Desmopressin to Prevent Rapid Sodium Correction in Severe Hyponatremia: A Systematic Review

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**ABSTRACT**

**BACKGROUND:** Hyponatremia is common among inpatients and is associated with severe adverse outcomes such as osmotic demyelination syndrome. Current guidelines recommend serum sodium concentration correction targets of no more than 8 mEq/L per day in patients at high risk of osmotic demyelination syndrome. Desmopressin is recommended to control high rates of serum sodium concentration correction in severe hyponatremia. However, recommendations are based on limited data. The objective of this study is to review current strategies for DDAVP use in severe hyponatremia.

**METHODS:** Systematic literature search of 4 databases of peer-reviewed studies was performed and study quality was appraised.

**RESULTS:** The literature search identified 17 observational studies with 80 patients. We found 3 strategies for desmopressin administration in hyponatremia: 1) proactive, where desmopressin is administered early based on initial serum sodium concentration; 2) reactive, where desmopressin is administered based on changes in serum sodium concentration or urine output; 3) rescue, where desmopressin is administered after serum sodium correction targets are exceeded or when osmotic demyelination appears imminent. A proactive strategy of desmopressin administration with hypertonic saline was associated with lower incidence of exceeding serum sodium concentration correction targets, although this evidence is derived from a small case series.

**CONCLUSIONS:** Three distinct strategies for desmopressin administration are described in the literature. Limitations in study design and sample size prevent definitive conclusions about the optimal strategy for desmopressin administration to correct hyponatremia. There is a pressing need for better quality research to guide clinicians in managing severe hyponatremia.

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**KEYWORDS:** DDAVP; Desmopressin; Fluid and electrolyte disorders; Hyponatremia

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**Authorship:** TEM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: TEM, TT, RBC.

Acquisition, analysis, or interpretation of data: TEM, TT.

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Study supervision: RBC.

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Hyponatremia is a common clinical problem among inpatients that is associated with adverse outcomes.1,2 Rapid correction of severe hyponatremia can lead to osmotic demyelination syndrome.3 Current guidelines, based on expert opinion, recommend correcting serum sodium concentration (sNa) by no more than 8 mEq/L/day for patients at high risk of osmotic demyelination syndrome, and 10-12 mEq/L in 24 hours and 18 mEq/L in 48 hours for patients at average risk of osmotic demyelination syndrome.4 The use of desmopressin (DDAVP) is recommended to prevent or slow high rates of sNa correction.4

There is uncertainty on the optimal timing, dose, and duration of DDAVP in hyponatremia. Some advocate for early DDAVP administration before changes in sNa.5 Others administer DDAVP at the onset of free water diuresis or when sNa correction has reached6 or exceeded7 targets. Co-interventions include normal saline, hypertonic saline, furosemide, and fluid restriction. DDAVP can be given with hypertonic fluids to re-lower sNa, which has been shown to reduce the incidence of osmotic demyelination syndrome in rats.8,9 DDAVP has potential adverse consequences, such as excessive re-lowering of sNa, neurologic deterioration, or delay in time to resolution of hyponatremia.10 There is no consensus on a preferred strategy, and the objective of this review is to examine current strategies for DDAVP use in hyponatremia.

**METHODS**

**Data Sources**

We searched Medline, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (from inception until October 2013) using a combination of keywords for hyponatremia and DDAVP (see Supplementary Methods, available online). We updated the search to include studies through October 17, 2014. We hand-searched guidelines, the Cochrane Database of Systematic reviews, and reference lists.

**Study Selection**

We included randomized controlled trials, observational studies, and systematic reviews in any language. Studies were included if any subjects had sNa < 125 mEq/L and were administered DDAVP. We excluded patients with any of the following: age <18 years, recent neurosurgery or traumatic brain injury, vasopressin-receptor antagonist use, hyponatremia complicating DDAVP use for another condition (eg, diabetes insipidus).

Two reviewers (TM and TT) independently screened abstracts to remove irrelevant or duplicate citations. We obtained full-text articles and independently applied inclusion criteria. Studies were excluded if there was insufficient clinical information for analysis. Where clarification was needed, we contacted study authors. For articles not in English or French, we used an online translator (Google Translate, Google Inc, Menlo Park, CA).

**Data Extraction and Analysis**

The 2 reviewers independently abstracted the data and resolved disagreements by consensus. We recorded the following characteristics: age, sex, diuretic use, psychoactive medication use (including selective serotonin release inhibitors, serotonin-norepinephrine release inhibitors, anticonvulsants, antipsychotic medications), syndrome of inappropriate antidiuretic hormone (SIADH), endocrine disorder (hyperthyroidism or adrenal insufficiency), low solute diet (or beer potomania), excess free water intake, liver disease, congestive heart failure, malignancy, alcohol use, seizure on presentation, initial sNa (sNa1), potassium, and urine osmolality.

We recorded the number, dose, and timing of DDAVP doses. We recorded co-interventions including hypertonic saline, normal saline, potassium, loop diuretics, hypotonic fluids, and fluid restriction.

We recorded the following outcomes: change in sNa at 24 hours (ΔsNa24), change in sNa at 48 hours (ΔsNa48), highest sNa within the first 24 hours, sNa before DDAVP (sNabeforeDDAVP), change from sNa to sNa before DDAVP (ΔsNa48beforeDDAVP), time of DDAVP from presentation, lowest sNa within 48 hours after DDAVP, and maximum lowering of sNa after DDAVP, and clinical or magnetic resonance imaging evidence of osmotic demyelination syndrome.

Based on our experience and literature review, we identified 3 strategies for DDAVP administration: 1) proactive, where DDAVP is administered based on the presenting sNa before changes in clinical parameters; 2) reactive, where DDAVP is administered after a change in clinical parameter (change in sNa or increased urine output); 3) rescue, where DDAVP is administered after exceeding sNa limits or upon development of neurologic symptoms. For the proactive and reactive strategies, DDAVP was used to prevent over-correction of sNa. In the rescue strategy, DDAVP was used to stabilize or re-lower sNa. We classified cases based on the stated intentions of the study authors where possible. Given that maximum sNa correction thresholds varied between studies, we applied sNa limits as defined by each study when categorizing DDAVP use as “reactive” or “rescue.”

For each case, we calculated whether sNa correction exceeded guideline-recommended limits (see Supplementary Methods, available online).1 High risk of osmotic demyelination syndrome included any of: presenting sNa < 106 mEq/L, hypokalemia, alcoholism, malnutrition, or advanced liver disease. For patients at high risk of osmotic demyelination syndrome, we defined the sNa correction limit as the sNa limit that is associated with adverse outcomes.1,2
as no more than 8 mEq/L in a 24-hour period. For patients at average risk of osmotic demyelination syndrome, we defined sNa correction limit as no more than 12 mEq/L in 24 hours and 18 mEq/L in 48 hours.4

We assessed the quality of included studies independently using an appraisal tool for case series.11 For case reports, given the absence of established quality guidelines, we used a relevant subset of variables from the same appraisal tool.

We compared continuous variables using the nonparametric Kruskal-Wallis test and categorical variables using the Fisher test. Post hoc between-group comparisons for continuous variables were performed with the Wilcoxon test using the Bonferroni correction. Statistical analysis was performed with R (The R Foundation for Statistical Computing, 2014).

RESULTS
Search Results and Study Sample
The search identified 1501 citations, of which 1407 were deemed irrelevant after initial review. Of the 94 articles reviewed in full text, 77 were excluded (44 did not meet inclusion criteria, 28 met exclusion criteria, and 5 had insufficient data). Seventeen articles were included, with 80 unique patients (Supplementary Figure, available online). Characteristics of included studies are shown in Table 1.5-8,12-24

Methodological Quality
All included studies were case reports or case series with retrospective data collection, indicating low-quality evidence. The appraised quality of studies was low to moderate (Supplementary Table, available online).5-8,12-24 Key parameters such as length of follow-up were described in fewer than half. Other clinical data were frequently lacking, such as serum potassium concentration (reported in 15% of patients).

DDAVP Strategy and Usage
Demographic and clinical characteristics are presented in Table 2, stratified by strategy of DDAVP administration. The mean presenting sNa was 111.7 mEq/L (SD 5.9).

A proactive strategy was used in 36.3% of patients, reactive in 41.3%, and rescue in 20.0%. In 2 patients (2.5%), we could not determine the strategy. There were no significant differences in age, baseline sNa, or risk of osmotic demyelination syndrome among the 3 strategies (Table 2). There were significant differences between groups in seizure at presentation, SIADH or psychoactive medication use, low solute diet, and excess free water intake. The proactive strategy had a higher proportion of patients with low solute diets, while the reactive strategy had a higher proportion of patients with excess free water intake. The rescue strategy had a higher proportion of patients with seizure and a lower proportion with SIADH or psychoactive medication use.

The number of doses of DDAVP used was reported in 42.5% of patients. Of these, 35.3% used one dose of DDAVP. The initial dose of DDAVP was reported in 20.0% (median dose 2 μg; interquartile range 1.25, range 1-8 μg).

### Table 1  Study Characteristics and Methodological Quality

<table>
<thead>
<tr>
<th>Author and Date</th>
<th>Type of Study</th>
<th>n *</th>
<th>Initial sNa, mEq/L</th>
<th>No. of Cases Using Each DDAVP Strategy</th>
<th>Quality Score (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proactive (n = 29)</td>
<td>Reactive (n = 33)</td>
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<tr>
<td>Cai et al, 201213</td>
<td>Case report</td>
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<td>Case report</td>
<td>1</td>
<td>110</td>
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<td>1</td>
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<tr>
<td>Dickson &amp; Luks, 201016</td>
<td>Case report</td>
<td>1</td>
<td>104</td>
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<td>1</td>
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<tr>
<td>Gharabeh et al, 201317</td>
<td>Case report</td>
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<td>107</td>
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<td>Goldszmidt &amp; Iliescu, 200018</td>
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<tr>
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<td>Case report</td>
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<td>112.6</td>
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<td>Tomlín et al, 20117</td>
<td>Case report</td>
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<td>109</td>
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</tbody>
</table>

DDAVP = desmopressin; sNa = serum sodium concentration.

* n represents the number of cases in the series where DDAVP was administered.

† For case reports, the highest possible score is 6, and for case series, the highest score is 18. See Supplementary Table, available online for additional details.
Time to first DDAVP dose was reported in 62.5% (mean 18.2 hours; SD 17.1). The time of first DDAVP dose was reported in only 3.4% of the proactive group, although these studies stated that DDAVP was given early. In the reactive strategy, mean time to DDAVP was 12.3 hours (SD 7.8), compared with 31.9 hours (SD 24.2) in the rescue strategy.

Biochemical Outcomes
Changes in sNa at 24 hours (ΔsNa24) differed significantly between the strategies of DDAVP use (7.0 mEq/L, SD 3.6 for proactive vs 8.75 mEq/L, SD 2.6 for reactive vs 15.6 mEq/L, SD 3.1 for rescue; P < .001; Table 3). There was a significant difference in ΔsNa48 among the 3 groups, although the difference was not significant between proactive and reactive groups.

The mean change in sNa before DDAVP administration (ΔsNa BeforeDDAVP) was significantly lower in the proactive group (1.1 mEq/L, SD 2.0) compared with the reactive (9.0 mEq/L, SD 4.2; P < .001) and rescue (18.7 mEq/L, SD 4.4; P < .001) strategies. By definition, the ΔsNa BeforeDDAVP should be lowest in the proactive group and highest in the rescue group, validating our classification scheme. Patients in the rescue group should exceed sNa correction limits by definition, which was validated by the data (100% had sNa correction in excess of 8 mEq/L in any 24-hour period). Re-lowering of sNa after DDAVP administration, whether intentional or unintentional, was less common in the proactive group (6.9% compared with 57.6% and 93.8% in the reactive and rescue groups, respectively). Among patients with lowering of sNa after DDAVP, the maximum lowering differed significantly (1.5 mEq/L in the proactive group vs 5.3 mEq/L in reactive and 8.2 mEq/L in rescue).

In the proactive group, 27.6% exceeded the sNa correction limit of 8 mEq/L/day recommended for patients at high risk for osmotic demyelination syndrome, compared with 87.9% of the reactive group. Similar numbers in the proactive and reactive groups exceeded the less stringent limits of 12 mEq/L in 24 hours and 18/mEq/L in 48 hours (10.3% and 15.2%, respectively). Using sNa correction limits based on the individual risk of osmotic demyelination syndrome using the available clinical information, similar numbers in the proactive and reactive groups exceeded the limit (24.1% and 33.3%, respectively).

Clinical Outcomes and Adverse Events
There was one case of magnetic resonance imaging-confirmed osmotic demyelination syndrome in a patient at high risk (presenting sNa of 100 mEq/L, hypokalemia, and alcoholism), in whom a reactive DDAVP strategy was used. In that case, ΔsNa24 was 10 mEq/L, ΔsNa48 was 16 mEq/L, and the maximum sNa correction rate was 0.73 mEq/L/hour, all of which exceeded the limits recommended for patients at high risk of osmotic demyelination syndrome.

In 4 patients (44%) in the rescue group, DDAVP and hypotonic fluids were administered after the development of acute neurologic symptoms suggestive of imminent osmotic demyelination syndrome. In all cases, the neurologic symptoms resolved after re-lowering of sNa (mean lowering of sNa of 11.8 mEq/L, SD 4.2). For these patients, mean sNa was 104 mEq/L (range 99-107 mEq/L), and mean ΔsNa24 was 15.3 mEq/L (range 12-21 mEq/L).
Biochemical outcomes

For patients in the proactive group, despite an intention to administer DDAVP before changes in sNa, sNa changed before DDAVP in 14 (48%; mean ΔsNa(beforeDDAVP) 2.5 mEq/L, SD 2.1).

For patients in the reactive group, 2 variables prompted clinicians to administer DDAVP: change in a urine parameter (elevated urine output or low urine osmolality) or change in sNa (absolute change or high rate of change). Most (51.5%) were administered DDAVP after change in sNa, 3 (9.1%) after change in urine, and 13 (39.4%) after change in sNa (absolute change or high rate of change).

The main adverse event reported in association with DDAVP therapy was unintentional re-lowering of sNa, which was generally mild and self-limited. There were no reports of any harm (such as seizures) resulting from re-lowering of sNa. One patient developed congestive heart failure after treatment with DDAVP and hypertonic saline according to a proactive strategy. That patient had preexisting severe valvular heart disease and had developed rapid atrial fibrillation, and responded well to diuretics.

Co-interventions

More patients in the proactive group received hypertonic saline infusions (89.7% vs 21.2% in reactive and 6.3% rescue). However, most patients in the proactive group (86%) were from a single study that used protocolized hypertonic saline. Other co-interventions, including intravenous fluids, potassium, furosemide, and fluid restriction, were not reported consistently.

In the proactive group, the median amount of hypertonic (3%) saline given in the first 48 hours was not significantly different between patients who exceeded a sNa correction of 8 mEq/L/24 hours and those who did not (7.1 mL/kg, interquartile range 2.95, vs 7.7 mL/kg, interquartile range 6.3; \( P = .19 \)). Of the 5 patients in the proactive group who received an initial bolus of hypertonic saline, none exceeded the sNa correction limit of 8 mEq/L/24 hours.

The use of hypertonic fluids in conjunction with DDAVP to re-lower sNa was less common in the proactive group (3.4%) than the reactive and rescue groups (72.3% and 100% respectively). In the rescue group, rates of hypertonic fluid administration were reported in only 3 (19%) patients (median rate 500 mL/h). Total amounts of hypertonic fluids given after DDAVP were reported in 6 patients (38%) in the rescue group (median 1000 mL). Three patients in the rescue group were given oral free water to help re-lower sodium, although amounts were not reported.

**DISCUSSION**

This is the first systematic review, to our knowledge, that addresses the use of DDAVP to treat severe hyponatremia.
Despite a broad search, we identified a limited amount of low-quality evidence to guide clinicians. Among existing case series and case reports, we categorized DDAVP use according to 3 strategies: 1) proactive, where DDAVP is administered based on the presenting sNa; 2) reactive, where DDAVP is administered based on a change in clinical parameter, either a change in sNa or urinary parameter; 3) rescue, where DDAVP is administered after exceeding sNa correction limits or with symptoms of imminent osmotic demyelination syndrome (Table 4).

For all 3 strategies, reported harms were small and we did not identify any reports of seizure attributable to DDAVP. The only case of osmotic demyelination syndrome occurred despite DDAVP use with a reactive strategy in a high-risk patient.

The use of a proactive strategy was associated with earlier administration of DDAVP, smaller change in sNa at 24 hours, lower incidence of exceeding sNa correction limits, and less use of hypotonic fluids to re-lower sNa. Patients treated with a proactive strategy were less likely to exceed the sNa correction limits recommended for patients at high risk of osmotic demyelination syndrome when compared with a reactive strategy (27.6% vs 87.9%). The 2 strategies did not differ in exceeding sNa correction limits for patients at average risk of osmotic demyelination syndrome (10.3% vs 15.2%).

These data suggest that proactive DDAVP use may provide more reliable control of sNa, and is likely preferable among high-risk patients. For patients at average risk of osmotic demyelination syndrome, however, the reactive strategy may be an acceptable approach. This is tempered by the fact that osmotic demyelination syndrome can occur even with sNa corrections within the limits recommended for average-risk patients.6,12,25 Some suggest more conservative sNa correction targets of 6-8 mEq/L in the first 24 hours for all patients with severe hyponatremia, with the exception of water intoxication or postsurgical hyponatremia.7,26 The present review suggests that a proactive strategy may be more likely to achieve these stringent sNa correction targets.

In theory, a proactive strategy can worsen severe hyponatremia if free fluid restriction is not strictly enforced. Studies we identified did not document this concern; however, the majority of our proactive cases come from one case series where concomitant hypertonic saline was used. Without this co-intervention, potential worsening of severe hyponatremia or prolonged duration of hyponatremia are more likely.

By definition, DDAVP for rescue occurred after exceeding sNa correction limits. The rescue strategy was associated with higher incidence of acute neurologic symptoms and increased use of hypotonic fluids to re-lower sNa. This option is not an optimal first choice, despite its value in situations where sNa correction limits have inadvertently been exceeded. Of note, there were no reported cases of osmotic demyelination syndrome when using DDAVP for rescue. Finally, the rescue strategy effectively alleviated acute neurologic symptoms in 4 patients, suggesting that DDAVP and re-lowering of sNa may have prevented permanent neurologic injury.

Limitations
No studies reported on potential adverse effects of DDAVP such as prolonged duration of hyponatremia, increased length of stay in the hospital, thrombosis, or more labile sNa. It is possible that some of these adverse events occurred but were not detected or reported in the studies we included.

Co-interventions administered with DDAVP must be carefully considered, because hypertonic saline was commonly used with the proactive strategy (89.7%). Hypertonic saline is a high-risk medication and may require additional precautions and training.8,27 Optimal monitoring for patients receiving these therapies has not been established.

### Table 4: Strategies for DDAVP Use

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Clinical or Biochemical Variables Prompting DDAVP Administration</th>
<th>Usual Co-interventions</th>
<th>Timing of First DDAVP Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proactive</td>
<td>Presenting serum sodium concentration (generally &lt;120 mEq/L)</td>
<td>Hypertonic saline infusion</td>
<td>Early</td>
</tr>
<tr>
<td>Reactive</td>
<td>Urine parameter change (high urine output or low urine osmolality) and/or: Sodium parameter change (high rate of change or absolute change)</td>
<td>±Hypotonic fluids to stabilize/re-lower serum sodium concentration</td>
<td>Mid</td>
</tr>
<tr>
<td>Rescue</td>
<td>Sodium change (absolute change exceeding correction limit) and/or: Neurologic symptoms of imminent osmotic demyelination syndrome</td>
<td>Hypotonic fluids to stabilize/re-lower serum sodium concentration</td>
<td>Late</td>
</tr>
</tbody>
</table>

DDAVP = desmopressin.
It is possible we misclassified the DDAVP strategy due to misinterpretation of the authors’ intentions. In some cases, authors explicitly stated their intentions, and in others it was implicit. To minimize misclassification, we predefined our classification scheme and 2 reviewers independently applied it. By classifying patients into strategies based on the authors’ intentions rather than specific sNa cutoffs, there may be significant heterogeneity in each group.

The data we used to classify patients as high risk for osmotic demyelination syndrome were often incomplete. For example, serum potassium concentration was reported in only 15%, which could result in some high-risk patients being misclassified as average-risk. The predictive ability of known risk factors in estimating risk of osmotic demyelination syndrome is currently poorly documented.

Twenty-five cases (86%) using a proactive strategy came from a single study\(^5\); therefore, the proactive strategy we have described heavily reflects the practices at a single center and replication is needed before generalizing to other settings. In that study, DDAVP and hypertonic saline were administered by nephrologists using an informal protocol. There were no adverse neurologic outcomes reported, although length of follow-up was not provided, and methods for adjudicating neurologic outcomes were not stated. Bias could have been introduced in the chart review process, and cases of osmotic demyelination syndrome could have been missed due to inadequate follow-up.

Due to the rarity of osmotic demyelination syndrome, definitive conclusions about the relative safety of the strategies cannot be made from the limited data in this review. Larger, prospective studies would be needed to address this important question.

As with any observational studies, significant differences in patient populations, such as comorbidities or illness severity, could have affected treatment selection and outcomes. For example, fewer patients presented with seizures in the proactive strategy studies than among rescue strategy reports. Patients in rescue strategy studies had a lower proportion of SIADH or psychosympathetic use, conditions that are less prone to rapid shifts in sNa compared with hypovolemic hyponatremia, possibly contributing to the higher incidence of over-correction in the rescue group. Other unmeasured variables, such as intensity of patient monitoring, could have impacted treatment selection and patient outcomes. Better research designs that account for such confounders are needed.

CONCLUSIONS

Three distinct approaches for DDAVP administration in patients with hyponatremia are described in the literature, which we have termed proactive, reactive, and rescue strategies. Limitations in study design and sample size prevent definitive conclusions about the optimal strategy for DDAVP administration in severe hyponatremia. The paucity of high-quality literature on the topic contrasts with the prevalence and impact of this clinical problem. There is a pressing need for better quality research to guide clinicians in managing severe hyponatremia.

ACKNOWLEDGMENT

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References


**SUPPLEMENTARY DATA**

Supplementary materials accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.ajmmed.2015.04.040.
SUPPLEMENTARY MATERIALS

Contents

1) Methods
   Medline search strategy
   Definitions of exceeding serum sodium correction limits
2) Table: Methodological Quality
3) Figure: Flow diagram of screening process and inclusion and exclusion criteria for articles

Methods
Medline Search Strategy.

1 Inappropriate ADH Syndrome/(2265)
2 siadh.mp. (1116)
3 (syndrome adj2 adh).mp. (2289)
4 (inappropriate adj2 adh).mp. (2351)
5 (antidiuretic adj2 hormone adj2 inappropriate adj2 secretion).mp. (716)
6 schwartz bar?t?er syndrome.mp. (97)
7 (inappropriate adj2 vasopressin adj2 secretion adj2 syndrome*).mp. (6)
8 hyponatremia(7178)
9 hyponatremia*.mp. (9544)
10 hyponatraemia*.mp. (1651)
11 hyponatriaemia*.mp. (9)
12 hyponatriemia*.mp. (28)
13 hyposodiumemia*.mp. (1)
14 or/1 (11,425)
15 Deamino Arginine Vasopressin/(3671)
16 desmopressin.mp. (2327)
17 1-desamino-8-D-arginine vasopressin.mp. (341)
18 DDAVP.mp. (2082)
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30 adiuretin.mp. (61)
31 arginine vasopressin deamino.mp. (2)
32 dav ritter.mp. (0)
33 deamino 8 dextro arginine vasopressin.mp. (0)
34 deamino 8d arginine vasopressin.mp. (14)
35 deamino arginine vasopressin.mp. (3676)
36 deamino dextro arginine vasopressin.mp. (0)
37 deaminovasopressin.mp. (6)
38 desmogalen.mp. (0)
39 desmopressine.mp. (27)
40 minirin.mp. (49)
41 minirinette.mp. (0)
42 minirin.mp. (3)
43 minurin.mp. (4)
44 nocutil.mp. (0)
45 octim.mp. (1)
46 octostim.mp. (2)
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49 (vasopressin adj3 desaminoarginine).mp. (1)
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52 (vasopressin1 adj2 mercaptopropionic adj3 dextro arginine).mp. (0)
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54 1 deamino 8 dextro arginine.mp. (0)
55 deamino 8 cysteine dextro arginine.mp. (0)
56 deamino 8 d arginine.mp. (417)
57 deamino 8 dextro arginine.mp. (0)
58 deamino dextro arginine.mp. (0)
59 16679-58-6.rn. (3671)
60 16679-58-6.mp. (1)
61 Stimate.mp. (11)
62 D-VOID.mp. (1)
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67 Nafiset.mp. (0)
68 Noctislon.mp. (0)
69 Octostin.mp. (0)
70 Pizzard.mp. (0)
71 Presinex.mp. (0)
72 Uremin.mp. (0)
73 dD-AVP.mp. (5)
74 (deamino and arginine vasopressin).mp. (3922)
75 (desamino and arginine vasopressin).mp. (519)
76 (vasopressin and (deamino adj2 arginine)).mp. (3709)
77 or/15—76 (5115)
78 14 and 77 (301)
79 remove duplicates from 78 (285)
80 animals/not (animals/and humans/) (3,962,474)
81 79 not 80 (222)
82 limit 79 to humans (221)
83 81 or 82 (222)

Definitions of Exceeding Serum Sodium Correction Limits.

Average risk of osmotic demyelination syndrome defined as any 1 of:
- Change in sNa at 24 hours >12
- (Maximum sNa value in first 24 hours—presenting sNa) >12
- Change in sNa at 48 hours >18
- Change in sNa before DDAVP >12 (if time of change was within 0-24 hours)
- Change in sNa from presentation to DDAVP dose >12 (if time from presentation to DDAVP is within 0-24 hours)
- Change in sNa from presentation to DDAVP dose >18 (if time from presentation to DDAVP is within 24-48 hours)
- (Change in sNa at 48 hours−Change in sNa at 24 hours) >12

High-risk of osmotic demyelination syndrome defined as any 1 of:
- Change in sNa at 24 hours >8
- (Maximum sNa value in first 24 hours−presenting sNa) >8
- (Change in sNa at 48 hours−Change in sNa at 24 hours) >8
- Change in sNa before DDAVP >8 (if time of change was within 0-24 hours)
- Change in sNa from presentation to DDAVP dose >8 (if time from presentation to DDAVP is within 0-24 hours)

sNa = serum sodium

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**Supplementary Table**  Methodological Quality

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Characteristics</th>
<th>Intervention Described</th>
<th>Co-intervention Described</th>
<th>Length of Follow-up Recorded</th>
<th>Adverse Events Described</th>
<th>Competing Interests Declaration</th>
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