CASE REPORT

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Challenging the Safety Threshold: Neurotoxicity in Bipolar Disorder Treatment with Lithium at Therapeutic Serum Levels

Jinbo Chen, Jun Zhu, Hehua Bao, Lijuan Tang, Benhan Li, Zixuan Chen, Yanli Zhang, Qiang Hu

Department of Psychiatry, Zhenjiang Mental Health Center, Zhenjiang, China

ABSTRACT

Bipolar disorder is a complex mental disorder that often requires long-term medication management. Lithium carbonate is widely used to prevent and treat the recurrence of bipolar disorder. However, even with normal serum lithium levels, some rare but serious side effects may occur. This case report describes a 42-year-old female patient with bipolar disorder who experienced "electrical shock-like" convulsions after taking lithium carbonate sustained-release tablets, despite having normal serum lithium concentrations. The patient had a history of emotional instability for 27 years, and no obvious psychotic symptoms such as hallucinations or delusions were found upon psychiatric examination at admission. On the 33rd day of medication, the patient began to experience frequent rapid convulsions in the head, neck, and upper body. Considering the possibility of drug side effects, lithium carbonate was discontinued, and the convulsions subsequently subsided. Electroencephalogram (EEG) examination showed no abnormalities. After 10 days of treatment, the convulsions had essentially disappeared. This case reminds clinicians that even with normal serum lithium levels, toxic symptoms may occur, and close monitoring of the patient's clinical manifestations and serum lithium levels is essential. Additionally, poor diet and reduced sodium intake may increase the risk of lithium toxicity, so these factors should also be taken into consideration.

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INTRODUCTION

Bipolar disorder (BD), also referred to as manic-depressive illness, is a severe mental condition characterized by profound mood fluctuations.[1,2] Patients often experience rapid shifts between extreme euphoria and deep depression within short timeframes.[2] This disorder significantly disrupts daily life, affecting one's work, academic pursuits, and interpersonal relationships, and in severe cases, it can precipitate suicidal tendencies. While the exact etiology of BD remains elusive, it is believed to involve intricate interactions among genetic, neurochemical, and environmental factors.[2,3]

Lithium carbonate is a first-line pharmacotherapy for BD, having been in clinical use for over 5 decades. It effectively ameliorates mood swings, particularly manic symptoms, in affected patients.[4,5] However, due to its narrow therapeutic range, lithium carbonate can induce toxic reactions when administered in excess, leading to manifestations such as muscle tremors, polyuria, and gastrointestinal discomfort, with severe cases posing life-threatening risks.[6,7] Consequently, rigorous monitoring of serum lithium levels is imperative to ensure they remain within the therapeutic threshold.

Lithium carbonate is associated with substantial side effects, some of which may occur even at standard therapeutic dosages.[8,9] In addition to common gastrointestinal symptoms and polyuria, central nervous system manifestations like tremors and muscle spasms may also transpire.[9] These side effects can occasionally be influenced by dietary sodium intake, renal function, and interactions with other medications. The prevention and management of these side effects are pivotal in enhancing patient compliance and overall quality of life.

This study presents an uncommon case of a BD patient experiencing electric shock-like convulsions despite maintaining normal serum lithium levels. It entails a comprehensive clinical assessment and literature review to elucidate the infrequent yet significant side effects that may arise from lithium carbonate usage. Additionally, this study underscores the impact of diet, sodium intake, and

Corresponding author: Qiang Hu, huqiang@sjtu.edu.cn; Yanli Zhang, ZYL_317@163.com

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individual variabilities on the efficacy of lithium carbonate treatment.

CASE PRESENTATION

A 42-year-old female patient presented with recurrent emotional instability for the past 2 months. She had been diagnosed with BD for 27 years. Medical history revealed a previous diagnosis of stage 2 hypertension, with no notable personal or family history. On admission, a neurological examination was unremarkable, and the mental status examination showed clear consciousness and cooperative interaction but exhibited low mood, decreased interest, reduced energy, and diminished activity. Although the patient displayed slow responses, her answers were relevant, and there were no apparent psychotic symptoms such as hallucinations or delusions. Her willpower was diminished, but her intellectual orientation was intact, although she acknowledged a lack of self-awareness. The patient admitted to past self-destructive behavior but denied any current negative thoughts. Routine laboratory tests showed no abnormalities; the serum lithium concentration was 0.47 mmol/L.

The treatment plan upon admission included early administration of paroxetine hydrochloride 20 mg, evening administration of quetiapine fumarate 100 mg and oxazepam 15 mg, and once-daily extended-release lithium carbonate 0.3 g. After 5 days, the lithium carbonate dose was increased to 0.3 g twice daily. On the 30th day of medication, the patient reported poor appetite and reduced food intake. On the 33rd day, she experienced electric shock-like convulsions characterized by rapid jerking movements of the head, neck, and upper body, rapid nodding and shaking movements occurring every 10-15 seconds, and slight tremors in the hands,Written informed consent was obtained from the patient for the publication of this case report and accompanying images. The patient was fully informed of the purpose of the case presentation and her right to confidentiality, and her identity was anonymized to ensure privacy. Ethical committee approval was receihelp_outlineved from the Ethics Committee of Zhenjiang Mental Health Center (Approval no: 2023L01).

Considering the symptoms above could be drug-related adverse reactions, lithium carbonate was discontinued on the same day and replaced with sodium valproate sustained-release tablets 0.5 g, once daily. The serum lithium concentration on that day was 0.67 mmol/L. The convulsions improved the following day, and intravenous fluid supplementation, metabolic therapy, and intravenous administration of diazepam 3 mg were initiated. On the fourth day, the convulsions were significantly improved, and there were no abnormal findings on the electroencephalogram (EEG). On the sixth day, there were only slight tremors in the hands, and the serum lithium concentration decreased to 0.38 mmol/L. By the 10th day, the electric shock-like convulsions mainly had disappeared.

The exploration of the EEG outcomes associated with the administration of lithium was conducted (as illustrated in Figure 1). Related research confirmed that minor alterations in the EEG could be detected as early as 3 hours after lithium administration (Figure 1, left panel), with significant synchronous electrical activity observable 20 hours post-administration (Figure 1, right panel). The EEGs obtained 20 hours after lithium administration exhibited synchronous and asynchronous activity, including unilateral spikes and other non-epileptiform changes. Furthermore, to assess the patient's brain function and the potential neurotoxic effects induced by lithium, power spectral analysis of continuous intracortical recordings of EEGs was performed 25 minutes before (depicted in black) and 3 hours after (depicted in red) the administration of lithium (3 mEq/kg) (Figure 2). The EEG results revealed a pronounced increase in 4-5 Hz brainwave activity following lithium treatment (Figure 2). The asterisks in Figure 2A denote a significant increase in brain electrical activity within the particular frequency range corresponding to θ wave activity, as demonstrated during the time interval shown in Figure 2B. All the above data analyses were carried out utilizing Origin software (Microcal, v 7.0).

Literature Review

Lithium has been recognized since the 19th century as a preventative treatment for recurrent depressive episodes.[10] Its mechanisms of action include the inhibition of glycogen synthase kinase 3 beta (GSK-3β), modulation

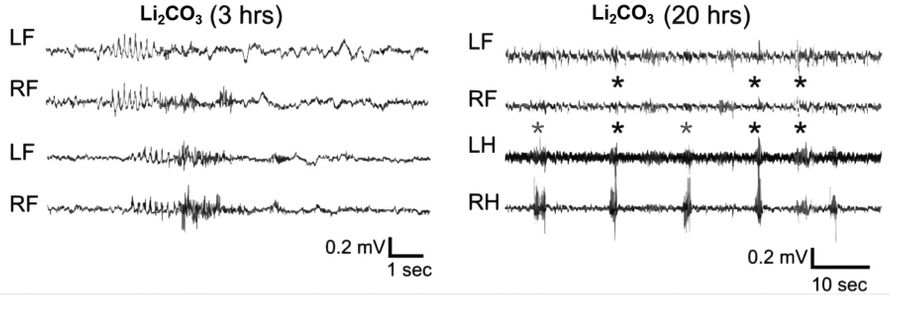

Figure 1. Changes in electroencephalogram patterns at different times after lithium administration in related research. Li_2CO_3 represents lithium.

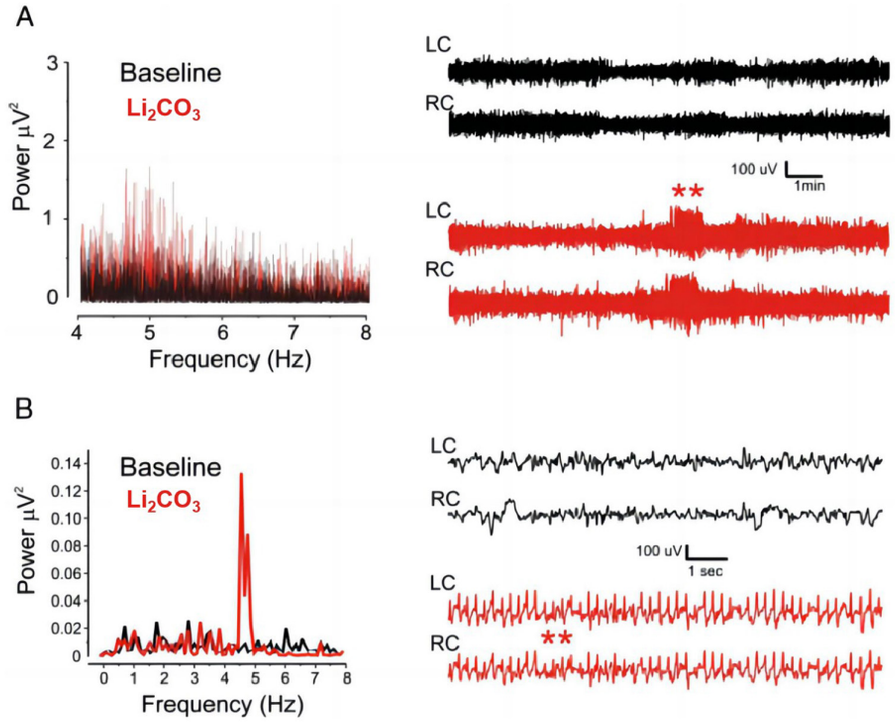

Figure 2. Alterations in theta wave activity in electroencephalogram following lithium administration in this study. (A) Brainwave activity after lithium administration. (B) The frequency range of theta wave activity during the most significant interval of brainwave activity post-treatment. Li_2CO_3 represents lithium.

of neurotrophic factors, and neurotransmitter systems.[11] These actions contribute to its therapeutic effects, particularly in neuronal plasticity.[12] Given its renal excretion, regular monitoring of kidney function is critical to avoid toxicity.[13] Lithium toxicity primarily affects the central nervous system and can lead to confusion, ataxia, and neuromuscular symptoms. Lithium's clinically recommended maintenance concentration is 0.6-0.8 mmol/L, though a commonly accepted range is 0.6-1.2 mmol/L. Lithium concentrations below 0.4 mmol/L are considered non-therapeutic in the treatment of BD.[14,15] Despite potential side effects, lithium remains a first-line treatment in BD.[16]

There have been cases where lithium toxicity does not directly correlate with serum levels. For example, reversible splenial lesions and neuroleptic malignant syndrome-like symptoms were reported despite normal lithium levels, suggesting that serum concentrations alone may not fully reflect neurotoxicity risks.[17] While tremor and polyuria are common side effects, rare cases of irreversible neurotoxicity have been documented.[18]

Due to the discrepancy between serum and brain lithium concentrations, convulsions and other adverse reactions may occur, with EEG serving as a sensitive tool for evaluating lithium-induced neurotoxicity.[19] Lithium's impact on brain function is further complicated by its interactions with other drugs, such as carbamazepine, which can exacerbate its neurotoxic effects.[5,20] Recent research also suggests that increased immune activity and disruption of the blood-brain barrier may contribute to lithium's pro-epileptic effects.[21]

DISCUSSION

This study uniquely illuminates a case of electric shock-like convulsions in a patient with BD under normal serum lithium concentrations, thereby establishing a potential link between lithium carbonate treatment and such convulsions. Through a detailed examination of the patient's clinical presentation and treatment regimen, this case offers novel observations and insights, enhancing the understanding of the complexities and challenges in treating BD. Herein, we delve into the main findings of this study, comparing them with existing literature in the field.

Lithium, commonly utilized as a mood stabilizer for treating Bipolar Affective Disorder, is known for its efficacy in many patients. However, it is also associated with a spectrum of side effects, including but not limited to renal function impairment, thyroid issues, tremors, increased thirst and urination, weight gain, and cognitive function decline. Studies have indicated that discontinuation of long-term lithium treatment significantly increases the risk of disease relapse, hospitalization need, and suicidal behaviors, especially if the treatment is stopped abruptly or quickly,[22] with the first 6-12 months post-discontinuation being particularly critical. This case underscores the importance

of careful monitoring and management of BD patients considering cessation of lithium treatment to prevent severe relapse. While previous studies have reported various side effects of lithium carbonate, observations of electric shock-like convulsions are relatively rare in the literature. Our findings offer a fresh perspective on the interactions between lithium carbonate and the nervous system. Compared to other studies on the side effects of lithium carbonate, our case emphasizes the importance of closely monitoring patient symptoms and the necessity for timely treatment adjustments. Moreover, the patient's diet and sodium intake were analyzed, factors possibly associated with the risk of lithium toxicity, an aspect not fully discussed in the existing literature.

Despite normal serum lithium levels, poor diet and reduced sodium intake could elevate the risk of lithium toxicity. This finding and existing research further underscore the importance of assessing and monitoring the dietary habits and electrolyte balance of patients undergoing lithium treatment. Additionally, this study highlights how individual differences and sensitivity to lithium salts may significantly impact the risk of lithium toxicity. These factors, possibly overlooked in previous research, hold significant value for optimizing personalized treatment strategies for patients with BD.

Although the precise mechanisms underlying the effects of lithium in emotional regulation remain incompletely elucidated, recent studies suggest its role in fostering emotional stability through its influence on cellular targets and subsequent neuroprotective effects.[23] The GSK-3 signaling pathway regulates cell apoptosis, synaptic plasticity, and cellular adaptability.[24] Research indicates that modulating the GSK-3 signaling pathway can yield anti-manic and antidepressant effects, and genetic regulation of GSK-3 is also implicated in the pathogenesis of BD.[25-27] Lithium can mitigate its excitotoxic effects by increasing phosphorylated GSK-3β activity and influencing multiple neuroprotective pathways while inhibiting its function.[28] Previous studies have shown that the response to lithium treatment can be predicted by GSK-3β gene expression and phosphorylation levels.[29,30] Increased phosphorylated GSK-3β induced by lithium is associated with clinical symptom improvement.[28]

This study's therapeutic approach, which included prompt medication adjustments and fluid supplementation, effectively mitigated electric shock-like convulsions. Lithium treatment can potentially disrupt electrolyte balance within the body, particularly levels of sodium and potassium, which play crucial roles in neuronal excitability. Imbalances in these electrolytes may lead to aberrant neuronal discharge, culminating in epileptic convulsions. Compared to treatment methodologies discussed in other literature, our strategy underscores the importance of a flexible and rapid response to clinical changes. Additionally, using sodium valproate as an alternative to lithium carbonate presented an effective pathway for alleviating side effects, offering practical insights for improving treatment methodologies for BD.

Additionally, it is worth noting that, although rare, the combination of lithium and selective serotonin reuptake inhibitors (SSRIs) may induce serotonin syndrome. The symptoms of this syndrome include fever, sweating, tachycardia, altered mental status, and muscle rigidity, some of which overlap with the symptoms described in this case. Previous studies have reported that lithium can increase sensitivity to serotonin, thereby contributing to the onset of serotonin syndrome.[31,32] Therefore, during the combined use of lithium and SSRIs, it is important to be vigilant for this potential complication, closely monitor the patient's clinical manifestations, and adjust the treatment regimen as necessary.

With the widespread application of lithium (Figure 3), it has been extensively utilized in the clinical treatment of various neurological disorders, including mood disorders, adjunctive antidepressant therapy, prophylactic anti-dementia, and neurodegenerative diseases.[5] The effects of lithium on the brain involve multiple pathways, including neurotransmitter regulation, alteration of ion transport, and impact on second messenger systems such as cyclic Adenosine Monophosphate (AMP). In this study, the

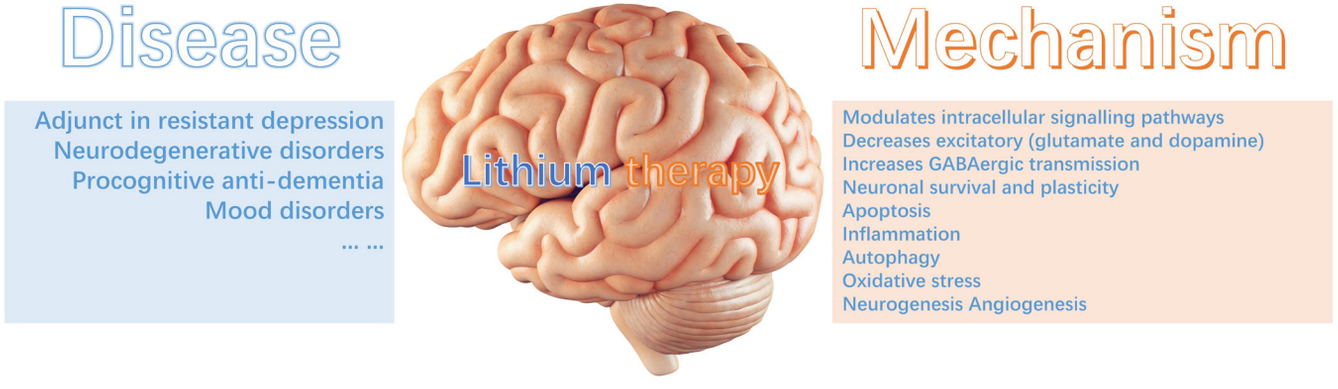

Figure 3. Neurological disorders treatable with lithium. The left side of the figure lists the types of treatable disorders, while the right side outlines the related molecular mechanisms of action.

electric shock-like epileptic convulsions experienced by the patient represent a rare phenomenon characterized by rapid muscular twitching while the patient remained conscious. Such convulsions typically affect the head, neck, and upper body and may implicate the intricate brain network responsible for controlling muscle activity. This generalized convulsion and a normal EEG post-convulsion suggest an issue with the central nervous system rather than a simple disorder of the peripheral or neuromuscular system. It involves partial epileptic convulsions, possibly due to lithium's impact on certain brain regions while sparing those involved in consciousness maintenance, thus affecting motor functions without impairing consciousness. In numerous animal studies, acute lithium treatment has been shown to facilitate dose-dependent proconvulsant effects through various mechanisms, including increased neuronal excitability, enhancement of the cholinergic pathway, inhibition of phosphoinositide signaling, and promotion of peripheral inflammation. Indeed, lithium-induced inhibition of GSK-3β in controlling convulsions and epilepsy is a double-edged sword, occasionally resulting in epileptic-like convulsions during its use. Figure 4 depicts the pathways associated with lithium-mediated anticonvulsant and neuroprotective effects. Lithium has neuroprotective properties, promoting the expression of certain neuroprotective proteins, such as brain-derived neurotrophic factor (BDNF). However, this neuroprotective action may, under certain circumstances, lead to hyperactivation of the nervous system, thereby increasing the risk of epileptic convulsions.[5] It can be inferred that electric shock-like convulsions following lithium treatment are also related to abnormalities in the above signals.

This study emphasizes the importance of personalized treatment for patients with BD. The response to lithium salts may vary significantly among different patients, and individualized treatment and monitoring plans can help minimize side effects and maximize therapeutic efficacy.

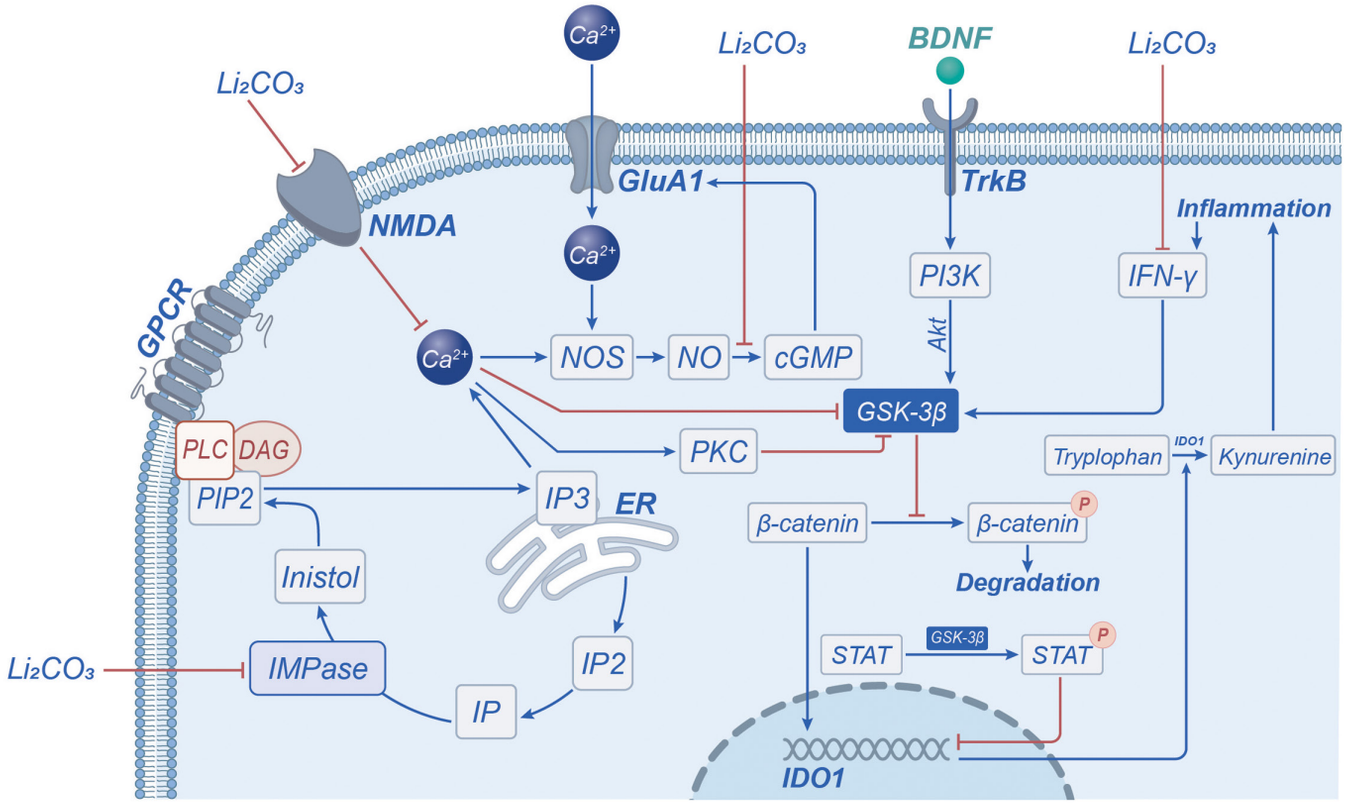

Figure 4. Molecular signaling pathways involved in the effects of lithium. (A) Lithium carbonate inhibits inositol monophosphatase (IMPase), reducing IP3-mediated intracellular Ca^{2+} elevation. (B) Lithium regulates the NMDA receptor 2B subunit and inhibits NMDAR-mediated Ca^{2+} influx. (C) Lithium suppresses the nitric oxide (NO)/cyclic GMP (cGMP) pathway, inhibiting Ca^{2+} influx mediated by glutamate ionotropic receptor AMPA type subunit 1 (GluA1). (D) Lithium activates the brain-derived neurotrophic factor (BDNF)/TrkB-mediated Akt pathway, where Akt inhibits glycogen synthase kinase 3 beta (GSK-3β). (E) Lithium can inhibit IFN-γ-mediated GSK-3β signaling. (F) GSK-3β phosphorylates and thereby facilitates the degradation of β-catenin; lithium, through various pathways (A, B, E), mediates the inhibition of GSK-3β, preventing β-catenin degradation. β-catenin nuclear translocation induces transcription of cyclin D1, a cell cycle regulator. (G) Lithium-mediated inhibition of GSK-3β blocks the nuclear translocation of signal transducer and activator of transcription factors, downregulating the transcription of indoleamine 2,3-dioxygenase (IDO1); inhibiting IDO1 prevents tryptophan metabolism, thus inhibiting the kynurenine pathway and reducing pro-inflammatory cytokine activity. Li_2CO_3, lithium carbonate; Ca^{2+}, calcium ion; GluA1, glutamate receptor AMPA type subunit 1.

Moreover, our research highlights the crucial role of continuous and meticulous safety monitoring in lithium salt treatment, facilitating the timely identification and management of potential issues. The primary limitation of this study is its limited sample size, being based on a single case observation. Furthermore, the lack of comparative groups restricts our ability to explain the phenomena observed more deeply. While we have endeavored to interpret the unique phenomena of this case, it must be acknowledged that these findings may not be universally applicable. Future clinical trials and mechanistic studies with larger samples will aid in validating and deepening our understanding.

Overall, this study provides new insights into the use of lithium carbonate in the treatment of BD through a unique case. Our findings underscore the importance of personalized treatment, continuous monitoring, and the flexibility to adjust treatment plans. Despite some limitations, this study contributes valuable insights into the complex challenges of treating BD and offers guidance for future clinical practice and research directions.

Data Availability Statement: Data availabilty statement The datasets generated and/or analysed during the current study are available in the manuscript and supplementary materials.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Zhenjiang Mental Health Center (Approval no: 2023L01).

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J.C., Y.Z.; Design – J.C., Q.H.; Supervision – Q.H., Y.Z.; Resources – H.B., Z.C.; Materials – H.B., Z.C.; Data Collection and/or Processing – H.B., Z.C.; Analysis and/or Interpretation – J.Z., B.L.; Literature Search – Y.Z., J.C.; Writing Manuscript – J.C., Y.Z.; Critical Review – Q.H., L.T.

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Declaration of Interests: The authors have no conflict of interest to declare.

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