

## Case Report

# Lithium Toxicity and Neuroleptic Malignant Syndrome in a Patient with Bipolar Disorder

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## Abstract

A combination of treatments are usually preferred by psychiatrists in managing acute manic exacerbations in patients with bipolar disorder. The most commonly used mix of psychotropic drugs to control mania consists of a known mood stabilizer - such as lithium or divalproex - plus an antipsychotic, though, these drugs can cause serious side effects. Neuroleptic Malignant Syndrome (NMS) occurs rarely in patients taking antipsychotic drugs and this infrequency makes diagnosis difficult in critically ill, Intensive Care Unit (ICU) patients. On the other hand, lithium toxicity can occur frequently in patients with bipolar disorder due to its narrow therapeutic index. Although rare, lithium toxicity and NMS may occur simultaneously in patients using antipsychotics and lithium together, resulting in severe morbidity or even mortality. The following research describes a patient on concomitant olanzapine and lithium treatment, who was diagnosed with NMS and lithium toxicity.

**Keywords:** Lithium; Olanzapine; Antipsychotic; Toxicity; Intensive care unit

## Introduction

NMS is a life-threatening, neurological and psychiatric danger, which typically manifests as altered mental status, muscular rigidity, hyperthermia and autonomic system dysfunction [1]. It occurs in 0.02–3% of patients taking antipsychotic drugs, a rarity that makes diagnosis difficult in critically ill ICU patients [2]. The mortality of patients with NMS has declined in recent years, with relevant studies reporting a mortality rate of 10–20% in untreated patients [3,4]. On the other hand, lithium toxicity occurs in 75–90% of patients receiving long-term lithium therapy [5]. While lithium toxicity shows mild side effects such as hand tremors in most patients, moderate to severe side effects including Central Nervous System (CNS) and renal involvement have also been seen in a sub-group of patients [6]. The mortality rate of lithium toxicity has decreased from 25% to less than 1% over the years [2,7], however, both incidence and mortality of the concurrent existence of lithium toxicity and NMS are unknown with only case reports found in literature. Herein, we examine a patient with bipolar disorder on concomitant olanzapine and lithium treatment, who was diagnosed with NMS and lithium toxicity.

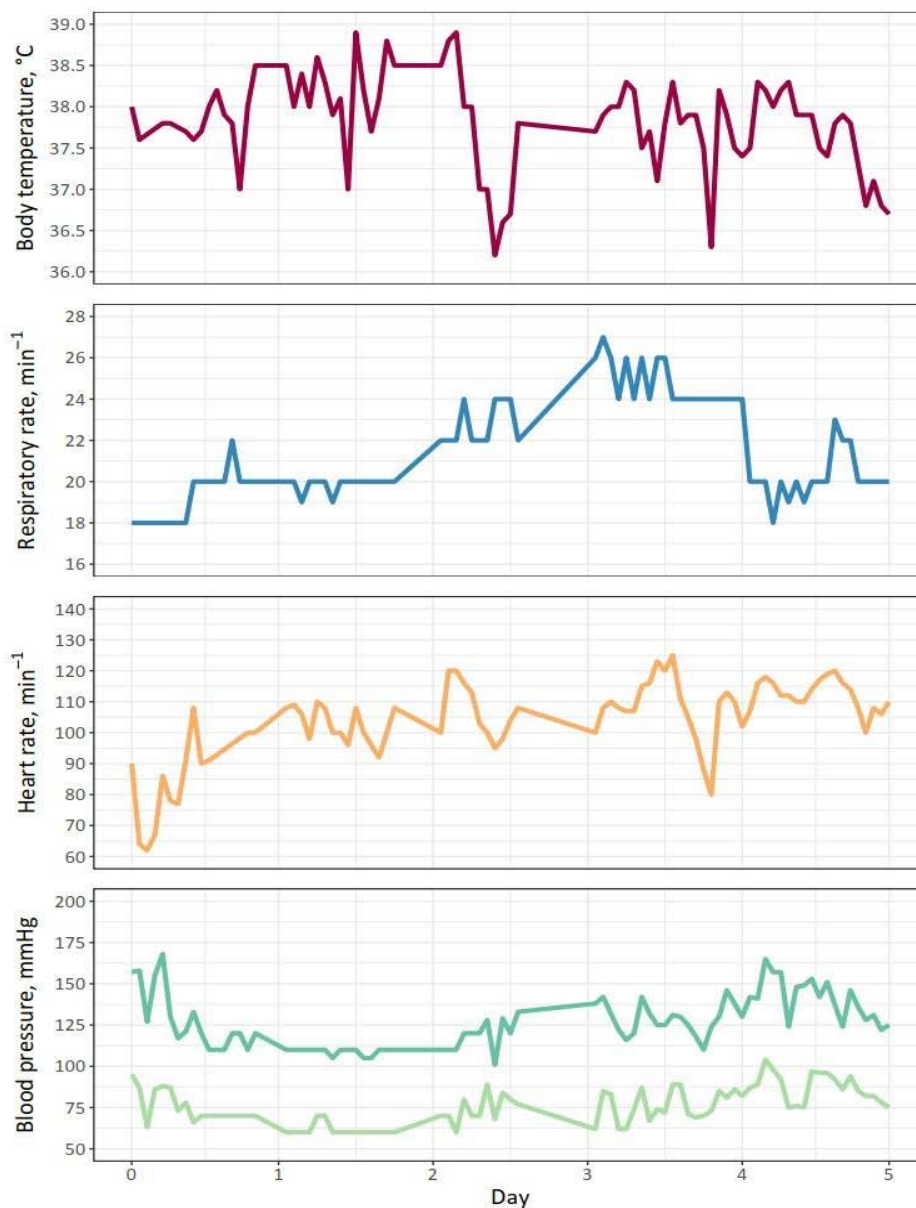
## Case Presentation

A 59-year-old female with a history of bipolar disorder for over 38 years was referred to our emergency department with speech impairment, lethargy, tremors and an altered mental state. Her medical history showed a significant risk of hypothyroidism, plus she had been taking 100mcg levothyroxine per day for 10 years. Her bipolar disorder medication was a weekly flupentixol depot dose of 20 mg, daily amisulpride of 600mg, 600mg of lithium and 3mg biperiden, for 2 years. About two weeks prior, after taking her last dose of flupentixol depot, these prescriptions were modified. The patient complaints began on the 10<sup>th</sup> day of the new therapy regimen, which consisted of lithium carbonate, 600mg twice daily, and olanzapine, 10mg/day.

Upon admission to the emergency department, the patient's body temperature was 38°C, pulse rate 90 beats/minute, respiratory rate was 18 breaths/minute and blood pressure was 157/95 mmHg. A neurological examination revealed slurred speech, rigidity and tremors, in addition to a time, place and person disorientation. Lithium and olanzapine were halted and an intravenous saline infusion was started at a rate of 75ml/hour. Firstly, serum creatinine was 2.99mg/dL (0.67–1.17 mg/dL) and lithium level was 2.16mmol/L (therapeutic level: 0.8–1.2 mmol/L), thus intermittent hemodialysis was performed. During the patient's hospital stay, her sodium level of 152mEq/L (136–146 mEq/L) was observed due to Nephrogenic Diabetes Insipidus (NDI). After the 6<sup>th</sup> day of hospitalization, the patient was transferred to the ICU due to a worsening of her general condition along with a decreasing Glasgow Coma Score (GCS) (9/15) and fluctuations in vital signs.

On admission to the ICU, she had persistent hyperthermia of about 38.5°C, pulse rate was 110 beats/minute, respiratory rate was 22 breaths/minute and blood pressure was 110/70 mmHg. Serum creatinine was 2.2mg/dL, serum Creatine Kinase (CK) was 524 IU/L (0–145 IU/L), sodium level was 154mEq/L and lithium level was 0.64mmol/L. In addition, serum C-reactive protein was 0.7mg/dL (0–0.8 mg/dL) and her white blood cell count was 10,400/mL (4300–103,00/mL). Infection was ruled out clinically and microbiologically. Cerebrospinal fluid analysis was normal with no signs of infection either. During her ICU stay, episodes of sinus tachycardia (120–130 beats per minute), unrelated to hyperthermia episodes, were observed. Electroencephalography revealed moderate to severe diffuse slow activity, diffuse triphasic sharp waves and focal epileptiform activities in both hemispheres, which are consistent with lithium toxicity, metabolic encephalopathy or non-convulsive status epilepticus. Magnetic resonance imaging of the brain revealed minimal cerebral atrophy.

In light of the clinical findings as shown in Table 1, NMS was



**Figure 1:** Fluctuation in vital signs for 5 days before ICU admission. There are 55% increase in systolic blood pressure and 65% increase in diastolic blood pressure above baseline.

diagnosed in addition to lithium toxicity. For treatment, dantrolene 400 mg/day for 18 days and bromocriptine 10 mg/day for 6 days were given during the ICU stay. Fluctuations in blood pressure, body temperature, heart rate and respiratory rate are shown in Figure 1. At the end of one month, as her renal functions and consciousness improved, she was discharged from the ICU. After one year of follow-up, lingering clinical signs of moderate cerebellar dysfunction (dysarthria, bilateral dysmetria, dysdiadokynesia) and asymmetric parkinsonism secondary to lithium toxicity were observed.

## Discussion

We report a case of both acute lithium toxicity and NMS in a patient with bipolar disorder. In addition, persistent cerebellar dysfunction and parkinsonism symptoms were observed in the

following year. Lithium toxicity is relatively easy to diagnose in patients on lithium treatment since serum lithium levels can be measured. However, NMS diagnosis might be problematic as its symptoms, such as hyperthermia, altered mental status, variability of blood pressure, heart rate and respiratory rate, are also frequently seen in critically ill patients. Also, a diagnostic delay of NMS in our patient could be related to severe lithium toxicity, including hypernatremia due to NDI. The simultaneous presentation of NMS and lithium toxicity can be under-diagnosed and under-treated in critically ill patients.

Lithium has a long history of the primary treatment option for bipolar disorders. This wide usage commonly causes toxicity, since the therapeutic range is narrow. Potential neurological symptoms and signs of acute lithium toxicity are sluggishness, ataxia, confusion

**Table 1:** NMS diagnostic criteria [8].

Diagnostic criteria	Score	Patient's score
Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours	20	20
Hyperthermia (>100.4°F or >38.0°C on at least 2 occasions, measured orally)	18	18
Rigidity	17	17
Mental status alteration (reduced or fluctuating level of consciousness)	13	13
CK elevation (at least 4 times the upper limit of normal)	10	0
Sympathetic nervous system lability, defined as at least 2 of the following: <ul style="list-style-type: none"> <li>• Blood pressure elevation (systolic or diastolic <math>\geq</math>25 percent above baseline)</li> <li>• Blood pressure fluctuation (<math>\geq</math>20 mmHg diastolic change or <math>\geq</math>25 mmHg systolic change within 24 hours)</li> <li>• Diaphoresis</li> <li>• Urinary incontinence</li> </ul>	10	10*
Hypermetabolism, defined as heart-rate increase ( $\geq$ 25 percent above baseline) AND respiratory-rate increase ( $\geq$ 50 percent above baseline)	5	0
Negative work-up for infectious, toxic, metabolic, or neurologic causes	7	7
Total score	100	85

\*10 points for 1 and 2.

and neuromuscular excitability, which can also manifest as an irregular course of tremors, fasciculations or myoclonic jerks [9]. Our patient responded to hemodialysis and fluid therapy as suggested in available literature, and the serum lithium level decreased to a normal value [10]. Since laboratory, findings were compatible with NDI, neurological deterioration was attributed to hypernatremia at first. In a follow-up examination, persistent hyperthermia, fluctuations in the vital signs and persistent unconsciousness despite improving hypernatremia that cannot be explained with isolated lithium toxicity led us to move towards additional diagnoses. After excluding central neurological system infections through laboratory and neuro-imaging test results, we considered NMS in our patient.

NMS is mostly associated with the use of antipsychotic agents, but it may also occur due to other drugs such as lithium, anti-emetics and antidepressants related by their anti-dopaminergic effects [11,12]. This is a rare condition in clinical practice, however, especially if there are fluctuations in body temperature, blood pressure, respiratory or heart rate in patients using these drugs, therefore the risk of NMS should be taken into account. Unfortunately, no threshold level was defined for the diagnosis of NMS in the international consensus report [8].

Since NMS occurs mainly due to the use of agents containing dopamine receptor blockade effects, as central dopamine receptor blocking is thought to be a key factor in pathogenesis. A hypothalamic blockade may lead to hyperthermia and other signs of dysautonomia, plus, nigrostriatal blockade is responsible for Parkinson's [13,14]. Besides the dopaminergic system, other neurotransmitter systems also appear to be involved [15]. A chronic use of lithium is one of the risk factors associated with NMS in patients taking antipsychotics. Acute lithium toxicity occurring during the course of chronic lithium use may lead to severe neurotoxicity, including Parkinson's disease [16,17].

Pharmacologically atypical antipsychotics differ in their receptor affinity profiles and accordingly, can be divided into three groups: amisulpride, a selective dopamine type-2/type-3 (D2/D3) receptor antagonist stands alone in the first group., the second group of atypical antipsychotics have an affinity mainly for dopamine and for serotonin (5-HT)-2A receptors, such as risperidone and ziprasidone,

and the third group of drugs such as clozapine, olanzapine, zotepine and quetiapine, have an affinity for a broad range of central receptors [18]. With the exception of amisulpride, all the uncommon antipsychotics exhibit a greater affinity for serotonergic receptors than dopamine receptors. Therefore, we cannot exclude the role of serotonergic pathways for the development of NMS, and further studies are needed in order to understand the role of dopaminergic and serotonergic pathways in the pathophysiology of NMS. Recommendations for specific medical treatments for NMS are based upon case reports and clinical experience, not upon data from clinical trials. Commonly used agents include dantrolene, bromocriptine, and benzodiazepines [19].

Considering all these options, prior to emergency department admission, the patient's medication was modified to olanzapine from amisulpride, she was given a depot flupenthixol just before 10 days her medication was changed and a daily lithium dose was also added at the same time. We speculate that both serotonin and dopamine antagonist olanzapine have aggravated NMS compared to amisulpride, which is a major dopamine antagonist, in addition to high dose lithium, which caused lithium toxicity and aggravated NMS due to an anti-dopamine action. Valproic acid was started for bipolar disorder maintenance therapy, as an atypical antipsychotic drug-lithium combination might be not a safe treatment choice in patients with a history of lithium-neuroleptictoxicity.

One year after discharge, the patient was examined in a psychiatry outpatient clinic. Clinical signs of moderate cerebellar dysfunction and asymmetric Parkinson's remained. In severely intoxicated patients, a syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) may develop, which is revealed by neuropsychiatric signs and symptoms including cognitive impairment, cerebellar dysfunction, brainstem dysfunction, extrapyramidal symptoms, choreoathetoid movements, myopathy and nystagmus. Risk factors for SILENT include age over 50, chronic lithium therapy, nephrogenic diabetes insipidus, hyperthyroidism and impaired renal function. Prolonged exposure of the central nervous system to sustained, high lithium concentrations can cause permanent neurologic conditions such as memory deficits, cerebellar dysfunction, Parkinson's disease and personality changes, as seen in our patient. Although the pathogenesis remains unclear, demyelination caused by lithium, neuronal loss and

gliosis in the cerebellar cortex and a prominent, spongy change in dentate nuclei are some possibilities [21,22]. Parkinson's symptoms, like tremors and rigidity, appear due to a dopaminergic blockade in the nigrostriatal pathways of the same direction.

## Conclusion

In conclusion, clinicians should consider lithium-neuroleptictoxicity and carefully evaluate daily fluctuations of vital signs in addition to changes in mental state in patients with psychiatric diseases taking a combination of drugs such as lithium and olanzapine. As was seen in our case, a diagnosis can be challenging because of interwoven and closely connected clinical characteristics. Patients should also be revisited for persistent neurological sequelae such as cerebellar dysfunction, dementia, Parkinson's syndrome, choreoathetosis, brain stem syndromes and peripheral neuropathies as side effects of lithium toxicity.

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