Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis

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Summary

Background Bipolar disorder affects up to one in 25 individuals and identification of early risk indicators of negative outcomes could facilitate early detection of patients with greatest clinical needs and risk. We aimed to investigate the association between childhood maltreatment and key negative outcomes in patients with bipolar disorder.

Methods For this systematic review and meta-analysis we searched MEDLINE, PsycINFO, and Embase to identify articles published before Jan 1, 2015, examining the association of maltreatment (physical, sexual, or emotional abuse, neglect, or family conflict) before age 18 years with clinical features and course of illness in bipolar disorder. Data were extracted from published reports and any missing information was requested from investigators. We did 12 independent random-effects meta-analyses to quantify the associations between childhood maltreatment and course of illness or clinical features.

Findings We initially identified 527 records and after unsuitable studies were removed, our search yielded 148 publications of which 30 were used in the meta-analysis. Patients with bipolar disorder and history of childhood maltreatment had greater mania severity (six studies, 780 participants; odds ratio [OR] 2·02, 95% CI 1·21–3·39, p=0·008), greater depression severity (eight studies, 1007 participants; 1·57, 1·25–1·99, p=0·0001), greater psychosis severity (seven studies, 1494 participants; 1·49, 1·10–2·04, p=0·011), higher risk of comorbidity with post-traumatic stress disorder (eight studies, 2494 participants; 3·60, 2·45–5·30, p<0·0001), anxiety disorders (seven studies, 5091 participants; 1·90, 1·39–2·61, p<0·0001), substance misuse disorders (11 studies, 5469 participants; 1·84, 1·41–2·39, p<0·0001), alcohol misuse disorder (eight studies, 5040 participants; 1·44, 1·13–1·83, p=0·003), earlier age of bipolar disorder onset (14 studies, 5733 participants; 1·85, 1·43–2·40, p<0·0001), higher risk of rapid cycling (eight studies, 3010 participants; 1·89, 1·45–2·48, p<0·0001), greater number of manic episodes (seven studies, 3909 participants; 1·26, 1·09–1·47, p=0·003), greater number of depressive episodes (eight studies, 4025 participants; 1·38, 1·07–1·79, p=0·013), and higher risk of suicide attempt (13 studies, 3422 participants; 2·25, 1·88–2·70, p<0·0001) compared with those with bipolar disorder without childhood maltreatment. Overall, these associations were not explained by publication bias, undue effects of individual studies, or variation in study quality.

Interpretation Childhood maltreatment predicts unfavourable clinical features and course of illness in patients with bipolar disorder.

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Introduction

Bipolar disorder is an impairing, progressive illness affecting up to one in 25 individuals.[1–5] The diagnosis encompasses a full range of chronic mood disorders with heterogeneous clinical presentation and longitudinal course.[6,7] In this heterogeneous clinical group, identification of early risk indicators of negative outcome is essential to deliver stratified early interventions and to improve prognosis.[6,7]

Previous research has identified measures of negative clinical outcome.[7] Patients with bipolar disorder who have severe symptoms,[8] comorbid anxiety disorders,[9,10] and substance or alcohol misuse disorders[11] have the poorest clinical course as characterised by early onset of disease, rapid cycling, and a large number of manic and depressive episodes. In turn, patients with a poor course of illness are at increased risk of completed suicide (in 10–15% of people with bipolar disorder) and non-suicidal self-injury (20–60%), which are tragically prevalent in this population.[12–15]

We did a meta-analysis to test whether a history of childhood maltreatment is associated with a heightened risk of the previously stated correlated measures of negative outcomes in patients with bipolar disorder and, thus, might be used as an early indicator of disease progression. A priori support for these associations was based on findings that maltreatment is highly prevalent, affecting up to 57% of patients with bipolar disorder,[16] predicts a doubled risk of unfavourable course of illness in unipolar depression,[17] is associated with biological abnormalities that could contribute to bipolar disorder progression (eg, systemic inflammation),[18–23] and has been connected to several of the previously stated outcomes in qualitative literature reviews.[24–26] We used meta-analytical techniques to gain sufficient statistical power in the context of the comparative low prevalence of bipolar disorder, to quantitatively summarise the associations of childhood maltreatment with course of illness and clinical features in bipolar disorder in published studies, to

Research in context

Evidence before this study

We searched MEDLINE, PsycINFO, and Embase databases for articles in English and published before Jan 1, 2015, that tested the association of childhood maltreatment with clinical features and course of illness in bipolar disorder, using the search terms "child* abuse", "child* neglect", "child* maltreatment", "early abuse", "early maltreatment", "early neglect", "sexual abuse", "physical abuse", "emotional abuse", and "family conflict" in combination with "bipolar", "mania/manic", "hypomania/hypomanic", "cyclothymia/cyclothymic", and "manic depress*". After excluding duplicates or unsuitable reports, we identified 30 studies that tested the association of a history of childhood maltreatment with 12 correlated clinical outcomes in patients with bipolar disorder.

Added value of this study

From our 12 independent meta-analyses, we showed that, compared with patients with bipolar disorder who did not experience childhood maltreatment, patients with bipolar disorder and a history of childhood maltreatment had greater mania severity, greater depression severity, greater psychosis severity, higher risk of comorbidity with post-traumatic stress disorder, anxiety disorders, substance misuse disorders, and alcohol misuse disorder, earlier age of bipolar disorder onset, higher risk of rapid cycling, greater number of manic episodes, greater number of depressive episodes, and higher risk of suicide attempt. Effect sizes varied across outcomes with odds ratios of 1·26 to 3·60. Overall, these associations were not accounted for by artifacts owing to publication bias, undue effect of individual studies, or variation in study quality.

Implications of all the available evidence

Results suggest that a history of childhood maltreatment can be used as an indicator for disease progression to identify patients with bipolar disorder who are at a higher risk of unfavourable clinical features and course of illness. Additional research is needed to test whether a history of childhood maltreatment can be used as an indicator for unfavourable treatment outcomes. Further research on the stratified, and possibly trans-diagnostic, biological abnormalities associated with a history of childhood maltreatment could uncover innovative treatment strategies.

examine the heterogeneity of findings in the published literature, and to test various possible sources of bias or artifacts.

Methods

Search strategy and selection criteria

See Online for appendix

We did a systematic review and meta-analysis in accordance with the PRISMA and MOOSE guidelines (appendix).

We searched MEDLINE, PsycINFO, and Embase databases for articles written in English and published before Jan 1, 2015, that tested the association of childhood maltreatment with clinical features and course of illness in bipolar disorder. We searched using the following terms: "child* abuse", "child* neglect", "child* maltreatment", "early abuse", "early maltreatment", "early neglect", "sexual abuse", "physical abuse", "emotional abuse", and "family conflict", combined with "bipolar", "mania/manic", "hypomania/hypomanic", "cyclothymia/cyclothymic", and "manic depress*".

We included articles that satisfied the following criteria: definition of childhood adversities consistent with maltreatment (physical abuse, sexual abuse, emotional abuse, neglect, or family conflict) before age of 18 years; and availability of data for target measures of clinical features and course of illness in bipolar disorder including mania severity, depression severity, psychosis severity, post-traumatic stress disorder (PTSD) comorbidity, anxiety disorders comorbidity, substance misuse disorders comorbidity, alcohol misuse disorder comorbidity, age of onset, rapid cycling, number of manic episodes, number of depressive episodes, and risk of suicide attempt.

Data analysis

We independently extracted data from included articles about mean age of the sample, sex distribution, prevalence of study sample with bipolar disorder type 1, maltreatment measure (eg, questionnaire, interview, or chart review), maltreatment definition (any maltreatment, physical abuse, sexual abuse, emotional abuse, physical neglect, or emotional neglect), measures of bipolar disorder outcomes (eg, interview, clinical diagnosis, or chart review), and study quality. Inconsistencies were resolved in consensus meetings. Authors were contacted to provide any missing information. We identified and computed effect sizes and coded the information about the listed key variables from every study (appendix).

The primary outcome of this study was the quantitative association between childhood maltreatment and clinical features or course of illness in bipolar disorder. We also assessed heterogeneity of findings and tested various possible sources of bias or artifacts.

Extracted data were converted to odds ratio (OR) effect sizes to indicate the probability of unfavourable outcomes, with ORs larger than 1 representing a greater likelihood of unfavourable clinical features and course of illness in patients with bipolar disorder who have a history of childhood maltreatment compared with patients with bipolar disorder but no history of childhood maltreatment. In articles in which only continuous outcomes were reported, risk of unfavourable outcomes was derived using a validated method based on the evidence that natural ln (OR) can be converted to standardised mean difference by dividing by 1·81.[27]

We tested heterogeneity between studies using the I^2 statistic[28,29] and Cochran's Q.[30] We systematically used random-effects models meta-analyses. Meta-analyses were done with the metan programs in Stata (version 13; StataCorp, College Station, TX, USA).

We visually assessed the presence of publication bias by drawing funnel plots[31] and statistically assessed using Begg's adjusted rank correlation test[32] and Egger's regression asymmetry test,[33] using the metabias program in Stata. Because these tests might be underpowered if only a few studies are available,[34] we systematically used a non-parametric trim-and-fill method,[35] using the metatrim program to examine the extent to which publication bias might have contributed to the meta-analysis results.

We assessed the undue effect of individual studies on the meta-analysis results through jack-knife sensitivity analyses, by testing changes in the estimate across permutations in which each study was omitted in turn using the metaninf program in Stata.

Finally, we assessed the moderation of the meta-analytical results by study quality, mean age of the sample, proportion of patients with bipolar disorder type 1, sex distribution (proportion of women), and ethnic origin (proportion of white people) through meta-regression using the metareg program in Stata. The quality of epidemiological studies was assessed with an adapted version of the Newcastle–Ottawa Scale,[36] which is recommended by the Cochrane Collaboration.[37] This quality scale was adapted to represent criteria based on expert opinion[24–26] (appendix).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

We initially identified 527 records. After removal of unsuitable studies, our search yielded 148 publications, of which 30 were used in the meta-analysis (figure 1). A description of included studies[16,38–66] is in the appendix. We undertook 12 independent meta-analyses for each of the clinical outcomes in bipolar disorder; table 1 and figure 2 summarise these results. Individual forest plots from meta-analyses of the association between childhood maltreatment and each clinical outcome are in the appendix. Table 2 summarises the meta-regression results addressing the role of study quality (see appendix for details of ratings), mean age of participants, prevalence of bipolar disorder type 1, prevalence of women in the sample, and prevalence of white participants.

The random-effects meta-analyses included a median of eight studies (IQR 7–9, range 6–14) and 3666 participants (IQR 2244–5053, range 780–5733). Across all meta-analyses, patients with bipolar disorder and a history of childhood maltreatment had unfavourable clinical features and course of illness compared with patients with bipolar disorder who had no maltreatment (median effect size OR 1·85; table 1). The smallest effect sizes were for greater number of manic episodes (OR 1·26, 95% CI 1·09–1·47) and greater number of depressive episodes (1·38, 1·07–1·79). The largest effect sizes were for risk of suicide attempt (2·25, 1·88–2·70) and comorbidity with PTSD (3·60, 2·45–5·30; table 1, figure 2).

Several meta-analyses were characterised by high heterogeneity (table 1), as also shown in the forest plots (appendix). Five (42%) of 12 meta-analyses had significant heterogeneity according to the Q test (Cochran's χ^2 test; table 1).[30] To compensate for the low statistical power of this test in the context of meta-analyses with a small number of studies, we also tested the I^2 index that describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[28,29] The median I^2 across meta-analyses was 48·2% (IQR 6·45–63·2, range 0–72·8%).

Overall, results highlighted scarce evidence for publication bias across meta-analyses. We tested publication bias through funnel-plot-based tests, such as the Begg's test[32] and the Egger's test.[31] These tests were not significant (table 1). This result suggests that, within each meta-analysis, the effect sizes from individual studies are symmetrically distributed around the overall effect size, and therefore that the overall results of the meta-analyses are not biased by selective publication of

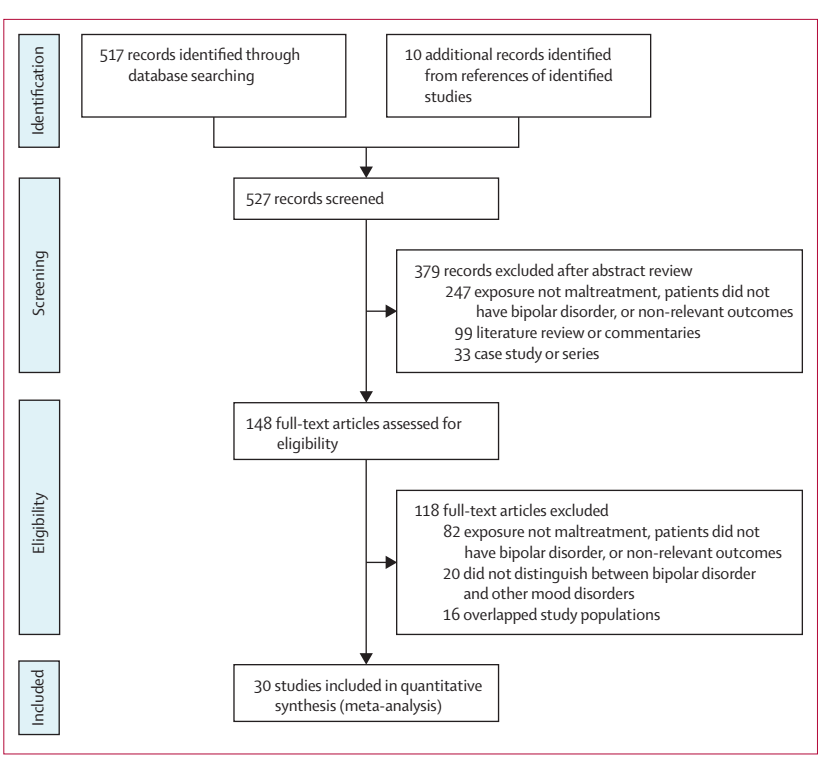

Figure 1: **Study selection**

	Number of studies (N=30)	Number of patients	Effect size estimate		Heterogeneity		Publication bias				Jack-knife sensitivity*
			OR (95% CI)	p value	Q test (p value)	I^2 (%)	Egger's p value	Begg's p value	Number filled	Trim-and-fill OR (95% CI)	
Mania severity	6	780	2·02 (1·21–3·39)	0·008	17·12 (0·004)	70·8%	0·513	0·348	0	NA	No
Depression severity	8	1007	1·57 (1·25–1·99)	0·0001	4·38 (0·735)	0%	0·069	0·083	1	1·53 (1·22–1·92)	No
Psychosis severity	7	1494	1·49 (1·10–2·04)	0·011	6·56 (0·363)	8·6%	0·615	0·453	1	1·42 (1·00–2·02)	Yes
PTSD comorbidity	8	2494	3·60 (2·45–5·30)	<0·0001	14·13 (0·049)	50·4%	0·542	0·621	2	2·94 (1·92–4·50)	No
Anxiety disorders comorbidity	7	5091	1·90 (1·39–2·61)	<0·0001	22·08 (0·001)	72·8%	0·229	0·652	0	NA	No
Substance misuse disorders comorbidity	11	5469	1·84 (1·41–2·39)	<0·0001	25·66 (0·004)	61·0%	0·216	0·243	0	NA	No
Alcohol misuse disorder comorbidity	8	5040	1·44 (1·13–1·83)	0·003	13·23 (0·067)	47·1%	0·993	0·621	1	1·43 (1·13–1·80)	No
Age of bipolar disorder onset	14	5733	1·85 (1·43–2·40)	<0·0001	42·90 (<0·0001)	69·7%	0·215	0·171	6	1·34 (1·00–1·80)	No
Rapid cycling	8	3010	1·89 (1·45–2·48)	<0·0001	11·46 (0·120)	38·9%	0·535	1·000	0	NA	No
Number of manic episodes	7	3909	1·26 (1·09–1·47)	0·003	4·72 (0·581)	0%	0·868	0·881	0	NA	No
Number of depressive episodes	8	4025	1·38 (1·07–1·79)	0·013	13·81 (0·055)	49·3%	0·899	0·805	1	1·33 (1·03–1·70)	Yes
Suicide attempt	13	3422	2·26 (1·88–2·70)	<0·0001	11·59 (0·479)	0%	0·173	0·272	4	2·11 (1·75–2·53)	No

OR=odds ratio. NA=not applicable. PTSD=post-traumatic stress disorder. *The jack-knife sensitivity analysis indicates whether evidence showed that individual studies might have had undue influence on the meta-analysis results.

Table 1: **Meta-analysis of clinical outcomes in patients with bipolar disorder who did or did not have a history of childhood maltreatment**

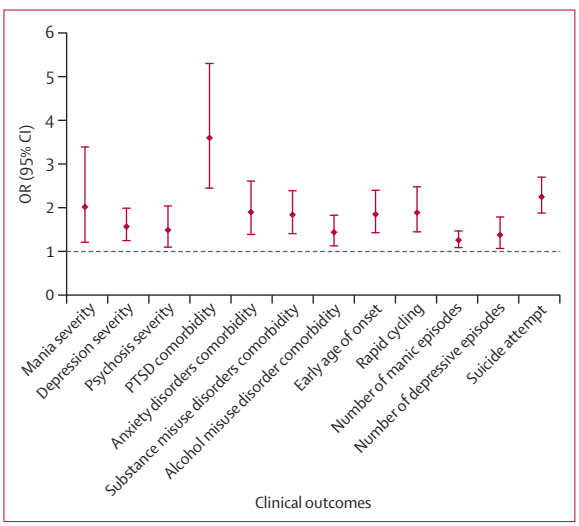

Figure 2: **Combined effect sizes and 95% CIs from 12 independent meta-analyses testing the association of childhood maltreatment with course of illness and clinical features in bipolar disorder**
Error bars show 95% CIs. OR=odds ratio. PTSD=post-traumatic stress disorder.

small (less precise) studies with inflated effect sizes. Because of the low statistical power of these tests, we used a trim-and-fill procedure[35] that aims to both identify and correct for funnel-plot asymmetry arising from publication bias via imputation strategies. The trim-and-fill results were similar to the results of our original meta-analyses (data not shown).

Jack-knife sensitivity analyses showed overall little evidence for undue effects of individual studies in the meta-analyses (table 1). Overall, childhood maltreatment predicted a significant increase in odds of the 12 outcomes investigated in automated permutations, whereby each study was omitted in turn (table 1). However, the permutation in which the study by Romero and colleagues[63] was eliminated resulted in a non-significant estimate for the meta-analysis of the association between childhood maltreatment and psychosis severity (OR 1·30, 95% CI 0·92–1·84, p=0·131). Omission of the studies by Brown and colleagues[39] and by Sala and colleagues[64] led to a non-significant estimate for the meta-analysis of the association between childhood maltreatment and number of depressive episodes (OR 1·34, 95% CI 0·98–1·83, p=0·066; 1·37, 0·96–1·96, p=0·079, respectively).

Overall, our meta-regression analyses showed that variation in study quality was not associated with variation in effect sizes across the 12 meta-analyses (table 2). However, studies of better quality identified stronger associations between childhood maltreatment and number of depressive episodes (table 2). Furthermore, studies that included a larger proportion of patients with bipolar disorder type 1 identified stronger associations between childhood maltreatment and number of depressive episodes (table 2). Variation in the mean age of participants, proportion of women in the sample, or proportion of white participants was generally not associated with variation in effect sizes across the meta-analyses.

Discussion

Our meta-analysis showed that a history of childhood maltreatment in patients with bipolar disorder is associated with a heightened risk of severity of manic, depressive, and

	Included studies	Meta-regression coefficient (95%CI)	p value
Mania severity			
Quality (NOS)	6	–0·137 (–0·703 to 0·430)	0·540
Mean age	6	–0·008 (–0·070 to 0·055)	0·747
Bipolar disorder type 1	5	–0·001 (–0·035 to 0·033)	0·926
Women	5	0·040 (–0·198 to 0·278)	0·630
White	2	NA	NA
Depression severity			
Quality (NOS)	8	0·154 (–0·045 to 0·353)	0·107
Mean age	7	0·005 (–0·020 to 0·030)	0·638
Bipolar disorder type 1	6	0·000 (–0·014 to 0·014)	0·982
Women	7	0·006 (–0·031 to 0·042)	0·759
White	2	NA	NA
Psychosis severity			
Quality (NOS)	7	0·031 (–0·357 to 0·419)	0·847
Mean age	7	–0·012 (–0·35 to 0·012)	0·260
Bipolar disorder type 1	4	–0·012 (–0·065 to 0·041)	0·441
Women	7	0·006 (–0·012 to 0·024)	0·416
White	5	–0·007 (–0·072 to 0·058)	0·749
PTSD comorbidity			
Quality (NOS)	8	0·000 (–0·043 to 0·043)	1·000
Mean age	8	–0·026 (–0·074 to 0·022)	0·235
Bipolar disorder type 1	7	–0·015 (–0·037 to 0·007)	0·179
Women	7	–0·001 (–0·038 to –0·036)	0·958
White	5	0·006 (–0·062 to 0·073)	0·812
Anxiety disorders comorbidity			
Quality (NOS)	7	0·122 (–0·155 to 0·398)	0·310
Mean age	7	0·008 (–0·038 to 0·053)	0·690
Bipolar disorder type 1	5	0·018 (–0·017 to 0·053)	0·308
Women	6	0·000 (–0·030 to 0·031)	0·979
White	3	–0·051 (–0·310 to –0·209)	0·245
Substance misuse disorders comorbidity			
Quality (NOS)	10	0·007 (–0·306 to 0·320)	0·961
Mean age	11	–0·016 (–0·046 to 0·015)	0·286
Bipolar disorder type 1	11	–0·005 (–0·020 to 0·010)	0·525
Women	10	–0·003 (–0·024 to 0·018)	0·758
White	5	–0·005 (–0·068 to 0·058)	0·803
Alcohol misuse disorder comorbidity			
Quality (NOS)	7	0·215 (–0·275 to 0·705)	0·311
Mean age	8	0·067 (–0·024 to 0·159)	0·122
Bipolar disorder type 1	8	0·012 (–0·005 to 0·029)	0·177
Women	8	–0·007 (–0·027 to 0·012)	0·407
White	3	0·032 (–0·254 to 0·318)	0·393
Age of bipolar disorder onset			
Quality (NOS)	14	–0·075 (–0·245 to 0·096)	0·358
Mean age	14	0·017 (–0·008 to 0·042)	0·160
Bipolar disorder type 1	10	0·007 (–0·004 to 0·017)	0·205
Women	13	0·005 (–0·010 to 0·019)	0·495
White	8	0·022 (–0·033 to 0·079)	0·352
Rapid cycling			
Quality (NOS)	8	–0·076 (–0·463 to 0·311)	0·649
Mean age	8	0·043 (–0·082 to 0·168)	0·431
Bipolar disorder type 1	7	0·010 (–0·014 to 0·034)	0·322
Women	7	–0·001 (–0·021 to 0·019)	0·928
White	3	0·041 (–0·344 to 0·426)	0·406
Number of manic episodes			
Quality (NOS)	7	0·058 (–0·213 to 0·328)	0·607
Mean age	7	0·019 (–0·032 to 0·071)	0·382
Bipolar disorder type 1	7	0·008 (–0·007 to 0·022)	0·320
Women	7	–0·001 (–0·017 to 0·004)	0·177
White	3	0·041 (–0·344 to 0·426)	0·406
Number of depressive episodes			
Quality (NOS)	8	0·265 (0·005 to 0·525)	0·047
Mean age	8	0·007 (–0·064 to 0·078)	0·812
Bipolar disorder type 1	8	0·018 (0·007 to 0·030)	0·002
Women	8	–0·005 (–0·024 to 0·015)	0·581
White	4	0·002 (–0·055 to 0·059)	0·888
Suicide attempt			
Quality (NOS)	13	–0·067 (–0·213 to 0·079)	0·336
Mean age	13	–0·004 (–0·024 to 0·017)	0·693
Bipolar disorder type 1	12	–0·004 (–0·017 to 0·009)	0·540
Women	12	0·008 (–0·019 to 0·034)	0·581
White	6	–0·007 (–0·039 to 0·026)	0·607

(Table 2 continues in next column)

(Continued from previous column)

NOS=Newcastle–Ottawa Scale.[36] NA=not applicable, not enough observations were available to do a meta-regression. PTSD=post-traumatic stress disorder.

Table 2: **Meta-regression of clinical outcomes in patients with bipolar disorder who did and did not have a history of childhood maltreatment**

psychotic symptoms, risk of comorbid PTSD, anxiety, substance or alcohol misuse disorders, early age of bipolar disorder onset, risk of rapid cycling, number of manic and depressive episodes, and risk of suicide attempt. Overall, these associations were not accounted for by artifacts owing to publications bias, undue effect of individual studies, or variation in study quality. Our results suggest that a history of childhood maltreatment might be useful as an early indicator of bipolar disorder progression in clinical practice to identify a prevalent subgroup of patients with bipolar disorder and unfavourable clinical features and course of illness.

These findings should be interpreted in the context of important limitations. Crucially, whether childhood maltreatment should be conceptualised as a causal risk factor or as a risk indicator or marker—namely an exposure that is statistically associated with an outcome but is not necessarily its cause[67]—is unclear. Although this question cannot be fully addressed on the basis of the published literature, features of the reported analyses begin to shed light on this issue. First, because included studies relied on retrospective reports of childhood experiences, the results might represent greater bias in the recall of maltreatment in patients with bipolar disorder with worse outcomes.[68] Recall bias, or a greater likelihood of reporting exposure in participants with the

outcome, has been noted in participants with unipolar depression—presumably linked to negative bias in autobiographical memory.[69] However, findings from our study generalise across depressive and manic symptoms, which are unlikely to affect recall in a similar way. Furthermore, significant findings were reported even in studies that assessed childhood maltreatment in patients during euthymic states.[43,45,55,62] Even if unbiased, recall could be inaccurate (ie, misclassification irrespective of outcome status or poor reliability). However, inaccuracy of recall would increase a measurement error and lead to underestimation of the real association between childhood maltreatment and bipolar disorder outcomes.[70]

Second, even if the association between childhood maltreatment and bipolar disorder outcomes were real, it might be accounted for by confounders. Genetic factors that are crucial in the pathophysiology of bipolar disorder[71] might have confounded the association between childhood maltreatment and unfavourable clinical outcomes in patients with bipolar disorder. However, evidence suggests that maltreatment is associated with key outcomes even in groups in which all patients had familial risk,[65] and that maltreatment has additive predictive value beyond familial risk in non-selected groups.[53] Furthermore, several studies have reported evidence of gene–environment interactions with childhood maltreatment in patients with bipolar disorder,[57,72] which require statistical independence of the genetic and environmental effects. An additional confounder is the presence of childhood psychopathology. The presence of psychopathology might result in an increased risk of maltreatment during childhood and lead to poor clinical outcomes in later life. However, the included studies did not examine pre-existing childhood psychopathology, thus, we were unable to test these possible confounding effects.

Finally, there was significant heterogeneity in meta-analyses for mania severity, anxiety disorders comorbidity, substance misuse disorders comorbidity, and age of bipolar disorder onset (table 1). Of note, this heterogeneity was not explained by study quality. It was difficult to identify other sources of heterogeneity in the published literature, which might have included gene–environment interactions and the effects of other environmental cues during patients' life-course. Notwithstanding the use of random-effects models that partly accounted for across-study heterogeneity, the main effects noted in the analyses with significant heterogeneity should therefore be interpreted cautiously. Despite these limitations, our findings have important implications for clinical practice and future research.

With respect to clinical practice, findings from this study suggest that a history of childhood maltreatment could be used as an indicator of disease progression to identify patients with bipolar disorder who are at a high risk of unfavourable clinical features and course of illness. This contribution to risk stratification could be used to improve the delivery of effective interventions.[6] Additional research is needed to directly test whether childhood maltreatment also predicts treatment response in patients with bipolar disorder, as suggested by preliminary results in clinical trials[73] and chart review studies.[74] Furthermore, these findings point to plausible treatment strategies. On the one hand, biological vulnerabilities in this group of patients could be targeted by pharmacological interventions.[6,57] This strategy has perhaps been best implemented in treatment of major depression. Patients with depression and a history of childhood maltreatment have raised inflammation levels,[75] and anti-inflammatory treatment in patients with depression with raised inflammation levels showed promising preliminary results.[22] Some patients with bipolar disorder are also characterised by increased inflammation levels, and similar strategies might be generalisable across mood disorders.[18–23] On the other hand, the identified patterns of comorbidity represent known negative prognostic features. Patients with bipolar disorder and a history of childhood maltreatment are at a high risk of PTSD and anxiety disorders, which have been associated with negative clinical outcomes,[9,10] suggesting that treatment of trauma-related symptoms and anxiety disorders might improve clinical outcomes in this subgroup of patients with bipolar disorder.

With respect to future research, if causal, findings from our study lend support to the notion that childhood maltreatment can affect neurobiological processes associated with bipolar disorder progression, which is consistent with the stress-sensitisation model.[76,77] Additional research is needed to increase understanding of the mechanisms through which maltreatment affects these processes, including immune mechanisms.[18–23] Even in the presence of unresolved questions on causal inference, childhood maltreatment can be usefully conceptualised as a risk indicator. Similar to unipolar depression[75,78] and other psychiatric conditions,[79–82] a history of childhood maltreatment could be used to help to identify a discrete group of patients with bipolar disorder with more homogeneous biological features with important implications for genetic research. Further research in these stratified, and possibly transdiagnostic,[82] biological features associated with childhood maltreatment might find innovative treatment strategies for patients with bipolar disorder.

Contributors

AD designed the study. Both authors contributed to the literature search, data collection, data analysis, data interpretation, and manuscript writing.

Declaration of interests

We declare no competing interests.

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