

Tolvaptan for the treatment of the syndrome of inappropriate antidiuresis (SIAD)

Ploutarchos Tzoulis^{ID}, Gregory Kaltsas, Stephanie E. Baldeweg, Pierre-Marc Bouloux and Ashley B. Grossman

*Ther Adv Endocrinol
Metab*

2023, Vol. 14: 1–17

DOI: 10.1177/

20420188231173327

© The Author(s), 2023.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract: The syndrome of inappropriate antidiuresis (SIAD), the commonest cause of hyponatraemia, is associated with significant morbidity and mortality. Tolvaptan, an oral vasopressin V₂-receptor antagonist, leads through aquaresis to an increase in serum sodium concentration and is the only medication licenced in Europe for the treatment of euvolaemic hyponatraemia. Randomised controlled trials have shown that tolvaptan is highly efficacious in correcting SIAD-related hyponatraemia. Real-world data have confirmed the marked efficacy of tolvaptan, but they have also reported a high risk of overly rapid sodium increase in patients with a very low baseline serum sodium. The lower the baseline serum sodium, the higher the tolvaptan-induced correction rate occurs. Therefore, a lower starting tolvaptan dose of 7.5 mg has been evaluated in small cohort studies, demonstrating its efficacy, but it still remains unclear as to whether it can reduce the risk of overcorrection. Most international guidelines, except for the European ones, recommend tolvaptan as second-line treatment for SIAD after fluid restriction. However, the risk of unduly rapid sodium correction in combination with its high cost have limited its routine use. Prospective controlled studies are warranted to evaluate whether tolvaptan-related sodium increase can improve patient-related clinical outcomes, such as mortality and length of hospital stay in the acute setting or neurocognitive symptoms and quality of life in the chronic setting. In addition, the potential role of a low tolvaptan starting dose needs to be further explored. Until then, tolvaptan should mainly be used as second-line treatment for SIAD, especially when there is a clinical need for prompt restoration of normonatraemia. Tolvaptan should be used with specialist input according to a structured clinical pathway, including rigorous monitoring of electrolyte and fluid balance and, if needed, implementation of appropriate measures to prevent, or when necessary reverse, overly rapid hyponatraemia correction.

Keywords: hyponatraemia, SIAD, sodium, tolvaptan, vaptans

Received: 7 February 2023; revised manuscript accepted: 15 April 2023.

Introduction

Hyponatraemia, the most frequent electrolyte abnormality encountered in hospital practice, is defined as a serum sodium concentration below 135 mmol/litre and is associated with significant morbidity and excess mortality, with its commonest cause being the syndrome of inappropriate antidiuresis (SIAD). Fluid restriction has been the mainstay treatment for SIAD in the last decades despite the limited evidence base supporting its use.¹ The modest efficacy of fluid restriction in increasing serum sodium, noted in large observational studies,² was also confirmed in the first and

only prospective randomised controlled trial (RCT) which reported a failure to respond in more than one-third of patients, highlighting the need for other therapies for SIAD.

Vaptans are non-peptide antagonists of arginine vasopressin (AVP) receptors that have been shown to be useful for the treatment of hyponatraemia by selectively increasing solute-free water excretion from the kidneys. Several vaptans have been developed and tested in humans, including tolvaptan, conivaptan, mozavaptan, lixivaptan and satavaptan.³ However, the only vaptan that is

Correspondence to:
Ploutarchos Tzoulis
Department of Metabolism
& Experimental
Therapeutics, Division of
Medicine, UCL Medical
School, University College
London, Gower Street,
London WC1E 6BT, UK.
ptzoulis@yahoo.co.uk

Gregory Kaltsas
First Department of
Propaedeutic and Internal
Medicine, Laiko University
Hospital, National and
Kapodistrian University of
Athens, Athens, Greece

Stephanie E. Baldeweg
Department of Diabetes &
Endocrinology, University
College London Hospitals
NHS Foundation Trust,
London, UK

Division of Medicine,
University College London,
London, UK

Pierre-Marc Bouloux
Centre for
Neuroendocrinology,
University College London,
London, UK

Ashley B. Grossman
Green Templeton College,
University of Oxford,
Oxford, UK

Neuroendocrine Tumour
Unit, Royal Free Hospital,
London, UK

Centre for Endocrinology,
Barts and the London
School of Medicine, Queen
Mary University of London,
London, UK

currently licenced and available in Europe is tolvaptan, but its role in the treatment of SIAD has been disputed, and its place in therapeutic strategies remains unclear. This review summarises the current state of knowledge on the use of tolvaptan for hyponatraemia due to SIAD, exploring its effectiveness and safety. It also attempts to define its place in the treatment armamentarium of SIAD and to form a protocol for its optimal use in clinical practice.

It should be noted that the United States Food and Drug Administration (FDA) licence of tolvaptan for the treatment of hyponatraemia, besides SIAD, includes individuals with hypervolaemic hyponatraemia, such as those with heart failure.⁴ The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) found that tolvaptan was effective in increasing serum sodium as well as in improving dyspnoea and reducing body weight in patients hospitalised with heart failure, but with no effect on long-term mortality, cardiovascular morbidity or rehospitalisation rate.^{5,6} These findings were confirmed by a recent meta-analysis,⁷ suggesting that tolvaptan may relieve water retention, but there is not enough evidence that it improves the long-term prognosis.⁸ Interestingly, data from recent RCTs showed that tolvaptan was superior to placebo in terms of achieving rapid and persistent weight loss,^{9,10} as well as reducing dyspnoea after 3 days,⁹ but without being associated with greater improvement in dyspnoea within first day.^{9,10} Finally, recent evidence suggests that long-term tolvaptan use in patients with hyponatraemia and heart failure is associated with better renal function, possibly due to its loop diuretic dose-sparing effect.¹¹ With respect to the use of tolvaptan in patients with hyponatraemia and cirrhosis, tolvaptan is effective in increasing the serum sodium concentration, as shown in the subgroup of cirrhotic patients with hyponatraemia in SALT (Study of Ascending Levels of Tolvaptan in hyponatremia) studies¹² and in the interim results from a large post-marketing surveillance study in Japan.¹³ However, and in view of the risk for liver injury, the FDA states cirrhosis as a contraindication for tolvaptan use because of impaired ability of these patients to recover in case of hepatotoxicity. In contrast, tolvaptan has been approved in Japan for the treatment of fluid retention in liver cirrhosis, regardless of serum sodium levels, with real-world data showing a

significant reduction in body weight and improvement in related symptoms.¹⁴

Mechanism of action

Tolvaptan is an orally administered AVP antagonist used at doses between 15 and 60 mg/day, undergoes hepatic metabolism, and has an elimination half-life of 6–8 h. *In vitro* receptor-binding studies have demonstrated that tolvaptan blocks the binding of AVP to V2 receptors with 29-fold greater selectivity than that for V1a receptors, the activation of the latter promoting vasoconstriction and myocardial contractility.¹⁵ In addition, it shows no inhibition of V3 (also known as V1b) receptors,¹⁶ which are involved in AVP-related adrenocorticotrophic hormone (ACTH) release from the anterior pituitary.^{15,16} Therefore, tolvaptan, a selective V2-receptor AVP antagonist, competitively blocks the binding of vasopressin to V2 receptors located on renal collecting duct cells. As a consequence of V2 receptor inactivation, there is inhibition of the synthesis and transport of aquaporin-2 water channel proteins into the apical membrane of the collecting duct cells, resulting in a decrease in free water reabsorption.³ As shown in the SALT-1 and SALT-2 trials, which evaluated the effect of tolvaptan on euvoaemic and hypervolaemic hyponatraemia, tolvaptan resulted in an average increase in urine output of 1200 ml during the first day after its administration.⁴ Tolvaptan-induced diuresis is quantitatively similar to that induced by the intravenous administration of 20 mg furosemide,¹⁷ albeit qualitatively different to furosemide because tolvaptan leads to increased water excretion without significant increases in the excretion of urine solutes, such as sodium or potassium.³ For this reason, tolvaptan has been termed an aquaretic in contrast to classic diuretics, which are also natriuretic and kaliuretic.¹⁸ Since 2009, tolvaptan has been approved for the treatment of euvoaemic hyponatraemia due to SIAD by both the regulatory authorities in the United States (FDA) and Europe (EMA; European Medicines Agency).

RCTs on tolvaptan for treatment of SIAD

The SALT-1 and SALT-2 trials were randomised, placebo-controlled, double-blind, multi-centre, phase III trials, which randomly assigned adult patients with a serum sodium concentration of less than 135 mmol/litre to oral

tolvaptan at a starting dose of 15 mg daily ($n=225$) or placebo ($n=223$).⁴ Within 8 h after initiation of tolvaptan, the serum sodium concentration was already significantly higher in the tolvaptan group than in the placebo group, and remained persistently higher over the 30-day study period, across all ranges of hyponatraemia, while the safe limit of 12 mmol/litre/day for sodium correction was exceeded in only 1.8% of cases.⁴ Regarding the effect of tolvaptan on health status, a prespecified combined analysis of Short-Form 12 (SF-12) Health Survey showed that scores on the physical component summary did not differ significantly, whereas scores on the mental component summary significantly improved in the tolvaptan group.⁴ Subsequently, an SIAD subgroup analysis of the SALT studies confirmed a significantly greater sodium increase with tolvaptan than placebo both on days 4 and 30 (mean serum sodium change 5.3 *versus* 0.5 mmol/litre and 8.1 *versus* 1.9 mmol/litre, respectively), with a rate of 5.9% for overly rapid sodium correction.¹⁹ In the SIAD subgroup, tolvaptan-treated patients showed a significant improvement of the physical component summary in the tolvaptan group after 30 days.¹⁹ These landmark studies provided the high-quality evidence basis for authorisation of tolvaptan use for hyponatraemia by regulatory authorities across the world.

SALTWATER was a multicentre, non-randomised, open-label extension of the SALT trials, including a total of 111 tolvaptan-treated patients for a mean follow-up period of 701 days.²⁰ The short-term effect of tolvaptan on sodium levels was sustained for a 2-year period, suggesting that tolvaptan retains its efficacy long-term with an acceptable safety margin.²⁰ An RCT, addressing the use of tolvaptan for the treatment of hyponatraemia in patients with cancer, showed that a 14-day course of tolvaptan led to hyponatraemia correction, defined as serum sodium above 135 mmol/litre, in 94% of patients compared with only 8% in the placebo arm, without any cases of too rapid sodium correction.²¹ However, tolvaptan did not improve the minimal state examination score (MMSE) or the length of hospital stay.²¹ The Investigation of the Neurocognitive Impact of Sodium Improvement in Geriatric Hyponatremia: Efficacy and Safety of Tolvaptan (INSIGHT) trial, a multicentre, randomised, double-blind, placebo-controlled, parallel group trial, assessed the effect of 21-day tolvaptan therapy in patients with chronic

euvolaemic or hypervolaemic hyponatraemia on cognition and gait.²² Despite a statistically significant increase in serum sodium levels in the tolvaptan group compared with placebo (136 *versus* 132 mmol/litre on day 21, $p < 0.01$), there was no significant difference in the primary endpoint of overall neurocognitive composite score of speed domains. The only neurocognitive measure to show statistically significant improvement after tolvaptan treatment was psychomotor speed, particularly rapid motor movements.²² In addition, the tolvaptan group showed an increase in serum osteocalcin, a bone formation marker, and a decrease in the urine N-telopeptide (NTx):creatinine ratio, a bone resorption marker. Despite these changes not being statistically significant, there was a highly significant decrease in the bone resorption index, calculated as change from baseline in the urine NTx:creatinine ratio divided by change in serum osteocalcin, suggesting that long-term treatment of hyponatraemia may potentially reverse hyponatraemia-induced resorptive bone loss.²² In total, data from RCTs, summarised in Table 1, have established tolvaptan as an agent, which is efficacious in increasing serum sodium levels and is associated with a low risk for overly rapid correction. In addition, some data support tolvaptan-related improvement of symptoms and quality of life.

Real-world data on the effectiveness and safety of tolvaptan use and predictors for rapidity of hyponatraemia correction

The *Hyponatraemia Registry*, the largest observational study in this field, examined the effectiveness and safety of various treatment modalities for a serum sodium level ≤ 130 mmol/litre in diverse real-life settings, both in the United States and Europe.² Real-world data analysis of 225 tolvaptan-treated SIAD patients with median baseline serum sodium levels of 127 mmol/litre recorded a median first 24-h sodium change of 4 mmol/litre following tolvaptan initiation.¹ The effectiveness of tolvaptan was similar with that of hypertonic saline and superior to fluid restriction. Tolvaptan was also significantly more successful compared with all other therapies for achieving correction benchmarks, such as a sodium levels increase of at least 5 mmol/litre (78% success rate), final serum sodium ≥ 130 mmol/litre (74%), and sodium ≥ 135 mmol/litre (40%). Overly rapid correction of hyponatraemia occurred in 12.1% of tolvaptan-treated patients,

Table 1. Randomised controlled trials and real-life studies of efficacy and safety of tolvaptan for the treatment of hyponatraemia.

Author Country	Study type population	Baseline Na (mmol/litre)	Change in Na	Rate of overly rapid Na correction ^a	Predictors of great Na response to tolvaptan	Effect on other outcomes
Schrier <i>et al.</i> ⁴ United States and Europe	RCT Inpatients Na <135 Euvolaemic and hypervolaemic N=225 (tolvaptan) N=223 (placebo) FU: 30 days	Tolvaptan Median 128.7 Placebo Median 128.8	Day 4 Tolvaptan + 5.8 Placebo + 0.7 <i>p</i> < 0.001	Tolvaptan 1.8% Placebo 0	Marked hypoNa (Na <130) compared with mild hypoNa (Na 130–134)	Improvement in mental component summary
Verbalis <i>et al.</i> ¹⁹ United States and Europe	RCT Inpatients with SIAD N=58 (tolvaptan) N=52 (placebo) FU: 30 days		Day 4 Tolvaptan + 5.3 Placebo + 0.5 <i>p</i> < 0.001	Tolvaptan 5.9% Placebo 0	NDA	Improvement in physical (<i>p</i> =0.019) and mental (<i>p</i> =0.051) component summary
Berl <i>et al.</i> ²⁰ United States and Europe	Open-label extension of SALT studies Outpatients N=111 (tolvaptan) Mean FU: 701 days	Mean 130.8	Mean 138	NDA	NDA	NDA
Chen <i>et al.</i> ²³ China	RCT Inpatients with SIAD N=19 (tolvaptan) N=18 (placebo) FU: 7 days	Tolvaptan Mean 127.1 Placebo Mean 125.3	Day 4 Tolvaptan + 8.4 Placebo + 3.3 <i>p</i> < 0.001	NDA	NDA	NDA
Salahudeen <i>et al.</i> ²¹ United States	RCT Inpatients Na <135 With cancer Euvolaemic or hypervolaemic N=17 (tolvaptan) N=13 (placebo) FU: 14 days	Tolvaptan Median 129 Placebo Median 129	Day 14 Tolvaptan + 10.2 Placebo + 3.9 <i>p</i> < 0.001	Tolvaptan 0 Placebo 0	NDA	No significant changes on MMSE (Mini-Mental State Examination) Score and length of hospital stay
Verbalis <i>et al.</i> ²² United States	RCT Outpatients With SIAD Na 122–134 >50 years old N=29 (tolvaptan) N=27 (placebo) FU: 21 days	Tolvaptan Median 129.4 Placebo Median 129.8	Median Day 21 Tolvaptan + 7 Placebo + 2 <i>p</i> < 0.01	Tolvaptan 0 Placebo 0	NDA	No difference in neurocognitive composite score Improvement in psychomotor speed domain Decrease in bone resorption index

(Continued)

Table 1. (Continued)

Author Country	Study type population	Baseline Na (mmol/litre)	Change in Na	Rate of overly rapid Na correction ^a	Predictors of great Na response to tolvaptan	Effect on other outcomes
Verbalis <i>et al.</i> ¹ United States and Europe	Real-world HypoNa Registry SIAD Na <130 N=225 (tolvaptan)	Median 127	Median Day 1 + 4	Tolvaptan 12.1%	Lower baseline Na Marked hypoNa (Na <120)	NDA
Rajendran <i>et al.</i> ²⁴ United Kingdom	Real-world One site Inpatients SIAD Na <125 N=15	Mean 120.1	Mean Day 1 + 6.7	0	NDA	NDA
Tzoulis <i>et al.</i> ²⁵ United Kingdom	Real-world Two sites Inpatients SIAD Na <130 N=61	Mean 119.9	Mean Day 1 + 9	23%	Lower baseline Na	NDA
Humayun and Cranston ²⁶ United Kingdom	Real-world One site Inpatients SIAD Na <125 N=31	Mean 117.8	Mean Day 1 + 7.2 Day 3 + 8.9	0	NDA	NDA
Han <i>et al.</i> ²⁷ South Korea	Real-world Multi-centre Inpatients SIAD Na <135 N=39	Mean 126.8	Mean Day 1 + 6.9 Day 4 + 8.8	13%	Lower baseline Na Severe hypoNa (Na <125) Low BMI	NDA
Estilo <i>et al.</i> ²⁸ Seven European countries	Pharmacovigilance study Inpatients SIAD Na <135 N=252	Mean 123.2	Mean Day 7 + 11.8	24.6%	Lower baseline Na	Improvement in hypoNa symptoms
Umbrello <i>et al.</i> ²⁹ Italy	ICU SIAD Na <135 N=38	Mean 133	Mean Day 1 + 6.7	10.5%	Lower baseline Na Lower urine Na Lower BUN	NDA
Morris <i>et al.</i> ³⁰ United States	Inpatients SIAD Na <130 N=28	Mean 120.6	Mean Day 1 + 8.3	25%	Lower baseline Na Lower BUN	NDA

BMI, body mass index; BUN, blood urea nitrogen; FU, follow-up; ICU, intensive care unit; Na, sodium; NDA, no data available; RCT, randomised controlled trial; SALT, Study of Ascending Levels of Tolvaptan; SIAD, syndrome of inappropriate antidiuresis.

^aDefined as rise of serum sodium concentration exceeding 12 mmol/litre in the first 24 h or 18 mmol/litre in the first 48 h after tolvaptan administration

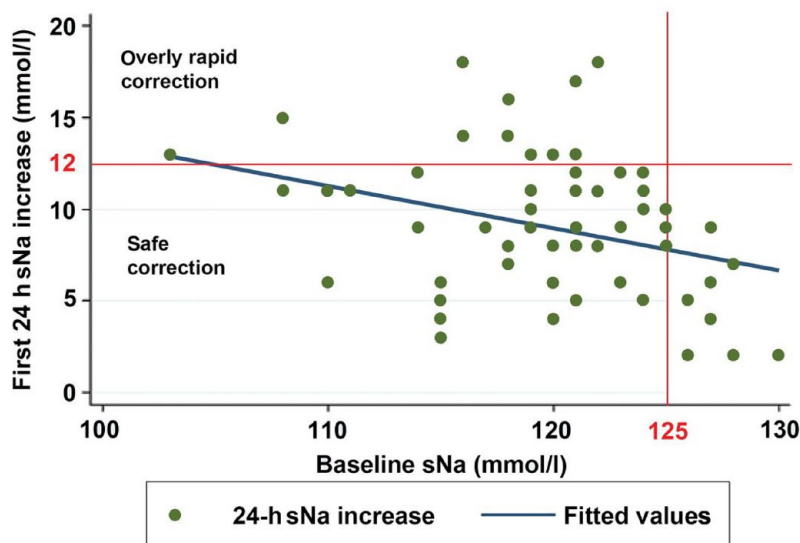


Figure 1. Linear regression between baseline serum sodium concentration (x-axis) and sodium correction in the first 24 h after initiation of tolvaptan (y-axis).

Adapted by Tzoulis *et al.*²⁵

Red vertical line indicates baseline serum sodium of 125 mmol/litre.

Red horizontal line indicates serum sodium increase of 12 mmol/litre in the first 24 h.

Correlation coefficient: -0.23 ($p=0.012$).

sNa, serum sodium.

with both the magnitude of correction and the rate of overly rapid sodium rise being higher than in RCTs.¹ Of note, the patients at greatest risk for unduly rapid sodium correction were those with severe baseline hyponatraemia, especially those with a sodium concentration <120 mmol/litre.² Subsequently, a retrospective study of 61 tolvaptan-treated SIAD patients with a mean starting sodium level of 119.9 mmol/litre reported a mean first day sodium increase of 9 mmol/litre and an unprecedented rate of overly rapid correction of 23%.²⁵ The baseline serum sodium concentration was lower compared with previous studies, while a significant negative correlation was found between baseline sodium value and its 24-h rise,²⁵ as illustrated in Figure 1.

A prospective study confirmed the inverse correlation between baseline serum sodium levels and tolvaptan-induced sodium change, but it also identified low weight and body mass index (BMI) as predictors for a more rapid sodium rise.²⁷ A prospective, observational, post-marketing, pharmacovigilance study, including 252 tolvaptan-treated patients with SIAD across several European countries, confirmed the great effectiveness of tolvaptan in sodium correction in combination with a high rate of around 25% for

overly rapid hyponatraemia correction, most commonly in those with a lower starting sodium.²⁸ The fact that the lower the baseline serum sodium concentration, the greater the magnitude of tolvaptan-induced sodium rise, was confirmed in further studies^{29,30} and may merely reflect that subjects with more severe degree of hyponatraemia have greater room for improvement.²⁹ Other biochemical parameters, such as urine sodium and blood urea nitrogen (BUN), were also identified as predictors for the rapidity of tolvaptan-induced sodium rise.^{29,30} The inverse correlation of baseline urine sodium with serum sodium rise may be explained by the competitive nature of the AVP antagonism exerted by tolvaptan, indicating that lower urine sodium represents lower degree of AVP activation and, therefore, predicting a higher response to tolvaptan.²⁹ A possible explanation for the negative correlation with BUN, an observation also shown in relation to conivaptan-induced response,³¹ is that subjects with the lowest BUN levels may have the largest increase in whole body water content, greatest extracellular fluid expansion, highest glomerular filtration rate (GFR), lowest proximal tubular reabsorption and greatest distal delivery of substrate, thereby making them more responsive to water diuresis.^{29,30} Therefore, BUN may serve as a useful

pre-treatment marker of response to vaptans, with patients with a very low BUN showing a larger sodium rise. Finally, acquired resistance to tolvaptan has rarely been described and has been attributed to escalating plasma AVP concentrations in the setting of progression of malignant disease, competing with tolvaptan at AVP kidney receptors.³²

In summary, several real-world studies have reported a substantial risk of overly rapid hyponatraemia correction, estimated at around 25% for individuals with a starting serum sodium of 120 mmol/litre.^{25,28,30} This significantly greater magnitude of sodium rise in real-life data compared with RCTs, as summarised in Table 1, is most likely explained by real-life tolvaptan use in individuals with much lower baseline serum sodium levels. The underlying explanation may be that patients starting with lower serum sodium have higher volumes of excess body water, which becomes available for renal excretion after tolvaptan administration, leading to a more pronounced aquaresis and a greater increase in serum sodium.

Efficacy and safety of low tolvaptan doses

The high therapeutic potency of tolvaptan is associated with a risk of unduly rapid correction of hyponatraemia, raising concerns about the likelihood of osmotic demyelination syndrome (ODS), a severe neurological condition associated with rapid increase of serum sodium levels. Tolvaptan doses, which are lower than the formally approved 15 mg starting dose, have been successfully used for other indications, such as an adjunct to standard treatment in symptomatic heart failure.^{33,34} A case series of 11 patients with paraneoplastic SIAD, who were treated with a low (7.5 mg) tolvaptan dose and achieved normonatraemia without any cases of too rapid sodium correction, in 2011 provided the first evidence that lower than suggested tolvaptan doses may be an effective and safe treatment, at least for malignant SIAD.³⁵ Following this report, several research groups have reported their real-world experience on the effectiveness and safety of low-dose tolvaptan for the treatment of SIAD. The largest study to date of low-dose tolvaptan reported the outcomes of using a starting 7.5 mg tolvaptan dose in 55 patients with malignant SIAD and a mean baseline serum sodium of 117.9 mmol/litre.³⁶ After the initiation of tolvaptan, the median serum sodium increase was 9 and 10 mmol/litre at 24

and 72 h, respectively, with the vast majority of patients (87.3%) achieving a serum sodium rise of at least 5 mmol/litre over 48 h. However, the high efficacy of low-dose tolvaptan was accompanied by a high rate (30.9%) of overly rapid hyponatraemia correction.³⁶

Post-marketing assessments of tolvaptan use in Europe have reported that a significant proportion of physicians use a low 7.5 mg tolvaptan starting dose on a patient-by-patient case basis, with the hope of lowering the risk of overly rapid sodium correction.^{37,38} All real-world studies suggest that a starting 7.5 mg dose, half the approved initiation dose of tolvaptan, is effective in treating hyponatraemia. With respect to the risk of overly rapid sodium correction, some studies suggest that a low dose may reduce it,^{35,39–41} whereas other studies still report high rates of too rapid correction.^{25,28,36,37,42} Critical review of these data suggests that tolvaptan at a 7.5 mg dose seems to be still associated with a substantial risk for overly rapid sodium correction, especially in individuals with more severe hyponatraemia and a basal serum sodium level below 120 mmol/litre.^{36,37} Finally, an even lower starting tolvaptan dose of 3.75 mg has been used anecdotally by some clinicians, but the only available data from 10 individuals in a pharmacodynamic study does not allow us to draw any conclusion about its efficacy and safety.³⁷ As a result, and until higher quality data become available, we recommend considering the use of 7.5 mg starting tolvaptan dose for patients with SIAD and a low baseline serum sodium <125 mmol/litre (see Table 2).

The position of tolvaptan in guidelines for the treatment of SIAD

In 2013, an expert panel published their recommendations for the evaluation and treatment of hyponatraemia,¹⁸ suggesting the use of vaptans as second-line therapy for SIAD after fluid restriction, but also as first-line therapeutic option in cases when fluid restriction cannot be adhered to or is unlikely to be effective.¹⁸ The authors of these recommendations favoured tolvaptan over other agents since tolvaptan has been the only pharmacological agent widely approved by the regulatory authorities with well-established efficacy in correcting hyponatraemia and a good safety record, while alternative therapies have a very limited evidence base for their efficacy and safety.¹⁸ Considering the paucity of data on

Table 2. Studies evaluating the efficacy and safety of low tolvaptan dose for the treatment of SIAD.

Author Country	Study type population	Low dose tolvaptan 7.5 mg initial Na	Change in Na	Rate of overly rapid Na correction*	Standard dose comparator	Conclusion
Kenz <i>et al.</i> ³⁵ United Kingdom	Case series Inpatients Na ≤126 Malignant SIAD	N=11 110–126	9/11 normal 7.5 mg on alternate days 2/11 needed higher dose	Low dose 0/11 <i>versus</i> standard dose 2/2	N = 2 2/2 too rapid correction	Effective Lower risk of rapid correction
Tzoulis <i>et al.</i> ²⁵ United Kingdom	Case series Inpatients Na <125 SIAD	N=6 Mean 115.3	Day 1 Mean + 9.8	Low dose 1/6 (16.6%) <i>versus</i> standard dose 10/43 (23.2%)	N=43 Mean 118.7 Day 1 Mean + 9.9 (<i>p</i> =0.989)	Effective Similar risk of rapid correction
Harbeck <i>et al.</i> ³⁹ Germany	Case series Inpatients Na <130 SIAD	N=22 Mean 124.0	Day 1 Mean + 6.0	Low dose 0/22 (0) <i>versus</i> standard dose 2/15 (13.3%)	N=15 Mean 120.4 Day 1 Mean + 6.5 Not significant	Effective Lower risk of rapid correction
Castello <i>et al.</i> ⁴⁰ Italy	Case series Inpatients Na <130 SIAD or hypervolaemic hypoNa	N=11 Mean 124	Day 1 Mean + 6	Low dose 0/11 <i>versus</i> standard dose 5/12 (41.3%) <i>p</i> =0.037	N=12 Mean 125 Day 1 Mean + 12 <i>p</i> =0.025	Effective Lower risk of rapid correction
Shoaf <i>et al.</i> ³⁷ United States/ Europe	RCT Inpatients Na 120–133 SIAD	N=10 Mean 129.7	Day 1 Mean + 5.3 Very low dose 3.75 N=10 Day 1 + 3.6	Low dose 1/10 (10%) <i>versus</i> standard dose 2/8 (25%) <i>versus</i> very low dose 1/10 (10%)	N=8 Mean 127.9 Day 1 Mean + 7.9	Lower dose will not reduce risk for too rapid correction
Barajas-Galindo <i>et al.</i> ⁴² Spain	Case series Inpatients Na <135 SIAD	N=9 Mean 125	Day 1 Mean + 5	Low dose 50% <i>versus</i> standard dose 25% <i>p</i> =0.501	N=7 Mean 125 Day 1 Mean + 5	Effective Similar risk of rapid correction
Hanna <i>et al.</i> ⁴¹ United States	Retrospective study Na <135 SIAD	N=18 Mean 123.7	Day 1 Mean + 5.6	Low dose 1/18 (5.6%) <i>versus</i> standard dose 8/28 (28.6%) <i>p</i> =0.07	N=28 Mean 120.6 Day 1 Mean + 8.3 <i>p</i> =0.1	Effective Lower risk of rapid correction
Estilo <i>et al.</i> ²⁸ Seven European countries	Pharmacovigilance study Inpatients Na <135 SIAD	N=106	Day 7 Mean + 7.3		N=189 Day 7 Mean + 11.8	Effective Similar efficacy of different doses
Chatzimavridou- Grigoriadou <i>et al.</i> ³⁶ United Kingdom	Retrospective study Na <130 Malignant SIAD	N=55 Mean 117.9	Day 1 Median + 9	Low dose 17/55 (30.9%)	No comparator	Effective High risk of rapid correction

Na, sodium; RCT, randomised controlled trial; SIAD, syndrome of inappropriate antidiuresis.

*Defined as rise of serum sodium concentration exceeding 12 mmol/litre in the first 24 h or 18 mmol/litre in the first 48 h after tolvaptan administration

tolvaptan use for severe hyponatraemia, they advised that one should use tolvaptan with caution and under stringent monitoring in cases with a serum sodium below 120 mmol/litre.¹⁸

A few months later, in 2014, a clinical practice guideline on treatment of hyponatraemia, developed as a joint venture of the *European Society of Endocrinology* (ESE), the *European Renal Association – European Dialysis and Transplant Association* (ERA-EDTA) and the *European Society of Intensive Care Medicine* (ESICM), did not recommend the use of tolvaptan for the treatment of SIAD.⁴³ They concluded that tolvaptan had a negative risk–benefit ratio because of the absence of proven hard clinical outcome benefit in combination with safety concerns about the risk of overly rapid sodium correction and potential hepatotoxicity. In fact, they specifically recommended against the use of vaptans in patients with a serum sodium <125 mmol/litre because of the high risk of over-rapid hyponatraemia correction in this subgroup. The overarching principle of the European guidelines was the absence of concrete evidence that correcting hyponatraemia itself improves patient-important outcomes, while active hyponatraemia treatment carries the risk of unduly rapid correction, which may expose patients to the risk of ODS with potentially devastating neurological sequelae.⁴³ Instead of vaptans, the authors of the European guidelines recommended as equal second-line treatment options oral urea or a combination of low-dose loop diuretic with oral sodium chloride.⁴³

Urea, an osmotic agent, which through water diuresis increases serum sodium concentration,⁴⁴ has been shown to be effective in the treatment of hyponatraemia.^{45,46} However, oral urea is not routinely used because of its poor palatability and the lack of an approved preparation. With regards to other therapeutic options for SIAD, demeclocycline is a tetracycline derivative licenced in the United Kingdom for the treatment of malignant SIAD, but its use is nowadays limited due to its unpredictable efficacy, slow onset of action and concerns regarding nephrotoxicity.⁴⁷ Finally, a well-known anti-diabetic medication, empagliflozin, has recently emerged as a promising novel treatment option for SIAD since sodium-glucose co-transport 2 (SGLT-2) inhibition increases urinary free water excretion.⁴⁸ Two small RCTs have shown that empagliflozin is effective in increasing serum sodium in inpatients as an

add-on to fluid restriction⁴⁹ as well as in outpatients as monotherapy.⁵⁰

This decision of the *European Clinical Practice Guidelines* not to recommend a place for tolvaptan within its licenced indication for SIAD, despite being the only pharmacological therapy approved across three continents for the treatment of SIAD, was highly controversial. The main arguments against this negative recommendation were that the negative benefit–risk profile was based on vaptans in general rather than tolvaptan; that only one case of tolvaptan-induced ODS had been reported globally despite cases of too rapid sodium correction; and that tolvaptan, in contrast to other therapeutic modalities, had been subjected to the rigours of a regulatory process and the scrutiny of RCTs.⁵¹ The European guidelines were also heavily criticised by a group of endocrinologists who argued that the exclusion of tolvaptan could remove the most evidence-based treatment option for SIAD from the armamentarium of physicians, constituting a disservice to patients.⁵² The main counter-argument on behalf of the European guideline development group was that they considered only patient-relevant hard outcomes.⁵³ Therefore, they could not recommend tolvaptan on the basis of improving a surrogate marker, such as serum sodium levels, since there was no proof that tolvaptan-induced sodium increase results in a meaningful change in such ‘hard’ patient-relevant outcomes.⁵³ Despite the divergence in recommendations between various guidelines, there has been unanimous agreement between authors of all guidelines on the lack of high-quality evidence in the field of hyponatraemia.^{43,54}

Besides the disagreement between the European guidelines⁴³ and US expert panel recommendations¹⁸ concerning the role of tolvaptan in clinical practice, several other guidelines from various professional organisations have been published, all recognising tolvaptan as a valuable pharmacological therapy for the treatment of SIAD.^{47,55} Two different algorithms, developed by a Spanish multidisciplinary group⁵⁵ and a group of senior UK clinicians with a special interest in hyponatraemia,⁴⁷ recommended the use of tolvaptan in patients with SIAD and mild-to-moderate symptoms, either as second-line treatment after failure to respond to 48-h fluid restriction or as first-line therapy when fluid restriction is not feasible or is predicted to fail, for example, when the urine/plasma electrolyte ratio is >1.^{47,55} In addition, an

Italian Task Force, generated by the *Italian Societies of Endocrinology, Nephrology and Oncology*, has recommended the use of tolvaptan in SIAD, either as first-line therapy for moderate symptoms or second-line therapy for mild symptoms.⁵⁶ Finally, the most recent guidance, published in 2022 by the *South Korean Society of Nephrology*, also recommends tolvaptan as second-line therapy for hyponatraemia due to SIAD.⁵⁷

Current role of tolvaptan in the management of SIAD

With the exception of the European guidelines,⁴³ all other published recommendations and consensus statements^{18,47,55–57} recommend tolvaptan as a second-line treatment option for SIAD in patients who do not respond to fluid restriction. Tolvaptan may also be used as a first-line agent in SIAD patients who are unlikely to respond to fluid restriction due to very limited renal excretion of solute-free water.³ Current data do not support the use of tolvaptan in patients with severe symptoms of hyponatraemia.⁵⁸ Mechanistically, tolvaptan offers an elegant and attractive treatment option for euvoalaemic hyponatraemia since it specifically reverses its pathophysiologic derangement.⁵⁹ However, for now, clinicians must rely on good judgement rather than unequivocal evidence to decide which patients with hyponatraemia should be given tolvaptan.⁶⁰ The reason for this is that the landmark SALT⁴ and SALTWATER²⁰ studies have provided high-quality evidence that tolvaptan is effective in correcting hyponatraemia, but they were not designed or powered enough to assess improvement in symptoms or survival, raising the key unanswered question whether treatment of hyponatraemia can improve hard endpoints.⁶⁰ Since the key question whether tolvaptan can improve patient-related clinical outcomes has not been answered as yet, tolvaptan cannot comprise the mainstay of therapy for SIAD.⁶¹ There is also considerable uncertainty as to which symptoms and what degree of severity of hyponatraemia should be considered indications for tolvaptan treatment.⁶¹ The current place of tolvaptan in the therapeutic armamentarium for treating SIAD is indeed heavily influenced by ‘expert opinions’. In total, despite its well-known efficacy in hyponatraemia correction, the risk of overly rapid sodium correction in combination with the high cost of tolvaptan have prohibited its widespread use. Thus, in most European countries, tolvaptan

is sparingly used in highly selected cases and for a limited duration. The extent to which tolvaptan might replace fluid restriction as first-line therapy will be predicated upon additional data about the cost-benefit ratio of these therapies.

Hepatotoxicity of tolvaptan

In 2013, the FDA issued a caution that tolvaptan-related hepatic injury had occurred in some patients being treated with tolvaptan in the TEMPO 3:4 trial, a multicentre, double-blind, placebo-controlled, 3-year trial, examining the effect of tolvaptan on autosomal dominant polycystic kidney disease (ADPKD).⁶² Three out of 957 ADPKD tolvaptan-treated patients developed severe liver injury and jaundice, which were probably caused by tolvaptan and were reversed on discontinuation of tolvaptan. Nevertheless, there were no reports of liver failure and all subjects experiencing hepatic injury recovered.⁶³ Since then, the FDA has recommended limiting the duration of tolvaptan treatment to 30 days, avoiding its use in patients with underlying liver disease, and discontinuing it if a patient develops signs of liver disease. On the contrary, the EMA has not suggested any restriction on the duration of tolvaptan treatment for SIAD.

With respect to the potential hepatotoxicity of tolvaptan, three points should be highlighted. First, the average daily tolvaptan dose in the TEMPO study (95 mg) was much higher than commonly used doses (15–30 mg) for SIAD. Second, the earliest case of serious liver damage was reported 3 months after starting tolvaptan treatment, indicating that liver toxicity is unlikely to occur with short-term use.^{62,63} Third, cases of liver damage have not been reported in clinical trials of tolvaptan treatment for hyponatraemia, not even in those with long follow-up, such as the SALTWATER²⁰ and EVEREST⁵ trials. In addition, tolvaptan has been approved in Japan for patients with liver cirrhosis, with post-marketing surveillance data showing a good safety profile.¹³ The absence of a liver safety signal in non-ADPKD patients treated with tolvaptan for hyponatraemia may suggest enhanced susceptibility of the ADPKD population to tolvaptan-associated liver injury,⁶³ indicating a minimal, if any, risk of tolvaptan-induced liver injury in the vast majority of patients with SIAD. Therefore, patients with SIAD remain candidates for long-term tolvaptan therapy if the benefit of tolvaptan

treatment outweighs the risks and they are either refractory or unable to tolerate other therapies for hyponatraemia.¹⁸ In such cases, caution should be exercised and there is no evidence-based algorithm for the optimal monitoring of liver function. Taking into account the prescribing information for tolvaptan in ADPKD patients as well as the lower risk for liver injury in tolvaptan use for SIAD, in our opinion transaminases and bilirubin should be measured prior to tolvaptan initiation, two weeks after and subsequently every 1–2 months.

Cost-effectiveness of tolvaptan

Taking into account that the annual direct costs of treating hyponatraemia in the United States have been estimated to range between US\$1.6 and US\$3.6 billion, with hospitalisation accounting for approximately 70% of the total costs,⁶⁴ it is essential to evaluate the impact of tolvaptan use on the costs associated with this condition. Based on a trend noticed in the SALT trials towards a reduced length of stay in the tolvaptan group (mean 4.98 days) compared with the placebo group (mean 6.19 days),¹⁹ a cost-offset model demonstrated that, despite the incremental cost of tolvaptan therapy, tolvaptan use resulted in an estimated mean US\$694 cost savings per admission among SIAD patients in the United States.⁶⁵ Based on real-world data from the Hyponatraemia Registry, and after factoring both the decrease in hospital costs and the increase in tolvaptan-related pharmacy costs, the same group concluded that tolvaptan is related to lower hospital-related costs than fluid restriction, indicating a cost-offset opportunity of US\$2296 per admission of patient with hyponatraemia.⁶⁶ From the European perspective, taking into consideration a reduction in length of hospitalisation observed in tolvaptan-treated patients in the SIAD population of the SALT studies,¹⁹ tolvaptan was associated with reduced costs (equivalent to €624 per patient) in adult patients with SIAD.⁶⁷ These studies have provided evidence that tolvaptan, on the basis of reduction of length of hospital stay, could represent a cost-effective treatment option for SIAD.^{65–67}

Key areas for further research in the use of tolvaptan

The first key, as yet unresolved, question remains regarding the clinical benefit of tolvaptan. Can

tolvaptan-mediated hyponatraemia correction improve hard clinical outcomes? This highlights the need for prospective studies, which will assess whether tolvaptan can save lives or improve quality of life or, at least, save money through shortening duration of hospitalisation.⁶¹ Given the dearth of evidence in many aspects of the management of hyponatraemia, our priority should be to undertake RCTs, exploring the key hypothesis that correction of hyponatraemia in the acute setting translates into improvement of patient-important outcomes, such as mortality, length of hospital stay, need for re-admission, and symptomatology. Similarly, in the outpatient setting, we need to evaluate whether long-term treatment of chronic hyponatraemia will result in improved neurocognitive function, quality of life and functional status, and whether correction of chronic hyponatraemia can improve bone mineral density, prevent falls and reduce fracture rates. So, we believe it is the time for a major paradigm shift, changing the endpoints of hyponatraemia studies from surrogate outcomes, such as magnitude of increase in serum sodium concentration, to real clinical outcomes, such as mortality and morbidity. Regulatory authorities, such as the FDA and EMA, should reinforce a transformation of pharmaceutical studies in the field of SIAD, by evaluating and approving drugs for hyponatraemia based on their ability to improve hard clinical outcomes. The new approach should follow that in the field of lipid-lowering medications, where regulatory authorities have demanded over the last 20 years from pharmaceutical companies and investigators that they design studies with endpoint cardiovascular events rather than simply lowering cholesterol values. In conclusion, multicentre prospective controlled studies are urgently warranted to evaluate whether tolvaptan-related sodium increase can improve hard clinical outcomes, demonstrating the future role of tolvaptan use for SIAD.

Second, the need for comparison head-to-head studies between different therapeutic options for SIAD, which was already highlighted in 2014,^{18,43} has not as yet been met, with the exception of a small prospective study comparing the efficacy and safety of vaptans with oral urea in patients with SIAD.⁶⁸ Prospective studies should compare tolvaptan *versus* other therapies, such as fluid restriction and urea, not only with regard to their ability to correct hyponatraemia, but also to alter patient-related outcomes and safety. Taking into

account the heterogeneity of SIAD, further studies are also warranted to evaluate the therapeutic role of tolvaptan in homogeneous cohorts, for example, in malignant SIAD or in neurosurgical settings, since tolvaptan may translate into reduced length of hospitalisation and use of hospital resources in these subgroups.

The third research question relates to the main safety concern of tolvaptan, the likelihood for overly rapid hyponatraemia correction. Specifically, we need to establish the effectiveness and safety of tolvaptan in patients with very low serum sodium, for example, below 120 mmol/litre, who are most in need of hyponatraemia correction, and at the same time are exposed to the greatest risk of overcorrection. What is the magnitude of this risk when tolvaptan is used under stringent protocols, encompassing close electrolyte/fluid balance monitoring and measures to halt/reverse too rapid correction? In the era of personalised medicine, large prospective studies are warranted to demonstrate the parameters that can predict the magnitude of response to tolvaptan and are associated with high likelihood for over-rapid sodium correction. These data would provide the evidence basis for the development of a risk calculator for tolvaptan-related overly rapid sodium increase, individualising the starting dose and monitoring of tolvaptan. Various protocols of tolvaptan initiation, titration, monitoring and corrective measures should be prospectively tested to develop an algorithm for tolvaptan use, readily applicable to clinical practice, achieving maximal drug efficacy and safety. For example, an open-label randomisation trial is in progress, randomising patients with non-hypovolaemic hyponatraemia to receive either 7.5 mg tolvaptan or fluid restriction imposed at 1000 ml/day, testing the hypothesis that tolvaptan can improve the rate of sodium correction as well as clinical outcomes, without exposing the patients at high risk of serum sodium overcorrection.⁶⁹ These studies will determine the utility of tolvaptan in clinical practice and provide an evidence-based framework for tolvaptan administration and monitoring.

The fourth question, that of optimal tolvaptan dose, remains topical, since it has so far been addressed only in retrospective studies with small cohorts. There has been criticism that tolvaptan, initiated at the current approved dose of 15 mg,

can often lead to overly rapid sodium correction through profound aquaresis. This raises the question as to whether tolvaptan may in some cases act as 'a cannon rather than a magic bullet' and highlights the need for a precision low-calibre weapon needed to treat hyponatraemia in an effective and safe manner.³⁸ For this reason, large prospective studies are needed to compare the efficacy and safety of lower tolvaptan doses, such as 7.5 and 3.75 mg, with the 'approved' starting dose of 15 mg, across different levels of baseline hyponatraemia.

Our recommendations about tolvaptan use

We recommend individualising treatment of SIAD, based on a benefit–risk analysis for each patient and several individual factors, including chronicity of hyponatraemia, aetiology of SIAD, comorbidities, symptoms and biochemical parameters.

We promote the use tolvaptan as the main pharmacotherapy for SIAD for the following reasons:

1. Tolvaptan is, undoubtedly, highly efficacious in correcting hyponatraemia. Evidence that tolvaptan improves hard clinical outcomes is currently lacking, but this applies to all treatment options for SIAD. Therefore, using our clinical judgement on a case-by-case basis, we decide whether each individual is likely to benefit from increasing serum sodium levels.
2. Tolvaptan is the sole treatment modality licenced for the treatment of SIAD in the United States and Europe, having undergone stringent review of risk–benefit balance by the regulatory authorities and based on high-quality evidence basis for efficacy and safety. On the contrary, the use of other agents is supported by low-quality data, derived primarily from retrospective uncontrolled studies and case series.
3. Regarding concerns about tolvaptan-related overly rapid hyponatraemia correction, greater effectiveness is associated with a higher risk for too rapid correction. However, it can be substantially reduced, provided patients undergo rigorous monitoring at frequent intervals and specific measures are implemented, when need arises, to prevent, or even reverse, overly rapid correction.

We recommend the use of tolvaptan for treatment of SIAD, mainly in hospitalised patients, and also in selected outpatients. The four scenarios of tolvaptan use are illustrated below.

1. As second-line therapy, after failure of patient to respond to at least 48-h fluid restriction.
2. As first-line therapy in selected cases when there is a clinical need for prompt correction of hyponatraemia. Classic examples are the need to render a patient fit for surgery or its use in patients with malignant SIAD who are waiting to start chemotherapy with drugs, which either can worsen hyponatraemia by themselves, such as platinum-based agents, or require infusion of large volumes of fluids.
3. As first-line therapy in patients who are highly unlikely to respond to fluid restriction, for example, when urine osmolality exceeds 500 mOsm/kg or the urine/plasma electrolyte ratio is above 1.¹⁸
4. For chronic use in outpatients. This only applies to selected complex cases who are either refractory or cannot adhere to other treatment modalities. A classic clinical scenario is that of patients with refractory malignant SIAD, most often due to lung cancer, who would otherwise require recurrent hospitalisations and experience a poor quality of life.

Based on the summary of product characteristics for tolvaptan and existing literature,^{3,18} we propose the following algorithm for the initiation of tolvaptan:

- Confirm the diagnosis of SIAD and exclude hypovolaemic hyponatraemia.
- Initiate tolvaptan only as an inpatient.
- To be prescribed and supervised only by an endocrinologist or nephrologist with a special interest in the field.
- Discontinue any concomitant therapy for hyponatraemia, such as fluid restriction, and wait at least 6 h after cessation of hypertonic saline infusion.
- Maintain *ad libitum* (as desired) fluid intake, after ensuring intact thirst and free access to fluids, since patient's thirst and fluid intake act as a 'break' on sodium rise.
- Do not administer tolvaptan in patients receiving strong CYP3A4 inhibitors

(grapefruit, ketoconazole, clarithromycin, protease inhibitors), while use with great caution a lower dose of 7.5 mg in case of concomitant administration of a moderate CYP3A4 inhibitor (fluconazole, erythromycin, diltiazem, verapamil).

- Initiate tolvaptan as a single stat dose in the early morning to facilitate face-to-face review within the first 6–8 h of initiation.
- Start tolvaptan at a dose of 15 mg for baseline serum sodium ≥ 125 mmol/litre and at a lower 'off label' dose of 7.5 mg for serum sodium < 125 mmol/litre in view of the high rate of overly rapid correction in severe hyponatraemia.

We follow a stringent protocol^{18,36,69} for the first 24 h of tolvaptan use:

- Monitor serum sodium 6-hourly (baseline, 6, 12, 18 and 24 h after initial dose).
- Keep an accurate fluid balance chart, recording fluid input and urine output at 2-h intervals.
- If 6-h sodium rise exceeds 6 mmol/litre or 12-h sodium rise exceeds 8 mmol/litre or 18-h sodium rise exceeds 10 mmol/litre or urine output exceeds 200 ml/h for two consecutive hours, notify the clinical team in charge of tolvaptan therapy and intensify monitoring. Halt further correction by administration of intravenous infusion of dextrose 5% at a rate equal to urine output or, alternatively, administer desmopressin 2 μ g as a stat dose intravenously and after 8 h.
- If the sodium rise is even more pronounced, requiring reversal of overly rapid correction, there are two ways for re-lowering serum sodium. The first regimen is intravenous infusion of dextrose 5% at a rate of 6–10 ml/kg over 2 h, recheck serum sodium in 2 h, and, if needed, continue infusion until target serum sodium is reached. Alternatively, administer desmopressin 2 μ g intravenously plus an intravenous infusion of dextrose 5% in water at a rate of 3–5 ml/kg over 2 h, recheck serum sodium in 2 h, and, if needed, continue infusion until the target sodium is reached.

Following the first day after tolvaptan initiation, the preferred strategy for most patients, especially those who receive active treatment for the underlying aetiology of SIAD, is daily evaluation and

decision to offer stat doses on a day-to-day basis, if and when required, since two to four doses in total are adequate treatment for most inpatients with SIAD of short duration.⁴⁷ Tolvaptan dose titration usually takes place during hospitalisation according to the serum sodium concentration. In patients with SIAD of long, or even indefinite, duration, daily tolvaptan administration as a repeat prescription can be considered. The tolvaptan dose can also be safely up-titrated on outpatient basis since the risk of overly rapid sodium correction applies to the first 48 h following tolvaptan initiation.

A suggested approach for the second tolvaptan dose is:

1. When the first 24-h serum sodium rise is 9 mmol/litre or above, withhold the next tolvaptan dose.
2. When it is 5–8 mmol/litre, continue the same tolvaptan dose.
3. When the first 24-h sodium rise is <5 mmol/litre, up-titrate the tolvaptan dose to 30 mg (if the initial dose was 15 mg) or 15 mg (if initial dose was 7.5 mg).

Conclusion

In view of the high-quality evidence that tolvaptan is a highly efficacious agent in increasing the serum sodium concentration, most guidelines, with exception of the European ones, recommend it as second-line treatment of hyponatraemia due to SIAD. The future use of tolvaptan and other pharmacotherapies for hyponatraemia will be determined to a great extent by prospective studies, evaluating its effect on patient-related outcomes, such as mortality and length of hospital stay in the acute setting, as well as neurocognition and quality of life in the chronic setting. The second key issue is related to the risk of overly rapid sodium correction, especially in patients with severe hyponatraemia. To address this safety issue, prospective studies are warranted to assess whether low starting doses of tolvaptan could reduce the risk for an unduly rapid correction of hyponatraemia and at the same time retain its efficacy. The development of risk calculators for overt sodium correction, incorporating clinical and biochemical parameters, would also be of paramount importance to facilitate clinical decision-making and the safe use of tolvaptan in routine care. Furthermore, there is an unmet need

for evidence-based protocols for tolvaptan initiation, dose titration and monitoring with established efficacy and safety, across different levels of severity for baseline hyponatraemia. Finally, the high cost of tolvaptan has been a key barrier to its routine use in clinical practice. Following the recent patent expiry of tolvaptan, the availability of tolvaptan as a generic medication may lead to a more attractive price to mitigate the substantial financial burden related to the care of hyponatraemic patients.⁷⁰ In total, all these factors will define the future role of tolvaptan in the treatment of hyponatraemia.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Ploutarchos Tzoulis: Conceptualisation; Data curation; Formal analysis; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

Gregory Kaltsas: Formal analysis; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Stephanie E. Baldeweg: Data curation; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Pierre-Marc Bouloux: Resources; Validation; Writing – original draft; Writing – review & editing.

Ashley B. Grossman: Conceptualisation; Resources; Validation; Writing – original draft; Writing – review & editing.

Acknowledgements

Not applicable.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

ORCID iD

Ploutarchos Tzoulis  <https://orcid.org/0000-0003-4228-071X>

References

1. Verbalis JG, Greenberg A, Burst V, *et al.* Diagnosing and treating the syndrome of inappropriate antidiuretic hormone secretion. *Am J Med* 2016; 129: 537.e9–537.e23.
2. Greenberg A, Verbalis JG, Amin AN, *et al.* Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int* 2015; 88: 167–177.
3. Peri A. Clinical review: the use of vaptans in clinical endocrinology. *J Clin Endocrinol Metab* 2013; 98: 1321–1332.
4. Schrier RW, Gross P, Gheorghiade M, *et al.* Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 2006; 355: 2099–2112.
5. Konstam MA, Gheorghiade M, Burnett JC Jr, *et al.* Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007; 297: 1319–1331.
6. Gheorghiade M, Konstam MA, Burnett JC Jr, *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: 1332–1343.
7. Wang L, Zhang Q, Liu M, *et al.* Tolvaptan in reversing worsening acute heart failure: a systematic review and meta-analysis. *J Int Med Res* 2019; 47: 5414–5425.
8. Ishikawa SE and Funayama H. Hyponatremia associated with congestive heart failure: involvement of vasopressin and efficacy of vasopressin receptor antagonists. *J Clin Med* 2023; 12: 1482.
9. Konstam MA, Kiernan M, Chandler A, *et al.* Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol* 2017; 69: 1409–1419.
10. Felker GM, Mentz RJ, Cole RT, *et al.* Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017; 69: 1399–1406.
11. Oka T, Hamano T, Ohtani T, *et al.* Renoprotection by long-term low-dose tolvaptan in patients with heart failure and hyponatremia. *ESC Heart Fail* 2021; 8: 4904–4914.
12. Cárdenas A, Ginès P, Marotta P, *et al.* Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. *J Hepatol* 2012; 56: 571–578.
13. Sakaida I, Terai S, Kurosaki M, *et al.* Effectiveness and safety of tolvaptan in liver cirrhosis patients with edema: interim results of post-marketing surveillance of tolvaptan in liver cirrhosis (START study). *Hepatol Res* 2017; 47: 1137–1146.
14. Sakaida I, Terai S, Kurosaki M, *et al.* Real-world effectiveness and safety of tolvaptan in liver cirrhosis patients with hepatic edema: results from a post-marketing surveillance study (START study). *J Gastroenterol* 2020; 55: 800–810.
15. Greenberg A and Verbalis JG. Vasopressin receptor antagonists. *Kidney Int* 2006; 69: 2124–2130.
16. Miyazaki T, Fujiki H, Yamamura Y, *et al.* Tolvaptan, an orally active vasopressin V(2)-receptor antagonist – pharmacology and clinical trials. *Cardiovasc Drug Rev* 2007; 25: 1–13.
17. Ohnishi A, Orita Y, Okahara R, *et al.* Potent aquaretic agent. A novel nonpeptide selective vasopressin 2 antagonist (OPC-31260) in men. *J Clin Invest* 1993; 92: 2653–2659.
18. Verbalis JG, Goldsmith SR, Greenberg A, *et al.* Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013; 126(Suppl 1): S1–S42.
19. Verbalis JG, Adler S, Schrier RW, *et al.* Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Endocrinol* 2011; 164: 725–732.
20. Berl T, Quittnat-Pelletier F, Verbalis JG, *et al.* Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* 2010; 21: 705–712.
21. Salahudeen AK, Ali N, George M, *et al.* Tolvaptan in hospitalized cancer patients with hyponatremia: a double-blind, randomized, placebo-controlled clinical trial on efficacy and safety. *Cancer* 2014; 120: 744–751.
22. Verbalis JG, Ellison H, Hobart M, *et al.* Tolvaptan and neurocognitive function in mild to moderate chronic hyponatremia: a randomized trial (INSIGHT). *Am J Kidney Dis* 2016; 67: 893–901.
23. Chen S, Zhao JJ, Tong NW, *et al.* Randomized, double blinded, placebo-controlled trial to

- evaluate the efficacy and safety of tolvaptan in Chinese patients with hyponatremia caused by SIADH. *J Clin Pharmacol* 2014; 54: 1362–1367.
24. Rajendran R, Grossman AB and Kar P. Vasopressin receptor antagonist in the treatment of the syndrome of inappropriate antidiuretic hormone in general hospital practice. *Endocr J* 2012; 59: 903–909.
 25. Tzoulis P, Waung JA, Bagkeris E, *et al.* Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion. *Clin Endocrinol (Oxf)* 2016; 84: 620–626.
 26. Humayun MA and Cranston IC. In-patient Tolvaptan use in SIADH: care audit, therapy observation and outcome analysis. *BMC Endocr Disord* 2017; 17: 69.
 27. Han SW, Yi JH, Kang KP, *et al.* Safety and efficacy of tolvaptan in Korean patients with hyponatremia caused by the syndrome of inappropriate antidiuretic hormone. *J Korean Med Sci* 2018; 33: e112.
 28. Estilo A, McCormick L and Rahman M. Using tolvaptan to treat hyponatremia: results from a post-authorization pharmacovigilance study. *Adv Ther* 2021; 38: 5721–5736.
 29. Umbrello M, Mantovani ES, Formenti P, *et al.* Tolvaptan for hyponatremia with preserved sodium pool in critically ill patients. *Ann Intensive Care* 2016; 6: 1.
 30. Morris JH, Bohm NM, Nemecek BD, *et al.* Rapidity of correction of hyponatremia due to syndrome of inappropriate secretion of antidiuretic hormone following tolvaptan. *Am J Kidney Dis* 2018; 71: 772–782.
 31. Velez JC, Dopson SJ, Sanders DS, *et al.* Intravenous conivaptan for the treatment of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone in hospitalized patients: a single-centre experience. *Nephrol Dial Transplant* 2010; 25: 1524–1531.
 32. Garrahy A, Hannon AM, Zia-Ul-Hussnain HM, *et al.* Secondary resistance to tolvaptan in two patients with SIAD due to small cell lung cancer. *Eur J Clin Pharmacol* 2018; 74: 245–246.
 33. Okabe T, Yakushiji T, Igawa W, *et al.* The efficacy of tolvaptan in congestive heart failure patients with and without hypoalbuminemia: a pilot study. *Cardiovasc Ther* 2015; 33: 275–281.
 34. Watanabe K, Dohi K, Sugimoto T, *et al.* Short-term effects of low-dose tolvaptan on hemodynamic parameters in patients with chronic heart failure. *J Cardiol* 2012; 60: 462–469.
 35. Kenz S, Haas CS, Werth SC, *et al.* High sensitivity to tolvaptan in paraneoplastic syndrome of inappropriate ADH secretion (SIADH). *Ann Oncol* 2011; 22: 2696.
 36. Chatzimavridou-Grigoriadou V, Al-Othman S, Brabant G, *et al.* Clinical experience of the efficacy and safety of low-dose tolvaptan therapy in a UK tertiary oncology setting. *J Clin Endocrinol Metab* 2021; 106: e4766–e4775.
 37. Shoaf SE, Bricmont P and Dandurand A. Low-dose tolvaptan PK/PD: comparison of patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion to healthy adults. *Eur J Clin Pharmacol* 2017; 73: 1399–1408.
 38. Sterns RH. Tolvaptan for the syndrome of inappropriate secretion of antidiuretic hormone: is the dose too high? *Am J Kidney Dis* 2018; 71: 763–765.
 39. Harbeck B, Lindner U and Haas CS. Low-dose tolvaptan for the treatment of hyponatremia in the syndrome of inappropriate ADH secretion (SIADH). *Endocrine* 2016; 53: 872–873.
 40. Castello LM, Baldrighi M, Panizza A, *et al.* Efficacy and safety of two different tolvaptan doses in the treatment of hyponatremia in the Emergency Department. *Intern Emerg Med* 2017; 12: 993–1001.
 41. Hanna RM, Velez JC, Rastogi A, *et al.* Equivalent efficacy and decreased rate of overcorrection in patients with syndrome of inappropriate secretion of antidiuretic hormone given very low-dose tolvaptan. *Kidney Med* 2020; 2: 20–28.
 42. Barajas-Galindo DE, Vidal-Casariago A, Gómez-Hoyos E, *et al.* Clinical experience with different initial doses of tolvaptan in SIADH. *Nefrologia (Engl Ed)* 2019; 39: 672–674.
 43. Spasovski G, Vanholder R, Allolio B, *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 2014; 170: G1–G47.
 44. Sterns RH, Silver SM and Hix JK. Urea for hyponatremia? *Kidney Int* 2015; 87: 268–270.
 45. Rondon-Berrios H, Tandukar S, Mor MK, *et al.* Urea for the treatment of hyponatremia. *Clin J Am Soc Nephrol* 2018; 13: 1627–1632.
 46. Nervo A, D'Angelo V, Rosso D, *et al.* Urea in cancer patients with chronic SIAD-induced hyponatremia: old drug, new evidence. *Clin Endocrinol (Oxf)* 2019; 90: 842–848.
 47. Grant P, Ayuk J, Bouloux PM, *et al.* The diagnosis and management of inpatient hyponatraemia and SIADH. *Eur J Clin Invest* 2015; 45: 888–894.

48. Refardt J, Winzeler B, Meienberg F, *et al.* Empagliflozin increases short-term urinary volume output in artificially induced syndrome of inappropriate antidiuresis. *Int J Endocrinol* 2017; 2017: 7815690.
49. Refardt J, Imber C, Sailer CO, *et al.* A randomized trial of empagliflozin to increase plasma sodium levels in patients with the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol* 2020; 31: 615–624.
50. Refardt J, Imber C, Nobbenhuis R, *et al.* Treatment effect of the SGLT2 inhibitor empagliflozin on chronic syndrome of inappropriate antidiuresis: results of a randomized, double-blind, placebo-controlled, crossover trial. *J Am Soc Nephrol* 2023; 34: 322–332.
51. Avila M. The Clinical Practice Guideline on diagnosis and treatment of hyponatraemia: a response from Otsuka Pharmaceutical Europe Ltd. *Eur J Endocrinol* 2014; 171: L1–L3.
52. Verbalis JG, Grossman A, Höybye C, *et al.* Review and analysis of differing regulatory indications and expert panel guidelines for the treatment of hyponatremia. *Curr Med Res Opin* 2014; 30: 1201–1207.
53. Van Biesen W and Vanholder R. Clinical Practice Guidelines on diagnosis and treatment of hyponatraemia: response to letter from Otsuka Ltd. *Eur J Endocrinol* 2014; 171: L5–L6.
54. Nagler EV, Vanmassenhove J, van der Veer SN, *et al.* Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements. *BMC Med* 2014; 12: 1.
55. Runkle I, Villabona C, Navarro A, *et al.* Treatment of hyponatremia induced by the syndrome of inappropriate antidiuretic hormone secretion: a multidisciplinary Spanish algorithm. *Nefrologia* 2014; 34: 439–450.
56. Sbardella E, Isidori AM, Arnaldi G, *et al.* Approach to hyponatremia according to the clinical setting: consensus statement from the Italian Society of Endocrinology (SIE), Italian Society of Nephrology (SIN), and Italian Association of Medical Oncology (AIOM). *J Endocrinol Invest* 2018; 41: 3–19.
57. Lee Y, Yoo KD, Baek SH, *et al.* Korean Society of Nephrology 2022 recommendations on controversial issues in diagnosis and management of hyponatremia. *Korean J Intern Med* 2022; 37: 1120–1137.
58. Jovanovich AJ and Berl T. Where vaptans do and do not fit in the treatment of hyponatremia. *Kidney Int* 2013; 83: 563–567.
59. Leirich RW and Greenberg A. When is it appropriate to use vasopressin receptor antagonists? *J Am Soc Nephrol* 2008; 19: 1054–1058.
60. Greenberg A and Leirich RW. Treatment of chronic hyponatremia: now we know how, but do we know when or if? *J Am Soc Nephrol* 2010; 21: 552–555.
61. Gross PA, Wagner A and Decaux G. Vaptans are not the mainstay of treatment in hyponatremia: perhaps not yet. *Kidney Int* 2011; 80: 594–600.
62. Torres VE, Chapman AB, Devuyst O, *et al.* Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–2418.
63. Watkins PB, Lewis JH, Kaplowitz N, *et al.* Clinical pattern of tolvaptan-associated liver injury in subjects with autosomal dominant polycystic kidney disease: analysis of clinical trials database. *Drug Saf* 2015; 38: 1103–1113.
64. Boscoe A, Paramore C and Verbalis JG. Cost of illness of hyponatremia in the United States. *Cost Eff Resour Alloc* 2006; 4: 10.
65. Dasta JF, Chiong JR, Christian R, *et al.* 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. *Hosp Pract* 2012; 40: 7–14.
66. Dasta JF, Sundar S, Chase S, *et al.* Economic impact of tolvaptan treatment vs. fluid restriction based on real-world data among hospitalized patients with heart failure and hyponatremia. *Hosp Pract* 2018; 46: 197–202.
67. Jamookeeah C, Robinson P, O'Reilly K, *et al.* Cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden. *BMC Endocr Disord* 2016; 16: 22.
68. Soupart A, Coffernils M, Couturier B, *et al.* Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 2012; 7: 742–747.
69. Warren AM, Grossmann M, Hoermann R, *et al.* Tolvaptan versus fluid restriction in acutely hospitalised patients with moderate-profound hyponatraemia (TVFR-HypoNa): design and implementation of an open-label randomised trial. *Trials* 2022; 23: 335.
70. Berl T. Vasopressin antagonists. *N Engl J Med* 2015; 372: 2207–2216.