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Research paper

Anxiety disorders and childhood maltreatment as predictors of outcome in bipolar disorder

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ABSTRACT

Background: Comorbid anxiety disorders and childhood maltreatment have each been linked with unfavourable outcomes in people with bipolar disorder. Because childhood maltreatment is associated with anxiety disorders in this population, their respective predictive value remains to be determined.
Methods: In 174 adults with bipolar disorder, we assessed childhood maltreatment using the Childhood Trauma Questionnaire and lifetime anxiety disorders with the MINI International Neuropsychiatric Interview. We constructed an overall index of severity of bipolar disorder as a sum of six indicators (unemployment, psychotic symptoms, more than five manic episodes, more than five depressive episodes, suicide attempt, and hospital admission). We tested the relationship between childhood maltreatment, the number of anxiety disorders and the overall severity index using ordered logistic regression.
Results: The number of lifetime anxiety disorders was associated with the overall severity index (OR = 1.43, 95%CI = 1.01–2.04, p = 0.047). This relationship was only slightly attenuated when controlled for childhood maltreatment (OR = 1.39, 95%CI = 0.97–2.00, p = 0.069). The relationship between childhood maltreatment and the overall severity index was not statistically significant (OR = 1.26, 95%CI = 0.92–1.74, p = 0.151). Secondary analyses revealed that childhood maltreatment was associated with suicide attempts (OR = 1.70, 95%CI = 1.15–2.51, p = 0.008) and obsessive compulsive disorder was associated with the overall severity index (OR = 9.56, 95%CI = 2.20–41.47, p = 0.003).
Limitations: This was a cross-sectional study with a moderate-sized sample recruited from a specialist program.
Conclusions: While comorbid anxiety disorders are associated with the overall severity of bipolar disorder, childhood maltreatment is specifically associated with suicide attempts. Clinicians should systematically assess both factors. Interventions to improve outcomes of people with bipolar disorder with comorbid anxiety disorders and history of childhood maltreatment are needed.

1. Introduction

Bipolar disorder is a heterogeneous illness with variable symptomatic and functional outcomes (Treuer and Tohen, 2010). Despite available treatments (Yatham et al., 2013), thirty to sixty percent of people with bipolar disorder do not return to their original levels of functioning (MacQueen et al., 2001) and nine to twenty percent die of suicide (Gonda et al., 2012; Medici et al., 2015).

Identifying those most at risk for adverse outcomes has become a focus of numerous studies. Comorbid anxiety disorders and history of childhood maltreatment have each been associated with negative outcomes and are very common in this population. Almost a half have a lifetime anxiety disorder (Pavlova et al., 2015) and a similar proportion have experienced childhood maltreatment (Garno et al., 2005). Compared to people with bipolar disorder who do not have comorbid anxiety disorders, those with anxiety disorders experience more frequent relapses and mania with more psychotic symptoms (Azorin et al., 2009). They are admitted to hospital more often (Goldstein and Levitt, 2008), their psychosocial functioning is more impaired (Hawke et al., 2013; Simon et al., 2004) and they are more likely to engage in suicidal behaviour (Azorin et al., 2009; Perroud et al., 2007; Simon et al., 2004). Bipolar disorder also starts earlier in individuals with anxiety disorders

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(Perlis et al., 2004). Additionally, those with two and more anxiety disorders have worse prognosis than those with one (Deckersbach et al., 2014; Simon et al., 2004). History of childhood maltreatment has a very similar impact on outcomes of bipolar disorder; it is associated with an earlier age of onset (Aas et al., 2016; Agnew-Blais and Danese, 2016), greater number of mood episodes (Agnew-Blais and Danese, 2016), suicide attempts (Aas et al., 2016; Agnew-Blais and Danese, 2016), more severe psychotic symptoms (Agnew-Blais and Danese, 2016), and impaired functioning (Sala et al., 2014).

However, none of the above-mentioned studies explored the relative contribution of comorbid anxiety disorders and childhood maltreatment to outcomes in bipolar disorder. Because comorbid anxiety disorders and history of childhood maltreatment in people with bipolar disorder are associated with each other (Agnew-Blais and Danese, 2016; Pavlova et al., 2016), their relative contribution to unfavourable outcomes is not clear. Disentangling this relationship would clarify whether both factors are equally important to assess in routine clinical practice and help appropriately target interventions to improve outcomes of people living with bipolar disorder. In the present study, we aim to answer the question whether we need to assess both factors to predict outcome of bipolar disorder.

2. Method

2.1. Sample

We used the same sample as in our previous study (Pavlova et al., 2016). The sample consisted of adults with bipolar I or bipolar II disorder who were recruited between January 2010 and December 2012 as consecutive referrals to the Mood Disorders Unit at the Geneva University Hospital. This is a tertiary specialist service which accepts referrals for diagnosis and treatment recommendations from various health professionals, including general practitioners and psychiatrists. The study was approved by the ethics committee of the Republic and Canton of Geneva.

2.2. Measures

2.2.1. Diagnoses

The diagnoses of bipolar I or bipolar II disorder were established according to the Diagnostic and Statistical Manual-fourth edition-text revision DSM-IV-TR (American Psychiatric Association, 2000) using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) and were confirmed in a consensus meeting with a psychiatrist with an expertise in mood disorders (JMA).

We also used the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) to diagnose DSM-IV-TR lifetime anxiety disorders. The assessed anxiety disorders included panic disorder, agoraphobia, social anxiety disorder, specific phobia, obsessive compulsive disorder (OCD) and post-traumatic stress disorder. As we used the DSM-IV-TR, we included OCD and post-traumatic stress disorder among anxiety disorders. To capture the role of multiple anxiety disorders in bipolar disorder outcomes (Deckersbach et al., 2014; Simon et al., 2004), we classified the presence of anxiety disorders on a three-point ordinal scale as no anxiety disorder, one anxiety disorder and two and more anxiety disorders. In secondary analyses, we explored each anxiety disorder separately.

2.2.2. Childhood maltreatment

History of childhood maltreatment was established using the Childhood Trauma Questionnaire (Bernstein et al., 1994). This is a validated self-report questionnaire that retrospectively assesses frequency of physical abuse, emotional abuse, sexual abuse, emotional neglect and physical neglect. It consists of 28 items. Each item is scored on a five-point ordinal scale based on how frequently the person experienced each event in childhood (never true, rarely true, sometimes true, often true, very often true). The questionnaire includes five questions for each maltreatment domain; the remaining three items form a denial score and are not included in the total score. We used the total score to capture the cumulative severity of childhood maltreatment in our analyses. The use of CTQ total score as an overall measure of childhood maltreatment has been supported by previous literature (Scher et al., 2001; Spinhoven et al., 2014). The total score can range between 25 and 125. Higher score reflects more severe maltreatment.

2.2.3. Severity

To assess the overall severity of bipolar disorder, we calculated the overall severity index by combining the following severity indicators that were established in an interview with a psychiatrist: age of onset before 21 years of age, more than five lifetime depressive episodes, more than five lifetime manic episodes, history of one or more suicide attempts, history of at least one hospital admission for bipolar disorder, history of psychotic symptoms and unemployment at the time of the interview. We rated each severity indicator on a binary scale (0 = indicator not present, 1 = indicator present). The overall severity index is a sum of all severity indicators and can range from 0 to 6. Higher ratings suggest greater severity. We used the overall severity index in the primary analyses and explored the individual severity indicators in the secondary analyses.

2.3. Statistical analysis

In the primary analyses, we used ordered logistic regression to test the effect of the number of lifetime anxiety disorders (0 = no anxiety disorder, 1 = one anxiety disorder, 2 = two and more anxiety disorders) and of history of childhood maltreatment (total CTQ score) on the overall severity index. We consider tests with a p-value smaller than 0.05 as statistically significant. In the secondary analyses we used logistic regression to explore the association of childhood maltreatment and the number of anxiety disorders with each severity indicator (i.e. unemployment, more than five lifetime depressive episodes, more than five lifetime manic episodes, history of psychotic symptoms, one or more hospital admission for bipolar disorder, and suicide attempts). Further secondary analyses explored the relationship between individual anxiety disorders and the overall severity index using ordered logistic regression. All analyses were controlled for age, sex and type of bipolar disorder (bipolar I or bipolar II disorder). We used Stata 12.1 to conduct all analyses.

2.4. Power calculation

We aimed to detect a moderate effect of predictors on the overall severity index, equivalent to odds ratio 1.4 in ordered logistic regression with five levels of the outcome variable. Power calculation by simulation in STATA suggested that a sample of 173 individuals is required to detect such effect with a power of 80% at an alpha level of 0.05. To achieve a similar power at alpha level 0.01, a sample of 260 individuals would be required. The available sample of 174 individuals with valid data was sufficient for a powered test at alpha 0.05 but not at alpha 0.01. Given these considerations and the available sample, we chose to carry out only one primary test per predictor and consider results with $p < 0.05$ as statistically significant.

3. Results

3.1. Sample description

We recruited 174 individuals. Ninety-eight (56.3%) were female and their mean age was 41.79 years (SD = 12.71). Eighty-one (46.6%) were diagnosed with bipolar I disorder. Fifty (28.7%) had one lifetime anxiety disorder and thirty-four (19.5%) had two or more lifetime anxiety disorders. Generalized anxiety disorder was the most commonly

Table 1
Individual severity indicators in the sample.

Severity indicator	N (%)[a]
Early age of onset	70 (40.2)
More than 5 depressive episodes	73 (47.4)
More than 5 manic episodes	17 (11.2)
Suicide attempt	69 (39.7)
Hospital admission	81 (50.9)
Psychotic symptoms	37 (23.3)
Unemployment	60 (35.7)

[a] The total number of individuals in whom the individual severity indicators were assessed does not always add up to 174 due to missing data.

diagnosed anxiety disorder (28%), followed by agoraphobia (16%), panic disorder (15%), social anxiety disorder (14%), post-traumatic stress disorder (5%) and obsessive compulsive disorder (4%). The mean CTQ total score was 46.2 (SD 16.5, range = 25–111), which falls between the 90th and the 95th percentile (Scher et al., 2001) and hence suggests higher severity of childhood maltreatment in our sample when compared to a community sample. The mean overall severity index was 2.33 (SD 1.17, IQR = 2–3; range = 0–5), corresponding to an average of over two severity indicators per person. The prevalence of individual severity indicators in the sample is described in Table 1.

3.2. Anxiety disorders, childhood maltreatment and severity of bipolar disorder

The number of anxiety disorders was associated with the overall severity index in this sample (OR 1.43, 95%CI = 1.01–2.04, p = 0.047). There was no significant association between the total CTQ score and the overall severity index (OR 1.26, 95%CI = 0.92–1.74, p = 0.151). When anxiety disorders and history of childhood maltreatment were considered together in a multiple logistic regression, there was a trend association between the number of anxiety disorders and the overall severity index (OR = 1.39, 95%CI = 0.97–2.00, p = 0.069) but no significant association between the total CTQ score and the overall severity index (OR = 1.22, 95%CI = 0.88–1.69, p = 0.234). See Tables 2, 3.

3.3. Secondary analyses

The only specific anxiety disorder associated with the overall severity index was OCD (OR = 9.56, 95%CI = 2.20–41.47, p = 0.003; Table 4). Out of the specific severity indicators, childhood maltreatment was significantly associated with a history of suicide attempts (OR = 1.70, 95%CI = 1.15–2.51, p = 0.008; Table 3). When considered in the regression together with the number of anxiety disorders, the relationship between childhood maltreatment and a history of suicide attempts remained significant (OR = 1.66, 95%CI = 1.12–2.46, p = 0.011; Table 3).

3.4. Sensitivity analysis

High scores on CTQ items 10, 16 and 22 are sometimes used to index individuals who may be minimizing or denying because of reluctance to report childhood adverse experiences. In the present sample, 29 (17%) endorsed the top score on one or more of these items and thus were identified as potential minimization-denial cases. Therefore, we have examined if minimization-denial might have influenced our results. Minimization-denial cases did not differ from the remainder of the sample in the overall severity index ($chi2_{[5]}$ = 7.86, p = 0.164). Sensitivity analyses restricted to the 145 participants with low probability of minimization-denial closely replicated the main results reported above: the number of anxiety disorders was associated with the overall severity index (OR 1.52, 95%CI = 1.03–2.22, p = 0.045), total CTQ score was not associated with the overall severity index (OR = 1.28, 95%CI = 0.87–1.89, p = 0.212), but remained strongly associated with suicide attempts (OR = 1.66, 95%CI = 1.05–2.62, p = 0.030). The similarity of these results to the main analyses suggests that potential reluctance to disclose history of adversity did not affect the associations between childhood maltreatment, anxiety and severity of bipolar disorder.

4. Discussion

We found that anxiety disorders and childhood maltreatment each play a unique role in predicting unfavourable outcomes in people with bipolar disorder: While anxiety disorders are a more powerful predictor of the overall negative outcome, maltreatment in childhood is specifically associated with suicide attempts.

Our finding that anxiety disorders are associated with unfavourable outcomes in people with bipolar disorder is in line with previous literature (Azorin et al., 2009; Hawke et al., 2013; Simon et al., 2004). There are several possible explanations of this association: First, anxiety disorders are associated with an earlier age of onset of bipolar disorder (Perlis et al., 2004) and hence are likely to interfere with developing supportive social networks and achieving one's academic potential (Van Ameringen et al., 2003; Woodward and Fergusson, 2001) at crucial times in development (adolescence and very early adulthood) which in turn may worsen the prognosis. Second, anxiety could contribute to sleep disruption (Hawke et al., 2013) and hence mood instability (Harvey et al., 2009). Third, it is possible that anxiety leads to the negative outcomes via the increased risk of substance abuse (Goodwin et al., 2002). Fourth, stressful life events are associated with depression in bipolar disorder (Gershon et al., 2013; Hosang et al., 2012; Simhandl et al., 2015) and it is possible that people with comorbid anxiety disorders are less resilient to stressors and hence more prone to negative outcomes. Fifth, there may be a common genetic susceptibility underlying anxiety and the more severe forms of bipolar disorder (Mackinnon et al., 2002). We also found that the effect of anxiety disorders on outcome in bipolar disorder is largely independent of the effect of maltreatment in childhood.

Table 2
Effect of anxiety disorders on severity indicators.

	Controlled for BD type, age and sex				Controlled for BD type, age, sex and CTQ			
	Odds ratio	**P > |z|**	**95% CI lower**	**95% CI upper**	**Odds ratio**	**P > |z|**	**95% CI lower**	**95% CI upper**
Overall severity index	1.43	0.047	1.01	2.04	1.39	0.069	0.97	2.00
Early age of onset	1.23	0.351	0.79	1.92	1.20	0.416	0.77	1.88
Number of depressive episodes	0.00	0.979	−0.36	0.37	−0.02	0.918	−0.39	0.35
Number of manic episodes	−0.01	0.934	−0.36	0.33	−0.04	0.824	−0.39	0.31
Suicide attempts	1.28	0.222	0.86	1.90	1.19	0.397	0.79	1.79
Hospital admissions	1.04	0.849	0.67	1.64	1.03	0.901	0.65	1.62
Psychotic symptoms	0.84	0.496	0.50	1.39	0.90	0.681	0.53	1.51
Unemployment	1.32	0.181	0.88	2.00	1.33	0.181	0.88	2.01

Table 3
Effect of childhood maltreatment on severity indicators.

	Controlled for BD type, age and sex				Controlled for BD type, age, sex and anxiety disorders			
	Odds ratio	**P > |z|**	**95% CI lower**	**95% CI upper**	**Odds ratio**	**P > |z|**	**95% CI lower**	**95% CI upper**
Overall severity index	1.26	0.151	0.92	1.74	1.22	0.234	0.88	1.69
Early age of onset	1.21	0.349	0.81	1.82	1.19	0.411	0.79	1.78
Number of depressive episodes	0.15	0.357	−0.17	0.47	0.15	0.355	−0.17	0.48
Number of manic episodes	0.14	0.404	−0.19	0.47	0.15	0.392	−0.19	0.48
Suicide attempts	1.70	0.008	1.15	2.51	1.66	0.011	1.12	2.46
Hospital admissions	1.10	0.638	0.74	1.65	1.10	0.655	0.73	1.65
Psychotic symptoms	0.69	0.167	0.41	1.17	0.71	0.202	0.42	1.20
Unemployment	1.02	0.926	0.70	1.49	0.98	0.915	0.66	1.45

Table 4
Effect of individual anxiety disorders on the overall severity index.

	Odds ratio	**P > |z|**	**95% CI lower**	**95% CI upper**
Panic disorder	1.54	0.281	0.70	3.36
Agoraphobia	1.43	0.348	0.68	3.01
Social phobia	1.49	0.330	0.67	3.32
GAD	1.40	0.276	0.76	2.59
OCD	9.56	0.003	2.20	41.47
PTSD	1.76	0.396	0.48	6.43

Note: All analyses controlled for BD type, age and sex.

We found that childhood maltreatment is specifically linked to suicide attempts. This is in agreement with findings from a general population sample (Hoertel et al., 2015), a sample of people with schizophrenia (Hassan et al., 2016) and a recent meta-analysis of impact of childhood maltreatment on outcomes in people with bipolar disorder (Agnew-Blais and Danese, 2016). Hoertel et al. (2015) found that this relationship is independent of psychopathology (Hoertel et al., 2015), which concurs with our finding that the association between childhood maltreatment and suicide attempts is not explained by anxiety disorders comorbidity. Several mechanisms could be involved: Affective lability and reactivity to failure experiences is associated with childhood maltreatment (Aas et al., 2014; Pavlova et al., 2011) and affective lability in people with bipolar disorder has been linked to suicidality (Palmier-Claus et al., 2012). It is possible that people who experienced childhood maltreatment are more likely to respond to stressful life events with large decreases in mood which may in turn make them more likely to attempt suicide. It has also been suggested that impulsivity may be the link between maltreatment in childhood and suicidality (Braquehais et al., 2010). Finally, maltreatment in childhood is also associated with poor social support (Sperry and Widom, 2013), which is likely to increase the risk of suicidal behaviour in people with bipolar disorder (Holma et al., 2014).

In our secondary analyses, we also found that a lifetime OCD diagnosis increased the likelihood of adverse outcomes nine times. This is in line with previous findings that out of all DSM-IV anxiety disorders, OCD is most strongly associated with unfavourable outcomes in bipolar disorder (Coryell et al., 2012; Goes et al., 2012) and that it prolongs time to remission from both depression and mania for longer than other anxiety disorders (Kim et al., 2014).

Because both anxiety disorders and a history of childhood maltreatment are relevant for the prognosis of bipolar disorder, they should be an integral part of clinical assessment. Presence of anxiety disorders, and particularly OCD, should alert clinicians to a higher likelihood of negative outcomes. Additionally, the risk of suicide should be monitored especially carefully in those who experienced childhood maltreatment. It is clear that a significant proportion of people with bipolar disorder need an effective intervention for anxiety disorders. As selective serotonin reuptake inhibitors can contribute to mood destabilization in people with bipolar disorder (Viktorin et al., 2014), cognitive behavioural therapy appears to be the treatment of choice in this population. Preliminary evidence suggests that it is safe and effective (Fracalanza et al., 2014; Provencher et al., 2011; Stratford et al., 2015). It also appears that many people with bipolar disorder may benefit from interventions to mitigate the sequelae of childhood trauma. Two small studies suggest that dialectic behavioural therapy can be a successful treatment in people with bipolar disorder and decrease suicidal ideation and affective instability (Goldstein et al., 2015; Van Dijk et al., 2013). Additionally, eye movement desensitization and reprocessing, therapy that specifically targets trauma symptoms, has had some promising results with people with bipolar disorder in a pilot study (Novo et al., 2014). Finally, trauma focussed cognitive behavioural therapy may be useful in this population, but has not been tested yet.

This study has significant strengths including consensus diagnoses made by an expert psychiatrist, use of reliable and valid measures, and the use of an overall measure of severity. However, our results need to be interpreted in the light of several limitations. First, our sample is modest. It is possible that some of the secondary analyses that revealed positive relationships did not reach statistical significance because of insufficient power. For example, while we showed that overall, anxiety disorders were associated with the severity of bipolar disorder, we did not find significant association between anxiety disorders and the individual severity indicators. Also, we did not capture all aspects of severity in our overall severity index. For example, we did not assess duration of mood episodes and chronicity of the course of bipolar disorder, which may be a stronger indicator of severity than the number of episodes (Angst et al., 2009). Additionally, our sample was recruited from a specialized tertiary centre and our results may not be applicable to other groups of people with bipolar disorder. We also did not assess personality disorders, which have been shown to increase severity of mood disorders (Frias et al., 2016; McDermid et al., 2015) and suicidality (Frias et al., 2016) and which are also linked to childhood maltreatment in this population (McDermid et al., 2015). As we included participants in various phases of bipolar disorder, it is possible that the reporting of childhood maltreatment may have been influenced by recall bias. Finally, while childhood maltreatment experiences and development of anxiety disorders usually precede the onset of bipolar disorder (Duffy et al., 2013), this was a retrospective study and hence we cannot make conclusions about causation. Future studies would benefit from prospective design, bigger numbers as well as assessment of chronicity.

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References

Aas, M., Aminoff, S.R., Vik, L.T., Etain, B., Agartz, I., Andreassen, O.A., Melle, I., 2014. Affective lability in patients with bipolar disorders is associated with high levels of childhood trauma. Psychiatry Res. 218, 252–255.

Aas, M., Henry, C., Andreassen, O.A., Bellivier, F., Melle, I., Etain, B., 2016. The role of childhood trauma in bipolar disorders. Int. J. Bipolar Disord. 4, 2.

Agnew-Blais, J., Danese, A., 2016. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 3, 342–349.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Author, Washington, DC (text rev.).

Angst, J., Gamma, A., Rossler, W., Ajdacic, V., Klein, D.N., 2009. Long-term depression versus episodic major depression: results from the prospective Zurich study of a community sample. J. Affect. Disord. 115, 112–121.

Azorin, J.M., Kaladjian, A., Adida, M., Hantouche, E.G., Hameg, A., Lancrenon, S., Akiskal, H.S., 2009. Psychopathological correlates of lifetime anxiety comorbidity in bipolar I patients: findings from a French national cohort. Psychopathology 42, 380–386.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., Ruggiero, J., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am. J. Psychiatry 151, 1132–1136.

Braquehais, M.D., Oquendo, M.A., Baca-Garcia, E., Sher, L., 2010. Is impulsivity a link between childhood abuse and suicide? Compr. Psychiatry 51, 121–129.

Coryell, W., Fiedorowicz, J.G., Solomon, D., Leon, A.C., Rice, J.P., Keller, M.B., 2012. Effects of anxiety on the long-term course of depressive disorders. Br. J. Psychiatry 200, 210–215.

Deckersbach, T., Peters, A.T., Sylvia, L., Urdahl, A., Magalhaes, P.V., Otto, M.W., Frank, E., Miklowitz, D.J., Berk, M., Kinrys, G., Nierenberg, A., 2014. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. Am. J. Psychiatry 171, 178–186.

Duffy, A., Horrocks, J., Doucette, S., Keown-Stoneman, C., McCloskey, S., Grof, P., 2013. Childhood anxiety: an early predictor of mood disorders in offspring of bipolar parents. J. Affect. Disord. 150, 363–369.

Fracalanza, K., McCabe, R.E., Taylor, V.H., Antony, M.M., 2014. The effect of comorbid major depressive disorder or bipolar disorder on cognitive behavioral therapy for social anxiety disorder. J. Affect. Disord. 162, 61–66.

Frias, A., Baltasar, I., Birmaher, B., 2016. Comorbidity between bipolar disorder and borderline personality disorder: prevalence, explanatory theories, and clinical impact. J. Affect. Disord. 202, 210–219.

Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2005. Impact of childhood abuse on the clinical course of bipolar disorder. Br. J. Psychiatry 186, 121–125.

Gershon, A., Johnson, S.L., Miller, I., 2013. Chronic stressors and trauma: prospective influences on the course of bipolar disorder. Psychol. Med. 43, 2583–2592.

Goes, F.S., McCusker, M.G., Bienvenu, O.J., Mackinnon, D.F., Mondimore, F.M., Schweizer, B., Depaulo, J.R., Potash, J.B., 2012. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. Psychol. Med. 42, 1449–1459.

Goldstein, B.I., Levitt, A.J., 2008. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. Bipolar Disord. 10, 67–78.

Goldstein, T.R., Fersch-Podrat, R.K., Rivera, M., Axelson, D.A., Merranko, J., Yu, H., Brent, D.A., Birmaher, B., 2015. Dialectical behavior therapy for adolescents with bipolar disorder: results from a pilot randomized trial. J. Child Adolesc. Psychopharmacol. 25, 140–149.

Gonda, X., Pompili, M., Serafini, G., Montebovi, F., Campi, S., Dome, P., Duleba, T., Girardi, P., Rihmer, Z., 2012. Suicidal behavior in bipolar disorder: epidemiology, characteristics and major risk factors. J. Affect. Disord. 143, 16–26.

Goodwin, R.D., Stayner, D.A., Chinman, M.J., Wu, P., Tebes, J.K., Davidson, L., 2002. The relationship between anxiety and substance use disorders among individuals with severe affective disorders. Compr. Psychiatry 43, 245–252.

Harvey, A.G., Talbot, L.S., Gershon, A., 2009. Sleep disturbance in bipolar disorder across lifespan. Clin. Psychol.:Sci. Pract. 16, 256–277.

Hassan, A.N., Stuart, E.A., De Luca, V., 2016. Childhood maltreatment and the risk of suicide attempt in schizophrenia. Schizophr. Res. 176, 572–577.

Hawke, L.D., Provencher, M.D., Parikh, S.V., Zagorski, B., 2013. Comorbid anxiety disorders in Canadians with bipolar disorder: clinical characteristics and service use. Can. J. Psychiatry 58, 393–401.

Hoertel, N., Franco, S., Wall, M.M., Oquendo, M.A., Wang, S., Limosin, F., Blanco, C., 2015. Childhood maltreatment and risk of suicide attempt: a nationally representative study. J. Clin. Psychiatry 76, 916–923.

Holma, K.M., Haukka, J., Suominen, K., Valtonen, H.M., Mantere, O., Melartin, T.K., Sokero, T.P., Oquendo, M.A., Isometsa, E.T., 2014. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. Bipolar Disord. 16, 652–661.

Hosang, G.M., Uher, R., Maughan, B., McGuffin, P., Farmer, A.E., 2012. The role of loss and danger events in symptom exacerbation in bipolar disorder. J. Psychiatr. Res. 46, 1584–1589.

Kim, S.W., Berk, L., Kulkarni, J., Dodd, S., de, C.A., Fitzgerald, P.B., Amminger, G.P., Berk, M., 2014. Impact of comorbid anxiety disorders and obsessive-compulsive disorder on 24-month clinical outcomes of bipolar I disorder. J. Affect. Disord. 166, 243–248.

Mackinnon, D.F., Zandi, P.P., Cooper, J., Potash, J.B., Simpson, S.G., Gershon, E., Nurnberger, J., Reich, T., Depaulo, J.R., 2002. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. Am. J. Psychiatry 159, 30–35.

MacQueen, G.M., Young, L.T., Joffe, R.T., 2001. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr. Scand. 103, 163–170.

McDermid, J., Sareen, J., El-Gabalawy, R., Pagura, J., Spiwak, R., Enns, M.W., 2015. Comorbidity of bipolar disorder and borderline personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Compr. Psychiatry 58, 18–28.

Medici, C.R., Videbech, P., Gustafsson, L.N., Munk-Jorgensen, P., 2015. Mortality and secular trend in the incidence of bipolar disorder. J. Affect. Disord. 183, 39–44.

Novo, P., Landin-Romero, R., Radua, J., Vicens, V., Fernandez, I., Garcia, F., Pomarol-Clotet, E., McKenna, P.J., Shapiro, F., Amann, B.L., 2014. Eye movement desensitization and reprocessing therapy in subsyndromal bipolar patients with a history of traumatic events: a randomized, controlled pilot-study. Psychiatry Res. 219, 122–128.

Palmier-Claus, J.E., Taylor, P.J., Varese, F., Pratt, D., 2012. Does unstable mood increase risk of suicide? Theory, research and practice. J. Affect. Disord. 143, 5–15.

Pavlova, B., Uher, R., Dennington, L., Wright, K., Donaldson, C., 2011. Reactivity of affect and self-esteem during remission in bipolar affective disorder: an experimental investigation. J. Affect. Disord. 134, 102–111.

Pavlova, B., Perlis, R.H., Alda, M., Uher, R., 2015. Lifetime prevalence rates of anxiety disorders in people with bipolar disorder: a meta-analysis. Lancet Psychiatry 2, 710–717.

Pavlova, B., Perroud, N., Cordera, P., Uher, R., Dayer, A., Aubry, J.-M., 2016. Childhood maltreatment and comorbid anxiety in people with bipolar disorder. J. Affect. Disord. 192, 22–27.

Perlis, R.H., Miyahara, S., Marangell, L.B., Wisniewski, S.R., Ostacher, M., Delbello, M.P., Bowden, C.L., Sachs, G.S., Nierenberg, A.A., 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 55, 875–881.

Perroud, N., Baud, P., Preisig, M., Etain, B., Bellivier, F., Favre, S., Reber, N., Ferrero, F., Leboyer, M., Malafosse, A., 2007. Social phobia is associated with suicide attempt history in bipolar inpatients. Bipolar Disord. 9, 713–721.

Provencher, M.D., Hawke, L.D., Thienot, E., 2011. Psychotherapies for comorbid anxiety in bipolar spectrum disorders. J. Affect. Disord. 133, 371–380.

Sala, R., Goldstein, B.I., Wang, S., Blanco, C., 2014. Childhood maltreatment and the course of bipolar disorders among adults: epidemiologic evidence of dose-response effects. J. Affect. Disord. 165, 74–80.

Scher, C.D., Stein, M.B., Asmundson, G.J., McCreary, D.R., Forde, D.R., 2001. The childhood trauma questionnaire in a community sample: psychometric properties and normative data. J. Trauma Stress 14, 843–857.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), 22–33.

Simhandl, C., Radua, J., Konig, B., Amann, B.L., 2015. The prevalence and effect of life events in 222 bipolar I and II patients: a prospective, naturalistic 4 year follow-up study. J. Affect. Disord. 170, 166–171.

Simon, N.M., Otto, M.W., Wisniewski, S.R., Fossey, M., Sagduyu, K., Frank, E., Sachs, G.S., Nierenberg, A.A., Thase, M.E., Pollack, M.H., 2004. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am. J. Psychiatry 161, 2222–2229.

Sperry, D.M., Widom, C.S., 2013. Child abuse and neglect, social support, and psychopathology in adulthood: a prospective investigation. Child Abus. Negl. 37, 415–425.

Spinhoven, P., Penninx, B.W., Hickendorff, M., van Hemert, A.M., Bernstein, D.P., Elzinga, B.M., 2014. Childhood Trauma Questionnaire: factor structure, measurement invariance, and validity across emotional disorders. Psychol. Assess. 26, 717–729.

Stratford, H.J., Cooper, M.J., Di Simplicio, M., Blackwell, S.E., Holmes, E.A., 2015. Psychological therapy for anxiety in bipolar spectrum disorders: a systematic review. Clin. Psychol. Rev. 35, 19–34.

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

Van Ameringen, M., Mancini, C., Farvolden, P., 2003. The impact of anxiety disorders on educational achievement. J. Anxiety Disord. 17, 561–571.

Van Dijk, S., Jeffrey, J., Katz, M.R., 2013. A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. J. Affect. Disord. 145, 386–393.

Viktorin, A., Lichtenstein, P., Thase, M.E., Larsson, H., Lundholm, C., Magnusson, P.K., Landen, M., 2014. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am. J. Psychiatry 171, 1067–1073.

Woodward, L.J., Fergusson, D.M., 2001. Life course outcomes of young people with anxiety disorders in adolescence. J. Am. Acad. Child Adolesc. Psychiatry 40, 1086–1093.

Yatham, L.N., Kennedy, S.H., Parikh, S.V., Schaffer, A., Beaulieu, S., Alda, M., O'Donovan, C., Macqueen, G., McIntyre, R.S., Sharma, V., Ravindran, A., Young, L.T., Milev, R., Bond, D.J., Frey, B.N., Goldstein, B.I., Lafer, B., Birmaher, B., Ha, K., Nolen, W.A., Berk, M., 2013. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 15, 1–44.