISCUSSION

To our knowledge, this is the first study to examine both the prevalence and outcomes for the range of co-occurring PD in first episode psychotic mania. The prevalence rate for PD observed in our cohort is almost twice that reported for general community but is substantially lower than rates reported in multi-episode cohorts. It is also noteworthy that, although Cluster B PD was the most frequent (including mainly antisocial and narcissistic PD, fewer borderline PD and no

histrionic PD), the rate of borderline PD in the current study (2.8%) was consistent with general population rates (Leichsenring, Leibing, Kruse, New, & Leweke, 2011), and is considerably lower than among other bipolar I samples, reporting rates of up to 40% (Preston, Marchant, Reimherr, Strong, & Hedges, 2004); this low prevalence could be explain in various ways. First, several authors have suggested that lower rates of co-occurring PD in the early phase of BD might indicate that the phenotype of PD develops over time as a consequence of BD. Chanen et al. (2016) have also noted that borderline and mood-related psychopathology can reinforce one another, and other authors have suggested that recurrent episodes or chronic state might induce the progressive development, or at least exacerbation, of pathological personality traits (Carpenter et al., 1995; Dunayevich et al., 1996). Second, individuals without PD might be more likely be accepted for treatment in primary care, where prevalence rates for PD are lower than in specialist mental health settings (Moran, Jenkins, Tylee, Blizard, & Mann, 2000), rather than at specialist treatment centres where previous studies have been conducted. Finally, it is possible that the higher relapse rates and more chronic course of illness among patients with PD would progressively lead to 'enrichment' of bipolar samples in specialist settings with patients displaying such comorbidity. This illustrates "Berkson's bias" (Berkson, 1946), whereby people who meet criteria for multiple disorders, compared to those with just one disorder, are more likely to be treatment seeking, and is likely to lead to inflated levels of co-occurrence.

The prevalence of co-occurring PD in this study is however lower than that reported in previous FEM studies (Dunayevich et al., 1996; Pica et al., 1990).This might be explained by the lower average age of the patients involved in our study, or by methodological and clinical setting differences. Specifically, both Dunayevich et al. (1996) and Pica et al. (1990) were based on assessment during acute episode. In contrast, our PD diagnostic procedure is based on a 18-

month longitudinal assessment, including information gathered not only with patients but also with numerous other sources (relatives), allowing a possibly more accurate distinction between 'state' and 'trait' features. Our method was consistent with that recommended by Bajaj and Tyrer (2005) who suggested that due to the potential confounding effect of state versus trait characteristics during acute bipolar episodes, the confirmation of PD diagnosis in BD patients should only occur during the euthymic phase. As such, the prevalence of PD comorbidity in the present study might be closer to what is likely to be found in centres treating youth.

Consistent with previous studies, co-occurring PD was associated with poorer outcomes early in the course of treatment, such as lower rates of remission of mood symptoms at 6 months. However, by 12 and 18 months there were no significant differences between groups. Reliable data on adherence to treatment were not available for most patients and therefore, we could not explore its influence upon outcome. Indeed, available data suggested that patients with PD are less likely to adhere to treatment, which should be explored in future studies. The observation of a higher rate of hospital admission is consistent with poorer clinical outcome, higher severity of mood episodes (Post et al., 2018), and might also be linked to differences in behaviour during relapses, mainly regarding risk of harm to self or others, which are common factors leading to inpatient admission. Lack of statistical power prevented stratifying analyses to explore if the type of PD had a differential impact on outcome.

Patients with co-occurring PD had a significantly poorer level of functioning at 6 months. Functional recovery after a FEM is generally poor and might lag behind symptom recovery (Conus et al., 2006; Strakowski et al., 1998). While targeted intervention addressing functional recovery

is an important aspect of treatment following a FEM (Macneil, Hasty, Conus, Berk, & Scott, 2010), this finding suggests it might be particularly important when PD co-occurs.

Despite some significant differences in the early phase of recovery, the current findings, consistent with Dunayevich et al. (1996), showed no difference between groups on any of the symptom or functioning measures at 12 and 18 months. Similarly, no differences were observed in the number of mood episodes or relapses rates between groups. It is possible that these encouraging findings might be attributed to the specialized comprehensive and early psychosocial intervention. Indeed, early intervention for youth with borderline PD, and for young people with BD, has been found to result in significant improvement across a broad range of outcomes (Chanen, Sharp, & Hoffman, 2017; Chanen & McCutcheon, 2013; Macneil et al., 2012). It might also be explained by a ceiling effect, BD patients without PD reaching recovery earlier but then failing to improve more, while BD patients with PD reach this level more progressively but finally close the gap and then stagnating as well.

There are various limitations to this study. First, the sample size was small and lacked statistical power to examine individual PDs and clinical phenomena of low effect size. Second, diagnosis of PD was not based on a structured diagnostic tool, such as the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 2007). However, our longitudinal and expert consensus diagnostic approach enabled us to incorporate numerous sources of information (family/patient reports, clinical observation/interaction) across 18 months, which were used in addition to specific clinical assessment regarding DSM-IV PD criteria. Westen (1997), who questioned the utility of direct questions in the assessment of PDs, suggested that the validity of PD diagnosis is

likely to be enhanced if observations and direct questions are combined. Third, this study is focused on patients with psychotic mania and therefore provides information only for this subgroup and might not be relevant to patients who present a FEM without psychotic features or with index depression. Finally, our study suggests a need for early, targeted interventions for BD patients with comorbid PD. Indeed, prolonged illness might have consequences, such as increased risk taking behaviour or exposure to negative life events and higher negative impact on caregivers and relatives (Berk et al., 2013; Perlick et al., 2016). However, such factors were not measured in the present study, and thus will need to be clarified in future research in order to develop specific interventions.

In conclusion, the prevalence of PD co-occurrence among young first-episode psychotic mania patients is greater than the population prevalence for PD. The co-occurrence of PD and BD led to delayed recovery and higher rates of hospital admissions over the treatment period, but did not lead to poorer 12- and 18-month outcomes, in the context of a specialized youth mental health service. This suggests a need for early, targeted interventions for this sub-group. Future research are required to explore the impact of such specific early interventions.

Acknowledgments

Research reported in this publication was supported by an unrestricted grant from Eli Lilly to PC. MB is supported by a NHMRC Senior Principal Research Fellowship (1059660 and 1156072). SC is supported by a NHMRC Career Development Fellowship. PC is partly supported by the Swiss National Science Foundation, NCCR SYNAPSY consortium.

Conflicts of interest

MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier – all unrelated to this work.

REFERENCES

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders, 4th ed*. Arlington, VA, US: American Psychiatric Publishing, Inc.

Bajaj, P., & Tyrer, P. (2005). Managing mood disorders and comorbid personality disorders. *Current opinion in psychiatry, 18*(1), 27-31.

Berk, L., Berk, M., Dodd, S., Kelly, C., Cvetkovski, S., & Jorm, A. F. (2013). Evaluation of the acceptability and usefulness of an information website for caregivers of people with bipolar disorder. *BMC medicine, 11*(1), 162.

Berkson, J. (1946). Limitations of the application of fourfold table analysis to hospital data. *Biometrics Bulletin, 2*(3), 47-53.

Bezerra-Filho, S., Galvao-de Almeida, A., Studart, P., Rocha, M. V., Lopes, F. L., & Miranda-Scippa, A. (2015). Personality disorders in euthymic bipolar patients: a systematic review. *Braz J Psychiatry, 37*(2), 162-167. doi:10.1590/1516-4446-2014-1459

Bieling, P. J., MacQueen, G. M., Marriot, M. J., Robb, J. C., Begin, H., Joffe, R. T., & Young, L. T. (2003). Longitudinal outcome in patients with bipolar disorder assessed by life-charting is influenced by DSM-IV personality disorder symptoms. *Bipolar Disord, 5*(1), 14-21. doi:10.1034/j.1399-5618.2003.00014.x

Blacker, D., & Tsuang, M. T. (1992). Contested boundaries of bipolar disorder and the limits of categorical diagnosis in psychiatry. *Am J Psychiatry, 149*(11), 1473-1483. doi:10.1176/ajp.149.11.1473

Carpenter, D., Clarkin, J. F., Glick, I. D., & Wilner, P. J. (1995). Personality pathology among married adults with bipolar disorder. *J Affect Disord, 34*(4), 269-274. doi:10.1016/0165-0327(95)00024-h

Chanen, A., Sharp, C., & Hoffman, P. (2017). Prevention and early intervention for borderline personality disorder: a novel public health priority. *World Psychiatry, 16*(2), 215-216. doi:10.1002/wps.20429

Chanen, A. M., Berk, M., & Thompson, K. (2016). Integrating Early Intervention for Borderline Personality Disorder and Mood Disorders. *Harv Rev Psychiatry, 24*(5), 330-341. doi:10.1097/hrp.0000000000000105

Chanen, A. M., & McCutcheon, L. (2013). Prevention and early intervention for borderline personality disorder: current status and recent evidence. *The British Journal of Psychiatry, 202*(s54), s24-s29.

Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Benabarre, A., & Gasto, C. (2000). Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *J Clin Psychiatry, 61*(8), 549-555. doi:10.4088/jcp.v61n0802

Conus, P., Berk, M., Cotton, S. M., Kader, L., Macneil, C., Hasty, M. K., . . . McGorry, P. D. (2015). Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: An 8-week randomised controlled trial. *Eur Psychiatry, 30*(8), 975-982. doi:10.1016/j.eurpsy.2015.09.009

Conus, P., Cotton, S., Abdel-Baki, A., Lambert, M., Berk, M., & McGorry, P. D. (2006). Symptomatic and functional outcome 12 months after a first episode of psychotic mania: Barriers to recovery in a catchment area sample. *Bipolar Disorders, 8*(3), 221-231. doi:10.1111/j.1399-5618.2006.00315.x

Conus, P., Cotton, S., Schimmelmann, B. G., Berk, M., Daglas, R., McGorry, P. D., & Lambert, M. (2010). Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. *Bipolar Disorders, 12*(3), 244-252. doi:10.1111/j.1399-5618.2010.00813.x

Conus, P., Macneil, C., & McGorry, P. D. (2014). Public health significance of bipolar disorder: implications for early intervention and prevention. *Bipolar Disord, 16*(5), 548-556. doi:10.1111/bdi.12137

Conus, P., & McGorry, P. D. (2002). First-episode mania: A neglected priority for early intervention. *Australian and New Zealand Journal of Psychiatry, 36*(2), 158-172. doi:10.1046/j.1440-1614.2002.00994.x

Dunayevich, E., Sax, K. W., Keck, P. E., Jr., McElroy, S. L., Sorter, M. T., McConville, B. J., & Strakowski, S. M. (2000). Twelve-month outcome in bipolar patients with and without personality disorders. *J Clin Psychiatry, 61*(2), 134-139.

Dunayevich, E., Strakowski, S. M., Sax, K. W., Sorter, M. T., Keck, P. E., Jr., McElroy, S. L., & McConville, B. J. (1996). Personality disorders in first- and multiple-episode mania. *Psychiatry Res, 64*(1), 69-75. doi:10.1016/0165-1781(96)02925-3

First, M., Spitzer, R., Gibbon, M., & Williams, J. (2007). Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition (SCID-I/P, 1/2007 Revision). *Biometrics Research, New York State Psychiatric Institute: New York*.

Gasperini, M., Scherillo, P., Manfredonia, M. G., Franchini, L., & Smeraldi, E. (1993). A study of relapses in subjects with mood disorder on lithium treatment. *Eur Neuropsychopharmacol, 3*(2), 103-110. doi:10.1016/0924-977x(93)90261-j

George, E. L., Miklowitz, D. J., Richards, J. A., Simoneau, T. L., & Taylor, D. O. (2003). The comorbidity of bipolar disorder and axis II personality disorders: prevalence and clinical correlates. *Bipolar Disord, 5*(2), 115-122. doi:10.1034/j.1399-5618.2003.00028.x

Ghaemi, S. N., & Barroilhet, S. (2015). Confusing borderline personality with severe bipolar illness. *Acta Psychiatr Scand, 132*(4), 281-282. doi:10.1111/acps.12428

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British journal of social and clinical psychology, 6*(4), 278-296.

Hasin, D., Fenton, M. C., Skodol, A., Krueger, R., Keyes, K., Geier, T., . . . Grant, B. (2011). Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Arch Gen Psychiatry, 68*(11), 1158-1167. doi:10.1001/archgenpsychiatry.2011.78

10.1001/archgenpsychiatry.2011.136

Kavanagh, B. E., Brennan-Olsen, S. L., Turner, A., Dean, O. M., Berk, M., Ashton, M. M., . . . Williams, L. J. (2019). Role of personality disorder in randomised controlled trials of pharmacological interventions for adults with mood disorders: a protocol for a systematic review and meta-analysis. *BMJ Open, 9*(4), e025145. doi:10.1136/bmjopen-2018-025145

Kavanagh, B. E., Williams, L. J., Berk, M., Turner, A., Jackson, H. J., Mohebbi, M., . . . Maes, M. (2019). Personality disorder and functioning in major depressive disorder: a nested study within a randomized controlled trial. *Brazilian Journal of Psychiatry*(AHEAD).

Kutcher, S. P., Marton, P., & Korenblum, M. (1990). Adolescent bipolar illness and personality disorder. *J Am Acad Child Adolesc Psychiatry, 29*(3), 355-358. doi:10.1097/00004583-199005000-00004

Leichsenring, F., Leibing, E., Kruse, J., New, A. S., & Leweke, F. (2011). Borderline personality disorder. *The Lancet, 377*(9759), 74-84.

Macneil, C., Hasty, M., Conus, P., Berk, M., & Scott, J. (2010). Bipolar Disorder in Young People. A Psychological Intervention Manual. *Tijdschrift voor Psychiatrie, 52*(7), 473-473.

Macneil, C. A., Hasty, M., Cotton, S., Berk, M., Hallam, K., Kader, L., . . . Conus, P. (2012). Can a targeted psychological intervention be effective for young people following a first manic episode? Results from an 18-month pilot study. *Early Intervention in Psychiatry, 6*(4), 380-388. doi:10.1111/j.1751-7893.2011.00336.x

Moran, P., Jenkins, R., Tylee, A., Blizard, R., & Mann, A. (2000). The prevalence of personality disorder among UK primary care attenders. *Acta Psychiatr Scand, 102*(1), 52-57.

Ng, T. H., Burke, T. A., Stange, J. P., Walshaw, P. D., Weiss, R. B., Urosevic, S., . . . Alloy, L. B. (2017). Personality disorder symptom severity predicts onset of mood episodes and conversion to bipolar I disorder in individuals with bipolar spectrum disorder. *J Abnorm Psychol, 126*(3), 271-284. doi:10.1037/abn0000255

Overall, J.E., Gorham, D.R. The Brief Psychiatric Rating Scale. Psychol Reports 1962;10:799-812

Perlick, D. A., Berk, L., Kaczynski, R., Gonzalez, J., Link, B., Dixon, L., . . . Miklowitz, D. J. (2016). Caregiver burden as a predictor of depression among family and friends who provide care for persons with bipolar disorder. *Bipolar Disord, 18*(2), 183-191.

Pica, S., Edwards, J., Jackson, H. J., Bell, R. C., Bates, G. W., & Rudd, R. P. (1990). Personality disorders in recent-onset bipolar disorder. *Compr Psychiatry, 31*(6), 499-510. doi:10.1016/0010-440x(90)90064-y

Post, R. M., Leverich, G. S., McElroy, S., Kupka, R., Suppes, T., Altshuler, L., . . . Hellemann, G. (2018). Prevalence of axis II comorbidities in bipolar disorder: relationship to mood state. *Bipolar Disord, 20*(4), 303-312. doi:10.1111/bdi.12596

Preston, G. A., Marchant, B. K., Reimherr, F. W., Strong, R. E., & Hedges, D. W. (2004). Borderline personality disorder in patients with bipolar disorder and response to lamotrigine. *J Affect Disord, 79*(1-3), 297-303. doi:10.1016/s0165-0327(02)00358-0

Quirk, S. E., Berk, M., Chanen, A. M., Koivumaa-Honkanen, H., Brennan-Olsen, S. L., Pasco, J. A., & Williams, L. J. (2016). Population prevalence of personality disorder and associations with physical health comorbidities and health care service utilization: A review. *Personal Disord, 7*(2), 136-146. doi:10.1037/per0000148

Quirk, S. E., Stuart, A. L., Berk, M., Pasco, J. A., Brennan Olsen, S. L., Koivumaa-Honkanen, H., . . . Williams, L. J. (2017). Personality disorder is an excess risk factor for physical multimorbidity among women with mental state disorders. *Psychiatry Res, 257*, 546-549. doi:10.1016/j.psychres.2017.08.010

Quirk, S. E., Stuart, A. L., Brennan-Olsen, S. L., Pasco, J. A., Berk, M., Chanen, A. M., . . . Williams, L. J. (2016). Physical health comorbidities in women with personality disorder: Data from

the Geelong Osteoporosis Study. *Eur Psychiatry, 34*, 29-35. doi:10.1016/j.eurpsy.2015.12.007

Skodol, A. E., Grilo, C. M., Keyes, K. M., Geier, T., Grant, B. F., & Hasin, D. S. (2011). Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. *Am J Psychiatry, 168*(3), 257-264. doi:10.1176/appi.ajp.2010.10050695

Strakowski, S. M., Keck, P. E., McElroy, S. L., West, S. A., Sax, K. W., Hawkins, J. M., . . . Bourne, M. L. (1998). Twelve-month outcome after a first hospitalization for affective psychosis. *Arch Gen Psychiatry, 55*(1), 49-55.

Tohen, M., Strakowski, S. M., Zarate Jr, C., Hennen, J., Stoll, A. L., Suppes, T., . . . Baldessarini, R. J. (2000). The McLean–Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biological psychiatry, 48*(6), 467-476.

Westen, D. (1997). Divergences between clinical and research methods for assessing personality disorders: Implications for research and the evolution of Axis II. *American Journal of Psychiatry, 154*(7), 895-903.

Winsper, C., Bilgin, A., Thompson, A., Marwaha, S., Chanen, A. M., Singh, S. P., . . . Furtado, V. (2020). The prevalence of personality disorders in the community: a global systematic review and meta-analysis. *Br J Psychiatry, 216*(2), 69-78. doi:10.1192/bjp.2019.166

Yen, S., Frazier, E., Hower, H., Weinstock, L. M., Topor, D. R., Hunt, J., . . . Keller, M. B. (2015). Borderline personality disorder in transition age youth with bipolar disorder. *Acta Psychiatr Scand, 132*(4), 270-280. doi:10.1111/acps.12415

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A Rating Scale for Mania: Reliability, Validity and Sensitivity. *British Journal of Psychiatry, 133*(5), 429-435. doi:10.1192/bjp.133.5.429

Zimmerman, M., Balling, C., Chelminski, I., & Dalrymple, K. (2020). Patients with borderline personality disorder and bipolar disorder: a descriptive and comparative study. *Psychol Med*, 1-12. doi:10.1017/s0033291720000215

Zimmerman, M., & Morgan, T. A. (2013). Problematic Boundaries in the Diagnosis of Bipolar Disorder: The Interface with Borderline Personality Disorder. *Current Psychiatry Reports, 15*(12), 422. doi:10.1007/s11920-013-0422-z