Cochrane
Library

Cochrane Database of Systematic Reviews

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC

Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC.
Interventions for chronic non-hypovolaemic hypotonic hyponatraemia.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD010965.
DOI: [10.1002/14651858.CD010965.pub2](https://doi.org/10.1002/14651858.CD010965.pub2).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	10
Figure 1.	11
Figure 2.	13
Figure 3.	14
Figure 4.	18
Figure 5.	19
Figure 6.	20
DISCUSSION	20
AUTHORS' CONCLUSIONS	22
ACKNOWLEDGEMENTS	23
REFERENCES	24
CHARACTERISTICS OF STUDIES	34
DATA AND ANALYSES	103
Analysis 1.1. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 1 Death at 6 months.	105
Analysis 1.2. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 2 Health-related quality of life.	106
Analysis 1.3. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 3 Cognitive function: trail making test Part B.	107
Analysis 1.4. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 4 Length of hospital stay.	107
Analysis 1.5. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 5 Change from baseline serum sodium concentration.	108
Analysis 1.6. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 6 Response in serum sodium concentration.	109
Analysis 1.7. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 7 Rapid increase in serum sodium concentration.	110
Analysis 1.8. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 8 Hyponatraemia during treatment.	111
Analysis 1.9. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 9 Thirst.	112
Analysis 1.10. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 10 Other adverse events.	112
Analysis 1.11. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 11 Injection-site complications at 2 to 7 days.	113
Analysis 1.12. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 12 Treatment discontinuation.	114
Analysis 1.13. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 13 Death during follow-up: sensitivity analysis.	115
Analysis 1.14. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 14 Rapid increase in serum sodium concentration: sensitivity analysis.	116
ADDITIONAL TABLES	117
APPENDICES	117
CONTRIBUTIONS OF AUTHORS	120
DECLARATIONS OF INTEREST	120
SOURCES OF SUPPORT	120
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	120

INDEX TERMS	121
-------------------	-----

[Intervention Review]

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia

Evi V Nagler^{1,2}, Maria C Haller^{2,3,4}, Wim Van Biesen^{1,2}, Raymond Vanholder^{1,2}, Jonathan C Craig^{5,6,7}, Angela C Webster^{5,6,8}

¹Renal Division, Sector Metabolic and Cardiovascular Conditions, Ghent University Hospital, Ghent, Belgium. ²European Renal Best Practice (ERBP), Guidance Body of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), London, UK. ³Section for Clinical Biometrics, Center for Medical Statistics, Informatics and Intelligent Systems, Medical University Vienna, Vienna, Austria. ⁴Department of Nephrology, Ordensklinikum Linz Elisabethinen, Linz, Austria. ⁵Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. ⁶Sydney School of Public Health, The University of Sydney, Sydney, Australia. ⁷College of Medicine and Public Health, Flinders University, Adelaide, Australia. ⁸Centre for Transplant and Renal Research, Westmead Millennium Institute, The University of Sydney at Westmead, Westmead, Australia

Contact address: Evi V Nagler, Renal Division, Sector Metabolic and Cardiovascular Conditions, Ghent University Hospital, De Pintelaan 185, Ghent, 9000, Belgium. Evi.Nagler@UGent.be.

Editorial group: Cochrane Kidney and Transplant Group.

Publication status and date: New, published in Issue 6, 2018.

Citation: Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC. Interventions for chronic non-hypovolaemic hypotonic hyponatraemia. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD010965. DOI: [10.1002/14651858.CD010965.pub2](https://doi.org/10.1002/14651858.CD010965.pub2).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Chronic (present > 48 hours) non-hypovolaemic hyponatraemia occurs frequently, can be caused by various conditions, and is associated with shorter survival and longer hospital stays. Many treatments, such as fluid restriction or vasopressin receptor antagonists can be used to improve the hyponatraemia, but whether that translates into improved patient-important outcomes is less certain.

Objectives

This review aimed to 1) look at the benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia when compared with placebo, no treatment or head-to-head; and 2) determine if benefits and harms vary in absolute or relative terms dependent on the specific compound within a drug class, on the dosage used, or the underlying disorder causing the hyponatraemia.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 1 December 2017 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov. We also screened the reference lists of potentially relevant studies, contacted authors, and screened the websites of regulatory agencies.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of any intervention with placebo, no treatment, standard care, or any other intervention in patients with chronic non-hypovolaemic hypotonic hyponatraemia. We also included subgroups with hyponatraemia from studies with broader inclusion criteria (e.g. people with chronic heart failure or people with cirrhosis with or without hyponatraemia), provided we could obtain outcomes for participants with hyponatraemia from the report or the study authors.

Data collection and analysis

Two authors independently extracted data and assessed risk of bias. We expressed treatment effects as mean difference (MD) for continuous outcomes (health-related quality of life, length of hospital stay, change from baseline in serum sodium concentration, cognitive function), and risk ratio (RR) for dichotomous outcomes (death, response and rapid increase in serum sodium concentration, hyponatraemia, polyuria, hypotension, acute kidney injury, liver function abnormalities) together with 95% confidence intervals (CI).

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Main results

We identified 35 studies, enrolling 3429 participants. Twenty-eight studies (3189 participants) compared a vasopressin receptor antagonist versus placebo, usual care, no treatment, or fluid restriction. In adults with chronic, non-hypovolaemic hypotonic hyponatraemia, vasopressin receptor antagonists have uncertain effects on death at six months (15 studies, 2330 participants: RR 1.11, 95% CI 0.92 to 1.33) due to risk of selective reporting and serious imprecision; and on health-related quality of life because results are at serious risk of performance, selective reporting and attrition bias, and suffer from indirectness related to the validity of the Short Form Health Survey (SF-12) in the setting of hyponatraemia. Vasopressin receptor antagonists may reduce hospital stay (low certainty evidence due to risk of performance bias and imprecision) (3 studies, 610 participants: MD -1.63 days, 95% CI -2.96 to -0.30), and may make little or no difference to cognitive function (low certainty evidence due to indirectness and imprecision). Vasopressin receptor antagonists probably increase the intermediate outcome of serum sodium concentration (21 studies, 2641 participants: MD 4.17 mmol/L, 95% CI 3.18 to 5.16), corresponding to two and a half as many people having a 5 to 6 mmol/L increase in sodium concentration compared with placebo at 4 to 180 days (moderate certainty evidence due to risk of attrition bias) (18 studies, 2014 participants: RR 2.49, 95% CI 1.95 to 3.18). But they probably also increase the risk of rapid serum sodium correction - most commonly defined as > 12 mmol/L/d (moderate certainty evidence due to indirectness) (14 studies, 2058 participants: RR 1.67, 95% CI 1.16 to 2.40) and commonly cause side-effects such as thirst (13 studies, 1666 participants: OR 2.77, 95% CI 1.80 to 4.27) and polyuria (6 studies, 1272 participants: RR 4.69, 95% CI 1.59 to 13.85) (high certainty evidence). The potential for liver toxicity remains uncertain due to large imprecision. Effects were generally consistent across the different agents, suggesting class effect.

Data for other interventions such as fluid restriction, urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin were largely absent.

Authors' conclusions

In people with chronic hyponatraemia, vasopressin receptor antagonists modestly raise serum sodium concentration at the cost of a 3% increased risk of it being rapid. To date there is very low certainty evidence for patient-important outcomes; the effects on mortality and health-related quality of life are unclear and do not rule out appreciable benefit or harm; there does not appear to be an important effect on cognitive function, but hospital stay may be slightly shorter, although available data are limited. Treatment decisions must weigh the value of an increase in serum sodium concentration against its short-term risks and unknown effects on patient-important outcomes. Evidence for other treatments is largely absent.

Further studies assessing standard treatments such as fluid restriction or urea against placebo and one-another would inform practice and are warranted. Given the limited available evidence for patient-important outcomes, any study should include these outcomes in a standardised manner.

PLAIN LANGUAGE SUMMARY

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia

What is the issue?

A low blood sodium concentration can be caused by many conditions and is linked to shorter survival and longer hospital stays. Many treatments, such as fluid restriction or certain water pills called vasopressin receptor antagonists can be used to increase the blood sodium concentration, as long as increases happen slowly enough to avoid brain damage. Whether these treatments also improve patient outcomes (the way patients feel, function and survive) is less clear.

What did we do?

We included randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of any intervention with placebo, no treatment, standard care, or any other intervention in patients with chronic non-hypovolaemic hypotonic hyponatraemia.

What did we find?

Our systematic search (to December 2017) identified 35 studies, enrolling 3429 patients. Vasopressin receptor antagonists have unclear effects on the risk of death and quality of life, with additional studies needed to answer these questions. They likely improve the blood sodium concentration, but it sometimes happens too quickly. In addition, people who take vasopressin receptor antagonists may experience increased thirst and urine output. There is very little information for any of the other available treatments.

Conclusions

In people with low blood sodium concentration, vasopressin receptor antagonists modestly raised the sodium concentration. The effects on mortality and health-related quality of life are unclear and do not rule out appreciable benefit or harm; there does not appear to be an important effect on cognitive function, but hospital stay may be slightly shorter, although available data are limited. Evidence for other treatments is largely absent.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Vasopressin receptor antagonists versus placebo or no treatment for chronic non-hypovolaemic hypotonic hyponatraemia

Vasopressin receptor antagonists versus placebo or no treatment for chronic non-hypovolaemic hypotonic hyponatraemia

Patient or population: chronic non-hypovolaemic hypotonic hyponatraemia

Intervention: Vasopressin receptor antagonists

Comparison: placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo or no treatment	Vasopressin receptor antagonists				
Death	Study population		RR 1.11 (0.92 to 1.33)	2330 (15)	⊕⊕⊕⊕ VERY LOW 2, 3	Interpretation: effect uncertain; may both result in 11/1000 fewer to 47/1000 more deaths within 6 months
Follow-up: range 2 to 180 days	143 per 1000 ¹	159 per 1000 (132 to 190)				
Health-related quality of life (assessed with mental component score of SF-12 ⁴)	The mean change from baseline in health-related quality of life in the control group ranged between 0.75 and 2.39 on a 0 to 100 point scale (worst to best) ⁵	The mean health-related quality of life in the intervention group was 4.76 higher (0.11 higher to 9.41 higher)	-	297 (2)	⊕⊕⊕⊕ VERY LOW 6, 7	Physical component score also measured in both studies; RR 1.04; CI -1.81 to 3.90 Interpretation: anywhere from 0.1 to 9.5/100 points higher increase with treatment, but questionable tool for QoL measurement in hyponatraemia and unclear minimally important clinical difference
Follow-up: 30 days						
Length of hospital stay	The mean length of hospital stay in the control group was 6 to 11 days ⁵	The mean length of hospital stay in the intervention group was 1.63 days lower (2.96 lower to 0.30 lower)	-	580 (2)	⊕⊕⊕⊕ LOW 8,9	
Cognitive function (assessed with various tools)		Across five studies, confidence intervals spanned the line of no effect and did not	-	1169 (5)	⊕⊕⊕⊕ LOW 10	Tools used to assess cognitive function: making test B; reaction time, psychomotor, processing speeds; Mini mental state exam;

Follow-up: 1 to 6 months	include a clinically meaningful effect		overall meta-analysis including all five studies not meaningfully possible		
Change from baseline in serum sodium concentration	The mean change from baseline in serum sodium concentration in the control group was 0.3 to 4.8 mmol/L ⁵	The mean change from baseline in serum sodium concentration in the intervention group was 4.17 mmol/L higher (3.18 higher to 5.16 higher)	-	2641 (21)	⊕⊕⊕⊖ MODERATE ¹¹
Follow-up: range 1 to 180 days					
Serum sodium concentration (response)	Study population		RR 2.49 (1.95 to 3.18)	2104 (18)	⊕⊕⊕⊖ MODERATE ¹¹
Follow-up: range 4 to 180 days	231 per 1000 ¹	576 per 1000 (454 to 597)	Response most commonly defined by investigators as > 5 to > 6 mmol/L increase or normalisation of serum sodium concentration		
Rapid sodium increase	Study population		RR 1.67 (1.16 to 2.40)	2058 (14)	⊕⊕⊕⊖ MODERATE ¹²
Follow-up: range 1 to 5 days	44 per 1000 ¹	73 per 1000 (51 to 105)	Rapid increase most commonly defined as > 12 mmol/d		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

¹ Source of assumed baseline risk was calculated as the unweighted summed event rate in the control groups of the trials included in the meta-analysis

² Downgraded one level because studies considered at serious risk of suffering from

* selective reporting: 6/16 studies with treatment duration > 1 week did not report death and had no protocol, accounting for 16% of the total number of participants in those studies

* commercial sponsorship; possible financial conflict of interest of the authors: all studies sponsored by pharmaceutical companies wanting to commercialize the treatment; all save one had author lists who featured people who had received money for presentations or consultancy, or were employed by the sponsor; only used as supporting reason for downgrading.

³ Downgraded two levels for imprecision. The 95% CI of the pooled estimate includes both important reduction (11/1000 fewer) and increase (47/1000 more) in death with vasopressin receptor antagonists.

⁴ Choice of the outcome-measure based on the fact that this was the only one reported in any of the studies. There are concerns around the validity of the SF-12 as a measure for health-related quality of life in the field of hyponatraemia as it gauges domains and symptoms not directly attributable to hyponatraemia.

- ⁵ Source of the assumed baseline risk was the range of outcomes in the control groups of the trials included in the meta-analysis
- ⁶ Downgraded one level because studies considered seriously at risk of suffering from
- * Performance bias: self-reported outcome, participants likely unblinded to treatment due to polyuria as side effect
 - * Selective reporting bias: both mental and physical component score of SF-12 measured; at week 1 or 2 and day 30 using two different analytic techniques. Only data at day 30 available for analysis.
 - * Attrition bias: overall 37% of data missing, unknown whether missing at random or not.
 - * Commercial sponsorship or possible financial conflict of interest of authors: both studies were sponsored by the company seeking to commercialise the treatment; both had author lists who featured people who had received money for presentations or consultancy, or were employed by the sponsor; only used as supporting argument for downgrading
- ⁷ Downgraded one level for indirectness due to concerns around validity of the SF-12 for measuring quality of life in the context of hyponatraemia and one level for imprecision: only studied in two studies.
- ⁸ Downgraded one level because studies considered seriously at risk of suffering from performance bias: participants and personnel likely unblinded to treatment due to polyuria as side effect; this could have influenced self-reported and professional appreciation of clinical condition and so have influenced decision to discharge from hospital.
- ⁹ Downgraded one level for imprecision. The 95% CI of the pooled estimate includes both negligible shortening (0.3 days shorter) and clinically important shortening (3 days shorter) of hospital stay with vasopressin receptor antagonists.
- ¹⁰ Downgraded two levels for indirectness and imprecision. Only studied in 5/28 studies, with most data for lixivaptan, and other studies not reaching the optimal information size.
- ¹¹ Downgraded one level because we considered studies seriously at risk of suffering from
- * Attrition bias: 7/21 studies, accounting for 53% of the total number of participants in those studies at high risk of bias either due to true attrition or because a repeated measures analytic technique was used with all measurements of serum sodium concentration included until patient attrition, which we judged would likely have overestimated the treatment effect.
 - * Commercial sponsorship; only used as supporting argument.
- ¹² Downgraded one level for indirectness; risks controlled in tightly organised randomised trial with several measurements of serum sodium concentration daily to avoid rapid correction. In real life, risk of rapid correction likely greater. Commercial sponsorship bias; only used as supporting argument.

BACKGROUND

Description of the condition

Hypotonic hyponatraemia is a common condition, occurring in up to 60% of people admitted to hospitals, depending on the definition of hyponatraemia, the types of patients who are studied and the healthcare facility to which these patients are admitted (Upadhyay 2009). Hypotonic hyponatraemia is usually defined as a serum sodium concentration < 135 mmol/L with an osmolality < 285 mOsm/kg (Reynolds 2006). It develops when the body retains an excess of water relative to the amount of sodium. It can be caused by intrinsic kidney disease but usually results from incomplete suppression of vasopressin activity despite decreased tonicity of the plasma. In situations of decreased circulating blood volume, vasopressin release is increased in a physiologic response to maintain haemodynamic homeostasis. This occurs either with true volume depletion or with reduced effective arterial circulating volume, as seen in heart failure, liver cirrhosis or nephrotic syndrome. In the syndrome of inappropriate antidiuretic hormone secretion, the increased release of vasopressin is non-haemodynamic and can have multiple causes including ectopic production of vasopressin by a variety of tumours (Verbalis 2013).

When plasma tonicity is low, water tends to enter the cells and causes them to swell. If blood sodium concentrations drop rapidly (within a 48 hour period), the swelling of brain cells may lead to brain oedema, brain stem herniation and eventually even death. Fortunately, when blood sodium concentrations drop more gradually, brain cells adapt to their hypo-osmolar surroundings and prevent swelling by the transport of solutes from the intracellular to the extracellular compartments. As a consequence, immediate symptoms attributable to chronic hyponatraemia are usually less severe than for acute hyponatraemia (Reynolds 2006). Nevertheless, people with chronic hyponatraemia have reduced attention and less stable gait than those without hyponatraemia (Renneboog 2006). They fall more often and have increased risk of osteoporosis and bone fractures (Arampatzis 2013; Hoorn 2011; Kinsella 2010; Renneboog 2006; Verbalis 2010). Finally, they stay in hospital longer and have an increased risk of death, even when sodium concentrations are only mildly decreased and underlying or comorbid conditions are adjusted for (Wald 2010).

Description of the intervention

It is accepted that acute hypotonic hyponatraemia requires an immediate increase in serum sodium concentration to prevent severe neurologic complications (Ellison 2007). What to do with chronic hypotonic hyponatraemia is less clear. Firstly, chronic non-hypovolaemic hypotonic hyponatraemia has been treated under the assumption that increasing the sodium concentration improves important health outcomes; that patients live longer, feel better and are hospitalised less frequently. Although several observational studies have indicated an association between hyponatraemia and undesirable outcomes, it is still unclear whether correcting the hyponatraemia improves them (Upadhyay 2009; Wald 2010). Secondly, once brain cells have adapted to their hypo-osmolar environment, they become vulnerable to osmotic demyelination in case the hypo-osmolar environment is restored. Although rare, osmotic demyelination is a devastating neurologic complication that may occur when the myelin sheath around pontine and extrapontine neurons breaks down after rapid rises in serum sodium concentration. It very rarely does if the increases

stay below 8 to 12 mmol/L/24 h and 18 mmol/L/48 h - accepted limits depending on risk factors such as older age, malnutrition and alcohol abuse (Adrogue 2012; Ellison 2007; Reynolds 2006). Treatment for chronic hypotonic hyponatraemia must balance the uncertain benefit of increasing the sodium concentration against the risk of complications due to overly rapid correction.

How the intervention might work

Whatever the underlying cause, chronic non-hypovolaemic hypotonic hyponatraemia usually results from urine being insufficiently dilute to maintain serum osmolality within the normal range (Adrogue 2000). Several treatment strategies can be used to try overcoming this (Adrogue 2012; Ellison 2007; Verbalis 2013).

1. Restriction of fluid intake aims to decrease the amount of free water needing excretion.
2. Urea and mannitol improve electrolyte-free water clearance by increasing urine osmolality and creating osmotic diuresis (Lindner 2012).
3. Loop diuretics, such as furosemide, bumetanide and ethacrynic acid, impair free-water absorption in the collecting duct by reducing the hypertonicity of the renal medulla.
4. Corticosteroids with a mineralocorticoid effect increase renal sodium retention by active reabsorption of sodium in the principal cells of the cortical collecting tubule.
5. Demeclocycline, lithium, phenytoin and vasopressin receptor antagonists act by pharmacologically inhibiting the effect of antidiuretic hormone on the principal cells of the collecting duct, thereby limiting insertion of water channels in the luminal membrane and thus preventing free water reabsorption.

As hyponatraemia with true volume depletion (chronic hypovolaemic hypotonic hyponatraemia) is treated by restoring volume with water and salt, we do not cover it in this review.

Why it is important to do this review

The benefits and harms of treatments for chronic non-hypovolaemic hypotonic hyponatraemia have not been formally evaluated in a systematic review. Two systematic reviews have explored the efficacy and safety of vasopressin receptor antagonists (e.g. conivaptan, lixivaptan, satavaptan, tolvaptan) versus placebo, no treatment or fluid restriction (Jaber 2011; Rozen-Zvi 2010), but to our knowledge there has been no attempt to compare them with any other intervention or to compare any of the other interventions versus placebo or against one another.

Both systematic reviews have found an early increase in serum sodium concentration, but no improvement in outcomes important to patients. Indeed, most randomised controlled trials (RCTs) have evaluated short-term and surrogate outcomes only, making it difficult to adequately assess any expected benefit in the long-term. Since the most recent systematic review was published, 12 additional RCTs comparing vasopressin receptor antagonists versus control have been completed, increasing the total sample size by at least 50%. Although outcomes are still mostly surrogate and short-term, the largest study was terminated early due to a numeric imbalance in the number of early deaths in the experimental group (FDA 2012). Two vasopressin receptor antagonists have received wide-spread regulatory approval, but indications and permitted treatment durations vary among

regions. Divergent interpretations of survival and harms data are a likely cause.

OBJECTIVES

This review aimed to:

1. Look at the benefits and harms of interventions for chronic non-hypovolaemic hypotonic hyponatraemia when compared with placebo, no treatment or head-to-head;
2. Determine if benefits and harms vary in absolute or relative terms dependent on the specific compound within a drug class, on the dosage used, or the underlying disorder causing the hyponatraemia.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at interventions for chronic, non-hypovolaemic hypotonic hyponatraemia.

We also included data for hyponatraemia subgroups within studies with broader inclusion criteria (e.g. people with chronic heart failure or people with cirrhosis with or without hyponatraemia) which report outcomes for participants with hyponatraemia, or where we could obtain these subgroup data from the study authors.

Types of participants

Inclusion criteria

- Adults and children beyond the neonatal period (the interval from birth to 28 days of age)
- Chronic, hypotonic hyponatraemia: presence of hyponatraemia > 48 hours, serum osmolality < 285 mOsm/kg and serum sodium concentration < 135 mmol/L, or as defined by authors); not requiring immediate treatment and due to:
 - * decreased effective circulating volume in the setting of heart failure, liver cirrhosis or nephrotic syndrome;
 - * inappropriate antidiuresis, associated with any underlying condition (includes syndrome of inappropriate antidiuretic hormone secretion and nephrogenic syndrome of inappropriate antidiuresis); or
 - * impaired renal dilutional capacity due to kidney disease.

Sodium concentrations can be measured in any type of blood sample (e.g. serum, plasma, whole blood, venous, arterial, capillary) using any measurement method (e.g. flame emission spectrophotometry, direct or indirect reading potentiometry by an ion-selective electrode) in any setting (e.g. central laboratory, local laboratory, point of care device).

Exclusion criteria

- Children in the neonatal period (the interval from birth to 28 days of age)
- Isotonic or hypertonic hyponatraemia (osmolality $\geq$ 285 mOsm/kg)
- Hyponatraemia due to true (extracellular) volume depletion, such as from third spacing (type of fluid leakage into interstitial

spaces seen in pancreatitis, bowel obstruction, sepsis), and gastrointestinal, or renal sodium loss

- Hyponatraemia due to secondary adrenal insufficiency or hypothyroidism
- Hyponatraemia due to primary psychogenic polydipsia
- Patients treated with any form of dialysis or extracorporeal ultrafiltration.

Types of interventions

We included studies of any degree of fluid restriction or any drug treatment that has the aim of increasing the sodium concentration. Any dose or route of administration is permitted, and interventions can be compared with placebo, no treatment, a different dose of the same or different interventions, different administration routes of the same or different interventions, or different combinations of interventions.

Treatments included (but were not limited to):

- vasopressin receptor antagonists (conivaptan, mozavaptan, lixivaptan, satavaptan, tolvaptan)
- fluid restriction
- urea
- mannitol
- loop diuretics (furosemide, bumetanide, ethacrynic acid)
- corticosteroids (hydrocortisone or equivalent, fludrocortisone)
- demeclocycline
- lithium
- phenytoin.

We excluded studies in which any form of dialysis treatment was given to correct serum sodium concentration.

Types of outcome measures

We assessed outcomes up to one week, up to one, two and six months, and up to one and five years.

Primary outcomes

- Death (all-cause mortality)
- Health-related quality of life and specifically symptoms attributed to hyponatraemia by trialists.

Secondary outcomes

- Length of hospital stay
- Serum sodium concentration (mmol/L) at end of treatment or change from beginning to end of treatment
- Response defined as increase of $\geq$ 5 mmol/L or normalisation of serum sodium concentration ($\geq$ 135 to 145 mmol/L, or as defined by the authors)

- Outcomes related to over-correction of serum sodium concentration
 - * Incidence of hypernatraemia (serum sodium concentration > 145 mmol/L, or as defined by the authors)
 - * Rapid increase in serum sodium concentration (increase in serum sodium concentration > 8 to 12 mmol/L in 24 h or > 18 mmol/L in 48h, or as defined by the authors)
 - * Incidence of osmotic demyelination syndrome, previously known as central pontine and extrapontine myelinolysis (diagnosed clinically, by MRI, or post mortem)
- Any treatment-specific side effects as defined by authors
 - * AKI (demeclocycline, mannitol, loop diuretics)
 - * Chronic kidney disease (lithium)
 - * Hypotension (mannitol, loop diuretics, vasopressin receptor antagonists)
 - * Thirst (mannitol, loop diuretics, fluid restriction, vasopressin receptor antagonists)
 - * Central nervous system symptoms (phenytoin)
 - * Polyuria (mannitol, loop diuretics, vasopressin receptor antagonists)
 - * Any other adverse event as reported by trialists
- Treatment discontinuation or switch

Search methods for identification of studies

Electronic searches

We searched the [Cochrane Kidney and Transplant Register of Studies](#) up to 1 December 2017 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about [Cochrane Kidney and Transplant](#).

See [Appendix 1](#) for search terms used in strategies for this review.

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

3. Point-of-care sources such as Dynamed and UpToDate as well as US Food and Drug Administration (FDA) and European Medicines Agency (EMA) applications.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies possibly relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however studies and reviews that possibly included relevant data or information on studies of interest for our analysis were retained initially. Two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions these data were used.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool ([Higgins 2011](#)) (see [Appendix 2](#)).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
 - * Participants and personnel (performance bias)
 - * Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. death, number of patients with serum sodium concentration increase of ≥ 5 mmol/L, number of patients that develop hypernatraemia, number of patients with rapid increase in serum sodium concentration, number of patients that develop osmotic demyelination syndrome), individual study results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. length of hospital stay, serum sodium concentration at the end of the study or its change from beginning to the end of treatment), results were expressed as the mean difference (MD). For outcomes reported both as dichotomous and continuous data (thirst), we presented individual study results as odds ratios (OR), by converting standardized mean differences to the natural logarithm of the odds ratios ([Higgins 2011](#)).

Unit of analysis issues

If studies had multiple treatment groups, we tried to collapse these into one where appropriate to enable single pair wise comparison (e.g. collapsing three groups of different doses of vasopressin receptor antagonists into one group and including them in single pair wise comparison versus placebo) (Higgins 2011).

Dealing with missing data

Any further information required from the original authors was requested by emailing the corresponding author. If no response or insufficient information was retrieved, we subsequently emailed the sponsor. Any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population was performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a χ^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Funnel plots were used to assess for the potential existence of small study bias. If we suspected asymmetry on visual inspection and the analysis included > 10 studies, we conducted formal hypothesis testing, using Egger's test for continuous outcomes and Peter's regression test for dichotomous outcomes (Higgins 2011).

Data synthesis

Where feasible and appropriate, data were pooled using the random-effects model. Dichotomous outcome results were expressed as risk ratio (RR) and continuous outcome results were expressed as mean difference (MD), both with 95% confidence intervals. For outcomes reported both as dichotomous and continuous data (thirst), we converted standardized mean differences to log-transformed odds ratios, combined them using the generic inverse-variance method and expressed the overall effect estimate as an odds ratio with its 95% confidence interval (Higgins 2011). Although the underlying conditions causing hyponatraemia are very different, the mechanism by which hyponatraemia develops is similar in that vasopressin activity plays a role in most forms of the disorder. We believe it justified pooled analysis across subgroups of participants with different underlying conditions.

We summarised the quality of the evidence together with absolute treatment effects based on estimated baseline risks by using the Grading of Recommendations Assessment, Development, and Evaluation guidelines (GRADE 2008). To estimate the absolute number of people with hyponatraemia who avoided death or incurred a rapid increase in serum sodium concentration with vasopressin receptor antagonists, the risk estimate and 95% CI were obtained from the control arm of the corresponding meta-analyses.

Subgroup analysis and investigation of heterogeneity

We analysed data for death, length of hospital stay, change from baseline and response in serum sodium concentration, cognitive function and outcomes related to over correction of serum sodium concentration within subgroups of participants dependent on the type of vasopressin receptor antagonist they were treated with. Additional prespecified subgroup analyses and univariate random effects meta-regression were conducted to explore potential sources of heterogeneity in effects of vasopressin receptor antagonists on death, change in serum sodium concentration and rapid increase in serum sodium concentration. The potential sources of heterogeneity included type of vasopressin receptor antagonist under evaluation, the underlying condition causing the hyponatraemia (with as non-prespecified categories studies only including participants with inappropriate antidiuresis; studies only including participants with heart failure or liver cirrhosis or studies including both), mean baseline serum sodium concentration, treatment duration and risk of selection bias. Meta-regression was undertaken on the log RR scale for categorical outcomes using Comprehensive Meta-Analysis® software, each study weighting equal to the inverse of the variance of the estimate for that study, with between study variance estimated using the restricted the method of moments. Results were expressed as the ratio of the RR within each subgroup for categorical explanatory variables and per one unit increase for continuous variables.

Sensitivity analysis

In addition to estimating treatment effects using random effects models, we also estimated fixed effects models to ensure robustness of the model chosen and susceptibility to outliers. Finally we also assessed whether including the number of deaths during follow-up (in contrast to only including those occurring during treatment) affected the estimate of the effect of treatment on all-cause mortality.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Death
- Health-related quality of life, assessed with the mental component score and physical component score of the Short Form Health Survey (SF-12)
- Cognitive function
- Length of hospital stay
- Change from baseline in serum sodium concentration

- Response of serum sodium concentration: defined as 4 to 6 mmol/L increase or normalisation
- Rapid sodium increase

the reference lists, contacting authors, conducting online searches for full reports of included abstracts, searching online trial registries, and screening the website of regulatory agencies. We reviewed in detail 157 reports, which led to the inclusion of 111 reports of 35 unique studies including 3429 participants ([Figure 1](#)).

RESULTS

Description of studies

Results of the search

We identified 1954 citations through electronic searches conducted in 1 December 2017. We found 16 additional reports by screening

Figure 1. Study flow diagram.

Included studies

Twenty-eight studies (providing data for 3189 participants) compared a vasopressin receptor antagonist versus placebo, usual care or no treatment ([ACTIV in CHF 2003](#); [Annane 2009](#); [BALANCE 2010](#); [Decaux 2006](#); [DILIPO 2011](#); [EVEREST 2005](#); [Ghali 2006](#); [Gheorghiade 2003](#); [Gines 2008b](#); [Gerbes 2003](#); [HARMONY 2012](#); [HYPOCAT 2008](#); [INSIGHT 2016](#); [Koren 2011](#); [LIBRA 2012](#); [Naidech 2010](#); [Nevens 2009](#); [Otsuka Study 2011a](#); [Otsuka Study 2011b](#); [Otsuka Study 2011c](#); [Salahudeen 2014](#); [SALT-1 2006](#); [SALT-2 2006](#); [Soupart 2006](#); [Wong 2003b](#); [Yang 2013](#); [Zeltser 2007](#)), or versus fluid restriction ([Gheorghiade 2006](#)). Studied vasopressin receptor antagonists included conivaptan ([Annane 2009](#); [Ghali 2006](#); [Koren 2011](#); [Naidech 2010](#); [Zeltser 2007](#)), lixivaptan ([BALANCE 2010](#); [Gerbes 2003](#); [HARMONY 2012](#); [LIBRA 2012](#); [Wong 2003b](#)), satavaptan ([Decaux 2006](#); [DILIPO 2011](#); [Gines 2008b](#); [HYPOCAT 2008](#); [Soupart 2006](#)), tolvaptan ([ACTIV in CHF 2003](#); [EVEREST 2005](#); [Gheorghiade 2003](#); [Gheorghiade 2006](#); [INSIGHT 2016](#); [Otsuka Study 2011a](#); [Otsuka Study 2011b](#); [Otsuka Study 2011c](#); [Salahudeen 2014](#); [SALT-1 2006](#); [SALT-2 2006](#); [Yang 2013](#)) and M0002 - also termed SPD556 or RWJ 351647 ([Nevens 2009](#)). Two studies assessed different doses conivaptan ([Kalra 2011](#)) or tolvaptan ([Shoaf 2017](#))

[Singhi 1995](#) (50 participants) compared fluid restriction with normal maintenance fluid in children with bacterial meningitis and reported data for the subgroup with hyponatraemia (26 participants). [Dzau 1984](#) (14 participants) compared captopril + furosemide versus furosemide alone in adults with decompensated heart failure. [Jalan 2007](#) (24 participants) compared infusion of human salt poor albumin in combination with fluid and sodium restriction versus fluid and sodium restriction alone in patients with liver cirrhosis and ascites. [Hayes 1987](#) (10 participants) compared early versus delayed administration of urea, and [NATRIPHAR 2013](#) (19 participants) compared a change in prescribed medications versus standard care in elderly patients admitted to the internal medicine ward or residents of the nursing home of the same institution.

Twenty-eight studies were conducted specifically in participants with hyponatraemia ([Annane 2009](#); [BALANCE 2010](#); [Decaux 2006](#); [Dzau 1984](#); [Ghali 2006](#); [Gheorghiade 2006](#); [Gines 2008b](#); [Gerbes 2003](#); [HARMONY 2012](#); [Hayes 1987](#); [HYPOCAT 2008](#); [INSIGHT 2016](#); [Jalan 2007](#); [Kalra 2011](#); [Koren 2011](#); [LIBRA 2012](#); [Naidech 2010](#); [Nevens 2009](#); [NATRIPHAR 2013](#); [Otsuka Study 2011b](#); [Otsuka Study 2011c](#); [Salahudeen 2014](#); [SALT-1 2006](#); [SALT-2 2006](#); [Soupart 2006](#); [Wong 2003b](#); [Yang 2013](#); [Zeltser 2007](#)). For five studies, participants with hyponatraemia formed a subgroup of a larger study including

both participants with and without hyponatraemia ([ACTIV in CHF 2003](#); [DILIPO 2011](#); [EVEREST 2005](#); [Gheorghiade 2003](#) [Singhi 1995](#)).

Studies included on average mostly older adults (median 65 years, interquartile range 5) with moderate hyponatraemia (median 129 mmol/L; range 124 to 133). Participants had as primary cause of hyponatraemia a syndrome of inappropriate antidiuresis in nine studies ([Decaux 2006](#); [HARMONY 2012](#); [LIBRA 2012](#); [Naidech 2010](#); [NATRIPHAR 2013](#); [Otsuka Study 2011a](#); [Salahudeen 2014](#); [Singhi 1995](#); [Soupart 2006](#)), heart failure in seven studies ([ACTIV in CHF 2003](#); [BALANCE 2010](#); [Dzau 1984](#); [EVEREST 2005](#); [Gheorghiade 2003](#); [Otsuka Study 2011b](#); [Yang 2013](#)) and liver cirrhosis in six studies ([Gines 2008b](#); [Hayes 1987](#); [HYPOCAT 2008](#); [Jalan 2007](#); [Nevens 2009](#); [Otsuka Study 2011c](#)). The others included a mixed group of patients. Sample sizes varied and were generally small (median 69 participants; range 6 to 652). Treatment was mostly short-term (median 8 days; range 1 to 365). Data for at least one outcome of interest were available from 31 studies and 3365 participants, two studies reported no numeric data ([Jalan 2007](#); [Otsuka Study 2011c](#)).

Excluded studies

We excluded 35 studies (46 reports). Thirty-three did not include the appropriate population, with participants either not having hyponatraemia at randomisation ([Albert 2013](#); [De Vita 2012](#); [Galton 2011](#); [Mori 1999](#); [Owen 2014](#); [Ramsay 1988](#); [Zamboli 2011](#); [Zellweger 2001](#)), some participants possibly having hyponatraemia but without available subgroup data ([Abraham 2006](#); [Angeli 2010](#); [Ghali 2012](#); [Guyader 2002](#); [K-STAR 2017](#); [Licata 2003](#); [Matsuzaki 2011a](#); [Matsuzaki 2011b](#); [Okita 2014](#); [Paterna 2000](#); [Sakaida 2014](#); [SECRET of CHF 2017](#); [Shanmugam 2016](#); [Suzuki 2013b](#); [TACT-ADHF 2016](#); [TACTICS-HF 2017](#); [Thuluvath 2006](#); [Wong 2009](#); [Wong 2010a](#); [Wong 2012](#); [Yang 2010b](#)); having hyponatraemia but caused by psychogenic polydipsia ([Alexander 1991](#)), prolonged exercise ([Rogers 2011](#)), or head and neck surgery ([Rajan 2015](#)); or having severe symptoms requiring immediate treatment [SALSA 2017](#)). One study compared two different salt-restricted diets in combination with step-wise increase of diuretic treatment for reducing weight and ascites in patients with decompensated liver cirrhosis ([Bernardi 1993](#)); and finally one study ([Gines 2007](#)) would have led to double counting of participants as it represented a second randomised trial built on top of a first included study ([HYPOCAT 2008](#)) using the same study medication.

Risk of bias in included studies

The risk of bias is described in ([Figure 2](#); [Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ACTIV in CHF 2003	?	+	-	+	+	-	-
Annane 2009	?	?	+	+	+	+	-
BALANCE 2010	+	+	?	+	+	+	-
Decaux 2006	?	?	?	+	?	+	-
DILIPO 2011	+	?	+	+	+	+	-
Dzau 1984	?	?	-	+	+	-	+
EVEREST 2005	+	+	-	+	-	-	-
Gerbes 2003	+	+	+	+	?	-	-
Ghali 2006	?	?	+	+	+	+	-
Gheorghiade 2003	?	+	-	+	-	-	-
Gheorghiade 2006	?	?	-	+	+	-	-
Gines 2008b	?	?	-	-	?	-	-
HARMONY 2012	?	?	+	+	-	+	-
Hayes 1987	?	?	?	?	?	?	?
HYPOCAT 2008	+	+	+	+	+	-	-
INSIGHT 2016	?	?	-	+	+	+	-
Jalan 2007	?	?	-	+	?	-	?
Kalra 2011	?	?	+	+	+	+	-
Koren 2011	?	?	+	+	+	+	-
LIBRA 2012	?	?	+	+	-	+	-

Figure 3. (Continued)

LIBRA 2012	?	?	+	+	-	+	-
Naidech 2010	+	+	-	+	+	+	?
NATRIPHAR 2013	+	+	-	+	-	+	+
Nevens 2009	?	?	?	+	?	-	-
Otsuka Study 2011a	+	?	+	+	+	-	-
Otsuka Study 2011b	+	?	?	+	+	-	-
Otsuka Study 2011c	?	?	?	+	?	-	-
Salahudeen 2014	+	+	+	+	+	-	-
SALT-1 2006	+	+	+	+	-	-	-
SALT-2 2006	+	+	+	+	-	-	-
Shoaf 2017	?	?	+	?	+	+	?
Singhi 1995	+	?	?	+	+	+	+
Soupart 2006	?	?	+	+	+	+	-
Wong 2003b	+	+	-	+	-	-	-
Yang 2013	?	?	?	?	?	-	?
Zeltser 2007	?	?	+	+	-	+	-

Allocation

The allocation sequence was adequately generated in 14 studies (BALANCE 2010; DILIPO 2011; EVEREST 2005; Gerbes 2003; HYPOCAT 2008; Naidech 2010; NATRIPHAR 2013; Otsuka Study 2011a; Otsuka Study 2011b; Salahudeen 2014; SALT-1 2006; SALT-2 2006; Singhi 1995; Wong 2003b). and adequately concealed in 12 studies (ACTIV in CHF 2003; BALANCE 2010; EVEREST 2005; Gheorghiade 2003; Gerbes 2003; HYPOCAT 2008; Naidech 2010; NATRIPHAR 2013; Salahudeen 2014; SALT-1 2006; SALT-2 2006; Wong 2003b). For the remaining studies the authors provided insufficient information about the procedures to permit a judgement of the risk of bias.

Blinding

In 26 studies, all assessing a vasopressin receptor antagonist, the investigators attempted to blind participants and personnel by providing a matching placebo (ACTIV in CHF 2003; Annane 2009; BALANCE 2010; Decaux 2006; DILIPO 2011; EVEREST 2005; Ghali 2006; Gheorghiade 2003; Gines 2008b; Gerbes 2003; HARMONY 2012; HYPOCAT 2008; INSIGHT 2016; Kalra 2011; Koren 2011; LIBRA 2012; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; SALT-1 2006; SALT-2 2006; Soupart 2006; Wong 2003b; Zeltser 2007). Although it was probably unlikely for participants and personnel to be fully blinded due to important increases in urine output when treated with a vasopressin receptor antagonist, co-interventions of fluid restriction or salt-intake were reported and similar in 12 studies (Annane 2009; DILIPO 2011; Ghali 2006; Gerbes 2003;

HARMONY 2012; HYPOCAT 2008; Kalra 2011; Koren 2011; LIBRA 2012; Salahudeen 2014; Soupart 2006; Zeltser 2007). For two studies, fluid restriction could be adapted by both participant and treating physician (e.g. based on urine output). We judged this would not have introduced important risk of bias for death and objective outcomes related to serum sodium concentration, but may have biased health-related quality of life measures and resulted in biased estimates of risk of rapid increase in serum sodium concentration (SALT-1 2006; SALT-2 2006).

Three studies explicitly reported blinding of outcomes assessors (BALANCE 2010; SALT-1 2006; SALT-2 2006). In 28 others we judged blinding of outcome assessors would likely have occurred or measured outcomes were objective enough so that the risk of bias was probably low (ACTIV in CHF 2003; Annane 2009; Decaux 2006; DILIPO 2011; Dzau 1984; EVEREST 2005; Ghali 2006; Gheorghiade 2003; Gheorghiade 2006; Gerbes 2003; HARMONY 2012; HYPOCAT 2008; INSIGHT 2016; Jalan 2007; Kalra 2011; Koren 2011; LIBRA 2012; Naidech 2010; NATRIPHAR 2013; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; Singhi 1995; Soupart 2006; Wong 2003b; Zeltser 2007).

Incomplete outcome data

In 17 studies, attrition stayed below 20% with either well documented reasons and/or limited opportunity for important bias (ACTIV in CHF 2003; Annane 2009; BALANCE 2010; DILIPO 2011; Dzau 1984; Ghali 2006; Gheorghiade 2006; HYPOCAT 2008; INSIGHT 2016; Kalra 2011; Koren 2011; Naidech 2010; Otsuka Study

2011a; Otsuka Study 2011b; Salahudeen 2014; Singhi 1995; Soupart 2006). Eight studies had attrition rates > 25% and either did not attempt to re-include participants in the analysis (EVEREST 2005; Gheorghiade 2003 NATRIPHAR 2013) or used imputation methods to deal with missing serum sodium concentration values that may have caused overestimation of the effect of the study medication - e.g. last observation carried forward, thus ignoring rebound hyponatraemia on cessation of treatment (HARMONY 2012; LIBRA 2012; SALT-1 2006; SALT-2 2006; Wong 2003b; Zeltser 2007). The others provided insufficient information to allow judgement of high or low risk of bias (Decaux 2006; Gheorghiade 2003; Gines 2008b; Gerbes 2003; Hayes 1987; Jalan 2007; Nevens 2009; Otsuka Study 2011c; Yang 2013).

Selective reporting

For 15 studies, we found a registered protocol in a trial registry (ACTIV in CHF 2003; BALANCE 2010; DILIPO 2011; EVEREST 2005; HARMONY 2012; HYPOCAT 2008; INSIGHT 2016; LIBRA 2012; Naidech 2010; NATRIPHAR 2013; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; SALT-1 2006; SALT-2 2006). The Otsuka Study was registered as a single study but reported as three separate studies (Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c). Investigators fully reported all expected pre-registered outcomes at pre-registered time-points in two studies (INSIGHT 2016; Naidech 2010). Whether a protocol was provided or not, for 12 studies investigators reported all expected outcomes related to benefit and harms at reasonable time-points (Annane 2009; Decaux 2006; DILIPO 2011; Ghali 2006; HARMONY 2012; Kalra 2011; Koren 2011; LIBRA 2012; NATRIPHAR 2013; Singhi 1995; Soupart 2006; Zeltser 2007). In seven studies with treatment duration > one week, authors did not report the primary outcomes all-cause mortality or health-related quality of life or any outcome related to rapid increases in serum sodium concentration (ACTIV in CHF 2003; Gheorghiade 2003; HYPOCAT 2008; Gines 2008b; Nevens 2009; Salahudeen 2014; Yang 2013). In eight studies with treatment duration ≤ 1 week, authors did not report any secondary outcome related to serum sodium concentration or rapid increases thereof (Dzau 1984; Gheorghiade 2006; Gerbes 2003; Jalan 2007; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Wong 2003b).

Other potential sources of bias

Bias through possible financial conflict of interest of the authors, sponsorship bias, or both

Industry funded 28 studies (ACTIV in CHF 2003; Annane 2009; BALANCE 2010; Decaux 2006; DILIPO 2011; EVEREST 2005; Ghali 2006; Gheorghiade 2003; Gheorghiade 2006; Gerbes 2003; HARMONY 2012; HYPOCAT 2008; INSIGHT 2016; Kalra 2011; LIBRA 2012; Koren 2011; Naidech 2010; Nevens 2009; Otsuka Study 2011a; Otsuka Study 2011b; Otsuka Study 2011c; Salahudeen 2014; Salahudeen 2014; SALT-1 2006; SALT-2 2006; Soupart 2006; Wong 2003b; Zeltser 2007). The funding source was unclear for six studies (Dzau 1984; Gines 2008b; Jalan 2007; NATRIPHAR 2013; Singhi 1995; Yang 2013). For 17 studies we retrieved a declaration of interest for the authors featuring on the reports (ACTIV in CHF 2003; Annane 2009; DILIPO 2011; EVEREST 2005; Ghali 2006; Gheorghiade 2003; Gines 2008b; Gerbes 2003; HARMONY 2012; HYPOCAT 2008; Kalra 2011; Koren 2011; LIBRA 2012; Naidech 2010; SALT-1 2006; SALT-2 2006; Zeltser 2007). All save one (Naidech 2010) had author lists who featured people who had received money for presentations or consultancy, or were employed by the sponsor.

Effects of interventions

See: [Summary of findings for the main comparison Vasopressin receptor antagonists versus placebo or no treatment for chronic non-hypovolaemic hypotonic hyponatraemia](#)

Vasopressin receptor antagonists versus placebo or no treatment

Primary outcomes

Vasopressin receptor antagonists had uncertain effects on mortality, results being compatible with both 11 in 1000 fewer to 47 in 1000 more deaths within six months ([Analysis 1.1](#) (15 studies, 2330 participants): RR 1.11, 95% CI 0.92 to 1.33; $I^2 = 0\%$). Using GRADE criteria, we downgraded the certainty of the evidence three levels from high to very low, partly because of this imprecision, partly for a risk of selective reporting ([Guyatt 2010](#)). Six of 16 long-term studies reasonably expected to measure death as an outcome did not, and the absence of a protocol did not allow to assess whether its measurement may have been planned, but not reported (Gheorghiade 2003; Gines 2008b; HYPOCAT 2008; Nevens 2009; Wong 2003b; Yang 2013).

Vasopressin receptor antagonists increased scores for the mental component summary of the SF-12 ([Analysis 1.2.1](#) (2 studies, 297 participants): MD 4.76, 95% CI 0.11 to 9.41, $I^2 = 63\%$), but had unclear effects on the physical component summary score ([Analysis 1.2.2](#) (2 studies, 297 participants): MD 1.04, 95% CI -1.81 to 3.90, $I^2 = 0\%$). We downgraded the certainty of the evidence for these outcomes one level because we judged the results to be at serious risk of performance bias due to likely unblinding of the participants with a self-reported outcome; of selective reporting bias due to outcomes being measured at two different time-points with only one time-point reported; of attrition bias due to more than one third of the overall data being missing. We downgraded two additional levels for imprecision and indirectness, because of concerns around the validity of the SF-12 for measuring quality of life in the context of hyponatraemia.

Five studies evaluated cognitive function (BALANCE 2010; HARMONY 2012; LIBRA 2012; INSIGHT 2016; Salahudeen 2014). In three studies, two of which provided data that could reliably contribute to meta-analysis ((BALANCE 2010; LIBRA 2012), investigators used the trail making test part B, a neuropsychological test of visual attention and task switching. They found lixivaptan did not shorten the time to complete the test ([Analysis 1.3](#) (858 participants): MD 6.89 sec, 95% CI -6.34 to 20.12). A fourth study tested reaction time, psychomotor and processing speeds and found no difference in change between the groups (INSIGHT 2016, 56 participants, 0.20, 95% CI -0.10 to 0.50). The fifth study, assessing the change in mini mental state exam with tolvaptan, found no change from baseline (Salahudeen 2014, 30 participants, MD -0.70, 95% CI -2.23, 0.83). We considered the evidence of moderate certainty, downgrading one level mainly because of some indirectness and imprecision as it is unclear to what extent the used tools reflect the impairment thought to be caused by hyponatraemia, and the outcome was infrequently studied.

Three studies found vasopressin receptor antagonists shortened hospital stay anywhere between 0.3 and 3 days ([Analysis 1.4](#) (3 studies, 610 participants): MD -1.63 days, 95% CI -2.96 to -0.30, $I^2 = 0\%$). We downgraded the certainty of the evidence one level

because we judged it at serious risk of suffering from performance bias, as participants and personnel were likely unblinded due to polyuria as a side-effect and this could have influenced self-reported and professional appreciation of clinical condition and so have influenced decision to discharge from hospital. We downgraded an additional level for imprecision as the confidence interval of the pooled effect included both a negligible effect and a clinically important one.

Secondary outcomes

Vasopressin receptor antagonists caused a modest increase in serum sodium concentration. At the end of treatment, participants treated with placebo had an average increase in serum sodium concentration ranging from 0.5 to 4.7 mmol/L. In comparison, people treated with a vasopressin receptor antagonist had an average increase that was approximately 4 mmol/L higher ([Analysis 1.5](#) (21 studies, 2641 participants): MD 4.17 mmol/L, 95% CI 3.18 to 5.16; $I^2 = 91\%$). These results were generally consistent for studies with shorter and longer follow-up. Although there was substantial heterogeneity among included studies as described by the I^2 , individual point estimates all favoured vasopressin receptor antagonists. Investigators often also analysed serum sodium concentration as a dichotomous outcome, defining response as an increase of 5 to 6 mmol/L or normalisation of the absolute value. Defined as such, the previous data translated into two and a half as many people having a response with vasopressin receptor antagonists compared with placebo ([Analysis 1.6](#) (18 studies, 2104 participants): RR 2.49, 95% CI 1.95 to 3.18; $I^2 = 56\%$). On average 23% of participants treated with placebo had a response versus 57% treated with a vasopressin receptor antagonist. Overall, in absolute terms this implies treating three adults with hyponatraemia with a vasopressin receptor antagonist could result in one more individual attaining an increase in serum sodium concentration of 5 mmol/L. We downgraded the certainty of the evidence from high to moderate because in 7/21 studies, accounting for 53% of the total number of participants in those studies, we harboured serious concerns around attrition bias; either because outcomes were not measured in the participants that dropped out, or because analytic techniques were used that included all measurements of serum sodium concentration included until patient attrition, both of which we judged would likely have overestimated the treatment effect.

Treatment with a vasopressin receptor antagonist raised the risk of rapid increases in serum sodium concentration by 67%, resulting in three additional people with a rapid increase per 100 treated with a vasopressin receptor antagonist versus placebo ([Analysis 1.7](#) (14 studies, 2058 participants): RR 1.67, 95% CI 1.16 to 2.40; $I^2 = 0\%$). The analysis showed no significant heterogeneity. Additional sensitivity analysis including only studies defining an increase in serum sodium concentration of > 12 mmol/L/24 h did not meaningfully change the results ([Analysis 1.14.2](#) (10 studies, 1801 participants): RR 1.63, 95% CI 1.09 to 2.43; $I^2 = 0\%$). The effects

for hypernatraemia were unclear ([Analysis 1.8](#) (10 studies, 1595 participants): RR 1.37, 95% CI 0.63 to 3.01; $I^2 = 1\%$). None of the included studies reported participants developing osmotic demyelination syndrome. For similar concerns related to attrition bias as, we considered the evidence to be of moderate certainty.

Overall, treatment with vasopressin receptor antagonists increased the odds for thirst nearly three times compared versus treatment with placebo ([Analysis 1.9](#) (13 studies, 1666 participants): OR 2.77, 95% CI 1.80 to 4.27; $I^2 = 66\%$). Other side-effects were generally less extensively reported. Nevertheless there was some evidence vasopressin receptor antagonists substantially increased the risk of polyuria ([Analysis 1.10.1](#) (6 studies, 1272 participants): RR 4.69, 95% CI 1.59 to 13.85, $I^2 = 0\%$). The risk remained uncertain for hypotension ([Analysis 1.10.2](#) (14 studies, 1748 participants): RR 1.11, 95% CI 0.75 to 1.63; $I^2 = 0\%$), AKI ([Analysis 1.10.3](#) (8 studies, 1920 participants): RR 0.89, 95% CI 0.67 to 1.18; $I^2 = 0\%$), and liver function abnormalities ([Analysis 1.10.4](#) (3 studies, 811 participants): RR 2.43, 95% CI 0.88 to 6.70; $I^2 = 0\%$). Half of the studies in which the vasopressin receptor antagonist was administered intravenously evaluated important adverse events related to the infusion itself. Overall there were almost three times as many patients developing infusion-site phlebitis ([Analysis 1.11.2](#) (2 studies, 133 participants): RR 3.52, 95% CI 1.00 to 12.41; $I^2 = 0\%$); the effects for infusion-site thrombosis were less clear ([Analysis 1.11.3](#) (2 studies, 133 participants): RR 1.75, 95% CI 0.21 to 14.80; $I^2 = 0\%$). There were slightly fewer people who discontinued treatment when given placebo than when given a vasopressin receptor antagonist ([Analysis 1.12](#) (14 studies, 2429 participants): RR 0.93, 95% CI 0.85 to 1.00; $I^2 = 0\%$).

Analysis of heterogeneity

Using univariate meta-regression and subgroup analyses, we explored possible sources of heterogeneity in the effect of vasopressin receptor antagonists on the change in serum sodium concentration. Our prespecified potential sources were: the specific vasopressin receptor antagonist compound, the underlying condition causing the hyponatraemia (with as non-prespecified categories studies only including participants with inappropriate antidiuresis; studies only including participants with heart failure or liver cirrhosis or studies including both), mean baseline serum sodium concentration, treatment duration and risk of selection bias as sources of heterogeneity. A higher serum sodium concentration at baseline resulted in smaller increases in serum sodium with treatment ([Figure 4](#)). Per 1 mmol/L increase in baseline serum sodium concentration between 124 and 133 mmol/L, the mean difference on average decreased from 5.7 by 0.33 mmol/L (95% CI -0.89 to -0.60) to 2.7 mmol/L ([Table 1](#)). There was no evidence that the compound, the cause of hyponatraemia, the treatment duration or risk of selection bias modified the effect of vasopressin receptor antagonists on change from baseline in serum sodium concentration.

Figure 4. Effect of baseline serum sodium concentration on change in natraemia: meta-regression

We observed asymmetry in the funnel plot for the outcomes of response, suggesting the presence of small-study effects or publication bias, such that studies with small or null effects are not in the public domain and were not uncovered by our sensitive searching (Figure 5, Peters' regression test, $P = 0.002$). Sensitivity analysis for this outcome excluding four studies with the largest effect estimates and largest estimate of variance reduced the

relative risk with 30% (RR 2.07, 95% CI 1.67 to 2.56). However, the funnel plots for other related outcomes were more symmetrical. No asymmetry was observed in funnel plots for change and rapid increase in serum sodium concentration, thirst, treatment discontinuation, and data for death, length of hospital stay, cognitive function, hypernatraemia or other adverse events were insufficient to allow for detection of small-study effects.

Figure 5. Funnel plot of comparison: 1 Vasopressin receptor antagonists versus placebo or no treatment, outcome: 1.6 Response in serum sodium concentration.

Sensitivity analysis

Including the number of deaths occurring during follow-up rather than during treatment had little effect on the estimate of the treatment effect ([Analysis 1.13](#) (16 studies, 2404 participants): RR 1.10, 95% CI 0.91 to 1.32).

For the serum sodium concentration analysis, when we excluded seven studies judged at high or unclear risk of performance bias, the summary treatment estimate remained unchanged (14 studies, 1458 participants: MD 4.89 mmol/L, 95% CI 4.02 to 5.76). When we excluded eight studies judged at high or unclear risk of attrition bias, we found similar treatment effect estimates (13 studies, 1342 participants: MD 4.71 mmol/L, 95% CI 3.34 to 6.08).

Conivaptan versus conivaptan

[Kalra 2011](#) (117 participants) compared four regimens with or without a loading dose with one another and found no significant difference in any of the measured outcomes (death, change from baseline serum sodium concentration, response in serum

sodium concentration, thirst, injection-site phlebitis, injection-site thrombosis, treatment discontinuation (data not shown).

Tolvaptan versus tolvaptan

[Shoaf 2017](#) (30 participants) compared 3 single doses with one another and found rapid correction in 1, 1 and 2 subjects in the 3.75, 7.5, and 15 mg dose groups respectively, but only abstract data was available and the number of participants in each group was not reported (data not shown).

Fluid restriction versus normal maintenance fluid treatment

[Singhi 1995](#) (26 participants) compared fluid restriction (calculated as 65% of normal) versus normal maintenance intravenous fluid administration in children with bacterial meningitis. At two days, administration of restricted volumes significantly increased the serum sodium concentration ([Figure 6](#) (1 study, 26 participants): MD 4.40 mmol/L, 95% CI 1.79 to 7.01), but had uncertain effects on the risk of death ([Figure 6](#) (1 study, 26 participants): RR 7.80, 95% CI 0.46 to 131.62).

Figure 6. Single study results

Comparisons and outcomes	No. of participants	Effect size (95% CI)
Fluid restriction versus normal maintenance fluid treatment		
Death	26	RR 7.80 (0.46 to 131.620)
Change from baseline serum sodium concentration	26	MD 4.40 mmol/L (1.79 to 7.01)
Captopril + furosemide versus furosemide		
Serum sodium concentration	14	MD 10.00 mmol/L (8.60 to 11.40)
Medication change versus standard care		
Death at 1 month	19	RR 0.37 (0.02 to 8.01)
Death at 3 months	14	RR 0.75 (0.06 to 9.72)
Change from baseline serum sodium concentration at 1 month	14	MD 1.70 mmol/L (-1.39 to 4.79)
Response in serum sodium concentration at 1 month	14	RR 10.11 (0.68 to 150.68)
Hyponatraemia at 1 month	14	Not estimable
Osmotic demyelinating syndrome	14	Not estimable

Captopril and furosemide versus captopril

Dzau 1984 (14 participants) found after five days of treatment, the combination of captopril and furosemide resulted in a 10 mmol/L higher serum sodium concentration compared with captopril alone (Figure 6 (1 study, 14 participants): MD 10.00 mmol/L, 95% CI 8.60 to 11.40). The report did not include outcomes related to death, quality of life or adverse events due to rapid increases in serum sodium concentration caused by treatment.

Albumin versus no treatment

Jalan 2007 (24 participants) compared infusion of human salt poor albumin in combination with fluid and sodium restriction versus fluid and sodium restriction alone in patients with refractory ascites caused by liver cirrhosis. We only identified an abstract and it did not include any comparative data.

Urea versus urea

Hayes 1987 (10 participants) compared urea given immediately after development of hyponatraemia in people with ascites under diuretics versus urea given after a 'no treatment interval' of three days. We only identified an abstract and it did not include any comparative data.

Medication change versus standard care

NATRIPHAR 2013 (19 participants) compared a change in medication regimen to standard care in older adults suspected of having drug-induced hyponatraemia. Compared with standard care, changing the medication regimen had uncertain effects on risk of death (Figure 6 (1 study, 19 participants): RR 0.37, 95% CI 0.02 to 8.01), response in serum sodium concentration (Figure 6 (1 study 14 participants): RR 10.11, 95% CI 0.68 to 150.68) and change from baseline in serum sodium concentration at one month (Figure 6 (1 study, 14 participants): MD 1.70, 95% CI -1.39 to 4.79). No participant in either group developed hyponatraemia or osmotic demyelination syndrome.

No studies evaluated the effects of urea, mannitol, loop diuretics with or without oral sodium chloride, corticosteroids, demeclocycline, lithium or phenytoin with regard to correction of hyponatraemia.

DISCUSSION

Summary of main results

This review included evidence from 35 randomised controlled trials involving 3429 participants, primarily covering vasopressin receptor antagonists. Generally, the evidence for patient-important outcomes was limited. Vasopressin receptor antagonists had very uncertain effects on mortality and health-related quality of life. There was low certainty evidence for a reduction in hospital stay (1.6 days) and for the absence of an important improvement in cognitive function.

Most studies have focused on the intermediate biochemical outcome and there was moderate certainty evidence that vasopressin receptor antagonists increased the serum sodium concentration (4 mmol/L). But they were also associated with an increased risk of rapid serum sodium correction and commonly caused adverse effects such as thirst and polyuria. On average, treating 1000 people would cause 290 additional people to have an increase in serum sodium concentration of at least 5 mmol/L, but it would come at a cost of an additional 29 people having an increase exceeding 8 to 12 mmol/L/d, considered as the threshold from which on there is an increased risk for osmotic demyelination, be it that no such cases were documented in any of included studies. Effects were generally consistent across the different drugs in this class. RCT data for other interventions such as fluid restriction, urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin were largely absent.

Overall completeness and applicability of evidence

Although the FDA and the EMA have approved certain vasopressin receptor antagonists for treating people with hyponatraemia, regulatory approval was largely based on intermediate outcomes in short-term studies. To date, clinically important outcomes (e.g. reduction in all-cause mortality or improvement in health-related quality of life, cognitive and general functional status) remain insufficiently investigated. The data we had, indicated with moderate confidence that vasopressin receptor antagonists modestly increased the serum sodium concentration, but there is insufficient evidence to conclude this truly translates in the improvement of patient-important outcomes.

In the context of intervention studies, a surrogate or intermediate is a measurable outcome such as a laboratory test, which responds to an intervention (e.g. lowering of cholesterol with statins) and is causally associated a clinically important outcome (e.g. reduction in mortality with statins) (Ballinger 2014). Investigators often use surrogates instead of important health outcomes because surrogates can substantially reduce the cost, sample size and duration of a randomised trial. However, not all are valid proxies of clinically important outcomes. It is true that in acute and profound hyponatraemia, the evidence from observational studies is so overwhelming that we readily accept that increasing the serum sodium concentration is life-saving. But as we move further from the extreme of acute, profound hyponatraemia into chronic, mild hyponatraemia, the evidence for such a consistent causal link weakens. Although it is true that a chronically low serum sodium concentration is strongly and consistently associated with increased mortality and risk of bone fractures (Wald 2010), there is currently insufficient evidence that aside from affecting the surrogate (e.g. increase in serum sodium concentration with a vasopressin receptor antagonist) treatment in case of more chronic hyponatraemia also changes the patient-important outcomes downstream of the surrogate in the same causal pathway (e.g. reduction in mortality as a consequence of raising serum sodium concentration with a vasopressin receptor antagonist). There are intuitive reasons to assume that such causality can reasonably be extrapolated to the entire spectrum of hypotonic hyponatraemia. But likewise, there are reasons for caution. Lixivaptan primarily failed to obtain regulatory approval by the FDA for hyponatraemia in chronic heart failure due to a numeric - be it statistically non-significant - imbalance in early deaths. The clinical review team argued that 'while the early death in participants with chronic heart failure and hyponatraemia could reflect the underlying disease, they could not exclude the possibility that some subjects with hyponatraemia associated with acute worsening congestive failure were exquisitely sensitive to intravascular free water shifts and did not tolerate even a small change in intravascular volume status or osmolality, induced by lixivaptan and/or effects resulting from a compensatory neurohumoral activation' (BALANCE 2010).

Studies contributing to this review included mostly participants with mild to moderate hyponatraemia (mean serum sodium concentration at study level ≥ 123 mmol/L). Meta-regression revealed a modifying effect of the serum sodium concentration at baseline, with lower values associated with larger increases in natraemia. Extrapolation of meta-regression data would suggest higher increases, but possibly higher risks of rapid correction as the baseline serum sodium decreases. Although no study reported osmotic demyelination, it is unclear what would happen if vasopressin receptor antagonists were used on a larger scale and in people with sodium concentrations below those included in the RCTs that contributed to this review. Likewise, it is possible that while improvements in cognitive function were not readily detected, they would emerge for people with lower serum sodium concentrations at baseline.

Finally, studies evaluating the effectiveness of alternative interventions for increasing serum sodium concentration in people with chronic, non-hypovolaemic hyponatraemia are largely absent.

Quality of the evidence

Overall, we considered the data evaluating the effects of vasopressin receptor antagonists for people with chronic, non-

hypovolaemic, hypotonic hyponatraemia on patient-important outcomes such as mortality, health-related quality of life, and hospital stay limited and of low certainty. Low certainty evidence suggests that additional studies are likely to change our confidence in the effects (GRADE 2008). According to GRADE, RCT data is considered high quality, but may be downgraded for several reasons (Guyatt 2010). These reasons varied for each outcome. For death it was largely driven by the width of the confidence interval, which captured both appreciable benefit and harm, and left us with considerably uncertainty around the treatment effect. For health-related quality of life, there was some evidence that vasopressin receptor antagonists increased the mental component summary score of the SF-12, and unclear effects on the physical component summary score. However, we seriously questioned the validity of this tool for measuring quality of life in the context of hyponatraemia. For one thing, many items included in the SF-12 do not reflect readily acknowledged signs and symptoms of hyponatraemia (e.g. bodily pain, anxiety) and similarly, the neurocognitive signs of hyponatraemia are not assessed by the tool. In addition to the general content validity issues, we also judged effects for this self-reported outcome may have been inflated because participants were likely unblinded due to polyuria as a side-effect; results were selectively reported for one in two measurement time-points; and more than one-third of the data were missing.

We had more extensive data for outcomes related to serum sodium concentration, resulting in moderate confidence in the effect estimates all around. Downgrading occurred mainly for missing outcome data, which we judged could have somewhat overestimated the treatment effect; as well as indirectness, in that tight follow-up during dose-titration, is likely to have avoided rapid correction somewhat in the trial setting. It may result in higher risk of rapid correction when used in clinical practice.

Of note, all studies assessing benefits and harms of vasopressin receptor antagonists were likely instigated and sponsored by the pharmaceutical company developing or seeking to commercialise the compound. For the studies that provided a declaration of interest for the authors of study reports, all save one had author lists that featured people who had received money for presentations or consultancy, or were employed by the sponsor. Industry sponsorship does not necessarily introduce bias into the design and conduct of clinical trials, but empiric evidence does show that pharmaceutical industry-sponsored studies are more likely to have favourable efficacy results (RR 1.32, 95% CI 1.21 to 1.44) and harm results (RR 1.87, 95% CI 1.54 to 2.27) than studies not sponsored by industry (Lundh 2012).

Data for other interventions such as fluid restriction, change in medical regimens, captopril or albumin were sparse and inconclusive.

Potential biases in the review process

Although this review was conducted by two or more independent authors, used a comprehensive search of the published and unpublished research designed by a specialist librarian, and examined all potentially relevant clinical outcomes, potential biases exist in the review process. The major weakness of this review is the paucity of data for treatments other than vasopressin receptor antagonists. First, summary of existing evidence therefore focusses the discourse on new, and expensive, treatments, rather than focusing on existing, and cheaper alternatives. RCTs are

extraordinarily expensive and consequently often conducted by the pharmaceutical industry. This results in a catch-22 situation of evidence being mostly created, and thus only available, for newer interventions in general. Many other interventions are or have been used in clinical practice, but were driven to the background because RCT data were largely absent. Notably, also for fluid restriction, despite it being the currently accepted first-line treatment for both hypervolaemic and euvoalaemic hyponatraemia, there are no randomised trial data available. Currently, there are limited opportunities for use of vasopressin receptor antagonists in practice. Only two vasopressin receptor antagonists have obtained large scale regulatory approval. Conivaptan is FDA approved for euvoalaemic and hypervolaemic hyponatraemia in hospitalised patients. It is available only as an intravenous preparation and treatment duration is limited to a maximum duration of four days because of drug-interaction effects with other agents metabolized by the cytochrome P450 3A4 hepatic isoenzyme (FDA 2012). Tolvaptan, an oral agent, is also FDA-approved for the treatment of euvoalaemic and hypervolaemic hyponatraemia. Although theoretically available for long-term treatment, recent concerns around the potential for severe liver injury in patients with autosomal dominant polycystic kidney disease - be it at doses far exceeding the ones used in hyponatraemia - has caused the FDA to restrict the use of tolvaptan to 30 days and issue a contra-indication for patients with underlying liver disease (Mirski 2013). Canadian regulatory authorities mandated monitoring liver injury tests at regular intervals, but did not limit duration of use. In the European Union, tolvaptan is approved only for the treatment of euvoalaemic hyponatraemia, due to safety concerns stemming from a numeric - be it statistically non-significant - difference in treatment-emergent fatalities in patients with hypervolaemia.

Agreements and disagreements with other studies or reviews

This review largely agreed with the findings of two earlier systematic reviews. However, neither of these previous reviews sought to examine any other treatments beyond vasopressin receptor antagonists for treating chronic non-hypovolaemic hypotonic hyponatraemia. The first, including 15 RCTs and 1619 participants found vasopressin antagonists on average increased the serum sodium concentration by approximately 5 mmol/L at one week (13 studies, 1119 participants: MD 5.27 mmol/L, 95% CI 4.27 to 6.26), and approximately 3.5 mmol/L beyond the first week (8 studies, 793 participants: MD 3.49 mmol/L, 95% CI 2.56 to 4.41), but it came at a cost of increased risk of overly rapid correction of the serum sodium concentration (8 studies, 860 participants: RR, 2.52, 95% CI 1.26 to 5.08) (Rozen-Zvi 2010). The second review, including 11 RCTs and 1094 participants, found vasopressin antagonists on average increased the serum sodium concentration by approximately 5 mmol/L at day 4 (11 studies, 1094 participants: MD 4.90 mmol/L, 95% CI 4.10 to 5.80), but was associated with a 6% increased risk of overly rapid correction of the serum sodium concentration (9 studies, 995 participants: RD 0.06, 95% CI 0.03 to 0.10) (Jaber 2011).

We also largely agreed with the interpretation of these data by the respective study authors as presented in their discussion: vasopressin receptor antagonists effectively raise the serum sodium concentration. But whether this translates to meaningful changes in outcomes that matter to patients is not clear. At this stage the available RCTs have insufficiently studied

clinical outcomes to conclude that people whose serum sodium concentration increases under treatment will experience changes in end-points such as general well-being, cognitive function, gait stability, bone fractures and survival.

In 2013, a guideline group consisting of seven authors (six Americans and one Irishman), published expert recommendations identifying several alternative treatments, including fluid restriction, demeclocycline, urea and vasopressin receptor antagonists. Driven by the emergence of RCT evidence for vasopressin receptor antagonists as effective means for increasing the serum sodium concentration, and the absence of such evidence for other treatments, they projected vasopressin receptor antagonists were likely to become a mainstay of treatment for euvoalaemic hyponatraemia and probably represented the best approach to treating hyponatraemia in most oedema-forming states (Verbalis 2013).

A European guideline published in 2014 - to which four authors of this review contributed - suggested that in moderate or profound hyponatraemia (serum sodium concentration < 130 mmol/L), restricting fluid intake was first-line treatment (2D); increasing solute intake with urea or a combination of low-dose loop diuretics and oral sodium chloride were equal second-line treatments (2D); and vasopressin receptor antagonists were not recommended (1C). (Spasovski 2014). There is almost no RCT evidence for treatments other than vasopressin receptor antagonists. The group's rationale to advocate some of these treatments anyway stemmed from the premise that in the absence of unequivocal evidence that increasing the serum sodium concentration leads to an improvement in patient-important outcomes, the focus should be on avoiding harm. They gave much weight to avoiding rapid increases in the serum sodium concentration, for it's - albeit very rare - association with osmotic demyelination syndrome. And based on the absence of observational evidence for rapid increases or other important harms for fluid restriction, urea and low-dose loop diuretics with oral sodium chloride, they formulated a weak recommendation to consider these for treating people with sodium concentrations below 130 mmol/L. Largely because of the documented risk of rapid increase and some concern around its potential for liver disease, a negative recommendation was formulated for vasopressin receptor antagonists.

AUTHORS' CONCLUSIONS

Implications for practice

In people with chronic hyponatraemia, vasopressin receptor antagonists modestly raise serum sodium concentration at the cost of an absolute 3% increased risk the increase being too rapid. To date there is insufficient evidence for patient-important outcomes; the effects on mortality and health-related quality of life are unclear and do not rule out appreciable benefit or harm; there does not appear to be an important effect on cognitive function, but hospital stay may be shorter, although available data are limited. Treatment decisions must weigh the value of an increase in serum sodium concentration against its short-term risks and unknown effects on patient-important outcomes. Evidence for other treatments is largely absent.

Implications for research

Further studies assessing commonly used treatments such as fluid restriction would inform practice and are warranted. Also, given the limited available evidence for patient-important outcomes, studies with vasopressin receptor antagonists and other treatments should include these outcomes in a standardised way. Importantly, this requires validation of health-related quality of life measures, tailored specifically to the context of hyponatraemia and international consensus on how to assess hyponatraemia-specific symptoms.

ACKNOWLEDGEMENTS

We wish to acknowledge Ruth Mitchell and Gail Higgins for their contributions in developing the search strategies, running the

searches and collecting the citations. We would like to thank Narelle Willis, Ann Jones and Fiona Russell for their editorial support in developing this review. We sincerely wish to acknowledge Otsuka, Dr Peyro Saint Paul, and Dr Naoto Tominaga for contributing unpublished data to this review. And finally we would like to thank the referees for their comments and feedback during the preparation of this review.

The authors acknowledge that the information provided in the questionnaires for studies sponsored by Otsuka comprises unpublished information owned by Otsuka. With respect to each of the responses, Otsuka grants the authors of this Cochrane review the non-exclusive, non-sublicensable right to use the information provided therein for the purpose of the Cochrane review entitled “Interventions for chronic non-hypovolaemic hypotonic hyponatraemia”.

Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC Jr, et al. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *Journal of the American College of Cardiology* 2008;**52**(20):1640-8. [MEDLINE: 18992654]

Chiong JR, Kim S, Lin J, Christian R, Dasta JF. Evaluation of costs associated with tolvaptan-mediated length-of-stay reduction among heart failure patients with hyponatremia in the US, based on the EVEREST trial. *Journal of Medical Economics* 2012;**15**(2):276-84. [MEDLINE: 22111754]

Cyr PL, Slawsky KA, Olchanski N, Krasa HB, Goss TF, Zimmer C, et al. Effect of serum sodium concentration and tolvaptan treatment on length of hospitalization in patients with heart failure. *American Journal of Health-System Pharmacy* 2011;**68**(4):328-33. [MEDLINE: 21289328]

Dasta J, Chiong J, Kim S, Lin J. Evaluation of the hospital resource utilization associated with tolvaptan usage among heart failure patients with hyponatremia from the EVEREST trial [abstract]. *Pharmacotherapy* 2011;**31**(10):370e. [EMBASE: 70648093]

Dasta JF, Chiong JR, Kim S, Lin J. Evaluation of the hospital resource utilization associated with tolvaptan usage among heart failure patients with hyponatremia from the EVEREST trial [abstract no: PCV36]. *Value in Health* 2011;**14**(3):A38-9. [EMBASE: 70490649]

Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007;**297**(12):1332-43. [MEDLINE: 17384438]

Gheorghiade M, Orlandi C, Burnett JC, Demets D, Grinfeld L, Maggioni A, et al. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). *Journal of Cardiac Failure* 2005;**11**(4):260-9. [MEDLINE: 15880334]

Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *Journal of Cardiac Failure* 2013;**19**(6):390-7. [MEDLINE: 23743487]

* Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**(12):1319-31. [MEDLINE: 17384437]

Mentz RJ, Greene SJ, Ambrosy AP, Vaduganathan M, Subacius HP, Swedberg K, et al. Clinical profile and prognostic value of anemia at the time of admission and discharge among patients hospitalized for heart failure with reduced ejection fraction: findings from the EVEREST trial. *Circulation: Heart Failure* 2014;**7**(3):401-8. [MEDLINE: 24737459]

O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC, et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program.[Erratum appears in *Am Heart J.* 2012 May;163(5):900]. *American Heart Journal* 2010;**159**(5):841-9. [MEDLINE: 20435194]

Pang PS, Gheorghiade M, DiHu J, Swedberg K, Khan S, Maggioni AP, et al. Effects of tolvaptan on physician-assessed symptoms and signs in patients hospitalized with acute heart failure syndromes: analysis from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) trials. *American Heart Journal* 2011;**161**(6):1067-72. [MEDLINE: 21641352]

Vaduganathan M, Gheorghiade M, Pang PS, Konstam MA, Zannad F, Swedberg K, et al. Efficacy of oral tolvaptan in acute heart failure patients with hypotension and renal impairment. *Journal of Cardiovascular Medicine* 2012;**13**(7):415-22. [MEDLINE: 22673023]

Gerbes 2003 {published data only (unpublished sought but not used)}

Decaux G, Hannotier P, Pennickx R, Soupart A, Djian J. Difference in solute excretion after treatment of hyponatremia related to SIADH or cirrhosis by the non peptide, oral active selective vasopressin V2 receptor antagonist, vpa-985 [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Abstracts):120A. [CENTRAL: CN-00550692]

* Gerbes AL, Gulberg V, Ginès P, Decaux G, Gross P, Gandjini H, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. *Gastroenterology* 2003;**124**(4):933-9. [MEDLINE: 12671890]

Gross P, Decaux G, Gerbes A, Djian J. Treatment of hyponatremia (hypo) with VPA-985 [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):121A.

Guelberg GV, Decaux G, Gross P, Massien C, Djian J. VPA-985, an orally active vasopressin receptor antagonist improves hyponatremia in patients with cirrhosis: a double-blind placebo controlled multicenter trial [abstract]. *Hepatology* 1999;**30**(4):419A. [CENTRAL: CN-00280911]

Ghali 2006 {published data only (unpublished sought but not used)}

* Ghali JK, Koren MJ, Taylor JR, Brooks-Asplund E, Fan K, Long WA, et al. Efficacy and safety of oral conivaptan: a V1A/V2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *Journal of Clinical Endocrinology & Metabolism* 2006;**91**(6):2145-52. [MEDLINE: 16522696]

Ghali JK, Verbalis JG, Gross P, Long WA, Smith N. Vasopressin V1A and V2 antagonist conivaptan increased serum sodium concentration in patients with hyponatremia secondary to congestive heart failure [abstract no: F-FC028]. *Journal of the American Society of Nephrology* 2005;**16**(Abstracts):43A. [CENTRAL: CN-00677109]

Gheorghiade 2003 {published and unpublished data}

- * Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation* 2003;**107**(21):2690-6. [MEDLINE: 12742979]

Gheorghiade 2006 {published data only (unpublished sought but not used)}

- * Gheorghiade M, Gottlieb SS, Udelson JE, Konstam MA, Czerwiec F, Ouyang J, et al. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *American Journal of Cardiology* 2006;**97**(7):1064-7. [MEDLINE: 16563917]

Gines 2008b {published data only (unpublished sought but not used)}

- Gines P, Wong F, Martin M, Lecorps G, Watson HR. Effects of satavaptan on hyponatremia, management of ascites and morbidity in liver cirrhosis in a long-term placebo-controlled study [abstract]. *Hepatology* 2008;**48**(Suppl 4):413A-4A. [CENTRAL: CN-00690109]

HARMONY 2012 {published data only (unpublished sought but not used)}

FDA briefing document for the Cardiovascular and Renal Drugs Advisory (CRDAC) 13 September 2012. [deals.bio/home/download?doc_id=911](https://www.fda.gov/downloads/CDRAC/13September2012/ucm318869.pdf) (accessed on 28 June 2018):1-217.

- * Abraham WT, Decaux G, Josiassen RC, Yagil Y, Kopyt N, Thacker HP, et al. Oral lixivaptan effectively increases serum sodium concentrations in outpatients with euvoletic hyponatremia. *Kidney International* 2012;**82**(11):1215-22. [MEDLINE: 22932122]

Cardiokine Biopharma LLC. Lixivaptan for the treatment of symptomatic euvoletic hyponatremia associated with syndrome of inappropriate antidiuretic hormone (SIADH) and symptomatic hypervolemic hyponatremia associated with heart failure. Advisory Committee Briefing Document. FDA Cardio-Renal Drugs Advisory Committee Meeting. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM318869.pdf (accessed on 15 March 2015):1-61.

FDA Center for Drug Evaluation and Research. A matter of record: Cardiovascular and renal drug advisory committee meeting 13 September 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm345074.pdf (accessed on 15 March 2015):1-203.

Hayes 1987 {published data only}

- Hayes PC, Williams R. Oral urea in the treatment of hyponatraemic ascites [abstract]. *Gut* 1987;**28**(10):A1386. [CENTRAL: CN-00221198]

HYPOCAT 2008 {published data only (unpublished sought but not used)}

- Cordoba J, Guevara M, Watson HR, Guennec S, Gines P. Improvement of hyponatremia in cirrhosis increases speed

of complex information processing [abstract]. *Hepatology* 2009;**50**(Suppl 4):451A-2A. [CENTRAL: CN-00739727]

Gines P, Wong F, Milutinovic S, del Arbol LR, Olteanu D. Effects of satavaptan (SR121463B), a selective vasopressin V2 receptor antagonist, on serum sodium concentration and ascites in patients with cirrhosis and hyponatraemia [abstract]. *Journal of Hepatology* 2006;**44**(Suppl 2):S270. [CENTRAL: CN-00581518]

- * Gines P, Wong F, Watson H, Milutinovic S, del Arbol LR, Olteanu D, et al. Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. *Hepatology* 2008;**48**(1):204-13. [MEDLINE: 18508290]

INSIGHT 2016 {published data only (unpublished sought but not used)}

- * Verbalis JG, Ellison H, Hobart M, Krasa H, Ouyang J, Czerwiec FS, et al. Tolvaptan and neurocognitive function in mild to moderate chronic hyponatremia: a randomized trial (INSIGHT). *American Journal of Kidney Diseases* 2016;**67**(6):893-901. [MEDLINE: 26874645]

Jalan 2007 {published data only (unpublished sought but not used)}

Jalan R, Mookerjee R, Cheshire L, Williams R, Davies N. Albumin infusion for severe hyponatremia in patients with refractory ascites: a randomized clinical trial [abstract]. *Journal of Hepatology* 2007;**46**(Suppl 1):S95. [CENTRAL: CN-00653262]

Kalra 2011 {published data only (unpublished sought but not used)}

- * Kalra S, Efrati S, Arthur JM, Oliven A, Velez JC, McNutt BE, et al. Effect of loading dose and formulation on safety and efficacy of conivaptan in treatment of euvoletic and hypervolemic hyponatremia. *American Journal of Health-System Pharmacy* 2011;**68**(7):590-8. [MEDLINE: 21411800]

Koren 2011 {published data only (unpublished sought but not used)}

- * Koren MJ, Hamad A, Klasen S, Abeyratne A, McNutt BE, Kalra S. Efficacy and safety of 30-minute infusions of conivaptan in euvoletic and hypervolemic hyponatremia. [Erratum appears in Am J Health Syst Pharm. 2011 Aug 1;**68**(15):1374]. *American Journal of Health-System Pharmacy* 2011;**68**(9):818-27. [MEDLINE: 21515866]

LIBRA 2012 {published data only (unpublished sought but not used)}

FDA briefing document for the Cardiovascular and Renal Drugs Advisory (CRDAC) 13 September 2012. [news.medlive.cn/uploadfile/2012/0523/20120523095216110.pdf](https://www.fda.gov/downloads/CDRAC/13September2012/news.medlive.cn/uploadfile/2012/0523/20120523095216110.pdf) (accessed on 5 March 2018):1-217.

Abraham W, Josiassen R, Bichet DG, Orlandi C. Safety and efficacy of the vasopressin V2-receptor antagonist, lixivaptan, in outpatients with euvoletic hyponatremia [abstract no: LB-PO3144]. *Journal of the American Society of Nephrology* 2011;**22**(Abstracts):3B.

- * Abraham WT, Hensen J, Gross PA, Bichet DG, Josiassen RC, Chafekar DS, et al. Lixivaptan safely and effectively corrects

serum sodium concentrations in hospitalized patients with euvolemic hyponatremia. *Kidney International* 2012;**82**(11):1223-30. [MEDLINE: 22932119]

Cardiokine Biopharma LLC. Lixivaptan for the treatment of symptomatic euvolemic hyponatremia associated with syndrome of inappropriate antidiuretic hormone (SIADH) and symptomatic hypervolemic hyponatremia associated with heart failure. Advisory Committee Briefing Document. FDA Cardio-Renal Drugs Advisory Committee Meeting. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM318869.pdf (accessed on 15 March 2015):1-61.

FDA Center for Drug Evaluation and Research. A matter of record: Cardiovascular and renal drug advisory committee meeting 13 September 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm345074.pdf (accessed on 15 March 2015):1-203.

Naidech 2010 {published data only (unpublished sought but not used)}

* Naidech AM, Paparello J, Liebling SM, Bassin SL, Levasseur K, Alberts MJ, et al. Use of Conivaptan (Vaprisol) for hyponatremic neuro-ICU patients. [Erratum appears in *Neurocrit Care*. 2011 Aug;15(1):210 Note: Leibling, Storm M [corrected to Liebling, Storm M]]. *Neurocritical Care* 2010;**13**(1):57-61. [MEDLINE: 20568023]

NATRIPHAR 2013 {published and unpublished data}

* Peyro Saint Paul L, Martin J, Gaillard C, Mosquet B, Coquerel A, de la Gastine B. Moderate potentially drug-induced hyponatremia in older adults: benefit in drug reduction [L'hyponatremie moderee potentiellement medicamenteuse du sujet age: benefice de la reduction des medicaments]. *Therapie* 2013;**68**(6):341-6. [MEDLINE: 24246119]

Peyro Saint Paul L, Martin J, Mosquet B, Gaillard C, De La Gastine B. Benefit of pharmacological intervention on drug-induced mild hyponatremia in elderly: a prospective randomised trial [abstract no: P229]. *Fundamental & Clinical Pharmacology* 2012;**26**(Suppl 1):74. [EMBASE: 70866717]

Nevens 2009 {published and unpublished data}

Nevens F, Moreno C, Cools M, Thielemans L, Kerstens R, Meulemans A. Effect of M0002, a novel V2 antagonist on sodium levels and weight gain affected by water accumulation in cirrhotic patients with ascites [abstract no: 182]. *Journal of Hepatology* 2009;**50**(Suppl 1):S76. [CENTRAL: CN-00715780]

Otsuka Study 2011a {published data only (unpublished sought but not used)}

* Chen S, Zhao JJ, Tong NW, Guo XH, Qiu MC, Yang GY, et al. Randomized, double blinded, placebo-controlled trial to evaluate the efficacy and safety of tolvaptan in Chinese patients with hyponatremia caused by SIADH. *Journal of Clinical Pharmacology* 2014;**54**(12):1362-7. [MEDLINE: 24906029]

Otsuka Study 2011b {published data only (unpublished sought but not used)}

* Li L, Bai H, Zhu WL. Tolvaptan Therapy in Hyponatremia with Heart Failure Collaborative Group. The efficacy and safety of tolvaptan on treating heart failure patients with hyponatremia. *Chung-Hua Hsin Hsueh Kuan Ping Tsa Chih [Chinese Journal of Cardiology]* 2011;**39**(10):936-40. [MEDLINE: 22321279]

Ling L, Wenling Z, Hua B. The efficacy and safety of tolvaptan on treating congestive heart failure patients with hyponatremia [abstract no: gw22-e0446]. *Heart* 2011;**97**(Suppl 3):A127. [EMBASE: 70739844]

Ling L, Wenling Z, Hua B. The efficacy and safety of tolvaptan on treating congestive heart failure patients with hyponatremia [abstract no: gw22-e0831]. *Heart* 2011;**97**(Suppl 3):A216-7. [EMBASE: 70740110]

Otsuka Study 2011c {published data only (unpublished sought but not used)}

* Jia J, Wang HF, Cheng W, Ye W, Ding H, Deng C. A multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of tolvaptan on hyponatremia in Chinese cirrhotic patients [abstract]. *Journal of Hepatology* 2012;**56**(Suppl 2):S249. [CENTRAL: CN-00844257]

Salahudeen 2014 {published data only (unpublished sought but not used)}

Ali N, Palla S, George M, Salahudeen A. A randomized, double blind, placebo-controlled trial of tolvaptan in hyponatremic patients with cancer [abstract]. *Journal of Investigative Medicine* 2013;**61**(2):501. [EMBASE: 70993379]

* Salahudeen AK, Ali N, George M, Lahoti A, Palla S. Tolvaptan in hospitalized cancer patients with hyponatremia: a double-blind, randomized, placebo-controlled clinical trial on efficacy and safety. *Cancer* 2014;**120**(5):744-51. [MEDLINE: 24895288]

SALT-1 2006 {published and unpublished data}

Bai S, Targum S, Thompson A. Combined clinical and statistical review. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-02.pdf (accessed 18 January 2018):1-120.

Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. [Erratum appears in *J Am Soc Nephrol*. 2010 Aug;21(8):1407]. *Journal of the American Society of Nephrology* 2010;**21**(4):705-12. [MEDLINE: 20185637]

Blais J, Ahmad F, Chiodo J, Glaser LA, Gralla RJ, Zhou W, et al. Efficacy of tolvaptan in cancer patients with hyponatremia due to SIADH: post-hoc analysis of SALT (study of ascending levels of tolvaptan) [abstract]. *Supportive Care in Cancer* 2014;**22**(1 Suppl 1):S156-7. [EMBASE: 71501979]

Cardenas A, Gines P, Marotta P, Czerwiec F, Ouyang J, Guevara M, et al. Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. *Journal of Hepatology* 2012;**56**(3):571-8. [MEDLINE: 22027579]

Cardenas A, Gines P, Marotta P, Czerwiec FS, Ouyang J, Sexton A, et al. The effects of a vasopressin V2 receptor antagonist in the management of patients with cirrhosis and hyponatremia.

Safety and efficacy of oral tolvaptan in the SALT trials [abstract]. *Hepatology* 2009;**50**(Suppl 4):467A-8A. [CENTRAL: CN-00739662]

Dasta J, Chiong J, Christian R, Lin J. Estimation of cost savings associated with tolvaptan-mediated length of stay (LOS) reduction among SIADH patients in the US, based on SALT-1 and SALT-2 trials [abstract no: 563]. *Critical Care Medicine* 2011;**39**(Suppl 12):155. [EMBASE: 71058874]

Dasta JF, Chiong JR, Christian R, Lin J. Evaluation of cost offset associated with tolvaptan usage among hyponatremic SIADH patients in the united states, based on the SALT-1 and SALT-2 trials [abstract]. *Value in Health* 2012;**15**(4):A176. [EMBASE: 71058874]

Dasta JF, Chiong JR, Christian R, Lin J. Evaluation of costs associated with tolvaptan-mediated hospital length of stay reduction among US patients with the syndrome of inappropriate antidiuretic hormone secretion, based on SALT-1 and SALT-2 trials. *Hospital Practice (1995)* 2012;**40**(1):7-14. [MEDLINE: 22406878]

Josiassen RC, Goldman M, Jessani M, Shaughnessy RA, Albazzaz A, Lee J, et al. Double-blind, placebo-controlled, multicenter trial of a vasopressin V2-receptor antagonist in patients with schizophrenia and hyponatremia. *Biological Psychiatry* 2008;**64**(12):1097-100. [MEDLINE: 18692175]

Otsuka Pharmaceutical Development & Commercialization. Treatment of hyponatremia: medical utility of vasopressin V2 receptor antagonism: briefing document. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-05.pdf (accessed 18 January 2018):1-131.

* Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *New England Journal of Medicine* 2006;**355**(20):2099-112. [MEDLINE: 17105757]

Trueman D, Hancock E, Robinson P, Dale P, O'Reilly K, Gisby M. EQ-5D scores in patients receiving tolvaptan for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion [abstract]. *Value in Health* 2014;**17**(7):A354. [MEDLINE: 27200696]

Trueman D, Robinson P, Dale P, O'Reilly K, Lundberg J, Jamookeah C. The cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden [abstract]. *Value in Health* 2014;**17**(7):A350. [MEDLINE: 27200675]

U.S. Food, Drug Administration. NDA 22-275: tolvaptan for the treatment of hypervolemic and euvoletic hyponatremia and for prevention of worsening hyponatremia FDA review of patient-reported outcome (PRO) measures for the hyponatremia indication. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-03.pdf (accessed 18 January 2018):1-7.

Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS, et al. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *European Journal of Endocrinology* 2011;**164**(5):725-32. [MEDLINE: 21317283]

SALT-2 2006 {published and unpublished data}

Afdhal N, Cardenas A, Gines P, Gross P, Verbalis J, Berl T. Randomized, placebo-controlled trial of tolvaptan, a novel v2-receptor antagonist, in hyponatremia: results of the SALT 2 trial with emphasis on efficacy and safety in cirrhosis [abstract]. *Hepatology* 2005;**42**(Suppl 1):756A. [CENTRAL: CN-00581716]

Bai S, Targum S, Thompson A. Combined clinical and statistical review. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-02.pdf (accessed 18 January 2018):1-120.

Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, et al. Oral tolvaptan is safe and effective in chronic hyponatremia.[Erratum appears in J Am Soc Nephrol. 2010 Aug;21(8):1407]. *Journal of the American Society of Nephrology* 2010;**21**(4):705-12. [MEDLINE: 20185637]

Blais J, Ahmad F, Chiodo J, Glaser LA, Gralla RJ, Zhou W, et al. Efficacy of tolvaptan in cancer patients with hyponatremia due to SIADH: Post-hoc analysis of SALT (study of ascending levels of tolvaptan) [abstract]. *Supportive Care in Cancer* 2014;**22**(1 Suppl 1):S156-7. [EMBASE: 71501979]

Cardenas A, Gines P, Marotta P, Czerwiec F, Ouyang J, Guevara M, et al. Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. *Journal of Hepatology* 2012;**56**(3):571-8. [MEDLINE: 22027579]

Cardenas A, Gines P, Marotta P, Czerwiec FS, Ouyang J, Sexton A. The effects of a vasopressin V2 receptor antagonist in the management of patients with cirrhosis and hyponatremia. Safety and efficacy of oral tolvaptan in the SALT trials [abstract]. *Hepatology* 2009;**50**(Suppl 4):467-8A. [CENTRAL: CN-00739662]

Dasta J, Chiong J, Christian R, Lin J. Estimation of cost savings associated with tolvaptan-mediated length of stay (LOS) reduction among SIADH patients in the US, based on SALT-1 and SALT-2 trials [abstract no: 563]. *Critical Care Medicine* 2011;**39**(Suppl 12):155. [EMBASE: 71058874]

Dasta JF, Chiong JR, Christian R, Lin J. Evaluation of cost offset associated with tolvaptan usage among hyponatremic SIADH patients in the united states, based on the SALT-1 and SALT-2 trials [abstract]. *Value in Health* 2012;**15**(4):A176. [EMBASE: 70763929]

Dasta JF, Chiong JR, Christian R, Lin J. Evaluation of costs associated with tolvaptan-mediated hospital length of stay reduction among US patients with the syndrome of inappropriate antidiuretic hormone secretion, based on SALT-1 and SALT-2 trials. *Hospital Practice (1995)* 2012;**40**(1):7-14. [MEDLINE: 22406878]

Josiassen RC, Goldman M, Jessani M, Shaughnessy RA, Albazzaz A, Lee J, et al. Double-blind, placebo-controlled, multicenter trial of a vasopressin V2-receptor antagonist in patients with schizophrenia and hyponatremia. *Biological Psychiatry* 2008;**64**(12):1097-100. [MEDLINE: 18692175]

Otsuka Pharmaceutical Development & Commercialization. Treatment of hyponatremia: medical utility of vasopressin V2 receptor antagonism: briefing document. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-05.pdf (accessed 18 January 2018):1-131.

- * Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *New England Journal of Medicine* 2006;**355**(20):2099-112. [MEDLINE: 17105757]
- Trueman D, Hancock E, Robinson P, Dale P, O'Reilly K, Gisby M. EQ-5D scores in patients receiving tolvaptan for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion [abstract]. *Value in Health* 2014;**17**(7):A354. [MEDLINE: 27200696]
- Trueman D, Robinson P, Dale P, O'Reilly K, Lundberg J, Jamookeeah C. The cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden [abstract]. *Value in Health* 2014;**17**(7):A350. [MEDLINE: 27200675]
- U.S. Food, Drug Administration. NDA 22-275: tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia and for prevention of worsening hyponatremia. FDA review of patient-reported outcome (PRO) measures for the hyponatremia indication. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4373b1-03.pdf (accessed 18 January 2018):1-7.
- Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS, et al. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *European Journal of Endocrinology* 2011;**164**(5):725-32. [MEDLINE: 21317283]
- Shoaf 2017** {published data only}
- Shoaf SE, Bricmont P, Dandurand A. Low-dose tolvaptan PK/PD: Comparison of subjects with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) to healthy adults [abstract]. *Clinical Pharmacology and Therapeutics* 2017;**101**(Suppl 1):S88. [EMBASE: 614166327]
- Shoaf SE, Bricmont P, Dandurand A. Low-dose tolvaptan PK/PD: comparison of patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion to healthy adults. *European Journal of Clinical Pharmacology* 2017;**73**(11):1399-408. [MEDLINE: 28803333]
- Singhi 1995** {published data only (unpublished sought but not used)}
- * Singhi SC, Singhi PD, Srinivas B, Narakesri HP, Ganguli NK, Sialy R, et al. Fluid restriction does not improve the outcome of acute meningitis. *Pediatric Infectious Disease Journal* 1995;**14**(6):495-503. [MEDLINE: 7667054]
- Soupart 2006** {published data only (unpublished sought but not used)}
- Soupart A, Gross P, Legros J, Alfoldi S, Annane D, Heshmati HM, et al. Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with SR121463B, an orally active, nonpeptide, vasopressin V2-receptor antagonist [abstract no: SU-PO0140]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):563A. [CENTRAL: CN-00583147]
- * Soupart A, Gross P, Legros JJ, Alfoldi S, Annane D, Heshmati HM, et al. Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V2-receptor antagonist. *Clinical Journal of the American Society of Nephrology: CJASN* 2006;**1**(6):1154-60. [MEDLINE: 17699341]
- Wong 2003b** {published data only (unpublished sought but not used)}
- * Wong F, Blei AT, Blendis LM, Thuluvath PJ. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. *Hepatology* 2003;**37**(1):182-91. [MEDLINE: 12500203]
- Yang 2013** {published data only (unpublished sought but not used)}
- Yang P. Evaluation of tolvaptan in the treatment of hyponatremia in chronic heart failure patient [abstract]. *Heart* 2013;**99**(Suppl 3):A221. [EMBASE: 71317230]
- Zeltser 2007** {published data only (unpublished sought but not used)}
- Ghali JK, Verbalis JG, Gross P, Long WA, Smith N. Vasopressin V1A and V2 antagonist conivaptan increased serum sodium concentration in patients with hyponatremia secondary to congestive heart failure [abstract no: F-FC028]. *Journal of the American Society of Nephrology* 2005;**16**(Abstracts):43A. [CENTRAL: CN-00677109]
- Goldsmith SR, Verbalis JG, Barve A, Andoh M. Efficacy and safety of the vasopressin-receptor antagonist conivaptan hydrochloride injection in the treatment of hypervolemic hyponatremia [abstract no: SU-PO929]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):790A.
- Verbalis JG, Bisaha JG, Smith N. Novel vasopressin V1a and V2 antagonist conivaptan increases serum sodium concentration and effective water clearance in hyponatremia [abstract no: SA-PO254]. *Journal of the American Society of Nephrology* 2004;**15**(Abstracts):356A.
- Verbalis JG, Ghali JK, Gross P, Long WA, Smith N. Efficacy and safety of the vasopressin antagonist conivaptan in patients with euvolemic hyponatremia evaluated in a phase III clinical trial [abstract]. *Journal of Clinical Oncology* 2006;**24**(18 Suppl):480. [CENTRAL: CN-00616898]
- Verbalis JG, Rosansky S, Waggoner LE, McNutt B, Yan B. Efficacy and safety of conivaptan, a vasopressin v1a- and v2-receptor antagonist, during phase 3 trials of patients with euvolemic or hypervolemic hyponatremia [abstract]. *Chest* 2007;**132**(4 Suppl):562S. [CENTRAL: CN-00645592]
- Verbalis JG, Zeltser D, Smith N, Barve A, Andoh M. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolemic hyponatremia: subgroup analysis of a randomized, controlled study. *Clinical Endocrinology* 2008;**69**(1):159-68. [MEDLINE: 18034777]
- * Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N, Conivaptan Study Group. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *American Journal of Nephrology* 2007;**27**(5):447-57. [MEDLINE: 17664863]

References to studies excluded from this review

Abraham 2006 {published data only}

- * Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW. Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. *Journal of the American College of Cardiology* 2006;**47**(8):1615-21. [MEDLINE: 16630999]

Albert 2013 {published data only}

- * Albert NM, Nutter B, Forney J, Slifcak E, Tang WH. A randomized controlled pilot study of outcomes of strict allowance of fluid therapy in hyponatremic heart failure (SALT-HF). *Journal of Cardiac Failure* 2013;**19**(1):1-9. [MEDLINE: 23273588]

Alexander 1991 {published data only}

- Alexander RC, Karp BI, Thompson S, Khot V, Kirch DG. A double blind, placebo-controlled trial of demeclocycline treatment of polydipsia-hyponatremia in chronically psychotic patients. *Biological Psychiatry* 1991;**30**(4):417-20. [MEDLINE: 1912134]

Angeli 2010 {published data only}

- * Angeli P, Fasolato S, Mazza E, Okolicsanyi L, Maresio G, Velo E, et al. Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: Results of an open randomised clinical trial. *Gut* 2010;**59**(1):98-104. [MEDLINE: 19570764]

Bernardi 1993 {published data only}

- * Bernardi M, Laffi G, Salvagnini M, Azzena G, Bonato S, Marra F, et al. Efficacy and safety of the stepped care medical treatment of ascites in liver cirrhosis: a randomized controlled clinical trial comparing two diets with different sodium content. *Liver* 1993;**13**(3):156-62. [MEDLINE: 8336527]

De Vita 2012 {published data only}

- De Vita S, Quartuccio L, Isola M, Masolini P, Sacco S, De Marchi G, et al. A randomized, controlled, multicenter phase III study of the efficacy and safety of rituximab (RTX) monotherapy versus the best available treatment in patients with mixed cryoglobulinemia syndrome [abstract]. *Arthritis & Rheumatism* 2010; Vol. 62:2201. [EMBASE: 70380187]

- De Vita S, Quartuccio L, Isola M, Mazzaro C, Scaini P, Lenzi M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis & Rheumatism* 2012; Vol. 64, issue 3:843-53. [MEDLINE: 22147661]

- De Vita S, Quartuccio L, Masolini P, Stefania S, De Marchi G, Zabotti A, et al. A randomized, controlled, multicenter phase III study of the efficacy and safety of rituximab (RTX) monotherapy versus the best available treatment (BAT) in patients with mixed cryoglobulinemia syndrome [abstract no: OP0120]. *Annals of Rheumatic Diseases* 2010; Vol. 69:93.

- Quartuccio L, Zuliani F, Corazza L, Scaini P, Zani R, Lenzi M, et al. Retreatment regimen of rituximab monotherapy given at the relapse of severe HCV-related cryoglobulinemic vasculitis: Long-term follow up data of a randomized controlled multicentre

- study. *Journal of Autoimmunity* 2015;**63**:88-93. [MEDLINE: 26255249]

- Quartuccio L, Zuliani F, Corazza L, Scaini P, Zani R, Lenzi M, et al. Rituximab monotherapy of severe HCV-related cryoglobulinemic vasculitis for more than 2 years: follow-up of a randomized controlled multicentre study [abstract no: OP0228]. *Annals of the Rheumatic Diseases* 2014; Vol. 73. [EMBASE: 71551183]

Galton 2011 {published data only}

- Galton C, Deem S, Yanez ND, Souter M, Chesnut R, Dagal A, et al. Open-label randomized trial of the safety and efficacy of a single dose conivaptan to raise serum sodium in patients with traumatic brain injury. *Neurocritical Care* 2011;**14**(3):354-60. [MEDLINE: 21409494]

Ghali 2012 {published data only}

- * Ghali JK, Orlandi C, Abraham WT, CK-LX2401 Study Investigators. The efficacy and safety of lixivaptan in outpatients with heart failure and volume overload: results of a multicentre, randomized, double-blind, placebo-controlled, parallel-group study. *European Journal of Heart Failure* 2012;**14**(6):642-51. [MEDLINE: 22510424]

Gines 2007 {published data only}

- Gines P, Wong F, Watson H. Long-term improvement of serum sodium by the V2-receptor antagonist satavaptan in patients with cirrhosis and hyponatraemia [abstract]. *Journal of Hepatology* 2007;**46**(Suppl 1):S41. [CENTRAL: CN-00653239]

Guyader 2002 {published data only}

- * Guyader D, Patat A, Ellis-Grosse EJ, Orczyk GP. Pharmacodynamic effects of a nonpeptide antidiuretic hormone V2 antagonist in cirrhotic patients with ascites. *Hepatology* 2002;**36**(5):1197-205. [MEDLINE: 12395330]

K-STAR 2017 {published data only}

- Inomata T, Ikeda Y, Kida K, Shibagaki Y, Sato N, Kumagai Y, et al. Effects of additive tolvaptan vs. increased furosemide on heart failure with diuretic resistance and renal impairment- results from the K-STAR study. *Circulation Journal* 2017;**82**(1):159-67. [MEDLINE: 28835586]

- Inomata T, Ikeda Y, Shinagawa H, Kida K, Shibagaki Y, Sato N, et al. Effect of additive tolvaptan versus increased furosemide on refractory heart failure with renal impairment: Results from the K-STAR study [abstract no: P3742]. *European Heart Journal* 2015;**36**(Suppl 1):659. [EMBASE: 72021230]

- Tominaga N, Kida K, Inomata T, Sato N, Izumi T, Akashi YJ, et al. Significance of serum sodium concentration in the very early treatment phase of congestive heart failure complicated by advanced chronic kidney disease: Posthoc analysis of the K-STAR study [abstract]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i175. [EMBASE: 72326366]

Licata 2003 {published data only}

- * Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive

heart failure: long-term effects. *American Heart Journal* 2003;**145**(3):459-66. [MEDLINE: 12660669]

Matsuzaki 2011a {published data only}

* Matsuzaki M, Hori M, Izumi T, Asanoi H, Tsutamoto T. Effects of tolvaptan on volume overload in Japanese patients with heart failure: results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Cardiovascular Drugs & Therapy* 2011;**25** Suppl 1:S19-31. [MEDLINE: 22120091]

Matsuzaki 2011b {published data only}

* Matsuzaki M, Hori M, Izumi T, Fukunami M. Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: A phase III, randomized, double-blind, placebo-controlled study (QUEST study). *Cardiovascular Drugs & Therapy* 2011;**25** Suppl 1:S33-45. [MEDLINE: 22120092]

Mori 1999 {published data only}

Mori T. Hypervolemic therapy with fludrocortisone acetate for brain protection from cerebral vasospasm caused by subarachnoid hemorrhage. *Nihon University Journal of Medicine* 1999;**41**(1):39-54. [EMBASE: 29149014]

Okita 2014 {published data only}

* Okita K, Kawazoe S, Hasebe C, Kajimura K, Kaneko A, Okada M, et al. Dose-finding trial of tolvaptan in liver cirrhosis patients with hepatic edema: a randomized, double-blind, placebo-controlled trial. *Hepatology Research* 2014;**44**(1):83-91. [MEDLINE: 23530991]

Sakaida I, Nakajima K, Okita K, Hori M, Izumi T, Sakurai M, et al. Can serum albumin level affect the pharmacological action of tolvaptan in patients with liver cirrhosis? A post hoc analysis of previous clinical trials in Japan. *Journal of Gastroenterology* 2015;**50**(10):1047-53. [MEDLINE: 25689936]

Owen 2014 {published data only}

Owen BE, Rogers IR, Hoffman MD, Stuempfle KJ, Lewis D, Fogard K, et al. Efficacy of oral versus intravenous hypertonic saline in runners with hyponatremia. *Journal of Science & Medicine in Sport* 2014;**17**(5):457-62. [MEDLINE: 24148616]

Paterna 2000 {published data only}

* Paterna S, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *European Journal of Heart Failure* 2000;**2**(3):305-13. [MEDLINE: 10938493]

Rajan 2015 {published data only}

Rajan S, Srikumar S, Paul J, Kumar L. Effectiveness of single dose conivaptan for correction of hyponatraemia in post-operative patients following major head and neck surgeries. *Indian Journal of Anaesthesia* 2015;**59**(7):416-20. [MEDLINE: 26257414]

Ramsay 1988 {published data only}

Ramsay F, Crawford RJ, Allman S, Bailey R, Martin A. An open comparative study of two diuretic combinations, frusemide/

amiloride ('Frumil') and bumetanide/potassium chloride ('Burinex' K), in the treatment of congestive cardiac failure in hospital out-patients. *Current Medical Research & Opinion* 1988;**10**(10):682-9. [MEDLINE: 3371084]

Rogers 2011 {published data only}

Rogers IR, Hook G, Stuempfle KJ, Hoffman MD, Hew-Butler T. An intervention study of oral versus intravenous hypertonic saline administration in ultramarathon runners with exercise-associated hyponatremia: a preliminary randomized trial. *Clinical Journal of Sport Medicine* 2011;**21**(3):200-3. [MEDLINE: 21519296]

Sakaida 2014 {published data only}

* Sakaida I, Kawazoe S, Kajimura K, Saito T, Okuse C, Takaguchi K, et al. Tolvaptan for improvement of hepatic edema: A phase 3, multicenter, randomized, double-blind, placebo-controlled trial. *Hepatology Research* 2014;**44**(1):73-82. [MEDLINE: 23551935]

Sakaida I, Nakajima K, Okita K, Hori M, Izumi T, Sakurai M, et al. Can serum albumin level affect the pharmacological action of tolvaptan in patients with liver cirrhosis? A post hoc analysis of previous clinical trials in Japan. *Journal of Gastroenterology* 2015;**50**(10):1047-53. [MEDLINE: 25689936]

SALSA 2017 {published data only}

Lee A, Jo YH, Kim K, Ahn S, Oh YK, Lee H, et al. Efficacy and safety of rapid intermittent correction compared with slow continuous correction with hypertonic saline in patients with moderately severe or severe symptomatic hyponatremia: study protocol for a randomized controlled trial (SALSA trial). *Trials [Electronic Resource]* 2017;**18**(1):147. [MEDLINE: 28356136]

SECRET of CHF 2017 {published data only}

Felker GM, Mentz RJ, Adams KF, Cole RT, Egnaczyk GF, Patel CB, et al. Tolvaptan in patients hospitalized with acute heart failure: rationale and design of the TACTICS and the SECRET of CHF trials. *Circulation: Heart Failure* 2015;**8**(5):997-1005. [MEDLINE: 26374918]

Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *Journal of the American College of Cardiology* 2017;**69**(11):1409-19. [MEDLINE: 28302292]

Shanmugam 2016 {published data only}

* Shanmugam E, Doss CR, George M, Jena A, Rajaram M, Ramaraj B, et al. Effect of tolvaptan on acute heart failure with hyponatremia - a randomized, double blind, controlled clinical trial. *Indian Heart Journal* 2016;**68** Suppl 1:S15-21. [MEDLINE: 27056648]

Suzuki 2013b {published data only}

Suzuki S, Yoshihisa A, Abe Y, Saito T, Ohwada T, Kubota I, et al. Acute heart failure volume control trial: The comparison of tolvaptan and carperitide [abstract]. *European Heart Journal* 2013;**34**(Suppl 1):619. [EMBASE: 71259816]

* Suzuki S, Yoshihisa A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, et al. Acute Heart Failure Volume Control

Multicenter Randomized (AVCMA) Trial: comparison of tolvaptan and carperitide. *Journal of Clinical Pharmacology* 2013;**53**(12):1277-85. [MEDLINE: 24142853]

TACT-ADHF 2016 {published data only}

Kimura K, Momose T, Hasegawa T, Morita T, Misawa T, Motoki H, et al. Early administration of tolvaptan preserves renal function in elderly patients with acute decompensated heart failure. *Journal of Cardiology* 2016;**67**(5):399-405. [MEDLINE: 26692119]

TACTICS-HF 2017 {published data only}

Felker GM, Mentz RJ, Adams KF, Cole RT, Egnaczyk GF, Patel CB, et al. Tolvaptan in patients hospitalized with acute heart failure: rationale and design of the TACTICS and the SECRET of CHF trials. *Circulation: Heart Failure* 2015;**8**(5):997-1005. [MEDLINE: 26374918]

* Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *Journal of the American College of Cardiology* 2017;**69**(11):1399-406. [MEDLINE: 27654854]

Thuluvath 2006 {published data only}

Thuluvath PJ, Maheshwari A, Wong F, Yoo HW, Schrier RW, Parikh C, et al. Oral V2 receptor antagonist (RWJ-351647) in patients with cirrhosis and ascites: a randomized, double-blind, placebo-controlled, single ascending dose study. *Alimentary Pharmacology & Therapeutics* 2006;**24**(6):973-82. [MEDLINE: 16948809]

Wong 2009 {published data only}

Wong F, Bernardi M, Horsmans Y, Cabrijan Z, Watson H. Effects of Satavaptan, an oral vasopressin V2 receptor antagonist, on management of ascites and morbidity in liver cirrhosis in a long-term, placebo-controlled study [abstract]. *Journal of Hepatology* 2009;**50**(Suppl 1):S42-S43. [EMBASE: 70133362]

Wong 2010a {published data only}

* Wong F, Gines P, Watson H, Horsmans Y, Angeli P, Gow P, et al. Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. *Journal of Hepatology* 2010;**53**(2):283-90. [MEDLINE: 20541828]

Wong 2012 {published data only}

* Wong F, Watson H, Gerbes A, Vilstrup H, Badalamenti S, Bernardi M, et al. Satavaptan for the management of ascites in cirrhosis: efficacy and safety across the spectrum of ascites severity. *Gut* 2012;**61**(1):108-16. [MEDLINE: 21836029]

Yang 2010b {published data only}

* Yang YY, Lin HC, Lee WP, Chu CJ, Lin MW, Lee FY, et al. Association of the G-protein and alpha2-adrenergic receptor gene and plasma norepinephrine level with clonidine improvement of the effects of diuretics in patients with cirrhosis with refractory ascites: a randomised clinical trial. *Gut* 2010;**59**(11):1545-53. [MEDLINE: 20833658]

Zamboli 2011 {published data only}

Zamboli P, De Nicola L, Minutolo R, Chiodini P, Crivaro M, Tassinario S, et al. Effect of furosemide on left ventricular mass in non-dialysis chronic kidney disease patients: a randomized controlled trial. *Nephrology Dialysis Transplantation* 2011;**26**(5):1575-83. [MEDLINE: 20876366]

Zellweger 2001 {published data only}

Zellweger M, Saudan P, Saudan M, Hoffmeyer P, Martin P. Do COX-2 inhibitors induce more hyponatremia than non-selective NSAIDs? [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):141A. [CENTRAL: CN-00448525]

Additional references

Adrogue 2000

Adrogue HJ, Madias NE. Hyponatremia. *New England Journal of Medicine* 2000;**342**(21):1581-9. [MEDLINE: 10824078]

Adrogue 2012

Adrogue HJ, Madias NE. The challenge of hyponatremia. *Journal of the American Society of Nephrology* 2012;**23**(7):1140-8. [MEDLINE: 22626822]

Arampatzis 2013

Arampatzis S, Gaetcke LM, Funk GC, Schwartz C, Mohaupt M, Zimmermann H, et al. Diuretic-induced hyponatremia and osteoporotic fractures in patients admitted to the emergency department. *Maturitas* 2013;**75**(1):81-6. [MEDLINE: 23489552]

Ballinger 2014

Ballinger AE, Palmer SC, Nistor I, Craig JC, Strippoli GF. Calcimimetics for secondary hyperparathyroidism in chronic kidney disease patients. *Cochrane Database of Systematic Reviews* 2014, Issue 12. [DOI: [10.1002/14651858.CD006254.pub2](https://doi.org/10.1002/14651858.CD006254.pub2)]

Ellison 2007

Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *New England Journal of Medicine* 2007;**356**(20):2064-72. [MEDLINE: 17507705]

FDA 2012

US Food, Drug Administration. FDA briefing document for the Cardiovascular and Renal Drug Advisory (CRDAC) - Drug: Lixivaptan. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm318867.pdf (accessed 30 January 2014).

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

Guyatt 2010

Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: A new series of articles

in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2010;**64**:380-382. [MEDLINE: 21185693]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoorn 2011

Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, et al. Mild hyponatremia as a risk factor for fractures: the Rotterdam study. *Journal of Bone & Mineral Research* 2011;**26**(8):1822-8. [MEDLINE: 21381111]

Jaber 2011

Jaber BL, Almarzouqi L, Borgi L, Seabra VF, Balk EM, Madias NE. Short-term efficacy and safety of vasopressin receptor antagonists for treatment of hyponatremia. *American Journal of Medicine* 2011;**124**(10):977.e1-9. [MEDLINE: 21962320]

Kinsella 2010

Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clinical Journal of The American Society of Nephrology: CJASN* 2010;**5**(2):275-80. [MEDLINE: 20056759]

Lindner 2012

Lindner G, Schwarz C, Funk GC. Osmotic diuresis due to urea as the cause of hypernatraemia in critically ill patients. *Nephrology Dialysis Transplantation* 2012;**27**(3):962-7. [MEDLINE: 21810766]

Lundh 2012

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. [DOI: [10.1002/14651858.MR000033.pub3](https://doi.org/10.1002/14651858.MR000033.pub3)]

Mirski 2013

Mirski, D (Otsuka America Pharmaceutical, Inc). Potential risk of liver injury with use of SAMSCA® (tolvaptan). www.sefap.it/web/upload/UCM336675.pdf 22 January 2013.

Renneboog 2006

Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness and attention deficits. *American Journal of Medicine* 2006;**119**(71):e1-8. [MEDLINE: 16431193]

Reynolds 2006

Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. *BMJ* 2006;**332**(7543):702-5. [MEDLINE: 16565125]

Rozen-Zvi 2010

Rozen-Zvi B, Yahav D, Gheorghiade M, Korzets A, Leibovici L, Gaftor U. Vasopressin receptor antagonists for the treatment of

hyponatremia: systematic review and meta-analysis. *American Journal of Kidney Diseases* 2010;**56**(2):325-37. [MEDLINE: 20538391]

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Spasovski 2014

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. [Erratum appears in *Nephrol Dial Transplant*. 2014 Jun;40(6):924]. *Nephrology Dialysis Transplantation* 2014;**29**(Suppl 2):i1-i39. [MEDLINE: 24569496]

Upadhyay 2009

Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. *Seminars in Nephrology* 2009;**29**(3):227-38. [MEDLINE: 19523571]

Verbalis 2010

Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, et al. Hyponatremia-induced osteoporosis. *Journal of Bone & Mineral Research* 2010;**25**(3):554-63. [MEDLINE: 19751154]

Verbalis 2013

Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *American Journal of Medicine* 2013;**126**(10 Suppl 1):S1-42. [MEDLINE: 17981159]

Wald 2010

Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Archives of Internal Medicine* 2010;**170**(3):294-302. [MEDLINE: 20142578]

References to other published versions of this review

Nagler 2014

Nagler EV, Haller MC, Van Biesen W, Vanholder R, Craig JC, Webster AC. Interventions for chronic non-hypovolaemic hypotonic hyponatraemia. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: [10.1002/14651858.CD010965](https://doi.org/10.1002/14651858.CD010965)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ACTIV in CHF 2003

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2) Hyponatraemia subgroup: yes, but randomisation not stratified according to the subgroup Recruitment period: 2000 to 2001 Treatment duration: 60 days Follow-up: 60 days
Participants	<ul style="list-style-type: none"> Countries: Argentina; USA Number of centres: 44 Inclusion criteria: in-patients, hospitalised for acute exacerbation of CHF; ≥ 18 years; serum sodium concentration was not an inclusion criterion for primary study - we included subgroup with serum sodium concentration ≤ 135 mmol/L; NYHA class III or IV cardiac disease at screening - 2 of the following signs of heart failure: elevated jugular vein distention; rales; chest X-ray with signs of radiographic congestion, pedal oedema, increased abdominal girth, weight gain > 10 pounds above baseline; admission to hospital for heart failure within 96 hours of screening Exclusion criteria: women of childbearing age; cardiac surgery within 60 days; MI, sustained ventricular tachycardia, or ventricular fibrillation within 30 days; angina at rest; primary valvular disease; hypertrophic cardiomyopathy; stroke within last 6 months; significant hepatic, renal or haematologic dysfunction; systolic arterial BP < 110 mm Hg; use of drugs known to inhibit CYP3A4 within 7 days of randomisation; amiodarone within 10 weeks; nonsteroidal anti-inflammatory agents or aspirin > 700 mg/d; substance or alcohol abuse; uncontrolled diabetes mellitus; urinary tract obstruction; morbid obesity; malignancy or another terminal illness. Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group 1 (15); treatment group 2 (23); treatment group 3 (15); control group (16) * Number, % women: 23, 33%; numbers not reported for individual groups * Age: median 65, range 52-72 years; age not reported for individual groups * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group 1 (133 ± 3); treatment group 2 (131 ± 4); treatment group 3 (132 ± 3); control group (133 ± 2) * Cause of hyponatraemia: heart failure (100%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 90 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 60 mg/d <p>Treatment group 3</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 30 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: no Dietary sodium intake: no All received standard heart failure treatment including diuretics at the discretion of the investigator
Outcomes	<ul style="list-style-type: none"> Death

ACTIV in CHF 2003 (Continued)

- Response in serum sodium concentration: serum sodium concentration > 135 mmol/L. Insufficiently reported to allow contribution to meta-analysis
- Serum sodium concentration (continuous outcome): absolute values at discharge

Notes

- Funding source: Otsuka Maryland Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: 'Eligible patients were randomised ... using an interactive voice recognition system programmed with a computer-generated randomisation scheme. Randomization was stratified by study centre in blocks of 4.'</p> <p>Comment: the randomisation procedure produced groups in the overall study that were not entirely balanced in age and sex, but fairly well-balanced in terms of medical history and characteristics related to the heart failure. However, randomisation was not stratified for serum sodium concentration. Despite fairly similar numbers of participants in both the experimental and the control group, no baseline data available specifically for subgroup with hyponatraemia, making judgement on risk of bias difficult. The sequence generation in the overall study was good and low risk. However this is a subgroup analysis with low numbers relative to the number of groups and the sequence did not stratify for them.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: 'Patients were screened within 72 hours and randomised within 96 hours of admission. Randomization occurred between 8 and 9 AM; the study drug was to be administered at 9 AM.'</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: '...patients...randomised to receive ... tolvaptan or placebo. ' and '...was a multicenter, randomised, double-blind, placebo-controlled... trial'</p> <p>Additional info provided by the sponsor: 'Both OPC-41061 and placebo tablets were identical in appearance'.</p> <p>Comment: blinding attempted, although participants are unlikely to be fully blinded due to important increases in urine output. Also, co-interventions were not reported in detail and included standard heart failure treatment left at discretion of investigator and may have differed between groups according to baseline serum sodium concentration. This could have influenced outcome measurement of serum sodium concentrations.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Additional info provided by the sponsor: 'Did not have separate outcome assessors in this trial'.</p> <p>Comment: blinding outcome assessors attempted and measured outcome objective.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: 10% attrition for outcome death at 60 days; only 1 participant (1%) excluded from analysis because of missing follow-up serum sodium concentration measurement.</p>
Selective reporting (reporting bias)	High risk	<p>Comment: protocol available with matched primary and secondary outcomes for the overall study. However, results included in this review for the subgroup with hyponatraemia are based on post-hoc analyses of the data, with reported outcomes not matching the primary and secondary outcomes of the original study.</p>

ACTIV in CHF 2003 (Continued)

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * 'All authors served as consultants for Otsuka Maryland Research Institute, received grants or honoraria from the company, or both.' * Comment: senior authors of reports pertaining to this study are heavily linked to the company commercialising the study medication. Sponsorship bias <ul style="list-style-type: none"> * Quote: 'The ACTIV in CHF study and this analysis were funded by Otsuka Maryland Research Institute'
------------	-----------	--

Annane 2009

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 3) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 5 days Follow-up: 12 days
Participants	<ul style="list-style-type: none"> Countries: Belgium; Finland; France; Germany; Italy; Netherlands; Poland; Spain; UK Number of centres: 17 Inclusion criteria: aged ≥ 18 years; serum sodium concentration < 130 mmol/L; euvolaemia or hypervolaemia, plasma osmolality < 290 mOsmol/kg, fasting blood glucose < 126 mg/dL Exclusion criteria: females if breast-feeding or pregnant; clinical volume depletion or dehydration; symptomatic hypotension, uncontrolled hypertension, arrhythmias requiring pacemaker or emergency treatment; untreated thyroid disorders, adrenal insufficiency; known urinary outflow obstruction unless catheterized; SCr > 2.7 mg/dL, proteinuria > 3 g/24h, liver enzymes > 3 times upper limit of normal; bilirubin ≥ 2.5 mg/dL, $< 3 \times 10^3$ white blood cells/μL, humane immuno-deficiency virus infection or active hepatitis; symptomatic hyponatraemia, expected to require emergent treatment; any concurrent illness that could interfere with study treatment or its evaluation; arginine vasopressin, oxytocin, or desmopressin or drugs interacting with CYP450 3A4, including certain chemotherapeutic agents, calcium channel blockers, statins, benzodiazepines, and class III antiarrhythmic drugs; medications for SIADH discontinued for 1 week before screening; thiazide diuretics permitted if therapy initiated < 1 month before study enrolment Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group 1 (26); treatment group 2 (27); control group (30) * Number, % women: treatment group 1 (7, 27%); treatment group 2 (9, 33%); control group (12, 40%) * Mean age $\pm$ SD (years): treatment group 1 (63 ± 11); treatment group 2 (62 ± 15); control group (69 ± 13) * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group 1 (126 ± 4); treatment group 2 (125 ± 5); control group (126 ± 4) * Cause of hyponatraemia <ul style="list-style-type: none"> ☐ Treatment group 1: SIADH (12, 46%); heart failure (7, 27%); unclear (7, 27%) ☐ Treatment group 2: SIADH (7, 26%); heart failure (12, 44%); unclear (8, 30%) ☐ Control group: SIADH (12, 40%); heart failure (8, 40%); unclear (7, 23%); postsurgical (3, 10%)
Interventions	<p>treatment group 1</p> <ul style="list-style-type: none"> Oral conivaptan: 2 x 40 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral conivaptan: 2 x 20 mg/d <p>Control group</p> <ul style="list-style-type: none"> Placebo: not otherwise defined

Annane 2009 (Continued)

Co-interventions (all groups)

- fluid restriction: 500 mL in any 3-hour period or 2 L/d, unless changes required for safety reasons
- dietary sodium intake: not reported

Outcomes

- Death
- Response: serum sodium concentration ≥ 135 mmol/L or increase from baseline ≥ 6 mmol/L
- Serum sodium concentration (continuous outcome): change from baseline until end of treatment
- Outcomes related to over-correction of serum sodium concentration
 - * Hyponatraemia: serum sodium concentration ≥ 145 mmol/L during treatment
 - * Rapid increase in serum sodium concentration: serum sodium concentration ≥ 145 mmol/L or an increase in serum sodium concentration from baseline ≥ 12 mmol/L/d
- Treatment-specific side-effects
 - * Hypotension: not otherwise defined
 - * Thirst: not otherwise defined (no extractable data reported)
 - * Liver function abnormalities: elevated liver transaminase
 - * Serious adverse event: not otherwise defined
- Treatment discontinuation

Notes

- Funding source: Astellas Pharma US, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'Eligible patient ... were stratified according to volume status and then randomly assigned in a 1:1:1 ratio...' Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'This double-blind, placebo controlled ... study', and '...patients ... were...assigned to ... or placebo', and 'All patients were prescribed fluid restriction (not to exceed 500 mL in any 3-hour period or 2.0 L in a 24-hour period for both oral and parenteral fluids) prior to baseline and throughout the study, unless changes were necessary for safety reasons', and 'Four patients, 2 given conivaptan 80 mg/d and 2 given placebo, violated the 2-L/d fluid restriction.' Comment: blinding attempted, and although participants and personnel are unlikely to be fully blinded due to important increases in urine output, all measured outcomes short-term and generally objective. Fluid restriction was prescribed in both groups, violations reported and similar between groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: blinding outcome assessors probably attempted and main outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall 13% attrition; reasons well documented, most occurred in the placebo group due to adverse events. Given <20% attrition and limited opportunity for introducing bias in such a short-term study - we judged it 'Low risk'.
Selective reporting (reporting bias)	Low risk	Comment: no protocol, short term study (≤ 1 week), primary outcome death and secondary outcomes related to serum sodium concentration and rapid increase in serum sodium concentration reported

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Annane 2009 (Continued)

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Quote: 'Guy Decaux was a paid investigator for this trial. Neila Smith was employed by Astellas Pharma US, Inc.' * Comment: Senior author was an employee of the company commercialising the study medication Sponsorship bias <ul style="list-style-type: none"> * 'This study was supported by Astellas Pharma US, Inc.'
------------	-----------	---

BALANCE 2010

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 3) Hyponatraemia subgroup: no Recruitment period: 2008 to 2010 Treatment duration: 60 days Follow-up: 90 days
Participants	<ul style="list-style-type: none"> Country: Argentina; Canada; Chile; Czech Republic; Germany; India; Israel; Italy; Poland; Romania; Russia; Slovakia; Spain; USA Number of centres: 173 Inclusion criteria: inpatients, hospitalised for acute worsening of CHF; ≥ 18 years; serum sodium concentration 120 to < 135 mmol/L; NYHA III or IV; clinical or laboratory evidence of volume overload, baseline fluid restriction 1.5 L/d Exclusion criteria: severe symptoms requiring immediate intervention; supine systolic BP < 90 mm Hg; advanced liver disease/cirrhosis; adrenal insufficiency; uncorrected thyroid disease; uncontrolled diabetes mellitus; inability to respond to thirst with increased fluid intake Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (323); control group (329) * Number, % women: treatment group (90, 28%); control group (95, 29%) * Mean age $\pm$ SD (years): treatment group: (65 $\pm$ 14); control group (65 $\pm$ 13) * Serum sodium concentration: median 132 mmol/L; concentration not reported for groups * Cause of hyponatraemia: heart failure (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral lixivaptan: 1 x 50 mg/d up to 2 x 100 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1 capsule/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: discouraged during dose titration, at discretion of treating physician Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Death Response: serum sodium concentration ≥ 135 mmol/L Serum sodium concentration (continuous outcome): change from baseline Cognitive function: change from baseline time to complete the trial making test part B, a neuropsychological test of visual attention and task switching Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase ≥ 8 mmol/L during first 8 hours, > 12 mmol/L during first 24 hours or > 18 mmol/L during first 48 hours

BALANCE 2010 (Continued)

- Treatment-specific side-effects
 - * AKI: not otherwise defined
 - * Liver function abnormalities: elevated AST > 3 times the upper limit of normal
 - * Serious adverse events: not otherwise defined
- Treatment discontinuation

Notes

- Funding source: Cardiokine Inc.
- ClinicalTrials.gov: NCT00578695
- Data source: FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory (CRDAC)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: '...subjects were randomised by an Interactive Voice Response System...'. Comment: central allocation occurred.
Allocation concealment (selection bias)	Low risk	Quote: '...subjects were randomised by an Interactive Voice Response System...'. Comment: central allocation occurred.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: '... double-blind, placebo-controlled phase 3 trial...' Comment: Blinding of participants and personnel probably attempted, but insufficient information to assess the extent to which it was achieved or to permit judgement of 'High risk' or 'Low risk'. Co-interventions were left at the discretion of the treating physician.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'The Clinical Endpoints Committee was to perform a review (blinded to treatment group and serum sodium levels) and adjudicate all events assessed by the investigators as clinical endpoints using predetermined criteria for each end-point...'. Comment: blinding probably attempted and although un-blinding likely to have occurred for serum sodium concentration, assessment of other outcomes done by independent blinded adjudication committee.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: 'The FDA statistical reviewer, Dr Jialu Zhang, also performed a number of sensitivity analyses to assess the impact of missing values... All these sensitivity analyses showed consistent results: a statistically significant treatment effect on serum sodium with a modest effect size in the range 1.2 to 1.4 mEq/L.' Comment: overall 27% discontinuation at 30 days, < 1% of which never received treatment; 50% of discontinuations occurred in placebo group. Last observation carried forward method was used as imputation method for dealing with missing serum sodium concentration values, which could have caused overestimation of the effect of the study medication. However, sensitivity analyses conducted by the FDA statistical reviewer indicated this effect to be negligible. Cognitive function tests were taken at day 30 or the early termination visit. Given the better scores in the placebo group, any bias would only serve to increase the difference further in favour of the placebo group and would not change the conclusions drawn from the analysis.
Selective reporting (reporting bias)	Low risk	Comment: the study was registered with ClinicalTrials.gov, but no clear listing of predefined outcome measures and time-points. Given early stopping of trial due to numerically more deaths in treatment group, selective outcome reporting unlikely to be an issue.

BALANCE 2010 (Continued)

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * No declaration of interest: data used in this review is drawn from the FDA briefing document Sponsorship bias <ul style="list-style-type: none"> * Comment: The study sponsor was Cardiokine Inc.
------------	-----------	---

Decaux 2006

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 4 days Follow-up: 1 year
Participants	<ul style="list-style-type: none"> Countries: not reported Number of centres: not reported, but multi-centre Inclusion criteria: setting (not reported); age (not reported); serum sodium concentration 115 to ≤ 132 mmol/L; SIADH treated with fluid restriction up to 1.5 L/d Exclusion criteria: not reported Characteristics included participants <ul style="list-style-type: none"> * Number: treatment group 1 (22); treatment group 2 (24); control group (23) * Number, % women: not reported * Age: not reported * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group 1 (129 ± 3); treatment group 2 (129 ± 5); control group (128 ± 4) * Cause of hyponatraemia: SIADH not reported
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 50 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 25 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: not reported, participants were treated with fluid restriction at enrolment Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Response: serum sodium concentration ≥ 135 mmol/L or increase from baseline ≥ 5 mmol/L Serum sodium concentration (continuous outcome): change from baseline. Insufficiently reported to allow contribution to meta-analysis Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase ≥ 8 mmol/L during the first day * Osmotic demyelination syndrome: any neurological adverse event Treatment-specific side-effects: insufficiently reported to allow contribution to meta-analysis <ul style="list-style-type: none"> * Thirst: not otherwise defined * Adverse events: defined as treatment-emergent adverse events * Serious adverse events: not otherwise defined

Decaux 2006 (Continued)

- Treatment discontinuation

Notes

- Funding source: Sanofi Aventis
- Publication: abstract only; contact author confirmed the study was never published in any form other than abstract form

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'randomised... study', and 'Patients ... were randomly assigned'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: '...double-blind, placebo-controlled...study', and 'Patients...were... assigned to ... or placebo'. Comment: blinding probably attempted, but insufficient information to assess to what extent it was achieved or to permit judgement of 'High risk' or 'Low risk'.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: overall 16% attrition, reasons not documented. Given < 20% attrition in short-term study, we judged this not at high risk of bias per se, rather insufficient information to permit judgement of 'High risk' or 'Low risk'.
Selective reporting (reporting bias)	Low risk	Comment: no protocol, short-term study (≤ 1 week), secondary outcomes related to serum sodium concentration and over-correction of serum sodium concentration reported.
Other bias	High risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * No declaration of interest • Sponsorship bias <ul style="list-style-type: none"> * Quote: 'Grant/Research Support: Sanofi-Aventis; Consultant: Sanofi-Aventis'

DILIPO 2011

Methods

- Design: parallel RCT (phase 3)
- Hyponatraemia subgroup: no
- Recruitment period: not reported
- Treatment duration: 4 days
- Follow-up: not reported

Participants

- Countries: Argentina; Australia; Belgium; Canada; Chile; Denmark; Greece; Hungary; Israel; Poland; Portugal; Romania; South Africa; Sweden; USA
- Number of centres: 48

DILIPO 2011 (Continued)

- Inclusion criteria: setting not reported; ≥ 18 years; serum sodium concentration 115 to < 132 mmol/L; dilutional hyponatraemia not caused by SIADH or liver cirrhosis
- Exclusion criteria: adrenal insufficiency; untreated hypothyroidism; clinical or laboratory evidence of hypovolaemia; fasting glycaemia ≥ 200 mg/dL; Hb < 9 g/dL, neutrophil cell count $< 1500/\mu\text{L}$, platelet count $< 100,000/\mu\text{L}$; SCr > 2 mg/dL or CrCl < 30 mL/min; serum ALT or AST > 2 times upper limit of normal; QTcB interval ≥ 500 ms; serum potassium concentration > 5 mmol/L; having received inducers of CYP3A4 or potent and moderate inhibitors of CYP3A4 < 2 weeks before study; other AVP V2-receptor antagonists, lithium or demeclocycline < 1 month before study, urea < 2 days before study; positive pregnancy test and absence of medically approved contraceptive methods; pregnancy or breast-feeding
- Characteristics randomised participants
 - * Number: treatment group 1 (41); treatment group 2 (35); control group (42)
 - * Number, % women: treatment group 1 (16, 39%); treatment group 2 (19, 54%); control group (15, 36%)
 - * Mean age $\pm$ SD (years): treatment group 1 (71 ± 12); treatment group 2 (69 ± 16); control group (69 ± 11)
 - * Serum sodium concentration (mmol/L): treatment group 1 (128 ± 4); treatment group 2 (128 ± 4); control group (129 ± 3)
 - * Cause of hyponatraemia
 - ☐ Treatment group 1: heart failure 28 (68%); other 13 (32%)
 - ☐ Treatment group 2: heart failure 28 (80%); other 7 (20%)
 - ☐ Control group: heart failure 34 (81%); other 8 (19%)

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • Oral satavaptan: 1 x 50 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> • Oral satavaptan: 1 x 25 mg/d <p>Control group</p> <ul style="list-style-type: none"> • Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: 1 to 1.5 L/d • Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> • Response: serum sodium concentration ≥ 135 mmol/L or increase from baseline ≥ 5 mmol/L • Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: serum sodium concentration ≥ 145 mmol/L * Rapid increase in serum sodium concentration: serum sodium concentration increase ≥ 12 mmol/L/d * Osmotic demyelination syndrome: neurologic symptoms • Treatment-specific side-effects <ul style="list-style-type: none"> * Hypotension: not otherwise defined * Thirst: not otherwise defined * Adverse event: not otherwise defined * Serious adverse events: defined as serious treatment-emergent adverse events • Treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Sanofi-Aventis

Risk of bias
Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DILIPO 2011 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: '...eligible patients were randomly allocated to...', and '4 patients were not randomised through the interactive voice recognition system'. Comment: Central allocation probably occurred. The randomisation produced groups well-balanced in age and serum sodium concentration, less so in sex
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: '...patients were randomly allocated to ... or placebo', and 'The randomised, double-blind, placebo-controlled ...', and '...recommended fluid intake 1000-1500 mL'. Comment: blinding attempted, and although participants and personnel are unlikely to be fully blinded due to important increases in urine output, all measured outcomes short-term and fairly objective. Fluid restriction was prescribed in all groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: blinding outcome assessors probably attempted and all measured outcomes objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall 11% attrition, due to treatment discontinuation, reasons fairly well documented, asymmetrically in experimental group receiving highest dose due to adverse events. Missing data dealt with using last observation carried forward method. Given < 20% attrition and limited opportunity for introducing bias in such a short-term study - we judged it 'Low risk'
Selective reporting (reporting bias)	Low risk	Comment: study registered with ClinicalTrials.gov in 2005. Primary outcome matches, more outcomes reported than originally registered - predominantly outcomes related to harms. Short-term study (≤ 1 week), secondary outcomes related to serum sodium concentration and rapid increase in serum sodium concentration reported
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * M.M. was an employee of Sanofi-Aventis at the time of the study. All other listed authors have received research funds to conduct the DILIPO study.' * Comment: One of the authors was an employee of the company developing the study medication Sponsorship bias <ul style="list-style-type: none"> * Quote: 'This study was supported by a research grant from Sanofi-Aventis

Dzau 1984

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 5 days Follow-up: 8 days
Participants	<ul style="list-style-type: none"> Country: USA Number of centres: 1 Inclusion criteria: serum sodium concentration ≤ 135 mmol/L; heart failure - NYHA class III-IV

Dzau 1984 (Continued)

- Exclusion criteria: not reported
- Characteristics randomised participants
 - * Number: treatment group (8); control group (6)
 - * Number, % women: treatment group (2, 25%); control group (0, 0%)
 - * Mean age, range: 58, 3 to 72 years
 - * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group (129 ± 1); control group (130 ± 1)
 - * Cause of hyponatraemia: heart failure (100%)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Oral captopril 3 x 12.5 mg/d up to 3 x 150 mg/d • Furosemide: at doses adjusted to give a sustained diuretic effect without increasing azotaemia <p>Control group</p> <ul style="list-style-type: none"> • Oral captopril: 3 x 12.5 mg/d up to 3 x 150 mg/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: free access to water • Dietary sodium intake: 0.9 g/d
Outcomes	<ul style="list-style-type: none"> • Serum sodium concentration (continuous outcome): absolute value at end of treatment
Notes	<ul style="list-style-type: none"> • Funding source: National Institutes of Health and National Aeronautics and Space Administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: 'The patients were randomly divided in two groups...'</p> <p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Comment: blinding not attempted</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: blinding not attempted, but main outcomes objective such that unblinding of outcome detection unlikely to be an important source of bias</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: attrition or treatment discontinuation not specifically reported, but it appears as if all participants completed the treatment protocol</p>
Selective reporting (reporting bias)	High risk	<p>Comment: no protocol, short-term study (≤ 1 week), secondary outcomes related to rapid increase in serum sodium concentration not reported</p>
Other bias	Low risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: no declaration of interest

Dzau 1984 (Continued)

- Sponsorship bias
 - * Quote: 'Grant support: supported in part by grants ... from the National Institutes of Health andfrom the National Aeronautics and Space Administration.'
 - * Comment: no commercial sponsorship

EVEREST 2005

Methods	<ul style="list-style-type: none"> • Design: parallel RCT (phase 3) • Hyponatraemia subgroup: yes, randomisation not stratified based on serum sodium concentration • Recruitment period: 2003 to 2006 • Treatment duration: minimum 2 months • Follow-up: 2 years
Participants	<ul style="list-style-type: none"> • Countries: Argentina; Belgium; Brazil; Bulgaria; Canada; Czech Republic; France; Germany; Italy; Lithuania; Netherlands; Norway; Poland; Romania; Russian Federation; Spain; Sweden; Switzerland; UK; USA • Number of centres: 359 • Inclusion criteria: hospital in-patients recruited within 48 hours of hospitalisation; ≥ 18 years; serum sodium concentration not an inclusion criterion for primary study (we included subgroup with serum sodium concentration < 135 mmol/L); history of CHF - defined as requiring treatment for a minimum of 30 d before hospitalisation; left ventricular ejection fraction $\leq 40\%$; signs of volume expansion; NYHA III/IV; hospitalisation for exacerbation of chronic HF ≤ 48 h earlier • Exclusion criteria: cardiac surgery < 60 days of enrolment; cardiac mechanical support; biventricular pacemaker < 60 days; comorbid conditions with expected survival < 6 months; acute MI at the time of hospitalisation; haemodynamically significant uncorrected primary cardiac valvular disease; refractory end-stage heart failure; haemofiltration or dialysis; supine systolic arterial BP < 90 mm Hg; SCr > 3.5 mg/dL; serum potassium concentration > 5.5 mmol/L; Hb < 9 g/dL; history of hypersensitivity or idiosyncratic reaction to benzazepine derivatives; positive urine pregnancy test; inability to provide written informed consent; history of drug or medication abuse within the past year, or current alcohol abuse; previous participation in this or any other tolvaptan clinical trial; inability to take oral medications; participation in another clinical drug or device trial in which the last dose of drug was within the past 30 d or an investigation medical device is implanted • Characteristics included participants <ul style="list-style-type: none"> * Number: treatment group (243); control group (232) * Number, % women: treatment group (35, 14%); control group (52, 22%) * Mean age $\pm$ SD (years): treatment group (64 ± 14); control group (65 ± 14) * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group (131 ± 3); control group (130 ± 4) * Cause of hyponatraemia: heart failure (100%)
Interventions	<p>treatment group</p> <ul style="list-style-type: none"> • Oral tolvaptan: 1 x 30 mg/d <p>Control group</p> <ul style="list-style-type: none"> • Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: not reported • Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> • Death during follow-up • Length of hospital stay

EVEREST 2005 (Continued)

- Serum sodium concentration (continuous outcome): change from baseline until day 7
- Outcomes related to over-correction of serum sodium concentration
 - * Hyponatraemia: not otherwise defined
 - * Osmotic demyelination syndrome: not otherwise defined
- Treatment-specific side effects
 - * AKI: not otherwise defined
 - * Hypotension: not otherwise defined
 - * Thirst (categorical outcome): not otherwise defined
 - * Polyuria: not otherwise defined
- Treatment discontinuation

Notes

- Funding source: Otsuka

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: '...within each centre, patients were randomised to... according to a centralized, blocked randomization performed using a central Interactive Voice Response System'.</p> <p>Additional info provided by the sponsor: 'Subjects were not stratified by baseline serum sodium'.</p> <p>Comment: the randomisation procedure was adequate and produced well balanced groups in the overall study. Although randomisation was not stratified for serum sodium concentration, fairly similar numbers of participants in both the experimental and the control group, with similar ages and baseline serum sodium concentration</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: '...within each centre, patients were randomised to... according to a centralized, blocked randomisation performed using a central Interactive Voice Response System'</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: 'Patients...assigned to receive oral tolvaptan 30 mg or matching placebo.' and '...is and international, ..., double-blind, placebo-controlled study...'</p> <p>Additional info provided by the sponsor: 'The trial drug was packaged so that each subject received an identical number of tablets regardless of the treatment group assigned'.</p> <p>Comment: blinding attempted, although participants are unlikely to be fully blinded due to important increases in urine output. Also, co-interventions were not reported and may have differed between groups according to baseline serum sodium concentration. This could have influenced outcome measurement of serum sodium concentrations and length of hospital stay</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Additional info provided by the sponsor: 'Did not have separate outcome assessors in this trial'.</p> <p>Comment: blinding outcome assessors attempted and all measured outcomes objective</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Comment: 30% (33% in experimental group, 29% in control group) attrition from analysis of serum sodium concentration at day 7</p>
Selective reporting (reporting bias)	High risk	<p>Comment: protocol available with matched primary and secondary outcomes for the overall study. However, results included in this review for the subgroup</p>

EVEREST 2005 (Continued)

with hyponatraemia are based on post-hoc analyses of the data, with reported outcomes not matching the primary and secondary outcomes of the original study

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'Ms Krasa received compensation through her Otsuka salary and Ms Bechhofer received compensation through a contract between the University of Wisconsin and Otsuka Maryland Research Institute.', and 'Mr. Cyr, Ms. Olchanski, Ms. Slawsky, and Dr. Gross received research funding from Otsuka America Pharmaceutical, which markets tolvaptan. Ms. Krasa and Dr. Zimmer are employees of Otsuka Pharmaceutical Development and Commercialization. Dr. Hauptman is a clinical investigator for and a consultant to Otsuka Pharmaceutical Development and Commercialization' Comment: senior authors of reports pertaining to this study are heavily linked to the company commercialising the study medication Sponsorship bias <ul style="list-style-type: none"> Quote: 'Otsuka funded the EVEREST trial under the guidance of the EVEREST steering committee', and 'the data collection and management for this study was by Otsuka; analysis was by the University of Wisconsin Statistical Data Analysis centre and Otsuka'. Comment: Data collection, management and analysis was also done by the pharmaceutical company
------------	-----------	---

Gerbes 2003

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase II) Hyponatraemia subgroup: no Recruitment period: 1997 to 1998 Treatment duration: 7 days Follow-up: not reported
Participants	<ul style="list-style-type: none"> Country: not reported Number of centres: 17 Inclusion criteria: 18 to $\leq$ 80 years; serum sodium concentration 115 to $\leq$ 132 mmol/L; urine/plasma osmolality > 1; written informed consent Exclusion criteria: major haemodynamic or pulmonary insufficiency; creatinine concentration >200 μmol/L; systolic arterial pressure < 80 mm Hg; Hb < 9 g/dL; encephalopathy; any evidence of active myocardial ischaemia within past two months; heart failure NYHA IV; recent antibiotic treatment Characteristics included participants Number: treatment group 1 (36); treatment group 2 (37); control group (39) Number, % women: not reported Mean age: 58 years (not reported for individual groups) Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group 1 (128 ± 4); treatment group 2 (128 ± 4); control group (129 ± 4) Cause of hyponatraemia: SIADH (31, 28%); heart failure (14, 13%); liver cirrhosis (61, 54%) (not reported for individual groups)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral lixivaptan: 2 x 100 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral lixivaptan: 2 x 50 mg/d

Gerbes 2003 (Continued)

Control group

- Oral placebo: 2 x 1/d

Co-interventions (all groups)

- Fluid restriction: < 1 L/d
- Dietary sodium intake: not reported

Outcomes	<ul style="list-style-type: none"> • Response: serum sodium concentration ≥ 136 mmol/L • Serum sodium concentration (continuous outcome): absolute value at end of treatment • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Osmotic demyelination syndrome: any neurologic abnormality • Treatment-specific side-effects <ul style="list-style-type: none"> * AKI: SCr > 200 μmol/L * Thirst (continuous outcome): measured on a 0 to 100 VAS * Serious adverse events: requiring treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Wyeth Ayerst Research • Publication: abstract-only publication (full publication reports the subgroup of participants with cirrhosis only)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: 'A computer-generated randomisation table was available at each participating hospital. A patient number was assigned when a patient had qualified during the pre-study screening. Before administration of the first study medication, the patient was assigned a randomisation number by an unblinded site pharmacist. This unblinded dispenser did not administer the drug to patients, and the contact between him and the investigators and study nurses was kept to a minimum.'</p> <p>Comment: the randomisation procedure produced well balanced groups in terms of baseline serum sodium concentration, no information on other baseline characteristics</p>
Allocation concealment (selection bias)	Low risk	<p>Comment: the randomisation procedure produced well balanced groups in terms of baseline serum sodium concentration, no information on other baseline characteristics</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: '...randomised, double blind, placebo-controlled study...', and '...patients were randomised to placebo or 50 mg twice a day...'</p> <p>Comment: blinding attempted, and although participants and personnel are unlikely to be fully blinded due to important increases in urine output, all measured outcomes short-term and fairly objective. Co-intervention of fluid restriction similar in all groups</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Comment: published in abstract form only, insufficient information to permit judgement of 'High risk' or 'Low risk'</p>

Gerbes 2003 (Continued)

Selective reporting (reporting bias)	High risk	Comment: no protocol, short-term study (≤ 1 week) but no reporting of primary outcomes death or health-related quality of life or secondary outcomes related to rapid increase in serum sodium concentration in a way that permitted data extraction
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'P Ginès has been a consultant for Wyeth Ayerst Research, H. Gandjini and J. Djian are employees at Wyeth Ayerst Research.' Comment: senior author of all publications related to this study is an employee at the company developing the study medication Sponsorship bias <ul style="list-style-type: none"> Comment: this study was funded Wyeth Ayerst Research

Ghali 2006

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 5 days Follow-up: 14 days
Participants	<ul style="list-style-type: none"> Countries: Canada; Israel; USA Number of centres: 21 Inclusion criteria: ≥ 18 years; serum sodium concentration 115 to < 132 mmol/L; euvolaemia or hypervolaemia; plasma osmolality < 290 mOsm/kg Exclusion criteria: women if lactating, pregnant or not using barrier method of birth control; fasting serum glucose concentration ≥ 275 mg/dL; uncontrolled hypertension; orthostatic hypotension or supine systolic BP < 85 mm Hg; uncontrolled arrhythmia; untreated severe hypothyroidism, hyperthyroidism, adrenal insufficiency; estimated CrCl < 20 mL/min; ALT or AST > 5 times upper limit of normal; serum albumin concentration ≤ 1.5 g/dL; prothrombin time > 22 s or international normalised ratio > 2.0 without anticoagulants or ≥ 3.0 with therapy; WCC $< 3000/\mu\text{L}$; HIV infection or active hepatitis; patients expected to have hyponatraemia necessitating emergent treatment during study; concurrent illness that could interfere with study treatment or evaluation; participation in clinical trial with 30 days of screening <ul style="list-style-type: none"> Characteristics included participants Number: treatment group 1 (27); treatment group 2 (24); control group (23) Number, % women: treatment group 1 (13, 48); treatment group 21 (2, 50%); control group (13, 56%) Mean age, range (years): treatment group 1 (69, 35 to 90); treatment group 2 (66, 38 to 93); control group (73, 41 to 94) Serum sodium concentration (mmol/L): treatment group 1 (125 ± 4); treatment group 2 (125 ± 4); control group (123 ± 4) Cause of hyponatraemia <ul style="list-style-type: none"> Treatment group 1: heart failure (11, 41%); COPD (2, 7%); malignancy (3, 11%); idiopathic (7, 26%); other (4, 15%) Treatment group 2: heart failure (10, 42%); malignancy (2, 8%); idiopathic (5, 21%); other (7, 29%) Control group: heart failure (11, 48%); COPD (1, 4%); malignancy (3, 13%); idiopathic (3, 13%); other (5, 22%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral conivaptan: 2 x 40 mg/d <p>Treatment group 2</p>

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Ghali 2006 (Continued)

- Oral conivaptan: 2 x 20 mg/d

Control group

- Oral placebo: 2 x/d

Co-interventions (all groups)

- Fluid restriction: ≤ 500 mL in any 3-hour period or < 2 L/d; treatment group 1 (67%), treatment group 2 (75%), control group (61%) drank 2 to 3 L/d
- Dietary sodium intake: remained stable throughout the study

Outcomes	<ul style="list-style-type: none"> • Death • Response: serum sodium concentration ≥ 135 mmol/L or increase from baseline ≥ 6 mmol/L • Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L/d or total increase > 24 mmol/L or serum sodium concentration > 145 mmol/L or reduced or temporarily withheld treatment after increase in serum sodium concentration judged by investigator as too rapid • Treatment-specific side-effects <ul style="list-style-type: none"> * AKI: SCr > 1.6 mg/dL * Hypotension: not otherwise defined * Serious adverse events: not otherwise defined • Treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Astellas Pharma US, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'Eligible patients were stratified by volume status and assigned randomly in a 1:1:1 ratio...' Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'This double-blind, placebo-controlled ... study', and 'Fluid intake was limited to ...up to a maximum of 2.0 litres in 24h.and 24-h sodium intake remained stable throughout the study'. Comment: blinding attempted, and although participants and personnel are unlikely to be fully blinded due to important increases in urine output, all measured outcomes short-term and fairly objective. Fluid restriction and stable sodium intake were prescribed in all groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: blinding outcome assessors probably attempted and all measured outcomes objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall 9% attrition, 5% exclusions for never having received the drug, 4% due to treatment discontinuation, reasons well-documented. Missing data dealt with through analytic techniques for repeated measures using the last available measurement before discontinuation. Given $< 20\%$ attrition and

Ghali 2006 (Continued)

		limited opportunity for introducing bias in such a short-term study - we judged it 'Low risk'
Selective reporting (reporting bias)	Low risk	Comment: no protocol, short term study (≤ 1 week), secondary outcomes related to serum sodium concentration and rapid increase in serum sodium concentration reported
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> 'J.K.G. was a principal investigator from 1999-2004 for trials sponsored by Astellas Pharma US, Inc. N.S. is employed by Astellas Pharma US, Inc.' Comment: senior author is an employee of the company commercialising the study medication. Sponsorship bias <ul style="list-style-type: none"> Quote: 'This study was supported by Astellas Pharma US, Inc (formerly Yamanoushi Pharma America, Inc)

Gheorghiade 2003

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2) Hyponatraemia subgroup: yes, but randomisation not stratified according to the subgroup Recruitment period: 1998 to 1999 Treatment duration: 25 days Follow-up: 58 days
Participants	<ul style="list-style-type: none"> Countries: Argentina; USA Number of centres: 30 Inclusion criteria: outpatients recruitment from university, community and veterans affairs hospitals; ≥ 18 years; serum sodium concentration: not an inclusion criterion for primary study (we included subgroup with serum sodium concentration ≤ 135 mmol/L); CHF with clinical signs of volume overload; stable oral furosemide dose (40 to 240 mg) ≥ 7 days before enrolment Exclusion criteria: cardiac surgery < 90 days prior; MI < 60 days prior; sustained ventricular tachycardia, ventricular fibrillation or automatic implantable cardiac defibrillator discharge < 30 days prior; atrial fibrillation with ventricular rate 115 BPM; diastolic BP > 95 mm Hg; diuretics other than furosemide < 14 days prior; NSAIDs or aspirin 700 mg/d; SCr > 3.0 mg/dL or BUN > 60 mg/dL; serum potassium concentration < 3.4 mmol/L; serum digoxin concentration > 2.2 ng/mL; uncontrolled diabetes mellitus; urinary tract obstruction; morbid obesity; history of intrinsic hepatic disease or liver enzymes ≥ 3 times upper limit of normal; any disorder precluding participation or limiting survival; women if breast-feeding, of childbearing potential, and not using contraception Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group 1 (20); treatment group 2 (14); treatment group 3 (15); control group (21) Number, % women: not reported Mean age $\pm$ SD (years): not reported Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group 1 (133 ± 2); treatment group 2 (133 ± 2); treatment group 3 (134 ± 1); control group (133 ± 1) Cause of hyponatraemia: heart failure (100%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral tolvaptan: 1×60 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral tolvaptan: 1×45 mg/d <p>Treatment group 3</p>

Gheorghiade 2003 (Continued)

- Oral tolvaptan: 1 x 30 mg/d

Control group

- Oral placebo: 1 x 1/d

Co-interventions (all groups)

- Fluid restriction: no
- Dietary sodium intake: 'during the study patients were asked to follow a no-salt-added diet
- All received standard heart failure treatment including diuretics at the discretion of the investigator

Outcomes

- Response in serum sodium concentration: serum sodium concentration > 135 mmol/L at any time during treatment
- Serum sodium concentration (continuous outcome): defined as change from baseline
- Treatment-specific side-effects
 - * AKI: insufficiently reported to allow contribution to meta-analysis
 - * Thirst: insufficiently reported to allow contribution to meta-analysis
 - * Polyuria: insufficiently reported to allow contribution to meta-analysis
- Treatment discontinuation: insufficiently reported to allow contribution to meta-analysis

Notes

- Outcomes insufficiently reported to allow contribution to meta-analysis
- Funding source: Otsuka Maryland Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: '...central random assignment procedure ... by means of an Interactive Voice-Response System'</p> <p>Comment: the randomisation procedure produced groups in the overall study that were not entirely balanced in age and sex, not in terms of medical history or characteristics related to the heart failure. The randomisation was not stratified for serum sodium concentration. The large number of groups relative the total number of participants would have made it likely for the groups to be unbalanced in prognostic characteristics. However, the absence of baseline data specifically for the subgroup with hyponatraemia, make it difficult to judge both magnitude and direction of possible bias.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: '...central random assignment procedure ... by means of an Interactive Voice-Response System'.</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: '...were assigned to receive...or placebo...', and '...a double-blind, randomised trial'</p> <p>Additional info provided by sponsor: 'Both OPC-41061 and placebo tablets were identical in appearance'.</p> <p>Comment: blinding attempted, although participants are unlikely to be fully blinded due to important increases in urine output. Also, co-interventions were not reported in detail for the subgroup with hyponatraemia and included standard heart failure treatment left at discretion of investigator and may have differed between groups according to baseline serum sodium concentration. This could have influenced outcome measurement of serum sodium concentrations</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Additional info provided by sponsor: 'Did not have separate outcome assessors in this trial'.</p>

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Gheorghiade 2003 (Continued)

		Comment: blinding outcome assessors attempted, main outcome objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 34% attrition for outcomes related to serum sodium concentration measurements in comparison with numbers provided in the study report
Selective reporting (reporting bias)	High risk	Comment: no protocol available, long-term study (> 1 week), primary outcomes and secondary outcomes not reported in a way that allowed extraction of raw data
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Comment: 'Dr Gheorghiade is a consultant for and has received a grant support from Otsuka Maryland Research Institute (OMRI), Rockville, Md. Dr. Niazi has received grant support from OMRI, and Drs. Ouyang, Czerwicz, Kambayashi, and Orlandi are OMRI employees.' Comment: multiple authors, including the senior author, are employees of the company commercialising Sponsorship bias <ul style="list-style-type: none"> Comment: this study was industry instigated and supported by Otsuka Maryland Research Institute

Gheorghiade 2006

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2) Hyponatraemia subgroup: no Recruitment period: 1998 to 1999 Treatment duration: 12 days Follow-up: 65 days
Participants	<ul style="list-style-type: none"> Country: USA Number of centres: 9 Inclusion criteria: university and community hospital in-patients; ≥ 18 years; serum sodium concentration < 135 mmol/L; euvoalaemia or hypervolaemia Exclusion criteria: acute coronary ischaemic events < 60 days after randomisation; history of sustained ventricular tachycardia or ventricular fibrillation; $SCr > 2.8$ mg/dL Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group (17); control group (11) Number, % women: treatment group: (7, 41%); control group (5, 45%) Mean age $\pm$ SD (years): treatment group (66 ± 13); control group (67 ± 9) Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group (129 ± 3); control group (129 ± 4) Cause of hyponatraemia: SIADH 10 (36%); heart failure 14 (50%); liver cirrhosis 4 (14%) (not reported for individual groups)
Interventions	<p>treatment group</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 10 mg/d up to 1 x 60 mg/d <p>Control group</p> <ul style="list-style-type: none"> Fluid restriction: ≤ 1.2 L/d with changes left to discretion of investigator + 1 x 1/d <p>Co-interventions (all groups)</p>

Gheorghiade 2006 (Continued)

- Fluid restriction: see above
- Dietary sodium intake: a no salt added diet was recommended throughout the study

Outcomes	<ul style="list-style-type: none"> • Death • Response in serum sodium concentration (categorical outcome):serum sodium concentration $\geq$ 135 mmol/L or 10% increase from baseline • Serum sodium concentration (continuous outcome):change from baseline until day 5 • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: not otherwise defined • Treatment-specific side-effects <ul style="list-style-type: none"> * Thirst (continuous outcome): measured on a 0 to 100-point VAS * Hypotension: not otherwise defined
Notes	<ul style="list-style-type: none"> • Funding source: Otsuka Maryland Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: '...subjects were randomised...', and 'This study was a multicenter, prospective, randomised.... trial.'</p> <p>Additional info provided by the sponsor: 'The study was conducted using local (per site) randomisation.'</p> <p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: 'This study was a multicenter, prospective, randomised, open-label.... trial', and '...subjects were randomised ... to tolvaptan or fluid restriction plus placebo'.</p> <p>Additional info provided by the sponsor: 'The study drug was supplied as either 5 mg, 15 mg OPC-4 1061 tablets or matching placebo. All tablets were identical in appearance.' and '(investigators were) not concealed as separate instructions were given to investigators for subjects on fluid-restriction/placebo and those on active therapy.'</p> <p>Comment: blinding of participants attempted, and although participants are unlikely to have been fully blinded due to important increases in urine output, serum sodium concentration short-term and generally objective. Personnel were not blinded</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: blinding of outcome assessors not attempted, but main measured outcomes objective. Participants not blinded, and plausible 'high risk' of bias for self-reported outcome of thirst</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: 'Two of the 17 subjects assigned to the tolvaptan group and 3 of the 11 subjects assigned to the fluid restriction group were withdrawn during the run-in phase because of protocol violations or because withdrawal criteria were met.'</p> <p>Comment: overall 17% attrition -12% in experimental group, 27% in placebo group - due to protocol violation or because participants never received the study medication. Reasons not documented in detail. Given <20% attrition, short-term study, we judged risk of bias to be 'Low'</p>

Gheorghiade 2006 (Continued)

Selective reporting (reporting bias)	High risk	Comment: no protocol, short-term study (<1 week), secondary outcomes related to rapid increase in serum sodium concentration not reported. Treatment duration 12 days, yet primary outcome measured at 5 days; Thirst measured at last inpatient visit, which could have been anywhere between 5 and 12 days after study initiation and different for both groups
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Comment: Three authors, including the senior author are affiliated to Otsuka Maryland Research Institute, Rockville, Maryland Sponsorship bias <ul style="list-style-type: none"> Quote: 'This trial was funded by Otsuka Maryland Research Institute'.

Gines 2008b

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 1 year Follow-up: not reported
Participants	<ul style="list-style-type: none"> Country: not reported Number of centres: not reported Inclusion criteria: serum sodium concentration < 130 mmol/L; liver cirrhosis and ascites Exclusion criteria: not reported Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group (92); control group (47) Number, % women: not reported Mean age $\pm$ SD (years): not reported Serum sodium concentration (mmol/L): not reported Control group: liver cirrhosis 47 (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 5 mg/d up to 1 x 50 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: not reported Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Length of hospital stay: average number of days/year/patient Treatment-specific side-effects <ul style="list-style-type: none"> AKI: SCr increase > 50% from baseline or SCr > 1.5 mg/dL
Notes	<ul style="list-style-type: none"> Funding source: not reported Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Gines 2008b (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: 'Patients...were randomised...'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'. No baseline characteristics presented
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: 'Patients...were randomised into a multi-centre, single-blind study to receive in a 2:1 ratio either a flexible dose-regimen of satavaptan (5-50 mg once daily) or placebo'. Comment: blinding of participants probably attempted. However, insufficient information for assessing to what extent it was achieved, or to permit judgement of 'High risk' or 'Low risk'. Blinding of personnel not attempted. No information on how differential treatment and follow-up was avoided
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: 'Patients...were randomised into a multi-centre, single-blind study...'. Comment: outcome assessors not blinded and main outcome measure - objective outcome measures
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Selective reporting (reporting bias)	High risk	Comment: no protocol and long term (> 1 week) study, primary outcomes and secondary outcomes related to rapid increase in serum sodium concentration not reported
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: no declaration of interest. From declarations of interest from Gines 2008a it is clear that 'Dr. Ginès is a consultant for Sanofi-Aventis. Dr. Wong is a consultant for Sanofi-Aventis. Dr. Watson owns stock in Sanofi-Aventis' Sponsorship bias <ul style="list-style-type: none"> * Comment: all of the studies in which a vasopressin receptor antagonist was evaluated were industry sponsored. It seems very likely this one was industry sponsored too, but at this stage insufficient information

HARMONY 2012

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 3) Hyponatraemia subgroup: no Recruitment period: 2009 to 2010 Treatment duration: 6 months Follow-up: 7 months
Participants	<ul style="list-style-type: none"> Countries: Belgium; Czech Republic; Israel; India; Italy; Mexico; Peru; USA Number of centres: 61 Inclusion criteria: long-term care facilities and nursing homes; ≥ 18 years; serum sodium concentration < 135 mmol/L; euvoemia; willing to be observed in a monitored setting for the first 8 hours following treatment initiation; in the Investigator's judgement the patient has adequate visual and auditory acuity to allow participation in the trial Exclusion criteria: overt symptoms requiring immediate intervention; acute or transient hyponatraemia, pseudohyponatraemia, hypovolaemic hyponatraemia; drug-induced hyponatraemia; hy-

HARMONY 2012 (Continued)

	<p>ponatraemia due to hypothyroidism or adrenal insufficiency; hypertonic hyponatraemia, hypokalaemia; demeclocycline, lithium carbonate, urea, or any other vasopressin antagonist within 7 days of participation; supine systolic BP $\leq$ 90 mm Hg; SCr > 3 mg/dL; uncontrolled diabetes; severe malnutrition; documented cirrhosis or alcoholic liver disease; terminal illness; psychogenic polydipsia; urinary tract obstruction; myocardial ischaemia; MI or cerebrovascular accident within 30 days; neurologic impairment such as dementia; conditions causing inability to respond to thirst; NYHA class III or IV; women pregnant or breastfeeding or planning to</p> <ul style="list-style-type: none"> Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (154); control group (52) * Number, % women: treatment group (81, 53%); control group (25, 48%) * Mean age $\pm$ SD (years): treatment group (67 ± 14); control group (63 ± 14) * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group (130 ± 4); control group (130 ± 4) * Cause of hyponatraemia: SIADH (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral lixivaptan: 1 x 25 mg/d, titrated to 1 x 100 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral matching placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: investigators were instructed, when possible, to not institute fluid restriction for at least the first 72 hours of dosing. However, fluid restriction could be initiated at the investigator's discretion throughout the duration of the study Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Death Response: serum sodium concentration 135 to $\leq$ 145 mmol/L Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation Cognitive function (continuous outcome): measured by the time to complete the Trail Making Test - Part B; continuous outcome - as measured by change from baseline in the Medical Outcomes Study 6-Item Cognitive Function Scale (MOS-6) score - insufficiently reported to allow contribution to meta-analysis Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: serum sodium concentration $\geq$ 145 mmol/L * Rapid increase in serum sodium concentration: serum sodium concentration increase $\geq$ 8 mmol/L during first 8 hours, > 12 mmol/L during first 24 hours or > 18 mmol/L during first 48 hours * Osmotic demyelination syndrome: not otherwise defined Treatment-specific side-effects <ul style="list-style-type: none"> * Hypotension: not otherwise defined * Thirst: not otherwise defined * Polyuria: not otherwise defined * Adverse event: treatment-emergent adverse events, not otherwise defined * Serious adverse events: serious treatment-emergent adverse events, not otherwise defined Treatment discontinuation
Notes	<ul style="list-style-type: none"> Funding source: No clear statement about funding but from author affiliations and declarations of interest clear this is an industry instigated study Additional data source: FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory (CR-DAC)

Risk of bias

HARMONY 2012 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'The HARMONY study was a ... randomised study', and 'Subjects were initially randomised to ...'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'The HARMONY study was a ... double-blind, placebo-controlled ... study'. Comment: blinding probably attempted, although due to increase in urine output, un-blinding likely to have occurred. Fluid restriction was largely left to the discretion of the investigator, but fewer participants receiving the study medication had fluid restriction initiated or tightened by day 30 (11% versus 21%)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: overall 17% discontinuation at 8 weeks, numbers and reasons similarly distributed between experimental and placebo group. However, 67% discontinuation at 24 weeks, according to the FDA briefing document because, quote 'According to the applicant, because the primary and secondary efficacy endpoints targeted time points between the initial eight weeks from randomisation, therefore, when the last subject enrolled in the study had completed eight weeks of treatment, the applicant instructed the investigators to stop blinded therapy in all subjects in the study'
Selective reporting (reporting bias)	Low risk	Comment: the study was registered with ClinicalTrials.gov, but no clear listing of predefined outcome time-points. That said, all preregistered outcomes and outcomes related to over correction reported. Some additional outcomes were insufficiently reported for contribution to meta-analysis
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'WTA has received consulting fees from Cardiokine. GD has received consulting fees from Wyeth (Pfizer), Sonofi, Cardiokine, Otsuka Pharmaceuticals, and Yamanouchi. RCJ has served as a Principal Investigator on vaptan-related phase III clinical trials sponsored by Astellas, Otsuka, and Cardiokine. He has also served as a consultant for Otsuka and Cardiokine. NK has served on the speakers' bureau for Otsuka. DGB has received consulting fees from Cardiokine, received consulting fees from Cardiokine, receives grants from Otsuka, and is a paid consultant for Otsuka Canada. CO is an employee of Cardiokine. MM received consulting fees from Otsuka. HPT and YY have no relevant relationships to disclose.' Sponsorship bias <ul style="list-style-type: none"> Quote: 'Medical writing and editorial assistance, supported by Cardiokine, ...' No clear statement about funding but from author affiliations and declarations of interest clear this is an industry instigated study

Hayes 1987

Methods	<ul style="list-style-type: none"> Design: parallel RCT Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: not reported Follow-up: not reported
Participants	<ul style="list-style-type: none"> Country: UK Number of centres: not reported, presumably 1 Inclusion criteria: serum sodium concentration < 130 mmol/L; liver cirrhosis and ascites Exclusion criteria: not reported Characteristics randomised participants <ul style="list-style-type: none"> * Number: 10 (not reported for individual groups) * Number, % women: not reported * Mean age $\pm$ SD (years): not reported * Serum sodium concentration (mmol/L): not reported * Cause of hyponatraemia: liver cirrhosis (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral urea: 3 x 20 mg/d within 24 hours of development of hyponatraemia <p>Control group</p> <ul style="list-style-type: none"> Oral urea: 3 x 20 mg/d after 3 days of no treatment after development of hyponatraemia <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: not reported Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Serum sodium concentration (mmol/L) from beginning to end of treatment (no comparative data) Treatment-specific side-effects <ul style="list-style-type: none"> * Diarrhoea and vomiting: no data provided
Notes	<ul style="list-style-type: none"> Funding source: not reported Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'Patients...randomised...'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'. No baseline characteristics presented.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Hayes 1987 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.
Other bias	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'.

HYPOCAT 2008

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2) Hyponatraemia subgroup: no Recruitment period: 2004 to 2005 Treatment duration: 14 days Follow-up: 21 days
Participants	<ul style="list-style-type: none"> Countries: Argentina; Australia; Belgium; Canada; Croatia; Czech Republic; France; Germany; Hungary; Italy; Romania; Spain; USA Number of centres: 30 Inclusion criteria: ≥ 18 years; serum sodium concentration ≤ 130 mmol/L; cirrhosis diagnosed by liver biopsy or combination of clinical, biochemical, ultrasonographic and endoscopic findings; moderate/tense ascites defined as grade 2-3 ascites according to previously established criteria Exclusion criteria: serum bilirubin concentration > 8 mg/dL; INR > 3; platelet count $< 30,000/\text{mm}^3$; SCr $> 2\text{mg/dL}$; serum potassium concentration > 5.5 mmol/L; hepatocellular carcinoma $>$ Milan criteria; hepatic encephalopathy $>$ grade 1; bacterial infection/gastrointestinal bleeding < 10 days; large-volume paracentesis < 7 days prior; cardiac disease, systolic BP < 80 mm Hg; inducer or inhibitors of CYP450 CYP3A < 14 days prior Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group 1 (28); treatment group 2 (26); treatment group 3 (28); control group (28) * Number % women: treatment group 1 (8, 29%); treatment group 2 (7, 27%); treatment group 3 (12, 43%); control group (6, 21%) * Mean age $\pm$ SD (years): treatment group 1 (59 ± 10); treatment group 2 (56 ± 9); treatment group 3 (57 ± 8); control group (55 ± 10) * Mean serum sodium concentration $\pm$ SD (mmol/L): treatment group 1 (126 ± 6); treatment group 2 (128 ± 4); treatment group 3 (127 ± 5); control group (126 ± 4) * Cause of hyponatraemia: liver cirrhosis (100%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 25 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 12.5 mg/d <p>Treatment group 3</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 5 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p>

HYPOCAT 2008 (Continued)

- Fluid restriction: < 1.5 L/d, unless patients were thirsty or there was a medical need to increase fluid intake
- Dietary sodium intake: ≤ 2.7 g/d

Outcomes	<ul style="list-style-type: none"> • Response in serum sodium concentration (categorical outcome): increase from baseline in serum sodium concentration ≥ 5 mmol/L or serum sodium concentration ≥ 135 mmol/L at any time during treatment • Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase ≥ 8 mmol/L/24 h * Hyponatraemia: serum sodium concentration ≥ 145 mmol/L at any point during treatment * Osmotic demyelination syndrome: neurological symptoms • Treatment-specific side-effects <ul style="list-style-type: none"> * Thirst (categorical outcome): measured on a VAS (cut-offs for categorisation not reported) * Adverse events: not otherwise defined * Serious adverse events: not otherwise defined • Treatment discontinuation
----------	---

Notes	<ul style="list-style-type: none"> • Funding source: Sanofi-Aventis
-------	--

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: 'Each participating centre received blocks of study treatment which contained equal numbers of each of the four therapies on a random sequence generated by a computer program', and 'The median number of patients included in the 30 participating centres was 3 (range 1 to 14)'.</p> <p>Comment: The randomisation procedure generated groups well-balanced for age, sex and baseline serum sodium concentration. The severity of liver disease as assessed by the serum bilirubin concentration, Child-Pugh and MELD score was greater for the placebo group in comparison with the other groups. We assumed the influence of the imbalance thus generated would be negligible in practice</p>
Allocation concealment (selection bias)	Low risk	<p>Comment: considering randomisation procedure and extent of attempting to blind, likely adequate</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: 'This was a ...double-blind, placebo-controlled efficacy study', and 'all...were maintained on a low-sodium diet ... and daily fluid intake was limited to 1.5L unless patients were thirsty or there was a medical need to increase fluid intake'</p> <p>Comment: blinding attempted, and although participants and personnel are unlikely to be fully blinded due to important increases in urine output, all measured outcomes short-term and fairly objective. Fluid restriction occurred in all groups, any increase in fluid intake likely to have occurred in the intervention groups, with possible bias favouring the placebo group for outcomes related to serum sodium concentration</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: blinding outcome assessors probably attempted, main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst</p>

HYPOCAT 2008 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall 5% attrition, presumably due to treatment discontinuation, despite efforts to measure outcomes regardless. Reasons for treatment discontinuation well documented. Missing data dealt with through analytic techniques for repeated measures using the last available measurement before discontinuation. Given <20% attrition and limited opportunity for introducing bias in such a short-term study - we judged it 'Low risk'
Selective reporting (reporting bias)	High risk	Comment: protocol registered after completion of the study. Outcomes related to serum sodium concentration said to be measured at 14 days, yet only reported at day 5. Protocol also lists 'trail making test' and 'quality of life' as outcomes, which are not reported in the study publication
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'Dr. Ginès is a consultant for Sanofi-Aventis. Dr. Wong is a consultant for Sanofi-Aventis. Dr. Watson owns stock in Sanofi-Aventis.' Sponsorship bias <ul style="list-style-type: none"> Quote: 'The sponsor, Sanofi-Aventis, and the academic principal investigator designed the study, developed the protocol, and prepared the first and subsequent drafts of the manuscript', and 'The sponsor and the academic principal investigator held and analysed the data' Comment: the principal investigator is a consultant for the company developing the study drug

INSIGHT 2016

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 3) Hyponatraemia subgroup: no Recruitment period: 2007 to 2009 Treatment duration: 21 days Follow-up: 28 days
Participants	<ul style="list-style-type: none"> Country: USA Number of centres: 12 Inclusion criteria: ≥ 50 years; serum sodium concentration 123 to ≤ 134 mmol/L and for 118 to ≤ 122 mmol/L inclusion based on consultation and approval from the study medical monitor Exclusion criteria: conditions or history which may present a safety concern to the subject or their offspring or extreme susceptibility to hypotension with sudden fluid loss; hyponatraemia that is acute, easily reversible, artifactual, or due to a condition not associated with vasopressin excess; conditions associated with an independent imminent risk of morbidity and mortality; conditions which may confound the assessment of endpoints, history of poor compliance, participation in a clinical trial believed by the principal investigator or sponsor likely to confound endpoint assessments; conditions which may confound primary endpoints of cognitive function Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group (29); control group (28) Number, % women: treatment group (15, 52%); control group (19, 68%) Mean age $\pm$ SD (years): treatment group (71 ± 10); control group (71 ± 10) Serum sodium concentration (mmol/L): not reported Cause of hyponatraemia: not reported
Interventions	Treatment group <ul style="list-style-type: none"> Oral tolvaptan: 1 x 15 mg/d up to 1 x 60 mg/d Control group

INSIGHT 2016 (Continued)

- Oral matching placebo: 1 x 1/d

Co-interventions (all groups)

- Fluid restriction: fluid restrictions to be loosened during dose titration phase, reinstated at any time if serum sodium concentration fails to improve, left at discretion of investigator
- Dietary sodium intake: not reported

Outcomes	<ul style="list-style-type: none"> • Serum sodium concentration (continuous outcome): change from baseline until end of treatment • Cognitive function (Neurocognitive Composite Score of Speed Domains) change from baseline in sum of all speed domain Z-scores: reaction time (Simple = recognize "yes" 50 times; choice = recognize "yes" or "no" 50 times; digit vigilance = match 45 digits); psychomotor speed (morse tapping = tap button for 30 s with right & left hands); processing speed (rapid visual information processing = detect consecutive sequences of 3 odd or 3 even digits; numeric working memory = recognize numbers from series of 5 digits among 30; word recognition = remember 15 prior learned words from 30 total; results age-matched to healthy controls from Cognitive Drug Research normative data • Gait test: change from baseline timed get-up-and-go test = time it takes for a seated subject to rise from a chair, walk 3 m, walk around an object and return to sit in chair. Values: under 10 s (no difficulties), 10 to 20 s (starting to have balance difficulty), over 30 s (at high risk for falls and dependent in most activities of daily living and mobility); test assesses risk to elderly subjects of falling and higher scores in seconds indicate higher risk of falling • Treatment-specific side-effects <ul style="list-style-type: none"> * Thirst: not otherwise defined * Adverse event: not otherwise defined * Serious adverse events: serious treatment-emergent adverse events • Treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Otsuka Pharmaceutical Development & Commercialization • Publication: protocol registry only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'Subjects will be randomised...' Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: 'A pilot...double-blind, placebo-controlled ... study', and 'Subjects will be randomised to ... or matching placebo tablet', and 'during this period, fluid restrictions should be loosened or suspended, until the subject's response to therapy can be evaluated, typically over the first few days of therapy. Fluid restriction may be reinstated at any time in subjects whose sodium fails to improve or worsens with study therapy. Subjects entering ...with a serum sodium concentration less than 130 mEq/L may be fluid restricted if necessary at the discretion of the investigator'. Comment: blinding of both participants and personnel attempted. However, unlikely for participants to have been fully blinded due to likely important increases in urine output. Also, fluid restriction was not mandatory and could be adapted at the discretion of the investigator. This may have biased outcome measures at one month in favour of the study medication
Blinding of outcome assessment (detection bias)	Low risk	Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective. Unlikely for participants to

INSIGHT 2016 (Continued)

All outcomes		have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall 9% attrition, 8% due to treatment discontinuation, asymmetrical due to adverse events in the experimental group. Given < 10% attrition in long-term study, we judged opportunity for introducing attrition bias 'Low'
Selective reporting (reporting bias)	Low risk	Comment: study registered with ClinicalTrials.gov in 2007 before study initiation. Primary and secondary outcomes including time-points match
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * No declaration of interest Sponsorship bias <ul style="list-style-type: none"> * Quote: 'Sponsor: Otsuka Pharmaceutical Development & Commercialization' * Comment: no further information as study not published at this time

Jalan 2007

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 7 days Follow-up: not reported
Participants	<ul style="list-style-type: none"> Country: UK Number of centres: not reported (presumably 1) Inclusion criteria: serum sodium concentration < 130 mmol/L despite 3 days of fluid restriction; liver cirrhosis with refractory ascites Exclusion criteria: active infection; hepatic encephalopathy > grade 2; creatinine concentration >150 µmol/L; systolic BP < 80 mm Hg; alcoholic hepatitis; adrenal insufficiency; hypothyroidism; hyperthyroidism; diabetes; severe cardiovascular disease; head injury; diuretics within 7 days; paracentesis < 1 week Characteristics randomised participants <ul style="list-style-type: none"> * Number: 24 * Number, % women: not reported * Mean age ± SD (years): not reported * Serum sodium concentration (mmol/L): not reported * Cause of hyponatraemia: not reported; liver cirrhosis (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> IV human salt-poor albumin: 1 x 40 g/d <p>Control group</p> <ul style="list-style-type: none"> No treatment <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: < 1.5 L/d Dietary sodium intake: 1.8 g/d

Jalan 2007 (Continued)

Outcomes	<ul style="list-style-type: none"> Serum sodium concentration (continuous outcome): absolute values; insufficiently reported to allow contribution to meta-analysis
----------	--

Notes	<ul style="list-style-type: none"> Funding source: not reported Publication: abstract only
-------	--

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: '...a randomised clinical trial'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: 'treatment group 1: Fluid restriction (1.5 L)+Na restriction (80 mmol/d), Group 2: Human Salt Poor Albumin (40 gm/d) + Fluid (1.5 L) + Na restriction (80 mmol/d) Comment: attempts at blinding not mentioned, blinding unlikely to have happened
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Selective reporting (reporting bias)	High risk	Comment: no protocol, short-term study (≤ 1 week) but no reporting of primary outcomes death or health-related quality of life, and no reporting of secondary outcomes related to rapid increase in serum sodium concentration in a way that permitted data extraction
Other bias	Unclear risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * No declaration of interest Sponsorship bias <ul style="list-style-type: none"> * Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'

Kalra 2011

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 2 days Follow-up: 7 days
Participants	<ul style="list-style-type: none"> Countries: India; Israel; USA Number of centres: 25

Kalra 2011 (Continued)

- Inclusion criteria: ≥ 18 years; serum sodium concentration 115 to ≤ 134 mmol/L; euvolaemia or hypervolaemia
- Exclusion criteria: women of childbearing potential with positive pregnancy test; clinical evidence of volume depletion; mechanical circulatory or respiratory support; supine systolic BP < 85 mm Hg; history of significant orthostatic hypotension; requiring emergent treatment for hyponatraemia
- Characteristics included participants
 - * Number: treatment group 1 (29); treatment group 2 (30); treatment group 3 (30); control group (28)
 - * Number, % women: treatment group 1 (18, 62%); treatment group 2 (13, 43%); treatment group 3 (16, 53%); control group (14, 40%)
 - * Mean age $\pm$ SD (years): treatment group 1 (63 ± 22); treatment group 2 (61 ± 20); treatment group 3 (65 ± 14); control group (59 ± 20)
 - * Serum sodium concentration (mmol/L): treatment group 1 (124 ± 5); treatment group 2 (124 ± 4); treatment group 3 (125 ± 4); control group (125 ± 4)
 - * Cause of hyponatraemia
 - ☐ Treatment group 1: not specified; euvolaemia (27, 93%); hypervolaemia (2, 7%)
 - ☐ Treatment group 2: not specified; euvolaemia (28, 93%); hypervolaemia (2, 7%)
 - ☐ Treatment group 3: not specified; euvolaemia (27, 90%); hypervolaemia (3, 10%)
 - ☐ Control group: not specified; euvolaemia (25, 89%); hypervolaemia (3, 11%)

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • IV conivaptan: 20 mg loading dose in 30-min infusion + conivaptan 1 x 20 mg/d in premixed bag without propylene glycol solvent, in continuous infusion <p>Treatment group 2</p> <ul style="list-style-type: none"> • IV conivaptan: 20 mg loading dose in 30-min infusion + conivaptan 1 x 20 mg/d in ampoule with propylene glycol solvent, in continuous infusion <p>Treatment group 3</p> <ul style="list-style-type: none"> • IV placebo: loading dose in 30-min infusion + conivaptan 1 x 20 mg/d in premixed bag without propylene glycol solvent, in continuous infusion <p>Control group</p> <ul style="list-style-type: none"> • IV placebo: loading dose in 30-min infusion + conivaptan 1 x 20 mg/d in ampoule with propylene glycol solvent, in continuous infusion <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: < 2 L/d • Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> • Death: time-point measurement unclear • Response in serum sodium concentration (categorical outcome): increase from baseline in serum sodium concentration > 4 mmol/L at any time during treatment • Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L during the first day or serum sodium concentration > 145 mmol/L at any time during treatment • Treatment-specific side-effects <ul style="list-style-type: none"> * Adverse events: not otherwise defined * Serious adverse events: not otherwise defined * Injection-site reactions (continuous outcome): severity of injection-site reactions as measured by the ISR modified 5-point scale; and as categorical outcome not otherwise defined * Injection-site phlebitis: not otherwise defined * Injection-site thrombosis: not otherwise defined

Kalra 2011 (Continued)

- Treatment discontinuation

Notes

- Funding source: Astellas Pharma US, Inc.
- Request for additional information sent 27/10/2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'This was a randomised, parallel-group study.', and 'Eligible patients were... randomised to...' Comment: large number of groups relative to the number of included participants may have caused simple randomisation to fail: groups are not entirely balanced in terms of age and sex. Insufficient information to permit judgement of 'High risk' or 'Low risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'The placebo ampoules and premixed bags contained all the components of the active formulation except conivaptan. For the ampoule formulation, the contents of the 4 mL ampoule was added to a bag containing 96 mL of 5% dextrose injection, so that the final volume was 100 mL for the loading dose or a bag containing 246 mL of 5% dextrose injection for the continuous infusion.' Comment: blinding of participants and personnel attempted and given all groups included active ingredient, un-blinding due to differences in urine output not very likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: blinding outcome assessors adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: overall 17% attrition due to exclusion after randomisation (3%) and treatment discontinuation (14%); reasons well-documented. Missing data dealt with through analytic techniques for repeated measures using the last available measurement before discontinuation. Given < 20% attrition and limited opportunity for introducing bias in such a short-term study - we judged it 'Low risk'
Selective reporting (reporting bias)	Low risk	Comment: no protocol and short term study (< 1 week), secondary outcomes related to both serum sodium concentration and rapid increase in serum sodium correction reported. Because a repeated measures analytic technique was used, unclear at what time point serum sodium concentration was measured for all participants, yet given short term study, bias thus introduced probably negligible in practice
Other bias	High risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Quote: 'Dr. Velez has received a grant and honorarium from and served on the speakers bureau for Astellas Pharma. Drs McNutt and Abeyratne and Ms. Klasen are employed by Astellas Pharma US, Inc.' * Comment: Senior authors are employed by company commercialising the study medications • Sponsorship bias <ul style="list-style-type: none"> * Comment: this study was sponsored by Astellas Pharma, Inc

Koren 2011

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 2 days Follow-up: 30 days
Participants	<ul style="list-style-type: none"> Countries: India; USA Number of centres: 16 Inclusion criteria: hospital in-patients; ≥ 18 years; serum sodium concentration 115 to ≤ 130 mmol/L; euvoaemia or hypervolaemia Exclusion criteria: women of childbearing potential with positive pregnancy test; volume depletion or dehydration; haemodynamic instability; unable to provide consent due to significantly altered mental status; hypertonic saline administered in previous 24 h; expected to require emergent treatment of hyponatraemia supine systolic BP < 85 mm Hg; significant orthostatic hypotension; uncontrolled hypertension; uncontrolled arrhythmias requiring emergent pacemaker placement or treatment; severe hypothyroidism; hyperthyroidism; adrenal insufficiency; creatine clearance < 20 mL/min, urinary out-flow obstruction unless catheterized; alanine transaminase or aspartate transaminase > 5 times upper limit of normal, serum albumin concentration ≤ 15 g/L; white blood cell count $< 3 \times 10^9$/L, concomitant illness that could interfere with treatment or evaluation of safety; history of hepatic encephalopathy, hematemesis or melena, moderate-to-severe hepatic impairment, moderate ascites secondary to hepatic dysfunction, non-fasting blood glucose concentration ≥ 200 mg/dL Characteristics included participants <ul style="list-style-type: none"> * Number: treatment group 1 (20); treatment group 2 (20); control group (9) * Number, % women: treatment group 1 (11, 55%); treatment group 2 (7, 35%); control group (8, 89%) * Mean age $\pm$ SD (years): treatment group 1 (68 ± 15); treatment group 2 (59 ± 17); control group (62 ± 20) * Serum sodium concentration (mmol/L): treatment group 1 (126 ± 4); treatment group 2 (126 ± 4); control group (126 ± 4) * Cause of hyponatraemia <ul style="list-style-type: none"> ☐ Treatment group 1: SIADH (9, 45%); heart failure (6, 30%); unclear (5, 25%) ☐ Treatment group 2: SIADH (6, 30%); heart failure (5, 25%); nephrotic syndrome (1, 5%); alcoholism (1, 5%); unclear (6, 30%) ☐ Control group: SIADH (2, 22%); heart failure (3, 33%); impaired salt intake due to hypertension (1, 11%); unclear (3, 33%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> IV conivaptan: 2 x 20 mg/d in 30-min infusion <p>Treatment group 2</p> <ul style="list-style-type: none"> IV conivaptan: 1 x 20 mg/d in 30-min infusion <p>Control group</p> <ul style="list-style-type: none"> IV placebo: 2 x 100 mL 5% dextrose in water in 30-min infusion <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: < 2 L/d Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Death Response in serum sodium concentration (categorical outcome): increase from baseline in serum sodium concentration > 4 mmol/L at any time during treatment

Koren 2011 (Continued)

- Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation
- Outcomes related to over-correction of serum sodium concentration
 - * Hyponatraemia: serum sodium concentration > 145 mmol/L; insufficiently reported to allow contribution to meta-analysis
 - * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L during the first day
 - * Osmotic demyelination syndrome: not otherwise specified
- Treatment-specific side-effects
 - * Hypotension: supine systolic BP < 85 mm Hg
 - * Adverse events: not otherwise defined
 - * Serious adverse events: not otherwise defined
 - * Injection-site reactions
 - * Injection-site phlebitis
 - * Injection-site thrombosis
- Treatment discontinuation

Notes

- Funding source: Astellas Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: 'This randomised, double-blind...' and 'Eligible patients were stratified by baseline SSC (serum sodium concentration) ... and then randomly assigned...</p> <p>Comment: methods for sequence generation not reported. Due to the large number of groups relative to the number of included participants, adequate simple randomisation may have failed to produce groups with similar baseline prognosis. E.g. there is an imbalance in age, sex and volume status across the groups. We assumed the influence of the imbalance thus generated would be negligible in practice</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: 'In each dosing regimen, conivaptan or placebo was administered via a 30-minute i.v. infusion using a 100 mL plastic bag containing either 20 mg conivaptan hydrochloride in 5% dextrose injection or placebo (5% dextrose injection). In the once-daily regimen, conivaptan was administered at 0 and 24 hours, and placebo was administered at 12 and 36 hours to maintain blinding'</p> <p>Comment: blinding attempted, and although participants and personnel are unlikely to be fully blinded due to important increases in urine output, all measured outcomes very short-term and fairly objective</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: blinding outcome assessors probably attempted and all measured outcomes objective</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: overall 18% attrition due to exclusion after randomisation (2%) and treatment discontinuation (16%); reasons fairly well-documented. All save 1 were re-included in the analysis for sodium concentration measurements using the analytic techniques for repeated measures using the last available measurement before discontinuation. Given < 20% attrition and limited opportunity for introducing bias in such a short term study, we judged it 'Low risk of bias'</p>

Koren 2011 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: no protocol and short term study (≤ 1 week), secondary outcomes related to both serum sodium concentration and rapid increase in serum sodium correction reported
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'Ms. Klasen, Dr Abeyratne, and Dr. McNutt are employees of Astellas Pharma US Inc.' Comment: Several authors are employees of the company who commercialised the study drug Sponsorship bias <ul style="list-style-type: none"> Quote: 'Supported by a grant from Astellas Pharma Global Development, Inc.'

LIBRA 2012

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 3) Hyponatraemia subgroup: no Recruitment period: 2008 to 2010 Treatment duration: 30 days Follow-up: 60 days
Participants	<ul style="list-style-type: none"> Country: Belgium; Canada; Germany; India; Poland; USA Number of centres: 37 Inclusion criteria: ≥ 18 years; serum sodium concentration 120 to < 130 mmol/L; euvolaemia; hospitalised or willing to stay for 48 to 72 hours Exclusion criteria: overt symptoms requiring immediate intervention; acute or transient hyponatraemia, pseudohyponatraemia or hypertonic hyponatraemia; hyponatraemia due to hypothyroidism, adrenal insufficiency; psychogenic polydipsia; creatinine > 3 mg/dL, HbA1c $> 9\%$, urinary tract obstruction; severe pulmonary artery hypertension expected to deteriorate, NYHA III or IV; ST-segment elevation, MI previous 30 days, active myocardial ischaemia; cerebrovascular accident previous 30 days, significant neurological impairment; nephrotic syndrome, advanced liver disease, documented cirrhosis or alcoholic liver disease; terminal illness; radiotherapy or chemotherapy within 2 weeks; demeclocycline, lithium carbonate, urea, vasopressin antagonist within 7 days; women pregnant or breastfeeding or planning to Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group (54); control group (52) Number, % women: treatment group 1 (28, 52%); control group (22, 42%) Mean age $\pm$ SD (years): treatment group (66 ± 14); control group (65 ± 13) Serum sodium concentration (mmol/L): treatment group (125 ± 5); control group (124 ± 5) Cause of hyponatraemia: SIADH (100%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral lixivaptan: 1 x 50 mg/d, titrated to 1 x 25 mg/d or 1 x 100 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: investigators were instructed, when possible, to not institute fluid restriction for at least the first 72 hours of dosing. However, fluid restriction could be initiated at the investigator's discretion throughout the duration of the study Dietary sodium intake: not reported

LIBRA 2012 (Continued)

Outcomes	<ul style="list-style-type: none"> • Death • Response: serum sodium concentration ≥ 135 mmol/L • Serum sodium concentration (continuous outcome): change from baseline until treatment discontinuation • Cognitive function (continuous outcome): time to complete the Trail Making Test - Part B; (continuous outcome) change from baseline in the Medical Outcomes Study 6-Item Cognitive Function Scale (MOS-6) score; insufficiently reported to allow contribution to meta-analysis • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: serum sodium concentration ≥ 145 mmol/L * Rapid increase in serum sodium concentration: serum sodium concentration increase ≥ 8 mmol/L during first 8 h, > 12 mmol/L during first 24 hours or > 18 mmol/L during first 48 h * ODS: clinical signs and symptoms consistent with the diagnosis • Treatment-specific side-effects <ul style="list-style-type: none"> * Hypotension: not otherwise defined * Adverse event: treatment-emergent adverse events, not otherwise defined * Serious adverse events: serious treatment-emergent adverse events, not otherwise defined • Treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Cardiokine Biopharma. • Additional data source: FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory (CR-DAC)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: 'The LIBRA study was a ... randomised study', and 'Subjects were initially randomised to ...'</p> <p>Comment: Overall insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: 'The Libra study was a ... double-blind, placebo-controlled ... study'</p> <p>Comment: blinding probably attempted, although due to increase in urine output, un-blinding likely to have occurred. Fluid restriction was largely left to the discretion of the investigator, and more participants receiving the study medication had fluid restriction initiated or tightened by day 30 (32% versus 23%), but more participants in the placebo group were on fluid restriction at baseline (37% versus 65%) and at any time-point throughout the study</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: blinding insufficiently reported but main outcomes objective such that un-blinding of outcome detection unlikely to be an important source of bias</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Comment: overall 13% discontinuation at 7 days, 5% of which never received treatment; 67% of discontinuations occurred in placebo group. 31% discontinuation at 30 days, with last observation carried forward method as imputation method for dealing with missing serum sodium concentration values, which may have caused overestimation of the effect of the study medication. Cognitive function tests were taken at day 30 or the early termination visit. We judged outcomes measured at 7 days to at 'Low risk', but those at 30 days to be at 'High risk' of attrition bias</p>

LIBRA 2012 (Continued)

Selective reporting (reporting bias)	Low risk	Comment: protocol first registered with ClinicalTrials.gov in 2008. Primary registered outcome was average daily area under the curve (AUC) of change from baseline in serum sodium concentrations up to 72 hrs, whereas the reported primary outcome is change in serum sodium concentration at 7 days. That said, all reregistered outcomes were reported and secondary outcomes related to over-correction also reported
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'WTA has received consulting fees from Cardiokine. PA.... has received honoraria for this work and from Otsuka for presentations and participation in advisory committees. DGB has received consulting fees from Cardiokine and received grants from and is paid consultant for Otsuka Pharmaceuticals. RCJ has served as a principal investigator on vaptan-related phase-III clinical trials sponsored by Astellas, Otsuka, and Cardiokine. He has also served as a consultant for Otsuka and Cardiokine. At the time of the study and manuscript preparation, CO was an employee of Cardiokine Biopharma' Sponsorship bias <ul style="list-style-type: none"> Quote: 'Medical writing and editorial assistance, supported by Cardiokine Biopharma, ...' No clear statement about funding but from author affiliations and declarations of interest clear this is an industry instigated study

Naidech 2010

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 4) Hyponatraemia subgroup: no Recruitment period: 2008 to 2009 Treatment duration: 1 day Follow-up: until discharge from hospital
Participants	<ul style="list-style-type: none"> Country: USA Number of centres: 1 Inclusion criteria: patients admitted to a dedicated neuro/spine intensive care unit of a teaching hospital; ≥ 18 years: serum sodium concentration < 135 mmol/L and Glasgow Coma Scale < 15; or < 130 mmol/L Exclusion criteria: enrolment in the NMH high-risk spine protocol; expected death from any cause; known sensitivity or allergy to conivaptan; baseline creatinine > 1.5 mg/dL; clinical diagnosis of hypovolaemia, or by central venous pressure < 5 mm Hg if a central venous catheter is in place; concomitant use of potent inhibitors of cytochrome P-450 isoenzyme 3A4; clinical diagnosis of liver failure or insufficiency; pregnancy; intra-arterial vasodilators within 24 h; concern by the Neuro-intensive care unit pharmacist of a drug-drug interaction that would meaningfully impact care; diabetes insipidus or treated with vasopressin; congestive heart failure, inclusion declined by the attending physician or consulting study nephrologist Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group (3); control group (3) Number, % women: not reported Median age, range (years): treatment group (20, 45 to 64); control group (65, 67 to 69) Mean serum sodium concentration (mmol/L): treatment group (131); control group (132) Cause of hyponatraemia <ul style="list-style-type: none"> ☐ Treatment group 1: SIADH (100%) (central nervous system-infection (1); brain metastasis (1); tuberous sclerosis (1)) ☐ Control group: SIADH (100%) (central nervous system-infection (1); seizures (1); cerebrotrauma (1))

Naidech 2010 (Continued)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> IV conivaptan: 1 x 20 mg loading dose + 20 mg/d continuous infusion <p>Control group</p> <ul style="list-style-type: none"> Usual care <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: at discretion of treating physician sodium intake: at discretion of treating physician
Outcomes	<ul style="list-style-type: none"> Death Serum sodium concentration (continuous outcome): change from baseline Treatment-specific side-effects <ul style="list-style-type: none"> * Hypotension: systolic BP < 100 mm Hg or new vasopressor medication
Notes	<ul style="list-style-type: none"> Funding: Astellas Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: '...the patient was randomised by opening the lowest numbered, sealed envelope.'</p> <p>Comment: although methods for generating the sequence were not reported, we judged it likely for methods to have been adequate given researchers went to trouble of using sealed, numbered envelopes</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: '...the patient was randomised by opening the lowest numbered, sealed envelope.'</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Comment: participants nor personnel blinded to treatment allocation. Treatment consisted of the study drug added to standard care versus usual care alone. Usual care was left at the discretion of the treating physician with two participants treated with the study medication versus one participant treated with usual care receiving hypertonic saline. This differential treatment in the two groups could have influenced the outcome in favour of the study drug</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: from ClinicalTrials.gov 'Masking: single blind - outcomes assessor'</p> <p>Comment: still unclear whether outcome assessors of non patient-reported outcomes other than Glasgow Coma Scale and NHS Stroke Scale were blinded, but outcomes objective</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: 'all randomised patients completed the protocol'</p> <p>Comment: no attrition or exclusion</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: protocol registered with ClinicalTrials.gov, reported outcomes match those originally registered</p>
Other bias	Unclear risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Quote: 'AMN is responsible for data integrity and the statistical analysis. AMN acknowledges past research support from NovoNordisk, the Neurocritical Care Society, and the Northwestern Memorial Foundation for an unrelated project. AMN acknowledges research support from Gaymar Inc unrelated to this study.'

Naidech 2010 (Continued)

- * Comment: study commercially sponsored, but declaration of interest available and indicating limited further influence
- Sponsorship bias
 - * Quote: 'This study was funded by Astellas Pharma, US. The study sponsor had no role in the design of the protocol, recruitment of patients, analysis or decision to submit for publication. AMN is responsible for data integrity and the statistical analysis. AMN acknowledges past research support from NovoNordisk, the Neurocritical Care Society, and the Northwestern Memorial Foundation for an unrelated project. AMN acknowledges research support from Gaymar Inc unrelated to this study
 - * Comment: study commercially sponsored, but declaration of interest available and indicating limited further influence. We felt unclear on what this means for risk of bias

NATRIPHAR 2013

Methods	<ul style="list-style-type: none"> • Design: parallel RCT (phase not applicable) • Hyponatraemia subgroup: no • Recruitment period: 2010 to 2011 • Treatment duration: not reported • Follow-up: three months
Participants	<ul style="list-style-type: none"> • Country: France • Number of centres: 1 • Inclusion criteria: people admitted to the internal medicine ward or resident of the nursing home of the same institution; ≥ 65 years; serum sodium concentration 123 to ≤ 134 mmol/L; detected on routine biochemistry • Exclusion criteria: not receiving medications with the ability to cause hyponatraemia; hypervolaemia caused by heart failure or liver cirrhosis; treatment modification not possible according to treating physician; dementia • Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (9); control group (10) * Number, % women: treatment group (5, 56%); control group (6, 60%) * Mean age $\pm$ SD (years): treatment group (91 ± 4); control group (89 ± 7) * Serum sodium concentration (mmol/L): treatment group (132 ± 2); control group (130 ± 2) * Cause of hyponatraemia: drug-induced hyponatraemia (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Change in prescribed medications <p>Control group</p> <ul style="list-style-type: none"> • Standard care <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: no restriction • sodium intake: no restriction save for one patient in treatment group who stopped dietary salt restriction after pharmacologist advice.
Outcomes	<ul style="list-style-type: none"> • Death • Response in serum sodium concentration (categorical outcome): serum sodium concentration > 135 mmol/L • Serum sodium concentration (continuous outcome): change from baseline as well as absolute values

NATRIPHAR 2013 (Continued)

- Outcomes related to over-correction of serum sodium concentration
 - * Hyponatraemia: not otherwise defined
 - * Osmotic demyelination syndrome: not otherwise defined

Notes

- Funding source: 'a pharmacological association'
- Registration number: ID RCB 2010-A00778-31

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'Les patients ont été randomisés en deux bras...' Additional information provided by the authors: 'Random sequence was managed as a single randomisation list managed by the sponsor' Comment: the small number of participants may have caused simple randomisation to fail in producing balanced groups, participants in experimental group had slightly higher baseline serum sodium concentration and took more medications. Consequences for risk of bias judged to be low
Allocation concealment (selection bias)	Low risk	Additional information provided by the authors: 'Allocation was concealed using masking envelope'. Comment: Allocation concealment method considered adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Additional information provided by the authors: 'No measures were taken to prevent participants or personnel from knowing to which treatment participants had been allocated' Comment: blinding not attempted and difficult because of intervention type. There were no specific instructions concerning co-interventions. Differences in co-interventions may have influenced difference in outcome in favour of experimental treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Additional information provided by the authors: 'No measures were taken to prevent outcome assessors from knowing to which treatment participants had been allocated' Comment: blinding of outcome assessors not attempted, but main measured outcomes objective.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: overall 26% incomplete outcome data at four weeks; 1 attrition in control group, due to being released from hospital before four weeks; 1 exclusion in experimental group for gastrointestinal bleed after withdrawing proton pump inhibitor; 3 in control group: 2 for stopping a drug possibly causing hyponatraemia - hence possibly biasing results in favour of experimental treatment - 1 due to death
Selective reporting (reporting bias)	Low risk	Comment: protocol available, long-term study (> 1 week), and both primary outcome death and secondary outcomes related to serum sodium concentration reported. Given lowest serum sodium concentration equalled 129 mmol/L and the intervention consisted of medication withdrawal, potential for rapid increases in serum sodium concentration very limited
Other bias	Low risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors • Sponsorship bias <ul style="list-style-type: none"> * Additional information provided by the authors: 'The study was sponsored by a pharmacological association' * Comment: Unlikely for commercial sponsorship to be an issue

Nevens 2009

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2a) Hyponatraemia subgroup: yes Recruitment period: 2007 Treatment duration: 15 days Follow-up: 45 days
Participants	<ul style="list-style-type: none"> Country: Belgium Number of centres: 5 Inclusion criteria: hospitalised participants from university teaching hospitals; 18 to ≥ 75 years; liver cirrhosis and ascites Exclusion criteria: not reported Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (10); control group (5) * Number, % women: not reported * Mean age $\pm$ SD (years): not reported * Serum sodium concentration (mmol/L): not reported * Cause of hyponatraemia: liver cirrhosis (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral M0002 (RWJ-351647): 0.3 mg/d up to 6 mg/d titrated every 3 days <p>Control group</p> <ul style="list-style-type: none"> Oral placebo <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: not reported sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Response in serum sodium concentration (categorical outcome): normalisation of serum sodium concentrations = insufficiently reported to allow contribution to meta-analysis Treatment-specific side-effects <ul style="list-style-type: none"> * Adverse events: not otherwise defined * Serious adverse events: bacterial peritonitis, duodenal perforation and daydreaming
Notes	<ul style="list-style-type: none"> Funding source: Early Development, Movetis, Turnhout, Belgium Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: 'In a randomised, double-blind, placebo-controlled trial, 15...were treated...'</p> <p>Comment: insufficient information to permit judgement of 'Low risk' or 'High risk'</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'Low risk' or 'High risk'</p>

Nevens 2009 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: 'In a randomised, double-blind, placebo-controlled trial, 15...were treated...' Comment: blinding of participants and personnel attempted. However, lack of detail in reporting of outcomes makes it difficult to assess to what extent it was actually achieved. insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Selective reporting (reporting bias)	High risk	Comment: no protocol, long-term study (> 1 week) but no reporting of primary outcomes death or health-related quality of life, no reporting of secondary outcomes related to rapid increase in serum sodium concentration
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: No declaration of interest. Last two authors' affiliations are linked to the commercial company developing the medication Sponsorship bias <ul style="list-style-type: none"> * Quote: 'Early Development, Movetis, Turnhout, Belgium'

Otsuka Study 2011a

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2) Hyponatraemia subgroup: no Recruitment period: 2008 to 2009 Treatment duration: 7 days Follow-up: 14 days
Participants	<ul style="list-style-type: none"> Country: China Number of centres: 9 Inclusion criteria: 18 to 75 years; serum sodium concentration < 135 mmol/L; SIADH Exclusion criteria: serum sodium concentration < 120 mmol/L with apathy, clouded consciousness and convulsion; hypovolaemia; acute of transient hyponatraemia cause by brain trauma or surgery; uncontrolled hypothyroidism or adrenal insufficiency; cardiac surgery, sustained ventricular tachycardia or ventricular fibrillation and not using cardioverter defibrillator; severe stable or unstable angina, cerebrovascular accident within 30 days of recruitment; psychogenic polydipsia; systolic BP < 90 mm Hg; history of hypersensitivity of benzodiazepines; drug abuse; fasting glucose concentration > 220 mg/dL; advanced terminal illness or severe pulmonary hypertension; drug-induced hyponatraemia excluding diuretics; creatinine > 1.5 x upper limit; central nervous system diseases; transaminase > 2.5 x upper limit; requiring intravenous fluid for any reason; use of vasopressin analogues; treatment of hyponatraemia within 13 days of recruitment; nursing or pregnancy Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (21); control group (24) * Number, % women: treatment group (11, 52%); control group (9, 38%) * Mean age $\pm$ SD (years): treatment group (63 $\pm$ 14); control group (61 $\pm$ 13) * Serum sodium concentration (mmol/L): treatment group (127 $\pm$ 5); control group (125 $\pm$ 6) * Cause of hyponatraemia: SIADH (100%)
Interventions	Treatment group

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Otsuka Study 2011a (Continued)

- Oral tolvaptan: 1 x 15 mg/d up to 1 x 60 mg/d

Control group

- Oral placebo: 1 x 1/d

Co-interventions (all groups)

- Fluid restriction: 'fluid restriction (1500 mL/d) was added at the discretion of the investigator when the patient's serum sodium levels were below 130 mmol/L persistently'
- sodium intake: not reported

Outcomes	<ul style="list-style-type: none"> • Death • Response: serum sodium concentration ≥ 135 mmol/L • Serum sodium concentration (continuous outcome): change from baseline • Treatment-specific side-effects <ul style="list-style-type: none"> * Thirst: not otherwise defined; insufficiently reported to allow contribution to meta-analysis
Notes	<ul style="list-style-type: none"> • Funding source: Otsuka Pharmaceutical • Trial acronym: We allocated the trial acronym 'Otsuka study' from the quote 'the present study analysed SIADH patients recruited in theOtsuka study', to indicate the three separately reported subgroups belonged to the same trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: 'This randomised double-blind placebo-controlled trial...' and 'Randomisation was stratified by underlying disease and whether the hyponatraemia was mild...or marked...'</p> <p>Comment: since the investigators went to the trouble to stratify allocation, it seems probable enough that sequence generation was adequate</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: 'This randomised double-blind placebo-controlled trial...' and 'Patients received tolvaptan or matching placebo..'</p> <p>Comment: blinding probably attempted, although due to increase in urine output, un-blinding likely to have occurred. Fluid restriction was largely left to the discretion of the investigator, but fewer participants receiving the study medication had fluid restriction initiated or tightened by day 30 (11% versus 21%)</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: No attrition for main outcomes</p>
Selective reporting (reporting bias)	High risk	<p>Comment: the study was registered with ClinicalTrials.gov, but only primary efficacy outcome clearly listed, short-term study (≤ 1 week) death reported, but no reporting of secondary outcomes related to rapid increase in serum sodium concentration. Also study results - incompletely/differentially - reported for the subgroups of SIADH, heart failure and cirrhosis separately</p>

Otsuka Study 2011a (Continued)

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: Insufficient information to permit judgement of 'High risk' or 'Low risk' Sponsorship bias <ul style="list-style-type: none"> * Quote: 'This study was funded by Otsuka Pharmaceutical, which provided consultancy fees or honorarium, support for travel to meetings and for language polishing.'
------------	-----------	---

Otsuka Study 2011b

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 2) Hyponatraemia subgroup: no Recruitment period: 2008 to 2009 Treatment duration: 7 days Follow-up: not reported
Participants	<ul style="list-style-type: none"> Country: China Number of centres: 11 Inclusion criteria: inpatients, hospitalised for congestive heart failure; 18 to 80 years; serum sodium concentration < 135 mmol/L Exclusion criteria: hypovolaemia; haemodynamic instability; insertion of heart valves; open heart surgery or artificial pacemaker insertion within 60 days of recruitment; heart valve insertion or heart transplant within 30 days of recruitment; acute MI; cardiac hypertrophy; active myocarditis or amyloid cardiomyopathy; severe aortic stenosis; severe pulmonary hypertension; uncontrolled low function of thyroid or adrenal glands; epilepsy; Guillain-Barre Syndrome; anuria; ventricular tachycardia; ventricular fibrillation; implantable cardioverter defibrillators; cerebral vascular accidents within 30 days of recruitment; allergy to benzodiazepines; medication or alcohol abuse; BMI > 35 kg/m; supine systolic pressure < 90 mm Hg; abnormal laboratory results at the time of recruitment: fasting blood sugar > 12.2 mmol/L, haemoglobin < 80 g/L, total bilirubin > 85.5 µmol/L, SCr > 2 x the upper limit, potassium > 5.5 mmol/L, transaminases > 5 x the upper limit, sodium < 120 mmol/L Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (35); control group (30) * Number, % women: treatment group (15, 43%); control group (12, 40%) * Mean age ± SD (years): treatment group (63 ± 15); control group (65 ± 15) * Serum sodium concentration (mmol/L): treatment group (130 ± 4); control group (131 ± 3) * Cause of hyponatraemia: heart failure (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 15 mg/d up to 1 x 60 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: not reported sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Death Serum sodium concentration (continuous outcome): change from baseline Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: not otherwise defined

Otsuka Study 2011b (Continued)

- Treatment-specific side-effects
 - * Hypotension: systolic BP < 100 mm Hg or new vasopressor medication

Notes

- Funding source: Otsuka Pharmaceutical
- Primary paper in Mandarin - Translated by Sunny Wu

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'This randomised double-blind placebo-controlled trial...' and 'Randomisation was stratified by underlying disease and whether the hyponatraemia was mild...or marked...' Comment: since the investigators went to the trouble to stratify allocation, it seems probable enough that sequence generation was adequate
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: 'This randomised double-blind placebo-controlled trial...' Comment: blinding of participants and personnel attempted. However, lack of detail in reporting of outcomes makes it difficult to assess to what extent it was actually achieved. insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No attrition for main outcomes
Selective reporting (reporting bias)	High risk	Comment: the study was registered with ClinicalTrials.gov, but only primary efficacy outcome clearly listed, short-term study (≤ 1 week) but no reporting of primary outcomes death or health-related quality of life, no reporting of secondary outcomes related to rapid increase in serum sodium concentration in a way that permitted data extraction. Also study results - incompletely/differentially - reported for the subgroups of SIADH, heart failure and cirrhosis separately
Other bias	High risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: Insufficient information to permit judgement of 'High risk' or 'Low risk' • Sponsorship bias <ul style="list-style-type: none"> * Quote: 'The study was conducted by Otsuka Beijing Research Institute. The institute is funded by Otsuka Pharmaceutical CO., Ltd. Japan.'

Otsuka Study 2011c

Methods

- Design: parallel RCT (phase not reported)
- Hyponatraemia subgroup: no
- Recruitment period: not reported
- Treatment duration: 7 days

Otsuka Study 2011c (Continued)

- Follow-up: not reported

Participants	<ul style="list-style-type: none"> • Country: China • Number of centres: not reported • Inclusion criteria: liver cirrhosis • Exclusion criteria: not reported • Characteristics randomised participants <ul style="list-style-type: none"> * Number: not reported * Number, % women: not reported * Mean age $\pm$ SD (years): not reported * Serum sodium concentration (mmol/L): not reported * Cause of hyponatraemia: liver cirrhosis (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Oral tolvaptan: 1 x 30 mg/d up to 1 x 60 mg/d <p>Control group</p> <ul style="list-style-type: none"> • Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: not reported • Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> • Response: normalisation of serum sodium concentration; insufficiently reported to allow contribution to meta-analysis • Serum sodium concentration (continuous outcome) change from baseline until day 4 and 7; insufficiently reported to allow contribution to meta-analysis
Notes	<ul style="list-style-type: none"> • Funding source: Otsuka Pharmaceutical • Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: 'A multicenter, randomised, double-blind,...', and 'Patients were randomised to receive...'</p> <p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Quote: 'A multicenter,..., double-blind, placebo-controlled clinical trial...', and 'Patients were randomised to receive placebo or tolvaptan...'</p> <p>Comment: 'insufficient information to permit judgement of 'High risk' or 'Low risk'</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective</p>
Incomplete outcome data (attrition bias)	Unclear risk	<p>Comment: 'insufficient information to permit judgement of 'High risk' or 'Low risk'</p>

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Otsuka Study 2011c (Continued)

All outcomes

Selective reporting (reporting bias)	High risk	Comment: the study was registered with ClinicalTrials.gov, but only primary efficacy outcome clearly listed, short-term study (≤ 1 week) but no reporting of primary outcomes death or health-related quality of life, and no reporting of secondary outcomes related to rapid increase in serum sodium concentration in a way that permitted data extraction. Also study results - incompletely/differentially - reported for the subgroups of SIADH, heart failure and cirrhosis separately
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> No declaration of interest Sponsorship bias <ul style="list-style-type: none"> Quote: 'This study was funded by Otsuka Pharmaceutical, which provided consultancy fees or honorarium, support for travel to meetings and for language polishing.'

Salahudeen 2014

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase 3) Hyponatraemia subgroup: no Recruitment period: 2011 to 2012 Treatment duration: 14 days Follow-up: 30 days
Participants	<ul style="list-style-type: none"> Country: USA Number of centres: 1 Inclusion criteria: patients admitted to University of Texas MD Anderson cancer centre; ≥ 18 years; serum sodium concentration 125 to ≤ 130 mmol/L; non-hypovolaemia; Eastern Cooperative Oncology Group performance status from 0 (fully active) to 3 (capable of only limited self-care and confined to bed or chair $\geq 50\%$ of waking hours) Exclusion criteria: critical illness; GFR < 25 mL/min; correctable hyponatraemia; use of demeclocycline, lithium or CYP 3A4 modulators; life-expectancy < 3 months Characteristics randomised participants <ul style="list-style-type: none"> Number: treatment group (24); control group (24) % women: treatment group (47%); control group (46%) Median age, range (years): treatment group (69, 52 to 81); control group (60, 20 to 85) Serum sodium concentration (mmol/L): treatment group (128 ± 2); control group (129 ± 1) Cause of hyponatraemia: cancer (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 15 mg/d up to 60 mg/d <p>Control group</p> <ul style="list-style-type: none"> Oral matching placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: fluid restriction < 1.5 L/d, but participants were allowed to drink to thirst Dietary sodium intake: not reported
Outcomes	<ul style="list-style-type: none"> Death Length of hospital stay (continuous outcome): insufficiently reported to allow contribution to meta-analysis

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Salahudeen 2014 (Continued)

- Cognitive function (Mini Mental State Exam score (range 1 to 16)): change from baseline
- Response: serum sodium concentration ≥ 136 mmol/L
- Serum sodium concentration (continuous outcome): change from baseline
- Treatment-specific side-effects
 - * Hypotension: not otherwise defined
 - * Thirst: not otherwise defined
 - * Polyuria: increase urination frequency and volume
 - * Serious adverse events: not otherwise defined
- Treatment discontinuation: insufficiently reported to allow contribution to meta-analysis

Notes

- Funding source: Otsuka America Pharmaceuticals Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: '...we chose Bayesian adaptive randomisation for its several reported useful features.' and 'After obtaining the patient's consent, the research co-ordinator logged into the Clinical Trial Conduct website to register and randomise the patients.'</p> <p>Comment: valid randomisation methods produced imbalanced groups in terms of age due to small sample size, sex and baseline serum sodium concentration were well balanced and the imbalance in age was likely favouring the control group as they contained the younger participants</p>
Allocation concealment (selection bias)	Low risk	<p>Comment: 'After obtaining the patient's consent, the research coordinator logged into the Clinical Trial Conduct website to register and randomise the patients.'</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: 'All research personnel except therapy distributing pharmacy and biostatistician were blinded to the treatment allocation.'</p> <p>Comment: blinding probably attempted, and although participants are unlikely to be fully blinded due to important increases in urine output, measured outcomes were short-term and mostly objective for the data used in meta-analysis. Co-interventions were similar between groups</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: 'All research personnel except therapy distributing pharmacy and biostatistician were blinded to the treatment allocation.'</p> <p>Comment: Blinding of outcome assessors probably done</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: overall 42% attrition for serum sodium concentration, 46% in placebo group, 29% in tolvaptan group, extensive sensitivity analysis including worst case imputation methods still resulted in statistically significant results. No attrition for death</p>
Selective reporting (reporting bias)	High risk	<p>Comment: study protocol registered with ClinicalTrials.gov in 2010. Only study's primary outcome serum sodium concentration registered. Long-term study (>1 week) with primary outcome death reported. However secondary outcomes related to rapid increase in serum sodium concentration not reported</p>
Other bias	High risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Quote: 'Dr Salahudeen has received financial compensation in the form of honorarium for a lecture and a fee for attending 1 medical board meeting.'

Salahudeen 2014 (Continued)

- Sponsorship bias
 - * Quote: 'This investigator-initiated study was funded by Otsuka America Pharmaceuticals Inc.' and 'Dr Salahudeen has received financial compensation in the form of honorarium for a lecture and a fee for attending 1 medical board meeting.'

SALT-1 2006

Methods	<ul style="list-style-type: none"> • Design: parallel RCT (phase 3) • Hyponatraemia subgroup: no • Recruitment period: 2003 to 2005 • Treatment duration: 30 days • Follow-up: 37 days
Participants	<ul style="list-style-type: none"> • Country: USA • Number of centres: 42 • Inclusion criteria: recruitment from university hospitals, community hospitals and veteran's medical centres, both in- and outpatients; ≥ 18 years; serum sodium concentration < 135 mmol/L, with at least 50% of included participants < 130 mmol/L; hypervolaemia or euvolaemia • Exclusion criteria: psychogenic polydipsia, head trauma, postoperative conditions, uncontrolled hypothyroidism or adrenal insufficiency; any hyponatraemic condition associated with the use of medications that could have been safely withdrawn; hypovolaemic hyponatraemia; cerebrovascular accident, multiple strokes; sustained ventricular tachycardia or fibrillation, severe angina; systolic BP < 90 mm Hg; central venous pressure < 5 cm H₂O; PCW < 5 mm Hg; SCr > 3.5 mg/dL; Child-Pugh > 10; severe pulmonary hypertension, urinary tract obstruction; uncontrolled diabetes mellitus; progressive or episodic neurologic disease; little chance of short-term survival or those not tolerating sudden shifts in fluid volumes or pressures; serum sodium concentration < 120 mmol/L in association with neurologic impairment • Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (102); control group (103) * Number, % women: treatment group (50, 49%); control group (41, 40%) * Mean age $\pm$ SD (years): treatment group (60 ± 14); control group (60 ± 13) * Serum sodium concentration (mmol/L): treatment group (129 ± 5); control group (129 ± 4) * Cause of hyponatraemia <ul style="list-style-type: none"> ☐ Treatment group 1: SIADH (25, 25%); heart failure (36, 35%); liver cirrhosis (23, 22%); other (18, 18%) ☐ Control group: SIADH (23, 22%); heart failure (34, 33%); liver cirrhosis (19, 18%); other (27, 26%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Oral tolvaptan: 1 x 15 mg/d up to 1 x 60 mg/d <p>Control group</p> <ul style="list-style-type: none"> • Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: no restriction • sodium intake: no specific dietary requirements
Outcomes	<ul style="list-style-type: none"> • Death: death due to treatment-emergent adverse events started before 7 days follow-up • Health-related quality of life (continuous outcome): change from baseline measured by physical and mental component of the Medical Outcomes Study 12-item Short Form General Health Survey. Only the mental component score available for analysis

SALT-1 2006 (Continued)

- Response in serum sodium concentration (categorical outcome): serum sodium concentration > 135 mmol/L at any time during treatment
- Serum sodium concentration (continuous outcome): change from baseline as well as absolute values
- Outcomes related to over-correction of serum sodium concentration
 - * Hyponatraemia: serum sodium concentration > 145 mmol/L
 - * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L during the first day
 - * Osmotic demyelination syndrome
- Treatment-specific side-effects (insufficiently reported for contribution to meta-analysis)
 - * AKI: not otherwise defined
 - * Hypotension: not otherwise defined
 - * Thirst: not otherwise defined
 - * Adverse events: not otherwise defined
 - * Serious adverse events: not otherwise defined
- Treatment discontinuation

Notes

- Funding source: Otsuka Maryland Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: 'Patients...underwent central randomisation with the use of random permuted blocks and stratification according to whether the hyponatraemia was mild or marked...' Comment: the randomisation procedure produced well balanced groups
Allocation concealment (selection bias)	Low risk	Quote: 'Patients...underwent central randomisation with the use of random permuted blocks and stratification according to whether the hyponatraemia was mild or marked...'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: '...trials were...randomised, double-blind, placebo-controlled efficacy studies...' and 'Patients were assigned...to receive oral tolvaptan...or matching placebo...', and 'Fluid restriction was not mandatory'. Additional info supplied by sponsor: 'Study medication was supplied for each subject in monthly kits per randomisation number, each labelled with a two-panel double-blind disclosure label specifying the treatment assignment (i.e., the compound name, strength, and lot number) in the concealed portion of the label. The study drug was packaged so that each subject received an identical number of tablets regardless of the treatment group assignment. All tablets were identical in appearance. The investigator was instructed to not open the treatment assignment code unless knowledge of the subject's treatment was required for the subject's clinical care and safety. In this event, the investigator was to contact OMRI by telephone with an explanation of the need for opening the treatment assignment code before or within 24 hours of opening the code.' Comment: blinding of both participants and personnel attempted. However, unlikely for participants to have been fully blinded due to important increases in urine output. We judged this would not have introduced important risk of bias for death and the outcomes related to serum sodium concentration, but may have biased health-related quality of life measures in favour of the study medication. Also, fluid restriction was not mandatory and could be adapted by both participant and treating physician - e.g. based on urine output. This may have resulted in underestimation of the risk of rapid increase in serum sodium concentration

SALT-1 2006 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Additional info provided by the sponsor: 'Serum sodium samples were collected and analysed at the site's local hospital laboratory. All serum sodium samples were collected and analysed at the same local hospital for purposes of consistency of efficacy analysis. Local laboratory results for serum sodium were captured in the electronic case report form (CRF). Study personnel measuring secondary endpoints were blinded as above and recorded results in the electronic CRF.'</p> <p>Comment: outcome assessors of non patient-reported outcomes were blinded. However, unlikely for participants to have been fully blinded given important increases in urine output, which may have biased the self-reported outcome health-related quality of life</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Quote: 'Patients who received at least one dose of the study medication were included in the safety analyses. Patients whose serum sodium concentrations were evaluated at baseline and one or more times after baseline were included in the efficacy analysis'. And 'serum sodium concentrations were measured at days 2, 3, 4, 11, 18, 25, 30, and 37'</p> <p>Comment: overall 26% attrition at 30 days, 25% in treatment group 1, 26% in the placebo group; reasons not reported in detail. Repeated measures analytic technique was used with all measurements of serum sodium concentration included until patient attrition. We judged this may likely have overestimated the change in serum sodium concentration in favour of the study medication. For the mental component score of the SF-12 health survey, measured at 30 days, attrition reached 30% in treatment group 1 and 44% in the placebo group</p>
Selective reporting (reporting bias)	High risk	<p>Comment: study protocol registered with ClinicalTrials.gov. Outcome measures were only registered in September 2005. Health-related quality of life not registered as one of the outcomes; both the mental and physical component of the SF-12 health survey were reported separately and measured at day 4 and day 30 using two analytic techniques, but only data for the statistically significant mental component score at day 30 were available for analysis from the published paper. Also because a repeated measures analytic technique was used, unclear at what time point serum sodium concentration was measured for all participants</p>
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'Dr. Schrier reports having served as a consultant to Otsuka, Astellas, Bayer, and Amgen. Dr. Gross reports having served as a consultant to Sanofi-Synthelabo, having received lecture fees from Astellas, and having received grant support from GlaxoSmithKline, Takeda, Amgen, Roche, and Fresenius. Dr. Gheorghiade reports having served as a consultant to Otsuka, PDL, Sigma Tau, Medtronic, and GlaxoSmithKline and having received honoraria from Medtronic, Astra Zeneca, Scios, GlaxoSmithKline, Otsuka, PDL, Abbott, and Sigma Tau. Dr. Berl reports having served as a consultant to Bayer and Astellas and having received grant support from Otsuka. Dr. Verbalis reports having served as a consultant to Otsuka, Yamanouchi Pharma American, Astellas, Ferring Research, Bristol-Myers Squibb, and Sanofi Aventis and having received grant support from Yamanouchi Pharma American and Astellas. Drs. Czerwiec and Orlandi are employees of Otsuka Maryland Research Institute. No other potential conflict of interest relevant to this article was reported.' Comment: senior author is an employee of the company commercialising the compound Sponsorship bias <ul style="list-style-type: none"> Quote: 'Supported by the Otsuka Maryland Research Institute.'

SALT-2 2006

Methods	<ul style="list-style-type: none"> • Design: parallel RCT (phase 3) • Hyponatraemia subgroup: no • Recruitment period: 2003 to 2005 • Treatment duration: 30 days • Follow-up: 37 days
Participants	<ul style="list-style-type: none"> • Countries: Belgium; Canada; Czech Republic; Germany; Hungary; Italy; Poland; Spain; USA • Number of centres: 50 • Inclusion criteria: recruitment from university hospitals, community hospitals and veteran's medical centres; both in- and outpatients; ≥ 18 years; serum sodium concentration < 135 mmol/L, with at least 50% of included participants < 130 mmol/L; hypervolaemia or euvolaemia • Exclusion criteria: psychogenic polydipsia, head trauma, postoperative conditions, uncontrolled hypothyroidism or adrenal insufficiency; any hyponatraemic condition associated with the use of medications that could have been safely withdrawn; hypovolaemic hyponatraemia; cerebrovascular accident, multiple strokes; sustained ventricular tachycardia or fibrillation, severe angina; systolic BP < 90 mm Hg; central venous pressure < 5 cm H₂O; PCW < 5 mm Hg; SCr > 3.5 mg/dL; Child-Pugh > 10; severe pulmonary hypertension, urinary tract obstruction; uncontrolled diabetes mellitus; progressive or episodic neurologic disease; little chance of short-term survival or those not tolerating sudden shifts in fluid volumes or pressures; serum sodium concentration < 120 mmol/L in association with neurologic impairment • Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (123); control group (120) * Number, % women: treatment group (48, 39%); control group (47, 39%) * Mean age $\pm$ SD (years): treatment group (62 ± 15); control group (63 ± 14) * Serum sodium concentration (mmol/L): treatment group (130 ± 4); control group (129 ± 5) * Cause of hyponatraemia <ul style="list-style-type: none"> ☐ Treatment group: SIADH (24, 20%); heart failure (36, 29%); liver cirrhosis (37, 30%); other (26, 21%) ☐ Control group: SIADH (30, 25%); heart failure (34, 28%); liver cirrhosis (33, 28%); other (49, 20%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Oral tolvaptan: 1 x 15 mg/d up to 1 x 60 mg/d <p>Control group</p> <ul style="list-style-type: none"> • Oral placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: no restriction • sodium intake: no restriction
Outcomes	<ul style="list-style-type: none"> • Death • Health-related quality of life (continuous outcome): change from baseline measured by physical and mental component of the Medical Outcomes Study 12-item Short Form General Health Survey • Response in serum sodium concentration (categorical outcome): serum sodium concentration > 135 mmol/L at any time during treatment • Serum sodium concentration (continuous outcome): change from baseline as well as absolute values • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: serum sodium concentration > 145 mmol/L * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L during the first day * Osmotic demyelination syndrome

SALT-2 2006 (Continued)

- Treatment-specific side-effects
 - * AKI: not otherwise defined
 - * Hypotension: not otherwise defined
 - * Thirst: not otherwise defined
 - * Adverse events: not otherwise defined
 - * Serious adverse events: not otherwise defined
- Treatment discontinuation

Notes

- Funding source: Otsuka Maryland Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: 'Patients...underwent central randomisation with the use of random permuted blocks and stratification according to whether the hyponatraemia was mild or marked...'</p> <p>Comment: the randomisation procedure produced well balanced groups</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: 'Patients...underwent central randomisation with the use of random permuted blocks and stratification according to whether the hyponatraemia was mild or marked...'</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: '...trials were...randomised, double-blind, placebo-controlled efficacy studies...' and 'Patients were assigned...to receive oral tolvaptan...or matching placebo...', and 'Fluid restriction was not mandatory'</p> <p>Comment: blinding of both participants and personnel attempted. However, unlikely for participants to have been fully blinded due to important increases in urine output. We judged this would not have introduced important risk of bias for death and the outcomes related to serum sodium concentration, but may have biased health-related quality of life measures in favour of the study medication. Also, fluid restriction was not mandatory and could be adapted by both participant and treating physician - e.g. based on urine output. This may have resulted in underestimation of the risk of rapid increase in serum sodium concentration</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: unclear whether outcome assessors of non patient-reported outcomes were blinded, but outcomes fairly objective. However, unlikely for participants to have been fully blinded given important increases in urine output, which may have biased the self-reported outcome health-related quality of life</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Quote: 'Patients who received at least one dose of the study medication were included in the safety analyses. Patients whose serum sodium concentrations were evaluated at baseline and one or more times after baseline were included in the efficacy analysis'. And 'serum sodium concentrations were measured at days 2,3,4,11,18,25,30, and 37'</p> <p>Comment: overall 26% attrition at 30 days, 25% in treatment group 1, 26% in placebo group; reasons not reported in detail. Repeated measures analytic technique was used with all measurements of serum sodium concentration included until patient attrition. We judged this may likely have overestimated the change in serum sodium concentration. For the mental component score of the SF-12 health survey, measured at 30 days, attrition reached 31% in treatment group 1 and 29% in the placebo group</p>
Selective reporting (reporting bias)	High risk	<p>Comment: study protocol registered with ClinicalTrials.gov. Outcome measures were only registered in September 2005. Health-related quality of life not</p>

SALT-2 2006 (Continued)

registered as one of the outcomes. Note that the study was registered as separate trial, but the health-related quality of life outcomes and adverse events were reported in a joint analysis for the two studies together without data allowing separation for the purpose of this review. Also because a repeated measures analytic technique was used, unclear at what time point serum sodium concentration was measured for all participants

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'Dr. Schrier reports having served as a consultant to Otsuka, Astellas, Bayer, and Amgen. Dr. Gross reports having served as a consultant to Sanofi-Synthelabo, having received lecture fees from Astellas, and having received grant support from GlaxoSmithKline, Takeda, Amgen, Roche, and Fresenius. Dr. Gheorghiade reports having served as a consultant to Otsuka, PDL, Sigma Tau, Medtronic, and GlaxoSmithKline and having received honoraria from Medtronic, Astra Zeneca, Scios, GlaxoSmithKline, Otsuka, PDL, Abbott, and Sigma Tau. Dr. Berl reports having served as a consultant to Bayer and Astellas and having received grant support from Otsuka. Dr. Verbalis reports having served as a consultant to Otsuka, Yamanouchi Pharma American, Astellas, Ferring Research, Bristol-Myers Squibb, and Sanofi Aventis and having received grant support from Yamanouchi Pharma American and Astellas. Drs. Czerwiec and Orlandi are employees of Otsuka Maryland Research Institute. No other potential conflict of interest relevant to this article was reported.' Comment: senior author is an employee of the company commercialising the compound Sponsorship bias <ul style="list-style-type: none"> Quote: 'Supported by the Otsuka Maryland Research Institute.'
------------	-----------	--

Shoaf 2017

Methods	<ul style="list-style-type: none"> Design: parallel RCT (initiated after licensing) Hyponatraemia subgroup: no Recruitment period: not reported Treatment duration: 1 dose Follow-up: 1 day
Participants	<ul style="list-style-type: none"> Country: not reported Number of centres: > 1 Inclusion criteria: ≥ 18 years; serum sodium concentration > 120 mmol/L and < 133 mmol/L; SIADH Exclusion criteria: not reported Characteristics randomised participants (data not provided for individual groups) <ul style="list-style-type: none"> Number: 30 Number, % women: not reported Mean age $\pm$ SD (years): not reported Serum sodium concentration (mmol/L): not reported Cause of hyponatraemia: SIADH (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 15 mg <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral tolvaptan: 1 x 7.5 mg <p>Control group</p>

Shoaf 2017 (Continued)

- Oral tolvaptan: 1 x 3.75 mg

Co-interventions (all groups)

- Fluid restriction: no restriction
- sodium intake: not reported

Outcomes

- Outcomes related to over-correction of serum sodium concentration
 - * Rapid increase in serum sodium concentration: serum sodium concentration increase > 8 mmol/L in the first 8 hours or ≥ 12 mmol/L during the first day

Notes

- Funding source: not reported
- Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'subjects...were randomised'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'In a multi-center...double blind trial'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: 'In a multi-center...double blind trial'. Comment: insufficient information to permit judgement of 'High risk' or 'Low risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: attrition or treatment discontinuation not specifically reported, but given single dose study, risk of bias seems low nonetheless
Selective reporting (reporting bias)	Low risk	Comment: no protocol, short-term study (single dose), secondary outcomes related to over-correction of serum sodium concentration reported
Other bias	Unclear risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: Insufficient information to permit judgement of 'High risk' or 'Low risk' • Sponsorship bias <ul style="list-style-type: none"> * Comment: sponsorship not reported

Singhi 1995
Methods

- Design: parallel RCT (phase not applicable)
- Hyponatraemia subgroup: yes, with randomisation stratified according to the subgroup
- Recruitment period: not reported
- Treatment duration: 2 days
- Follow-up: 2 days

Singhi 1995 (Continued)

Participants	<ul style="list-style-type: none"> Country: India Number of centres: 1 Inclusion criteria: consecutive admissions to a paediatric emergency service of a teaching hospital; 2 months to 7 years; serum sodium concentration < 130 mmol/L; previously healthy children with acute bacterial meningitis Exclusion criteria: heart disease; respiratory illness including pneumonia; gastrointestinal illness; renal disease; central nervous system disease other than meningitis; weight for age < 60% of expected; endocrinopathy; malignancy; immunodeficiency; previous anticonvulsant therapy Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (15); control group (11) * Number, % girls: treatment group (6, 40%); control group (4, 36%) * Mean age $\pm$ SD: treatment group (11 years $\pm$ 13 months); control group (9 years $\pm$ 12 months) * Serum sodium concentration (mmol/L): treatment group (126 $\pm$ 4); control group (126 $\pm$ 4) * Cause of hyponatraemia: SIADH (100%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> IV one-fifth NaCl 0.9% in dextrose 5%, 65% of calculated normal daily maintenance requirement calculated according to 110 mL/kg for first 10 kg, 50 mL/kg for next 10 kg, 25 mL/kg for subsequent weight - increased to 10 mL/kg/8 hours after 24 hours; 100% of calculated requirement after 48 hours <p>Control group</p> <ul style="list-style-type: none"> IV one-fifth NaCl 0.9% in dextrose 5%, 100% of calculated normal daily maintenance requirement calculated according to 110 mL/kg for first 10 kg, 50 mL/kg for next 10 kg, 25 mL/kg for subsequent weight <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Not reported
Outcomes	<ul style="list-style-type: none"> Death Serum sodium concentration (continuous outcome): change from baseline to the end of treatment
Notes	<ul style="list-style-type: none"> Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: 'Patients in both groups were assigned randomly to receive...' and 'a randomisation list was prepared with help of random tables before initiation of the study.'</p> <p>Comment: valid randomisation methods may have produced imbalanced groups due to small sample size, but any imbalance was likely favouring the experimental group as control group contained the sicker children</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'Low risk' or 'High risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Comment: blinding of participants probably not relevant given setting, short-term study and objective outcomes. Attempts to blind personnel not reported, probably not done, may have influenced administration of co-interventions not reported in the paper</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: blinding of outcome assessors probably not done, but unlikely this will have caused substantial bias given short-term study and objectivity of outcomes</p>

Singhi 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no attrition
Selective reporting (reporting bias)	Low risk	Comment: no protocol, but primary outcome and secondary outcome related to serum sodium concentration reported
Other bias	Low risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors Sponsorship bias <ul style="list-style-type: none"> * Not reported, but given nature of the intervention, unlikely that sponsorship bias would have occurred

Soupart 2006

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: 2001 to 2003 Treatment duration: 5 days Follow-up: 5 days
Participants	<ul style="list-style-type: none"> Countries: Belgium; France; Germany; Hungary Number of centres: not reported Inclusion criteria: ≥ 18 years; serum sodium concentration 115 to ≤ 130 mmol/L; Other: SIADH secretion based on true serum hypo-osmolality; inappropriate urinary osmolality; clinical euvolaemia; elevated urinary sodium excretion while on a normal salt and water intake; normal renal, adrenal and thyroid functions - including participants with sodium excretion ≤ 20 mmol/L as a result of low solute intake Exclusion criteria: cardiac failure; symptomatic liver disease; ALT or AST $> 2 \times$ upper limit of normal; blood glucose ≥ 200 mg/dL; creatinine > 1.7 mg/dL; Hb < 9 g/dL, neutrophils $< 1500/\text{mm}^3$, platelets $< 100,000/\text{mm}^3$, hypothyroidism or adrenal deficiency; radiotherapy or chemotherapy < 2 weeks before drug administration; demeclocycline < 1 month or lithium < 2 days; women of childbearing potential with positive pregnancy test or medically approved contraception method Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group 1 (12); treatment group 2 (14); control group (9) * Number, % women: treatment group 1 (8, 67%); treatment group 2 (7, 50%); control group (7, 78%) * Mean age $\pm$ SD (years): treatment group 1 (69 ± 14); treatment group 2 (71 ± 11); control group (62 ± 19) * Serum sodium concentration (mmol/L): treatment group 1 (127 ± 5); treatment group 2 (125 ± 6); control group (126 ± 3) * Cause of hyponatraemia: SIADH (100%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 50 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral satavaptan: 1 x 25 mg/d <p>Control group</p> <ul style="list-style-type: none"> Placebo: 1 x 1/d <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> Fluid restriction: < 1.5 L/d

Soupart 2006 (Continued)

- Dietary sodium intake: no restriction, kept at levels consistent with baseline

Outcomes	<ul style="list-style-type: none"> Response in serum sodium concentration (categorical outcome): serum sodium concentration increase ≥ 5 mmol/L or serum sodium concentration ≥ 135 mmol/L at any time during treatment Serum sodium concentration (continuous outcome): change from baseline to the end of treatment Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Hyponatraemia: serum sodium concentration > 145 mmol/L * Rapid increase in serum sodium concentration: serum sodium concentration increase > 8 mmol/L during the first day * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L/d at any time point during study Treatment-specific side-effects <ul style="list-style-type: none"> * Hypotension (orthostatic hypotension): systolic BP standing - supine ≤ -20 mm Hg * Thirst (continuous outcome): expressed on a VAS * Adverse events: not otherwise defined * Serious adverse events: not otherwise defined Treatment discontinuation
Notes	<ul style="list-style-type: none"> Funding source: Sanofi-Aventis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: '...patients were randomly assigned to take placebo or a once-daily dose...'</p> <p>Comment: due to the large number of groups relative to the number of included participants, the randomisation procedure may have failed to produce groups with similar baseline prognosis. E.g. there is an imbalance in age, SCr, urinary sodium across the groups. We assumed the influence of the imbalance thus generated would be negligible in practice</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: insufficient information to permit judgement of 'Low risk' or 'High risk'</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: '...patients were randomly assigned to take placebo or a once-daily dose of 25 or 50 mg of sataavaptan during a double-blind period of up to 5 days...', and 'The double-blind period was followed by 23 d of open-label treatment...'</p> <p>Comment: blinding probably attempted, and although participants are unlikely to be fully blinded due to important increases in urine output, all measured outcomes are short-term and fairly objective. Co-interventions similar for all groups</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: only 1 participant (3%), in the placebo group, dropped out due to worsening of pre-existing vasculitis</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: no protocol, but short-term study (≤ 1 week) and both secondary outcomes related to serum sodium concentration and rapid increase in serum sodium concentration reported</p>

Soupart 2006 (Continued)

Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Quote: 'This study was designed by H.M.H., G.D. and Dr. J.G. Verbalis.' * Comment: No declaration of interest. H.M.H - Hassan M. Heshmati's affiliations: Clinical Development, Sanofi-Aventis, Malvern, Pennsylvania Sponsorship bias <ul style="list-style-type: none"> * Quote: 'This study was sponsored by Sanofi-Aventis.' * Comment: H.M.H - Hassan M. Heshmati's affiliations: Clinical Development, Sanofi-Aventis, Malvern, Pennsylvania
------------	-----------	--

Wong 2003b

Methods	<ul style="list-style-type: none"> Design: parallel RCT (phase not reported) Hyponatraemia subgroup: no Recruitment period: 1998 to 1999 Treatment duration: 8 days Follow-up: 8 days
Participants	<ul style="list-style-type: none"> Countries: Canada, USA Number of centres: 13 Inclusion criteria: serum sodium concentration < 130 mmol/L Exclusion criteria: Child-Pugh > 12; creatinine ≥ 3 mg/dL without cirrhosis; creatinine ≥ 2 mg/dL with cirrhosis; adrenal insufficiency, thyroid dysfunction; fasting blood glucose > 13.8 mmol/L; infection ≤ 2 weeks; MI ≤ 2 months; surgery or head trauma; systolic BP < 80 mm Hg; symptomatic orthostatic hypotension; lithium, vasopressin analogues, demeclocycline, desmopressin, oncologic agents salt tablets or hypertonic saline Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group 1 (10); treatment group 2 (11); treatment group 3 (12); control group (11) * Number, % women: treatment group 1 (2, 20%); treatment group 2 (3, 40%); treatment group 3 (7, 60%); control group (1, 9%) * Mean age ± SD (years): treatment group 1 (51 ± 3); treatment group 2 (55 ± 4); treatment group 3 (48 ± 3); control group (52 ± 3) * Serum sodium concentration (mmol/L): treatment group 1 (126 ± 1); treatment group 2 (121 ± 1); treatment group 3 (126 ± 0.4); control group (127 ± 1) * Cause of hyponatraemia <ul style="list-style-type: none"> ☐ Treatment group 1: SIADH (1, 10%); heart failure (2, 20%); liver cirrhosis (7, 70%) ☐ Treatment group 2: heart failure (1, 9%); liver cirrhosis (10, 91%) ☐ Treatment group 3: SIADH (3, 25%); heart failure (1, 8%); liver cirrhosis (8, 67%) ☐ Control group: SIADH (1, 9%); heart failure (1, 9%); liver cirrhosis (8, 73%); heart failure and cirrhosis (1, 9%)
Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> Oral lixivaptan: 2 x 250 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> Oral lixivaptan: 2 x 125 mg/d <p>Treatment group 3</p> <ul style="list-style-type: none"> Oral lixivaptan: 2 x 25 mg/d <p>Control group</p> <ul style="list-style-type: none"> Placebo: 2 x 1/d

Interventions for chronic non-hypovolaemic hypotonic hyponatraemia (Review)

Wong 2003b (Continued)

Co-interventions (all groups)

- Fluid restriction: < 1.5 L/d, adapted according to urine output
- Dietary sodium intake: no restriction, sodium intake determined by each investigator and kept at levels constant throughout study

Outcomes	<ul style="list-style-type: none"> • Serum sodium concentration (continuous outcome): change from baseline to the end of treatment • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase > 8 mmol/L/d throughout the study; or serum sodium concentration > 142 mmol/L • Treatment-specific side-effects <ul style="list-style-type: none"> * Thirst (continuous outcome): expressed on a 0 to 100 mm VAS • Treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Wyeth-Ayerst

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: 'patients were randomised at a central site by the Computerized Randomization/Enrollment (CORE) system'</p> <p>Comment: due to the large number of groups relative to the number of included participants, randomisation procedure may have failed to produce groups with similar baseline prognosis. E.g. there is an imbalance in age across the groups. We assumed the influence of the imbalance thus generated would be negligible in practice</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: 'patients were randomised at a central site by the Computerized Randomization/Enrollment (CORE) system'</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: '...randomised...to receive twice daily per os either placebo, ...'</p> <p>Comment: blinding probably attempted, but due to increase in urine output, un-blinding likely to have occurred and as fluid intake was adjusted to urine output, this may likely have resulted in underestimation of the incidence of rapid increase in sodium concentration as well as influenced thirst measurements</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: unclear whether assessors of non patient-reported outcomes were blinded, but main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Comment: 27% attrition, due to treatment discontinuation (21%); reasons well-documented. 'High risk' for sodium concentration measurements given re-inclusion occurred using last available measurement before discontinuation</p>
Selective reporting (reporting bias)	High risk	<p>Comment: no protocol - study duration 8 days without adequate reporting of secondary outcomes related serum sodium concentration permitting data</p> <ul style="list-style-type: none"> • Timing outcome assessment <ul style="list-style-type: none"> * Comment: Last-observation carried forward method may have caused measurements at different time-points
Other bias	High risk	<ul style="list-style-type: none"> • Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> * Comment: No declaration of interest

Wong 2003b (Continued)

- Sponsorship bias
 - * Quote: 'Data were collected centrally at Wyeth-Ayerst Laboratories and initially analysed at Wyeth-Ayerst'
 - * Comment: the sponsor initiated and funded the study, and had direct control over data and their analysis

Yang 2013

Methods	<ul style="list-style-type: none"> • Design: parallel RCT (phase not reported) • Hyponatraemia subgroup: no • Recruitment period: not reported • Treatment duration: 8 days • Follow-up: 8 days
Participants	<ul style="list-style-type: none"> • Country: China • Number of centres: not reported • Inclusion criteria: > 18 years; CHF • Exclusion criteria: not reported • Characteristics randomised participants <ul style="list-style-type: none"> * Number: treatment group (8); control group (8) * Number, % women: not reported * Mean age $\pm$ SD (years): not reported * Serum sodium concentration (mmol/L): not reported * Cause of hyponatraemia: CHF (100%)
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Oral tolvaptan: dose and duration not reported <p>Control group</p> <ul style="list-style-type: none"> • Not reported <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Not reported
Outcomes	<ul style="list-style-type: none"> • Health-related quality of life: (measured by the Minnesota quality of life score): insufficiently reported to allow contribution to meta-analysis • Serum sodium concentration (continuous outcome) • Treatment-specific side-effects (insufficiently reported to allow contribution to meta-analysis) <ul style="list-style-type: none"> * Thirst: dry mouth * Serious adverse events: not otherwise specified
Notes	<ul style="list-style-type: none"> • Funding source: not reported • Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: '...they were randomly divided...' Comment: insufficient evidence to permit judgement of 'Low risk' or 'High risk'

Yang 2013 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: insufficient evidence to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient evidence to permit judgement of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient evidence to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient evidence to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias)	High risk	Comment: no protocol, study duration > 1 week, primary and secondary outcomes insufficiently reported
Other bias	Unclear risk	Comment: insufficient evidence to permit judgement of 'Low risk' or 'High risk'

Zeltser 2007

Methods	<ul style="list-style-type: none"> • Design: parallel RCT (phase 3) • Hyponatraemia subgroup: no • Recruitment period: 2000 to 2003 • Treatment duration: 2 days • Follow-up: not reported
Participants	<ul style="list-style-type: none"> • Countries: Canada, Israel, South Africa, USA • Number of centres: not reported • Inclusion criteria: ≥ 18 years; serum sodium concentration: 115 to ≤ 130 mmol/L; plasma osmolality < 290 mOsm/kg H₂O; fasting blood glycaemia < 275; euvolaemia (defined as absence of pitting oedema or ascites determined by clinical assessment); hypervolaemia (defined as presence of oedema determined by clinical assessment) • Exclusion criteria: hypovolaemia; supine systolic BP < 85 mm Hg; orthostatic hypotension - systolic BP < 80 mm Hg on standing or decrease of > 20 mm Hg from supine to standing; uncontrolled hypertension; bradyarrhythmia or tachyarrhythmia necessitating emergent pacemaker implantation or treatment; untreated severe thyroid disease or adrenal insufficiency; severe renal dysfunction (CrCl < 20 mL/min); medications known to interact with cytochrome P450 3A4, AVP, oxytocin, desmopressin and other medications used to treat hyponatraemia, specifically, lithium salts, urea, and demeclocycline; hyponatraemia necessitating emergent treatment during the study

Zeltser 2007 (Continued)

- Characteristics included participants
 - * Number: treatment group 1 (29); treatment group 2 (29); control group (26)
 - * Number, % women: treatment group 1 (12, 46%); treatment group 2 (17, 59%); control group (14, 48%)
 - * Mean age $\pm$ SD (years): treatment group 1 (73 ± 14); treatment group 2 (74 ± 12); control group (76 ± 12)
 - * Serum sodium concentration (mmol/L): treatment group 1 (125 ± 3); treatment group 2 (123 ± 5); control group (124 ± 4)
 - * Cause of hyponatraemia
 - ☐ Treatment group 1: SIADH (7, 27%); heart failure (8, 31%); malignancy (2, 8%); post-surgery (1, 4%); idiopathic (6, 23%); unclear (2, 8%)
 - ☐ Treatment group 2: SIADH (7, 24%); heart failure (10, 35%); malignancy (3, 10%); post-surgery (1, 3%); idiopathic (5, 17%); unclear (3, 10%)
 - ☐ Control group: SIADH (4, 14%); heart failure (7, 24%); malignancy (2, 7%), post-surgery (1, 3%), COPD (2, 7%); idiopathic (4, 14%); unclear (9, 31%)

Interventions	<p>Treatment group 1</p> <ul style="list-style-type: none"> • IV conivaptan: 20 mg loading dose + 80 mg/d continuous infusion <p>Treatment group 2</p> <ul style="list-style-type: none"> • IV conivaptan: 20 mg loading dose + 40 mg/d continuous infusion <p>Control group</p> <ul style="list-style-type: none"> • IV Placebo: 100 mL 5% dextrose in water + 250 mL/d 5% dextrose in water continuous infusion <p>Co-interventions (all groups)</p> <ul style="list-style-type: none"> • Fluid restriction: <2 L/d • Dietary sodium intake: no restriction, sodium intake kept at levels consistent with baseline
Outcomes	<ul style="list-style-type: none"> • Death • Response in serum sodium concentration (categorical outcome): serum sodium concentration increase ≥ 6 mmol/L or serum sodium concentration ≥ 135 mmol/L at any time during treatment • Serum sodium concentration (continuous outcome): change from baseline to the end of treatment • Outcomes related to over-correction of serum sodium concentration <ul style="list-style-type: none"> * Rapid increase in serum sodium concentration: serum sodium concentration increase > 12 mmol/L on day 1; or serum sodium concentration increase > 24 mmol/L in total; or serum sodium concentration > 145 mmol/L; or treatment reduced or withheld following increase in serum sodium concentration judged by the investigator as too rapid * Osmotic demyelination syndrome • Treatment-specific side-effects <ul style="list-style-type: none"> * AKI: kidney dysfunction or worsening kidney function * Hypotension * Thirst (insufficiently reported to allow contribution to meta-analysis) * Serious adverse events: not otherwise defined * Injection-site phlebitis * Injection-site thrombosis * Liver function abnormalities: significantly elevated liver enzymes • Treatment discontinuation
Notes	<ul style="list-style-type: none"> • Funding source: Astellas Pharma US, Inc. • 88 were randomised - 4 excluded after randomisation for not having received the study drug

Risk of bias

Zeltser 2007 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: 'patients were stratified by volume status and randomly assigned to...' Comment: insufficient information to permit judgement of 'Low risk' or 'High risk'
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: '...double-blind, placebo-controlled study,...' and 'The placebo group received a 100-ml loading dose of D5W on day 1 followed by continuous infusion of 250 ml D5W...' Comment: blinding probably attempted, and although participants are unlikely to be fully blinded due to important increases in urine output, all measured outcomes fairly objective. Co-interventions Fluid-restriction and salt intake were similar for all groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: blinding outcome assessors for non patient-reported outcomes probably attempted and main measured outcomes objective. Unlikely for participants to have been fully blinded, and plausible 'high risk' of bias for self-reported outcome of thirst
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: overall 25% attrition due to exclusion after randomisation (4%) and treatment discontinuation (21%); reasons well-documented. 'Low risk' for death, but 'high risk' for sodium concentration measurements given re-inclusion occurred using last available measurement before discontinuation. Although the opportunity for introducing bias is probably limited in such a short-term study - we judged it 'high risk' as matter of principle
Selective reporting (reporting bias)	Low risk	Comment: no protocol, but death, serum sodium concentration and outcomes related to rapid increase in serum sodium concentration reported. However, violation intention to treat analysis may be an issue. Quote: 'The efficacy analyses were conducted using a modified intent-to-treat approach and included all randomised patients who had at least 1 baseline serum [Na ⁺] measurement, received at least 1 dose of study medication, and had at least 1 valid efficacy measurement.' Comment: 4 (4%) excluded after randomisation for not having received the study drug
Other bias	High risk	<ul style="list-style-type: none"> Bias through possible financial conflict of interest of the authors <ul style="list-style-type: none"> Quote: 'Neila Smith: Astellas Pharma US, Inc., Deerfield, Ill., USA'; 'Disclosure - Grant/Research support: Yamanouchi Pharma America, Inc - grant (Verbalis), employee (Bisaha and Smith), consultant: Yamanouchi Pharma America, Inc.; J.G.V. is a consultant for Astellas Pharma US, Inc., Otsuka Pharmaceutical Co., Ltd and Sanofi-Aventis; has received funds for research from Yamanouchi Pharma America, Inc. and Astellas Pharma US, Inc; and has received fees for speaking from Astellas Pharma US, Inc. D.Z. has nothing to declare. N.S., A.B. and M.A. are employed by Astellas Pharma US, Inc.'; 'Joseph Verbalis, No Product/Research Disclosure Information; Grant monies (from industry related sources) Joseph G. Verbalis, Astellas Pharma US, Inc; Employee Bruce McNutt, Bo Yan, Astellas Pharma US, Inc.; Consultant fee, speaker bureau, advisory committee, etc. Joseph G. Verbalis is a consultant for Astellas Pharma US, Inc., Otsuka Pharmaceutical Co., Ltd., and Sanofi-Aventis, and has received fees for speaking from Astellas Pharma US, Inc.' Comment: senior author's affiliation: Astellas Pharma; several authors affiliated with the company commercialising the compound

Zeltser 2007 (Continued)

- Sponsorship bias
 - * Quote: 'This study was supported by Astellas Pharma US, Inc. (formerly Yamanouchi Pharma America, Inc.)
 - * Comment: senior author's affiliation: Astellas Pharma; several authors affiliated with the company commercialising the compound

AKI - acute kidney injury; ALT - alanine aminotransferase; AST - aspartate aminotransferase; AVP - Arginine vasopressin; BP - blood pressure; BPM - beats per minute; BUN - blood urea nitrogen; CHF - chronic heart failure; COPD - chronic obstructive pulmonary disease; CrCl - creatinine clearance; FDA - food and Drug Administration; GFR - glomerular filtration rate; Hb - haemoglobin; INR - international normalised ratio; MI - myocardial infarction; NYHA - New York Heart Association; PCW - pulmonary capillary wedge; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; SF-12 - Short Form Health Survey; SIADH - syndrome of inappropriate antidiuretic hormone; VAS - visual analogue scale; WCC - white cell count

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abraham 2006	Wrong population: RCT comparing lixivaptan versus placebo in participants with heart failure. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Albert 2013	Wrong population: RCT comparing fluid restriction versus usual care after discharge in patients hospitalised for acute decompensation of chronic heart failure. Inclusion criteria state hyponatraemia - but defined as a serum sodium concentration ≤ 137 mmol/L. At discharge, and hence start of the intervention, the median serum sodium concentration in both groups equalled 135.5 mmol/L with interquartile ranges 134 to 137 mmol/L. This means hardly no participants had hyponatraemia as defined in this review. Consequently, any treatment given does not have the same harms (rapid increases in serum sodium concentration, osmotic demyelination syndrome) to consider. We judged the studied participants in this trial did not meet the projected characteristics of the patient group targeted by this review
Alexander 1991	Wrong population: people with hyponatraemia due to primary psychogenic polydipsia are excluded from the review
Angeli 2010	Wrong population: RCT comparing combined versus sequential diuretic treatment in participants with cirrhosis. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 23/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Bernardi 1993	Wrong intervention: RCT in which in patients with liver cirrhosis and ascites two different salt-restricted diets are evaluated in combination with step-wise increase of diuretic treatment in both groups in order to reduce weight and ascites
De Vita 2012	Wrong population: RCT comparing rituximab monotherapy versus the best available treatment in patients with mixed cryoglobulinaemia syndrome
Galton 2011	Wrong population: RCT in which a single dose of conivaptan was given to normonatraemic critically ill patients with severe traumatic brain injury
Ghali 2012	Wrong population: RCT comparing lixivaptan versus placebo in participants with heart failure. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 23/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response

Study	Reason for exclusion
Gines 2007	Double counting of included participants. Study represents a second RCT built on top of a first included RCT (Gines 2008b) using the same study drug. Including the trial would give rise to double counting of participants
Guyader 2002	Wrong population: RCT comparing satavaptan with placebo in participants with liver cirrhosis. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors with a request for the outcome data for the subgroup of participants with hyponatraemia. We received a response from the sponsor with inclusion of the full text. However, no additional data were provided
K-STAR 2017	Wrong population: Post-hoc analysis of RCT comparing tolvaptan versus placebo in participants with heart failure. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia. As the primary study data have not yet been published, primary author unable to supply raw data
Licata 2003	Wrong population: RCT comparing high-dose furosemide + low volume hypertonic saline versus high-dose furosemide in participants with heart failure. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Matsuzaki 2011a	Wrong population: RCT comparing tolvaptan versus placebo in participants with heart failure. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Matsuzaki 2011b	Wrong population: RCT comparing tolvaptan versus placebo in participants with heart failure. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Mori 1999	Wrong population: study evaluating fludrocortisone for preventing hyponatraemia in people with subarachnoidal bleeding. Patients were not hyponatraemic at randomisation
Okita 2014	Wrong population: RCT comparing tolvaptan versus placebo in participants with liver cirrhosis and hepatic oedema. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Owen 2014	Wrong population: RCT in people with acute hyponatraemia after an ultra-distance run
Paterna 2000	Wrong population: RCT comparing high-dose furosemide + low volume hypertonic saline versus high-dose furosemide in participants with heart failure. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Rajan 2015	Wrong population: RCT on conivaptan in people with acute hyponatraemia
Ramsay 1988	Wrong population: RCT in people with congestive heart failure, but none had hyponatraemia at the start of the study
Rogers 2011	Wrong population: RCT in people with exercise-associated hyponatraemia, which is to be seen as a form of acute hyponatraemia present < 48 hours, requiring immediate intervention. Only chronic hyponatraemia, defined as present > 48 hours is included in the review

Study	Reason for exclusion
Sakaida 2014	Wrong population: RCT comparing tolvaptan versus placebo in participants with liver cirrhosis and hepatic oedema. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
SALSA 2017	Wrong population: RCT comparing intermittent infusion of small volumes of NaCl 3% versus slow continuous infusion of NaCl 3% in people with moderately severe or severe symptoms attributed to hyponatraemia. These people are considered requiring immediate intervention to increase the serum sodium concentration. Only those that did not require immediate treatment were considered in the review
SECRET of CHF 2017	Wrong population: RCT comparing tolvaptan versus placebo in participants with heart failure. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Shanmugam 2016	Wrong population: RCT comparing tolvaptan versus placebo in participants with heart failure. Abstract title implies all participants had hyponatraemia, but investigators actually included everyone with serum sodium concentration below 140 mmol/L. Study population included both participants with and without hyponatraemia according to our definition. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Suzuki 2013b	Wrong population: RCT comparing tolvaptan versus carperitide in participants with heart failure. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
TACT-ADHF 2016	Wrong population: RCT comparing tolvaptan versus placebo in participants with heart failure. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
TACTICS-HF 2017	Wrong population: RCT comparing tolvaptan versus placebo in participants with heart failure. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Thuluvath 2006	Wrong population: RCT comparing tolvaptan versus placebo in participants with liver cirrhosis and ascites. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Wong 2009	Wrong population: RCT comparing satavaptan versus placebo in participants with liver cirrhosis and hepatic oedema. Study population included both participants with and without hyponatraemia. We attempted to contact the authors on 04/12/2016 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Wong 2010a	Wrong population: RCT comparing satavaptan with placebo in participants with liver cirrhosis. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors with a request for the outcome data for the subgroup of participants with hyponatraemia. Dr Wong referred us to the sponsor, who was subsequently contacted on 24/10/2014. The sponsor agreed to provide the data but to date we received no further communication
Wong 2012	Wrong population: RCT comparing satavaptan versus placebo in participants with liver cirrhosis. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response

Study	Reason for exclusion
	pants with hyponatraemia. Dr. Ginès referred us to the sponsor, who was subsequently contacted on 24/10/2014, but we received no response
Yang 2010b	Wrong population: RCT comparing clonidine versus placebo in participants with liver cirrhosis. Study population possibly included both participants with and without hyponatraemia. We attempted to contact the authors on 24/10/2014 with a request for the outcome data for the subgroup of participants with hyponatraemia, but received no response
Zamboli 2011	Wrong population: RCT in people with CKD stage 3 or 4. This is not a group that likely contains a substantial number of people with hyponatraemia
Zellweger 2001	Wrong population: RCT comparing cyclooxygenase-2 inhibitors versus non-selective NSAID and the risk of developing hyponatraemia

CKD - chronic kidney disease; NSAID - non-steroidal anti-inflammatory drugs; RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. Vasopressin receptor antagonists (VRA) versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 6 months	15	2330	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.92, 1.33]
1.1 Conivaptan	4	222	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.13, 1.17]
1.2 Lixivaptan	3	950	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.85, 1.80]
1.3 Tolvaptan	8	1158	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.89, 1.39]
2 Health-related quality of life	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Mental component SF-12	2	297	Mean Difference (IV, Random, 95% CI)	4.76 [0.11, 9.41]
2.2 Physical component SF-12	2	300	Mean Difference (IV, Random, 95% CI)	1.04 [-1.81, 3.90]
3 Cognitive function: trail making test Part B	2	858	Mean Difference (IV, Random, 95% CI)	6.89 [-6.34, 20.12]
4 Length of hospital stay	3	610	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.96, -0.30]
4.1 Satavaptan	1	139	Mean Difference (IV, Random, 95% CI)	-1.80 [-3.80, 0.20]
4.2 Tolvaptan	2	471	Mean Difference (IV, Random, 95% CI)	-1.50 [-3.28, 0.29]
5 Change from baseline serum sodium concentration	21	2641	Mean Difference (IV, Random, 95% CI)	4.17 [3.18, 5.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Conivaptan	5	292	Mean Difference (IV, Random, 95% CI)	5.17 [2.65, 7.69]
5.2 Lixivaptan	4	1070	Mean Difference (IV, Random, 95% CI)	2.24 [0.78, 3.70]
5.3 Satavaptan	3	257	Mean Difference (IV, Random, 95% CI)	4.91 [2.88, 6.94]
5.4 Tolvaptan	9	1022	Mean Difference (IV, Random, 95% CI)	4.22 [3.55, 4.89]
6 Response in serum sodium concentration	18	2104	Risk Ratio (M-H, Random, 95% CI)	2.49 [1.95, 3.18]
6.1 Conivaptan	4	282	Risk Ratio (M-H, Random, 95% CI)	2.48 [1.54, 4.01]
6.2 Lixivaptan	4	1024	Risk Ratio (M-H, Random, 95% CI)	2.21 [1.19, 4.10]
6.3 Satavaptan	4	331	Risk Ratio (M-H, Random, 95% CI)	3.33 [1.88, 5.89]
6.4 Tolvaptan	6	467	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.75, 3.18]
7 Rapid increase in serum sodium concentration	14	2058	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.16, 2.40]
7.1 Conivaptan	4	290	Risk Ratio (M-H, Random, 95% CI)	3.77 [0.89, 15.98]
7.2 Lixivaptan	4	994	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.90, 2.17]
7.3 Satavaptan	4	331	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.73, 9.30]
7.4 Tolvaptan	2	443	Risk Ratio (M-H, Random, 95% CI)	6.70 [0.82, 54.56]
8 Hypernatraemia during treatment	10	1592	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.63, 3.01]
8.1 Conivaptan	1	83	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.14, 57.89]
8.2 Lixivaptan	2	306	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.04, 5.78]
8.3 Satavaptan	3	262	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.35, 11.11]
8.4 Tolvaptan	4	941	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.81, 9.22]
9 Thirst	13		Odds Ratio (Random, 95% CI)	2.77 [1.80, 4.27]
10 Other adverse events	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Polyuria	6	1272	Risk Ratio (M-H, Random, 95% CI)	4.69 [1.59, 13.85]
10.2 Hypotension	14	1748	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.75, 1.63]
10.3 Acute kidney injury	8	1920	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.67, 1.18]
10.4 Liver function abnormalities	3	811	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.88, 6.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Injection-site complications at 2 to 7 days	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Reactions	1	49	Risk Ratio (M-H, Random, 95% CI)	7.56 [0.49, 115.93]
11.2 Phlebitis	2	133	Risk Ratio (M-H, Random, 95% CI)	3.52 [1.00, 12.41]
11.3 Thrombosis	2	133	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.21, 14.80]
12 Treatment discontinuation	14	2429	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.00]
12.1 Conivaptan	4	288	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.39, 1.30]
12.2 Lixivaptan	4	1008	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
12.3 Satavaptan	2	145	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.17, 1.46]
12.4 Tolvaptan	4	988	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.66, 1.13]
13 Death during follow-up: sensitivity analysis	16	2404	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.91, 1.32]
13.1 Conivaptan	5	296	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.19, 1.15]
13.2 Lixivaptan	3	950	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.37, 3.15]
13.3 Tolvaptan	8	1158	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.89, 1.39]
14 Rapid increase in serum sodium concentration: sensitivity analysis	14	2058	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.16, 2.40]
14.1 > 8 mmol/L/d	4	257	Risk Ratio (M-H, Random, 95% CI)	3.22 [0.65, 15.94]
14.2 > 12 mmol/L/d	10	1801	Risk Ratio (M-H, Random, 95% CI)	1.63 [1.09, 2.43]

Analysis 1.1. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 1 Death at 6 months.

Study or subgroup	VRA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Conivaptan					
Naidech 2010	0/3	0/3			Not estimable
Koren 2011	0/40	0/9			Not estimable
Annan 2009	2/53	3/30		1.18%	0.38[0.07,2.13]
Zeltser 2007	3/55	4/29		1.74%	0.4[0.09,1.65]
Subtotal (95% CI)	151	71		2.92%	0.39[0.13,1.17]

**Analysis 1.2. Comparison 1 Vasopressin receptor antagonists (VRA)
versus placebo or no treatment, Outcome 2 Health-related quality of life.**

Analysis 1.3. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 3 Cognitive function: trail making test Part B.

Analysis 1.4. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 4 Length of hospital stay.

Analysis 1.5. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 5 Change from baseline serum sodium concentration.

Analysis 1.6. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 6 Response in serum sodium concentration.

Analysis 1.7. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 7 Rapid increase in serum sodium concentration.

Analysis 1.8. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 8 Hypernatraemia during treatment.

Analysis 1.9. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 9 Thirst. **Analysis 1.10. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 10 Other adverse events.**

Analysis 1.11. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 11 Injection-site complications at 2 to 7 days.

Analysis 1.12. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 12 Treatment discontinuation.

Analysis 1.13. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 13 Death during follow-up: sensitivity analysis.

Analysis 1.14. Comparison 1 Vasopressin receptor antagonists (VRA) versus placebo or no treatment, Outcome 14 Rapid increase in serum sodium concentration: sensitivity analysis.

ADDITIONAL TABLES

Table 1. Change in serum sodium concentration: meta-regression and confounding

Covariate	Number of studies included in meta-regression	Scale	Absolute change in mean difference	P value
Baseline serum sodium concentration	21	Per 1 mmol/L increase	-0.33 (-0.65 to -0.02)	0.04
<i>Compound</i>	21	Relative to conivaptan	-	0.17
Conivaptan	5	-	-	-
Lixivaptan	4	-	-2.79 (-5.47 to -0.10)	-
Satavaptan	3	-	-0.23 (-3.34 to 2.87)	-
Tolvaptan	9	-	-0.82 (-3.13 to 1.50)	-
<i>Cause of hyponatraemia</i>	21	Relative to SIADH	-	0.18
SIADH	5	-	-	-
Combined SIADH - Heart failure, cirrhosis	10	-	0.67 (-1.77 to 3.13)	-
Heart failure	6	-	-1.19 (-3.84 to 1.47)	-
<i>Treatment duration</i>	21	Per day increase	-0.02 (-0.04 to 0.00)	0.1
<i>Risk of selection bias</i>	21	Relative to low risk	-	0.86
Low risk	8	-	-	-
High risk	13	-	0.18 (-1.90 to 2.27)	-

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. hyponatr*emi*:ti,ab,kw 2. "inappropriate ADH syndrome":ti,ab,kw 3. "inappropriate vasopressin secretion":ti,ab,kw 4. {or #1-#3}
MEDLINE	<ol style="list-style-type: none"> 1. Hyponatremia/ 2. Inappropriate ADH Syndrome/ 3. hyponatr?emi*.tw. 4. inappropriate ADH syndrome.tw. 5. inappropriate vasopressin secretion.tw. 6. or/1-5
EMBASE	<ol style="list-style-type: none"> 1. hyponatremia/ 2. inappropriate vasopressin secretion/ 3. hyponatr?emi*.tw. 4. inappropriate ADH syndrome.tw. 5. inappropriate vasopressin secretion.tw. 6. or/1-5

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	<p><i>Low risk of bias:</i> Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).</p> <p><i>High risk of bias:</i> Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available.</p>
Blinding of participants and personnel	<p><i>Low risk of bias:</i> No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</p>

(Continued)

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>High risk of bias:</i> No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<p><i>Low risk of bias:</i> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.</p> <p><i>High risk of bias:</i> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	<p><i>Low risk of bias:</i> No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.</p> <p><i>High risk of bias:</i> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Selective reporting Reporting bias due to selective outcome reporting	<p><i>Low risk of bias:</i> The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).</p> <p><i>High risk of bias:</i> Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Other bias Bias due to problems not covered elsewhere in the table	<p><i>Low risk of bias:</i> The study appears to be free of other sources of bias.</p> <p><i>High risk of bias:</i> Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.</p>

(Continued)

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: EVN, MCH, WVB, RVH, JC, ACW
2. Study selection: EVN, MCH
3. Extract data from studies: EVN, MCH
4. Enter data into RevMan: EVN
5. Carry out the analysis: EVN
6. Interpret the analysis: EVN, ACW
7. Wrote the review: EVN
8. Revised the review: MCH, ACW, WVB, RVH, JC, ACW
9. Advised on presentation of results: ACW
10. Disagreement resolution: ACW
11. Update the review: EVN, MCH, WVB, RVH, JC, ACW

DECLARATIONS OF INTEREST

Evi V Nagler, Maria C Haller, Wim Van Biesen and Raymond Vanholder are members of European Renal Best Practice (ERBP), the guidance issuing body of the European Renal Association/ European Dialysis and Transplant Association (ERA-EDTA). ERBP has recently developed a clinical practice guideline on diagnosis and treatment of hyponatraemia in a joint venture with the European Society of Endocrinology and the European Society of Intensive Care Medicine. ERBP receives their annual budget from the ERA-EDTA. The ERA-EDTA council does not interfere with topic choice or any other part of the guideline development process of ERBP.

Evi V Nagler and Maria C Haller received an ERBP grant to fund their research programs. They have no commercial interests to declare.

Wim Van Biesen has no commercial interests related to the treatment of hyponatraemia or this review.

Raymond Vanholder has acted as consultant for Baxter Healthcare, Bellco and Mitsubishi; as expert advisor for Relitech, Dutch Kidney Foundation, Bellco, Amgen, Mitsubishi, DOPPS, Hoffman Laroche, Fresenius Medical Care; has received research grants from Fresenius Medical Care, Baxter Healthcare, Gambro, Astellas, Hoffman Laroche and Amgen. He has no specific commercial interests related to the treatment of hyponatraemia.

Jonathan C Craig and Angela C Webster have no intellectual or commercial interests to declare.

SOURCES OF SUPPORT

Internal sources

- European Renal Best Practice (ERBP), the guidance issuing body of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), Other.

Provided a grant that funded this research

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Liver function abnormalities were not anticipated as an adverse effect attributable to vasopressin receptor antagonists. A communication issued by Otsuka, indicating concerns around possibility for liver failure - be it in patients with autosomal polycystic kidney disease and at doses higher than those given for hyponatraemia - highlighted the outcome for inclusion in our review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidiuretic Hormone Receptor Antagonists [*therapeutic use]; Chronic Disease; Hyponatremia [blood] [*drug therapy] [mortality]; Length of Stay; Quality of Life; Randomized Controlled Trials as Topic; Sodium [blood]

MeSH check words

Humans