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Original Article

Clozapine for Treatment of Polydipsia and Hyponatremia in Chronic Schizophrenia Patients: A Systematic Review

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Abstract
Objectives: T Systematic review of evidence regarding the effect of clozapine on binge drinking and hyponatremia in patients with schizophrenia.
Design: systematic review
Setting(s): Schizophrenia patients
Participants: 8 studies
Interventions: Clozapine treatment
Outcome Measures: polydipsia and hyponatremia
Results: Based on the findings, clozapine treatment was consistently associated with significant improvements in both polydipsia and hyponatremia among patients with schizophrenia or schizoaffective disorder.
Conclusions: Clozapine appears to consistently ameliorate the dysregulation of thirst and sodium balance in patients with schizophrenia. These findings support the potential of clozapine as a promising targeted therapy and pharmacological strategy and provide a basis for future mechanistic and controlled efficacy studies in this challenging clinical domain, potentially informing evidence-based management of polydipsia-related hyponatremia.
Keywords: Clozapine, Schizophrenia, Polydipsia, Hyponatremia

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Introduction

Schizophrenia is a chronic and debilitating mental disorder that affects about 1% of the worldwide population.[1] Psychogenic polydipsia is a major concern among individuals diagnosed with this condition, as it can lead to hyponatremia.[2-4] Although the exact pathophysiology of polydipsia in these patients remains unclear,[5] several risk factors seem to be linked to this condition, including the use of diuretics, male gender, longer duration of the psychiatric disorder, a diagnosis of schizophrenia, smoking, and possibly racial background.[2-6]

Hyponatremia occurs in approximately 4% of unmedicated patients with schizophrenia and up to 10% of those on antipsychotic treatment.[7] In addition, older adults are particularly vulnerable due to an increased risk of falls and other complications.

Hyponatremia is defined as a serum sodium concentration below 135 mmol/L, with severe cases (< 125 mmol/L) carrying a substantial risk of irreversible neurological damage and serious clinical outcomes, including coma, seizures, rhabdomyolysis and death.[8-10] Milder forms, which affect about 29% of patients, may present with dizziness, nausea, confusion, gait instability, or other indigestion-related symptoms. However, severe cases can rapidly progress to delirium and life-threatening outcomes, including coma or death.[11]

While antipsychotics can occasionally worsen polydipsia, evidence indicates that clozapine may improve both polydipsia and hyponatremia, particularly in frail older adults.[12] The study by Canuso et al, involving eight schizophrenia patients, demonstrated that this drug was effective in reducing psychogenic polydipsia and akathisia, with significant improvements in psychiatric symptoms. Doses of 300 mg/day were sufficient to normalize plasma osmolality, and lower doses of around 100 mg/day were also effective.[13]

Addressing hyponatremia is crucial to prevent potential secondary complications in patients with schizophrenia. Given the lack of recent systematic reviews on this topic, to the best of our knowledge, and its clinical importance, this review aims to examine studies evaluating the positive effects of clozapine on the symptoms of polydipsia and hyponatremia in patients with schizophrenia. Moreover, it is important to accurately diagnose polydipsia, as it may overlap with other conditions presenting similar clinical features. Additionally, the review attempts to investigate its effects in adults, focusing on geriatric implications.

Methods

Protocol and Eligibility Criteria

This systematic review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement, which guided the identification, screening, eligibility, and inclusion of studies (checklist provided as supplementary material). It should be noted that the protocol was not prospectively registered.

Studies were eligible if they met several inclusion criteria. Eligible studies included randomized controlled trials (RCTs) or case reports/series involving adults aged ≥ 18 years diagnosed with schizophrenia or schizoaffective disorder (with a subgroup analysis for those aged ≥ 60 years). Likewise, the studies were required to evaluate clozapine treatment for polydipsia/hyponatremia, report changes in sodium levels and polydipsia symptoms, and have full-text articles available in English.

However, the exclusion criteria included (1) studies with insufficient scientific data or ambiguous statistical analyses, (2) articles in languages other than English, and (3) conference abstracts or proceedings without full-text peer-reviewed publications.

Information Sources and Search Strategy

Multiple electronic databases were searched, including PubMed, Scopus, and Web of Science, PsycINFO, and EMBASE; the last search was performed on December 31, 2024. Additional sources were identified by searching the reference lists of the included studies and relevant review articles, as well as grey literature via Google Scholar and OpenGrey. Moreover, the search utilized Medical Subject Headings (MeSH) terms and free-text keywords. The full strategy for PubMed was ((“schizophrenia” [Title/Abstract] OR “schizophrenia, catatonic” [MeSH Terms] OR “schizoaffective” [Title/Abstract] OR “schizophrenia spectrum and other psychotic disorders” [MeSH Terms] OR “Schizophrenia, treatment resistant” [MeSH Terms]) AND “Clozapine” [Title/Abstract] AND (“Hyponatremia” [Title/Abstract] OR “polydipsia” [Title/Abstract])). Equivalent strategies were adapted for Scopus and Web of Science, with no language filters applied initially, and date limits were set from inception to December 31, 2024. Full search strings for all databases are provided in the supplement.

Eligibility

The review included studies involving adults aged 18 years or older diagnosed with schizophrenia or schizoaffective disorder. A specific subgroup analysis was planned for geriatric patients aged 60 years or older. In addition, administration of clozapine was the intervention of interest. Furthermore, primary outcomes were changes in serum sodium levels and the severity of polydipsia symptoms. Eligible study designs comprised RCTs, case series, and case reports.

Study Selection

Retrieved records were imported into ENDNOTE X7 software for deduplication. Two reviewers independently screened titles and abstracts against eligibility criteria. Further, disagreements were resolved through discussion, and unresolved cases advanced to full-text review. In the full-text phase, two reviewers independently assessed articles, with discrepancies resolved by consensus or consultation with a third reviewer. Additionally, risk-of-bias was assessed using the Cochrane RoB 2 tool for the RCT and JBI checklists for case reports/series; it should be noted that a meta-analysis was not feasible due to heterogeneity.

Data Collection

Data were independently extracted by two reviewers using a standardized Excel version 2021 form piloted on three studies. Extracted items included extraction date, study title, country, sample size (n), methodology details, outcomes (e.g., changes in serum sodium, plasma osmolality, and polydipsia symptoms), findings, and clozapine-related side effects. Finally, discrepancies were reconciled through discussion.

Synthesis Methods

The certainty of the evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. This assessment considered five domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results

Based on the GRADE assessment, the certainty of the evidence regarding the effect of clozapine on polydipsia and serum sodium levels was rated as very low. Overall, 315 records were identified through a systematic search using predetermined key terms across electronic databases. After removing 46 duplicates, 269 records were screened by title and abstract, of which 223 were excluded as irrelevant. Then, 46 full texts were assessed for eligibility, of which 8 met the inclusion criteria (insufficient data: n = 20; non-English: n = 10; abstract-only: n = 6; full-text unobtainable: n = 2). Figure 1 displays the selection process and exclusion reasons.

Eight studies were included in this systematic review, including one RCT and seven case reports/series (total n = 18; 3 females,15 males; age range: 31–68 years). The studies (1995-2022) mainly involved patients with schizophrenia; one had schizoaffective disorder (bipolar type).

Baseline serum sodium levels indicated hyponatremia (e.g., as low as 113 mmol/L); post-treatment levels were normalized (135–143 mmol/L, where reported). In several reports, psychogenic polydipsia and associated hyponatremia were frequently severe and refractory, sometimes accompanied by catatonia or suspected syndrome of inappropriate antidiuretic hormone secretion

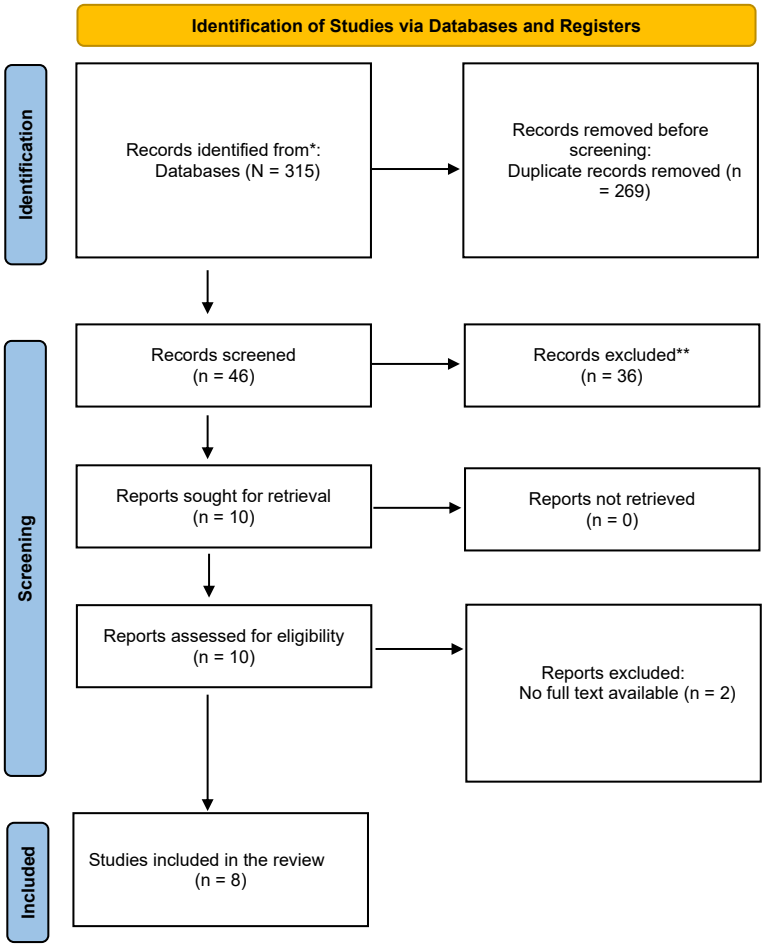

Figure 1. PRISMA Flow Diagram of the Selection Process and Exclusion Reasons
Note. PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *Consider, if feasible to do so, report the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
Source. Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

(SIADH). Moreover, one case report documented worsening of hyponatremia when clozapine was combined with amisulpride and indapamide, emphasizing the need for co-medication review.

Despite these complexities, all studies indicated the beneficial effects of polydipsia/hyponatremia in schizophrenia-spectrum disorders. In the RCT, doses of 100–300 mg/day normalized osmolality, reduced polydipsia, and improved psychiatric symptoms. In addition, case reports demonstrated similar improvements in serum sodium levels, a drop in water intake, and avoidance of invasive interventions, including electroconvulsive therapy. In a randomized trial, typical sodium normalization occurred with doses of 100–300 mg/day over 1–4-weeks, with follow-up periods of 1–12 months (noting inconsistencies, such as one case suggesting clozapine-induced hyponatremia).[17]

Overall, the available evidence, although limited to one trial and a small number of case-based studies, consistently suggested that clozapine is a valuable therapeutic option for managing psychogenic polydipsia and hyponatremia in patients with schizophrenia and related disorders, particularly in refractory or high-risk cases. The detailed clinical and biochemical outcomes of the individual studies are summarized in Table 1.

Discussion

Despite the limited available evidence, existing findings support the potential efficacy of clozapine in managing polydipsia and hyponatremia in patients with chronic schizophrenia. The analytical synthesis revealed that refractory cases better responded to clozapine than to prior treatments, demonstrating its superiority across all studies.

Overall, the data support the argument that clozapine can not only decrease the occurrence and intensity of excessive thirst but also improve the body's ability to maintain appropriate sodium levels, allowing patients to be discharged from an extended hospitalization.

Studies have shown that clozapine at relatively low doses (approximately 300 mg/day) restores normal serum sodium levels and reduces fluid retention, as shown by decreases in diurnal weight gain.[21] Even though some individuals might benefit from higher doses, there is no consistent evidence representing that gradually increasing dosages provides any better efficacy for either sodium levels or fluid balance compared with lower doses.[9, 10] In general, conventional neuroleptic agents have demonstrated unpredictable results with respect to these two symptoms and often fail to correct

Table 1. Summary of Selected Studies Evaluating the Effect of Clozapine on Polydipsia and Hyponatremia

First Author (Year)	Disorder	Gender	Age	Type of Study	Sodium Level Before	Sodium Level After	Results
Arany Shanmugalingam (2022) [14]	Schizoaffective disorder – bipolar type	Woman	68	Case report	113 mmol/L	143 mmol/L	Clozapine is a valuable pharmacologic option to treat PPD in schizoaffective disorder, especially in refractory cases or when polydipsia leads to dangerous hyponatremia.
Nurazah Ismail (2022) [15]	Schizophrenia	Man	48	Case report	113 mmol/L	Normalized	Two atypical antipsychotics were started: clozapine and amisulpride, along with indapamide, a thiazide-like diuretic used as an antihypertensive medication. Discontinuing indapamide while continuing the antipsychotics led to an improvement in the serum sodium level of the patient.
Carla M Canuso (1999) [13]	Schizophrenia	8 Males	-	RCT	125 mEq/L in the previous month	Normalized	Clozapine was effective in reducing psychogenic polydipsia and akathisia in a schizophrenic patient. A significant improvement was observed in psychiatric symptoms, indicating that a dose of 300 mg/day is sufficient to normalize plasma osmolality clozapine dosages as low as 100 mg per day.
Juliana Belo Diniz (2010) [16]	Schizophrenia	Man	33	Case report	130	Normalized	The use of clozapine when psychogenic polydipsia evolves in schizophrenic patients could improve the polydipsia and akathisia
Mehmet Hamdi Orum (2019) [17]	Schizophrenia	Man	31	Case report	122 mmol/L	135	Clozapine and amisulpride combination can cause hyponatremia, potentially through SIADH
Inderpreet Virk (2016) [18]	Schizophrenia	Man	53	Case report	128-131	Normalized	A significant improvement was found with clozapine treatment. Clozapine may be a viable alternative to ECT for patients with catatonia and polydipsia.
Michiko Fujimoto (2016) [19]	Schizophrenia	Man	56	Case report	122-134 mEq/L	138	Clozapine could improve hyponatremia caused by SIADH in schizophrenia patients.
J de Leon (1995) [20]	Schizophrenia	Two females Two males	aged 31-39 years	Case report	Below normal range (specific values not reported)	Normalized	In this case study, which reported 4 chronic schizophrenic patients with severe polydipsia, treatment with clozapine significantly improved the symptoms of polydipsia and hyponatremia.

Note. ECT: Electroconvulsive therapy; PPD: Psychogenic polydipsia; RCT: Randomized controlled trial; SIADH: Syndrome of inappropriate antidiuretic hormone secretion

fluid imbalances.

By contrast, conventional antipsychotics have shown inconsistent and frequently restricted efficacy in correcting these disturbances. Their effectiveness, in addition to dosage limitations available to patients, commonly requires fluid restrictions along with close clinical monitoring in order to prevent complications.[22]

Clozapine's unique therapeutic effects may be attributed to its broad receptor profile, including potent antagonism at dopamine D4 and serotonin 5-HT2A/2C receptors.[23] Based on pharmacodynamic studies, although the evidence is limited, clozapine's D4/5-HT2 antagonism may describe these effects.[23-26] Clozapine exhibits notably high affinity for dopamine D4 receptors and antagonizes serotonin 5-HT2A and 5-HT2C receptors, collectively contributing to its potent antipsychotic efficacy with reduced extrapyramidal side effects compared to D2 receptor antagonists.[24] Additionally, clozapine modulates muscarinic, adrenergic, and histaminergic receptors, which may underlie both its clinical effectiveness and complex side effect profile.[25, 26]

Likewise, clozapine stabilizes sodium levels and may reduce excessive water intake by increasing free water excretion, thereby leading to a reduction in polydipsic fluid intake and a more stable serum sodium level. Improvement in psychiatric symptoms is usually accompanied by a decrease in excessive water intake behavior, suggesting that stabilization of the psychiatric condition often helps achieve normal physiological function. Thus, clozapine can treat both the fluid-electrolyte imbalance and the neuropsychiatric phenotype of chronic psychosis. Nonetheless, further studies are needed to understand the precise mechanism of action.[14, 15]

This comprehensive pharmacodynamic action underscores clozapine's unique suitability in managing psychogenic polydipsia and hyponatremia, conditions that remain challenging with traditional antipsychotic treatments.

This study had some limitations, including a small number of clinical trials, case reports with a limited sample size of 18 participants, the absence of evaluation of confounding factors (e. g., co-medications and SIADH), a limited geriatric focus, and the lack of long-term follow-ups.

Due to the life-threatening potential of hyponatremia

and polydipsia, it is vital to monitor the electrolyte balance during clozapine use. However, assessment challenges and methodological inconsistencies limit the strength of the available evidence. Accordingly, further studies, including RCTs in older adults comparing clozapine to standard care, are required, with primary results including water intake and sodium normalization.

Conclusions

Our findings revealed that clozapine may benefit refractory polydipsia and hyponatremia in schizophrenia, with significant implications for geriatric populations. It demonstrated its multifaceted action beyond its purely antipsychotic effects; nevertheless, this method needs additional trials and careful monitoring. By affecting sodium metabolism and fluid regulation, clozapine offers a therapeutic option for patients who experience these complications alongside severe psychiatric disorders. However, due to potential risks, its use requires close monitoring. Therefore, future research should investigate the precise mechanisms involved and establish clearer guidelines for the use of this drug in these conditions.

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Data availability statement

Not applicable.

Ethical approval

The Medical Ethics Committee of Tabriz University of Medical Sciences approved the protocol of this study (IR.TBZMED.REC.1403.280(.

Consent for publication

Not applicable.

Conflict of interests

The authors declare they have no competing interests.

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