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PATTERN OF ADVERSE DRUG REACTION ASSOCIATED TO ANTIPSYCHOTIC DRUGS WITH SPECIAL REFERENCE TO HYPONATRAEMIA IN MEDICAL COLLEGE, KOLKATA: AN OBSERVATIONAL, PROSPECTIVE STUDY

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INTRODUCTION

The therapeutic armamentarium for psychotic spectrum disorders has undergone a profound metamorphosis with the advent of antipsychotic pharmacotherapeutics. The evolution from classical first-generation dopamine D2 antagonists, such as haloperidol and chlorpromazine, to more receptor-diverse second-generation antipsychotics (SGAs) including risperidone, olanzapine, and aripiprazole, has redefined the neuropsychopharmacology paradigm[2,3,22]. However, this progress has not been without the collateral burden of a diverse array of adverse drug reactions (ADRs), which complicate long-term clinical management, impede compliance, and potentiate iatrogenic morbidity[1,3,4,22].

While first-generation antipsychotics (FGAs) are unequivocally notorious for eliciting extrapyramidal symptoms due to antagonism of the nigrostriatal dopaminergic tract[2,3], SGAs, though initially considered to have a benign side-effect profile, are now increasingly implicated in multifaceted disruptions such as glucose dysregulation, lipid abnormalities, and notably,

perturbations of osmoregulatory homeostasis manifesting as hyponatremia—an electrolyte imbalance whose clinical significance is often obscured by its protean neuropsychiatric manifestations[1,3,4,5,6].

Within the Indian pharmacovigilance milieu—characterized by variable reporting fidelity, infrastructural limitations, and clinical heterogeneity—the underdiagnosis of ADRs like drug-induced hyponatremia assumes heightened importance[1,3,7]. This is especially pertinent given the paucity of routine electrolyte monitoring in psychiatric settings[3,8]. Tertiary-care data from Delhi implicate risperidone and olanzapine in ADRs such as tremors and weight gain[3], while corroborative evidence from South Indian cohorts underscores sedation and menstrual irregularities as frequent sequelae—yet these findings remain largely silent on the electrophysiological consequences of sodium dysregulation[1,3].

Hyponatremia, defined pathophysiologically as a serum sodium concentration below 135 mmol/L, and clinically significant below 125 mmol/L, often masquerades in psychiatric populations with cognitive clouding, psychomotor slowing, and, in extremis, seizures or coma[4,8,9,15]. These symptoms can blur the diagnostic boundary between psychiatric decompensation and metabolic encephalopathy—a phenomenon that demands clinical discernment but is frequently overlooked[4,8,10].

Although previously ascribed to non-pharmacological etiologies such as psychogenic polydipsia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH)[8,9,15], emerging literature increasingly identifies a sinister iatrogenic vector. Antipsychotics may dysregulate water-electrolyte balance via serotonergic and dopaminergic receptor interactions that disrupt hypothalamic-pituitary signaling and alter renal aquaporin channel expression[4,5,6,16,23].

A seminal in silico pharmacodynamic analysis using data from the FDA Adverse Event Reporting System (FAERS) by Guo et al. revealed that receptor activity at dopaminergic D3 and D4 sites correlated positively with hyponatremia, whereas antagonism at 5-HT2A and α1-adrenergic receptors was inversely related, suggesting a receptor-specific susceptibility index[6]. Olanzapine, risperidone, and aripiprazole emerged as predominant offenders in this model[6].

Pathophysiological plausibility is further supported by hypotheses indicating that hypothalamic dopaminergic blockade increases arginine vasopressin (AVP) secretion, resulting in inappropriate water retention and dilutional hyponatremia[4,5,16]. Meanwhile, serotonergic modulation via 5-HT1A, 5-HT2A, and 5-HT2C receptors may synergistically or antagonistically influence thirst, ADH release, and renal sodium handling, situating SGAs within a neuroendocrine framework of electrolyte dysregulation[4,5,16,23,27].

Despite mechanistic coherence, empirical substantiation remains limited, particularly in low- and middle-income countries where systematic case documentation is sparse[1,4,10]. However, a systematic review of case reports noted a rapid onset of hyponatremia following SGA administration—including risperidone, clozapine, and ziprasidone—with resolution upon drug withdrawal, thereby establishing a pharmacovigilance signal[1,4,10,24].

Larger pharmacoepidemiological datasets, such as those from China analyzing over 3,000 ADRs, corroborate this risk[2,11,12]. These studies identify a vulnerability during the initial treatment quarter and highlight risk amplifiers including advanced age, institutional care, and polypharmacy—factors highly relevant to Indian psychiatric practice[11,12,13,21].

The dichotomy portraying SGAs as inherently safer than FGAs regarding electrolyte homeostasis is now increasingly contested[5,6,28]. Observational data suggest both classes may disrupt sodium equilibrium through distinct receptor-mediated and renal-central mechanisms, necessitating a reevaluation of pharmacotherapeutic hierarchies and the myth of "atypical safety"[5,6,16,28].

Moreover, the symptomatology of mild-to-moderate hyponatremia—such as irritability, cognitive dulling, or affective lability—overlaps with primary psychopathology[8,14,18,19]. This overlap invites misattribution and delays intervention, emphasizing the need for proactive electrolyte monitoring during initiation and titration of antipsychotic therapy[10,14,18,19].

Pharmacogenomic variability, including polymorphisms in cytochrome P450 enzymes, receptor isoforms, renal sodium transporters, and neuroendocrine regulators, may influence individual

susceptibility to hyponatremia[14,17,20]. These biomolecular dimensions remain largely unexplored in the Indian context and represent a frontier for personalized psychiatry[17,20].
In light of these complexities, the present prospective observational study at Medical College Kolkata aims to delineate the phenotypic spectrum and prevalence of ADRs induced by antipsychotic therapy, with a special emphasis on the biochemical hazard of hyponatremia[1,3,4]. This endeavor aspires to enrich Indian psycho pharmacovigilance with empirically grounded insights and inform risk-adaptive therapeutic strategies[3,11,14].

AIMS & OBJECTIVES

Aim

To rigorously elucidate the clinico-biochemical trajectory and pattern of antipsychotic-induced hyponatremia in ambulatory psychiatric patients, with special emphasis on the temporal kinetics of serum sodium derangement, agent-specific pharmacovigilance profiling, and age-stratified susceptibility analysis.

Objectives

1. To quantitatively characterize the evolution of serum sodium concentrations in adult psychiatric outpatients initiated on risperidone, olanzapine, or aripiprazole over a 24-week observation period, thereby delineating both intra- and inter-drug variability in hyponatremic potential.
2. To determine the statistical correlation between patient age and serum sodium levels at defined temporal checkpoints (baseline, 4 weeks, 12 weeks, and 24 weeks), with the objective of elucidating age as an independent modifier of antipsychotic-associated dysnatremia.
3. To document and classify treatment-emergent adverse drug reactions (ADRs) using the WHO–UMC causality assessment framework, thereby enabling structured attribution of hyponatremic events to specific pharmacotherapeutic agents.
4. To evaluate the symptomatic burden and clinical sequelae of hyponatremia, including neuropsychiatric, neuromuscular, and seizure-related outcomes, with the aim of identifying early-warning clinical phenotypes within the asymptomatic biochemical deterioration window.
5. To compare the hyponatremic risk profiles among the three antipsychotic agents, thereby facilitating evidence-based pharmacological stratification and guiding future psychotropic prescribing practices in vulnerable populations, particularly the elderly.
6. To propose a systematic biochemical monitoring protocol for outpatient psychopharmacological regimens involving second-generation antipsychotics, with the dual intent of minimizing iatrogenic morbidity and informing national-level psychiatric safety guidelines.

MATERIALS AND METHODS

In the context of an intricate and methodologically robust pharmacoepidemiological inquiry, this investigation—conducted as a single-center, longitudinal, prospective, clinico-biochemical o study within the Departments of Pharmacology and Psychiatry at the Medical College Kolkata over a six-month horizon—was specifically architected to elucidate the trajectory and prevalence of antipsychotic-induced hyponatremia, as well as to characterize its clinical and biochemical manifestations within a demographically heterogeneous outpatient psychiatric population. The study recruited 100 adult individuals (aged 28–74 years), each initiating de novo monotherapy with risperidone, olanzapine, or aripiprazole, and rigorously screened for baseline normonatremia (serum sodium range: 136–144 mmol/L), with psychiatric diagnoses adhering strictly to DSM-5 criteria as validated under consultant psychiatric oversight. Sampling was purposive, involving only those who provided informed consent and fulfilled all inclusion criteria, and the recruitment was executed without randomization but followed a structured and ethically approved protocol, sanctioned by the Institutional Ethics Committee, with informed assent obtained from patients or their legal guardians as per the ethical requirements stipulated by national regulatory norms.

Under the rubric of Biochemical and Clinical Monitoring, the study employed a meticulous timeline of sodium surveillance—via ion-selective electrode assays in NABL-accredited laboratories—at four critical intervals: baseline, 4 weeks, 12 weeks, and 24 weeks. Simultaneously, adverse drug reactions (ADRs), encompassing both symptomatic and asymptomatic spectrums, were diligently recorded using the WHO-Uppsala Monitoring Centre (UMC) causality algorithm, thereby categorizing each ADR as probable, possible, unlikely, unclassified, or unassessable. Notably, due to ethical limitations, no ADR was categorized as "certain," as rechallenge protocols were precluded. Adverse event documentation was systematically entered into both CRFs (Case Report Forms) and the CDSCO Suspected ADR Reporting Form v1.4, ensuring regulatory compliance and scientific fidelity. The study technique involved serial clinical assessments, exhaustive anamnesis, and relevant hematological and biochemical investigations, with follow-up visits fixed at 4th, 12th, and 24th weeks, and each subject underwent evaluations based on pre-designed diagnostic proformas to assure intersubjective uniformity and reproducibility. The Statistical Analysis Framework was anchored in a multidimensional methodological paradigm that incorporated both parametric and non-parametric tools, enabling a comprehensive understanding of sodium kinetics over time and across pharmacological groups. Intra-group longitudinal sodium fluctuations were interrogated using repeated-measures ANOVA, bolstered by post hoc Neuman–Keuls corrections, while intergroup comparisons at each follow-up point were subjected to one-way ANOVA. For distributions lacking Gaussian normality, the Kruskal–Wallis and Friedman's tests were utilized. Moreover, a Pearson's correlation coefficient computation delineated the relationship between advancing chronological age and progressive sodium decrement, which emerged as statistically robust, with r-values ranging from –0.7448 to –0.8009, thereby positing a strong inverse correlation between age and hyponatremia susceptibility. All analyses adhered to a significance threshold of $p < 0.05$, with descriptive statistics represented as mean ± standard deviation, medians, and percentages within a 95% confidence interval, processed via SPSS v23 and Microsoft Excel (Office 2022). The Demographic and Clinical Results section reveals a gender-equitable cohort (M:F ≈ 1:1), predominantly middle-aged (mean age: 45 years), with no significant baseline variation in age ($p = 0.100$) or sex ($p = 0.177$) between treatment groups. Baseline serum sodium values were also statistically homogeneous ($p = 0.666$). However, follow-up assessments indicated a progressive decrement in sodium levels across all antipsychotic groups, culminating in definitive hyponatremia at 24 weeks, with values as follows: Olanzapine: 129.61 ± 3.34 mmol/L, Risperidone: 130.60 ± 3.34 mmol/L, and Aripiprazole: 130.72 ± 3.44 mmol/L, all reaching extremely significant intra-group differences ($p < 0.0001$) and intergroup statistical significance by the third follow-up ($p = 0.003$), thereby indicating drug-specific as well as class-wide risk profiles.

Furthermore, ADRs were prevalent in 84% of subjects, though only 90 ADRs in 68 individuals were retained after excluding "unlikely" outcomes. The causality analysis delineated the ADRs as follows: 38.09% "probable," 2.64% "possible," 45.50% "unlikely," 5.29% "unclassified," and 8.46% "unassessable." Despite the high incidence, 92% of hyponatremia cases were asymptomatic, but a small fraction presented with nonspecific symptoms such as headache (4%), lethargy (3%), nausea/vomiting (3%), and seizures (2%), the latter necessitating hospitalization and therapy cessation, both in risperidone recipients. No statistically significant variance was noted in symptomatic hyponatremia incidence across pharmacologic groups ($p = 0.280$).

Finally, the sample size determination, grounded in epidemiologic formulae $N=4pq/l2N = 4pq/l^2$ with a projected prevalence of ADRs at 64%, and incorporating a 10% attrition rate, yielded a final cohort of 100 patients. Data collection was spearheaded by the principal investigator through direct clinical interface in psychiatric outpatient settings, where all biochemical indices favoring hyponatremia were meticulously recorded and subsequently processed within the Department of Pharmacology. Hence, this investigation not only provides a high-resolution view of iatrogenic sodium derangements in the psychiatric milieu but also imparts crucial pharmacovigilance insights pertinent to the geriatric and polypharmacy-prone subpopulations, urging clinicians to monitor electrolyte homeostasis vigilantly during antipsychotic therapy.

Time Point	Risperidone (Mean ± SD, mmol/L)	Olanzapine (Mean ± SD, mmol/L)	Aripiprazole (Mean ± SD, mmol/L)	Intergroup p-value
Baseline	138.76 ± 1.92	138.68 ± 2.04	138.71 ± 1.98	0.666
4 Weeks	133.42 ± 2.87	132.81 ± 3.09	133.23 ± 3.11	0.221
12 Weeks	131.02 ± 3.28	130.14 ± 3.17	130.68 ± 3.44	0.135
24 Weeks	130.60 ± 3.34	129.61 ± 3.34	130.72 ± 3.44	0.003*

Table 1: Temporal Decline in Serum Sodium Across Antipsychotic Groups(Statistically significant at $p < 0.05$)

Time Point	Pearson's Correlation Coefficient (r)	p-value	Interpretation
4 Weeks	-0.7448	<0.001*	Strong inverse correlation
12 Weeks	-0.7812	<0.001*	Strong inverse correlation
24 Weeks	-0.8009	<0.001*	Very strong inverse correlation

Table 2: Correlation Between Age and Serum Sodium Levels (Statistically significant at $p < 0.05$)

Symptom	Number of Patients	Percentage (%)
Headache	4	4.3%
Lethargy	3	3.2%
Nausea/Vomiting	3	3.2%
Seizures	2	2.1%
Asymptomatic	85	92.4%

Table 3: Symptomatic Profile of Hyponatremia Cases (n = 92)

Antipsychotic Agent	Symptomatic Cases (n)	Total Hyponatremia Cases (n)	Percentage Symptomatic (%)
Risperidone	4	31	12.9%
Olanzapine	2	30	6.7%
Aripiprazole	2	31	6.5%
Total	8	92	8.7%

Table 4: Incidence of Symptomatic Hyponatremia by Drug Group($p = 0.280$ (Chi-square test applied; no significant intergroup difference)

Causality Category	Number of ADRs	Percentage (%)
Probable	34	38.09%
Possible	2	2.64%
Unlikely	41	45.50%
Unclassified	5	5.29%
Unassessable	8	8.46%

Table 5: Causality Assessment of All Documented ADRs (n = 90)

Adverse Drug Reaction (ADR)	Risperidone (n = 34)	Olanzapine (n = 33)	Aripiprazole (n = 33)	Chi-Square (χ^2)	p-value
Sexual Dysfunction	8 (23.5%)	6 (18.2%)	5 (15.1%)	1.19	0.550
Extrapyramidal Syndrome (EPS)	5 (14.7%)	3 (9.1%)	4 (12.1%)	0.64	0.725
Neuroleptic Malignant Syndrome (NMS)	1 (2.9%)	1 (3.0%)	0 (0.0%)	1.67	0.434
Weight Gain (>5% from baseline)	9 (26.4%)	11 (33.3%)	6 (18.2%)	2.23	0.328

Galactorrhoea	4 (11.7%)	3 (9.1%)	2 (6.1%)	0.85	0.654
Increased Salivation	6 (17.6%)	5 (15.2%)	3 (9.1%)	1.38	0.501
Suicidal Ideation (Post-initiation)	3 (8.8%)	4 (12.1%)	2 (6.1%)	0.68	0.711

Table 6 - Comparative Cross-Sectional Pharmacotoxicovigilant Profiling of Non-Hyponatremia-Associated Adverse Drug Reactions among Atypical Antipsychotic Agents: A Chi-Square-Based Intergroup Evaluation of Risperidone, Olanzapine, and Aripiprazole within a Normonatremic Psychiatric Cohort .Comparative Incidence of Non-Hyponatraemic Adverse Drug Effects Among Antipsychotic Groups (n=100). Chi-square test applied; p-values > 0.05 (statistically insignificant)

DISCUSSION

The phenomenon of **antipsychotic-induced hyponatremia**—though historically regarded as a pharmacological aberration of marginal incidence—demands renewed scrutiny in light of emerging data suggesting both a quantitatively underappreciated prevalence and a qualitatively underestimated pathophysiological impact. The present prospective cohort study unveils a disconcerting trend: a precipitous, temporally synchronized decline in serum sodium concentrations across all three evaluated antipsychotic agents (risperidone, olanzapine, aripiprazole), culminating in a biochemical state of hyponatremia in a staggering 92% of subjects, the vast majority of whom were clinically asymptomatic, thereby escaping routine clinical detection. Such asymptomatic progression is, in essence, a **pharmacoepidemiological iceberg**—the visible tip being overt seizures, and the submerged mass comprising subclinical neurocognitive impairment, osteoporotic fragility, and cumulative morbidity[1, 8 ,9].

The crux of this electrolyte dysregulation resides in the **antidiuretic hormone (ADH) axis**, with the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**) serving as the biochemical substrate of culpability[4]. Second-generation antipsychotics (SGAs), through their nuanced modulation of central serotonergic (5-HT2A) and dopaminergic (D2/D3) circuits, appear to perturb hypothalamic osmoreceptor thresholds, thereby precipitating non-osmotic vasopressin release and promoting aquaporin-2–mediated renal water reabsorption—culminating in dilutional hyponatremia[4–7].

Risperidone and olanzapine, owing to their high D2/D3 receptor binding affinity and minimal 5-HT2A antagonism, exhibit a higher propension for such derangements, whereas aripiprazole, by virtue of partial agonism at D2 receptors, is often presumed to be less culpable—an assumption partially rebutted by the current findings[6–9].

Of considerable import is the **temporal trajectory of sodium decline**: our data reveal a statistically significant nadir in serum sodium as early as the first month of therapy, with continued decrement observed across the 24-week monitoring horizon. This temporal pattern is concordant with published pharmacovigilance data wherein hyponatremia often manifests within 3–14 days of initiation and stabilizes or exacerbates based on dose titration and individual susceptibilities[10–13]. In a notable subset of our cohort, the magnitude of hyponatremia was sufficient to induce generalized tonic-clonic seizures—exemplifying the capacity of antipsychotic agents to cross the boundary from subclinical disturbance to overt neurological catastrophe[13].

Perhaps most sobering is the **age-associated correlation**; the inverse Pearson's coefficients ($r \approx -0.78$) across all follow-up intervals underscore the **geriatric neuroendocrine milieu** as intrinsically predisposed to sodium imbalance. Aging is accompanied by blunted thirst perception, impaired renal concentrating capacity, and a dysregulated hypothalamic-pituitary axis—all of which synergistically augment vulnerability to drug-induced SIADH[14–17]. In this context, antipsychotics function not as isolated etiological agents but rather as final perturbative insults within a pre-fragilized homeostatic network.

Beyond the biochemical terrain, the **clinical phenomenology of hyponatremia** is heterogenous and insidiously deceptive: ranging from fatigue, malaise, confusion, and gait instability to cataclysmic

seizures and coma[18–20]. The absence of florid symptomatology in 92% of hyponatremic cases in our sample raises grave concerns regarding the sufficiency of symptom-driven diagnostic paradigms and compels the implementation of **routine electrolyte surveillance** as a non-negotiable standard in antipsychotic pharmacotherapy[6 10 19].

The **ADR causality evaluation**, conducted using WHO-UMC algorithms, lends additional credence to pharmacological culpability, with over 38% of ADRs categorized as 'probable'[21]. Notably, the absence of 'certain' ADRs reflects the ethical and logistical impossibility of rechallenge testing in a neurotoxic context—an epistemological limitation endemic to psychopharmacological research[22].

These findings also resurrect the discourse on **agent-specific risk stratification**. While all three SGAs were implicated, the incidence of symptomatic hyponatremia and seizure was disproportionately higher in the risperidone cohort, warranting circumspect prescribing in populations with concurrent hyponatremic predispositions (e.g., SSRIs, diuretics, heart failure, hypothyroidism)[23–26]. Moreover, olanzapine's well-documented **metabolic sequelae** and aripiprazole's **neuro activation potential** may serve as collateral modulators of SIADH risk. The existing literature underscores the importance of **receptor occupancy dynamics**,particularly D3 and 5-HT1A receptor interactions—in modulating vasopressinergic tone[27 28].

Limitations of this study, while acknowledged, are not without their own academic utility. The inability to quantify osmolality, vasopressin titers, or conduct rechallenge paradigms precludes a complete mechanistic model. Nevertheless, the robust intra-patient longitudinal sodium tracking, complemented by structured ADR analysis, renders this study among the more methodologically rigorous assessments of this pharmacological complication[6 7 21].

The tabular schema delineates a multidimensional comparative landscape of non-electrolyte-based pharmaco toxicological sequelae manifesting secondary to monotherapeutic administration of second-generation antipsychotics,namely **risperidone, olanzapine, and aripiprazole**,within a neuropsychiatric outpatient cohort stringently filtered for psychotropic naïveté and biochemical euvolemic at baseline.

Despite the empirical heterogeneity in the phenotypic expression of adverse drug reactions such as **hyperprolactinemia-induced galactorrhea, dopaminergic antagonism-mediated extrapyramidal symptomatology, serotonergic disinhibition–linked sexual dysfunction, and serotonergic-dopaminergic instability resulting in suicidal ideation**, the **Chi-square inferential analytics** failed to demonstrate statistically robust intergroup divergence ($p > 0.05$ across all ADR domains), thereby underscoring the **equivocal pharmacotoxic liability spectrum** shared among these agents in the context of these specific non-sodium-centric endpoints.

The **neuroleptic malignant syndrome (NMS)**—although an idiosyncratic pharmacy neurological catastrophe of high lethality, was observed at a **negligibly low incidence**, insufficient for inferential robustness due to constrained event frequency and inadequate statistical power. **Weight gain**, a cardinal metabolic adversogenic parameter associated with olanzapine's orexigenic receptor profile (notably H1 and 5HT2C blockade), manifested more prominently in that subgroup; however, this variation failed to traverse the threshold of statistical significance ($p = 0.328$), suggesting potential Type II error and necessitating larger sample sizes for validation.

Similarly, **increased salivation**, typically attributed to α2-adrenergic receptor antagonism, and **sexual dysfunction**, often arising from serotonergic excess and dopaminergic suppression, were omnipresent across all pharmacologic strata, reflecting a **class-wide neurotransmitter-mediated iatro dysfunction** rather than a molecule-specific idiosyncrasy.

In essence, this matrix typifies a pharmacovigilant equilibrium across the atypical antipsychotic classes with respect to these adverse sequelae,**signifying non-differential toxicodynamic burdens**—and thereby guides the clinician toward **individualized risk–benefit stratification based on patient-specific variables** rather than presumptive drug superiority in ADR mitigation.

Ultimately, our findings argue not merely for heightened awareness but for a **paradigmatic shift in psychiatric prescribing practices**,one that operationalizes **routine electrolyte monitoring**, patient stratification based on hyponatremia risk, and thoughtful agent selection. We advocate for the integration of **sodium surveillance into national psychotropic safety guidelines**, particularly for geriatric populations[19] [20]. Furthermore, investment in future trials exploring **pharmacogenetic susceptibilities**, **ADH polymorphisms**, and **real-time osmoregulatory biomarkers** would dramatically enhance clinical predictability[17] [20] [28].

CONCLUSION

Our prospective surveillance confirms that SGAs—especially olanzapine, risperidone, and aripiprazole—can precipitate early, often asymptomatic hyponatremia, with potential neurologic sequelae. The elderly population is particularly susceptible due to inherent osmoregulatory decline and polypharmacy. We strongly advocate:

1. Baseline and weekly serum sodium monitoring during first four weeks of therapy, especially in patients >60 years.
2. Education of clinicians regarding the SIADH risk profile in SGAs, and its mechanistic underpinnings.
3. Prompt action on falling sodium: consider dose reduction, medication substitution, fluid restriction, or hypertonic management.
4. Investment in multicenter trials to better quantify risk stratification and preventive strategies, including receptor occupancy profiling.
5. Integration of these measures into psychiatric pharmacotherapy protocols will optimize patient safety while preserving therapeutic gains.

RERERENCES

1. Uchiyama M, et al. Hyponatremia secondary to psychotropic medications: a systematic review. J Clin Psychopharmacol. 2018;38(5):443-450.
2. Falhammar H, et al. Antipsychotic-associated hyponatremia in the Swedish population: a nationwide case-control study. J Psychopharmacol. 2018;32(12):1308-1316.
3. Sahoo S, et al. Hyponatremia in elderly psychiatric patients: clinical and pharmacological implications. Asian J Psychiatr. 2016;21:17-22.
4. Stachnik JM, et al. The syndrome of inappropriate antidiuretic hormone (SIADH) in psychiatry: pharmacologic associations and management strategies. US Pharm. 2024;49(3):HS11-HS16.
5. Dube D, et al. Olanzapine-induced SIADH: a case report and review of literature. Rev Colomb Psiquiatr. 2020;49(4):277-282.
6. Guo Y, et al. Pharmacodynamic profiles of atypical antipsychotics and hyponatremia risk. Psychopharmacology. 2021;238(2):451-463.
7. Spigset O. Mechanisms of psychotropic drug-induced SIADH. Acta Psychiatr Scand. 1994;89(6):451-459.
8. Ayus JC, et al. Chronic hyponatremia in the elderly: associations with falls, fractures, and mortality. Am J Med. 2013;126(12):1127-1133.
9. Babar SM, et al. Hyponatremia and the geriatric syndrome: a review. Curr Geriatr Rep. 2018;7(1):1-7.
10. Rahman M, et al. Early-onset hyponatremia with risperidone: clinical pharmacology and outcomes. Clin Neuropharmacol. 2010;33(2):105-108.
11. Sköldunger A, et al. Antipsychotics and electrolyte disorders: a pharmacoepidemiological perspective. J Clin Med. 2020;9(4):1144.
12. Lin CH, et al. Delayed-onset hyponatremia in elderly patients with schizophrenia. Int Psychogeriatr. 2011;23(3):461-468.
13. Yamamoto K, et al. Aripiprazole and SIADH: case-based evidence. Clin Psychopharmacol Neurosci. 2008;6(3):157-160.

14. Filippatos TD, et al. Electrolyte and acid–base disorders in psychiatric illness: pathophysiology and clinical implications. World J Psychiatr. 2016;6(1):1-10.
15. Ayus JC, et al. Neurologic sequelae of hyponatremia in elderly populations. Neurology. 2000;54(3):1305-1312.
16. Verbalis JG, et al. Pathogenesis of hyponatremia: vasopressin and water homeostasis. Am J Med. 2013;126(10 Suppl 1):S1-S7.
17. Miller M. Hyponatremia and bone health in the elderly. J Clin Endocrinol Metab. 2006;91(4):1229-1233.
18. Renneboog B, et al. Mild chronic hyponatremia is associated with falls and fractures in elderly. Am J Med. 2006;119(1):71.e1-71.e8.
19. Liamis G, et al. Hyponatremia in clinical practice: causes, implications, and management. Eur J Intern Med. 2008;19(6):407-413.
20. Spasovski G, et al. Clinical practice guideline on diagnosis and treatment of hyponatremia. Nephrol Dial Transplant. 2014;29 Suppl 2:i1-i39.
21. Naranjo CA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245.
22. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259.
23. Leung AA, et al. Drug-induced SIADH: a review. QJM. 2008;101(8):569-575.
24. Balestrieri M, et al. Hyponatremia associated with antipsychotics: evidence from pharmacovigilance data. Drug Saf. 2012;35(6):481-488.
25. Movig KLL, et al. Hyponatremia associated with antidepressants and antipsychotics. Pharmacoepidemiol Drug Saf. 2002;11(8):689-694.
26. Hix JK, et al. Diagnosing SIADH: essential and emerging tests. Am Fam Physician. 2006;73(5):769-776.
27. Miyamoto S, et al. D2/D3 receptor blockade and clinical psychopharmacology. J Psychopharmacol. 2005;19(4):403-419.
28. Remington G, et al. Receptor affinity and side effect profiles of antipsychotics. Can J Psychiatry. 2006;51(10):631-643.