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SYSTEMATIC REVIEW AND META-ANALYSIS

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# Efficacy and Safety of Vasopressin Receptor Antagonists for Euvolemic or Hypervolemic Hyponatremia

## *A Meta-Analysis*

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**Abstract:** Hyponatremia, defined as a nonartifactual serum sodium level <135 mmol/L, is the most common fluid and electrolyte abnormality in clinical practice. Traditional managements (fluid restriction, hypertonic saline and loop diuretics, etc.) are difficult to maintain or ineffective. Recently, vasopressin receptor antagonists (VRAs) have shown promise for the treatment of hyponatremia.

We aimed to conduct a meta-analysis to evaluate the efficacy and safety of VRAs in patients with euvolemic or hypervolemic hyponatremia. We searched Pubmed, Cochrane Library, Web of Science and Springer, etc. (latest search on June 4, 2015) for English publications with randomized controlled trials. Two authors independently screened the citations and extracted data. We calculated pooled relative risk (RR), risk difference (RD), weighted mean difference (WMD) or standard mean difference (SMD), and 95% confidence intervals (CIs) by using random and fixed effect models.

We collected data from 18 trials involving 1806 patients. Both random and fixed effect meta-analyses showed that VRAs significantly increased the net change of serum sodium concentration ($WMD_{random}$ = 4.89 mEq/L, 95%CIs = 4.35–5.43 and $WMD_{fixed}$ = 4.70 mEq/L, 95%CIs = 4.45–4.95), response rate ($RR_{random}$ = 2.77, 95%CIs = 2.29–3.36 and $RR_{fixed}$ = 2.95, 95%CIs = 2.56–3.41), and 24-hour urine output ($SMD_{random}$ = 0.82, 95%CIs = 0.65–1.00 and $SMD_{fixed}$ = 0.79, 95%CIs = 0.66–0.93) compared to placebo. Furthermore, VRAs significantly decreased body weight ($WMD_{random}$ = −0.87 kg, 95%CIs = −1.24 to −0.49 and $WMD_{fixed}$ = −0.91 kg, 95%CIs = −1.22 to −0.59). In terms of safety, rates of drug-related adverse events (AEs), rapid sodium level correction, constipation, dry mouth, thirst, and phlebitis in the VRA-treated group were greater than those in control group. However, there was no difference in the total number of AEs, discontinuations due to AEs, serious AEs, death, headache, hypotension, nausea, anemia, hypernatremia, urinary tract infection, renal failure, pyrexia, upper gastrointestinal bleeding, diarrhea, vomiting, peripheral edema, and dizziness between the 2 groups. Random effect meta-analyses showed that post treatment urine osmolality, supine systolic blood pressure, and diastolic blood pressure were lowered ($WMD_{random}$ = −233.07 mOsmol/kg, 95%CIs = −298.20–147.94; $WMD_{random}$ = −6.11 mmHg, 95%CIs = −9.810 to −2.41; $WMD_{random}$ = −2.59 mmHg, 95%CIs = −4.06 to −1.11, respectively), but serum osmolality was increased ($WMD_{random}$ = 9.29 mOsmol/kg, 95%CIs = 5.56–13.03). There was no significant change from baseline in serum potassium concentration between the 2 groups ($WMD_{fixed}$ = 0.00 mmHg, 95%CIs = −0.07–0.06).

VRAs are relatively effective and safe for the treatment of hypervolemic and euvolemic hyponatremia.

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**Abbreviations**: AE = adverse event, CI = confidence interval, RD = risk difference, RR = relative risk, SIADH = inappropriate release of arginine vasopressin, SMD = standard mean difference, VRA = vasopressin receptor antagonist, WMD = weighted mean difference.

## INTRODUCTION

Hyponatremia, defined as a nonartifactual serum sodium level of less than 135 mmol/L, is the most common fluid and electrolyte abnormality in clinical practice.[1,2] Decreases in serum sodium concentration may be a result of excess water intake, which contributes to a dilution effect, or sodium loss may exceed body water excretion.[3] Hyponatremia is frequently caused by heart failure, cirrhosis, and the inappropriate release of arginine vasopressin (SIADH).[4,5] It leads to various clinical symptoms, ranging from subtle to severe or even life threatening, and is associated with increased mortality, morbidity, and length of hospital stay for patients presenting with a range of conditions.[6] Traditional managements (fluid restriction, hypertonic saline and loop diuretics, etc.) are the main but suboptimal treatment option since it is poorly tolerated, difficult to maintain, and has variable efficacy, slow responses, severe side effects.[6–8] Vasopressin receptor antagonists (VRAs) are promising new agents for the treatment of the hypervolemic or euvolemic forms of hyponatremia. These agents are nonpeptide VRAs that interfere with the antidiuretic effect of the hormone by competitively binding to $V_2$ receptors in the kidney. They induce the excretion of electrolyte-free water without changing the total level of electrolyte excretion, thereby increasing serum sodium concentration.[9] Conivaptan is a $V_{1a}/V_2$ receptor antagonist, while tolvaptan, satavaptan, and lixivaptan are selective $V_2$ receptor antagonists. Current randomized controlled trials have proven the relatively reliable efficacy and safety of VRAs in treating mild and moderate hyponatremia. However, the correction rate of serum sodium in acute severe hyponatremia has remained uncertain. In addition, although thirst and dry mouth have been the most frequent adverse events

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(AEs) reported to date, severe AEs have also occasionally occurred, including liver and kidney damage, nerve damage, severe infection, upper gastrointestinal bleeding, etc. Therefore, a meta-analysis was undertaken to evaluate the clinical efficacy and safety of VRAs in patients with hyponatremia.

## METHODS

### Literature Search

Pubmed, Cochrane Library, Web of Science and Springer, etc. were searched with the MeSH terms ''hyponatremia,'' ''vasopressin receptor antagonists,'' ''conivaptan,'' ''lixivaptan,'' ''satavaptan,'' and ''tolvaptan'' (the latest search was performed on June 4, 2015) to identify English publications from randomized controlled trials assessing the efficacy and safety of VRAs for euvolemic or hypervolemic hyponatremia.

### Eligibility Criteria

Patients, 18 years of age or older, diagnosed with euvolemic or hypervolemic hyponatremia (defined as a nonartifactual serum sodium level of less than 135 mmol/L) were eligible for inclusion. The intervention comparisons were made between VRAs (conivaptan, lixivaptan, satavaptan, tolvaptan, etc.) and no intervention, placebo, other diuretics (furosemide, spironolactone, etc.). No specific criteria were made regarding the dose or duration of treatment. The primary efficacy outcome was the change from baseline in serum sodium concentration. Secondary efficacy outcomes were the response rate (variable definitions to characterize this endpoint were used by the authors of the original studies), net change in body weight, and 24-hour urine output. The safety outcomes included the incidence of discontinuations, discontinuations due to AEs, AEs, serious AEs, drug-related AEs, death, and common AEs (dry mouth, thirst, headache, hypotension, nausea, constipation, etc.). Excluded trials were listed with the reason for exclusion.

### Data Extraction

Data were extracted from full-text articles by 2 of the authors (XZ and WD) independently. Disagreements were resolved through consensus and arbitration by a 3rd author (DZ). For each included trial, the following basic characteristics were extracted from the full-text article: first author, country of patients, year of publication, concomitant disease of patients, amount of fluid restriction (if any), dose of drugs and route of administration, mean age or range, female percentage, the number of patients, duration of intervention, and hyponatremia type. Outcomes were extracted preferentially by intention to treat. In addition, we obtained mean ± standard deviation values for continuous variables in the original manuscripts for the meta-analysis. When mean ± standard deviation values were not available, calculation of mean and standard deviation values is based on 95% confidence intervals (CIs) or standard deviation values within subgroups. Trials in which specific endpoints were not reported were excluded only from the pooled analyses of the specific endpoints that were reported.

### Quality Assessment

Study quality was assessed by the Jadad scale, which assesses adequacy of randomization, blinding, and attrition.[10] The Jadad scale ranges from 0 to 5 points, with a low-quality study receiving a score of 2 or less and a high-quality study having a score of at least 3.[11] Furthermore, we used the Schulz approach to evaluate the allocation concealment, which is defined as adequate (such as central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other descriptions that contained convincing elements of concealment), inadequate (such as alternation or reference to case record numbers or to dates of birth), and unclear (not reported).[12] There was low correlation between assessments of overall risk of bias and 2 common approaches to quality assessment: the Jadad scale and the Schulz approach to allocation concealment.[13]

### Statistical Analysis

Data analyses were performed in R 3.1.3 and STATA SE version 12.0 software. Main analyses used all trials with available quantitative information for every outcome. Random and fixed effect models were used for pooling data. The results were expressed as relative risk (RR), risk difference (RD), weighted mean difference (WMD), or standard mean difference (SMD) with 95%CIs, $I^2$ value, and Egger test $P$ value. The $I^2$ value serves as a marker of intertrial heterogeneity, and intertrial heterogeneity was not considered with $I^2 \leq 50\%$ (with $I^2 > 50\%$ defined as high heterogeneity).[14] The sources of intertrial heterogeneity were assessed in subgroup and sensitivity analyses. Subgroup analyses evaluated the influence of various VRAs, hyponatremia type, and fluid restriction. In sensitivity analyses, we serially left 1 study out and analyzed heterogeneity on the basis of masking within the trial in order to judge the stability of effective values. Finally, publication bias was formally assessed by using funnel plots and Egger regression analysis (with $P < 0.05$ defined as having publication bias).[15]

## RESULTS

### Study Characteristics

A total of 1147 potentially relevant citations were identified and screened, using the process shown in Figure 1. We retrieved 60 full-text articles for detailed evaluation, out of which 18 reports involving 1806 patients satisfied the selection criteria.[16–33] The included trials were published between 2003 and 2014. The median number of patients was 100 (range 28–243), with 8 trials having more than 100 patients. Treatment duration ranged from 2 to 30 days. These trials generally focused on comparisons of 4 drugs (conivaptan, lixivaptan, satavaptan, and tolvaptan) with placebo. Conivaptan was used in 5 trials,[16–20] lixivaptan in 4 trials,[21–24] satavaptan in 3 trials,[25–27] and tolvaptan in 6 trials.[28–33] (Table 1 and Figure 1) There was 1 publication which included 2 trials and combined some results.[29] When the results were reported for the 2 trials collectively, we regarded them as 1 trial.

### Study Quality

Overall study quality scores were fair to good (Jadad score of 2–5, Table 1). Seventeen of the 18 trials were double-blind, randomized, controlled studies, and randomization procedures were adequately described in 3 trials.[21,22,31] One of the 18 trials was a prospective, multicenter, randomized, active-controlled, and open-label trial.[30] The mean attrition rate reported in 17 trials[16–21,23–33] was 30.84% and allocation concealment was reported in 8 trials.[17,20–22,26,27,29,30] Finally, the intention-to-treat principle was used in 8 trials.[16–18,20,23,25,27,33]

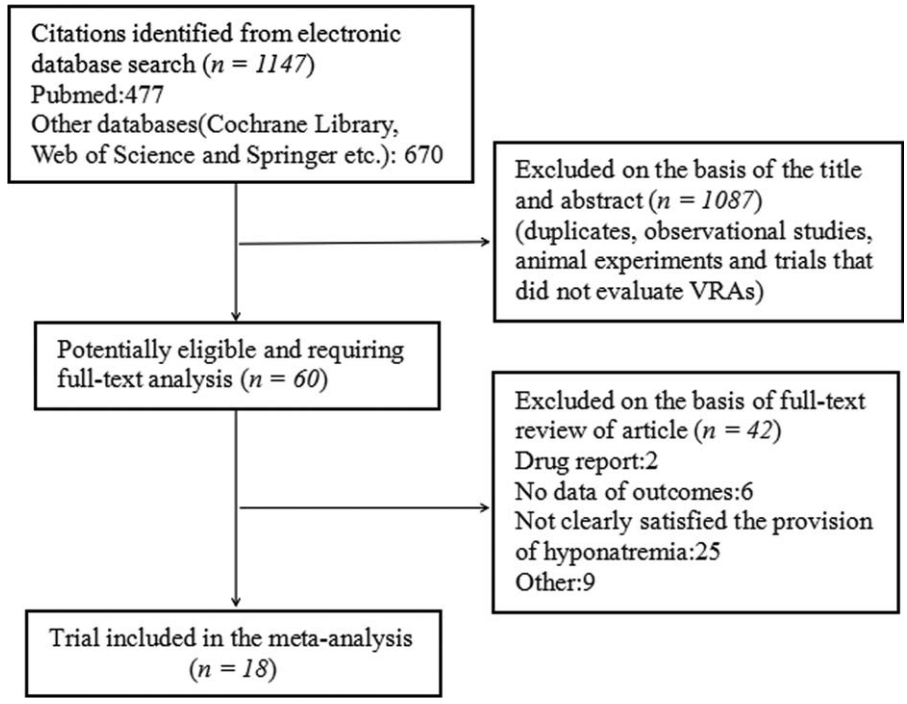


**FIGURE 1.** Flow diagram of the literature search and selection procedure.

## Effect of VRAs on Net Change of Serum Sodium Concentration

A total of 13 studies[16–20,22–24,27,28,30,31,33] including 30 comparisons of 1725 patients reported net changes of serum sodium concentration. Using random and fixed effect meta-analyses (Figure 2), we found that use of VRAs resulted in a significant net increase in serum sodium concentration relative to the control group ($WMD_{random} = 4.89$ mEq/L, 95%CIs = 4.35–5.43 and $WMD_{fixed} = 4.70$ mEq/L, 95%CIs = 4.45–4.95). The heterogeneity was significant ($I^2 = 67.2\%$). We found similar overall results after excluding each individual study. Egger regression analysis found no evidence of publication bias in the assessment ($P_{Egger} = 0.45$).

In subgroup analyses (Figure 2), net changes of serum sodium concentration were larger in each drug-treated group (conivaptan, $WMD_{random} = 5.43$ mEq/L, 95%CIs = 4.73–6.13 and $WMD_{fixed} = 4.86$ mEq/L, 95%CIs = 4.59–5.14, $I^2 = 75.7\%$, 5 trials;[16–20] lixivaptan, $WMD_{random} = 2.44$ mEq/L, 95%CIs = 1.24–3.64 and $WMD_{fixed} = 2.44$ mEq/L, 95%CIs = 1.24–3.64, $I^2 = 0\%$, 3 trials;[22–24] satavaptan, $WMD_{random} = 3.89$ mEq/L, 95%CIs = 2.52–5.26 and $WMD_{fixed} = 3.89$ mEq/L, 95%CIs = 2.61–5.16, $I^2 = 13.1\%$, 1 trial;[27] and tolvaptan, $WMD_{random} = 4.72$ mEq/L, 95%CIs = 3.78–5.66 and $WMD_{fixed} = 4.70$ mEq/L, 95%CIs = 3.87–5.52, $I^2 = 17.5\%$, 4 trials)[28,30,31,33] than those in the placebo-treated group. Furthermore, the largest net changes of serum sodium concentration were found in conivaptan-treated patients. Each of the included studies had its own definitions of fluid restriction; in most of the studies, daily fluid intake was limited to 1.0 to 2.5 L. Net changes in trials that restricted fluid intake ($WMD_{random} = 5.22$ mEq/L, 95%CIs = 4.63–5.80 and $WMD_{fixed} = 4.85$ mEq/L, 95%CIs = 4.58–5.11, $I^2 = 66.5\%$, 8 trials)[16,17,20,28,30,31,33] were larger than the changes in trials without fluid restriction ($WMD_{random} = 3.53$ mEq/L, 95%CIs = 2.42–4.65 and $WMD_{fixed} = 3.44$ mEq/L, 95%CIs = 2.65–4.23, $I^2 = 43.8\%$, 4 trials).[23,24,28,31] Compared with placebo-treated patients, net changes of serum sodium concentration were significantly larger in VRA-treated patients in trials assessing patients mostly with cirrhosis ($WMD_{random} = 3.88$ mEq/L, 95%CIs = 3.030–4.73, $I^2 = 17.8\%$, 3 trials)[22,27,31] and SIADH ($WMD_{random} = 5.56$ mEq/L, 95%CIs = 3.35–7.76, $I^2 = 0\%$, 1 trial).[28]

## Effect of VRAs on the Response Rate

A total of 16 studies,[16–20,22–31,33] including 23 comparisons of 2333 patients, reported the response rate of patients with hyponatremia. Variable definitions were used to characterize this endpoint, such as the proportion of patients who achieved a confirmed normal serum sodium level (≥135 mEq/L) or an increase of 6 mEq/L,[16–20] or who achieved a confirmed normal serum sodium level (≥135 mEq/L) or an increase of 5 mEq/L,[25–27] or who achieved a sodium level ≥135 mmol/L,[23,24,28–30] or who achieved a sodium level ≥136 mmol/L.[22,31] The results of random and fixed effect meta-analyses (Figure 3) proved that the administration of VRAs resulted in a significantly increased response rate compared to placebo ($RR_{random} = 2.77$, 95%CIs = 2.29–3.36 and $RR_{fixed} = 2.95$, 95%CIs = 2.56–3.41). There was no heterogeneity among the included studies ($I^2 = 33.5\%$). The result of Egger regression analysis proved that publication bias existed ($P_{Egger} < 0.001$). All 16 trials included showed a beneficial effect of the study drug (RR > 1) and varied in sample size; thus, the bias probably stemmed from different degrees of benefit and small-study effects.[34] Sensitivity analysis did not show a significant change in the results.

In subgroup analyses (Figure 3), the response rate was higher for each drug (conivaptan, $RR_{random} = 3.00$, 95%CIs = 1.74–5.16 and $RR_{fixed} = 3.11$, 95%CIs = 2.26–4.28, $I^2 = 56.5\%$, 5 trials;[16–20] lixivaptan, $RR_{random} = 2.70$,

**TABLE 1.** Characteristics of Eligible Studies Included in the Meta-Analysis

| Author | Year | Country | Concomitant Disease | Restrictions of Fluid Intake | Dose, mg | Baseline of Serum Sodium, Mean ± SD or Range, mEq/L | Age (Range/ SD), year | Male/ Female | Total | Course | Hyponatremia Type | Jadad Score | Allocation Concealment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ghali et al[16] | 2006 | United States, Canada, and Israel | COPD/malignancy/ idiopathic/HF/ other | ≤0.5 L/3 h or 2.0 L/24 h | Conivaptan, 40 mg, qd, p.o. | 125.3 ± 3.5 | 38.0–93.0 | 12/12 | 74 | 5d | Euvolemic/ hypervolemic | 4 | Unclear |
| | | | | | Conivaptan, 80 mg, qd, p.o. | 125.4 ± 4.0 | 35.0–90.0 | 14/13 | | | | | |
| | | | | | Placebo | 123.4 ± 4.1 | 41.0–94.0 | 10/13 | | | | | |
| Annane et al[17] | 2009 | Belgium, Finland, France, Germany, Italy, Spain, etc. | CHF/malignancy/ idiopathic/COPD/ postsurgical/other/ unknown | ≤0.5 L/3 h or 2.0 L/24 h | Conivaptan, 40 mg, qd, p.o. | 125.1 ± 5.1 | 61.5 ± 15.0 | 18/9 | 83 | 5d | Euvolemic/ hypervolemic | 4 | Adequate |
| | | | | | Conivaptan, 80 mg, qd, p.o. | 125.6 ± 3.6 | 63.2 ± 10.7 | 19/7 | | | | | |
| | | | | | Placebo | 125.6 ± 3.9 | 68.3 ± 12.7 | 18/12 | | | | | |
| Verbalis et al[18] | 2008 | United States | SIADH/idiopathic/ CHF/malignancy/ postsurgery/COPD/ other | ≤2.0 L/24 h | Conivaptan, 40 mg, qd, i.v. | 123.5 ± 4.3 | 74.3 ± 12.8 | 7/11 | 56 | 4d | Euvolemic | 4 | Unclear |
| | | | | | Conivaptan, 80 mg, qd, i.v. | 125.1 ± 3.1 | 74.1 ± 11.7 | 9/8 | | | | | |
| | | | | | Placebo | 124.4 ± 3.9 | 76.8 ± 12.5 | 9/12 | | | | | |
| Koren et al[19] | 2011 | North America, India | CHF/SIADH/ alcoholism/ nephrotic / hypertension/renal failure/unknown, etc. | ≤2.0 L/48 h | Conivaptan, 20 mg, qd, i.v. | 126.0 ± 4.0 | 126.0 ± 4.0 | 13/7 | 49 | 2d | Euvolemic/ hypervolemic | 4 | Unclear |
| | | | | | Conivaptan, 20 mg, bid, i.v. | 126.4 ± 3.6 | 126.4 ± 3.6 | 9/11 | | | | | |
| | | | | | Placebo | 125.5 ± 3.7 | 125.5 ± 3.7 | 1/8 | | | | | |
| Zeltser et al[20] | 2007 | Israel, Columbia, United States, South Africa | CHF/SIADH/ idiopathic/COPD/ other | ≤2.0 L/24 h | Conivaptan, 40 mg,qd, i.v. | 123.3 ± 84.7 | 73.8 ± 11.5 | 12/17 | 84 | 4d | Euvolemic/ hypervolemic | 4 | Adequate |
| | | | | | Conivaptan, 80 mg, qd, i.v. | 124.8 ± 83.4 | 72.5 ± 13.8 | 14/12 | | | | | |
| | | | | | Placebo | 124.3 ± 84.0 | 75.7 ± 1.6 | 15/14 | | | | | |
| Wong et al[21] | 2003 | Canada | Cirrhosis/CHF/SIADH | 1.5–2.5 L, according to previous 24 h urinary outputs | VPA-985, 25 mg, bid, p.o. | 126.0 ± 0.4 | 48.1 ± 3.2 | 5/7 | 44 | 7d | Euvolemic/ hypervolemic | 5 | Adequate |
| | | | | | VPA-985, 125 mg, bid, p.o. | 121.0 ± 1.0 | 54.8 ± 4.0 | 8/3 | | | | | |
| | | | | | VPA-98, 250 mg, bid, p.o. | 126.0 ± 1.0 | 51.3 ± 3.3 | 8/2 | | | | | |
| | | | | | Placebo | 127.0 ± 1.0 | 51.5 ± 2.9 | 10/1 | | | | | |
| Gerbes et al[22] | 2003 | Germany, Spain, Belgium, France | Cirrhosis | 1.0 L/24 h | VPA-985, 100 mg, bid, p.o. | 128.0 ± 1.0 | 54.0 ± 3.0 | 15/5 | 60 | 7d | Hypervolemic | 4 | Adequate |
| | | | | | VPA-985, 200 mg, bid, p.o. | 127.0 ± 1.0 | 56.0 ± 3.0 | 17/5 | | | | | |
| | | | | | Placebo | 127.0 ± 1.0 | 58.0 ± 2.0 | 14/4 | | | | | |

| Author | Year | Country | Concomitant Disease | Restrictions of Fluid Intake | Dose, mg | Baseline of Serum Sodium, Mean ± SD or Range, mEq/L | Age (Range/ SD), year | Male/ Female | Total | Course | Hyponatremia Type | Jadad Score | Allocation Concealment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abraham et al[23] | 2012 | USA, India, Europe, Israel | Lung cancer/HIV infection/ Guillain–Barre syndrome/other, but no SIADH | Unclear | Lixivaptan, 25–100 mg, qd, p.o. | 129.7 ± 4.4 | 66.6 ± 14.1 | 73/81 | 206 | 7d | Euvolemic | 4 | Unclear |
| | | | | | Placebo | 129.9 ± 4.3 | 62.7 ± 13.6 | 27/25 | | | | | |
| Abraham et al[24] | 2012 | North America, Europe, Asia | SIADH/other | Unclear | Lixivaptan, 25–100 mg, qd, p.o. | 124.7 ± 5.2 | 66.4 ± 14.1 | 26/28 | 106 | 7d | Euvolemic | 4 | Unclear |
| | | | | | Placebo | 124.1 ± 5.4 | 65.2 ± 13.3 | 30/22 | | | | | |
| Aronson et al[25] | 2011 | Europe, America, Israel, Australia | CHF/postoperative/ other | 1.0–1.5 L/24 h | Satavaptan, 25 mg, qd, p.o. | 127.6 ± 3.8 | 68.6 ± 15.8 | 16/19 | 118 | 4d | Hypervolemic | 4 | Unclear |
| | | | | | Satavaptan, 50 mg, qd, p.o. | 127.9 ± 3.8 | 70.8 ± 11.7 | 25/16 | | | | | |
| | | | | | Placebo | 128.5 ± 3.2 | 68.8 ± 11.3 | 27/15 | | | | | |
| Soupart et al[26] | 2006 | Belgium, France, Germany, Hungary | SIADH | 1.5 L/24 h | Satavaptan, 25 mg, qd, p.o. | 125.0 ± 6.0 | 71.1 ± 10.8 | 7/7 | 35 | 5d | Euvolemic | 4 | Adequate |
| | | | | | Satavaptan, 50 mg, qd, p.o. | 127.0 ± 5.0 | 68.9 ± 14.0 | 4/8 | | | | | |
| | | | | | Placebo | 126.0 ± 3.0 | 62.0 ± 18.9 | 2/7 | | | | | |
| Gines et al[27] | 2008 | Spain, Canada, Romania, Croatia, France | Cirrhosis | 1.5 L/24 h | Satavaptan, 5 mg, qd, p.o. | 127.0 ± 5.0 | 57.0 ± 8.0 | 16/12 | 110 | 14d | Hypervolemic | 5 | Adequate |
| | | | | | Satavaptan, 12.5 mg, qd, p.o. | 128.0 ± 4.0 | 56.0 ± 9.0 | 19/7 | | | | | |
| | | | | | Satavaptan, 25 mg,qd, p.o. | 126.0 ± 6.0 | 59.0 ± 10.0 | 20/8 | | | | | |
| | | | | | Placebo | 126.0 ± 4.0 | 55.0 ± 10.0 | 22/6 | | | | | |
| Chen et al[28] | 2014 | China | SIADH | Unclear | Tolvaptan, 15–60 mg, qd, p.o. | 127.1 ± 4.9 | 62.8 ± 14.2 | 10/11 | 45 | 7d | Euvolemic/ hypervolemic | 4 | Unclear |
| | | | | | Placebo | 125.3 ± 6.2 | 61.4 ± 12.8 | 15/9 | | | | | |
| Schrier et al[29] | 2006 | United States | Cirrhosis/CHF/ SIADH/other | Unclear | Tolvaptan, 15–60 mg, qd, p.o. | 128.7 ± 4.5 | 60.0 ± 14.0 | 52/50 | 205 | 30d | Euvolemic/ hypervolemic | 4 | Adequate |
| | | | | | Placebo | 128.8 ± 4.1 | 60.0 ± 13.0 | 62/41 | | | | | |
| Schrier et al[29] | 2006 | United States | Cirrhosis/CHF/ SIADH/other | Unclear | Tolvaptan, 15–60 mg, qd, p.o. | 129.5 ± 3.5 | 62.0 ± 15.0 | 75/48 | 243 | 30d | Euvolemic/ hypervolemic | 4 | Adequate |
| | | | | | Placebo | 129.1 ± 4.5 | 63.0 ± 14.0 | 73/47 | | | | | |
| Gheorghiade et al[30] | 2006 | United States | HF/liver cirrhosis/ SIADH | 1.2 L/24 h in placebo group | Tolvaptan, 10–60 mg, qd, p.o. | 129.0 ± 3.0 | 66.0 ± 13.0 | 10/7 | 28 | 27d | Euvolemic/ hypervolemic | 2 | Adequate |
| | | | | | Placebo | 129.0 ± 4.0 | 67.0 ± 9.0 | 6/5 | | | | | |
| Cárdenas et al[31] | 2011 | United States | Cirrhosis | Unclear | Tolvaptan, 15–60 mg, qd, p.o. | 128.8 ± 4.3 | 52.0 ± 8.0 | 50/13 | 120 | 30d | Euvolemic/ hypervolemic | 5 | Unclear |
| | | | | | Placebo | 128.6 ± 4.4 | 55.0 ± 9.0 | 38/19 | | | | | |
| Verbalis et al[32] | 2011 | United States | SIADH | Unclear | Tolvaptan, 15–60 mg, qd, p.o. | NA | 64.0 ± 15.0 | NA | 110 | 30d | Euvolemic/ hypervolemic | 4 | Unclear |
| | | | | | Placebo | NA | 65.0 ± 14.0 | NA | | | | | |
| Salahudeen et al[33] | 2013 | United States | Cancer | 1.5 L/24 h | Tolvaptan, 15–60 mg, qd, p.o. | 125.0–130.0 | 52.0–81.0 | 9/8 | 30 | 14d | Euvolemic/ hypervolemic | 4 | Unclear |
| | | | | | Placebo | 126.0–130.0 | 36.0–60.0 | 7/6 | | | | | |

CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, HF = heart failure, HIV = human immunodeficiency virus, NA = not available, SD = standard deviation, SIADH = inappropriate release of arginine vasopressin.

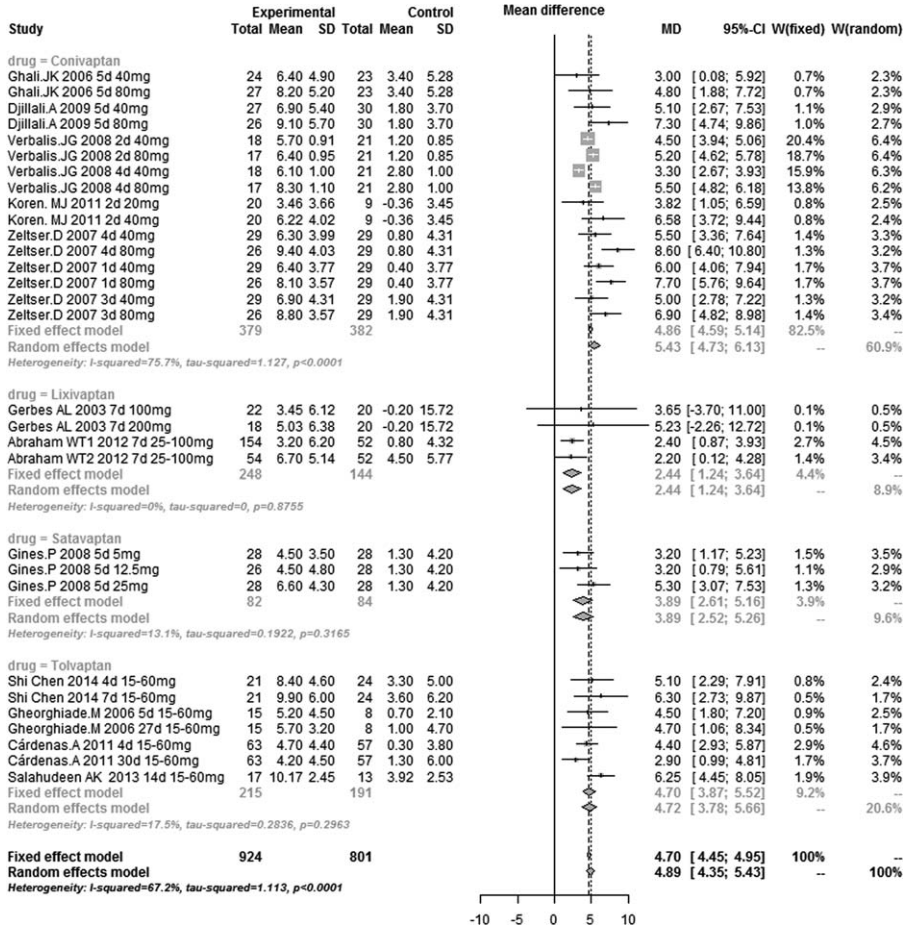


**FIGURE 2.** Meta-analysis of randomized trials comparing the effect of vasopressin receptor antagonists versus placebo on net change of serum sodium concentration of patients with hyponatremia.

95%CIs = 1.34–5.43 and $RR_{fixed} = 2.88$, 95%CIs = 1.80–4.61, $I^2 = 40.8\%$, 3 trials;[22–24] satavaptan, $RR_{random} = 2.54$, 95%CIs = 1.77–3.65 and $RR_{fixed} = 2.70$, 95%CIs = 1.87–3.91, $I^2 = 0\%$, 3 trials;[25–27] and tolvaptan, $RR_{random} = 2.93$, 95%CIs = 2.17–3.96 and $RR_{fixed} = 2.99$, 95%CIs = 2.46–3.63, $I^2 = 45.6\%$, 5 trials)[28–31,33] than for placebo. The response rate in trials of euvolemic hyponatremia was significantly higher than in trials of hypervolemic and euvolemic/hypervolemic hyponatremia ($RR_{fixed}$, 3.08 vs 2.79 vs 2.96). The response rate in trials that restricted fluid intake ($RR_{random} = 2.86$, 95%CIs = 2.09–3.91 and $RR_{fixed} = 3.12$, 95%CIs = 2.47–3.93, $I^2 = 36.6\%$, 11 trials)[16–20,22,25–27] was higher than in trials without fluid restriction ($RR_{random} = 2.77$, 95%CIs = 2.15–3.58 and $RR_{fixed} = 2.84$, 95%CIs = 2.36–3.42, $I^2 = 39.1\%$, 5 trials).[23,24,28,29,31] In addition, the response rate was also higher in VRA-treated patients than that in placebo-treated patients of trials assessing mostly patients with cirrhosis ($RR_{random} = 2.70$, 95%CIs = 1.80–4.05 and $RR_{fixed} = 2.91$, 95%CIs = 2.04–4.16, $I^2 = 17.8\%$, 3 trials)[22,27,31] and SIADH ($RR_{random} = 6.00$, 95%CIs = 2.44–14.76 and $RR_{fixed} = 6.61$, 95%CIs = 2.64–16.58, $I^2 = 0\%$, 2 trials).[26,28]

## Effect of VRAs on Net Change in Body Weight

A total of 4 studies,[17,18,26,27] including 13 comparisons of 576 patients, reported net changes in body weight of patients with hyponatremia. By random and fixed effect meta-analyses (Figure 4), the use of VRAs resulted in a significant net decrease in body weight relative to the control group ($WMD_{random} = -0.87$ kg, 95%CIs = −1.24 to −0.49 and $WMD_{fixed} = -0.91$ kg, 95%CIs = −1.22 to −0.59). There was no significant heterogeneity ($I^2 = 17.3\%$) or publication bias in the assessments ($P_{Egger} = 0.69$). Sensitivity analysis did not show any significant change.

## Effect of VRAs on 24-hour Urine Output

A total of 6 studies,[18,27–30,32] including 12 comparisons of 945 patients, reported 24-hour urine output of patients with hyponatremia. By random and fixed effects meta-analyses (Figure 5), the use of VRAs resulted in a significant net increase in 24-hour urine output relative to the control group ($SMD_{random} = 0.82$, 95%CIs = 0.65–1.00 and $SMD_{fixed} = 0.79$, 0.79, 95%CIs = 0.66–0.93). The tests for heterogeneity were not significant ($I^2 = 27.9\%$). Egger regression analysis found no evidence of publication bias in the assessment ($P_{Egger} = 0.24$). Sensitivity analysis did not show any change in the result.

## Safety Analysis of VRAs

As shown in Table 2 and Figure 6, there were no differences between VRAs and control groups regarding the total

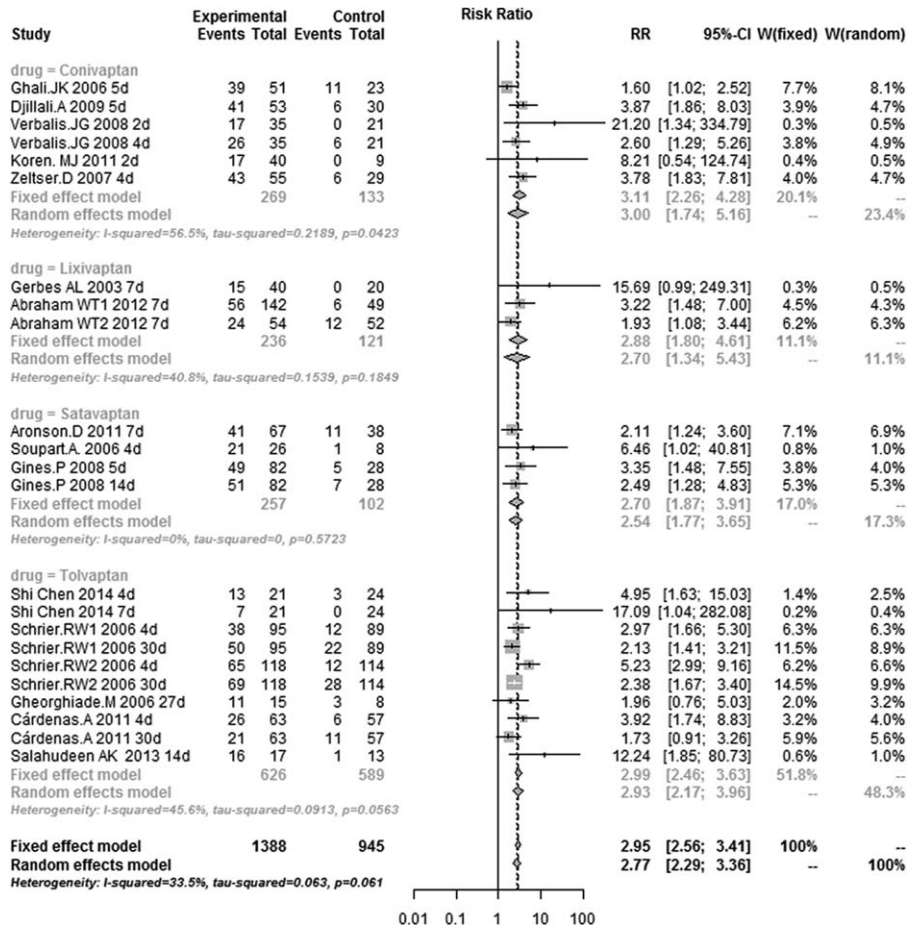


**FIGURE 3.** Meta-analysis of randomized trials comparing the effect of vasopressin receptor antagonists versus placebo on the response rate of patients with hyponatremia.

number of AEs ($RR_{fixed} = 1.03$, 95%CIs = 0.96–1.10, $I^2 = 0\%$, $P_{Egger} = 0.42$),[19,23–29,31] discontinuations due to AEs ($RR_{fixed} = 0.91$, 95%CIs = 0.67–1.24, $I^2 = 5\%$, $P_{Egger} = 0.35$),[16–20,22–25,28,29,31,32] serious AEs ($RR_{fixed} = 0.92$, 95%CIs = 0.76–1.12, $I^2 = 0\%$, $P_{Egger} = 0.55$),[16–20,23–29,31,32] or death ($RR_{fixed} = 0.97$, 95%CIs = 0.68–1.40, $I^2 = 17\%$, $P_{Egger} = 0.07$).[16–20,23,24,28,29,31–33] The use of VRAs was associated with 0.78-fold decreased odds of discontinuations ($RR_{fixed} = 0.78$, 95%CIs = 0.65–0.94, $I^2 = 10.2\%$, $P_{Egger} = 0.76$)[16–21,23–33] and 1.64-fold increased odds of drug-related AEs in the control group ($RR_{fixed} = 1.64$, 95%CIs = 1.33–2.02, $I^2 = 0\%$, $P_{Egger} = 0.46$).[16–18,20,22,28,29]

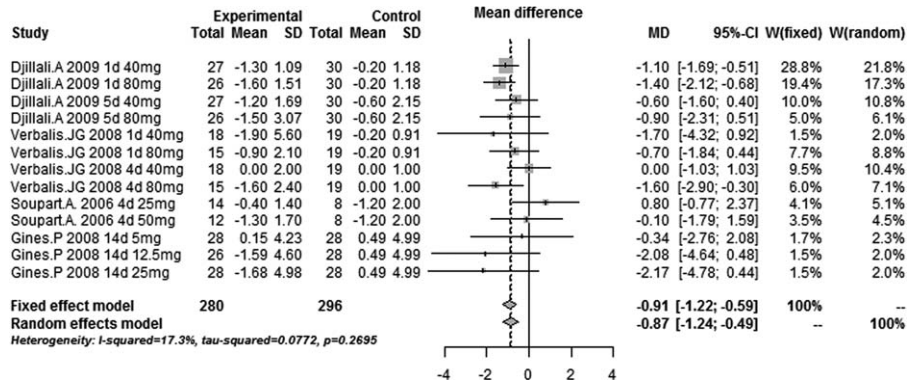


**FIGURE 4.** Meta-analysis of randomized trials comparing the effect of vasopressin receptor antagonists versus placebo on net change in body weight of patients with hyponatremia.

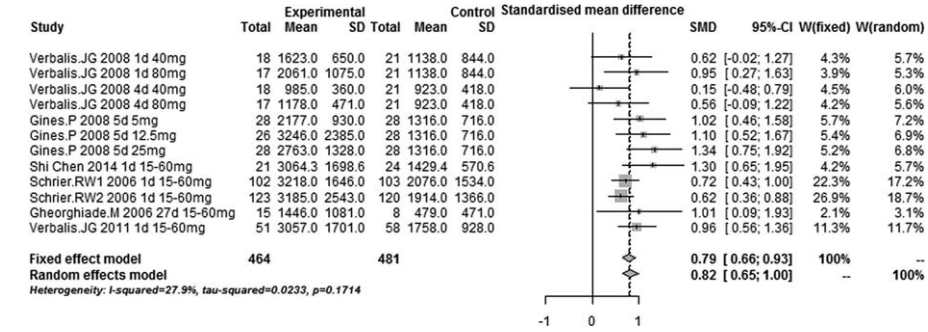


**FIGURE 5.** Meta-analysis of randomized controlled trials comparing the effect of vasopressin receptor antagonists versus placebo on 24-hour urine output of patients with hyponatremia.

The common AEs occurring during the studies were overly rapid correction of hyponatremia,[16–21,24–27,29,32] constipation,[16,19,24,29,32] dry mouth,[24,28,29,32] thirst,[27,29,32] phlebitis,[18–20] headache,[16,23,24,29,32] hypotension,[16–20,24,25,29,32] nausea,[16,19,23,24,29,32] anemia,[17–19,23] hypernatremia,[23,24,26,27] urinary tract infection,[17,19,23,24,26,29] renal failure,[18,20,22,29,31] pyrexia,[17,20,24,25] upper gastrointestinal bleeding,[22,31] diarrhea,[18,23,24,29,32] vomiting,[19,23,24,26,29,32] peripheral edema, and dizziness.[23,24,29,32] A total of 12 studies including 1300 patients reported overly rapid correction of serum sodium; in these studies, the authors used variable definitions to characterize the endpoint, with the serum sodium correction rate ranging from >8 mEq/L over 8 hours on the 1st day of therapy, or >12 mEq/L in 24 hours[29] to >12 mEq/L in 1 day or >24 mEq/L in total.[18] The results of the meta-analysis showed a significant increase in the rate of rapid sodium correction in the VRA-treated group without significant heterogeneity ($RR_{fixed} = 2.56$, 95%CIs = 1.45–4.53, $I^2 = 0\%$, $P_{Egger} < 0.05$), especially in patients with SIADH ($RR_{fixed} = 8.05$, 95%CIs = 1.07–60.53, $I^2 = 0\%$, 2 trials).[26,32] Moreover, in the VRA-treated group, more patients developed constipation ($RD_{fixed} = 0.06$, 95%CIs = 0.02–0.09, $I^2 = 0\%$, $P_{Egger} = 0.38$), dry mouth ($RD_{fixed} = 0.08$, 95%CIs = 0.04–0.13, $I^2 = 0\%$, $P_{Egger} = 0.76$), thirst ($RD_{fixed} = 0.10$, 95%CIs = 0.05–0.14, $I^2 = 0\%$, $P_{Egger} = 0.50$), and phlebitis ($RD_{fixed} = 0.13$, 95%CIs = 0.04–0.23, $I^2 = 38.1\%$, $P_{Egger} = 0.11$) than those in the control group. However, no significant difference was found between the 2 groups with regard to headache, hypotension, nausea, anemia, hypernatremia, urinary tract infection, renal failure, pyrexia, upper gastrointestinal bleeding, diarrhea, vomiting, peripheral edema, and dizziness (Table 2).

Effects of VRAs on osmolality, blood pressure, and serum potassium concentration were also taken into account in this meta-analysis. As shown in Table 3, changes in urine osmolality and serum osmolality, reported in 5 trials[16,17,20,27,30] including 10 comparisons (512 patients), showed a considerably larger change with VRAs than placebo (urine osmolality, $WMD_{random} = -233.07$ mOsmol/kg, 95%CIs = −298.20 to −147.94, $I^2 = 87.7\%$, $P_{Egger} = 0.07$; serum osmolality, $WMD_{random} = 9.29$ mOsmol/kg, 95%CIs = 5.56–13.03, $I^2 = 79.1\%$, $P_{Egger} = 0.15$). Changes in supine systolic blood pressure and supine diastolic blood pressure from baseline were reported in 6 trials[16–18,20,26,27] including 20 comparisons (986 patients). Meta-analysis of 20 comparisons showed that both supine systolic blood pressure and supine diastolic blood pressure were lowered after VRA treatment (supine systolic blood pressure, $WMD_{random} = -6.11$ mmHg, 95%CIs = −9.81 to −2.41, $I^2 = 63.4\%$, $P_{Egger} < 0.05$; supine diastolic blood pressure, $WMD_{random} = -2.59$ mmHg, 95%CIs = −4.06 to −1.11, $I^2 = 6.5\%$, $P_{Egger} = 0.51$). There was no significant change from baseline in serum potassium concentration between groups ($WMD_{random} = 0.00$ mmHg, 95%CIs = −0.07–0.07, $I^2 = 12.1\%$, $P_{Egger} = 0.75$, 6 trials).[16–18,20,26,27]

## DISCUSSION

The aim of this meta-analysis of 18 trials was to present the most comprehensive evaluation to date of the clinical efficacy and safety of VRAs in patients with euvolemic or hypervolemic hyponatremia. The results confirmed that the serum sodium concentration, the response rate, and 24-hour urine output were significantly increased, while the body weight of patients was significantly decreased by the VRAs regimen. These effects do not depend on the specific drug that was used, the type of hyponatremia, or whether fluid intake was restricted. Correspondingly, VRAs significantly increase the possibility of drug-related AEs, including a rapid rate of rapid sodium level correction, constipation, dry mouth, thirst, and phlebitis. The urine osmolality and supine systolic and diastolic blood pressure were decreased, while the serum osmolality was elevated; these changes might result from the aquaretic effect of VRAs. Concerning the change in serum potassium concentration, however, no significant difference existed between the VRA-treated group and the control group.

It is well known that in contrast to conventional diuretic agents, which block distal tubule sodium transporters and cause simultaneous loss of electrolytes and water, VRAs produce a solute-sparing water excretion, due to their antagonizing effect on the vasopressin $V_2$ receptors which are located only on the principal cells of the tubules.[35–37] Therefore, the increases in serum sodium concentration and 24-hour urine output, or the decreases in body weight in patients, have been viewed as primary indicators of the pharmacodynamic action of VRAs. Our study provides more convincing evidence than the previous reports,[38,39] by summarizing large amounts of clinical data and including meticulous subgroup analyses. We found that VRAs were definitely effective since they could induce meaningful increases in serum sodium concentration and response rate (defined as normalization of serum sodium level) in patients. The effect seemed more significant when each VRA was assessed separately. VRAs also exerted statistically significant effects in both fluid-restricted groups and fluid-unrestricted groups, although their effects seemed much stronger in groups where the fluid intake was restricted. In particular, the response

**TABLE 2.** Safety Analysis of Vasopressin Receptor Antagonists

| Outcome Index | No. Trials (Patients) | RR (95% CI) Random Effects Model | RR (95% CI) Fixed Effects Model | $I^2$, % | *P* (Egger) | RD (95% CI) Random Effects Model | RD (95% CI) Fixed Effects Model | $I^2$, % | *P* (Egger) |
|---|---|---|---|---|---|---|---|---|---|
| ADR | 10 (1229) | 1.04 (0.98,1.11) | 1.03 (0.96,1.10) | 0 | 0.4169 | 0.03 (−0.02,0.07) | 0.02 (−0.03,0.07) | 0 | 0.3243 |
| DCT | 18 (1752) | 0.78 (0.63,0.96) | 0.78 (0.65,0.94) | 10.2 | 0.7586 | 0.05 (−0.09,−0.00) | −0.05 (−0.09,−0.01) | 28.5 | 0.508 |
| DAE | 14 (1557) | 0.87 (0.62,1.22) | 0.91 (0.67,1.24) | 5 | 0.3469 | 0.00 (−0.03,0.03) | −0.01 (−0.04,0.02) | 23.9 | 0.8724 |
| SAE | 15 (1636) | 0.94 (0.77,1.14) | 0.92 (0.76,1.12) | 0 | 0.5471 | −0.02 (−0.06,0.02) | −0.02 (−0.05,0.01) | 0 | 0.4203 |
| DEA | 12 (1317) | 0.94 (0.59,1.50) | 0.97 (0.68,1.40) | 17 | 0.0670 | −0.01 (−0.04,0.02) | 0.00 (−0.03,0.03) | 24.9 | 0.4104 |
| DRE | 8 (845) | 1.61 (1.30,1.98) | 1.64 (1.33,2.02) | 0 | 0.4638 | 0.15 (0.06,0.25) | 0.15 (0.09,0.21) | 58.2 | 0.1239 |
| Common adverse events | | | | | | | | | |
| Overly rapid correction of hyponatremia | 12 (1300) | 1.95 (1.06,3.58) | 2.56 (1.45,4.53) | 0 | 0.0085 | 0.06 (0.02,010) | 0.05 (0.03,0.07) | 12.3 | 0.0231 |
| Constipation | 5 (776) | 2.57 (1.33,4.96) | 2.67 (1.39,5.12) | 0 | 0.5924 | 0.05 (0.02,0.09) | 0.06 (0.02,0.09) | 0 | 0.3766 |
| Dry mouth | 4 (698) | 2.27 (1.41,3.66) | 2.34 (1.46,3.77) | 0 | 0.4599 | 0.08 (0.03,0.12) | 0.08 (0.04,0.13) | 0 | 0.7626 |
| Thirst | 3 (662) | 2.83 (1.63,4.89) | 2.89 (1.67,5.01) | 0 | 0.9712 | 0.10 (0.05,0.14) | 0.10 (0.05,0.14) | 0 | 0.4999 |
| Phlebitis* | 3 (189) | 2.97 (1.00,8.83) | 3.14 (1.08,9.16) | 0 | 0.2008 | 0.11 (0.00,0.22) | 0.13 (0.04,0.23) | 38.1 | 0.1139 |
| Headache | 5 (932) | 0.90 (0.58,1.40) | 0.91 (0.59,1.41) | 0 | 0.9355 | −0.01 (−0.04,0.03) | −0.01 (−0.04,0.03) | 0 | 0.9117 |
| Hypotension | 9 (1121) | 1.07 (0.66,1.75) | 1.11 (0.69,1.78) | 0 | 0.9374 | 0.01 (−0.02,0.03) | 0.01 (−0.02,0.04) | 0 | 0.9702 |
| Nausea | 6 (981) | 1.08 (0.69,1.70) | 1.11 (0.71,1.74) | 0 | 0.7576 | 0.02 (−0.02,0.05) | 0.01 (−0.03,0.04) | 0 | 0.8975 |
| Anemia | 4 (393) | 0.61 (0.26,1.45) | 0.62 (0.26,1.47) | 0 | 0.1328 | −0.02 (−0.07,0.03) | −0.03 (−0.08,0.03) | 0 | 0.7062 |
| Hypernatremia | 4 (450) | 1.50 (0.42,5.44) | 1.53 (0.43,5.49) | 0 | 0.5781 | 0.01 (−0.02,0.04) | 0.02 (−0.02,0.05) | 0 | 0.0861 |
| Urinary tract infection | 6 (916) | 1.26 (0.51,3.09) | 1.40 (0.80,2.43) | 40.5 | 0.9466 | 0.03 (−0.03,0.09) | 0.02 (−0.01,0.05) | 57.9 | 0.8295 |
| Renal failure | 5 (763) | 1.03 (0.38,2.77) | 1.00 (0.42,2.37) | 0 | 0.7613 | 0.00 (−0.04,0.04) | 0.00 (−0.02,0.02) | 36.5 | 0.5995 |
| Pyrexia | 4 (390) | 1.73 (0.51,5.82) | 2.10 (0.68,6.46) | 0 | 0.0435 | 0.03 (0.00,0.07) | 0.03 (0.00,0.07) | 12.8 | 0.7183 |
| Upper gastrointestinal bleeding | 2 (180) | 3.32 (0.75,14.73) | 3.51 (0.82,15.01) | 0 | NA | 0.07 (0.00,0.14) | 0.07 (0.00,0.14) | 0 | NA |
| Diarrhea | 5 (914) | 0.90 (0.52,1.54) | 0.94 (0.55,1.58) | 0 | 0.6764 | 0.00 (−0.04,0.04) | 0.00 (−0.04,0.03) | 14.7 | 0.7548 |
| Vomit | 6 (942) | 0.48 (0.27,0.88) | 0.47 (0.26,0.84) | 0 | 0.2818 | −0.04 (−0.07,−0.01) | −0.04 (−0.07,−0.01) | 0 | 0.0416 |
| Peripheral edema | 4 (858) | 1.02 (0.63,1.66) | 1.03 (0.63,1.66 | 0 | 0.6683 | 0.00 (−0.03,0.04) | 0.00 (−0.03,0.04) | 0 | 0.9131 |
| Dizziness | 4 (858) | 1.32 (0.60,2.88) | 1.35 (0.78,2.34) | 33.1 | 0.6645 | 0.02 (−0.02,0.07) | 0.02 (−0.01,0.05) | 39.6 | 0.9828 |

ADR = overall adverse events, CI = confidence interval, DAE = discontinuations due to adverse events, DCT = discontinuations, DEA = death, DRE = drug-related adverse events, SAE = serious adverse events.

*Specific to intravenous conivaptan, NA = number of studies (k = 2) too small to test for small study effects.

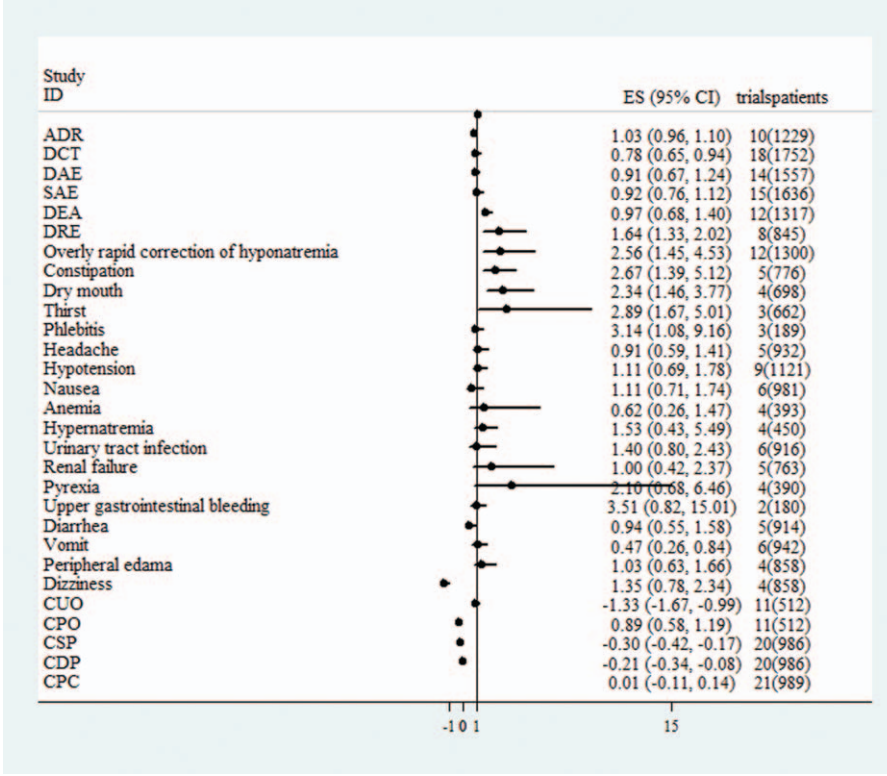


**FIGURE 6.** Random effects meta-analysis of vasopressin receptor antagonists versus placebo for safety. ADR = overall adverse events, CDP = change from baseline in supine diastolic blood pressure, CPC = change from baseline in serum potassium concentration, CPO = change from baseline in plasma osmolality, CSP = change from baseline in supine systolic blood pressure, CUO = change from baseline in urine osmolality, DAE = discontinuations due to adverse events, DCT = discontinuations, DEA = death, DRE = drug-related adverse events, SAE = serious adverse events, trials (patients) = the number of included studies and included patients.

rate to VRAs was significantly higher in patients with euvolemic hyponatremia (i.e., SIADH) than in patients with hypervolemic (i.e., heart failure, cirrhosis) and euvolemic/hypervolemic hyponatremia. The high response rate in patients with SIADH has been reported previously and is believed to be possibly related to the increased glomerular filtration rate and decreased proximal sodium reabsorption, which caused good free-water clearance, even in absence of arginine vasopressin.[38,39] However, this explanation needs to be further verified with more experimental or clinical data. It should be noted that around 15% of patients with SIADH do not significantly increase their serum sodium concentration when treated with VRAs.[40] Gain-of-function mutations in the vasopressin $V_2$ receptor of patients with SIADH[40–42] and resetting of osmosis could explain this nonresponsive behavior.[40]

Our meta-analysis suggested the administration of VRAs is associated with an increased occurrence rate of drug-related AEs, such as dry mouth, thirst, phlebitis, and overly rapid sodium level correction, etc. However, VRAs were generally well tolerated, since the side effects were mostly consistent with the physiological activity of the drugs. Dry mouth and thirst occurred significantly and frequently in patients treated with VRAs, which might theoretically be associated with the expected physiological response to an increase in plasma osmolality secondary to high urine volumes. These high urine volumes should probably be avoided by reducing the dose of the drug in clinical practice. The daily fluid intake was limited to 1.0 to 2.5 L in most of the trials, which would increase the risk of overly rapid correction of serum sodium and development of hypernatremia. As expected, our study showed a more frequent occurrence of excessive correction of serum sodium in the VRA-treated groups, especially in patients with SIADH. According to current clinical guidelines, in the treatment of chronic hyponatremia, a slow correction rate of 4 to 8 mmol/L/day in normal-risk patients, or 4 to 6 mmol/L/day in high-risk patients, is the recommended procedure to avoid the risk of osmotic demyelination.[43] Despite the fact that overall neurologic side effects were occasionally reported, no cases of osmotic demyelination syndrome were reported in the studies included in our meta-analysis. Nonetheless, it is prudent for clinicians to remain vigilant when using VRAs to treat patients with chronic hyponatremia, especially in patients with fluid intake limitation. Significantly more patients in the conivaptan-treated groups experienced phlebitis than in the placebo group, although most of the cases of phlebitis were rated mild or moderate. Koren et al[19] indicated that a simplified regimen, in which conivaptan was administered once or twice daily via 30-minute intravenous infusion, might reduce the incidence of infusion-site phlebitis when compared with placebo. However, a direct comparison study might be required to further confirm this finding. Compared with the placebo, VRAs were associated with greater but clinically unimportant changes in supine systolic and diastolic blood pressure on day 1, day 4, and day 5. The incidence of other AEs, including changes in serum

**TABLE 3.** Effects of VRAs on Osmolality, Blood Pressure, Serum Potassium Concentration

| Outcome Index | No.Trials (Patients) | WMD (95% CI) | | | | SMD (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Random Effects Model | Fixed Effects Model | $I^2$, % | *P* (Egger) | Random Effects Model | Fixed Effects Model | $I^2$, % | *P* (Egger) |
| CUO | 11 (512) | −233.07 (−298.20,−147.94) | −193.64 (−219.35,−167.93) | 87.7 | 0.0739 | −1.33 (−1.67,−0.99) | −1.30 (−1.50,−1.11) | 66 | 0.4088 |
| CPO | 11 (512) | 9.29 (5.56,13.03) | 8.34 (6.68,10.01) | 79.1 | 0.1452 | 0.89 (0.58,1.19) | 0.88 (0.70,1.07) | 62.8 | 0.9314 |
| CSP | 20 (986) | −6.11 (−9.81,−2.41) | −5.06 (−7.26,−2.86) | 63.4 | 0.0073 | −0.30 (−0.42,−0.17) | −0.32 (−0.52,−0.13) | 57.1 | 0.0380 |
| CDP | 20 (986) | −2.59 (−4.06,−1.11) | −2.57 (−3.99,−1.15) | 6.5 | 0.5137 | −0.21 (−0.34,−0.08) | −0.21 (−0.34,−0.08) | 2.6 | 0.0276 |
| CPC | 21 (989) | 0.00 (−0.07,0.07) | 0.00 (−0.07,0.06) | 12.1 | 0.7471 | 0.01 (−0.12,0.14) | 0.01 (−0.11,0.14) | 2.8 | 0.3187 |

CDP = supine diastolic blood pressure, CPC = change from baseline in serum potassium concentration, CPO = change from baseline in plasma osmolality, CSP = change from baseline in supine systolic blood pressure, CUO = change from baseline in urine osmolality.

potassium concentration, did not differ significantly between the 2 groups.

Our meta-analysis systematically evaluated the clinical efficacy and possible safety of VRAs in patients with euvolemic or hypervolemic hyponatremia, but there were still several limitations. First, long-term (>30 days) and clinical outcome data are too scarce for a meta-analysis to be fully implemented at the present time. However, several studies reporting the results of trials evaluating the efficacy of VRAs at 27 to 30 days[26,29–31] and of open-label trials spanning 1 to 4 years[26,44] indicate the long-term and continued efficacy of VRAs. Also, VRAs have been reported to shorten the length of hospital stay for patients with severe hyponatremia, and to improve their physical and mental condition, perhaps even including cognitive function.[23,32] Thus, as more and more long-term and clinical outcome data become available, a dedicated analysis would be helpful. Second, the exclusion of trials published as abstracts might increase the risk of publication bias. Third, mostly potential sources of heterogeneity has been identified by subgroup and sensitivity analyses, but some residual heterogeneity still existed in this meta-analysis, which might originated from the study size, variations in populations, and conventional interventions, etc.

In summary, the present paper convincingly suggests that VRAs are relatively effective and safe for the treatment of hypervolemic and euvolemic hyponatremia, and also provides a scientific and quantitative basis to guide clinicians in the clinical use of VRAs.

## ACKNOWLEDGMENTS

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