Original Article

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

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Acta Psychiatr Scand. 2022;145:615–627.

wileyonlinelibrary.com/journal/acps | 615
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Funding information
ALW is supported by a Deakin University Centre of Research Excellence in Psychiatric Treatment Postgraduate Research Scholarship. SER is supported by an Australian Government Research Training Program Scholarship. OMD is supported by a NHMRC R.D. Wright Biomedical Career Development Fellowship (APP1145634). SMC is supported by a NHMRC Senior Research Fellowship (APP1136344). MT is supported by the Atlas Foundation. MGM is supported by the Heinz C Prechter Bipolar Research Program and the Richard Tam Foundation. MB is supported by a NHMRC Senior Principal Research Fellowship (APP1156072). The Bipolar CHOICE trial was funded by the Agency for Healthcare Research and Quality (AHRQ): 1R01HS019371-01.

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.

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

1 INTRODUCTION

Treatment outcomes—including symptomatic remission and social and occupational functioning—among individuals with bipolar disorder are often suboptimal. Therefore, identifying factors that contribute to poor treatment outcomes is of considerable clinical relevance. It is well-established that childhood trauma plays a role in the course of bipolar disorder. The large meta-analysis by Agnew-Blais and Danese, for example, suggested that childhood trauma is related to an earlier onset and a greater number of mood episodes 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. 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. Although there are only few small-scale studies that examined a similar association in bipolar disorder, initial findings highlight that childhood trauma might also moderate treatment outcomes in this population.

For instance, Cakir et al. 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 with 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.\textsuperscript{13} contrasts with that of Cakir et al.\textsuperscript{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.\textsuperscript{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\textsuperscript{18-20} and non-adherence significantly reduces treatment effectiveness.\textsuperscript{8,21} Moreover, experiences of childhood trauma may impede individuals’ likelihood of establishing an adaptive therapeutic alliance;\textsuperscript{8,22,23} a strong and positive therapeutic alliance greatly facilitates adherence to pharmacological treatments.\textsuperscript{24-26}

\subsection*{1.1 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 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.\textsuperscript{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).

\section*{2 METHODS AND MATERIALS}

\subsection*{2.1 Study design}

We completed secondary analyses using data from the Clinical Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE) study.\textsuperscript{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.\textsuperscript{28} Bipolar CHOICE was registered (see ClinicalTrials.gov identifier NCT01331304).

\subsection*{2.2 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) 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— at entry to the study.

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).

2.3 | Assessments

2.3.1 | Diagnostic assessment

At baseline, diagnostic assessments were performed with an electronic version of the extended Mini-International Neuropsychiatric Interview (MINI) — 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.

2.3.2 | 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, and the assumption that those experiences are likely to be perceived as traumatic by most people.

2.3.3 | Assessment of symptom severity

At baseline and all follow-up visits, symptom severity was assessed with the Bipolar Inventory of Symptoms Scale (BISS) and the CGI-BP. 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 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).

2.3.4 | Assessment of functional impairment

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). 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).

2.3.5 | Assessment of necessary clinical adjustments

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

2.4 | Statistical analysis

2.4.1 | Primary analysis

All statistical analyses were conducted with STATA 14.0. 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.

2.4.2 Secondary analyses

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

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

3 RESULTS

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

The baseline characteristics for participants with and without a history of any childhood trauma are presented in Table 1. There was no significant difference between groups in age but participants with a history of any childhood trauma were more likely to be female. Childhood trauma was also associated with an earlier age at symptom onset (depression and mania), higher number of depressive episodes, higher rates and number of suicide attempts, higher rates of prior psychiatric hospitalisation, and higher rates of comorbidity with posttraumatic stress disorder and lifetime substance abuse. At baseline, participants with a history of any childhood trauma presented with greater symptom severity (depression, mania, anxiety, irritability and psychosis) as well as greater functional impairment. At week 2, there was no significant difference between groups in maximum dose of lithium (no childhood trauma: M = 995 mg, SD = 87 mg; any childhood trauma: M = 1040 mg; SD = 351 mg) or quetiapine (no childhood trauma: M = 340 mg, SD = 171 mg; any childhood trauma: M = 349 mg; SD = 167 mg) received (all p > 0.1).

3.1 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-RIFT 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 with 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.

**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 (%)**

| **** | No childhood trauma | Any childhood trauma | OR (95% CI) |
|------|----------------------|----------------------|-------------|
| 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**

| **** | No childhood trauma | Any childhood trauma | OR (95% CI) |
|------|----------------------|----------------------|-------------|
| 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**

| **** | No childhood trauma | Any childhood trauma | OR (95% CI) |
|------|----------------------|----------------------|-------------|
| 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**

| **** | No childhood trauma | Any childhood trauma | OR (95% CI) |
|------|----------------------|----------------------|-------------|
| LIFE-RIFT | 13.8 ± 3.2 | 14.4 ± 3.2 | 1.05 (1.00–1.11) |

**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., $p < 0.05$).

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.
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 lithium or quetiapine. Abbreviations: BISS, Bipolar Inventory of Symptoms Scale; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool.

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 or quetiapine, divided according to the type of childhood trauma experienced. Abbreviations: BISS, Bipolar Inventory of Symptoms Scale; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool.

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 or quetiapine, divided according to the number of childhood trauma types experienced. Abbreviations: BISS, Bipolar Inventory of Symptoms Scale; LIFE-RIFT, Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool. 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 3_Type group to all three types.
3.1.1 | The effect of treatment arm, type of childhood trauma and number of childhood trauma types experienced

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 with 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).

3.1.2 | 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 $p > 0.1$).

3.1.3 | 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 ($p = 0.34$).

4 | 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.

4.1 | 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.\(^\text{15}\) 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 among patients with bipolar disorder treated with various antipsychotics and/or mood stabilisers (including quetiapine).\(^\text{17}\) In line with our results, Perugi et al.\(^\text{17}\) reported that childhood trauma was not associated with participants’ remission rates after 12 weeks of pharmacotherapy.

### 4.2 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.\(^\text{16}\) and Conus et al.\(^\text{42}\) 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.\(^\text{42}\) 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.\(^\text{16}\) 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.\(^\text{16}\) 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).

### 4.3 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.\(^\text{13,15}\) Both Etain et al.\(^\text{13}\) and Cascino et al.\(^\text{15}\) 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.\(^\text{13}\) Specifically, Etain et al.\(^\text{13}\) 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.

Methodological differences may partly explain the inconsistent results. Etain et al.\(^\text{13}\) and Cascino et al.\(^\text{15}\) 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.

### 4.4 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.\(^\text{43-45}\) 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.12,48 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 antipsychotics than quetiapine could not be prescribed in either treatment arm limiting the ecological validity of Bipolar CHOICE.

4.5 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.

ACKNOWLEDGEMENT

Open access publishing facilitated by Deakin University, as part of the Wiley - Deakin University agreement via the Council of Australian University Librarians. [Correction added on 22 May 2022, after first online publication: CAUL funding statement has been added.]

CONFLICT OF INTEREST

ALW has received grant/research support from Deakin University. OKF has received speaker fees from Lundbeck. LS has received personal fees from United Biosource Corporation, Clintara, Bracket, and Clinical Trials Network and Institute; royalty fees from New Harbinger; grants from National Institute of Mental Health, Patient-Centered Outcomes Research Institute, American Foundation for Suicide Prevention, and Takeda. SER has received grant/research support from Deakin University. OMD has received grant/research support from the Brain and Behavior Foundation, Simons Autism Foundation, Stanley Medical Research Institute, Deakin University, Lilly, NHMRC and Australasian Society for Bipolar and Depressive Disorders (ASBDD)/Servier. OMD has also received kind support from BioMedica Nutraceuticals, NutritionCare and Biocelutical. MT is a former full-time employee at Lilly (1997–2008); he has been a consultant for AstraZeneca, Abbott, BMS, Lilly, GSK, J&J, Otsuka, Roche, Lundbeck, Elan, Allergan, AbbVie, Intracellular Therapies, Merck, Minerva, Neurocrine, Pamlab, Alexza, Forest, Teva, Sunovion and Gedeon Richter; his spouse is a former employee at Lilly (1998–2013). MM has consulted for Janssen and Otsuka Pharmaceuticals and has received research funding from Janssen Pharmaceuticals. TAK has received grant/research support from AstraZeneca Pharmaceuticals LP, Cephalon Inc., Eli Lilly and Company, Pfizer Inc., Dainippon Sumitomo Pharmaceuticals/Sepracor, Inc. Sepracor, Inc; he has also consulted for Bristol Myers Squibb Company, Cephalon Inc., Dainippon Sumitomo Pharmaceuticals/Sepracor, Inc., Merck & Co., Inc. and has received honoraria or royalties from AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, American Psychiatric Publishing, Inc; his spouse is an employee at Johnson & Johnson. RCS has received grant/research support from Acadia Pharmaceuticals, Allergan, Inc., Allergan, Inc., Assurex, Inc., Avanir Pharmaceuticals, Inc., Cerecor, Inc., Intracellular Therapies, Janssen Pharmaceutica, LivaNova PLC, Navitor Pharmaceuticals, Neurox, Novartis Pharmaceuticals, Otsuka America, Takeda Pharmaceuticals. RCS has also consulted for Acadia Pharmaceuticals, Allergan plc, Alfasigma USA Inc., Myriad Neuroscience, Novartis International AG, Evecxia Therapeutics, Sunovion Pharmaceuticals Inc., Neurorx, Inc., Seelos Therapeutics. MJO is a full-time
employee of the United States Department of Veterans Affairs and has received research support from Otsuka. MJO has also consulted for Janssen and Neurocrine. In the last five years, DVI has received consulting honors from Alkermes, Allergan, Axsome, Biogen, Centers for Psychiatric Excellence, Jazz, Lundbeck, Otsuka, Precision Neuroscience, Sage, Sunovion; he has received research support (through his academic institutions) from Alkermes, Astra Zeneca, Brainsway, Litecure, Neosync, Otsuka, Roche, Shire. MB has received grant/research support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier. AT has received travel/grant support from NHMRC, AMP Foundation, Stroke Foundation, Hunter Medical Research Institute, Helen Macpherson Smith Trust, Schizophrenia Fellowship NSW, SMHR, ISAD, the University of Newcastle and Deakin University. AAN is a consultant for the Abbott Laboratories, Alkermes, American Psychiatric Association, Appliance Computing Inc. (Mindsite), Basilea, Brain Cells, Inc., Brandeis University, Bristol Myers Squibb, Clintara, Corcept, Dey Pharmaceuticals, Dainippon Sumitomo (now Sunovion), Eli Lilly and Company, EpiQ, L.P./Mylan Inc., Forest, Genaissance, Genentech, GlaxoSmithKline, Hoffman LaRoche, Infomedic, Intra-Cellular Therapies, Lundbeck, Janssen Pharmaceutica, Jazz Pharmaceuticals, Medavante, Merck, Methylation Sciences, Naurex, NeuroRx, Novartis, Otsuka, PamLabs, Parexel, Pfizer, PGx Health, Ridge Diagnostics Shire, Schering-Plough, Somerset, Sunovion, Takeda Pharmaceuticals, Targacept and Teva; consulted through the MGH Clinical Trials Network and Institute (CTNI) for Astra Zeneca, Brain Cells, Inc, Dianippon Sumitomo/Sepracor, Johnson and Johnson, Labopharm, Merck, Methylation Science, Novartis, PGx Health, Shire, Schering-Plough, Targacept and Takeda/Lundbeck Pharmaceuticals. He receives grant/research support from American Foundation for Suicide Prevention, AHRQ, Brain and Behavior Research Foundation, Bristol Myers Squibb, Cederroth, Cephalon, Cyberonics, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen Pharmaceutica, Intra-Cellular Therapies, Lichtwer Pharma, Marriott Foundation, Mylan, NIMH, PamLabs, PCORI, Pfizer Pharmaceuticals, Shire, Stanley Foundation, Takeda and Wyeth-Ayerst. Honoraria include Belvoir Publishing, University of Texas Southwestern Dallas, Brandeis University, Bristol Myers Squibb, Hillside Hospital, American Drug Utilization Review, American Society for Clinical Psychopharmacology, Baystate Medical Center, Columbia University, CRICO, Dartmouth Medical School, Health New England, Harold Grinspoon Charitable Foundation, IMEDEX, Israel Society for Biological Psychiatry, Johns Hopkins University, MJ Consulting, New York State, Medscape, MBL Publishing, MGH Psychiatry Academy, National Association of Continuing Education, Physicians Postgraduate Press, SUNY Buffalo, University of Wisconsin, University of Pisa, University of Michigan, University of Wisconsin at Madison, World Congress of Brain Behavior and Emotion, APSARD, ISBD, SciMed, Slack Publishing and Wolters Kluwer Publishing ASCP, NCDEU, Rush Medical College, Yale University School of Medicine, NNDC, Nova Southeastern University, NAMI, Institute of Medicine, CME Institute, ISCTM. He was currently or formerly on the advisory boards of Appliance Computing, Inc., Brain Cells, Inc., Eli Lilly and Company, Genentech, Johnson and Johnson, Takeda/Lundbeck, Targacept, and InfoMedic. He owns stock options in Appliance Computing, Inc., Brain Cells, Inc, and MedAvante; has copyrights to the Clinical Positive Affect Scale and the MGH Structured Clinical Interview for the Montgomery Asberg Depression Scale exclusively licensed to the MGH Clinical Trials Network and Institute (CTNI).

AUTHOR CONTRIBUTIONS
ALW developed the research question and drafted/editd/approved the final version of the manuscript. OKF developed the research question, completed all quantitative analyses and edited/approved the final version of the manuscript. OMD, SMC, MB, AT and AAN developed the research question and edited/approved the final version of the manuscript. All other authors edited/approved the final version of the manuscript.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13420.

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.

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REFERENCES

1. Nierenberg AA. Strategies for achieving full remission when first-line antidepressants are not enough. J Clin Psychiatry. 2013;74:e26. doi:10.4088/JCP.13018tx3c

2. Judd LL, Schettler PJ, Akiskal HS, et al. Residual symptom recovery from major affective episodes in bipolar disorders and rapid episode relapse/recurrence. Arch Gen Psychiatry. 2008;65:386-394. doi:10.1001/archpsyc.65.4.386

3. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. Psychiatry Clin Neurosci. 2017;71:6-17. doi:10.1111/pcn.12433

4. Palmier-Claus JE, Berry K, Bucci S, Mansell W, Varese F. Childhood trauma and bipolar affective disorder: systematic review and meta-analysis. Br J Psychiatry. 2016;209:454-459. doi:10.1192/bjp.bp.115.179655

5. Sahle BW, Reavley NJ, Li W, et al. The association between adverse childhood experiences and common mental disorders and suicidality: an umbrella review of systematic reviews and meta-analyses. Eur Child Adolesc Psychiatry. 2021. doi:10.1007/s10578-021-01745-2

6. Copeland WE, Shanahan L, Hinesley J, et al. Association of childhood trauma exposure with adult psychiatric disorders and functional outcomes. JAMA Network Open. 2018;1:e184493. doi:10.1001/jamaneurol.2018.4493

7. Agnew-Blais J, Danese A. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry. 2016;3:342-349. doi:10.1016/s2215-0366(15)00544-1

8. Cotter J, Kaess M, Yung AR. Childhood trauma and functional disability in psychosis, bipolar disorder and borderline personality disorder: a review of the literature. Ir J Psychol Med. 2015;32:21-30. doi:10.1017/ijpm.2014.74

9. Klein DN, Arnow BA, Barkin JL, et al. Early adversity in chronic depression: clinical correlates and response to pharmacotherapy. Depress Anxiety. 2009;26:701-710. doi:10.1002/da.20577

10. Shamseddeen W, Asarнов JR, Clarke G, et al. Impact of physical and sexual abuse on treatment response in the Treatment of Resistant Depression in Adolescent Study (TORDIA). J Am Acad Child Adolesc Psychiatry. 2011;50:293-301. doi:10.1016/j.jaac.2010.11.019

11. Douglas KM, Porter RJ. The effect of childhood trauma on pharmacological treatment response in depressed inpatients. Psychi atr Res. 2012;200:1058-1061. doi:10.1016/j.psychres.2012.06.015

12. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry. 2012;169:141-151.

13. Etain B, Lajnef M, Brichant- Petitjean C, et al. Childhood trauma and mixed episodes are associated with poor response to lithium in bipolar disorders. Acta Psychiatr Scand. 2017;135:319-327. doi:10.1111/acps.12684

14. Cakir S, Tasdelen Durak R, Ozyildirim I, Ince E, Sar V. Childhood trauma and treatment outcome in bipolar disorder. J Trauma Dissociation. 2016;17:397-409. doi:10.1080/15299732.2015.1132489

15. Cascino G, D'Agostino G, Monteleone AM, et al. Childhood maltreatment and clinical response to mood stabilizers in patients with bipolar disorder. Hum Psychopharmacol. 2021;36(4):e2783. doi:10.1002/hup.2783

16. Benarous X, Raffin M, Bodeau N, Dhossche D, Cohen D, Consoli A. Adverse childhood experiences among inpatient youths with severe and early-onset psychiatric disorders: prevalence and clinical correlates. Child Psychiatry Hum Dev. 2017;48:248-259. doi:10.1007/s10578-016-0637-4

17. Perugi G, Vannucci G, Barbuti M, et al. Outcome and predictors of remission in bipolar-I patients experiencing manic episode and treated with oral antipsychotics and/or mood stabilizers: a prospective observational study in Italy. J Clin Psychopharmacol. 2018;33:131-139. doi:10.1097/YJC.0000000000000211

18. Spidel A, Greaves C, Yuille J, Lecomte T. A comparison of treatment adherence in individuals with a first episode of psychosis and inpatients with psychosis. Int J Law Psychiatry. 2015;39:90-98. doi:10.1016/j.ijlp.2015.01.026

19. Lecomte T, Spidel A, Leclerc C, MacEwan GW, Greaves C, Bentall RP. Predictors and profiles of treatment non-adherence and engagement in services problems in early psychosis. Schizophr Res. 2008;102:295-302. doi:10.1016/j.schres.2008.01.024

20. Rakosky JJ, Levy ST, Dunlop BW. Conceptualizing treatment nonadherence in patients with bipolar disorder and PTSD. CNS Spectr. 2011;16:11-20. doi:10.1016/j.schres.2012.00119

21. Baeza-Velasco C, Olie B, Bezait S, Guillaume S, Courtet P. Determinants of suboptimal medication adherence in patients with a major depressive episode. Depress Anxiety. 2019;36:244-251. doi:10.1002/da.22852

22. Lafrenaye-Dugas AJ, Godbout N, Hebert M. Cumulative childhood trauma and therapeutic alliance: the moderator role of attachment in adult patients consulting in sex therapy. J Sex Marital Ther. 2018;44:667-678. doi:10.1080/0092623X.2018.1447057

23. Lawson DM, Davis D, Brandon S. Treating complex trauma: critical interventions with adults who experienced ongoing trauma in childhood. Psychotherapy (Chic). 2013;50:331-335. doi:10.1037/a0032677

24. Strauss JL, Johnson SL. Role of treatment alliance in the clinical management of bipolar disorder: stronger alliances prospectively predict fewer manic symptoms. Psychiatry Res. 2006;145:215-223. doi:10.1016/j.psychres.2006.01.007

25. Sylvia LG, Hay A, Ostacher MJ, et al. Association between therapeutic alliance, care satisfaction, and pharmacological adherence in bipolar disorder. J Clin Psychopharmacol. 2013;33:343-350. doi:10.1097/JCP.0b013e3182900c6f

26. Zeber JE, Copeland LA, Good CB, Fine MJ, Bauer MS, Kilbourne AM. Therapeutic alliance perceptions and medication adherence in patients with bipolar disorder. J Affect Disord. 2008;107:53-62. doi:10.1016/j.jad.2007.07.026

27. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANNMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20:97-170. doi:10.1111/bdi.12609

28. Nierenberg AA, Sylvia LG, Leon AC, et al. Clinical and health outcomes initiative in comparative effectiveness for bipolar disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. Clin Trials. 2014;11:114-127. doi:10.1177/1740774513512184

29. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision ed. American Psychiatric Association; 2000.
30. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the clinical global impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 1997;73:159-171. doi:10.1016/s0165-1781(97)00123-6
31. Sheehan DV, Lecrubier Y, Sheehan KH, et al. 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. 1998;59(suppl 20):22-33.
32. Alameda L, Golay P, Baumann PS, Ferrari C, Do KQ, Conus P. Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. J Clin Psychiatry. 2016;77:e612-e618. doi:10.4088/JCP.15m09947
33. Gonzalez JM, Bowden CL, Katz MM, et al. Development of the bipolar inventory of symptoms scale: concurrent validity, discriminant validity and retest reliability. Int J Methods Psychiatr Res. 2008;17:198-209. doi:10.1002/mpr.262
34. Bowden CL, Singh V, Thompson P, et al. Development of the bipolar inventory of symptoms scale. Acta Psychiatr Scand. 2007;116:189-194. doi:10.1111/j.1600-0447.2006.00955.x
35. Leon AC, Solomon DA, Mueller TI, Turvey CL, Endicott J, Keller MB. The Range of Impaired Functioning Tool (LIFE-RIFT): a brief measure of functional impairment. Psychol Med. 1999;29:869-878. doi:10.1017/s0033291799008570
36. Leon AC, Solomon DA, Mueller TI, et al. A brief assessment of psychosocial functioning of subjects with bipolar I disorder: the LIFE-RIFT. Longitudinal Interval Follow-up Evaluation-Range Impaired Functioning Tool. J Nerv Ment Dis. 2000;188:805-812. doi:10.1097/00005053-200012000-00003
37. Stata Statistical Software. Version 14. StataCorp LP, 2015. https://www.stata.com/stata14/
38. Gueorguieva R, Krystal JH. Move over ANOVA: Progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. Arch Gen Psychiatry. 2004;61:310-317. doi:10.1001/archpsyc.61.3.310
39. Maniglio R. The impact of child sexual abuse on the course of bipolar disorder: a systematic review. Bipolar Disord. 2013;15:341-358. doi:10.1111/bdi.12050
40. Dualibe AL, Osório FL. Bipolar disorder and early emotional trauma: a critical literature review on indicators of prevalence rates and clinical outcomes. Harv Rev Psychiatry. 2017;25:198-208. doi:10.1097/hrp.0000000000000154
41. Etaín B, Aas M, Andreassen OA, et al. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. J Clin Psychiatry. 2013;74:991-998. doi:10.4088/JCP.13m08353
42. Conus P, Cotton S, Schimmelmann BG, et al. Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. Bipolar Disord. 2010;12:244-252. doi:10.1111/j.1399-5618.2010.00813.x
43. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. Br J Psychiatry. 2005;186(2):121-125. 10.1092/bjp.186.2.121
44. Sala R, Goldstein BI, Wang S, Blanco C. Childhood maltreatment and the course of bipolar disorders among adults: epidemiologic evidence of dose-response effects. J Affect Disord. 2014;165:74-80. doi:10.1016/j.jad.2014.04.035
45. Etaín B, Mathieu F, Henry C, et al. Preferential association between childhood emotional abuse and bipolar disorder. J Trauma Stress. 2010;23:376-383. doi:10.1002/jts.20532
46. Shannon C, Hanna D, Tumelty L, et al. Reliability of reports of childhood trauma in bipolar disorder: a test-retest study over 18 months. J Trauma Dissociation. 2016;17:511-519. doi:10.1080/15299732.2016.1141147
47. Fisher HL, Craig TK, Fearon P, et al. Reliability and comparability of psychosis patients’ retrospective reports of childhood abuse. Schizophr Bull. 2011;37:546-553. doi:10.1093/schbul/sbp103
48. Alameda L, Ferrari C, Baumann PS, Gholam-Rezaee M, Do KQ, Conus P. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. Psychol Med. 2015;45:2727-2736. doi:10.1017/s0033291715000690
49. Isobel S, Gladstone B, Goodyear M, Furness T, Foster K. A qualitative inquiry into psychiatrists’ perspectives on the relationship of psychological trauma to mental illness and treatment: implications for trauma-informed care. J Mental Health. 2021;30(6):667-673. doi:10.1080/09638237.2020.1714012

How to cite this article: Wrobel AL, Köhler-Forsberg O, Sylvia LG, et al. Childhood trauma and treatment outcomes during mood-stabilising treatment with lithium or quetiapine among outpatients with bipolar disorder. Acta Psychiatr Scand. 2022;145:615–627. doi:10.1111/acps.13420