Olanzapine-Induced Hyponatremia Secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) : A Rare Antipsychotic-Related Adverse Drug Reaction

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ABSTRACT

Olanzapine is a widely prescribed atypical antipsychotic with a generally favorable safety profile; however, rare but clinically significant electrolyte disturbances such as Hyponatremia have been reported. This case report describes olanzapine-associated hyponatremia secondary to Syndrome of Inappropriate Antidiuretic Hormone Secretion in an elderly patient. A 74-year-old female with a history of Pseudodementia presented with altered sensorium, irritability, sleep disturbances, and progressive cognitive decline. Laboratory investigations revealed severe hyponatremia with a serum sodium concentration of 117 mmol/L. A comprehensive clinical evaluation and detailed review of the patient's medication history suggested a drug-induced etiology associated with prolonged olanzapine therapy. The suspected medication was promptly discontinued, and the patient was managed with hypertonic saline infusion, electrolyte supplementation, and supportive care. Subsequent monitoring demonstrated gradual correction of serum sodium levels to 139 mmol/L, accompanied by marked clinical improvement. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale yielded a score of 7 (probable adverse drug reaction), while evaluation with the WHO–UMC Causality Assessment System classified the reaction as "probable/likely." This case highlights the importance of vigilant electrolyte monitoring in elderly patients receiving long-term antipsychotic therapy.

Key words :- Olanzapine, Hyponatremia, Naranjo Adverse Drug Reaction Probability Scale, Pseudodementia, Syndrome of Inappropriate Antidiuretic Hormone Secretion

I. INTRODUCTION

Rapidly developing hyponatremia is rare but clinically significant adverse reaction associated with olanzapine therapy. Several case reports have documented hyponatremia related to the use of atypical antipsychotics, and

this electrolyte disturbance is often attributed to the development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[1]

Epidemiology –

Analyses of pharmacovigilance databases show that about 1.1% of antipsychotic-related adverse event reports involve hyponatremia.[2] According to WHO pharmacovigilance data from VigiBase, olanzapine has been reported as the second most frequently reported atypical antipsychotic associated with hyponatremia.[3]

HYPONATREMIA

Hyponatremia is defined as serum sodium levels <135mEq/L and is the most common electrolyte imbalance encountered in clinical practice. Approximately 15-30% of hospitalized patients have hyponatremia.[4]

Classification –

The European clinical practice guidelines for the diagnosis and management of hyponatremia provide specific classification criteria, which are presented in Figure 1.

Clinical Classification—According to symptomatology				
Moderately severe	Nausea without vomiting; confusion; headache; cognition impairment; gait deficits; falls.			
Life threatening	Vomiting; cardiorespiratory distress; abnormal and deep somnolence; seizures; coma (Glasgow Coma Scale ≤ 8).			
Biochemical classification—According to serum sodium concentration				
Mild	130–135 mmol/L			
Moderate	125–129 mmol/L			
Profound	<125 mmol/L			
Time-based classification—According to time of development				
Acute	Development within <48 h (associated with higher risk of brain edema and neurological complications)			
Chronic	Development over ≥48 h (allowing partial cerebral adaptation to hypo-osmolality)			
Serum osmolality-based—According to serum osmolality				
Non-hypotonic	Hypertonic			>290 mOsm/kg
	Isotonic			275–290 mOsm/kg
Hypotonic	According to volume status	Hypovolemic	↓ H_2O ↓↓ Na^+	<275 mOsm/kg
		Hypervolemic	↑↑ H_2O ↑ Na^+	
		Euvolemic	↑ H_2O ↔ Na^+ excretion	
Pseudo-hyponatremia	Laboratory artifact			

↓, decreased; ↑, increased; ↓↓/↑↑, decrease/increase predominates; ↔, normal.

Fig 01 - Classification of Hyponatremia Based on Clinical Parameters[5]

Etiology –

Category	Etiology / Causes
Excess Water Intake or Dilution	• Excessive water consumption (psychogenic polydipsia) • Administration of hypotonic intravenous fluids • Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)
Loss of Sodium from the Body	• Vomiting, Diarrhea, Excessive sweating, Burns and Kidney diseases causing sodium loss
Drug-Induced Hyponatremia	• Antipsychotics such as olanzapine • Antidepressants (SSRIs) • Diuretics such as hydrochlorothiazide • Antiepileptics like carbamazepine • Chemotherapy drugs
Hormonal Disorders	• Adrenal insufficiency • Hypothyroidism
Organ Failure Conditions	• Congestive heart failure • Cirrhosis • Chronic kidney disease
Severe Illness or Stress	• Infections • Post-surgical states

Table 01 - Etiological Factors Associated with Hyponatremia[6]

Pathophysiology –

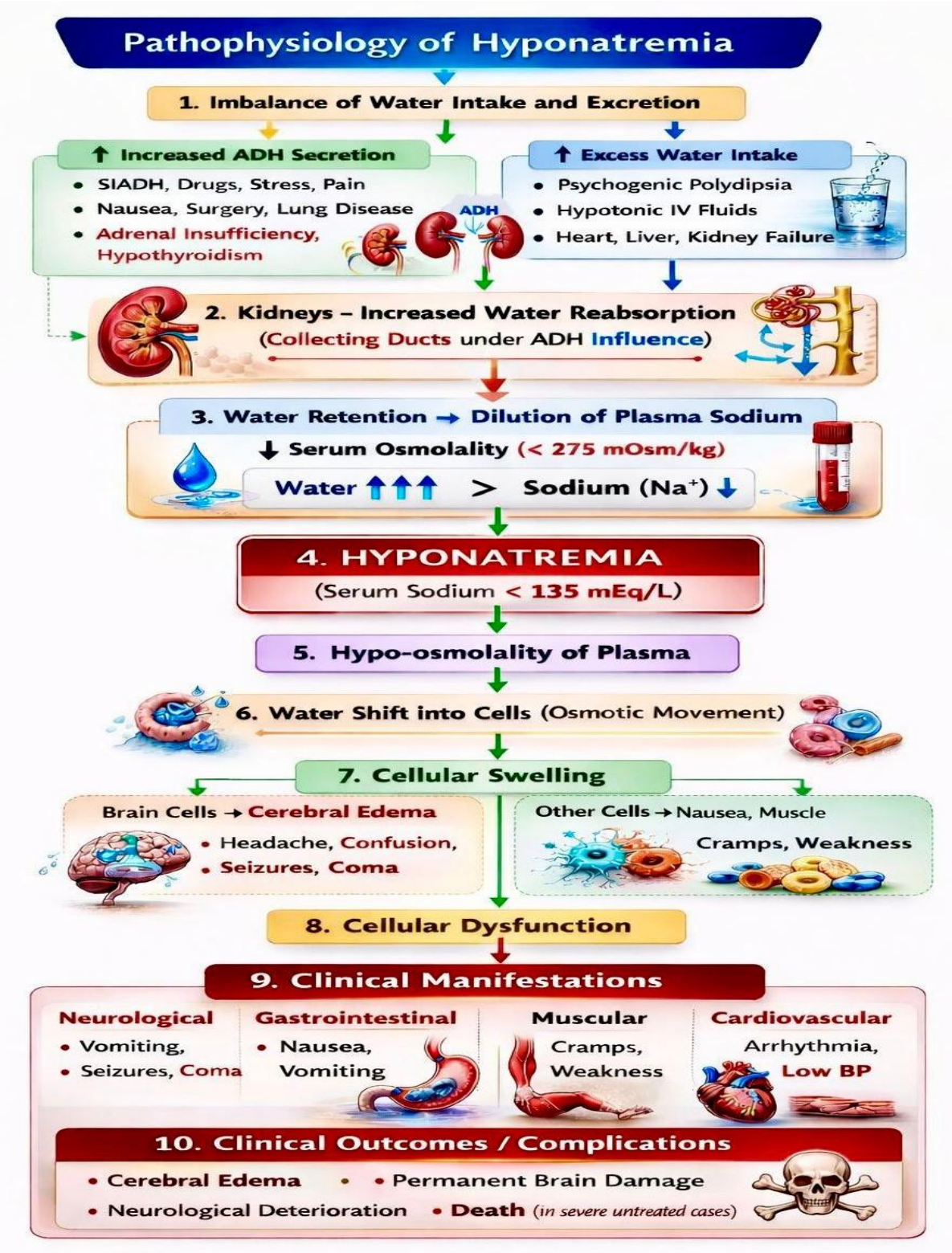


Fig 02 - Pathophysiological Mechanisms and Clinical Consequences of Hyponatremia[7]

Diagnosis –

Step	Investigation / Assessment	Interpretation / Possible Causes
1	**Confirm serum sodium**	Hyponatremia defined as Plasma Na^+ <135 mmol/L
2	**Measure Serum Osmolality**	• <275 mOsm/kg: Hypotonic hyponatremia (true hyponatremia) • 275–295 mOsm/kg: Isotonic hyponatremia (pseudohyponatremia – hyperlipidemia, hyperproteinemia) • >295 mOsm/kg: Hypertonic hyponatremia (hyperglycemia, mannitol)
3	**Assess Volume Status**	• Hypovolemic: Vomiting, diarrhea, diuretics, adrenal insufficiency • Euvolemic: SIADH, hypothyroidism, glucocorticoid deficiency • Hypervolemic: Heart failure, cirrhosis, nephrotic syndrome
4	**Measure Urine Osmolality**	• <100 mOsm/kg: Excess water intake (primary polydipsia, low solute intake) • >100 mOsm/kg: Impaired water excretion (SIADH, renal causes)
5	**Measure Urine Sodium**	• <20 mmol/L: Extrarenal sodium loss (vomiting, diarrhea) • >40 mmol/L: Renal sodium loss or SIADH
6	**Additional Investigations**	Thyroid function tests, serum cortisol, renal function tests, serum uric acid, blood urea nitrogen, plasma glucose

Table 02 - Stepwise Diagnostic Evaluation of Hyponatremia Leading to SIADH Identification.

Schwartz Diagnostic Criteria and Supporting Findings for SIADH Diagnosis

Category	Diagnostic Criteria
Schwartz Diagnostic Criteria for SIADH	• Decreased measured serum osmolality (<275 mOsm/kg H_2O) • Clinical euvolemia • Urinary osmolality >100 mOsm/kg H_2O • Urinary sodium (Na^+) >40 mmol/L with normal dietary sodium intake • Normal thyroid and adrenal function • Normal renal function • No use of diuretic agents within one week prior to evaluation • Absence of hypokalemia and acid–base disorders
Supporting Diagnostic Criteria for SIADH	• Serum uric acid <4 mg/dL • Blood urea nitrogen (BUN) <10 mg/dL • Fractional sodium excretion >1%; Fractional urea excretion >55% • Failure to improve or worsening of hyponatremia after 0.9% saline infusion • Improvement of hyponatremia with fluid restriction

Table 03 – Diagnostic criteria of SIADH

Treatment –

Principles of treatment of hyponatremia

- Treatment depends on :
  - ✓ Volume status.
  - ✓ Duration of hyponatremia (whether acute/48 h)).
  - ✓ Presence or absence of symptoms.
  - ✓ Etiology of hyponatremia.[8]

Guideline-Recommended Treatment of Severely Symptomatic Hyponatremia with Hypertonic Saline

Parameter	US Guideline	European Guideline
Patients requiring treatment with hypertonic saline	Regardless of duration : • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress). • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progression to life-threatening complications.	Regardless of duration : • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress). • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progression to life-threatening complications.
Rate of increase in serum sodium level desired	4–6 mEq/L within 1–2 h.	5 mEq/L within 1–2 h.
Recommended treatment with hypertonic saline (3% sodium chloride)	100-mL bolus via central or peripheral vein over 10 min; may repeat up to 3 times as needed to reach target serum sodium level.	150-mL bolus via central or peripheral vein over 20 min; repeat twice until desired serum sodium level is achieved.
Recommended frequency of measuring serum sodium level	After each bolus and every 4–6 h during the first 24 h.	After each bolus and every 6 h during the first 24 h.
Recommended increase in serum sodium level that should not be exceeded (correction limit)	**Low risk of osmotic demyelination :** • 10 mEq/L in first 24 h. • 18 mEq/L in first 48 h. **High risk of osmotic demyelination :** • 8 mEq/L during any 24-h period.	**Low risk of osmotic demyelination:** • 10 mEq/L in first 24 h. • 18 mEq/L in first 48 h. **High risk of osmotic demyelination:** • 8 mEq/L during any 24-h period.

Tale 04 - Comparison of US and European Guideline-Recommended Treatment of Severe Symptomatic Hyponatremia with Hypertonic Saline[9]

OLANZAPINE

Olanzapine is a second-generation (atypical) antipsychotic medication. It is a member of the thienobenzodiazepine class of serotonin-dopamine antagonists which have potent 5-HT_2 and weaker D_2 receptor binding properties.

Safety profile of Olanzapine –

Category	Adverse Effects
Common Adverse Effects	Somnolence, weight gain, increased appetite, dry mouth, constipation, dizziness and pharyngitis.
Neurological Effects	Minimal extrapyramidal symptoms (EPS), low incidence of akathisia and parkinsonism and rare dystonia.
Metabolic Effects	Significant weight gain; ~40.5% of patients gained ≥7% body weight.
Cardiovascular Effects	Mild increase in sinus heart rate; no clinically significant changes in blood pressure or ECG.
Hepatic Effects	Transient elevation of liver transaminases (ALT/SGPT), usually asymptomatic.
Endocrine Effects	Mild and transient increase in serum prolactin levels.
Hematological Effects	No evidence of hematotoxicity.
Rare Adverse Effects	Seizures and sexual dysfunction.

Table 05 - Comprehensive Safety Profile of Olanzapine Based on Clinical Trial Data

Overall, compared with typical antipsychotics, olanzapine demonstrates a favorable safety and tolerability profile with a lower incidence of extrapyramidal side effects; however, metabolic effects, particularly weight gain, remain a notable concern.[10]

II. CASE PRESENTATION

A 74-year-old female with a prior diagnosis of pseudodementia was admitted to the Department of General Medicine, BMCRC, Ballari (Karnataka) with complaints of altered sensorium, which manifested as irritability, reduced speech, decreased sleep, and progressive memory impairment for approximately one month. The

patient also had a history of chronic alcohol use. Her psychiatric history revealed long-term treatment with olanzapine, and she was additionally receiving quetiapine for the management of pseudodementia.

Initial laboratory evaluation at admission revealed marked hyponatremia with a serum sodium concentration of 117 mmol/L. After reviewing the patient's clinical history and medication profile, a drug-induced etiology was suspected, and the condition was diagnosed as acute hyponatremia likely associated with olanzapine therapy.

In view of the suspected adverse drug reaction, olanzapine was discontinued immediately. The patient was treated with hypertonic saline infusion, along with oral potassium supplementation (syrup potassium chloride) and regular monitoring of serum electrolytes. Supportive management and appropriate fluid regulation were maintained throughout the hospital stay.

Following therapeutic intervention and withdrawal of the suspected medication, a gradual correction of serum sodium levels was observed, rising from 117 mmol/L at admission to 139 mmol/L. This biochemical improvement was accompanied by noticeable recovery in the patient's mental status and cognitive function.

CAUSALITY ASSESSMENT

1. Naranjo Adverse Drug Reaction Probability Scale

Naranjo Criteria	Response	Score
Previous conclusive reports on this reaction	Yes	+1
Adverse event appeared after the drug was administered	Yes	+2
Adverse reaction improved after drug withdrawal (dechallenge)	Yes	+1
Adverse reaction reappeared on re-administration	Not done	0
Alternative causes that could have caused the reaction	Unlikely	+2
Reaction reappeared with placebo	Not done	0
Drug detected in toxic concentration	Not done	0
Reaction worsened with dose increase or improved with decrease	Not known	0
Similar reaction to same or similar drugs previously	Not known	0
Adverse event confirmed by objective evidence (lab reports)	Yes (serum Na^+ 117 mmol/L)	+1

Table 06 - Causality Assessment of the Suspected Adverse Drug Reaction Using the Naranjo Probability Scale

✓ Total Score : 7

✓ Interpretation:

According to the Naranjo ADR Probability Scale, a score of **7** indicates a ***Probable*** adverse drug reaction.

2. WHO–UMC Causality Assessment

Criteria	Observation in the Case
Reasonable time relationship to drug administration	Long-term olanzapine therapy before onset
Alternative explanations	No strong alternative cause identified
Response to withdrawal (dechallenge)	Serum sodium improved after olanzapine discontinuation
Objective evidence	Laboratory confirmation of severe hyponatremia

Table 07 - Causality Assessment of the Suspected Adverse Drug Reaction Using the WHO–UMC Criteria

✓ Causality Category : Probable/Likely.

Causality Assessment Tools : The relationship between olanzapine and the development of hyponatremia was evaluated using two standard causality assessment methods: the Naranjo Adverse Drug Reaction Probability Scale and the WHO–UMC causality assessment system.

1. Naranjo Scale Result :

   A total score of **7**, indicating a "**Probable"** adverse drug reaction.

2. WHO–UMC Assessment :

   Based on the WHO–UMC causality criteria, the association between olanzapine and hyponatremia was categorized as **"Probable/Likely."**

3. Supporting Evidence :

   This classification was supported by a clear temporal relationship between drug administration and onset of symptoms**,** lack of strong alternative etiologies and clinical improvement after discontinuation of olanzapine (positive dechallenge).

III. DISCUSSION

Hyponatremia is a common electrolyte disturbance, particularly in elderly patients. Age-related physiological changes, comorbid conditions and exposure to medications increase the risk of its occurrence. Psychotropic drugs, especially second-generation antipsychotics such as olanzapine, have been reported to contribute to disturbances in sodium balance.

Olanzapine, an atypical antipsychotic widely prescribed for psychiatric disorders, has occasionally been associated with the development of hyponatremia. Although the exact mechanism remains unclear, it is proposed that olanzapine may affect central neurotransmitter pathways that regulate the secretion of antidiuretic hormone (ADH). Increased ADH activity leads to water retention and dilution of serum sodium, resulting in dilutional hyponatremia. In severe cases, this electrolyte imbalance may present with neurological manifestations such as confusion, irritability, cognitive impairment and altered sensorium.

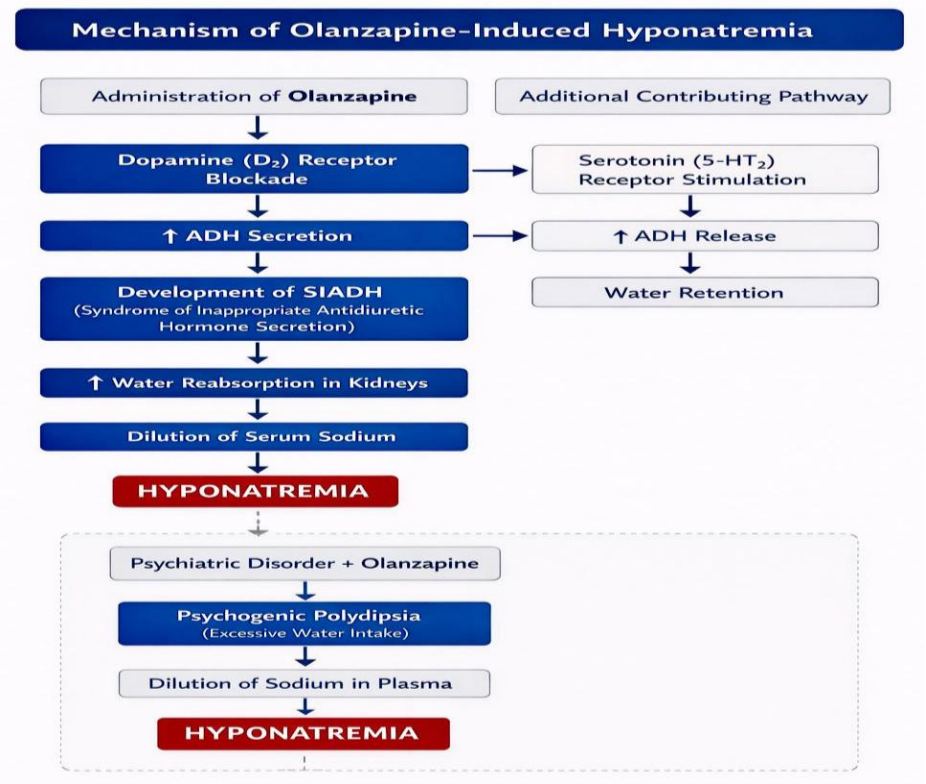


Fig 03 – Schematic flow chart representing mechanism of action of Olanzapine induced hyponatremia

Older individuals are particularly susceptible to drug-induced hyponatremia due to age-related physiological changes and increased exposure to long-term pharmacotherapy. Therefore, careful monitoring of electrolyte levels becomes essential in patients receiving antipsychotic medications for extended durations.

In the present case, the patient developed marked hyponatremia with a serum sodium level of 117 mmol/L along with clinical features including irritability, reduced communication, sleep disturbance, and cognitive

decline. The chronological relationship between prolonged olanzapine therapy and the onset of symptoms suggested a possible drug-related etiology. Following withdrawal of olanzapine and initiation of appropriate corrective measures, including hypertonic saline and electrolyte supplementation, the patient showed progressive clinical improvement with normalization of serum sodium levels to 139 mmol/L.

The favorable response observed after discontinuation of the suspected drug further strengthens the likelihood of olanzapine-associated hyponatremia in this patient. This case emphasizes the need for clinicians to remain vigilant regarding electrolyte abnormalities in elderly patients receiving antipsychotic therapy. Routine monitoring and early recognition of symptoms can help prevent serious complications and improve patient outcomes.

A similar case of olanzapine-associated hyponatremia was reported by Sethulakshmi Sreevalsam Anil et al, in which rapid-onset hyponatremia occurred following the administration of low-dose olanzapine in a patient undergoing inpatient treatment for bipolar disorder. In that report, hyponatremia developed shortly after initiation of the medication and was attributed to syndrome of inappropriate antidiuretic hormone secretion (SIADH). The authors emphasized the importance of clinician awareness regarding potentially serious electrolyte disturbances associated with atypical antipsychotics.

In contrast, the present case demonstrates hyponatremia associated with long-term olanzapine therapy in an elderly female patient. Unlike the previously reported rapid-onset presentation, the current patient developed symptoms gradually over a period of one month, presenting with altered sensorium, irritability, reduced speech, decreased sleep, and forgetfulness. Laboratory evaluation revealed severe hyponatremia with a serum sodium level of 117 mmol/L.

Another important distinction between the two cases lies in the patient population and associated risk factors. The earlier report involved a patient with bipolar disorder receiving low-dose olanzapine during inpatient psychiatric treatment, whereas the present case involved an elderly patient with pseudodementia and a history of chronic psychiatric medication use. Advanced age is a well-recognized risk factor for drug-induced hyponatremia due to age-related physiological changes, altered renal function, polypharmacy, and increased sensitivity to medications.

Therefore, while the previously reported case highlights rapid-onset hyponatremia associated with low-dose olanzapine, the present case demonstrates that severe hyponatremia may also occur during long-term therapy, particularly in elderly patients. This finding underscores the importance of regular electrolyte monitoring and careful clinical observation in patients receiving atypical antipsychotic medications.

IV. CONCLUSION

The study concludes that while olanzapine generally has a favorable safety profile, clinicians must remain vigilant. This is especially true for elderly patients, as age-related physiological changes increase the risk of drug-induced electrolyte imbalances. Regular monitoring is essential to prevent serious neurological complications and ensure patient safety.

V. REFERENCES

1. N'joumi Y, et al. Olanzapine induced hyponatremia and rhabdomyolysis. *Rabat (Morocco): Faculty of Medicine and Pharmacy of Rabat, Mohammed V University*; 2024 Apr 16.
2. Mazhar F, et al. Hyponatremia following antipsychotic treatment: in silico pharmacodynamics analysis of spontaneous reports from the US Food and Drug Administration Adverse Event Reporting System database and an updated systematic review. *Int J Neuropsychopharmacol.* 2021;24(6):477–489. doi:10.1093/ijnp/pyab005.
3. Sreevalsam Anil S, et al. A case report of rapid-onset hyponatremia induced by low-dose olanzapine. *J Family Med Prim Care.* 2018;7(4):895–898. doi:10.4103/jfmpc.jfmpc_205_17.
4. Pinkhasov A, et al. Management of SIADH-related hyponatremia due to psychotropic medications – an expert consensus from the Association of Medicine and Psychiatry. *J Psychosom Res.* 2021;151:110654. doi:10.1016/j.jpsychores.2021.110654.
5. Capinha M, et al. Drug-induced hyponatremia: insights into pharmacological mechanisms and clinical practice management. *J Clin Med.* 2025;14:6584. doi:10.3390/jcm14186584.
6. Spasovski G. Etiology, clinical approach, and therapeutic consequences of hyponatremia. *Kidney Dial.* 2024;4:37–45. doi:10.3390/kidneydial4010004.
7. Mannheimer B, et al. Drug-induced hyponatremia in clinical care. *Eur J Intern Med.* 2024;113:106–118. doi:10.1016/j.ejim.2024.09.002.
8. Sahay M, Sahay R. Hyponatremia: a practical approach. *Indian J Endocrinol Metab.* 2014;18(6):760–767. doi:10.4103/2230-8210.141320.
9. Adrogué HJ, Tucker BM, Madias NE. Diagnosis and management of hyponatremia: a review. *JAMA.* 2022;328(3):280–291. doi:10.1001/jama.2022.11176.
10. Beasley CM Jr, Tollefson GD, Tran PV. Safety of olanzapine. *J Clin Psychiatry*. 1997;58(Suppl 10):13–17.