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Review article

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Arginine vasopressin deficiency: diagnosis, management and the relevance of oxytocin deficiency

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Abstract

Polyuria–polydipsia syndrome can be caused by central diabetes insipidus, nephrogenic diabetes insipidus or primary polydipsia. To avoid confusion with diabetes mellitus, the name 'central diabetes insipidus' was changed in 2022 to arginine vasopressin (AVP) deficiency and 'nephrogenic diabetes insipidus' was renamed as AVP resistance. To differentiate the three entities, various osmotic and non-osmotic copeptin-based stimulation tests have been introduced in the past decade. The hypertonic saline test plus plasma copeptin measurement emerged as the test with highest diagnostic accuracy, replacing the water deprivation test as the gold standard in differential diagnosis of the polyuria–polydipsia syndrome. The mainstay of treatment for AVP deficiency is AVP replacement with desmopressin, a synthetic analogue of AVP specific for AVP receptor 2 (AVPR2), which usually leads to rapid improvements in polyuria and polydipsia. The main adverse effect of desmopressin is dilutional hyponatraemia, which can be reduced by regularly performing the so-called desmopressin escape method. Evidence from the past few years suggests an additional oxytocin deficiency in patients with AVP deficiency. This potential deficiency should be further evaluated in future studies, including feasible provocation tests for clinical practice and interventional trials with oxytocin substitution.

Sections

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Key points

- Central diabetes insipidus has been renamed to arginine vasopressin (AVP) deficiency and nephrogenic diabetes insipidus to AVP resistance.
- Polyuria–polydipsia syndrome comprises AVP deficiency or resistance and primary polydipsia.
- Copeptin-based stimulation tests have simplified and improved the diagnostic procedure for AVP deficiency and of these, the hypertonic saline test with measurement of plasma levels of copeptin has the highest diagnostic accuracy.
- AVP deficiency can be treated with desmopressin, but this treatment confers a risk of hyponatraemia; patients should be instructed to use the desmopressin escape method to decrease the risk of hyponatraemia.
- Oxytocin deficiency can occur in patients with AVP deficiency and can be assessed via stimulation with 3,4-methylenedioxymethamphetamine (that is, MDMA); whether oxytocin treatment is a future option for patients with AVP deficiency should be investigated in larger studies.

Introduction

Arginine vasopressin (AVP) deficiency (formerly known as central diabetes insipidus) is one of the three conditions that cause the polyuria–polydipsia syndrome, which is characterized by hypotonic polyuria (40–50 ml/kg body weight per 24 h) and polydipsia (excessive drinking; >3 l per day)[1]. In the differential diagnosis of polyuria–polydipsia syndrome, secondary causes such as osmotic diuresis (primarily owing to uncontrolled diabetes mellitus), electrolyte disturbances (primarily owing to hypercalcaemia or hypokalaemia) or chronic kidney disease must first be excluded. Once these diagnoses have been excluded, AVP deficiency and AVP resistance (formerly known as nephrogenic diabetes insipidus) have to be differentiated from primary polydipsia. The exact incidence of polyuria–polydipsia syndrome is unknown; however, AVP deficiency is rare, affecting around 1 in 25,000 people[2].

The use of the common term 'diabetes' for both diabetes insipidus and diabetes mellitus has led to confusion and, most importantly, to adverse patient outcomes in patients with diabetes insipidus[3]. In addition, the largest survey of its kind among patients with 'central diabetes insipidus' demonstrated that the majority of patients support a name change[4]. Accordingly, the new terms AVP deficiency and AVP resistance are now used[5].

As treatment approaches for polyuria–polydipsia syndrome vary and using the incorrect treatment can be harmful, distinguishing between the various causes is critically important. In the past decade, new test methods for the differential diagnosis were introduced based on the measurement of plasma levels of copeptin, an osmosensitive surrogate marker of AVP levels (Fig. 1). A lack of increase in the plasma concentration of copeptin (with a cut-off of ≤4.9 pmol/l) upon hypertonic saline stimulation showed high diagnostic accuracy for AVP deficiency; however, this test requires constant sodium monitoring and surveillance of patients[6]. Using an infusion of arginine to stimulate copeptin secretion was generally better tolerated, with a similar high diagnostic accuracy[7]. A head-to-head trial published in 2023 directly compared these stimulation tests[8].

Treatment of AVP deficiency is usually straightforward, consisting of the symptom-dependent application of desmopressin (a synthetic form of AVP) once or several times daily. However, hyponatraemia is an important and neglected adverse effect of desmopressin that should be taken into account. Furthermore, patients often report residual psychological symptoms, such as elevated anxiety, even after receiving adequate desmopressin treatment. Owing to the close anatomical proximity of the neurons that produce AVP and oxytocin, disruptions of the hypothalamic–pituitary axis, which cause AVP deficiency, could also lead to additional oxytocin deficiency (Fig. 1). Unfortunately, oxytocin deficiency is difficult to assess, as plasma levels of oxytocin are difficult to measure owing to unavailability of accurate commercial assays, and baseline levels, as well as established pituitary stimulation tests, are not useful in detecting oxytocin deficiency. Of note, a 2023 study investigated plasma levels of oxytocin upon stimulation with 3,4-methylenedioxymethamphetamine (MDMA), a stimulant that is widely recognized for strongly activating the central oxytocinergic system[9].

In this Review, we describe the reasons for the name change for this clinical entity and advances from the past decade in diagnosis, focusing on new copeptin-based diagnostic tests. For treatment, we highlight the importance of desmopressin escape and the future potential of oxytocin treatment.

The name change

The term diabetes means 'passing water like a siphon' and was already in use to describe individuals with polyuria in the first and second century BC. Later, the word 'mellitus', meaning 'honey sweet', was added by Thomas Willis in 1675 after discovering the sweetness of urine in patients with diabetes mellitus. Only in 1794 was the term 'insipidus' introduced, meaning 'tasteless', to differentiate patients with diabetes insipidus from those with diabetes mellitus[10]. However, the common term diabetes between these distinct clinical entities still leads to confusion. For example, some physicians and nurses often do not recognize the difference, which has led to adverse outcomes during hospitalization, including death in the past[3].

In a large web-based survey published in 2022 of 1,034 patients with AVP deficiency, 80% of the respondents indicated that on at least one occasion, health-care professionals had confused their condition with diabetes mellitus. Moreover, 84% of the participants thought that physicians, in general, have insufficient understanding of their disease and rated the general knowledge of physicians as low. In addition, 87% of the participants believed that this poor knowledge and confusion with 'diabetes mellitus' had an effect on how their condition was managed; for example, with repeated and unnecessary measurements of blood concentrations of glucose. Importantly, 85% of the participants preferred a renaming of the condition, with the clear wish that the term diabetes should not be used in the name of the disease[4]. Taking these findings together, patients with AVP deficiency have a notably increased risk of mismanagement during hospitalization owing to confusion among health-care professionals, and physicians and nurses have low levels of knowledge about diabetes insipidus[4]. Importantly, the patients who participated in this survey, along with a number of patient representative associations and foundations, are strongly in favour of changing the name and discarding the term diabetes; a change aimed at helping health-care professionals understand that patients with AVP deficiency or resistance require specialist therapy.

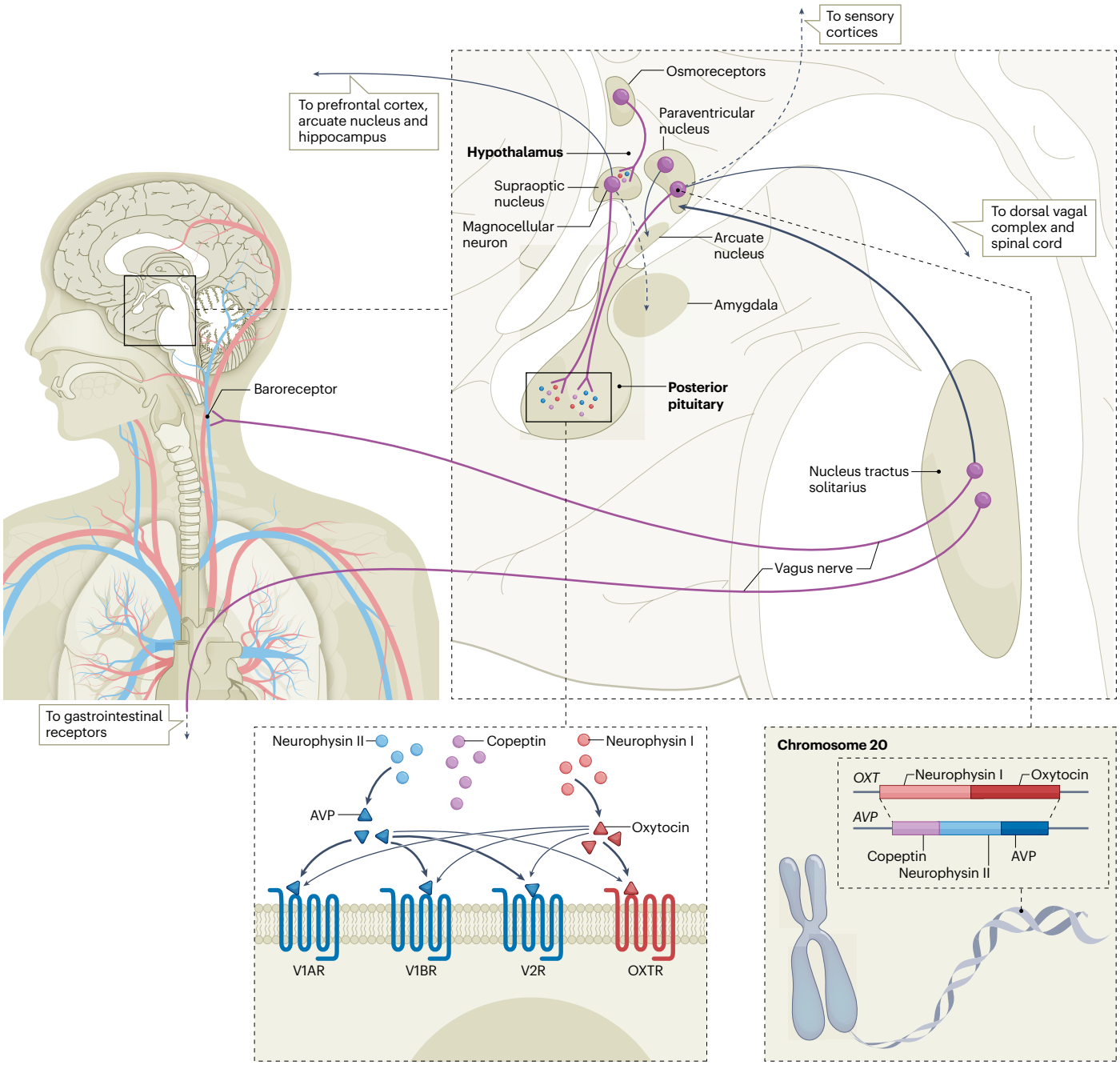

Fig. 1 | The hypothalamic–posterior pituitary axis. Arginine vasopressin (AVP) and oxytocin are synthesized by magnocellular and parvocellular neurons in overlapping hypothalamic nuclei (the paraventricular nucleus and supraoptic nucleus) and their projections to the posterior lobe of the pituitary. The genes encoding arginine vasopressin (*AVP*) and oxytocin (*OXT*) are in close proximity to each other on chromosome 20. These genes lie on opposite strands and have opposite transcriptional orientations. The gene product of *AVP* is proteolytically cleaved to form copeptin, neurophysin II and AVP, whereas the gene product of *OXT* yields neurophysin I and oxytocin. AVP and oxytocin signal through G protein-coupled receptors (V1AR, V1BR, V2R and OXTR), which have fairly high sequence homology, thereby leading to cross-reactivity between the peptides and their receptors.

To define a new name, the main endocrinology societies in the world formed a working group in 2022. As the names of medical conditions should ideally reflect the underlying pathophysiology, 'AVP deficiency' was chosen to replace central diabetes insipidus to reflect the deficient secretion of the hormone AVP. By contrast, the name AVP resistance was chosen to replace 'nephrogenic diabetes insipidus', to reflect the insensitivity of the kidneys to AVP. The new names are now used throughout manuscripts and book chapters, with the old name

in parentheses, to ease the transition in terms of online searches and to avoid confusion in the literature[5].

Diagnosis of AVP deficiency

Polyuria–polydipsia syndrome is a disorder that challenges internists, endocrinologists and nephrologists alike. The main problem lies in the distinction among AVP deficiency, AVP resistance and primary polydipsia. If AVP function is lacking, either due to insufficient release (deficiency) or due to renal insensitivity to AVP (resistance)[11–13], hypotonic polyuria and compensatory polydipsia will ensue; however, the mechanisms behind primary polydipsia are less clear. Historically, primary polydipsia was mainly associated with psychiatric disorders, but we now know it can be habitual; for example, in health-conscious persons who exhibit fluid intake above the normal thirst threshold[14]. Chronic polydipsia gradually leads to reduced renal concentration capacity, as well as suppression of AVP release, thereby mimicking AVP deficiency or resistance[15].

AVP deficiency can result from a number of disorders that affect the hypothalamic–neurohypophyseal system. The most frequent ones include injuries caused by tumours or surgery, as well as infiltrative disorders[16,17]. Traditionally, AVP deficiency is further categorized into a complete or partial form, depending on the amount of AVP secretion from the pituitary upon osmotic stimulation and consecutive urinary concentration capacity[11,12]. As long as patients with AVP deficiency are able to compensate for polyuria with polydipsia, electrolyte disturbances rarely occur. However, in states of altered consciousness (for example, during surgery or unconsciousness), patients are at risk of severe hypernatraemia. This complication is also seen in conscious and awake patients in whom thirst perception is affected, known as adipsic osmo-insensitive AVP deficiency. In this type of AVP deficiency, central hypothalamic osmoreceptors are impaired, for example, owing to direct tumour infiltration or surgical damage[18].

In line with the differences in underlying causes between AVP deficiency or resistance and primary polydipsia, the recommended treatment also differs; therefore, a reliable diagnostic assessment is crucial.

Clinical symptoms and MRI data

In all three entities that cause polyuria–polydipsia syndrome, the lead symptoms are increased thirst, polyuria and polydipsia, thus these symptoms are not helpful for discrimination. According to the two largest prospective studies in patients with polyuria–polydipsia syndrome, a clear overlap was observed between the amount of polyuria and polydipsia in patients with AVP deficiency and those with primary polydipsia[6,8]. Similar findings were seen when looking at baseline plasma sodium and osmolality. Psychiatric disorders (including depression) are reported to be more common in patients with primary polydipsia than those with AVP deficiency[19]; however, other studies have shown a similar prevalence (~30%) of psychiatric disorders between the two patient groups[6,8]. Of note, our 2022 survey results suggest that psychiatric conditions are underdiagnosed in patients with AVP deficiency[4].

If AVP deficiency is suspected, MRI of the hypothalamic–pituitary region is usually performed. The absence of the pituitary bright spot (an area of hyperintensity in the posterior lobe of the pituitary, possibly resulting from stored AVP in neurosecretory granules) has been described in MRI scans as pathognomonic for patients with AVP deficiency[20,21]. However, a larger study in 1,017 individuals receiving an MRI for unspecific neurological symptoms found an age-related absence of the bright spot in 4.1% (ref. 22). In addition, several patients with AVP deficiency with a persistent bright spot have been reported[23,24]. In two prospective evaluations in 2018 and 2023, the bright spot was absent not only in up to 70% of patients with AVP deficiency but also in 14–39% of patients with primary polydipsia[6,8]. Accordingly, the presence or absence of the bright spot on MRI should not be used as a sole criterion for the assumed underlying disorder.

The second characteristic radiological finding for AVP deficiency is a thickened pituitary stalk[25]. The presence of this feature is also not pathognomonic[8,26], but should lead to a thorough investigation for conditions affecting the pituitary or hypothalamus.

Diagnostic tests

Polydipsia occurring in the absence of other causes (such as uncontrolled diabetes mellitus or hypercalcaemia) should be further investigated by 24-h urine collection to confirm the presence of hypotonic polyuria. A urine osmolality level >800 mOsm/kg indicates solute diuresis, possibly caused by glucose (for example, in diabetes mellitus or in patients treated with sodium–glucose cotransporter 2 inhibitors), urea (for example, by high protein intake, tissue catabolism or steroid administration), mannitol (for example, from the treatment of increased intracranial pressure) or medications such as diuretics. In patients with hypotonic polyuria <800 mOsm/kg, further evaluation of plasma concentrations and osmolality levels of sodium could assist in indicating the underlying aetiology. Elevated concentration of plasma sodium (>147mmol/l) and levels of osmolality (≥300 mOsm/kg) suggest AVP deficiency or resistance, whereas low levels of plasma sodium (<135 mmol/l) and osmolality (≤280 mOsm/kg) point to primary polydipsia. However, in most patients, such a clear constellation of signs is not present and further evaluations are needed.

Indirect water deprivation test. For many years, the standard test for the polyuria–polydipsia syndrome was the indirect water deprivation test[12]. This test distinguishes between the different entities based on two main criteria. First, urine concentration capacity is measured after a period of water deprivation (usually 16 h) to indirectly assess AVP activity. Second, following a desmopressin injection, any changes in urine osmolality are evaluated (Fig. 2).

Diagnosing patients with complete AVP deficiency or resistance is usually straightforward using this test, yet it lacks diagnostic accuracy in distinguishing partial forms from primary polydipsia, in which the concentration gradient in the renal medulla is reduced. In addition, some patients with AVP deficiency might have higher than expected urine concentrations owing to a compensatory increase in *AVPR2* expression in the kidney[27], whereas partial resistance to AVP can mimic partial AVP deficiency. Importantly, urine osmolality cut-offs used for the water deprivation test were derived from a single study involving only 36 patients with post hoc assessment and have never been prospectively validated[12,28]. This limitation explains the low diagnostic accuracy of 70–77% for AVP deficiency versus primary polydipsia[6,29] (Table 1), and the test is particularly poor in diagnosing patients with primary polydipsia.

Direct measurements of plasma AVP. A logical way to overcome the limitations of the indirect water deprivation test is to directly measure plasma concentrations of AVP. Initial data with plasma AVP measurements after osmotic stimulation showed promising results in patients with polyuria–polydipsia syndrome[30]. However, plasma levels of AVP are not directly measured in clinical practice owing to its instability in plasma, technical limitations of the AVP assay[31–33] and the insufficient diagnostic accuracy of commercially available assays[28,29].

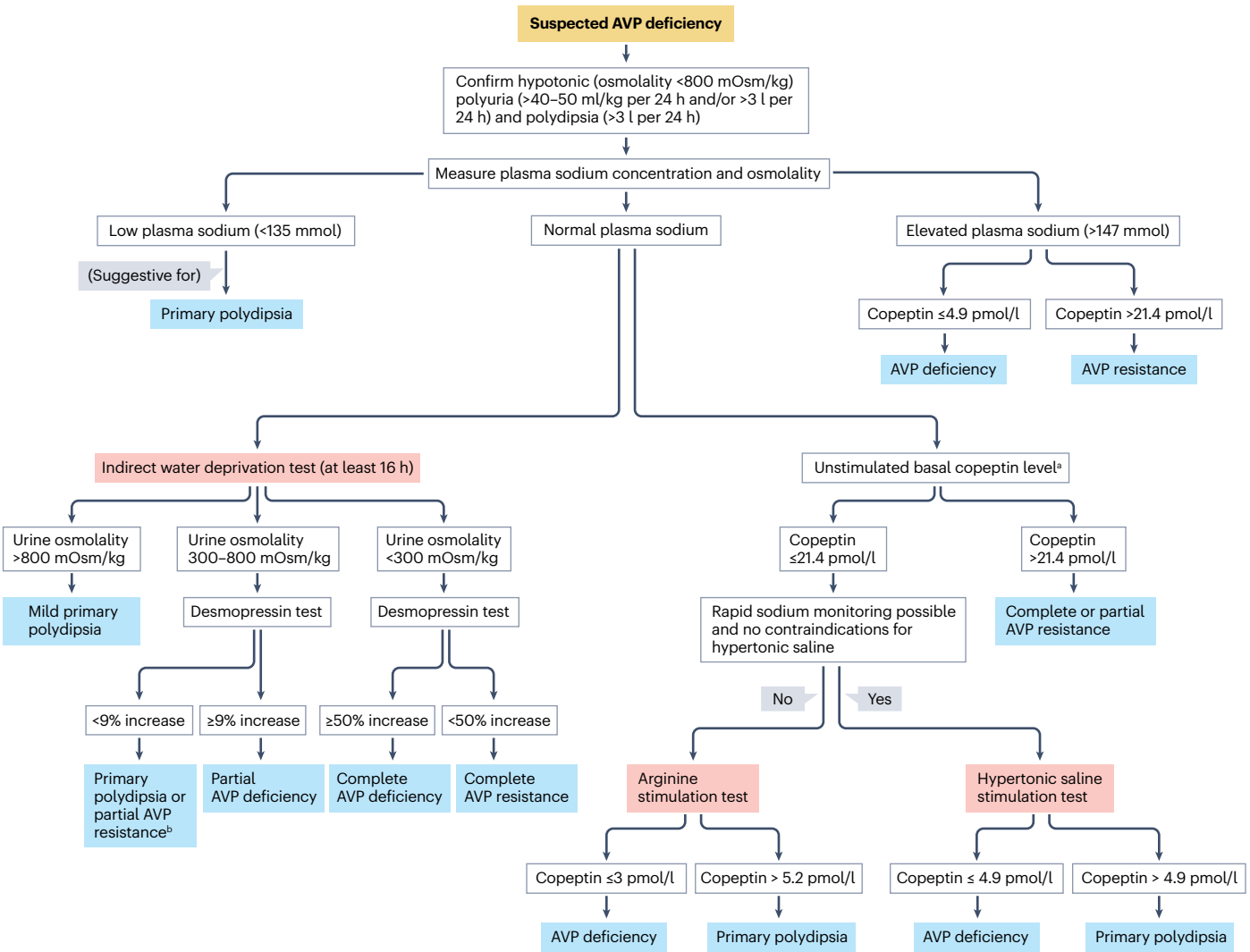

Fig. 2 | Algorithm for diagnostic approach in patients with suspected arginine vasopressin deficiency. In patients with polyuria–polydipsia syndrome, plasma concentrations of sodium and osmolality are measured. If these levels are in the normal range, further assessment is performed using either the indirect water deprivation test or copeptin-based testing. For the indirect water deprivation test, arginine vasopressin (AVP) activity is assessed indirectly by measuring the urine concentration capacity over a ≥16-h period of water deprivation. If urine osmolality remains below 300 mOsm/kg during water deprivation, a complete lack of adequate AVP release or action is likely. Following the administration of desmopressin, urine osmolality of patients with complete AVP deficiency should increase by more than 50%, whereas it remains below this threshold in patients with AVP resistance. Urine concentration is expected to increase to 300–800 mOsm/kg during water deprivation in patients with partial AVP deficiency or primary polydipsia. Showing an additional increase in urine osmolality ≥9% upon desmopressin injection diagnoses patients with partial AVP deficiency, whereas an increase of less than 9% diagnoses patients with either partial AVP resistance or primary polydipsia. An unstimulated basal plasma concentration of copeptin >21.4 pmol/l can indicate complete or partial AVP resistance. If plasma levels of copeptin are lower than this, copeptin measurement after the hypertonic saline stimulation test is recommended, as long as rapid sodium measurements and constant monitoring are available and no contraindications are present[8]. Alternatively, the arginine-stimulated copeptin test can be used, using the proposed lower (≤3.0 pmol/l) and upper (>5.2 pmol/l) plasma copeptin cut-offs; however, severe nausea or vomiting occurring during the test can interfere with copeptin measurements[7,8]. [a]Basal copeptin can only be validly evaluated if the patients had no distress (including physical and psychological) and had no severe nausea. [b]Plasma osmolality measurement might be needed to differentiate between both entities.

General considerations for copeptin-based tests. Copeptin is released from secretory granules in the posterior pituitary together with AVP and neurophysin II, from the precursor protein pre-pro-vasopressin[34,35]. Although its plasma concentrations are similar to those of AVP, copeptin is stable and simple to measure using commercially available assays[36]. Currently available are two CE-certified (that is, approved for sale in the European Union) assays: the automated immunofluorescent assay (using the KRYPTOR platform) and the original manual sandwich immunoluminometric assay[32]. Commercial tests are also available that are not approved for diagnostic use, mostly enzyme-linked immunosorbent assays, and they have poor correlations with immunoassays[37].

Table 1 | Diagnostic performance of tests for arginine vasopressin deficiency

Study	Diagnostic accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	*n*
AVP deficiency versus primary polydipsia: indirect water deprivation test				
Fenske et al.[29]: single centre study, prospective evaluation	70 (NA)	54 (NA)	88 (NA)	48
Fenske, Refardt et al.[6]: multicentre study, prospective evaluation	77 (69, 83)	86 (75, 94)	70 (58, 79)	141
AVP deficiency versus primary polydipsia: arginine-stimulated copeptin (cut-off 3.8 pmol/l)				
Winzeler et al.[7]: single centre study, cut-off derived from pooled patient data set	93 (86, 97)	93 (86, 98)	92 (84, 100)	96
Refardt et al.[8]: multicentre study, prospective cut-off validation	74 (67, 81)	75 (64, 84)	74 (63, 82)	156
AVP deficiency versus primary polydipsia: hypertonic saline-stimulated copeptin (cut-off 4.9 pmol/l)				
Fenske, Refardt et al.[6]: multicentre study, prospective cut-off validation	97 (92, 99)	93 (84, 98)	100 (96, 100)	141
Refardt et al.[8]: multicentre study, prospective cut-off validation	96 (91, 98)	91 (82, 96)	99 (94, 100)	158
Partial AVP deficiency versus primary polydipsia: indirect water deprivation test				
Fenske et al.[29]: single centre study, prospective evaluation	NA	NA	NA	37
Fenske, Refardt et al.[6]: multicentre study, prospective evaluation	73 (64, 81)	87 (66, 97)	70 (58, 79)	105
Partial AVP deficiency versus primary polydipsia: arginine-stimulated copeptin (cut-off 3.8 pmol/l)				
Winzeler et al.[7]: single centre study, cut-off derived from pooled patient data set	90 (82, 96)	93 (86, 98)	80 (60, 100)	73
Refardt et al.[8]: multicentre study, prospective cut-off validation	69 (60, 77)	54 (36, 71)	74 (63, 82)	115
Partial AVP deficiency versus primary polydipsia: hypertonic saline-stimulated copeptin (cut-off 4.9 pmol/l)				
Fenske, Refardt et al.[6]: multicentre study, prospective cut-off validation	95 (89, 98)	83 (61, 95)	100 (96, 100)	104
Refardt et al.[8]: multicentre study, prospective cut-off validation	95 (89, 98)	83 (64, 93)	99 (93, 100)	117

AVP, arginine vasopressin; *n*, sample size; NA, not available.

Owing to their shared neurosecretory granule storage, copeptin and AVP are co-secreted in response to increases in plasma osmolality or volume depletion, and the secretion of both factors is suppressed in response to fluid intake[36,38,39]. Copeptin is a nonspecific stress marker that can be used to assess both psychological and somatic stress[40–44]. Owing to these stimuli, preventing physical or emotional stress before drawing blood samples for basal copeptin analysis is crucially important.

The reliability of copeptin measurement as an alternative marker for plasma AVP concentrations has led to a reassessment of direct testing[45]. The initial finding from two prospective studies in patients with polyuria–polydipsia syndrome indicated that AVP resistance can be diagnosed in patients with a basal unstimulated plasma copeptin level of ≥21.4 pmol/l, negating the need for additional testing in these patients[29,46] (Fig. 2). However, considering the possible interfering factors discussed earlier, unstimulated plasma copeptin levels must be interpreted cautiously. Importantly, basal plasma copeptin concentrations usually show a large overlap between patients with AVP deficiency and those with primary polydipsia[6,46] and therefore stimulation testing is required.

Hypertonic saline stimulation test. Initial data in patients with polyuria–polydipsia syndrome for osmotically stimulated plasma copeptin values showed promise for the accurate diagnosis of AVP deficiency[46]. These findings were confirmed in two large prospective studies, including 320 patients with AVP deficiency or primary polydipsia[6,8]. To achieve sufficient osmotic stimulation, infusion of hypertonic (3%) saline is required as a bolus of 250 ml over 15 min, followed by a body-weight-adapted infusion. Plasma levels of sodium must be controlled at least every 30 min through rapid sodium measurements (for example, through venous blood gas analysis), with the aim of increasing plasma sodium levels above 149 mmol/l. Once this threshold is exceeded, blood samples are obtained for copeptin measurements, followed by quick re-lowering of plasma sodium levels through oral and parenteral rehydration. Using the copeptin plasma concentration cut-off of >4.9 pmol/l, patients with primary polydipsia can be distinguished from patients with AVP deficiency, with a high diagnostic accuracy of 96–97% (refs. 6,8) (91–93% sensitivity and 99–100% specificity; Fig. 2 and Table 1). By contrast, the indirect water deprivation test demonstrated a low diagnostic accuracy of 77% (86% sensitivity and 70% specificity), which was further reduced when copeptin measurements taken at the end of the deprivation phase were included into the diagnosis. These differences in accuracy highlight the drawbacks of the indirect water deprivation test, which frequently fails to produce an adequate osmotic stimulus, even when fluid is withheld for an extended period of time[6].

In addition to the higher diagnostic accuracy, hypertonic saline stimulation has a shorter duration than the water deprivation test and can be performed in the outpatient setting. Although adverse symptoms such as headache and malaise were more frequent and more pronounced during the hypertonic saline infusion test, patients preferred it over the indirect water deprivation test[6]. However, clinicians must have access to rapid sodium measurements (for example, via venous blood gas analysis) and closely monitor plasma sodium levels to prevent osmotic overstimulation. For reliable sodium measurements, two appropriate venous forms of accesses must be placed: one for the infusion and one for blood sampling. The test should not be performed in patients with heart failure or epilepsy, and limited safety data are available for older patients[6,8]. Patients with corticotroph insufficiency require stress dosing with exogenous corticosteroids[6,8].

Arginine-stimulation test. To overcome the limitations of the hypertonic saline stimulation test, the effect of arginine infusion was evaluated as arginine is a known stimulus for the anterior pituitary[47,48]. In a prospective study involving healthy volunteers and 96 patients with polyuria–polydipsia syndrome[7], a standard body-weight-adapted infusion of arginine (0.5 g per kg body weight diluted in 500 ml normal saline) administered over 30 min led to an increase in plasma levels of copeptin from a median of 5.2 pmol/l (interquartile range, 3.3–10.9) to 9.8 pmol/l (6.4–19.6) in healthy volunteers. In patients, a plasma copeptin cut-off of 3.8 pmol/l taken 60 min after the start of the arginine infusion had a diagnostic accuracy of 93% to distinguish between AVP deficiency and primary polydipsia[7]. The most common adverse effect was mild nausea, which occurred in half of the patients. Compared with hypertonic saline, arginine stimulation is the preferred test owing to its better test tolerance, the shorter duration of 1 h and the lack of need for constant laboratory monitoring.

Another growth hormone secretagogue is glucagon. In a 2022 study, an injection of 1 mg glucagon led to a notable increase in plasma copeptin levels in healthy participants and 10 patients with primary polydipsia, whereas no relevant increase was seen in patients with AVP deficiency[49]. A plasma copeptin cut-off of 4.6 pmol/l measured 150 min after glucagon injection had a sensitivity of 100% and a specificity of 90% to discriminate AVP deficiency from primary polydipsia; however, confirmation of these results in a larger cohort is pending.

Given the effect of arginine (a potent growth hormone secretagogue) stimulation on plasma copeptin levels, an oral stimulation test with macimorelin (an oral ghrelin agonist) was evaluated in a study with 28 healthy participants[50]. However, no effect on plasma copeptin levels was observed.

Hypertonic saline versus arginine stimulation. In 2023, a prospective diagnostic multicentre study directly compared the diagnostic accuracy of hypertonic saline versus arginine-stimulated copeptin. In total, 164 patients with AVP deficiency or primary polydipsia were included and underwent both hypertonic saline stimulation and arginine stimulation on two different days[8]. The diagnostic accuracy of the hypertonic saline stimulation test (plasma copeptin concentration threshold: 4.9 pmol/l) was confirmed to be 95.6% for discriminating between the two conditions (sensitivity 91.3% and specificity 98.9%). By contrast, the arginine-stimulation test (plasma copeptin concentration threshold: 3.8 pmol/l) was less discriminatory than expected, with a diagnostic accuracy of only 74.4% (sensitivity 75.4% and specificity 73.6%). Nevertheless, an arginine-stimulated plasma copeptin concentration ≤3.0 pmol/l or >5.2 pmol/l diagnosed over half of the patients with AVP deficiency and primary polydipsia, respectively, with a specificity of >90% (Fig. 2). Of note, 72% of the patients preferred arginine stimulation to hypertonic saline stimulation, as adverse effects were less frequent and milder.

In view of these results, we propose the following summary and algorithm (Fig. 2) for copeptin-based tests in patients with suspected AVP deficiency. The hypertonic saline-stimulated copeptin test has the highest diagnostic accuracy. Therefore, this test is recommended if rapid sodium measurements and constant monitoring are available and if there are no contraindications[8]. Arginine-stimulated copeptin can be used as an alternative simple test, using the proposed lower (≤3.0 pmol/l) and upper (>5.2 pmol/l) plasma copeptin concentration cut-offs. If severe nausea or vomiting occurs during arginine infusion, test results can only be used if plasma copeptin concentrations remain low; if not, a confirmation test (preferably hypertonic saline stimulation) is recommended[7,8].

Management of AVP deficiency

General goals in treatment

In patients with AVP deficiency, the correction of pre-existing water deficits and reduction of ongoing excessive urinary water loss are the treatment goals. Usually, severe hyperosmolality is not a risk in patients who are alert, ambulatory, have access to fluids and are able to drink in response to perceived thirst[51].

To reduce polyuria and polydipsia and therefore enable maintenance of a normal lifestyle, desmopressin is usually prescribed as the current standard of care for AVP deficiency, owing to its long half-life, selectivity for AVPR2 and the availability of multiple preparations[52]. The preferred formulations for long-term treatment are oral preparations (as swallowable tablets or sublingual melting tablets) and nasal formulations. Other options include nasal tubes or parenteral formulations (as intravenous or subcutaneous administration), the latter of which are more commonly used in hospital settings[53]. Optimal dosage and dosing intervals should be determined for each patient, beginning with a night-time dose to reduce nocturia. Sometimes, a morning or midday dose must be added, dependent on symptoms of the patient[1]. In clinical practice, the total required dose of desmopressin is not always clearly correlated with the degree of AVP deficiency and, thus, the severity of polyuria[52]. This discrepancy is probably caused by a number of variables that can affect the antidiuretic effect of desmopressin, such as solute intake and excretion as well as variable bioavailability (for example, owing to nasal congestion affecting the nasal route or concurrent meal intake for the oral route)[54]. Nevertheless, patients commonly adhere to a consistent dosing regimen at scheduled intervals.

Desmopressin escape method

Although desmopressin treatment offers immediate relief from polyuria and polydipsia, it is crucial to consider its main adverse effect of dilutional hyponatraemia and the related complications[55]. Fluid intake typically inhibits the secretion of AVP, allowing aquaresis to prevent water retention[56]. With the antidiuretic effects of desmopressin, however, even a modest intake of fluids is retained and therefore dilutional hyponatraemia is a prevalent adverse effect[57].

Hyponatraemia in patients with AVP deficiency is particularly frequent in outpatient settings, and some retrospective studies indicate a prevalence of ~30% in routine laboratory checks[51]. In a 2023 retrospective study of 222 patients with AVP deficiency, 31% had plasma sodium levels in the hyponatraemic range, including 9%

with pronounced hyponatraemia (≤130 mmol/l)[52]. In line with these data, in a survey study of 1,034 patients with AVP deficiency, 22% reported that they had experienced episodes of hyponatraemia in the outpatient setting and 26% experienced hyponatraemia leading to hospitalization[4].

In the initial phase of desmopressin treatment, patients should therefore receive advice on limiting excessive fluid intake and be educated about symptoms of hyponatraemia, including nausea, vomiting, headaches or lethargy. To avoid hyponatraemia, plasma sodium levels should be regularly monitored during the first few days of treatment[58–60].

To reduce the risk of hyponatraemia for long-term follow-up, recommendations have been made for patients with AVP deficiency to delay a desmopressin dose up to several times per week or omit a dose once a week to allow aquaresis; a method that is referred to as the desmopressin escape method[61] (Fig. 3). This method can be

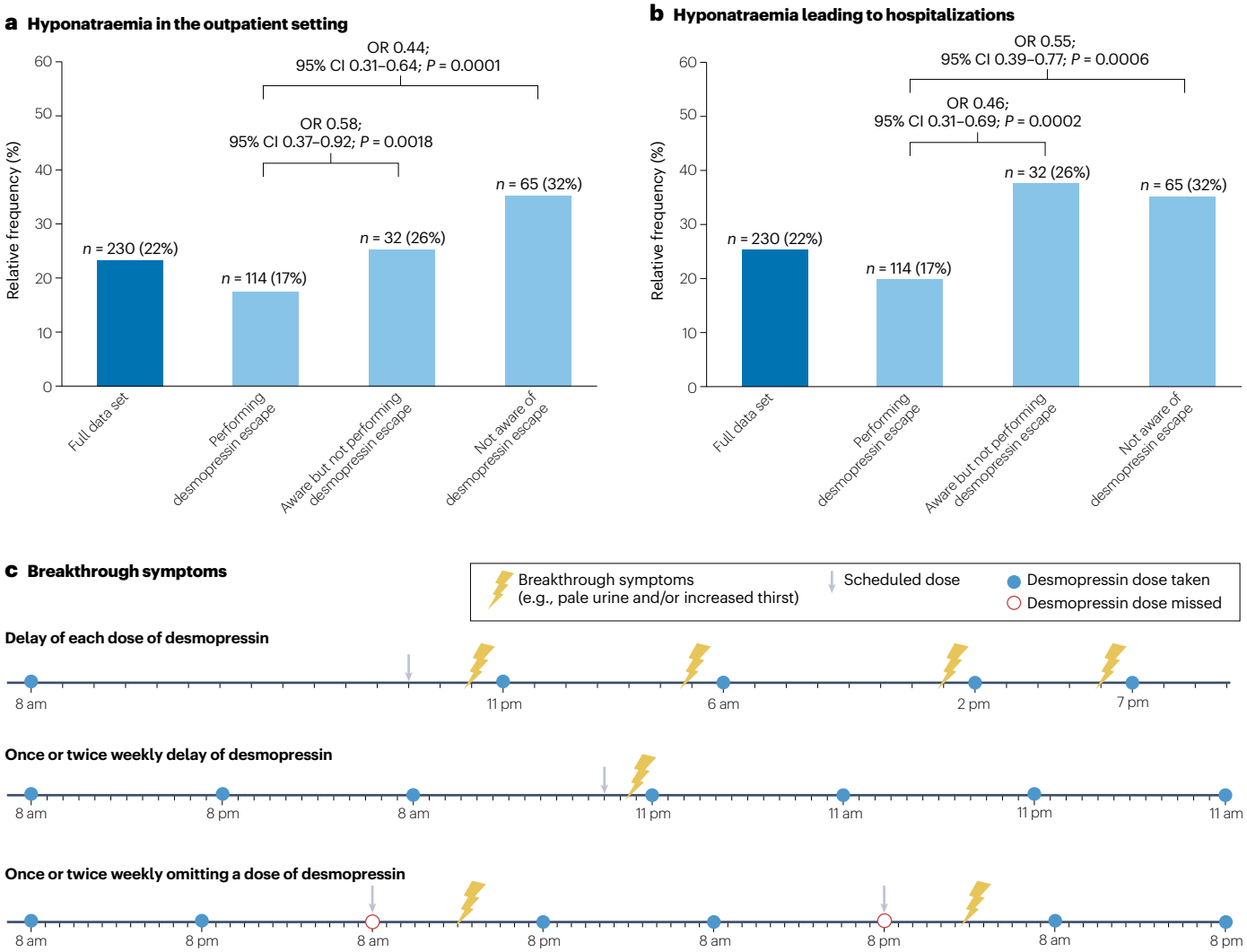

Fig. 3 | Prevalence of hyponatraemia in patients with arginine vasopressin deficiency and strategies for the desmopressin escape method. Survey data of 1,034 patients with arginine vasopressin deficiency[4]: 67% of the patients treated with desmopressin used desmopressin escape, a treatment approach that involves delaying or omitting a desmopressin dose to allow aquaresis. About 21% of the patients were unaware of this approach, and 12% were aware but did not use it. A univariate logistic regression model was performed to assess the association of desmopressin escape performance on hyponatraemia risk and reported by odds ratios (ORs) with 95% confidence intervals (CIs). Patients aware of the desmopressin escape method and following this approach were compared with patients aware of the need of desmopressin escape, but not following this approach, and with patients not aware of desmopressin escape and not following this approach. **a**, In the outpatient setting, performing desmopressin escape led to lower prevalence of hyponatraemia compared with patients not being aware of this approach and with those aware of desmopressin escape but not performing this method. **b**, Similarly, for hyponatraemia leading to hospitalization, patients performing desmopressin escape had a significantly lower prevalence of hyponatraemia than those who were not aware of this method and also to those aware of desmopressin escape but not performing this approach. **c**, Several options to perform the desmopressin escape method. Delaying each desmopressin dose or few doses up to several times per week until aquaresis and breakthrough symptoms (that is, strong thirst, full bladder, pale urine and frequent urination) occur or omitting a desmopressin dose once or several times per week for patients preferring to take desmopressin on a scheduled basis. Data in parts **a** and **b** were originally presented in ref. 4.

performed in one of the several ways, and physicians should follow an individualized approach when initiating desmopressin treatment.

The effectiveness of this simple clinical approach to reduce the risk of hyponatraemia was shown in our 2022 survey-based study of patients with AVP deficiency[4]. In both the outpatient setting or in cases of hyponatraemia leading to hospitalization, patients who used the desmopressin escape approach demonstrated a reduced risk of hyponatraemia compared with patients unaware of this method and with those aware of desmopressin escape but not following this strategy.

Evidence suggests that the formulation of desmopressin can affect the risk of hyponatraemia, with reports of increased risks associated with nasal desmopressin[62,63]. Interestingly, in another study, switching from nasal to oral formulations of desmopressin conferred a 60% reduction in the risk of hyponatraemia in patients with AVP deficiency[63]. Compared with these post-marketing safety data[62], data from the survey study and a recent retrospective analysis showed no difference in the prevalence of hyponatraemia in both types of preparations[4,52]. Although these findings are controversial, one should highlight the considerable number of patients who switch from nasal to oral formulations of desmopressin, mainly driven by patient preference, thereby suggesting overall better control of symptoms[4].

Oxytocin deficiency in patients with AVP deficiency

Oxytocinergic and vasopressinergic neurons have been categorized depending on their size, location, function and projection in magnocellular and parvocellular cells[64–66] (Fig. 1). Research in the past two decades from animal models on oxytocinergic transmission reconstructed neuronal connectivity, demonstrating that most magnocellular neurons project collaterals from the hypothalamic–posterior pituitary axons to more than 50 forebrain regions[67–69]. Together with associated limbic networks, these complex central circuits regulate contextual socio-emotional behaviour in mammals, including in-group favouritism and protection against social threats, emotional transfer between conspecifics, fostering trust and attachment, as well as promoting empathy and emotion recognition[70–73]. Circuits of smaller parvocellular oxytocinergic neurons that project to the midbrain, brainstem and spinal cord are suggested to be involved in autonomic functions including regulation of food intake, cardiovascular reflexes, erection and pain processing[74–78]. The parvocellular and magnocellular neurons seem to show strong interconnectivity, with parvocellular neurons acting as 'first-responders', conveying somatosensory signals onto magnocellular neurons[79–81]. Global oxytocin knockout mouse models have been used to assess disturbances in social interactions, with the observation of deficits in the formation of social memories and more anxiety-related behaviours[82,83].

Oxytocin in patients with hypothalamic–pituitary dysfunction

In contrast to patients with AVP deficiency, patients with anterior pituitary dysfunction have well-recognized socio-emotional deficits and impaired quality of life[84,85]. Although desmopressin therapy improves clinical outcomes in patients with AVP deficiency, evidence indicates that they still might not attain population norms in terms of quality of life and socio-emotional abilities[86]. Craniopharyngioma is also a condition associated with a high risk of causing damage to vasopressinergic and oxytocinergic neurons[87], and a long-term 10-year study of patients with craniopharyngioma identified changes in personality and social deficits[87–90]. Of note, data from our survey study in patients with AVP deficiency showed a high prevalence of self-reported psychological problems: 25% reported heightened anxiety, 25% sleep disturbances, 23% depressed mood, 18% stress management disturbance and 12% personality change[4]. In total, 64% reported lower quality of life, with recreation and fun, social activities and both physical and mental well-being being affected[4]. These findings were observed in patients with AVP deficiency with and without additional anterior pituitary hormone dysfunction, which challenges the notion that anterior pituitary dysfunction is the primary cause of psychological changes.

Vasopressinergic neuron disruption can cause AVP deficiency but could also potentially result in an impairment of oxytocinergic cells, thereby causing an additional oxytocin deficiency owing to the close proximity of both systems[91]. Hence, a plausible hypothesis is to assume that patients with AVP deficiency have a concomitant accompanying oxytocin deficiency that is partly responsible for their increased psychopathology and decreased quality of life[91]. A few initial studies measured oxytocin in these patients, mainly focusing on basal measurements[92–95]. One of the first studies assessed fasting and postprandial saliva levels of oxytocin in long-term survivors of craniopharyngioma and healthy control individuals, with no noteworthy difference between the groups. By contrast, in another study, patients with hypopituitarism demonstrated lower basal saliva oxytocin levels than healthy control individuals, regardless of the presence of AVP deficiency[94]. The lower level of oxytocin in these patients was also associated with an impaired ability to identify facial expressions accurately[94]. In a study that focused on male patients with AVP deficiency, the symptoms and signs of depression, anxiety and alexithymia were greater compared with either patients with hypopituitarism but without AVP deficiency or healthy control individuals[96]. Baseline plasma oxytocin levels were similar in all groups; however, patients with AVP deficiency had a slightly lower level, when plasma oxytocin was pooled over an hour[96]. On the contrary, another study noted increased baseline oxytocin levels in patients with AVP deficiency compared with healthy control individuals, once again raising doubts about the reliability of baseline oxytocin levels as an indicator of a potential deficiency[92,97].

These controversial findings might partly be explained by difficulties in accurately measuring oxytocin, given its technical complexities, and ideal sampling methods are currently the subject of ongoing research. Various assay methods have been used and included different samples; for example, plasma, saliva, cerebrospinal fluid and urine[97]. Importantly, as indicated by a meta-analysis in humans and animals, central levels of oxytocin correlate with peripheral levels only following physiological stimuli such as experimentally induced stress, not at baseline[98]. Therefore, a provocation test is crucial in assessing a possible oxytocin deficiency.

Provocation tests for oxytocin deficiency

Various provocation tests have already been examined for oxytocin. The insulin–hypoglycaemia test was shown to statistically significantly increase plasma oxytocin levels from around ~3 pmol/l to 6 pmol/l, in response to 30 min of severe hypoglycaemia in healthy adults[99]. Other established pituitary provocation tests, such as the hypertonic saline test, arginine test or oral macimorelin test, were tested in healthy adults[100]. Although plasma levels of oxytocin showed a statistically significant increase in response to hypertonic saline infusion, this increase was insufficient to qualify it as a diagnostic provocation test[100].

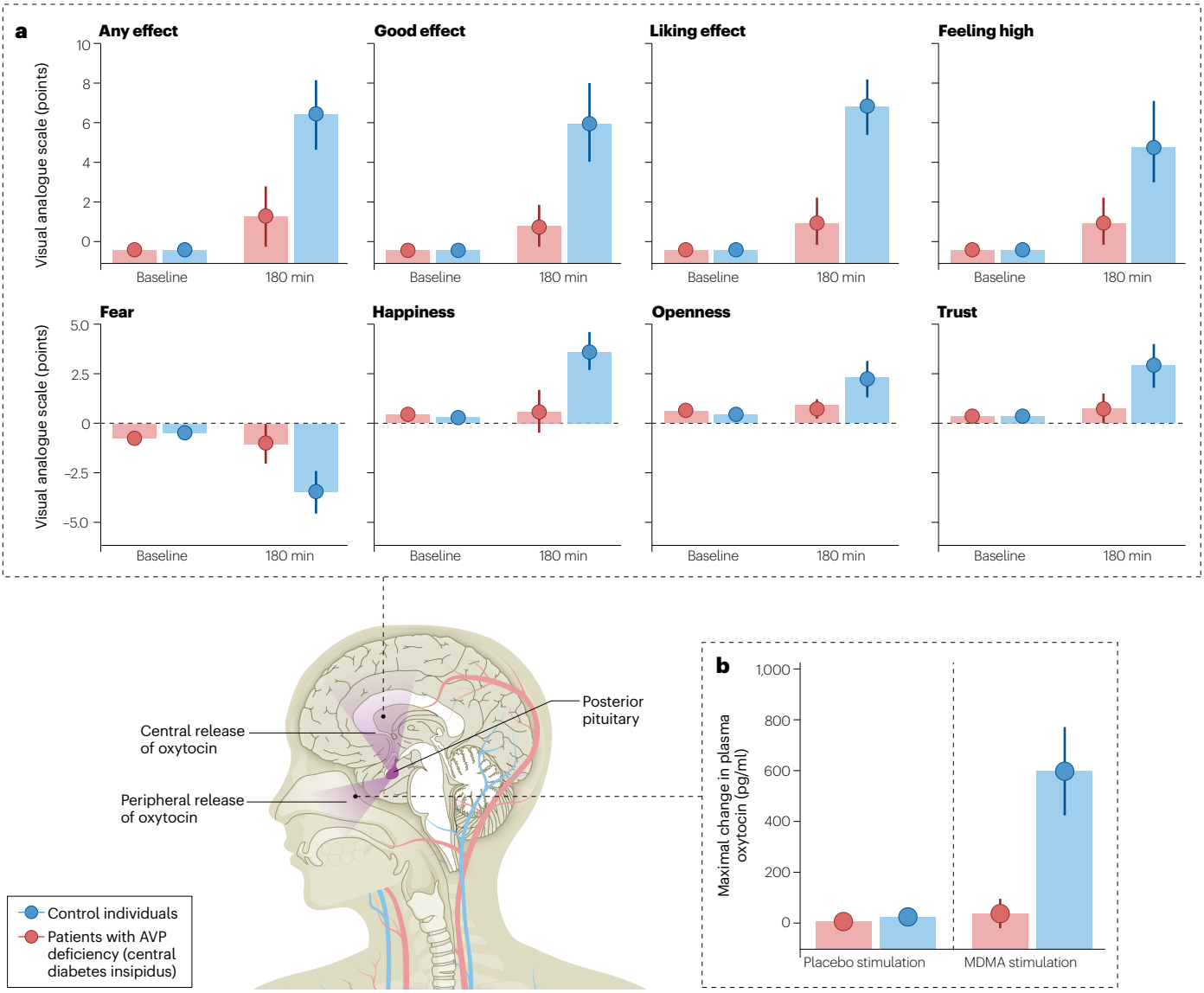

Fig. 4 | Psychoactive behavioural responses and plasma concentrations of oxytocin in response to the MDMA provocation test. Data from a placebo-controlled, crossover trial included 15 patients with arginine vasopressin (AVP) deficiency and 15 matched healthy control individuals (by age, sex, BMI, contraceptive use and menopause status) assigned to a single oral dose of 100 mg 3,4-methylenedioxymethamphetamine (MDMA)[9]. The data are presented as mean ± standard deviation for patients (in red) and healthy controls (in blue) at baseline and 180 min after administration of the drug. **a**, Subjective drug effects were assessed using 10-point visual analogue scales, ranging from 0 ('not at all') to 10 ('extremely'), or were bidirectionally ranging from −5 to +5, with 0 being the neutral measure (that is, 'no effect'). The MDMA-induced acute subjective psychoactive effects were blunted or absent in patients with AVP deficiency (red) compared with healthy control individuals (blue). **b**, The plasma concentration of oxytocin was also measured after the MDMA intake. In healthy control individuals, plasma levels of oxytocin increased eight-fold in response to MDMA, whereas in patients with AVP deficiency, plasma levels of oxytocin showed no major response. Data were originally presented in ref. 9.

An alternative approach investigated exercise-induced oxytocin stimulation. In healthy adults, an exercise stimulus on a bicycle ergometer increased saliva levels of oxytocin by 1.25-fold, whereas patients with hypopituitarism showed a diminished oxytocin response[93]. The presence of AVP deficiency was not a predictor for lower oxytocin levels in response to exercise. A subsequent study investigated a subgroup of patients with craniopharyngioma who showed diminished oxytocin release after exercise; compared with control individuals, these patients also demonstrated reduced enjoyment during social interactions, higher prevalence of self-reported autistic traits and they also performed worse on an emotional recognition task[101]. However, the weak oxytocin stimulation observed after exercise is again considered to be insufficient to diagnose oxytocin deficiency. For a valid provocation test, the stimulus must induce supraphysiological increases in oxytocin secretion and to evaluate the central action, psycho-active stimulation is necessary.

To this purpose, MDMA (also known as the recreational drug 'ecstasy') was assessed in a 2023 study as a stimulus for oxytocin[9] (Fig. 4). MDMA increases peripheral oxytocin levels and central oxytocin-mediated behavioural effects, which are associated with its empathic and prosocial profile. These effects include increased closeness and openness to others, enhanced trust, elevated happiness and an overall sense of well-being[102–105]. In the 2023 study, patients with AVP deficiency showed no difference in basal plasma oxytocin levels compared with matched healthy control individuals. In response to MDMA administration, control individuals showed an eight-fold increase in plasma levels of oxytocin, whereas no response was seen in patients[9]. In patients, psychoactive effects induced by MDMA (for example, 'good effect', 'liking effect' or 'feeling high') were either blunted or absent compared with control individuals (Fig. 4).

Before MDMA was administered, both patients and control individuals exhibited comparable increase in state anxiety, which decreased after MDMA intake in control individuals at the peak plasma concentration of oxytocin, whereas patients did not experience an anxiolytic effect[9]. The strong rise in peripheral levels and subsequent action of oxytocin in central key areas linked to fear processing, such as the amygdala, might be responsible for the anxiolytic effects seen during MDMA stimulation. Supporting this observation, control individuals but not patients showed decreased recognition of negative emotions (such as 'fearful') in the 'Facial Emotion Recognition Task'. Notably, half of the patients exhibited clinically relevant anxiety and symptoms of emotional blindness, although this study only included patients without actively treated psychological comorbidities[9].

Thus, in contrast to the predicted effects in control individuals, nearly all of the psychoactive effects of MDMA were either blunted or absent in patients[9]. This pattern is indicative of the absence of a rise in central oxytocin and the ensuing dysfunction in key brain areas that are essential for socio-emotional processing. In the light of these results, the question was raised in 2023 of whether oxytocin deficiency should be considered as a 'new' human disease[106].

Not all patients, particularly those with cardiovascular conditions, can undergo MDMA stimulation, and its implementation into clinical routine poses challenges. Therefore, future research should focus on developing alternative simplified approaches. One possibility could be to mimic the action of MDMA using substances that have already obtained approval; for example, by combining a selective serotonin receptor reuptake inhibitor and a serotonin-1A receptor agonist[107,108].

Oxytocin replacement therapy

Intranasal administration of oxytocin is the preferred method for studying its effects on social cognition[109–111]. The effects of oxytocin are probably mediated by its action on brain regions involved in processing social and emotional stimuli, including the amygdala, insula and striatum[112–116]. Some doubt has been raised about whether intranasal oxytocin effectively penetrates the central nervous system and whether the amounts applied for clinical studies produce functionally significant effects[117–119]. However, a growing body of evidence from animal studies indicates that a functionally relevant central level of oxytocin is achieved after intranasal application. In 2018 and 2020, two studies measured cerebrospinal fluid concentrations after intranasal administration of labelled oxytocin to rhesus macaques and provided direct evidence for cerebrospinal fluid entrance via trigeminal and olfactory nerve fibres[120]. These findings are corroborated by the observation that global oxytocin knockout mice showed increases in central oxytocin concentrations following exogenous administration of oxytocin[121], with accumulation in the amygdala and the hippocampus to a degree, which was assumed to be functionally relevant[122].

In patients with AVP deficiency, exogenous oxytocin effects have only been investigated and reported in one case report and a study of 10 patients[123,124]. Following pituitary surgery, the parents of a 6-year-old child observed behavioural changes, including tendencies towards social withdrawal and reduced interest in physical interaction. After receiving intranasal oxytocin, the patient resumed in play activities and demonstrated social interactions with peers[123]. In line with this observation, ten patients with childhood-onset craniopharyngioma (nine of whom had AVP deficiency) showed improvements in the categorization of negative emotions after receiving intranasal oxytocin[124]. Further studies will be needed to investigate the long-term therapeutic use of oxytocin in this patient population, as data are currently unavailable.

Potential effects during birth and lactation

Oxytocin has well-known obstetric functions[125,126]. The current data are limited to case series involving patients with hypopituitarism, and insufficient investigations have been made into difficulties with breastfeeding or complications during labour in patients with AVP deficiency[127–131]. Some patients reported successful spontaneous labour[127,128] without the need for oxytocin administration. Furthermore, at hospital discharge, only half of the patients with hypopituitarism were breastfeeding, implying that oxytocin from the pituitary might not be mandatory or might be partially preserved for the initiation of spontaneous labour or milk let-down[131–133]. Further investigation of larger cohorts is needed.

Conclusions

Although proposed only in 2022, the new name of AVP deficiency has already been widely adopted in clinical practice to replace central diabetes insipidus[8,9,134] and should be further propagated to increase the safety of our patients.

For many years, the differential diagnosis of polyuria–polydipsia syndrome has been based on the indirect water deprivation test. Over the past decade, copeptin-based test methods have notably improved the diagnostic accuracy. In 2018, hypertonic saline-stimulated copeptin emerged as a new test with high diagnostic accuracy and was proposed to be the new gold standard[6]. A study in 2023 comparing this test with the arginine-stimulation test (a simpler test method owing to its better tolerability and adverse effect profile) confirmed the superiority of hypertonic saline-stimulated copeptin[8]. As close sodium monitoring is mandatory and contraindications for this test exist, new test methods should be evaluated. Glucagon stimulation has shown promising results in a small patient cohort, but validation studies are needed. Other possible osmotic or non-osmotic stimuli of copeptin should be further explored.

Treatment of AVP deficiency has not changed much over the past few years, and the mainstay remains AVP replacement with desmopressin. Survey data underline the importance of regularly performing desmopressin escape to decrease the risk of hyponatraemia as an important adverse effect[4]. Evidence suggests that some patients with AVP deficiency could also be affected by oxytocin deficiency. Whether patients could benefit from additional oxytocin treatment will have to be shown in future intervention studies.

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