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Childhood trauma and treatment outcomes during mood-stabilising treatment with lithium or quetiapine among outpatients with bipolar disorder

Running title: CHILDHOOD TRAUMA AND TREATMENT OUTCOMES IN BIPOLAR DISORDER

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ABSTRACT

Background: Childhood trauma affects the course of mood disorders. Researchers are now considering childhood trauma as an influential factor in the treatment of mood disorders. However, the role of childhood trauma in the treatment of bipolar disorder remains understudied.

Methods: The effect of childhood trauma on treatment outcomes was evaluated among participants randomised to treatment with lithium or quetiapine in the Clinical and Health Outcomes Initiatives in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE) study by clinician assessment. Mixed effects linear regression models were used to analyse rates of improvement in symptom severity (assessed with the Bipolar Inventory of Symptoms Scale and the Clinical Global Impression Scale for Bipolar Disorder) and functional impairment (assessed with the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool).

Results: A history of any childhood trauma was reported by 52.7% of the sample (*N* = 476). Although participants with a history of any childhood trauma presented with greater symptom severity and functional impairment at most study visits, participants with and without a history of any childhood trauma showed similar rates of improvement in symptom severity and functional impairment over the 24 weeks of treatment.

Conclusion: This is the first study to explore the association between childhood trauma and treatment outcomes during treatment with lithium or quetiapine in the context of a randomised trial. In Bipolar CHOICE, a history of childhood trauma did not inhibit improvement in symptom severity or functional impairment. Nevertheless, these findings need replication across different settings.

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Keywords: bipolar disorder, childhood abuse, lithium, quetiapine, treatment outcomes

SIGNIFICANT OUTCOMES AND LIMITATIONS

Significant outcomes

A history of any childhood trauma was reported by more than 50% of the current sample.

Although participants with a history of childhood trauma experienced more severe symptoms and greater functional impairment at most study visits, participants with and without a history of childhood trauma did not differ in rates of improvement during mood-stabilising treatment with lithium or quetiapine as assessed in the Bipolar CHOICE study.

The data were collected as part of a randomised trial; hence, our findings require replication across different settings. Nevertheless, the present study adds to the scarce body of literature on the role of childhood trauma in the treatment of bipolar disorder.

Limitations

Bipolar CHOICE had no placebo group; therefore, regression to the mean cannot be excluded as a plausible reason for the present findings.

Only outpatients participated in Bipolar CHOICE; hence, the current results are not applicable to an inpatient population.

Childhood trauma was not assessed with a validated questionnaire, potentially underestimating the number of participants with a history of childhood trauma.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

INTRODUCTION

Treatment outcomes – including symptomatic remission and social and occupational functioning – among individuals with bipolar disorder are often suboptimal [1, 2]. Therefore, identifying factors that contribute to poor treatment outcomes is of considerable clinical relevance [3, 4]. It is well-established that childhood trauma plays a role in the course of bipolar disorder [5, 6]. The large meta-analysis by Agnew-Blais and Danese [7], for example, suggested that childhood trauma is related to an earlier onset and a greater number of mood episodes

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as well as to higher rates of rapid cycling, psychotic symptoms, and psychiatric comorbidities in bipolar disorder.

More recently, researchers have considered childhood trauma as a potentially important factor in the treatment of mood disorders [7, 8]. Several studies have demonstrated an association between childhood trauma and poorer response to pharmacotherapy in both adolescent and adult samples diagnosed with major depressive disorder [9-12]. Although there are only few small-scale studies that examined a similar association in bipolar disorder [13-17], initial findings highlight that childhood trauma might also moderate treatment outcomes in this population.

For instance, Cakir et al. [14] evaluated data from a sample of 135 euthymic outpatients with bipolar disorder who either received anticonvulsants (i.e., valproate or carbamazepine) or lithium as maintenance treatment (i.e., for at least 3 years). The researchers showed that participants who responded poorly to long-term treatment with anticonvulsants – in comparison to participants who responded adequately – had experienced more severe physical and/or emotional abuse in childhood. In contrast to these findings, no association was found between childhood trauma and participants' response to long-term lithium treatment.

The study by Etain et al. [13] contrasts with that of Cakir et al. [14]. These researchers reported that childhood physical abuse – but not sexual or emotional abuse – was inversely related to response to treatment with lithium among 148 euthymic participants with bipolar disorder. Additionally, Etain et al. [13] indicated that participants who experienced multiple types of childhood trauma (i.e., physical, sexual, or emotional abuse) were more likely to have an inadequate response to lithium than those participants who were not exposed to any trauma during childhood.

To note, whether these associations with childhood trauma are direct or indirect remains an unexplored issue. However, several plausible mediators have been proposed. For instance, survivors of childhood trauma are less likely to adhere to pharmacological treatments [18-20] and non-adherence significantly reduces treatment effectiveness [8, 21]. Moreover, experiences of childhood trauma may impede individuals' likelihood of establishing an adaptive therapeutic alliance [8, 22, 23]; a strong and positive therapeutic alliance greatly facilitates adherence to pharmacological treatments [24-26].

Aim of the study

As the existing evidence on the differential response to lithium treatment among individuals with bipolar disorder who have a history of childhood trauma is underscored by conflicting

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results, additional examination is warranted. Furthermore, there is a lack of clinical studies that investigate whether childhood trauma affects treatment with antipsychotics. This is despite both conventional and atypical antipsychotics being guideline recommended therapies for bipolar disorder [27]. Hence, we explored the association between childhood trauma and treatment outcomes (including improvements in symptom severity and functional impairment) among outpatients with bipolar disorder who were randomised to mood-stabilising treatment with lithium (a classic mood stabiliser) or quetiapine (a second-generation atypical antipsychotic).

METHODS AND MATERIALS

Study design

We completed secondary analyses using data from the Clinical Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE) study [28]. Bipolar CHOICE, a randomised comparative effectiveness trial, was conducted over 6 months at multiple sites to compare the efficacy of lithium and quetiapine for the treatment of bipolar disorder. Lithium and quetiapine were combined with evidence-based and guideline-informed treatments (referred to as Adjunctive Personalised Treatment [APT]). The APTs were personalised according to the participants' current symptomatology, course of the condition, and treatment history.

The Institutional Review Boards at all sites provided ethical approval for Bipolar CHOICE. Participants gave written informed consent in the presence of a study clinician before completing any research assessments. Further details pertaining to the study protocol developed for Bipolar CHOICE, including its rationale and design, have been previously reported [28]. Bipolar CHOICE was registered (see ClinicalTrials.gov identifier NCT01331304).

Participants

A total of 692 adult outpatients (between 18 and 62 years of age) were screened for participation in Bipolar CHOICE; 482 of these were randomised. Participants were required to meet the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [29] criteria for bipolar I or bipolar II disorder and present with at least mild depressive or (hypo)manic symptoms – as indicated by a Clinical Global Impression Scale for Bipolar Disorder (CGI-BP) score of ≥ 3 [30] – at entry to the study [28]. Limited exclusion criteria were applied to facilitate 'real-world' scenarios and increase the generalisability of the findings. The participants completed clinical assessments at baseline and eight follow-up visits (i.e., at weeks 2, 4, 6, 8, 12, 16, 20, and 24).

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Assessments

Diagnostic assessment

At baseline, diagnostic assessments were performed with an electronic version of the extended Mini-International Neuropsychiatric Interview (MINI) [31] – a validated but brief structured interview for psychiatric and substance use disorders (including current and lifetime diagnoses). During a clinical interview, study clinicians also collected demographic information and details on participants' psychiatric history.

Assessment of childhood trauma

Based on a question included in the clinical interview (i.e., "Did the patient experience abuse during childhood?"), study clinicians recorded: (1) whether participants had experienced any abuse during childhood (i.e., rated as present or absent); and (2) what type of childhood abuse (i.e., physical, sexual, emotional, other), if applicable. The study clinicians did not inquire about the participants' subjective perception of the abuse; therefore, participants were coded as having a history of any childhood trauma if they were exposed to at least one of the following: physical abuse, sexual abuse, or emotional abuse. This conceptualisation of childhood trauma is in line with previous research [13, 32] and the assumption that those experiences are likely to be perceived as traumatic by most people [32].

Assessment of symptom severity

At baseline and all follow-up visits, symptom severity was assessed with the Bipolar Inventory of Symptoms Scale (BISS) [33, 34] and the CGI-BP [30]. The BISS is a structured interview for the assessment of mood symptoms that consists of 44 items, each rated on a scale from 0 to 4. Higher scores indicate greater symptom severity. The BISS yields an overall illness severity score as well as five domain scores (depression, mania, anxiety, irritability, and psychosis). For their ratings, study clinicians used information provided by participants via self-report but also considered observations made during the interview and outside the assessment.

The CGI-BP [30] is a clinician-rated scale for the assessment of illness severity which is scored on a scale from 1 ('normal, not at all ill') to 7 ('among the most extremely ill patients'). Similar to the BISS, the CGI-BP yields a score for the overall illness severity as well as domain scores for depression and mania severity. Assessments with the CGI-BP are based on the study clinicians' overall impression of the participants' presentation (including reported and observed symptoms). Both the BISS and the CGI-BP have demonstrated adequate psychometric properties (for detailed discussions, see [30, 33, 34]).

Assessment of functional impairment

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At baseline and weeks 12 and 24, functional impairment was measured with the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) [35, 36]. The LIFE-RIFT is a semi-structured interview for the assessment of impairment in functioning, specifically due to psychopathology, in four domains (work, interpersonal relationships, recreation, and life satisfaction). Impairment in these domains is rated on a scale from 1 ('no impairment') to 5 ('severe impairment'). Scores of 0 ('not applicable') and 6 ('no information') are coded as missing. The LIFE-RIFT has also shown adequate psychometric properties (for detailed discussions, see [35, 36]).

Assessment of Necessary Clinical Adjustments

At all follow-up visits, the number of Necessary Clinical Adjustments (NCAs; i.e., required medication changes) were recorded indicating treatment complexity.

Statistical analysis

Primary analysis

All statistical analyses were conducted with STATA 14.0 [37]. For our primary analysis, we distinguished between (1) participants with a history of any childhood trauma and (2) participants without a history of any childhood trauma. To study differences between these two groups at entry to Bipolar CHOICE (i.e., baseline), we conducted several logistic regressions and obtained odds ratios (OR) including 95% confidence intervals (CI) of the ORs from these models. We conducted additional logistic regressions to explore differences between the two groups in maximum dose of lithium/quetiapine received at week 2.

To explore differences in treatment outcomes between participants with and without a history of any childhood trauma, we completed a series of mixed effects linear regression models using a repeated measures approach; *β*-coefficients including 95% CI were estimated. These models allow the inclusion of all available data collected across multiple time points and can adequately handle missing data [38].

We examined the association of childhood trauma with clinical outcomes (i.e., symptom severity *and* functional impairment) during the 24-week follow-up. We then examined rates of improvement in participants with and without a history of any childhood trauma over the course of the entire study period; treatment outcomes were indicated by participants' change in total scores on the following measures: BISS (overall severity), CGI-BP (overall severity), and LIFE-RIFT (overall impairment). We adjusted all models for age, sex, and participants' baseline score on the relevant outcome measure. To test the robustness of the models, we reran the analyses excluding participants with a diagnosis of posttraumatic stress disorder.

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340

341 ***Secondary analyses***

342 A range of secondary analyses using additional mixed effects linear regression models was
343 conducted. First, we completed similar models among individuals randomised to lithium or
344 quetiapine, respectively. Second, we wanted to distinguish between the different types of
345 childhood trauma and compared individuals who were exposed to physical abuse, sexual
346 abuse, or emotional abuse to participants without a history of any childhood trauma. Finally,
347 we conducted a secondary analysis considering the number of childhood trauma types (i.e., 0
348 vs. 1, 2, or 3) experienced. In all secondary analyses, participants without a history of any
349 childhood trauma were used as the reference group.

350

351 As exploratory analyses, we completed similar models among men and women. Finally, we
352 also calculated mixed effects linear regression models (adjusted for age and sex) to
353 investigate differences in number of NCAs required over the course of 24 weeks of treatment
354 between participants with and without a history of any childhood trauma.

355

356 **RESULTS**

357 Of the 482 patients who were randomised for Bipolar CHOICE, six participants were excluded
358 from the current analyses because they had not experienced physical, sexual, and/or
359 emotional abuse in childhood but were exposed to "other" abuse. Details about the
360 participants' "other" abuse experiences were not available. Among the remaining 476
361 participants, 52.7% (*n* = 251) were exposed to any childhood trauma. Of these, 47.0% (*n* =
362 118) were exposed to one type of childhood trauma, 24.7% (*n* = 62) were exposed to two
363 types of childhood trauma, and 28.3% (*n* = 71) were exposed to all three types of childhood
364 trauma. Specifically, 49.4% (*n* = 124) participants were exposed to physical abuse, 56.2% (*n*
365 = 141) participants were exposed to sexual abuse, and 75.7% (*n* = 190) participants were
366 exposed to emotional abuse.

367

368 The baseline characteristics for participants with and without a history of any childhood trauma
369 are presented in Table 1. There was no significant difference between groups in age but
370 participants with a history of any childhood trauma were more likely to be female. Childhood
371 trauma was also associated with an earlier age at symptom onset (depression and mania),
372 higher number of depressive episodes, higher rates and number of suicide attempts, higher
373 rates of prior psychiatric hospitalisation, and higher rates of comorbidity with posttraumatic
374 stress disorder and lifetime substance abuse. At baseline, participants with a history of any
375 childhood trauma presented with greater symptom severity (depression, mania, anxiety,
376 irritability, and psychosis) as well as greater functional impairment. At week 2, there was no

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significant difference between groups in maximum dose of lithium (no childhood trauma: *M* = 995mg, *SD* = 387mg; any childhood trauma: *M* = 1040mg; *SD* = 351mg) or quetiapine (no childhood trauma: *M* = 340mg, *SD* = 171mg; any childhood trauma: *M* = 349mg; *SD* = 167mg) received (all $p > 0.1$).

The effect of any childhood trauma on symptom severity and functional impairment

The adjusted mixed effects linear regression models showed significant reductions in symptom severity among participants with and without a history of any childhood trauma. After 24 weeks of treatment with lithium or quetiapine, participants with a history of any childhood trauma had a mean BISS score of 31.3 (*SD* = 22.8) and a mean CGI-BP score of 2.92 (*SD* = 1.31). Participants without a history of any childhood trauma had a mean BISS score of 27.1 (*SD* = 21.0) and a mean CGI-BP score of 2.76 (*SD* = 1.37).

Participants with a history of any childhood trauma had significantly higher mean BISS and CGI-BP scores at each study visit (all $p < 0.05$) except the 24-week follow-up visit (BISS: $p = 0.12$; CGI-BP: $p = 0.10$), than participants without a history of any childhood trauma. Regarding rates of improvement or symptom reduction during the 24 weeks of treatment, there was no significant difference between participants with and without a history of any childhood trauma as indicated by both the BISS ($\beta = -0.33$, 95% CI = -0.18 – 0.12, $p = 0.68$) and the CGI-BP ($\beta = 0.003$, 95% CI = -0.005 – 0.01, $p = 0.45$; see Figure 1).

The adjusted mixed effects linear regression models also showed significant reductions in functional impairment among participants with and without a history of any childhood trauma. At the 24-week follow-up visit, participants with a history of any childhood trauma had a mean LIFE-RFT score of 10.8 (*SD* = 3.7) whereas participants without a history of any childhood trauma had a mean LIFE-RIFT score of 9.9 (*SD* = 3.8).

In comparison to participants without a history of any childhood trauma, participants with a history of any childhood trauma had significantly higher mean LIFE-RIFT scores at week 12 and 24 (all $p < 0.05$). Similar to symptom severity, there was no significant difference between participants with and without a history of any childhood trauma in rates of improvement or reduction in functional impairment as indicated by the LIFE-RIFT ($\beta = 0.01$, 95% CI = -0.22 – 0.04, $p = 0.56$; see Figure 1). This pattern of findings was unaffected by the exclusion of participants with a diagnosis of posttraumatic stress disorder.

The effect of treatment arm, type of childhood trauma, and number of childhood trauma types experienced

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In the initial secondary analysis, we distinguished between participants randomised to lithium or quetiapine. In both treatment arms, participants with a history of any childhood trauma had significantly higher BISS and CGI-BP scores at each study visit (all $p < 0.05$) except the 24-week follow-up (lithium: BISS: $p = 0.21$; CGI-BP: $p = 0.18$; quetiapine: BISS: $p = 0.33$; CGI-BP: $p = 0.73$) as well as higher LIFE-RIFT scores at each study visit (all $p < 0.05$), than participants without a history of any childhood trauma. For either treatment arm, there was no significant difference in rates of improvement between participants with and without a history of any childhood trauma on the BISS, the CGI-BP, and the LIFE-RIFT (all $p > 0.1$).

Next, we distinguished by the type of childhood trauma experienced. In comparison to participants without a history of any childhood trauma, participants with a history of physical abuse, sexual abuse, and emotional abuse had significantly higher BISS, CGI-BP, and LIFE-RIFT scores at each study visit (all $p < 0.05$). Participants with a history of physical abuse, sexual abuse, or emotional abuse and participants without a history of any childhood trauma did not differ in rates of improvement on the BISS, the CGI-BP, and the LIFE-RIFT (all $p > 0.1$; see Figure 2).

Finally, we distinguished by the number of childhood trauma types experienced. Participants with a history of childhood trauma consisting of exposure to both a single or multiple childhood trauma types (2 or 3) had significantly higher BISS, CGI-BP, and LIFE-RIFT scores at each study visit (all $p < 0.05$), than participants without a history of any childhood trauma. There was no significant difference in rates of improvement in functional impairment between participants who were exposed to a single or multiple childhood trauma types and participants without a history of any childhood trauma as indicated by the LIFE-RIFT ($p > 0.1$; see Figure 3).

However, participants who were exposed to all three childhood trauma types – but not participants who were exposed to one or two types (all $p > 0.3$) – showed significantly higher rates of improvement in symptom severity on the BISS ($\beta = 4.99$, 95% CI = 0.21 – 9.77, $p = 0.04$) but not on the CGI-BP ($\beta = 0.03$, 95% CI = -0.26 – 0.32, $p = 0.83$), than participants without a history of any childhood trauma (see Figure 3).

The exploration of the effect of sex

For both men and women, there was no significant difference in rates of improvement between participants with and without a history of any childhood trauma on the BISS, the CGI-BP, and the LIFE-RIFT (all $p > 0.1$).

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The exploration of treatment complexity

Over the course of 24 weeks of treatment with lithium or quetiapine, participants with a history of any childhood trauma had a mean of 8.90 (*SD* = 6.12) NCAs while participants without a history of any childhood trauma had a mean of 9.44 (*SD* = 6.30) NCAs; there was no significant difference ($p = 0.34$).

DISCUSSION

To our knowledge, this is the first study to explore the effect of childhood trauma on treatment outcomes during mood-stabilising treatment with lithium or quetiapine provided in the context of a randomised trial. More than 50% of our sample reported a history of any childhood trauma; those participants were more likely to be female. Childhood trauma was related to several indicators of a worse course and prognosis of bipolar disorder including an earlier age at symptom onset, greater number of episodes, and higher rates of comorbidities. These observations are in line with the existing body of research [7, 39-41].

Participants with a history of any childhood trauma presented with greater symptom severity and functional impairment at most study visits. However, participants with and without a history of any childhood trauma showed *similar* rates of improvement in symptom severity and functional impairment over the 24 weeks of treatment. Neither treatment allocation (i.e., lithium or quetiapine) nor type of childhood trauma (i.e., physical, sexual, or emotional abuse) affected the aforementioned pattern of findings. In contrast, we found an effect of the number of childhood trauma types experienced with participants who were exposed to all three types of childhood abuse showing *greater* improvement in symptom severity – but not functional impairment – than participants without a history of any childhood trauma.

Childhood trauma and change in symptom severity during treatment with lithium or quetiapine

Our findings are consistent with two observational studies that were unable to demonstrate an association between participants' history of any childhood trauma and response to lithium treatment [13, 14]. Our findings are discordant with a recent study by Cascino et al. [15]. In a sample of 37 outpatients with bipolar disorder, participants with a history of childhood trauma ($n = 24$) responded more poorly to lithium (i.e., showed less symptom improvement). However, studies with small sample sizes need to be interpreted cautiously.

The present study is the first to investigate differences in treatment outcomes between participants with and without a history of any childhood trauma during treatment with quetiapine, specifically. Nevertheless, a previous study evaluated symptomatic remission

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among patients with bipolar disorder treated with various antipsychotics and/or mood stabilisers (including quetiapine) [17]. In line with our results, Perugi et al. [17] reported that childhood trauma was not associated with participants' remission rates after 12 weeks of pharmacotherapy.

Childhood trauma and change in functional impairment during treatment with lithium or quetiapine

This is also the first study to examine the effect of childhood trauma on improvement in functional impairment during treatment with lithium or quetiapine, specifically. Benarous et al. [16] and Conus et al. [42], however, evaluated the association between childhood trauma and global functioning in the context of service models (inpatient treatment and early intervention program, respectively). Our findings support the study by Conus et al. [42] in which no association between childhood trauma and functional remission at discharge from the service was found.

Interestingly, our results contrast with Benarous et al. [16] who demonstrated *greater* improvement in global functioning among participants with a history of childhood trauma. Differences in sample characteristics may be responsible for the conflicting findings. Contrary to our study, Benarous et al. [16] recruited children and adolescents with bipolar I disorder who were admitted for treatment to a psychiatric hospital. Thus, patients with a history of childhood trauma may especially benefit from receiving treatment early and in an inpatient setting (rather than an outpatient setting).

Childhood trauma – type and number of abuse experiences

Our null result pertaining to the type of childhood trauma (physical, sexual, or emotional abuse) is surprising in the context of previously published research [13, 15]. Both Etain et al. [13] and Cascino et al. [15] suggested that physical abuse – not sexual or emotional abuse – was negatively associated with treatment outcome after treatment with lithium. Unlike these studies, we were unable to provide evidence of the specific implication of one childhood trauma type.

Similarly, our finding that participants who were exposed to multiple types of childhood trauma (physical, sexual, *and* emotional abuse) showed *greater* improvement in symptom severity than participants without a history of childhood trauma is discordant with previous research [13]. Specifically, Etain et al. [13] reported that participants who experienced two or three types of childhood trauma had a *poorer* response to lithium treatment than participants without a history of childhood trauma.

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Methodological differences may partly explain the inconsistent results. Etain et al. [13] and Cascino et al. [15] conducted observational studies in which they retrospectively assessed response to lithium treatment among currently euthymic patients. In contrast, in Bipolar CHOICE, the treatment outcomes of symptomatic patients were prospectively monitored over the course of 24 weeks in the context of a randomised trial of lithium and quetiapine. Therefore, the direct comparison of the three studies is limited.

Strengths and limitations

This is the first study to comprehensively examine the association between childhood trauma and treatment outcomes (including improvements in symptom severity *and* functional impairment) during treatment with lithium or quetiapine in the context of a randomised trial (i.e., Bipolar CHOICE). As a pragmatic trial, Bipolar CHOICE was designed to collect data from a representative and generalisable sample of adult outpatients with bipolar disorder receiving treatment in a 'real-world' context, which greatly increases the translational value of the present findings. Additionally, with 476 participants, this is the largest study to date investigating the role of childhood trauma in the treatment of bipolar disorder.

However, some limitations must also be considered. The data on childhood trauma were not collected with a validated questionnaire (e.g., Childhood Trauma Questionnaire), potentially leading to systematic measurement error. Consequently, the number of participants with a history of childhood trauma may have been underestimated or overestimated. However, the prevalence of childhood trauma in our sample (52.7%) is comparable to that reported in previous studies [43-45]. Additionally, the retrospective assessment of childhood trauma may be influenced by recall bias. Nevertheless, previous research suggests that individuals with a serious mental illness (including bipolar disorder) are able to provide reliable information on experiences of childhood trauma in adulthood [46, 47].

Then, details pertaining to participants' exposure to childhood trauma (e.g., age at exposure, frequency/duration of exposure) were not collected. Exposure characteristics have been implicated as moderators of the effect of childhood trauma in participants with other serious mental illnesses [32, 48]. Thus, their consideration may also be a useful addition to future clinical research on bipolar disorder. Moreover, Bipolar CHOICE had no placebo group; therefore, we cannot exclude regression to the mean as a plausible reason for the present findings. Furthermore, only outpatients were considered for participation in the study; hence, the current results are not applicable to an inpatient population. Finally, other second-generation

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antipsychotics than quetiapine could not be prescribed in either treatment arm limiting the ecological validity of Bipolar CHOICE.

Implications and future directions

The administration of Adjunctive Personalised Treatment (APT) during Bipolar CHOICE was coordinated by highly trained clinicians with extensive experience in the treatment of bipolar disorder. These clinicians were specifically instructed to use APT to facilitate sustained remission [28]. Treatment decisions were based on comprehensive diagnostic assessments and made according to evidence-based guidelines [28]. As such, the findings of the present study suggest that a history of childhood trauma does not inhibit improvement in symptom severity or functional impairment in the context of *evidence-based pharmacotherapy administered by a skilled clinician*. This is important to emphasise as psychiatrists perceive "treatment [to be] made more challenging by trauma" [49; p. 3].

What remains unclear, however, is whether a history of childhood trauma impacts treatment outcomes in a more naturalistic (i.e., "less ideal") treatment setting; previous studies in this area are hampered by small sample sizes and methodological limitations. Furthermore, considering its high prevalence among people diagnosed with bipolar disorder, childhood trauma may affect other treatment-related factors (e.g., treatment engagement, treatment adherence, treatment alliance), if it is not directly related to treatment outcomes. For instance, while Conus et al. [42] found no association between childhood trauma and symptomatic remission, participants with a history of childhood trauma were more likely to prematurely disengage from the service.

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735 **Figure 1.** Mean BISS (left) and LIFE-RIFT (right) scores for participants with and without a history of any childhood trauma during 24 weeks of treatment with
736 lithium or quetiapine.

737 Abbreviations: BISS = Bipolar Inventory of Symptoms Scale; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool

738 **Figure 2.** Mean BISS (left) and LIFE-RIFT (right) scores for participants with and without a history of childhood trauma during 24 weeks of treatment with lithium
739 or quetiapine, divided according to the type of childhood trauma experienced.

740 Abbreviations: BISS = Bipolar Inventory of Symptoms Scale; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool.

741 **Figure 3.** Mean BISS (left) and LIFE-RIFT (right) scores for participants with and without a history of childhood trauma during 24 weeks of treatment with lithium
742 or quetiapine, divided according to the number of childhood trauma types experienced.

743 Abbreviations: BISS = Bipolar Inventory of Symptoms Scale; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool.
744 Note: Participants in the 1_Type group were exposed to a single childhood trauma type, participants in the 2_Type group to two types, and participants in the
745 3_Type group to all three types.

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Table 1. Baseline characteristics among 476 outpatients with bipolar disorder with and without a history of any childhood trauma.

	No childhood trauma	Any childhood trauma	OR (95% CI)
Total N (%)	225 (47.3)	251 (52.7)	-
Mean age ± SD	38.7 ± 13.0	39.0 ± 11.3	1.00 (0.98-1.02)
Female sex, n (%)	113 (50.2)	169 (67.3)	**2.04 (1.40-2.96)**
Age at onset of depressive symptoms, mean ± SD	18.3 ± 8.7	14.8 ± 6.9	**0.94 (0.91-0.96)**
Age at onset of manic symptoms, mean ± SD	21.3 ± 10.0	18.4 ± 8.7	**0.96 (0.94-0.98)**
Number of depressive episodes, mean ± SD	35.5 ± 37.5	43.2 ± 44.4	**1.01 (1.00-1.01)**
Number of manic episodes, mean ± SD	34.0 ± 43.3	41.1 ± 50.9	1.00 (1.00-1.01)
Any previous suicide attempt, n (%)	60 (26.7)	128 (51.0)	**2.69 (1.84-3.94)**
Number of suicide attempts, mean ± SD	0.48 ± 1.06	1.56 ± 3.96	**1.49 (1.25-1.78)**
Any previous psychiatric hospitalisation, n (%)	93 (41.3)	131 (52.2)	**1.48 (1.03-2.12)**
Number of hospitalisations, mean ± SD	2.64 ± 3.04	3.85 ± 6.33	1.07 (0.98-1.16)
Psychiatric comorbidities, n (%)			
Posttraumatic stress disorder	15 (6.7)	43 (17.2)	**2.89 (1.55-5.37)**
Generalised anxiety disorder	43 (19.1)	64 (24.7)	1.40 (0.90-2.17)
Social phobia/anxiety	49 (21.8)	69 (27.5)	1.34 (0.88-2.04)
Any substance dependence (past 12 months)	18 (8.0)	24 (9.6)	1.21 (0.64-2.30)
Any substance dependence (lifetime)	13 (5.8)	14 (5.6)	0.96 (0.44-2.09)
Any substance abuse (past 12 months)	39 (17.3)	38 (15.1)	0.85 (0.52-1.38)
Any substance abuse (lifetime)	70 (31.1)	103 (41.0)	**1.54 (1.05-2.25)**
Baseline BISS score overall, mean ± SD	52.9 ± 19.2	60.1 ± 18.7	**1.02 (1.01-1.03)**
BISS Depression	29.3 ± 12.7	31.6 ± 13.1	**1.01 (1.00-1.02)**
BISS Mania	13.6 ± 10.3	15.8 ± 10.6	**1.02 (1.00-1.03)**
BISS Anxiety	7.48 ± 4.19	8.44 ± 4.28	**1.05 (1.01-1.10)**
BISS Irritability	5.84 ± 3.48	7.47 ± 3.16	**1.15 (1.09-1.22)**
BISS Psychosis	0.82 ± 1.58	1.23 ± 1.90	**1.15 (1.03-1.28)**
Baseline CGI-BP score overall, mean ± SD	4.45 ± 0.89	4.52 ± 0.82	1.09 (0.88-1.34)

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CGI-BP Depression	4.24 ±1.09	4.24 ±1.16	1.00 (0.84-1.16)
CGI-BP Mania	2.86 ±1.27	3.10 ±1.24	**1.15 (1.00-1.33)**
Baseline LIFE-RIFT score, mean ± SD	13.8 ± 3.2	14.4 ± 3.2	**1.05 (1.00-1.11)**

Abbreviations: BISS = Bipolar Inventory of Symptoms Scale; CGI-BP = Clinical Global Impression Scale for Bipolar Disorder; LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool.

Note. Of the 251 participants with a history of any childhood trauma, 124 (49.4%) were randomised to receive lithium and 127 (50.6%) to receive quetiapine. **Bold** values indicate significant differences (i.e., $p < 0.05$).

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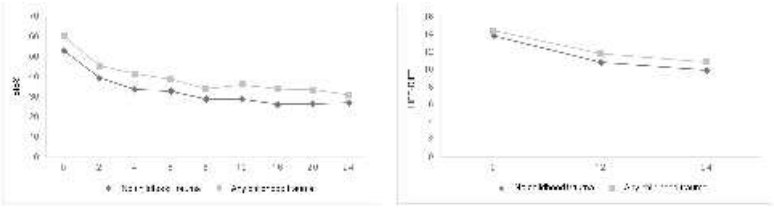

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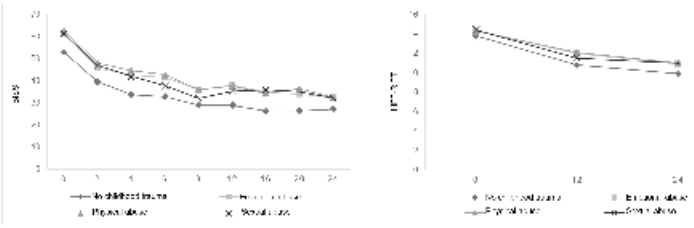

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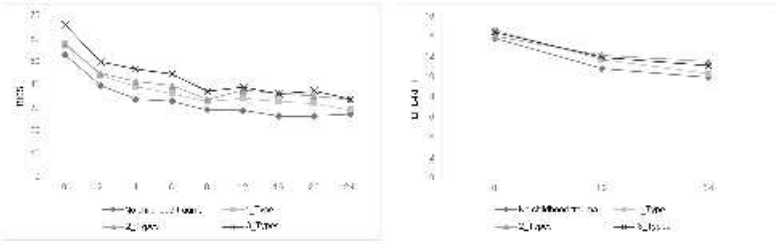

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