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Lurasidone response in bipolar type I depression with childhood trauma exposure

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Abstract

Importance: Childhood trauma (CT) worse the course of bipolar disorder (BD) and negatively impacts treatment outcomes. Despite the recognized influence of CT on clinical trajectories, limited evidence exists on how it affects specific pharmacological responses in BD.

Objective: This study aimed to investigate the effectiveness of lurasidone in BD type I depression, with a focus on how CT exposure impacts treatment response and remission.

Design: A multisite, observational, prospective, comparative effectiveness study over an 8-week period was conducted.

Setting: A multisite in 4 clinical research sites in Colombia.

Participants: A total of 84 adults with BD type I depression were enrolled (lurasidone = 41, lurasidone with lithium = 43).

Intervention: Over an 8-week period, 41 participants were assigned to the lurasidone arm and 43 to the lurasidone plus lithium arm.

Exposure: Childhood trauma exposure was measured with the Childhood Trauma Questionnaire-Short Form. BD with CT (n = 40) and BD without CT (n = 44) were included.

Main outcome and measures: The primary outcome was changes in Montgomery-Åsberg Depression Rating Scale (MADRS) scores. Secondary outcomes included changes in Clinical Global Impression-Bipolar depression severity scores and responder rates.

Results: Bipolar disorder with CT exposure demonstrated a smaller mean reduction in MADRS scores compared to those without CT exposure for both treatments (monotherapy: Least Square (LS) −3.4, 95% CI, −6.03 to −0.76, P = .013; combination therapy: LS −3.1, 95% CI, −5.36 to −0.63, P = .014). The presence of CT exposure, particularly physical abuse (PA), was associated with poorer response rates. Notably, lurasidone in combination with lithium showed superior outcomes compared to monotherapy, although effectiveness was attenuated in participants with documented CT exposure.

Conclusions: This study provides real-world evidence suggesting that CT exposure may modify treatment response in BD type I depression. Our findings underscore the importance of CT screening to guide personalized treatment strategies.

Relevance: This study provides evidence that CT, particularly PA, attenuates the antidepressant effects of lurasidone in BD type I depression, leading to lower response and remission rates in both monotherapy and combination therapy with lithium. These findings underscore the clinical importance of screening for CT in BD to guide personalized treatment strategies. Identifying trauma history may help clinicians optimize treatment selection, considering the potential need for combination pharmacotherapy and adjunctive trauma-focused psychotherapeutic interventions to improve outcomes in this vulnerable population.

Keywords: bipolar disorder; childhood trauma; lurasidone; lithium; treatment response.

Significance Statement

Bipolar disorder (BD) is a severe mental illness that can be challenging to treat, particularly when individuals have experienced childhood trauma (CT). While trauma is known to worsen the course of BD, its impact on specific medication responses remains unclear. This study provides real-world evidence that CT exposure, especially physical abuse, reduces the effectiveness of lurasidone in treating BD type I depression. Patients with a history of CT showed smaller improvements in depressive symptoms and lower treatment response rates, even when lurasidone was combined with lithium. These findings highlight the need for clinicians to screen for CT in BD patients to personalize treatment strategies. Recognizing a patient's trauma history may help guide medication choices and emphasize the importance of integrating trauma-focused therapy. By addressing both biological and psychological factors, this approach could improve treatment outcomes and quality of life for individuals living with BD.

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INTRODUCTION

Bipolar disorder (BD) is a multifactorial psychiatric disorder characterized by episodic mood dysregulation, cognitive impairment, cardiometabolic dysfunction, and an increased risk of premature mortality due to suicide or physical comorbidities.[1,2] Childhood trauma (CT) has been increasingly recognized as a key factor influencing the clinical course of BD, contributing to greater illness severity, poorer treatment response, and worse functional outcomes.[Guillen-Burgos et al., 2025] According to a recent meta-analysis, few studies have elucidated the effect of CT on pharmacological response in BD.[9]

Childhood trauma exposure has been shown to significantly impact metabolic and cardiovascular health in individuals with mood disorders, often manifesting as elevated blood pressure and increased rates of overweight or obesity.[10] In the context of BD, CT exposure is particularly consequential, as it has been identified as a key factor influencing immunomodulatory response, as demonstrated in a randomized controlled trial assessing adjunctive infliximab treatment in BD.[11] Given these findings, optimizing metabolic outcomes is essential when selecting treatment approaches for BD patients with a history of CT.

Lurasidone is a U.S Food and Drug Administration (FDA)-approved medication to treat bipolar depression in both monotherapy or as an adjunctive to lithium or valproate.[12] The multireceptor antagonist/partial agonist action over both dopamine and serotonin receptors is responsible for lurasidone antipsychotic and antidepressant properties to treat bipolar depression in children, adolescents, and adults.[13-16] Given their favorable metabolic profile, lurasidone may offer distinct advantages for managing bipolar depression in subgroup population such as BD with a risk of metabolic dysfunctions as evidenced in BD with CT exposure. Its minimal impact on weight and metabolic parameters positions it as a potentially suitable option for BD patients with CT exposure.[17] However, to date, no studies have specifically examined the effects of CT on lurasidone response, either as monotherapy or in combination with mood stabilizers, in bipolar depression.

While lurasidone is typically prescribed for complex clinical scenarios in BD, it has been included as monotherapy or in combination with lithium or valproate to treat acute bipolar depression type I in BD treatment guidelines available.[18] Childhood trauma exposure represents a prevalent and clinically significant factor in the presentation and course of BD, necessitating comprehensive consideration in clinical and research contexts.[3-5,19,20] In fact, BD participants with previous CT exposure are considered to have a more severe course of illness.[3,4,20] Moreover, several studies have reported that CT exposure, especially physical abuse (PA), was associated with poorer response to lithium treatment in BD.[7] These findings were replicated by Etain and colleagues in BD participants with multiple subtypes of CT exposure who were more likely to be considered lithium non-responders.[6] Furthermore, a meta-analysis by Wrobel et al. also reported an association between the number and subtypes of CT exposure and poor response to treatment.[9]

Atypical antipsychotic prescriptions for the treatment of bipolar depression such as quetiapine, lurasidone, olanzapine, and cariprazine are considered first-line psychopharmacological treatments.[21] However, research has not yet elucidated the modifying effects of CT exposure over BD treatment in participants with depressive episodes.

Perhaps, being able to explore associations of CT exposure over response and remission during acute treatment of bipolar depression is noteworthy. Although existing evidence remains inconclusive and has been more extensively examined in mood stabilizers than in antipsychotics, CT may potentially attenuate treatment response to antipsychotic medication, such as lurasidone for bipolar type I depression.

Therefore, this gap in the literature underscores the need for further research to assess whether lurasidone's clinical benefits extend to this vulnerable subgroup. We hypothesized that CT exposure may attenuate the effectiveness of antipsychotics during bipolar depression. In this sense, this study primarily aimed to examine the impact of CT exposure on treatment response and remission in BD type I depression. As part of this investigation, we conducted a comparative effectiveness analysis to explore whether the effect of CT exposure differed between lurasidone monotherapy and lurasidone plus lithium during an 8-week follow-up.

METHODS

Study Design

This multisite, observational, prospective, comparative effectiveness study over an 8-week period was conducted between January 2022 and June 2023 at the Center for Clinical and Translational Research in Barranquilla and Bogota DC, Colombia. The study evaluated the effectiveness of lurasidone monotherapy or lurasidone plus adjunctive lithium in bipolar type I depression with CT exposure in a real-world evidence (RWE) setting. The study protocol was designed according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[22]

Participants

The Center for Clinical and Translational Research is currently carrying out a longitudinal cohort study in BD, with a total of 305 BD participants enrolled.[3] We also identified 84 BD participants between 18 and 59 years of age diagnosed with BD type I experiencing a major depressive episode according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria, without psychotic symptoms prescribed with 20-60 mg daily of lurasidone in monotherapy or 20-60 mg of lurasidone adjunctive to lithium 600-1500 mg daily. Additionally, during the prescreening, a Montgomery-Åsberg Depression Rating Scale (MADRS)[23] score ≥ 20 and a Young Mania Rating Scale[24] score ≤ 12 were required.

Effectiveness Outcomes

The effectiveness of lurasidone monotherapy or adjunctive to lithium over 8 weeks was assessed in BD participants, comparing BD participants with a history of CT exposure to those without (non-CT exposure). The primary outcome was the least square mean change from baseline to week 8 in the MADRS total score. The secondary outcome was the least square mean change from baseline to week 8 in depression severity score on the Clinical Global Impression scale for Bipolar Illness (CGI-BP).[25]

CT Exposure

Childhood trauma exposure was administered at baseline with the Childhood Trauma Questionnaire-Short Form (CTQ-SF), a 28-item Likert-type, with a 5-factor structure: emotional abuse (EA), PA, sexual abuse (SA), physical neglect (PN), and emotional neglect (EN), self-administered instrument in order to assess multiple types of trauma during childhood.[26] **Thus, the cutoff scores**

for moderate to severe exposure on each CTQ-SF subtype—previously described in the literature—were used to classify participants as having or not having a history of childhood trauma (≥13 for emotional abuse, ≥10 for physical abuse, ≥8 for sexual abuse, ≥15 for emotional neglect, and ≥10 for physical neglect) .[26] A participant is classified as having CT exposure if their score exceeds the established cutoff for any CTQ-SF subtype.

Safety and Tolerability

Adverse events (AEs) during the study were evaluated by the incidence and severity of the events. Suicidal ideation and behavior were assessed using the Columbia Suicide Severity Rating Scale.[27]

Statistical Analysis

All statistical analyses were conducted using R (version 4.2.3) free software. Descriptive statistics were employed to summarize baseline demographic and clinical characteristics. An intention-to-treat analysis was performed, including all participants who received at least one dose of medication and had at least one post-baseline assessment. Missing data for week 8 effectiveness measures were handled using the last observation carried forward approach, while sensitivity analyses using multiple imputations were conducted to assess robustness.

Primary and secondary outcomes were analyzed using a mixed-effects model for repeated measures (MMRMs), with treatment, visit, baseline score, bipolar subtype, gender, age, presence of any comorbidity, body mass index (BMI), and a treatment-by-visit interaction as fixed effects. To account for within-subject correlation, an unstructured covariance matrix was selected based on model fit criteria (using Akaike Information Criterion and Bayesian Information Criterion). Potential multicollinearity among predictors was assessed using variance inflation factors, and collinear variables were addressed accordingly to ensure model stability.

Between-group effect sizes were estimated using least square means analysis, quantifying the change from baseline to week 8 for both treatment regimen and visit interaction. The proportions of responders (≥50% reduction from baseline in MADRS total) and remitters (MADRS total ≤ 12) were compared between the lurasidone monotherapy and lurasidone plus lithium treatment groups using logistic regression models to adjust for covariates, rather than independent *t*-tests, to account for potential confounding factors. Cohen's d effect sizes were computed for primary and secondary outcomes as the difference in change scores divided by the pooled SD.

Sample size was based on power calculations to detect clinically meaningful differences in the primary outcome (MADRS total score change) with 80% power at a 2-sided alpha level of 0.05. Participants were matched on age and gender, but not explicitly on childhood trauma (CT) exposure; however, groups were stratified post hoc to ensure comparability. Baseline demographic and clinical characteristics, including age, gender, bipolar subtype, BMI, and comorbidities, were assessed between the BD with CT and BD without CT groups to confirm the absence of significant differences. Any potential residual confounding was addressed by including these covariates in the mixed-effects model. All statistical tests were 2-tailed, with an alpha level of 0.05, and 95% CIs were reported for effect estimates.

Ethical Consideration

The study was approved by the Ethics Committee for the Universidad Simon Bolivar at Barranquilla, Colombia (Reference: CEI-USB-CE-0385-00-00). This study was conducted in accordance with the ethical considerations of the Declaration of Helsinki, Council for International Organizations of Medical Sciences, and Good Clinical Practices. All participants signed an informed consent to participate in the study research and authorized the publication.

RESULTS

The overall sample size of 84 participants with BD and a major depressive episode was divided into 2 groups: those with CT exposure (BD-CT, $n = 40$) and those without it (BD-non-CT, $n = 44$). The mean overall age was 32.1 ± 5.0 (32.2 ± 5.3 years in BD-CT vs 31.8 ± 5.1 years in BD-non-CT), and the overall age at onset was 14.5 ± 2.2 years (13.5 ± 2.5 years in BD-CT vs 15.3 ± 2.2 years in BD-non-CT). More than half (57.0%) of BD participants were female (55.0% in BD-CT vs 59.0% in BD-non-CT). With regards to CT exposure, the overall participants showed a score of 38.5 ± 4.5 (44.6 ± 5.8 in BD-CT vs 32.5 ± 4.1 in BD-non-CT). See all features in Table 1. Study completion rates were similar for the lurasidone (90%), lurasidone plus lithium (88.4%) (Figure 1).

Effectiveness of Lurasidone Monotherapy in BD with CT Exposure

At week 8, BD participants with CT exposure showed a LS mean change in MADRS total score of −12.0 (SE = 1.0), while BD participants without CT exposure showed a larger reduction of −15.4 (SE = 0.9). The LS mean difference between the groups was −3.4 (95% CI, −6.03 to −0.76), indicating a significantly greater reduction in MADRS total score for BD participants without CT exposure. The effect size was −3.57, with a *P* value of .013, demonstrating a statistically significant difference in response to treatment between groups. In terms of CGI-BP depression severity, BD participants with CT exposure had a LS mean change of −1.98 (SE = 0.12), compared to −2.5 (SE = 0.1) in BD participants without CT exposure at week 8. The LS mean difference between the groups was −0.52 (95% CI, −0.82 to −0.21), with an effect size of −4.70 and a *P* value < .001. A significant improvement with regard to depressive symptoms in BD participants without CT exposure was reported. Results are summarized in Table 2 and Figure 2.

Effectiveness of Lurasidone Plus Lithium in BD with CT Exposure

At week 8, the BD-CT exposure participants showed a LS mean change in MADRS total score of −14.5 (SE = 0.80), while the BD-non-CT exposure participants showed a greater reduction of −17.6 (SE = 0.91). The LS mean difference between the groups was −3.1 (95% CI, −5.36 to −0.63). A significantly larger improvement in MADRS total score was reported for BD participants without CT exposure compared to BD participants exposed to CT. The effect size was −3.52, with a *P* value of.014. This highlights a statistically significant difference in the treatment response between the groups. With regard to CGI-BP depression severity score, BD participants with CT exposure exhibited a LS mean change of −2.10 (SE = 0.12), compared to −2.67 (SE = 0.13) BD participants with non-CT exposure at week 8. The LS mean difference was −0.56 (95% CI, −0.91 to −0.22), with an effect size of −4.55 and a *P* value of.002. Likewise, CGI-BP change in score highlights a significantly greater reduction in depressive symptoms for BD participants without CT exposure. The results are summarized in Table 3 and Figure 3.

Table 1. Baseline and clinical features.

Variable	BD with CT (*n* = 40)	BD without CT (*n* = 44)	Total (*n* = 84)	*P* value
Age (years), mean ± SD	32.2 ± 4.6	31.8 ± 5.3	32.1 ± 5.0	<.001
Age at onset (years), mean ± SD	13.5 ± 2.0	15.3 ± 1.9	14.5 ± 2.2	<.001
Gender, *n*%				
Male	18 (45.0)	18 (41.0)	36 (43.0)	.875
Female	22 (55.0)	26 (59.0)	48 (57.0)	
Ethnicity, *n*%				
Hispanic	32 (80.0)	29 (66.0)	61 (72.6)	.988
African American	8 (20.0)	15 (34.0)	23 (27.4)	
Socioeconomic, *n*%				
Low	26 (65.0)	23 (52.3)	49 (58.3)	.958
Middle	8 (20.0)	13 (29.5)	21(25.0)	
High	6 (15.0)	8 (18.2)	14 (16.7)	
Education, *n*%				
High school	20 (50.0)	21(47.7)	41 (48.8)	.649
Technician	11 (27.5)	14 (31.8)	25 (29.8)	
Graduate	9 (22.5)	9 (20.5)	18 (21.4)	
Lurasidone	20 (50.0)	21 (47.7)	41 (48.8)	.834
Lurasidone plus lithium	20 (50.0)	23 (52.3)	43 (51.2)	.819
MADRS, mean ± SD	30.8 (4.8)	30.3 (5.1)	30.5 (4.9)	.645
CGI-BP depression severity, mean ± SD	4.5 (0.3)	4.3 (0.6)	4.4 (0.4)	.060
BMI (kg/m^2), mean ± SD	30.3 ± 2.9	27.7 ± 2.8	29.0 ± 2.8	<.001
Childhood trauma score, mean ± SD	44.6 ± 5.8	32.5 ± 4.1	38.5 ± 4.5	<.001
Emotional abuse	11.5 ± 3.6	7.1 ± 2.3	9.5 ± 3.4	<.001
Physical abuse	10.2 ± 4.2	5.9 ± 2.6	8.2 ± 2.9	<.001
Sexual abuse	11.3 ± 3.7	6.6 ± 2.1	9.0 ± 3.1	<.001
Emotional neglect	9.1 ± 2.7	5.5 ± 1.9	7.8 ± 2.8	<.001
Physical neglect	9.9 ± 3.0	6.0 ± 2.3	8.1 ± 2.7	<.001
AUD, *n*%	17 (42.5)	14 (31.8)	31 (36.9)	.001
BPD, *n*%	9 (22.5)	6 (13.6)	17 (20.2)	<.001
AD, *n*%	11(27.5)	9 (20.4)	20 (23.8)	.016
PTSD, *n*%	14 (35.0)	10 (22.7)	24 (28.6)	.011

Abbreviations: AD, anxiety disorders; AUD, alcohol use disorder; BMI, body mass index; BPD, borderline personality disorder; CGI-BP, clinical global impression-bipolar disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; PTSD, post-traumatic stress disorder.

Response and Remission Rates of Lurasidone Monotherapy and Lurasidone Plus Lithium

Although there are no statistical differences in the response rate of lurasidone monotherapy or combination therapy in BD with or without CT, in monotherapy, BD participants without CT exposure demonstrated a higher response rate, with 49.8% achieving a ≥ 50% reduction in MADRS scores, compared to 39.9% in BD participants with CT exposure. In the same line, BD participants in whom add-on lithium to lurasidone was prescribed, response rates also improved in all BD participants regardless of CT exposure; however, BD participants without CT exposure continued to report a trend of superior response rate, with 57.7% achieving a ≥ 50% reduction in MADRS scores, compared to 47.7% in BD participants with CT exposure (see Figure 4).

For both treatment conditions, the BD without CT group demonstrated higher remission rates compared to the BD with CT group. Notably, the combination of lurasidone with lithium yielded a greater remission rate in both groups compared to lurasidone alone, unfortunately, statistical differences were not found (see Figure 5).

Results also showed that PA is associated with the lowest response rates among CT exposure subtypes for both treatments. We reported response rates of 30.3% for BD participants with a history of PA-prescribed lurasidone monotherapy and 35.1% for BD participants prescribed with combination therapy. Conversely, EA and EN were associated with higher response rates. We reported response rates of 55.2% for combination therapy and 45.3% for monotherapy in BD participants with a history of EA and EN. Similarly, PN and SA were associated with attenuated response rates, with higher response rates reported in the combination therapy group; however, statistical differences were not found (see Figure 6).

Safety and Tolerability of Lurasidone During the Follow-up

The most prevalent AEs included nausea (10.71%), somnolence (9.52%), and akathisia (7.14%). Weight gain was less common (4.76%). Other notable AEs included dizziness (4.76%) and vomiting (1.2%). These findings underscore the generally well-tolerated profile of Lurasidone alone or in combination, with most AEs being mild to moderate in severity (see Table 4).

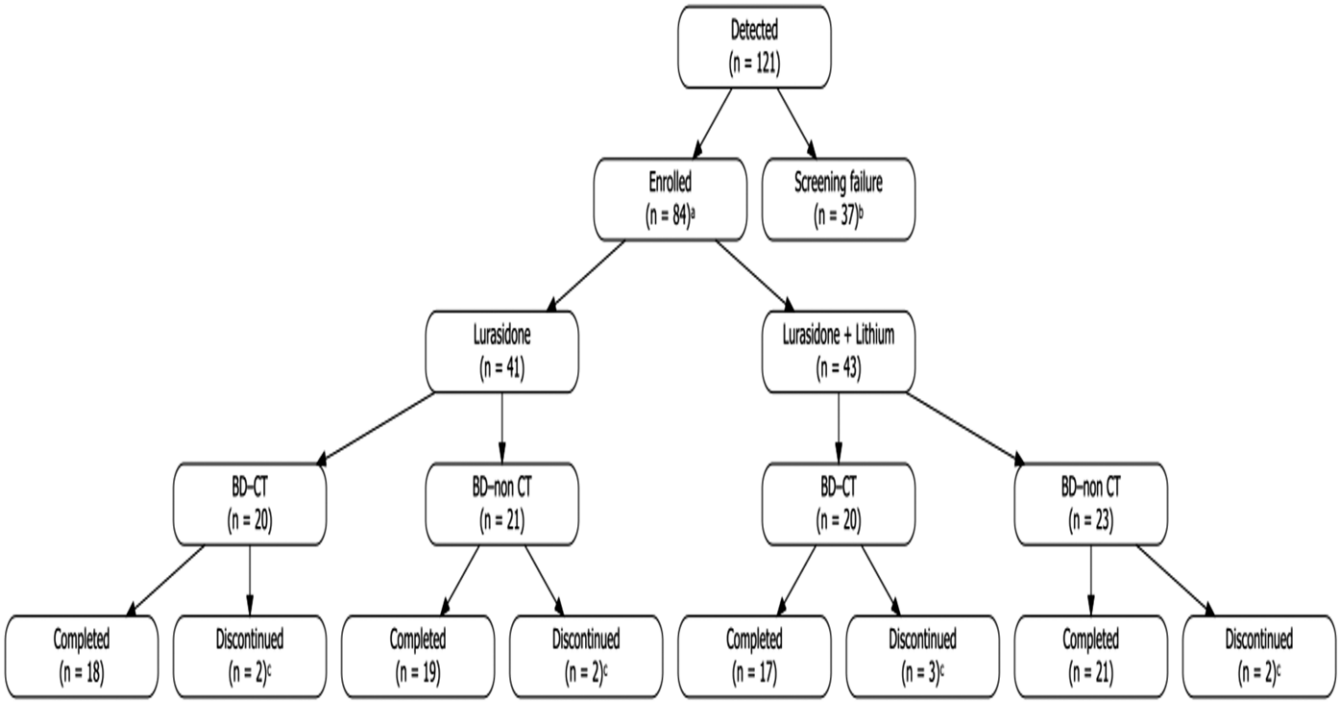

Figure 1. Patient disposition in a multisite, observational, prospective, comparative effectiveness study of both monotherapy and combination therapy of lurasidone for bipolar I depression with or without CT exposure. CT, childhood trauma.

Table 2. Effectiveness outcomes from baseline to week 8 in BD with or without childhood trauma exposure and treated with lurasidone.

	CT (n = 40)	Non-CT (n = 44)	Comparison	
	LS mean change at week 8 (MMRM), mean (SE)		LS mean difference (95% CI)	Effect size; P value
MADRS total score	−12.0 (1.0)	−15.4 (0.9)	−3.4 (−6.03, −0.76)	−3.57; P = .013
CGI-BP depression	−1.98 (0.12)	−2.5 (0.1)	−0.52 (−0.82, −0.21)	−4.70; P < .001

Abbreviations: BD, bipolar disorder; CGI-BP, clinical global impression-bipolar disorder; CT, childhood trauma; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

DISCUSSION

This is the first study exploring response and remission rates of lurasidone in participants with bipolar type I depression taking into account modifying effects of CT exposure over treatment outcomes. Our findings suggest that BD participants without CT exposure exhibited greater reductions in both depressive symptom severity and overall depression response reflected in MADRS and CGI-BP depression scores reported over an 8-week follow-up. Additionally, our findings suggest that while both treatment strategies are effective, patients without CT exposure reported higher response and remission rates for both lurasidone monotherapy and combination therapy with lithium.

Lurasidone is a second-generation antipsychotic with FDA approval for the treatment of schizophrenia and bipolar depression.[15,16,28-30] In bipolar depression, lurasidone in monotherapy significantly reduces depressive symptoms measured with MADRS compared to placebo in both low (20-60 mg) and high (80-120 mg) doses.[16] In combination therapy with mood stabilizers such as lithium or valproate, lurasidone also has shown efficacy to improve depressive symptoms compared to placebo, with a moderate effect size.[15] These effects have also been replicated in children and adolescents with bipolar depression.[31] In the same line, lurasidone has reported efficacy in the treatment of bipolar depression with mixed features without any risk of treatment-emergent mania in a post hoc analysis.[14] Therefore, lurasidone is effective in reducing depressive symptoms, treatment response, and remission rates in bipolar depression.[32]

Thus far, evidence for a response of lurasidone in bipolar depression with CT exposure is limited. Given the high prevalence of CT exposure among individuals with BD,[3,4,20,33] which is associated with a more severe course of illness,[5,34] it is imperative to roughly screen for CT exposure and keep in mind the potential diminished response and remission rates for treatments prescribed in bipolar depression. Thus, understanding the role of CT exposure over treatment response may guide researchers to tailor better therapeutic approaches for specific populations such as those exposed to CT.

We were able to report significant changes from baseline to endpoint with regard to improvement of depressive symptoms assessed with MADRS and CGI-BP depression severity scores in both lurasidone monotherapy and combination therapy with lithium. Our findings from RWE settings supported the previous reported effectiveness of lurasidone in bipolar depression, with a significant effect modification mediated by CT exposure toward

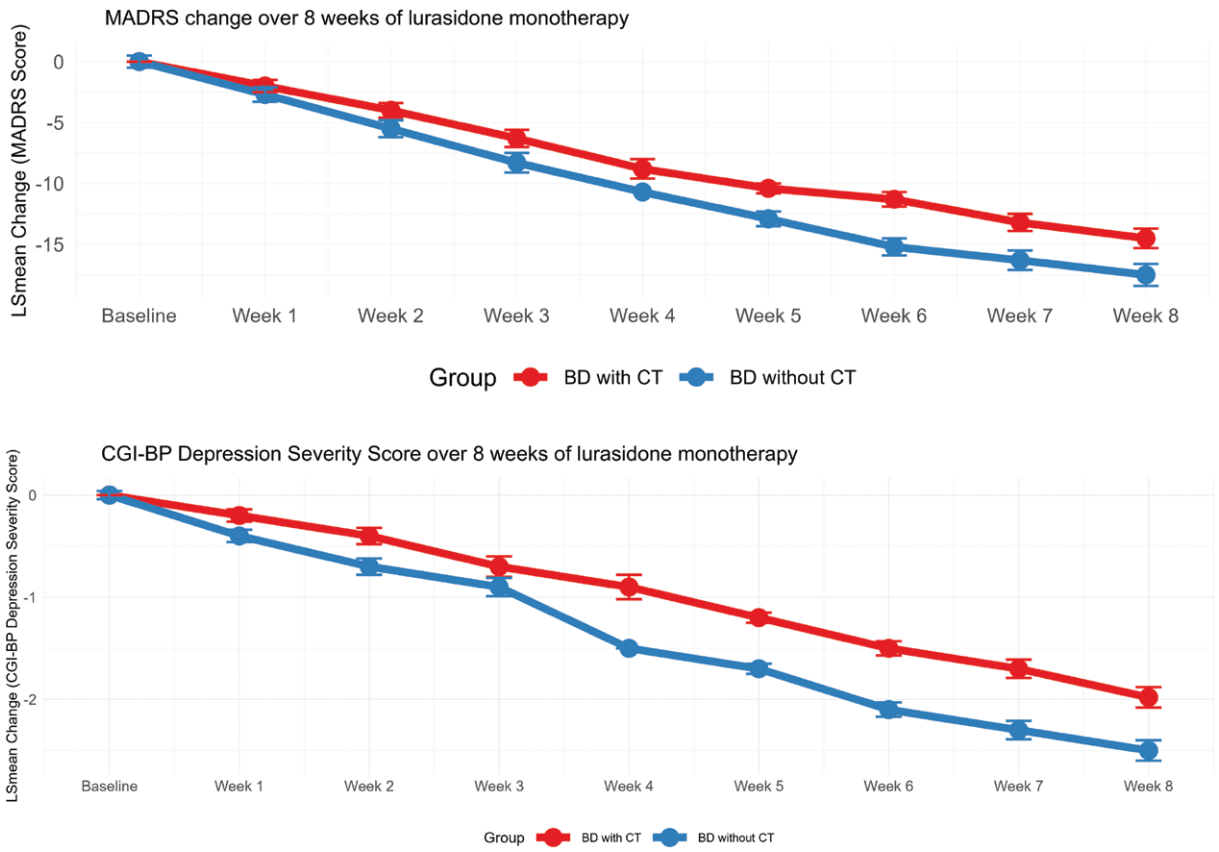

Figure 2. MADRS and CGI-BP depression severity change over 8 weeks with lurasidone monotherapy. CGI-BP, clinical global impression-bipolar disorder; MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 3. Effectiveness outcomes from baseline to week 8 in BD with or without CT exposure treated with lurasidone plus lithium.

	CT (*n* = 40	Non-CT (n = 44)	Comparison	
	LS mean change at week 8 (MMRM), mean (SE)		LS mean difference (95% CI)	Effect size; *P* value
MADRS total score	−14.5 (0.80)	−17.6 (0.91)	−3.1 (−5.36, −0.63)	−3.52; *P* = .014
CGI-BP depression	−2.10 (0.12)	−2.67 (0.13)	−0.56 (−0.91, −0.22)	−4.55; *P* = .002

Abbreviations: BD, bipolar disorder; CGI-BP, clinical global impression-bipolar disorder; CT, childhood trauma; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

lower response and remission rates. Additionally, we reported a significant *P* value obtained when comparing the response rates between CT exposure and non-CT exposure in both monotherapy and combination therapy (see Figure 4).

With regard to treatment response and subtypes of CT exposure, research has reported mixed results. For example, PA has been associated with a poorer response for anticonvulsants and lithium in BD participants[6,7,35-37] A recent meta-analysis, also reported a poorer treatment response rate among BD participants with CT exposure in non-randomized studies (OR 0.47, 95% CI, 0.27 to 0.83, *P* = .009).[9] However, the same research group had reported previously that CT exposure was not significantly related to symptomatic remission in BD. Our results showed that PA exposure is associated with a lower response to treatment for both monotherapy and combination therapy with lithium (see Figure 5). It is possible that some CT subtypes may be associated with a more severe course of BD and thus a poorer response to conventional therapeutic strategies such as lurasidone monotherapy and combination therapy with lithium. It may also be true that recurrent and/or mixed CT exposure early during the life cycle generates BD endophenotypes associated with premature markers of severity and thus attenuated, diminished responses. In recent studies conducted by our research group, we reported that PA is a higher risk factor for early age at onset, rapid cycling, suicide ideation/behavior, and early readmission in BD.[3] Although the severity of BD does not have standardized clinical criteria, the above outcomes may be considered as severe clinical factors.[3,19] While lurasidone plus lithium offers a therapeutic advantage across most CT subtypes, patients with a history of PA may exhibit a more attenuated response to both treatment approaches, indicating the need for targeted or complex interventions in this subgroup.

Childhood trauma exerts significant neurobiological effects in individuals with BD, contributing to structural, functional, and neuroendocrine alterations that may influence pathophysiology, clinical presentation, and treatment response. Structurally,

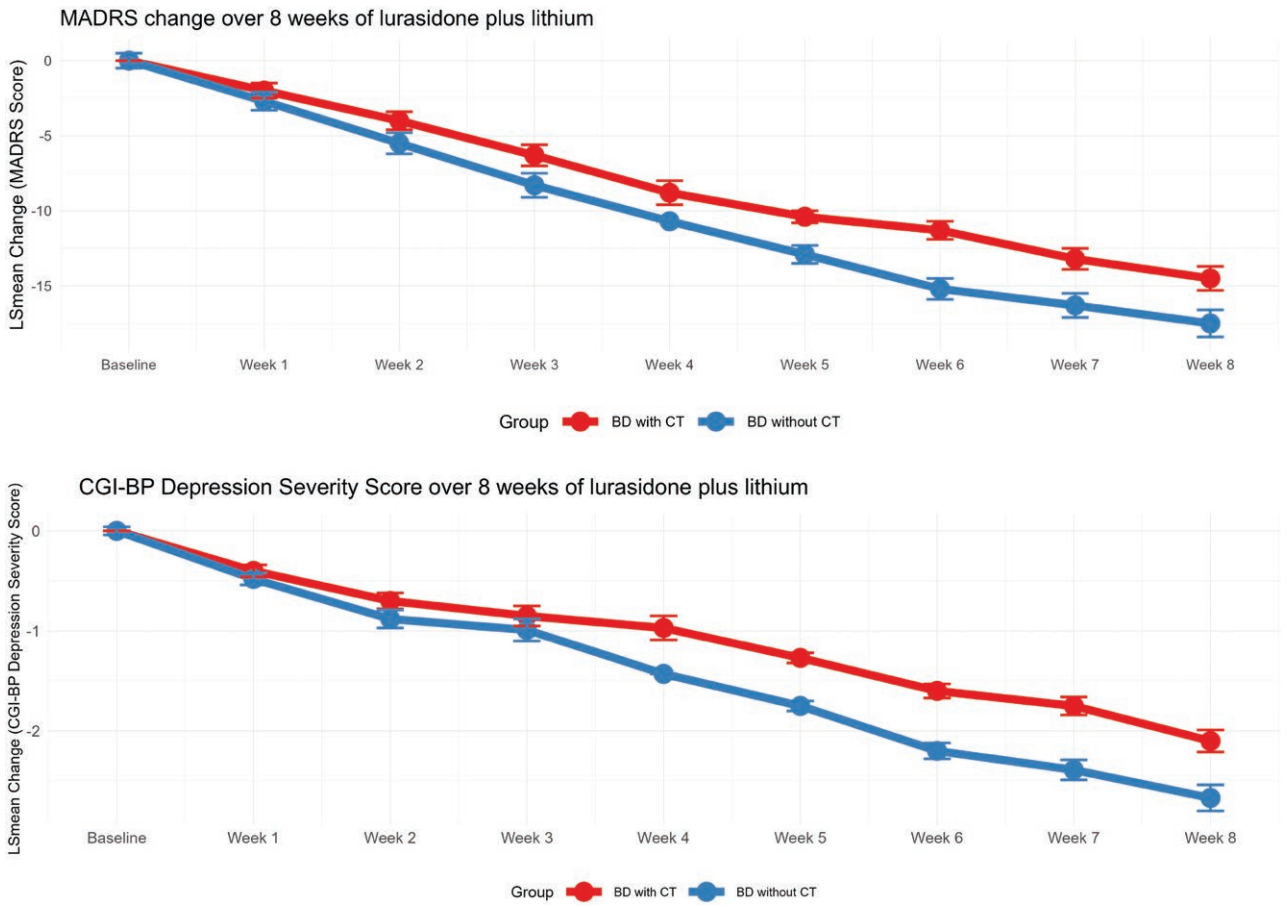

Figure 3. MADRS and CGI-BP depression severity change over 8 weeks with lurasidone plus lithium. CGI-BP, clinical global impression-bipolar disorder; MADRS, Montgomery-Åsberg Depression Rating Scale.

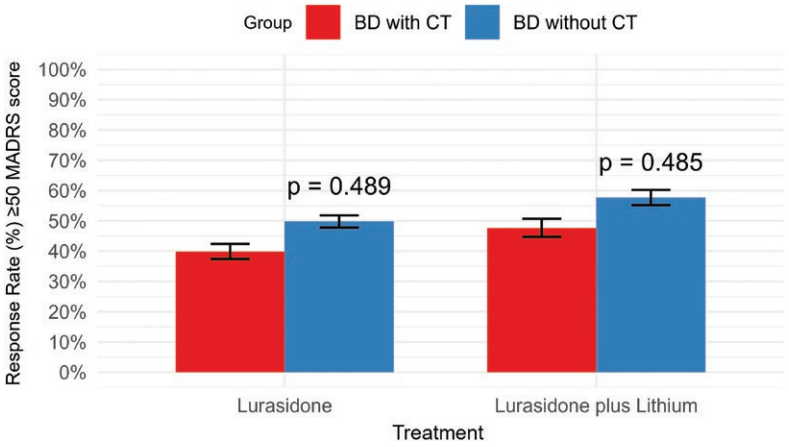

Figure 4. Response rate ≥50 MADRS score for lurasidone monotherapy and lurasidone plus lithium in bipolar disorder with and without childhood trauma exposure. MADRS, Montgomery-Åsberg Depression Rating Scale.

trauma is associated with reduced gray matter volume in prefrontal-paralimbic regions, altered hippocampal subfields, and compromised white matter integrity, as evidenced by lower fractional anisotropy values, which reflect disrupted microstructural connectivity.[38-40] Functionally, trauma exposure is linked to corticostriatal and limbic network dysfunction, impairing executive functions, emotional regulation, and cognitive performance.[41,42] Additionally, HPA axis dysregulation has been observed, with alterations in cortisol levels potentially mediating stress vulnerability and mood instability.[43,44] These neurobiological disruptions contribute to cognitive impairments, with trauma-exposed individuals exhibiting lower white matter volume and altered gray matter in frontopolar regions, correlating with poorer cognitive performance as well as emotional/social stress, self-referential thought, memory, unexpected stimuli, and avoidance behaviors in youths with CT exposure.[45,46]

Collectively, these findings highlight the profound impact of CT on brain development and function in BD, emphasizing the need for trauma-informed treatment strategies to address its neurobiological consequences.[42,45,47-53]

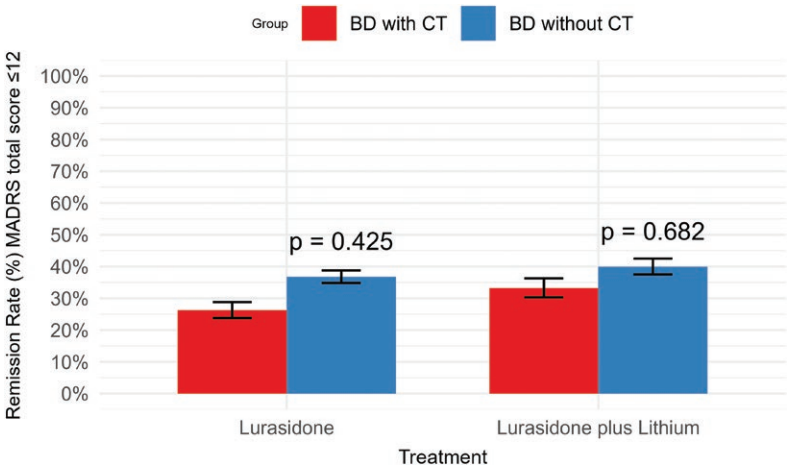

Figure 5. Remission rate (MADRS total ≤12) for lurasidone monotherapy and lurasidone plus lithium in bipolar disorder with and without childhood trauma exposure. MADRS, Montgomery-Åsberg Depression Rating Scale.

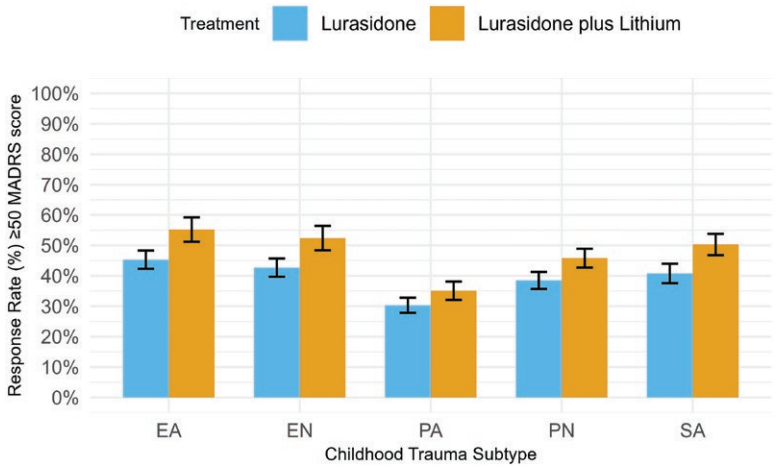

Figure 6. Response rates ≥50 MADRS score for monotherapy and combination therapy in childhood trauma subtypes. MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 4. Safety and tolerability of lurasidone during the follow-up ($n = 84$).

Adverse events	Prevalence, *n* (%)
Nausea	9 (10.71%)
Somnolence	8 (9.52%)
Akathisia	6 (7.14%)
Weight gain	4 (4.76%)
Dizziness	4 (4.76%)
Vomiting	1 (1.2%)

The limbic system, hippocampus, and frontal cortex are key brain regions implicated in mood regulation, where 5-HT7 and 5-HT1A receptors play a critical role in the antidepressant effects of lurasidone. Preclinical and clinical studies suggest that lurasidone's partial agonism at 5-HT1A receptors and antagonism at 5-HT7 receptors contribute to its therapeutic effects in bipolar depression.[54-59] However, CT exposure has been associated with neurodevelopmental disruptions, including alterations in serotonergic signaling, which may lead to increased emotional dysregulation and impaired stress response mechanisms.[60-63]

These serotoninergic alterations may potentially contribute to reduced treatment efficacy in individuals with BD and exposure to CT, possibly explaining the attenuated antidepressant response observed in this study. However, translational studies associating CT, serotoninergic receptor alterations, and diminished lurasidone response in BD remain limited. Future research should explore functional neuroimaging and pharmacogenetic analyses to elucidate the mechanistic role of serotonergic dysfunction in trauma-exposed BD populations.

Our findings highlight the clinical relevance of screening for CT exposure before initiating pharmacological treatment for bipolar type I depression, as trauma history may influence treatment response. Over the past decade, lurasidone prescriptions have increased, likely due to its proven efficacy, favorable tolerability, and superior metabolic profile compared to other second-generation antipsychotics. Notably, it is now the second most commonly prescribed antipsychotic for bipolar depression, following quetiapine.[21]

Although both treatment options demonstrated significant response rates, CT exposure was associated with a diminished response to lurasidone, whether used as monotherapy or in combination with lithium. This attenuated response may reflect a distinct neurobiological signature associated with CT exposure, consistent with prior findings on lithium non-responders in trauma-exposed BD populations.[6] Our findings suggest that CT exposure may influence treatment response beyond lithium, potentially extending to other pharmacological strategies in BD.

Future research should further characterize response and remission patterns in BD based on CT exposure, facilitating a more targeted and personalized treatment approach.

Our findings highlight the attenuating effects of CT particularly PA, on treatment response in BD type I depression, emphasizing the need for personalized treatment strategies. Clinicians should consider CT history when selecting pharmacological interventions, as individuals with a history of trauma may exhibit differential responses to treatment, requiring closer monitoring and potential treatment modifications. Given that lurasidone plus lithium demonstrated superior outcomes compared to monotherapy, combination strategies may be preferable in CT-exposed patients, though effectiveness remains attenuated in this subgroup.

Beyond pharmacological adjustments, integrating psychotherapeutic interventions tailored for trauma-related psychopathology may enhance treatment outcomes.[64,65] Approaches such as trauma-focused cognitive behavioral therapy,[66] dialectical behavior therapy,[67] or eye movement desensitization and reprocessing[68] may help address maladaptive cognitive patterns, emotional dysregulation, and residual depressive symptoms that may contribute to poorer pharmacological response. Future studies should explore multimodal treatment approaches, incorporating both pharmacotherapy and trauma-informed psychotherapy, to optimize outcomes in BD patients with CT exposure.

Another important aspect regarding a social risk factor such as CT is the social context where the study was conducted. While our findings provide valuable insights into the influence of CT on treatment response in BD type I depression, the sociocultural, socioeconomic, and healthcare context in Colombia may influence the generalizability of our results. Differences in access to specialized psychiatric care, healthcare coverage, and treatment-seeking behaviors could impact pharmacological response and adherence. Furthermore, cultural differences in trauma perception and reporting may shape both symptom expression and treatment response, as Latin American populations may experience childhood adversity and resilience differently from those in North America or Europe.

Despite these considerations, the real-world nature of our study strengthens its external validity within Latin American clinical settings. The findings highlight the importance of screening for CT exposure in BD treatment and underscore the need for further studies to assess whether these results extend to other sociocultural contexts. Future research should explore cross-cultural comparisons to determine whether the observed impact of CT on treatment response is consistent across diverse psychiatric populations.

Although demographic variables were balanced between treatment groups, the potential for residual confounding cannot be ruled out. Factors such as socioeconomic status, healthcare access, and medical comorbidities may influence both treatment response and clinical outcomes. While we adjusted for key covariates in our analyses, unmeasured and contrafactual confounders could still contribute to variability in outcomes. Future studies should incorporate sensitivity analyses or propensity score methods to further account for these potential confounders and enhance causal inferences.

As this study is observational and non-randomized, the absence of random treatment allocation may introduce selection bias and residual confounding despite our efforts to adjust for main covariates, including baseline depression severity, bipolar subtype, age, gender, comorbidities, and BMI. While MMRMs were used to account for within-subject variability and mitigate confounding, the findings should be interpreted with caution, as causal inferences cannot be drawn. Future studies employing randomized designs or advanced propensity score methods could further validate these comparative effectiveness findings.

In conclusion, BD participants without CT exposure reported higher response and remission rates to both lurasidone monotherapy and combination therapy with lithium. Statistical comparisons also revealed significant differences in response rates between BD participants with and without CT exposure when prescribed combination treatment. This highlights the potential influence of CT on the BD course of illness and thus treatment outcomes. Further studies with larger sample sizes, randomization or target trial emulation strategies for real-world evidence (RWE), as well as investigations of other psychopharmacological agents and adjunctive psychotherapy approaches, are needed to minimize potential bias..

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Conflicts of interest

H.F.G.B.: He has received research grant support from the Ministry of Science, Technology, and Innovation (Minciencias) in Colombia, UKRI in the United Kingdom; and speaker fees from Abbott, GSK, Roche, Pfizer, Synergy R&D.

J.F.G.F., S.M.L.: The authors declare no conflict of interest to report.

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Data availability

Data are available upon request from the corresponding authors

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