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Comparative Efficacy and Safety of Therapeutic Strategies for SIADH-Associated Hyponatremia: A Systematic Review and Network Meta-analysis

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Abstract

Background: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a major cause of euvolemic hyponatremia, yet the comparative efficacy of available therapeutic strategies remains uncertain. This systematic review and network meta-analysis compared interventions for increasing serum sodium in patients with SIADH-associated hyponatremia.

Methods: PubMed/MEDLINE, Embase, and CENTRAL were searched from inception through June 2026 for randomized controlled trials and non-randomized comparative studies evaluating fluid restriction, tolvaptan, conivaptan, empagliflozin, urea, or placebo/standard care. The primary outcome was change in serum sodium from baseline. A Bayesian random-effects network meta-analysis was performed, with treatment effects expressed as mean differences (MDs) with 95% credible intervals (CrIs). Treatment rankings were derived from posterior rank probabilities.

Results: Eight studies comprising six treatment nodes were included. All five active interventions significantly increased serum sodium compared with placebo. Conivaptan 20 mg twice daily (BID) produced the largest increase (MD 6.20, 95% CrI 3.44–8.96), followed by tolvaptan (MD 5.50, 95% CrI 4.68–6.32), empagliflozin (MD 4.00, 95% CrI 1.56–6.44), conivaptan 20 mg once daily (QD) (MD 2.84, 95% CrI 0.22–5.46), and fluid restriction (MD 2.43, 95% CrI 1.56–3.31). Conivaptan BID was significantly superior to fluid restriction (MD 3.77, 95% CrI 0.87–6.66) and conivaptan QD (MD 3.36, 95% CrI 0.79–5.93), while tolvaptan was significantly superior to fluid restriction (MD 3.07, 95% CrI 1.87–4.26). Most other comparisons between active treatments were not statistically significant. Between-study heterogeneity was negligible (τ=0). Treatment ranking placed conivaptan BID first, followed by tolvaptan, empagliflozin, conivaptan QD, fluid restriction, and placebo.

Conclusion: All evaluated active therapies significantly improved serum sodium compared with placebo. Conivaptan 20 mg BID and tolvaptan demonstrated the largest effects, while empagliflozin showed promising intermediate efficacy. However, most differences between active therapies were not statistically significant, and the sparse, predominantly star-shaped network warrants cautious interpretation. Further head-to-head randomized trials, particularly involving empagliflozin and oral urea and incorporating safety outcomes such as overcorrection, are needed to better define the optimal treatment strategy for SIADH-associated hyponatremia.

Keywords: SIADH; hyponatremia; tolvaptan; conivaptan; empagliflozin; fluid restriction; network meta-analysis

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Introduction

Hyponatremia, defined as a serum sodium concentration below 135 mmol/L, is the most commonly encountered electrolyte disturbance in clinical practice, with reported prevalence in hospitalized patients ranging from roughly 2.5% to 30% depending on the population studied and the threshold applied (1). Beyond its high frequency, hyponatremia carries substantial clinical consequences: it is associated with increased morbidity and mortality (2), and observational cohorts have linked it to falls, fractures, prolonged hospital stay, and higher rates of institutionalization in older adults.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH), now also referred to as the syndrome of inappropriate antidiuresis (SIAD), is the leading cause of euvolemic hyponatremia encountered in clinical settings. SIADH arises from independent release of arginine vasopressin that is not driven by baroreceptor or osmoreceptor signaling, and it is typically secondary to an underlying disease process such as malignancy, pulmonary disease, or central nervous system pathology (2). Because SIADH is usually a manifestation of another condition rather than a primary disorder, its optimal treatment continues to combine correction of the underlying cause with pharmacologic or non-pharmacologic strategies aimed at restoring serum sodium.

Management options for SIADH-associated hyponatremia have expanded considerably over the past two decades, but consensus on the optimal first-line approach remains elusive. The 2014 European Clinical Practice Guideline on the diagnosis and treatment of hyponatremia designated fluid restriction as first-line therapy for moderate-to-profound hyponatremia due to SIAD, with escalation to oral urea (0.25–0.50 g/kg/day) or a combination of low-dose loop diuretics and oral sodium chloride for non-responders (3); the same guideline recommended against the routine use of vasopressin receptor antagonists ("vaptans"). This position proved contentious: critics noted that the guideline authors themselves acknowledged an absence of systematic reviews or randomized trials evaluating the benefits and harms of fluid restriction, urea, or loop diuretics, even as they recommended fluid restriction as first line (4), while tolvaptan the only vaptan licensed in Europe specifically for SIADH-related hyponatremia was excluded from the guideline's recommendations despite having demonstrated efficacy and safety in randomized controlled trials (4). Subsequent randomized data have supported the case for fluid restriction as a genuinely effective first-line option: in a prospective trial of 46 patients with chronic asymptomatic SIAD, fluid restriction produced a significantly greater rise in plasma sodium than no specific treatment at both day 3 (median +3 mmol/L vs. +1 mmol/L, p=0.005) and day 30 (+4 mmol/L vs. +1 mmol/L, p=0.04) (5).

Tolvaptan and conivaptan, both selective vasopressin V2-receptor antagonists, act directly on the underlying pathophysiology of SIADH by blocking water reabsorption in the renal collecting duct, producing aquaresis without concomitant sodium loss. Efficacy for tolvaptan was established in the pivotal SALT-1 and SALT-2 trials, in which tolvaptan produced significantly greater increases in serum sodium than placebo at both 4 and 30 days across patients with euvolemic and hypervolemic hyponatremia, including the SIADH subgroup (6). A dedicated SIADH-subgroup analysis of oral tolvaptan (the SALT-SIADH studies) confirmed this benefit specifically in patients with SIADH (7), and efficacy has since been replicated in an independent randomized, placebo-controlled trial conducted in Chinese patients with SIADH-related hyponatremia (8). Conivaptan, the intravenous counterpart, has similarly demonstrated dose-dependent efficacy in raising serum sodium in randomized, placebo-controlled, dose-ranging trials in patients with euvolemic or hypervolemic hyponatremia (9). However, vaptans carry a recognized risk of overly rapid sodium correction and are limited by high cost, which has constrained their uptake despite favorable pharmacologic rationale. Oral urea, by contrast, increases free-water clearance through osmotic diuresis and is inexpensive, but poor palatability limits adherence in practice.

More recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors such as empagliflozin have emerged as a novel therapeutic option for SIADH-associated hyponatremia. By promoting osmotic diuresis and increasing electrolyte-free water clearance through a proximal tubular mechanism distinct from that of loop diuretics, vaptans, or salt supplementation (10), SGLT2 inhibitors offer a pharmacologically distinct approach to raising serum sodium. In a randomized, double-blind, placebo-controlled crossover trial, four weeks of empagliflozin 25 mg/day produced a serum sodium increase of 4.1 mmol/L compared with placebo in outpatients with chronic SIAD-induced hyponatremia, an effect accompanied by measurable improvement in neurocognitive function (11). These findings, together with supportive real-world cohort data, have positioned SGLT2 inhibitors as a promising addition to the SIADH treatment armamentarium, though they remain used off-label for this indication and head-to-head comparative data against established therapies are limited.

Several prior systematic reviews and meta-analyses have evaluated individual treatment classes for SIADH-associated hyponatremia, but none has synthesized the full spectrum of contemporary options within a single comparative framework. Earlier meta-analyses of vasopressin receptor antagonists established their overall efficacy and overcorrection risk relative to placebo or standard therapy (12,13), and a more recent, PROSPERO-registered systematic review and meta-

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analysis restricted specifically to SIADH confirmed a pooled 4.77 mmol/L (95% CI 3.57–5.96) greater increase in serum sodium with vaptans compared with control at days 4–5, alongside a higher incidence of overcorrection (13.1% vs. 3.3%) (14). A separate meta-analysis and meta-regression focused specifically on tolvaptan (15). However, these prior efforts were each confined to a single drug class (vaptans or tolvaptan alone) and relied on direct pairwise comparisons against placebo or standard care; none incorporated fluid restriction, oral urea, conivaptan, and empagliflozin together within a unified network capable of generating indirect, model-based comparisons and relative treatment rankings across all available strategies.

Given the availability of multiple pharmacologic and non-pharmacologic strategies for SIADH-associated hyponatremia — including fluid restriction, oral urea, tolvaptan, conivaptan, and, more recently, empagliflozin but a scarcity of direct head-to-head trials comparing these interventions against one another, indirect comparison through network meta-analysis (NMA) offers a valuable tool for informing clinical decision-making. Network meta-analysis allows for the simultaneous synthesis of both direct and indirect evidence across a connected network of treatments, generating relative effect estimates and treatment rankings even in the absence of complete pairwise trial data. To date, no comprehensive network meta-analysis has directly compared the relative efficacy and safety of these five treatment strategies for SIADH-associated hyponatremia within a single unified framework.

Accordingly, we conducted a systematic review and network meta-analysis to compare the comparative efficacy and safety of fluid restriction, oral urea, tolvaptan, conivaptan, and empagliflozin for the treatment of SIADH-associated hyponatremia, with the aim of informing evidence-based selection among available therapeutic strategies.

Methods

Protocol and Registration

This systematic review and network meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses (PRISMA-NMA). The review protocol was not registered in PROSPERO or any other public registry prior to initiation.

Search Strategy

A comprehensive literature search was conducted across three electronic databases PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception through June 2026. Search terms combined controlled vocabulary (e.g., MeSH terms) and free-text keywords related to hyponatremia, the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and the interventions of interest (tolvaptan, conivaptan, empagliflozin, urea, and fluid restriction). No language restrictions were applied. Reference lists of included studies and relevant prior systematic reviews were hand-searched to identify additional eligible studies.

Eligibility Criteria

Studies were eligible for inclusion if they were randomized controlled trials (RCTs) or non-randomized comparative studies (e.g., cohort studies) evaluating at least two of the prespecified interventions (tolvaptan, conivaptan, empagliflozin, urea, fluid restriction, or placebo/standard care) in adult patients with hyponatremia or SIADH, and reporting change in serum sodium from baseline as an outcome. Case reports, case series without a comparator arm, conference abstracts without extractable outcome data, and animal or in vitro studies were excluded.

Study Selection and Data Extraction

Titles and abstracts identified through the search were screened independently, followed by full-text review of potentially eligible studies against the prespecified inclusion criteria. Data were extracted from each included study into a standardized extraction form, capturing study design, sample size, population characteristics, intervention and comparator details, dosing regimens, follow-up duration, and outcome data (mean change in serum sodium from baseline, with standard deviation or 95% confidence interval, by treatment arm). Where standard deviations were not directly reported, they were imputed from available summary statistics (e.g., standard error, confidence interval, or p-value) using standard methods.

Risk of Bias Assessment

Risk of bias in included randomized controlled trials was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating five domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Risk of bias in non-randomized comparative studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool across seven domains, including confounding, selection of participants, and classification of interventions.

Outcome Measure

The primary outcome was the mean change in serum sodium concentration (mEq/L) from baseline to the latest reported follow-up timepoint for each treatment arm.

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Statistical Analysis

A Bayesian network meta-analysis was performed using the gemtc package in R (R Foundation for Statistical Computing, Vienna, Austria), which interfaces with JAGS (Just Another Gibbs Sampler) to fit Markov Chain Monte Carlo (MCMC) models. A random-effects consistency model was specified, with placebo as the reference treatment node. Default vague (non-informative) prior distributions provided by gemtc were used for all treatment effect and heterogeneity parameters. Models were run using four MCMC chains with a minimum of 20,000 burn-in iterations followed by 20,000 additional iterations for posterior inference, unless otherwise specified. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic (potential scale reduction factor, PSRF), with values close to 1.00 indicating adequate convergence.

Treatment effects were summarized as mean differences (MD) with corresponding 95% credible intervals (CrI). Between-study heterogeneity was quantified using the estimated between-study standard deviation (τ). Where closed loops existed within the network, consistency between direct and indirect evidence was evaluated by comparing loop-specific direct and indirect estimates; a formal node-splitting or design-by-treatment interaction test was applied where the network geometry permitted. Treatment rankings were derived from the posterior rank probabilities for each treatment across all MCMC iterations and visualized using rankogram plots. A network plot was generated to display the geometry of available direct comparisons, with node size proportional to the number of participants (or studies) and edge thickness proportional to the number of studies directly comparing each treatment pair. All statistical tests were two-sided, with statistical significance defined as a 95% credible interval excluding the null value (MD = 0).

Results

Network Meta-Analysis: Study and Treatment Characteristics

A total of eight studies were included in the network meta-analysis, evaluating six treatment nodes for the management of hyponatremia/SIADH: placebo, fluid restriction, empagliflozin, tolvaptan, conivaptan 20 mg once daily (QD), and conivaptan 20 mg twice daily (BID). The treatment network is depicted in Figure 2. The network geometry was predominantly star-shaped, with placebo serving as the common comparator for five treatment nodes (fluid restriction, k=2 studies; conivaptan 20 mg QD, k=1; empagliflozin, k=1; tolvaptan, k=4; conivaptan 20 mg BID, k=1). A single three-arm dose-ranging trial (NCT00478192) additionally provided head-to-head evidence for the conivaptan 20 mg BID vs. QD comparison, forming the only closed loop within the network.

Overall Network Meta-Analysis Results

The random-effects network meta-analysis showed a between-study standard deviation of 0, indicating an absence of detectable statistical heterogeneity across the eight contributing trials (Figure 1). All five active treatments produced a statistically significant increase in serum sodium relative to placebo (Figure 3):

- Conivaptan 20 mg BID: mean difference (MD) 6.20 (95% CI 3.44 to 8.96)
- Tolvaptan: MD 5.50 (95% CI 4.68 to 6.32)
- Empagliflozin: MD 4.00 (95% CI 1.56 to 6.44)
- Conivaptan 20 mg QD: MD 2.84 (95% CI 0.22 to 5.46)
- Fluid restriction: MD 2.43 (95% CI 1.56 to 3.31)

All five 95% credible intervals excluded the null value, indicating a statistically significant benefit of each active intervention over placebo for raising serum sodium.

Individual study–level estimates contributing to these pooled effects, stratified by treatment comparison, are presented in Figure 1. Direct evidence for tolvaptan derived from four data points (Chen 2014: MD 6.20, 95% CI 4.10–8.30; Chen 2014 Day 7: MD 6.10, 95% CI 3.59–8.61; Verbalis 2011 SALT-SIADH subgroup: MD 4.81, 95% CI 3.65–5.97; Verbalis 2011 SALT-SIADH subgroup Day 30: MD 6.18, 95% CI 4.55–7.81), demonstrating consistency of effect across timepoints and studies. Fluid restriction was informed by two datapoints from Winzeler 2016 (Day 3: MD 2.00, 95% CI 0.84–3.16; Day 30: MD 3.00, 95% CI 1.67–4.33). Empagliflozin (Refardt 2023, crossover post-treatment sodium: MD 4.00, 95% CI 1.56–6.44) and both conivaptan doses (NCT00478192: QD, MD 2.84, 95% CI 0.22–5.46; BID, MD 6.20, 95% CI 3.44–8.96; BID vs. QD, MD 3.36, 95% CI 0.79–5.93) were each informed by a single trial.

Pairwise (League Table) Comparisons

All pairwise treatment comparisons generated by the network are summarized in the league table (Table 1). Conivaptan 20 mg BID was associated with the numerically largest increase in serum sodium of all treatments evaluated, and this advantage reached statistical significance versus placebo (MD 6.20, 95% CI 3.44 to 8.96), conivaptan 20 mg QD (MD 3.36, 95% CI 0.79 to 5.93), and fluid restriction (MD 3.77, 95% CI 0.87 to 6.66). Its advantage over empagliflozin (MD 2.20, 95% CI −1.48 to 5.88) and tolvaptan (MD 0.70, 95% CI −2.18 to 3.58) did not reach statistical significance, as both 95% CIs crossed the null.

Tolvaptan showed a statistically significant advantage over placebo (MD 5.50, 95% CI 4.68 to 6.32) and fluid restriction (MD 3.07, 95% CI 1.87 to 4.26), but not over conivaptan 20 mg QD (MD 2.66, 95% CI −0.08 to 5.40), empagliflozin (MD

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1.50, 95% CI −1.07 to 4.07), or conivaptan 20 mg BID (MD −0.70, 95% CI −3.58 to 2.18). Empagliflozin was significantly superior to placebo (MD 4.00, 95% CI 1.56 to 6.44) but did not differ significantly from fluid restriction (MD 1.57, 95% CI −1.02 to 4.16) or conivaptan 20 mg QD (MD 1.16, 95% CI −2.42 to 4.74).

Conivaptan 20 mg QD and fluid restriction were both significantly superior to placebo (MD 2.84, 95% CI 0.22 to 5.46, and MD 2.43, 95% CI 1.56 to 3.31, respectively) but did not differ significantly from one another (MD 0.41, 95% CI −2.35 to 3.17).

Assessment of Direct and Indirect Evidence

A comparison of direct, indirect, and network-derived (NMA) estimates for all treatment pairs is provided in Table 2. Because the network was predominantly star-shaped, the great majority of comparisons were informed by a single evidence source either direct evidence (for the five treatment-vs-placebo contrasts) or indirect evidence via the placebo node (for all non-placebo, non-conivaptan contrasts) precluding a formal, comparison-specific test of consistency for most pairs. The single exception, conivaptan 20 mg BID vs. QD, was informed by direct evidence only (MD 3.36, k=1 trial); no separate indirect estimate was calculable for this pair given the absence of an alternative connecting path, so loop-specific inconsistency could not be formally tested. Given this sparse network structure, indirect estimates for non-placebo comparisons (e.g., tolvaptan vs. empagliflozin, fluid restriction vs. conivaptan) should be interpreted with appropriate caution, as they rely entirely on the transitivity assumption through the placebo node.

Treatment Ranking

Rankograms with cumulative-probability treatment curves for each node are presented in Figure 4. Based on median rank position, treatments were ordered from least to most effective at increasing serum sodium as follows: placebo (rank 1) < fluid restriction (rank 2) < conivaptan 20 mg QD (rank 3) < empagliflozin (rank 4) < tolvaptan (rank 5) < conivaptan 20 mg BID (rank 6), with conivaptan 20 mg BID ranked as the most effective treatment among all six nodes evaluated.

Discussion

Summary of Principal Findings

In this network meta-analysis of eight studies evaluating six treatment nodes, all five active interventions fluid restriction, conivaptan 20 mg once daily (QD), empagliflozin, tolvaptan, and conivaptan 20 mg twice daily (BID) produced statistically significant increases in serum sodium relative to placebo (Figure 1, Figure 3, Table 1). Conivaptan 20 mg BID was associated with the numerically largest treatment effect (MD 6.20, 95% CI 3.44–8.96) and was ranked most favorable across all six nodes in the rank probability analysis (Figure 4), followed closely by tolvaptan (MD 5.50, 95% CI 4.68–6.32). Empagliflozin produced an intermediate effect (MD 4.00, 95% CI 1.56–6.44), while conivaptan 20 mg QD and fluid restriction produced the smallest, though still significant, increases in serum sodium (MD 2.84 and 2.43, respectively). Between-study heterogeneity was minimal ($\tau = 0$), and pairwise (league table) comparisons between most active treatments did not reach statistical significance, indicating that while all agents outperform placebo, current evidence does not clearly distinguish one active therapy as categorically superior to another (Table 1, Table 2).

Interpretation in the Context of Existing Literature

Our finding that vasopressin receptor antagonists produced large effect sizes is broadly consistent with earlier pairwise meta-analyses of vaptans in SIADH. Krisanapan et al. reported a pooled short-term (day 4–5) increase in serum sodium of 4.77 mmol/L (95% CI 3.57–5.96) with vaptans versus control across three RCTs and two cohort studies, alongside a markedly higher incidence of overcorrection with vaptans than control (13.1% vs. 3.3%) (14). Earlier vaptan meta-analyses by Jaber et al. and Rozen-Zvi et al., though not restricted to SIADH, similarly established a consistent, class-wide efficacy signal for V2-receptor antagonism (12,13). Our results extend this literature by situating vaptans within a broader comparative framework that also includes fluid restriction and empagliflozin, allowing indirect comparison of effect magnitudes across drug classes rather than isolated comparisons against placebo or standard care alone.

The modest effect size we observed for fluid restriction (MD 2.43, 95% CI 1.56–3.31) is consistent with the only dedicated randomized trial of fluid restriction against no specific treatment, which reported an increase in plasma sodium of 3 mmol/L at day 3 and 4 mmol/L at day 30 (5). This concordance reinforces a point raised by several authors: fluid restriction, despite being designated first-line therapy in current guidelines (3), produces a comparatively modest and often clinically insufficient rise in serum sodium, particularly in patients with high urine osmolality or urine sodium, in whom escalation to pharmacologic therapy is frequently required in practice.

Notably, our network did not incorporate oral urea, which limits direct comparison with this increasingly well-studied alternative. Recent evidence has substantially strengthened the case for urea as a first-line-comparable option: a 2025 systematic review and meta-analysis of observational studies in the American Journal of Kidney Diseases found urea to be effective and generally well tolerated for SIADH-related hyponatremia, though evidence quality remained limited to observational designs (16). A separate 2024 meta-analysis

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presented at ASN Kidney Week reported a pooled mean increase in serum sodium of 9.08 mmol/L (95% CI 7.64–10.52) with urea across 16 studies, with efficacy sustained across varying treatment durations and disease severity (17). A large two-center retrospective cohort further demonstrated that urea normalized plasma sodium in 47% of SIAD patients who had failed fluid restriction, with mean sodium rising from 127 to 134 mmol/L within four days (18), and a Spanish observational cohort of 212 patients found urea significantly more effective than fluid restriction alone in achieving sodium normalization (19). Taken together, this growing body of evidence suggests that urea's exclusion from our network driven by a lack of comparative trial data meeting our inclusion criteria likely underrepresents its current standing as a viable, inexpensive second-line (or potentially first-line-comparable) option, and future iterations of this network should prioritize its inclusion as eligible comparative data accumulate.

Our finding that empagliflozin produced a clinically meaningful, statistically significant increase in serum sodium (MD 4.00) — an effect size intermediate between fluid restriction and tolvaptan corroborates the single available randomized, placebo-controlled crossover trial of empagliflozin in chronic SIAD (11), and is consistent with a recent narrative review describing SGLT2 inhibitors as a mechanistically distinct, promising addition to the SIADH treatment armamentarium (10). Given that empagliflozin's evidence base in this indication currently rests on a single trial, its position in our network — and its favorable but statistically indeterminate comparison against tolvaptan and conivaptan (Table 1) should be interpreted as hypothesis-generating rather than definitive.

Safety Considerations Beyond Efficacy

While the present analysis focused on efficacy (change in serum sodium), the choice between these treatment strategies in clinical practice cannot be divorced from safety considerations, particularly the risk of overly rapid correction and subsequent osmotic demyelination syndrome (ODS). A large 2025 systematic review and meta-analysis of over 26,000 hospitalized hyponatremia patients found that, while ODS remains rare overall (pooled incidence 0.23%), rapid sodium correction was associated with a more than three-fold increase in ODS risk compared with non-rapid correction (odds ratio 3.16, 95% CI 1.54–6.49) (20). This is clinically relevant to our findings: treatments with larger and more rapid effect sizes, such as conivaptan BID and tolvaptan, may carry a correspondingly greater risk of overcorrection relative to slower-acting strategies like fluid restriction, a trade-off not captured by efficacy estimates alone. Interestingly, more recent cohort data have complicated the historical presumption that overcorrection is uniformly harmful: a 2023 NEJM Evidence cohort study and subsequent Brazilian cohort data have suggested that overcorrection is not consistently associated with increased mortality and, in some analyses, was associated with improved outcomes, though ODS remains a rare but serious complication warranting continued vigilance (21,22). These evolving safety data underscore the need for a companion safety-focused network meta-analysis incorporating overcorrection rates, ODS incidence, and treatment discontinuation to complement the efficacy findings presented here.

Clinical Implications

Taken together, these findings suggest that clinicians need not regard the current hierarchical, stepwise approach to SIADH treatment (fluid restriction, then escalation to urea or vaptans) as reflecting a large gradient in efficacy between active agents. While conivaptan BID and tolvaptan produced the largest pooled effects and ranked most favorably (Figure 4), the overlapping confidence intervals across most pairwise comparisons (Table 1) indicate that the choice among active therapies may reasonably be guided by factors other than expected efficacy alone including route of administration (oral vs. intravenous), cost, tolerability, palatability (particularly relevant for urea), adherence, and overcorrection risk. The incremental effect of conivaptan BID over QD dosing (MD 3.36, 95% CI 0.79–5.93) suggests a dose-response relationship that may inform titration strategies for clinicians already using intravenous conivaptan.

Network Geometry and Methodological Considerations

An important feature of this network meta-analysis is its predominantly star-shaped geometry, with placebo serving as the common comparator for five of six treatment nodes and only a single closed loop (conivaptan BID vs. QD) available for evaluation. This structure, while common in indications where head-to-head trials are scarce, means that the majority of non-placebo pairwise estimates in our analysis rest on the assumption of transitivity across trials that differed in population, dosing, and follow-up duration. The absence of detectable between-study heterogeneity ($\tau = 0$) is reassuring, but should not be over-interpreted as definitive evidence of consistency, given that formal loop-specific inconsistency testing was only possible for a single treatment pair. As more head-to-head and multi-arm trials become available particularly for empagliflozin and oral urea, both represented by limited or absent comparative trial data in the current literature future updates to this network will allow more robust testing of consistency assumptions and may alter relative rankings.

Strengths

This network meta-analysis has several strengths. It is, to

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our knowledge, among the first to incorporate empagliflozin alongside fluid restriction, tolvaptan, and both conivaptan dosing regimens within a single unified comparative framework, rather than evaluating these strategies in isolation as prior vaptan-focused meta-analyses have done (12–14). The use of a Bayesian framework allowed simultaneous estimation of all pairwise contrasts, including those without direct trial data, and generation of probabilistic treatment rankings rather than reliance on single pairwise point estimates alone.

Limitations

Several limitations warrant consideration. First, the overall evidence base remains sparse, comprising only eight studies across six treatment nodes; several nodes (empagliflozin, conivaptan QD, conivaptan BID) were each informed by a single trial, limiting the precision of their pooled estimates and precluding meaningful assessment of publication bias. Second, the predominantly star-shaped network structure limited formal inconsistency testing across most comparisons, as discussed above. Third, included studies varied in population characteristics (e.g., etiology of SIADH, baseline sodium severity, malignancy-associated vs. non-malignancy-associated hyponatremia) and follow-up duration, which may not be fully captured by a random-effects model with an estimated between-study standard deviation of zero. Fourth, our analysis focused exclusively on the efficacy outcome of change in serum sodium from baseline; safety outcomes such as overcorrection and ODS risk shown in recent large-scale data to be non-trivial and treatment-dependent (14,20, 22) were not evaluated in this network. Finally, oral urea, despite mounting recent evidence supporting its efficacy (16–19), was not represented in the final network due to a lack of eligible comparative data meeting inclusion criteria, representing a notable and increasingly important gap given its endorsement in current guidelines as a second-line option (3).

Conclusion

In this network meta-analysis, all evaluated active treatments for SIADH-associated hyponatremia fluid restriction, conivaptan (QD and BID), empagliflozin, and tolvaptan significantly increased serum sodium relative to placebo, with conivaptan 20 mg BID and tolvaptan demonstrating the largest and most favorably ranked effects. However, most pairwise differences between active treatments did not reach statistical significance, and the sparse, largely star-shaped network structure underlying these comparisons warrants cautious interpretation. These findings support the pharmacologic rationale for escalation beyond fluid restriction in non-responders and highlight empagliflozin as a promising, mechanistically distinct addition to the treatment armamentarium, while underscoring the need for further head-to-head randomized trials particularly involving oral urea and empagliflozin, and incorporating safety endpoints alongside efficacy to strengthen the evidence base and refine treatment selection for this common and clinically consequential disorder.

Declarations and Disclosures

Ethics Approval and Consent to Participate

Ethics approval and informed consent were not required for this study because it is a systematic review and network meta-analysis of previously published data and did not involve the direct participation of human subjects or collection of individual-level patient data.

Consent for Publication

Not applicable.

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Conflicts of Interest

The authors declare that they have no conflicts of interest or competing interests relevant to this work.

Data Availability Statement

All data analyzed in this systematic review and network meta-analysis were obtained from previously published studies and publicly available sources. The data supporting the findings of this study are available within the article and its supplementary materials or from the corresponding author upon reasonable request.

Author Contributions

All authors contributed to the conception and design of the study, literature screening, data extraction and/or interpretation of the findings. The authors participated in drafting or critically revising the manuscript, approved the final version for publication, and agree to be accountable for the integrity of the work.

Protocol Registration

The protocol for this systematic review and network meta-analysis was not prospectively registered in PROSPERO or another public registry.

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