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REVIEW ARTICLE

A systematic review of known interventions for the treatment of chronic nonhypovolaemic hypotonic hyponatraemia and a meta-analysis of the vaptans

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Abstract

International and national guidelines on the treatment of chronic nonhypovolaemic hypotonic hyponatraemia differ; therefore, we have undertaken this systematic review and meta-analysis to investigate the efficacy and safety of interventions for the treatment of chronic nonhypovolaemic hypotonic hyponatraemia. Following registration of the review protocol with PROSPERO, systematic literature searches were conducted to identify randomized and quasi-randomized controlled trials assessing any degree of fluid restriction or any drug treatment with the aim of increasing serum sodium concentration in patients with chronic nonhypovolaemic hypotonic hyponatraemia. Where appropriate, outcome data were synthesized in a meta-analysis. A total of 45 716 bibliographic records were identified from the searches and 18 trials (assessing conivaptan, lixivaptan, tolvaptan and satavaptan) met the eligibility criteria. Results suggest that all four vasopressin receptor agonists ("vaptans") significantly improve serum sodium concentration. Lixivaptan, satavaptan and tolvaptan were associated with greater rates of response versus placebo. There was no evidence of a difference between each of the vaptans compared with placebo for mortality, discontinuation and rates of hypernatraemia. No RCT evidence of treatments other than the vaptans for hyponatraemia such as oral urea, salt tablets, mannitol, loop diuretics demeclocycline or lithium was identified. Vaptans demonstrated superiority over placebo for outcomes relating to serum sodium correction. Few trials documented the potential benefit of vaptans on change in health-related quality of life as a result of treatment. There was also a lack of high-quality RCT evidence on the comparative efficacy of the vaptans and other treatment strategies for the treatment of chronic nonhypovolaemic hypotonic hyponatraemia.

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Introduction

Hyponatraemia (HN) serum sodium concentration <135 mmol/l is the most common disorder of body fluid and electrolyte imbalance.[1–3] It is associated with various clinical conditions[1–3] and reportedly occurs in 15–30% of hospital admissions.[2,3] Hyponatraemia may be associated with iatrogenic causes or, in approximately 35% of cases,[4] be caused by the kidneys retaining water because of excess vasopressin secretion.[5]

The most common noniatrogenic cause of nonhypovolaemic hypotonic hyponatraemia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH), a disorder of impaired water excretion due to the inability to suppress the secretion of vasopressin resulting in reduced urinary volumes. If water intake exceeds the reduced urine output, the resulting water retention leads to the development of hyponatraemia.[3,5] Other causes include excessive fluid intake, excessive solute losses, renal failure, hormonal abnormalities and low solute intake.[3]

Nonhypovolaemic hyponatraemia is not a single diagnosis but a combination of a very heterogeneous group of clinical circumstances with variable clinical outcome depending on the hyponatraemia aetiology. Current treatment of nonhypovolaemic hyponatraemia depends primarily on ascertaining the underlying cause and must be undertaken carefully to avoid too rapid an increase in serum sodium concentration. Overly rapid correction can result in osmotic demyelination syndrome.[3,6] Fluid restriction is generally the first-line treatment for chronic hyponatraemia in the absence of relevant symptoms, including HN secondary to SIADH. Hypertonic saline should be administered

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in acute HN and in chronic HN in the presence of severe or moderate symptoms. However, there is no consensus regarding the optimal second-line options when fluid restriction is not appropriate or does not adequately correct the hyponatraemia.[1,3,5] Alternative treatment strategies include oral urea, salt tablets, mannitol, loop diuretics demeclocycline, lithium and recently vasopressin receptor antagonists (vaptans).[1,3,5]

Vaptans block the V2 receptors in the kidney facilitating aquaresis and restoring serum sodium level through restoration of normal circulating volume.[3,6] Advice in national and international guidelines on recommended treatments varies. A number of national guidelines recommend tolvaptan as a second-line option for treating hyponatraemia secondary to SIADH when fluid restriction is unsuitable,[3,7,8] but European guidelines in endocrinology, nephrology and intensive care medicine do not recommend the use of vaptans for this indication.[1,9,10]

Given this difference in published guidelines, this systematic review was undertaken to identify the randomized and quasi-randomized controlled trial evidence for the effectiveness of interventions to treat chronic nonhypovolaemic hypotonic hyponatraemia by assessing outcomes relating to change in serum sodium concentration, all-cause mortality, health-related quality of life outcomes, outcomes potentially related to over-correction of serum sodium concentration, treatment-specific side effects and treatment discontinuation.

Methods

A systematic review was undertaken according to the principles of systematic reviewing in the Cochrane handbook.[11] Two independent clinical experts (not involved in the conduct of the systematic review) peer-reviewed the protocol, statistical plan and draft report. The protocol was registered on PROSPERO[12] (CRD42015016670).

Studies were eligible for inclusion if they assessed the treatment of patients over 14 years of age. Children (aged 28 days to 14 years) were ineligible because they have significantly different physiological requirements and clinical circumstances to adults. Chronic nonhypovolaemic hypotonic hyponatraemia was defined as the presence of three criteria:

- Hyponatraemia >48 h;
- Serum osmolality <280 mOsm/kg;
- Serum sodium concentration <135 mmol/l.

Populations in the identified studies were not always clearly defined, particularly in relation to the duration of chronic hyponatraemia. For this reason, the inclusion criteria were broadened to include studies where hyponatraemia of more than 48 h had not been explicitly reported, but in which chronic hyponatraemia was a known feature of the chronic disease states being assessed (e.g. SIADH or chronic uncontrolled heart failure) on the assumption of a chronic process. A protocol amendment was recorded.

Randomized or quasi-randomized (i.e. trials in which the methods of allocating people to a treatment arm were not random, but were intended to produce similar groups[11]) controlled trials published as full reports were eligible for review. Eligible trials compared any degree of fluid restriction or any drug treatments with the aim of increasing serum sodium concentration in patients with chronic nonhypovolaemic hypotonic hyponatraemia. Outcomes of interest to the review included: all-cause mortality, health-related quality of life outcomes, length of hospital stay, response (an increase in serum sodium of ≥5 mmol/l or normalization of serum sodium concentration (≥135–145 mmol/l)), serum sodium concentration (mmol/l) at end of treatment or change from beginning to end of treatment, outcomes potentially related to over-correction of serum sodium concentration or rapid increase in serum sodium (i.e. more than 12 mmol/l in 24 h or more than 18 mmol/l in 48 h), any treatment-specific side effects and treatment discontinuation.

Searches were conducted in MEDLINE, EMBASE, PubMed, Cochrane Library, Science Citation Index, World Health Organisation International Clinical Trials Registry Platform and clinicaltrials.gov. Selected conference proceedings were searched. The detailed search strategies are provided in the Appendix S1–S3.

Two independent reviewers screened the search results against the eligibility criteria in the protocol. Any disagreements were discussed with a third reviewer. Studies excluded following full-text review are listed in the Appendix S1–S3.

Two independent reviewers conducted data extraction and quality assessment. Details of the funding source, trial design and methodology, patient characteristics, treatment and permitted dose adjustments, statistical methods used and prespecified outcomes (including the unit of measurement, analysis population and effect size) were extracted. The Cochrane Assessment of Risk of Bias tool[11] was used to assess risk of bias at the study level. High risk of bias was assumed if at least one quality criterion was not adequately met.

The results of similar studies were statistically pooled using both fixed-effects and random-effects models. RevMan (version 5·3) was used to calculate pairwise meta-analysis using standard frequentist approaches.[11]

Studies were drawn from the published literature; therefore, the effects being estimated in each study are likely to vary. There is also a degree of heterogeneity among studies in how outcomes are measured and in the ways that missing data were handled. Consequently, we report the most appropriate meta-analysis model: the random-effects model. Risk ratio (RR) has been used as a summary statistic (with 95% confidence intervals (CI)). RR has been shown to be more understandable and easier to interpret.[11]

Statistical heterogeneity was assessed for each pairwise comparison informed by at least two trials. Forest plots assess heterogeneity and present the *I*-squared statistic, between-study variance (tau-squared) and the *P*-value of the heterogeneity statistic Q. *I*-squared values of 25%, 50% and 75% were defined as representing low, moderate and high heterogeneity.[11]

Following data extraction, an assessment of the studies identified, and after consultation with independent clinical experts, it was agreed that in studies with more than one treatment group receiving different doses of the same drug, the treatment groups were collapsed into one single pairwise comparison versus placebo.[11]

It was also agreed that it was appropriate to combine data at any time point after 4 days of treatment initiation, on the understanding that the treatment effect of vaptans plateaus at 4 days and any additional treatment is effectively maintaining this effect. For the change from baseline outcomes and for incidence of response, some trials reported data at a number of time points and the data were not always consistent over time. Where this was the case, data for all time points are reported and the trials are grouped by similar time point for the meta-analyses. A post hoc 'end-point' analysis, (i.e. meta-analysis including the end of study data for each trial) was also conducted for these outcomes.

We planned to analyse publication bias using funnel plots.[11] Subgroup analyses were prespecified in relation to the underlying condition associated with hyponatraemia. Sensitivity analyses were explored for each meta-analysis excluding the following trials in turn:

- Average serum sodium concentration at baseline >130 mmol/l;
- >50 patients per treatment arm to explore how larger trials influence the results;
- Imposed mandatory fluid restriction;
- High risk of bias;
- Non-English language studies;
- Unpublished studies;
- Industry funding;
- Based on country;
- Based on diagnostic criteria.

The primary meta-analyses for each comparison include all eligible trials that reported data for that outcome, regardless of underlying condition. Results of the SIADH and cancer subgroups are also reported here, where data were available.

Results

The searches retrieved 45 716 records. Following study selection (Fig. 1), 18 trials met the eligibility criteria or reported data for an eligible subgroup. Two trials assessed conivaptan,[13,14] four assessed lixivaptan,[15–18] three assessed satavaptan[19–21] and nine assessed tolvaptan.[22–29] There were no RCTs published assessing other known interventions such as urea, sodium tablets or mannitol.

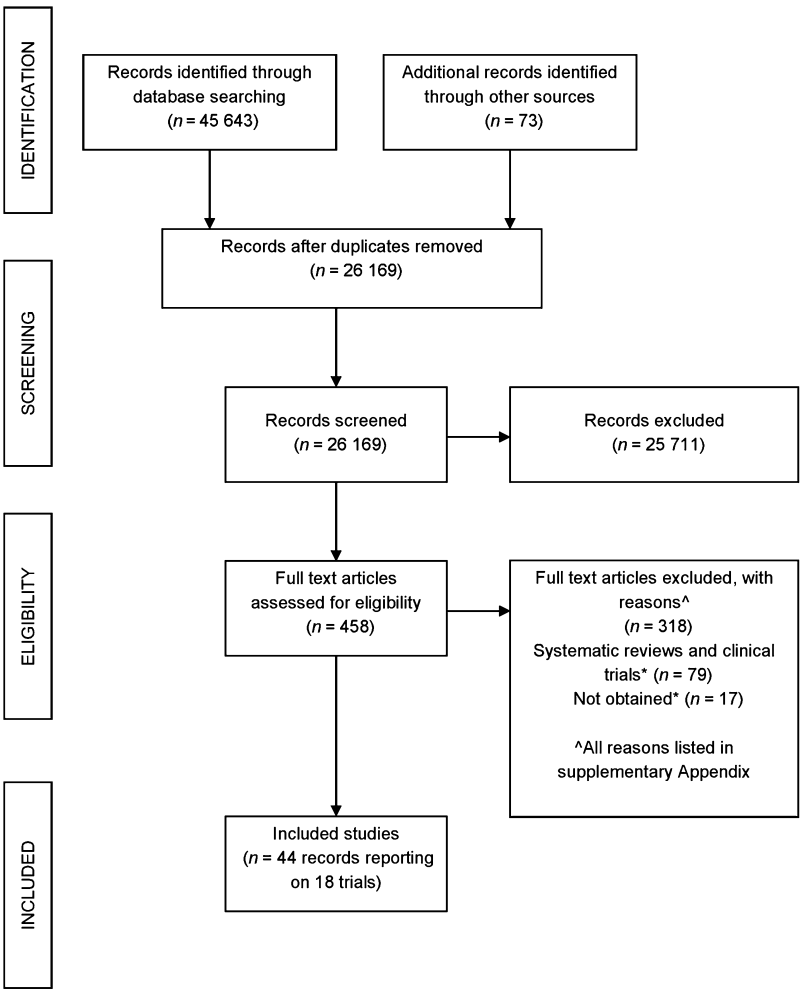

Fig. 1 Study selection process.

We contacted the authors of ten studies and Otsuka, to seek additional information about the trials' design and outcomes. Otsuka (manufacturer of tolvaptan and funder of this review) provided information for six trials of tolvaptan *vs* placebo and the authors of two further trials responded.[14,20]

A summary of the characteristics of the included trials is presented in Table 1. All 18 trials were randomized multicentre trials. Seventeen were double-blind trials and reported to be placebo-controlled. One trial was open label describing fluid restriction as an active control.[23] In two trials, the double-blind period was followed by a 1-year open-label noncomparative extension with flexible dosing: for this review, only results reported throughout the double-blind period were extracted.[19,21] All trials were supported or funded by pharmaceutical companies.

The underlying cause of hyponatraemia varied across the trials. Some trials reported data for a specific population and others included patients with various underlying causes. Three trials assessed hyponatraemia in patients with SIADH,[15,21,22] four assessed hyponatraemia in patients with congestive heart failure,[24–27] two assessed hyponatraemia in patients with cirrhosis,[17,20] and one assessed hyponatraemia in patients with cancer.[28] The other eight trials assessed hyponatraemia in patients with a range of underlying conditions. In these trials, results were reported for subgroups of patients in the Study of Ascending Levels of Tolvaptan in hyponatraemia (SALT 1 and SALT 2) trials with SIADH,[30] cirrhosis,[31] SIADH and cancer,[32] and schizophrenia[33]; one trial reported some results for a subgroup of patients with cirrhosis and SIADH[18] and one trial reported some results for a subgroup of patients with congestive heart failure (CHF).[19]

All trials reported assessing patients with nonhypovolaemic hyponatraemia, but only five trials specifically reported patients' fluid status. In two trials,[15,16] all patients were categorized as euvolaemic. In the other three trials, 50–70% of patients in each treatment arm were euvolaemic and the remainder were hypervolaemic.[13,14,29]

Sixteen trials reported primary outcomes related to serum sodium correction, serum sodium normalization or change from baseline. Two trials reported weight change[24,27] and worsening heart failure[27] as primary outcomes and reported results for the hyponatraemia subgroup in a larger CHF population.[27]

The majority of trials used the last observation carried forward (LOCF) method to impute missing data. LOCF can lead to bias and is only appropriate in cases where a relatively recent observation has been carried forward.[11] The majority of trials did not report this and therefore studies using this method of imputation were categorized as having an unclear risk of bias. Two trials had low risk of bias,[14,20] five had high risk of bias[21,23,27,28] and 11 did not report adequate detail and were categorized as unclear risk of bias indicating that there is a substantial risk of bias across the data set as a whole.

There were no significant differences between the fixed- and random-effects results for any outcome assessed.

Results are shown in Tables 2 and 3. The I^2 statistic presented in the tables indicates the level of statistical heterogeneity for each meta-analysis. All of the comparisons had low to moderate levels of heterogeneity unless otherwise stated.

Response was defined in the protocol as an increase in serum sodium of ≥5 mmol/l and/or normalization of serum sodium concentration (≥135–145 mmol/l). A random-effects meta-analysis suggests that patients randomized to lixivaptan,[15–17] satavaptan[19–21] and tolvaptan[22,26,29] are significantly more likely to experience a response compared to placebo, with tolvaptan showing the largest treatment effect (RR 3·30 [1·97, 5·54]). Tolvaptan data were available up to 30 days[24,29] and in all cases tolvaptan was significantly superior to placebo, with the exception of day 14.[23,28] The trials at day 30 showed high levels of heterogeneity (I^2 = 74%). Results were similar for tolvaptan compared to placebo when considering SIADH population/subgroups only at day 4.[22,30]

For the change in the daily area under the curve (AUC) of serum sodium, in the random-effects meta-analyses, patients randomized to lixivaptan at day 3[15,16] and tolvaptan at day 4,[22,26,29] day 7,[22,26] day 30[29] and in the end of study analysis[22,26,29] had significantly greater changes in daily AUC compared with placebo. Two trials of conivaptan did not show any differences between conivaptan and placebo.[13,14] Trials of conivaptan at day 7 (I^2 = 93%), and trials of tolvaptan (I^2 = 77%) showed high heterogeneity. Subgroup analysis in SIADH patients also found a significantly greater change in daily AUC among tolvaptan patients[22,30] compared to placebo.

For the change in serum sodium, pooled analyses of conivaptan,[13,14] lixivaptan,[15–18] satavaptan[19–21] and tolvaptan[22–25,27–29] versus placebo all reported significantly greater changes in patients randomized to vaptans. Trials assessing tolvaptan at days 10–14 had high levels of heterogeneity (I^2 = 75%).

There was no significant difference between patients receiving any of the vaptans compared to placebo in single trials or pooled analyses for mortality, treatment discontinuation and incidence of hypernatraemia.

Four trials comparing tolvaptan and placebo documented the incidence of osmotic demyelination syndrome.[23,25,29] No incidents were reported in either treatment arm by these trials.

A rapid increase in serum sodium was defined as an increase of more than 12 mmol/l in 24 h or more than 18 mmol/l in 48 h. Pooled analyses of two trials of conivaptan[13,14] and three trials of satavaptan[19–21] found no differences in the incidence of a rapid increase in serum sodium in patients randomized to either intervention or placebo. While there were no differences individually in the three tolvaptan trials,[23,29] when pooled, the incidence of a rapid rise in serum sodium levels was significantly greater in patients randomized to tolvaptan than placebo (RR 9·85 [95% CI: 1·27, 76·35] P = 0·03). However, because of the low number of events in the treatment arm (5 and 4 events in SALT 1 and SALT 2, respectively) and no events in the placebo arm of each trial, the size of the treatment effect is uncertain. Gheorghaide (2006) reported zero events in both treatment arms and did not contribute to the meta-analysis.[23]

Few trials reported health-related quality of life and, those that did, used various generic instruments none of which are specifically designed to assess hyponatraemia (see Appendix S1–S3). One trial of lixivaptan[15] reported change from baseline in

Table 1. Trial characteristics

Author, date, reference	Trial identifier	Trial design	Funding source	Study location and number of participating centres
Conivaptan trials				
Annane 2009[13]	NR	Placebo-controlled randomized, double-blind, multicentre trial	Astellas Pharma US (formerly Yamanouchi Pharma America Inc.)	17 sites in 9 European countries (Belgium, Finland, France, Germany, Italy, the Netherlands, Poland, Spain and UK)
Ghali 2006[14]	Convi-oral study USA/Canada/Israel	Placebo-controlled randomized, double-blind, multicentre trial	Astellas Pharma US (formerly Yamanouchi Pharma America Inc.)	21 sites (USA, Canada and Israel)
Lixivaptan trials				
Abraham 2012[15]	NCT00876798; HARMONY	Multicentre randomized, double-blind, placebocontrolled, phase III trial	CardioKine Inc.	61 sites in 8 countries (Belgium, Czech Republic, Israel, India, Italy, Mexico, Peru and USA)
Abraham 2012[16]	NCT00660959; LIBRA	Multicentre, randomized, double-blind, placebocontrolled, phase III trial	Supported by CardioKine Biopharma.	37 sites in 6 countries (USA, Canada, Belgium, Germany, Poland, India)
Gerbes 2003[17]	VPA-985 Study	Phase II multicentre randomized, placebo-controlled double-blind trial	Supported by Wyeth-Ayerst Research.	17 hospitals participated in the main trial (multiple countries – authors from Belgium, France, Germany and Spain). This study has a subset of patients from the main trial
Wong 2003[18]	North American VPA-985 Study	Multicentre randomized placebo-controlled trial	Study was sponsored by Wyeth-Ayerst Laboratories, USA.	Multicentre but number of hospitals not reported (Canada and USA)
Satavaptan trials				
Aronson 2011[19]	DILIPO	Randomized, double-blind, placebo-controlled trial with a 1-year open-label non-comparative extension with flexible dosing	Supported by a research grant from Sanofi-Aventis.	48 centres in Europe, North and South America, Israel, and Australia
Gines 2008[20]	NCT00501722; HypoCAT	Prospective, multicentre, randomized, double-blind, placebo-controlled efficacy trial	Sanofi-Aventis	Multicentre; locations not reported
Soupart 2006[21]	NR	Randomized, double-blind, placebo-controlled trial with a 1-year open-label noncomparative extension with flexible dosing	Sanofi-Aventis	Multicentre: four countries (Belgium, Germany, Hungary, France)
Tolvaptan trials				
Chen 2014[22]	NCT00664014	Multicentre, randomized, double-blind, placebo-controlled trial	Otsuka Pharmaceutical	49 sites (9 sites for SIADH) in China
Li 2011[26]	Chinese Tolvaptan study	Multicentre, randomized, double-blind placebo-controlled trial	Otsuka Pharmaceutical R & D Beijing Co., Ltd	11 centres in China
Salahudeen 2014[28]	NCT01199198	Double-blind, randomized placebo-controlled trial of tolvaptan in hyponatraemic patients with cancer	Otsuka Pharmaceutical	MD Anderson Cancer Centre, University of Texas, USA
Rossi 2007[27]	ACTIV in CHF: HN SG	Multicentre, randomized, double-blind, placebocontrolled, parallel group, dose-ranging phase II feasibility trial	Otsuka Maryland Research Institute	34 centres (USA) and 11 centres (Argentina)
Schrier 2006[29]	SALT 1 and SALT 2	Multicentre, randomized, double-blind, placebo-controlled trials	Otsuka Maryland Research Institute	SALT 1: 42 sites (USA) SALT 2: 50 international sites

(continued)

Table 1. (continued)

Author, date, reference	Trial identifier	Trial design	Funding source	Study location and number of participating centres
Gheorghiade 2006[23]	NR	Multicentre, randomized, active-controlled, open-label trial.	Otsuka Maryland Research Institute	Nine centres (USA)
Gheorghiade 2003[24]	Tolvaptan-CHF: HN SG	Randomized, double-blind placebo-controlled trial. Phase 2B trial	Otsuka Inc.	30 centres (USA)
Hauptman 2013[25]	NCT00071331; EVEREST	Prospective, multicentre, randomized, double-blind, placebo-controlled programme	Otsuka Inc.	359 sites (North America, South America and Europe)

NR, not reported; SIADH, syndrome of inappropriate antidiuretic hormone secretion; UK, United Kingdom; USA, United States of America.

the Medical Outcomes Survey 6-item cognitive function scale; higher scores indicated less impairment of cognitive functioning. The trial was carried out in patients with SIADH. Data were reported at weeks 8 and 12. At both time points, significantly greater increases from baseline were observed in the lixivaptan group compared with placebo.

The two SALT trials reported change from baseline in the Short Form-12 mental health composite score (SF-12 MCS).[18,19,34,35] At day 30 in SALT 1 and in the SIADH subgroup of the two SALT trials, patients receiving tolvaptan had a significantly greater increase in SF-12 MCS score compared with patients receiving placebo. There was also a significant difference in favour of tolvaptan when data were pooled for the two SALT trials at day 30 mean difference: 4·76 (95% CI: 0·11 to 9·41).

With the exception of a greater incidence of serious adverse events in patients receiving tolvaptan in the EVEREST trial, which assessed the safety of tolvaptan 30 mg at 60 days in patients with heart failure, there was no evidence of a difference between any of the other treatments identified compared with placebo for the incidence of adverse and serious adverse events and withdrawal due to adverse events. Adverse event data could not be pooled because of differences in the underlying condition of patients across trials and the differences in the time point assessed.

Comparative length of hospital stay could not be assessed because of the different settings reported for the studies (some studies required patients to be hospitalized for some or all of the trial period, whereas others did not) and the variation in underlying conditions.

None of the sensitivity analyses significantly altered the meta-analyses results. Sensitivity analyses excluding unpublished studies were not undertaken because all of the included studies were identified in the published literature. Sensitivity analyses excluding studies using the following filters were not explored: diagnostic criteria (too much variation across trials and differences in underlying conditions), source of funding (all studies were industry funded), country (insufficient variation to warrant investigation).

We planned to analyse publication bias, but none of the analyses had a sufficient number of studies to conduct funnel plot analysis.[11]

Discussion

This systematic review and meta-analysis identified RCT evidence only for vaptans in the treatment of chronic nonhypovolaemic hypotonic hyponatraemia. No RCTs or quasi-RCT evidence was identified for any alternative interventional strategy. Vaptans are more effective than placebo for the treatment of hyponatraemia for outcomes related to serum sodium correction.

There was limited evidence on the impact of vaptans treating hyponatraemia on other relevant outcomes, such as quality of life. Patient-reported outcome measures were inconsistently and infrequently assessed across trials and, therefore, conclusions cannot be drawn regarding patients' experiences of the different vaptans.

Table 2. Summary of meta-analyses: Change in serum sodium outcomes

				Subgroups by underlying condition			
		All studies (mixed population)		SIADH		Cancer	
Intervention	Time point of assessment	Number of studies/number of participants	MD [95%CI], I^2 statistic	Number of studies/number of participants	MD [95%CI], I^2 statistic	Number of studies/number of participants	MD [95%CI], I^2 statistic
Change in Daily AUC							
Conivaptan	Day 5	2/157	4·22 [−1·31, 9·76], I^2 = 93%				
Lixivaptan	Day 3	2/312	1·06 [0·26, 1·86], I^2 = 14%	1/206	0·75 [-0·15, 1·65], I^2 = NA		
	Days 28–30	2/312	1·58 [0·53, 2·64], I^2 = 0%	1/206	1·45 [0·19, 2·71], I^2 = NA		
	Day 56			1/206	1·60 [0·07, 3·13], I^2 = NA		
Tolvaptan	Day 4	4/526	3·91 [3·03, 4·79], I^2 = 63%	2/154	5·29 [3·99, 6·58], I^2 = 31%		
	Day 7	2/110	4·49 [1·56, 7·42], I^2 = 77%	1/45	6·10 [3·82, 8·38], I^2 = NA		
	Day 30	2/416	4·45 [3·71, 5·19], I^2 = 0%	1/109	6·18 [4·54, 7·82], I^2 = NA		
	End of study	4/526	4·38 [3·53, 5·23], I^2 = 34%				
Change in serum sodium concentration							
Conivaptan	Day 5	2/157	5·34 [2·82, 7·86], I^2 = 56%				
Lixivaptan	Day 7	4/416	2·82 [1·70, 3·95], I^2 = 9%	1/206	2·40 [0·87, 3·93], I^2 = NA		
Tolvaptan	Days 4–5	5/524	3·98 [2·31, 5·65], I^2 = 56%	1/45	5·10 [2·29, 7·91], I^2 = NA		
	Day 7	2/521	2·70 [1·84, 3·57], I^2 = 5%				
	Days 10–14	4/167	4·22 [2·09, 6·34], I^2 = 75%			1/30	1·89 [0·15, 3·62], I^2 = NA
	Days 25–30	3/442	3·54 [2·15, 4·94], I^2 = 12%				
	End of study	8/1083	4·17 [3·15, 5·18], I^2 = 49%				
Satavaptan	Day 4/5	3/262	4·95 [2·81, 7·10], I^2 = 52%	1/17	8·92 [4·46, 13·38], I^2 = NA		

The results of the meta-analyses for each treatment at various time points for change in serum sodium outcomes. Results are presented as mean difference with 95% confidence intervals. Cells highlighted in grey are those in which there is a statistically significant difference in favour of the active treatment compared with placebo.
AUC, area under the curve; CI, confidence interval; MD, mean difference; SD, standard deviation; SIADH, syndrome of inappropriate antidiuretic hormone; SG, Subgroup.

Table 3. Summary of meta-analyses: Dichotomous outcomes

				Subgroups by underlying condition			
		All studies (mixed population)		SIADH		Cancer	
Intervention	Time point of assessment	Number of studies/number of participants	RR [95%CI], I^2 statistic	Number of studies/number of participants	RR [95%CI], I^2 statistic	Number of studies/number of participants	RR [95%CI], I^2 statistic
Response (defined as an increase in serum sodium of ≥5 mmol/l or normalization of serum sodium concentration (≥135–145 mmol/l))							
Conivaptan	Day 5	1/74	1·49 [1·02, 2·18], I^2 = NA				
Lixivaptan	Day 7	3/372	2·81 [1·34, 5·91], I^2 = 46%	1/206	3·43 [1·58, 7·47], I^2 = NA		
	8 Weeks			1/206	1·39 [1·03, 1·88], I^2 = NA		
Tolvaptan	Day 4	4/527	3·30 [1·97, 5·54], I^2 = 59%	2/147	5·12 [2·69, 9·72], I^2 = 0%		
	Day 7	4/615	2·22 [1·25, 3·93], I^2 = 60%	1/45	17·05 [1·03, 281·65], I^2 = NA	1/30	8·41 [1·24, 57·12], I^2 = NA
	Day 14	2/53	4·24 [0·55, 32·40], I^2 = 74%			1/30	12·24 [1·85, 80·73], I^2 = NA
	Days 25–30	3/460	2·25 [1·74, 2·89], I^2 = 0%	1/83	2·48 [1·44, 4·30], I^2 = NA		
	End of Study	8/1,098	2·14 [1·74, 2·64], I^2 = 25%				
Satavaptan	Day 1			1/34	6·33 [0·41, 98·27], I^2 = NA		
	Days 4–5	3/262	2·57 [1·66, 4·00], I^2 = 0%	1/34	6·46 [1·02, 40·81], I^2 = NA		
Mortality							
Conivaptan	Day 5	1/74	0·43 [0·06, 3·25], I^2 = NA				
Lixivaptan	Days 56–60	2/307	0·57 [0·03, 9·84], I^2 = 61%	1/206	2·03 [0·25, 16·44], I^2 = NA		
Tolvaptan	>Day 7	8/1158	1·06 [0·89, 1·26], I^2 = 0%	3/154	0·85 [0·11, 6·76], I^2 = 20%		
Satavaptan	Day 14	1/110	1·75 [0·09, 35·33], I^2 = NA				
Discontinuation							
Conivaptan	Day 5	2/157	0·39 [0·14, 1·10], I^2 = 0%				
Lixivaptan	>Day 9	3/355	1·19 [0·71, 1·99], I^2 = 21%	1/205	0·78 [0·40, 1·53], I^2 = NA		
Tolvaptan	>Day 27	4/951	0·88 [0·71, 1·08], I^2 = 38%	1/109	0·71 [0·35, 1·42], I^2 = NA		
Satavaptan	>Day 4	3/263	0·76 [0·33, 1·76], I^2 = 10%	1/35	0·12 [0·01, 2·79], I^2 = NA		
Incidence of hypernatraemia							
Conivaptan	Day 5	1/74	Not estimable				
Lixivaptan	Day 30	1/106	1·93 [0·18, 20·60], I^2 = NA				
Tolvaptan	Days 30–65	4/941	2·34 [0·69, 7·99], I^2 = 0%				
Satavaptan	Days 4–14	3/266	2·04 [0·36, 11·44], I^2 = 0%	1/34	1·67 [0·09, 31·56], I^2 = NA		
Incidence of rapid increase in serum sodium (defined as an increase of more than 12 mmol/l in 24 h or more than 18 mmol/l in 48 h)							
Conivaptan	Days 2–5	2/157	Not estimable				
Lixivaptan	Day 7			1/196	0·82 [0·09, 7·66], I^2 = NA		
Tolvaptan	Days 30–65	2/443	9·85 [1·27, 76·35], I^2 = 0%				
Satavaptan	Days 2–4	3/265	1·65 [0·67, 4·04], I^2 = 0%	1/34	3·00 [0·18, 50·47], I^2 = NA		

The results of the meta-analyses for each treatment at various time points for response, mortality discontinuation, incidence of hypernatraemia and incidence of rapid increase in serum sodium. Results are presented as relative risk with 95% confidence intervals. Cells highlighted in grey are those in which there is a statistically significant difference in favour of the active treatment compared with placebo.
CI, confidence interval; RR, risk ratio; SIADH, syndrome of inappropriate antidiuretic hormone; SG, subgroup.

There was no evidence of a difference between placebo and any of the vaptans on mortality as an outcome but this was not a primary outcome in the studies examined. A recent review and meta-analysis[36] found that improvements in serum sodium, in hyponatraemic patients with a range of clinical conditions, are associated with a reduction in overall mortality. However, similar to other studies this observation does not establish a cause–effect relationship but is hypothesis-generating. The lack of correction might contribute directly to poor outcomes or might be a biomarker for the severity of the underlying comorbidities.

There is currently controversy regarding the optimal treatment of hyponatraemia related to SIADH and the guidelines available recommend a number of strategies to treat hyponatraemia.[1,3,8] The guidance is clear that in the acute setting hyponatraemia can be corrected relatively quickly without longer-term adverse consequences. However, it is less clear in the chronic setting (the presence of hyponatraemia >48 h). Similarly, severe hyponatraemia in which neurological symptoms are apparent requires intervention and most clinicians agree that hypertonic saline to elevate the serum sodium to a safe level of greater than 120 mmol/l is appropriate; however, in mild to moderate hyponatraemia as in the current analysis, optimal treatment strategies are less clear.

The main goal of therapy for moderate to severe hyponatraemia is to reliably increase the serum sodium concentration and safely minimize the risk of the brain swelling and also to improve hyponatraemic symptoms, while avoiding the devastating potential neurological sequelae caused by too rapid or too great a correction of the sodium concentration. To date, no therapy fulfilled these criteria; 3% saline improves serum sodium, but nearly 10% of patients will experience excessive correction, as a result of water diuresis that occurs during therapy. Some have advocated concomitant use of desmopressin to avoid this potential complication, but evidence from RCTs is lacking. Assessment of other parameters of patient-related outcomes is lacking and requires further study.

Thus, despite the observation in clinical care that hyponatraemia is the commonest occurring electrolyte disturbance, it is striking that the only intervention for which there are any data from RCTs are the vaptans. There are no data from RCTs on the efficacy and safety of other commonly used interventions such as oral urea tablets, salt tablets, hypertonic saline loop diuretics, mannitol, demeclocycline or lithium.

Implications for practice and further research recommendations

RCT evidence of the effectiveness of interventions to treat hyponatraemia was identified for conivaptan, lixivaptan, tolvaptan and satavaptan. Our analysis suggests that the efficacy profile across the vaptans is similar. Currently, tolvaptan has EU approval for the treatment of hyponatraemia secondary to SIADH and US approval for clinically significant nonhypovolaemic hyponatraemia (serum sodium <125 mEq/L or less). Satavaptan was withdrawn from the European Medicines Agency in 2008,[37] lixivaptan is not licensed, and conivaptan (IV) is approved for the treatment of euvolaemic hyponatraemia in hospitalized patients only in the United States.

Clinically the question remains regarding the relevance of the evolution and aetiology of hyponatraemia in different conditions; that is, is the hyponatraemia a "primary" feature in euvolaemic disorders which are often due to SIADH, or is it a "secondary" and variable feature, as seen in patients with heart failure, nephrotic syndrome and/or liver disease where there is often hypervolaemia. This is a complex concept but where the hyponatraemia is predominantly a secondary feature, the outcomes should be assessed as those of the underlying disease processes. Thus, management of the heart failure for example should lead to improved sodium levels. In the case where the intervention is for a "primary" feature such as in SIADH which responds to specific treatment to improve serum sodium such as fluid restriction or vaptans, the rate of change in serum sodium can be used as a surrogate biomarker of outcome of this therapy, particularly if there are no suggestions of adverse outcomes. It, however, is not a marker of overall outcome from the underlying disorder such as neoplasm or pneumonia which will be dictated by specific more prolonged therapy if feasible.

Thus, for future studies treating hyponatraemia we recommend standard measurement criteria of clinical status at inclusion. These measures should include the clinical hydration state, co-prescribed medications, nadir sodium levels and presence/absence of cognitive or other symptoms/signs associated with hyponatraemia. They should also include the underlying pathology for "secondary" hyponatraemia where known, and the pretreatment plasma/urine osmolalities and electrolytes that should be common to all studies. Further, a standard set of outcome measures should be agreed in relation to the sodium change and primary disease state. Such criteria are necessary to co-ordinate clinical research to facilitate a future clinical consensus in this complex but relatively common area of clinical practice, which is made more challenging because it intersects multiple medical and surgical specialties as well as primary care.

Recent clinical guidelines suggest that individualized care is optimal for treating patients. Tolerability is also a key component to effective therapy. There were little data available to determine which specific subgroups of patients might benefit from treatment with a vaptan and no data available on which patients would benefit from other interventions suggested in clinical guidelines.

All of the studies identified in this review were placebo-controlled trials. In the absence of direct evidence of the relative efficacy of vaptans for chronic nonhypovolaemic hypotonic hyponatraemia, there is potential for indirect treatment comparisons. Well-conducted RCTs comparing relevant comparators in use in current practice, such as vaptans, fluid restriction, urea, sodium tablets or hypertonic saline solution are required, to gain more evidence on the comparative effectiveness of different treatments and to explore which subgroups might benefit most from individual treatments. This will allow further revision of clinical guidelines.

This review was informed by extensive searches to ensure that as many relevant studies as possible were identified. None of the comparisons in these analyses had sufficient studies to assess publication bias reliably using funnel plots.

This review has benefited from the provision of additional data for six trials of tolvaptan,[34–39] one of conivaptan[14] and one of satavaptan.[20] Authors of the other studies did not provide similar data: we do not know how that missing data might impact on the risk of bias assessment or results.

This review considered all doses of each vaptan together and collapsed doses into a single treatment arm. This approach assumes that all doses of a drug have a similar treatment effect, which may not always be the case. The majority of trials adopted an approach allowing titration and dose adjustments at set points in the trial which may be more reflective of clinical practice. While there were some differences in the permitted dose adjustments and fluid restriction across trials, these differences were considered unlikely to impact on the overall treatment effect. Trials with mandatory fluid restriction were excluded from the meta-analyses in a sensitivity analysis and this had little impact on the treatment effect.

Flaws in the design, conduct and analysis of RCTs can lead to bias and raise questions about the validity of their findings. The trials in this review varied in design and quality; however, a sensitivity analysis excluding high risk of bias studies did not have a great impact on the direction or significance of the results. This review did not consider other types of evidence such as case series and case reports which may provide additional information, particularly in relation to safety and the lesser reported adverse events which may be under-estimated in published RCTs.

The trials varied in terms of the underlying causes of hyponatraemia. Some studies assessed a mixed population (i.e. any underlying cause), while others assessed hyponatraemia in specific populations of patients with heart failure, cirrhosis or SIADH. Where possible, subgroup analyses were also carried out by underlying condition.

Conclusions regarding the safety of each treatment should be drawn with care and should take into consideration the varying assessment time points and different underlying conditions.

Conclusions

Vaptans are an evidence-based treatment to increase serum sodium in patients with nonhypovolaemic hyponatraemia. The RCT evidence indicates that each of the vaptans significantly improves serum sodium concentration compared with placebo and is associated with greater rates of response than placebo. There was no evidence of a difference between any of the vaptans compared with placebo for mortality, discontinuation and rates of hypernatraemia; however, higher rates of a rapid increase in serum sodium were observed in the tolvaptan-treated patients in the pooled analysis. RCTs are required to determine the comparative efficacy of vaptans, fluid restriction and the other treatments currently used in clinical practice or recommended in guidelines for chronic hypotonic nonhypovolaemic hyponatraemia.

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