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Primary polydipsia in the medical and psychiatric patient: characteristics, complications and therapy

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Summary

Primary polydipsia (PP) has been defined as excessive intake of fluids. However, the pathogenesis of PP remains unexplored. Different theories include a dysfunction in the thirst mechanism, involvement of the hippocampus, stress-reducing behaviour and lesion occurrences in specific areas of the brain. Most studies have been performed in the psychiatric setting, indicating that PP coincides with schizophrenia, anxiety disorder and depression. However, an increasing number of case reports emphasise the incidence of PP in non-psychiatric patients. As often recommended by healthcare professions and in life-style programmes, the phenomenon of excessive fluid intake appears to be growing, especially in health-conscious and active people. PP is part of the polyuria-polydipsia syndrome, so the differential diagnosis diabetes insipidus (central or nephrogenic) must be excluded. The gold standard when differentiating between these disorders has been the water deprivation test. However, new options for distinguishing between these entities have been proposed e.g., measurement of copeptin, a reliable surrogate marker of the hormone arginine vasopressin (AVP). The major risk of excessive drinking is the development of hyponatraemia and the ensuing complications. In patients with PP, factors reducing the renal excretory capacity of the kidney such as acute illness, medications or low solute intake may accumulate in hyponatraemia. Treatment options for PP remain scarce. Different medication and behavioural therapy have been investigated, but never on a large scale and rarely in non-psychiatric patients. This review provides an overview of the pathophysiology, characteristics, complications, and outcomes of patients with PP in the medical and psychiatric patient.

Key words: *Polyuria-polydipsia syndrome, psychogenic polydipsia, dipsogenic polydipsia, beer potomania, water intoxication, hyponatraemia*

Author contributions
CS, BW and MCC wrote the manuscript and approved the final version of this manuscript. CS and BW are equally contributing first authors.

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Introduction

Primary polydipsia (PP) is characterised by an increased fluid intake and consistent excretion of profound quantities of dilute urine exceeding 40–50 ml/kg body weight (e.g., 3000 ml/day for a person of 60 kg) over an extended period, excluding reasons for secondary polydipsia [1–3]. It has most commonly been described in patients with schizophrenia spectrum disorder with an incidence of 11 to 20%, and has therefore been named psychogenic polydipsia [1–4]. With the increasing popularity of lifestyle programmes and the common conception that consuming several litres of fluid per day is healthy, the prevalence of this phenomenon is increasing, particularly outside of the psychiatric setting. However, the prevalence in the overall population is unknown and has yet to be studied. Presumably, a lack of knowledge regarding the burden, consequences and treatment options for this disorder has limited studies in this field until now.

A comparable disorder is beer potomania, which is also characterised by increased intake of beer, but in this condition urine output may be below the above-mentioned polyuria definition [5–8].

The most common and potentially severe complication of excessive fluid intake is the occurrence of hyponatraemia [1, 4, 9, 10]. Hyponatraemia is associated with increased morbidity and mortality and should therefore be prevented [11–14]. Different risk factors are thought to be associated with the development of hyponatraemia in PP such as medication, physical or psychological stress, and acute consumption of copious quantities of fluids [1, 4, 9].

Several treatment options for PP have been investigated, ranging from different medication to behavioural therapy [15–20]. Unfortunately, most studies were using explorative study designs, small sample sizes with limited success, and low generalisability.

This review is intended to give an overview of the current stage of research in the field of PP. We will describe causes, associated comorbidities, complications, and will discuss the diagnostic and therapeutic issues of this syndrome.

Pathophysiology

Maintaining a stable fluid level is a primary human need [21, 22]. Water balance is an incessant equilibrium of water

intake and excretion through the kidneys, the lungs, the bowels and the skin. This balance, in order to keep plasma osmolality within a close range, is primarily regulated by the interplay of thirst and the hormone arginine vasopressin (AVP) [23]. AVP, promoting water retention in the kidney, is released upon two main stimuli namely high serum osmolality and low arterial blood volume [21, 23, 24] (fig. 1).

In healthy people, drinking leads to a pleasant feeling in response to thirst with an activation of the prefrontal cortex, the pleasure and reward centre of the brain, as shown in functional magnet resonance imaging (fMRI) experiments. In contrast, increased drinking after thirst has been satisfied results in an unpleasant or even aversive sensation, which then stops the healthy participant from further fluid intake [26, 27].

The pathogenesis of insatiable thirst and excessive fluid intake as seen in PP remains largely unknown. According to the underlying or associated conditions, PP may be classified in two main categories, whereby different causal mechanisms are discussed: psychogenic polydipsia and dipsogenic polydipsia [2, 24, 28, 29] (table 1). A related disorder is beer potomania, which is characterised by the chronic or acute consumption of large amounts of beer [7, 30].

Most research has been done in patients with schizophrenia spectrum disorders and psychogenic polydipsia. In both, a central defect of thirst and a dysfunction in AVP regulation has been suggested [31, 32]. During acute psychotic episodes, worsening of polydiptic behaviour and increased levels of AVP have been observed [9]. It is speculated that during acute psychosis, the activation of the hypothalamic-pituitary-adrenal axis and AVP secretion influences behavioural traits and vice versa – probably through hippocampal involvement [9, 23, 33–37]. Interestingly, in cranial MRI, the hippocampus was found to have a diminished volume in patients with schizophrenia spectrum disorder and PP compared to those without PP [35].

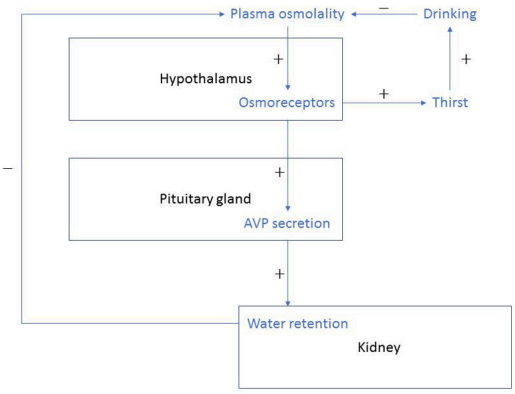
Furthermore, a stress-induced increase in dopamine levels may also play a role in acute psychotic patients. This hypothesis has been tested in animal studies, which showed that exogenous dopamine initiated drinking and increased AVP levels [38–41].

Other psychiatric conditions such as affective and dependency disorder (e.g., smoking, alcoholism) and anorexia nervosa also appear frequently in PP [29]. In these diseases, drinking might be perceived as a coping strategy to deal with psychological stress or, especially in patients with anorexia nervosa, increased liquid consumption may compensate for low food intake and to decrease the sensation of hunger [32, 42, 43].

Dipsogenic polydipsia includes patients with an increased sensation of thirst due to hypothalamic lesions and subjects with habitual polydipsia, which is typically seen in lifestyle conscious men and women, which is the use of water to detox the body. Abnormally high water consumption is also seen in people who perform excessive amounts of sport [44–48]. Alongside hypothalamic affection after traumatic brain injuries, vascular or infiltrative diseases (e.g., sarcoidosis) may lead to dipsogenic polydipsia [24, 49–52]. In habitual polydipsia, social conditioning with constant motivation to drink may modify drinking behaviour relative to actual water deficit, thus resulting in a downward resetting of the thirst threshold [26, 27].

Finally, while in beer potomania the underlying disorder is alcohol dependency, the motivation to drink is the effect of alcohol and thus different from other forms of primary polydipsia [5–8]. Psychogenic and dipsogenic polydipsia seem to occur preferentially in women, whereas beer potomania is more often seen in men [1, 4, 11, 29].

Figure 1: Physiology of thirst regulation. In the case of increased plasma osmolality, osmoreceptors in the hypothalamus are activated, which leads to secretion of the hormone arginine vasopressin (AVP). AVP thereafter stimulates water retention in the kidneys receptors. On the other hand, thirst is stimulated and leads to drinking.Adapted from Knepper et al. (2015) [25].



Diagnosis and differential diagnosis of PP

The differential diagnoses of primary polydipsia (PP) are central and nephrogenic diabetes insipidus (DI). While PP is primarily characterised by increased fluid intake, DI is determined by polyuria due to impaired AVP secretion

Table 1: Causes of primary polydipsia.<su>Table-Small</su>

Primary polydipsia (excessive water intake)		
	Psychogenic polydipsia (e.g., in patients with acute psychosis, chronic schizophrenia spectrum disorder, anxiety disorder, depression, anorexia nervosa and dependency disorder)	
	Dipsogenic polydipsia	
		Habitual polydipsia
		Health-conscious men and women
		Sporty people
		Somatic (damage of thirst centre)
		Cerebral lesion
		Granulomatous (sarcoidosis)
		Infectious (tuberculous meningitis)
		Vascular (vasculitis)

(central DI) or AVP resistance in the kidneys (nephrogenic DI) [24]. Central DI may be acquired after e.g., pituitary trauma (surgery), infections, auto-immune disease or congenital factors [2, 3, 24, 53]. Nephrogenic DI can be due to inherited mutations in the AVP-receptor-2 and aquaporine-2 gene, or acquired (e.g., chronic lithium use or metabolic/vascular kidney injuries) [3, 53].

The first step in the diagnosis and differential diagnosis of PP is a thorough history, including medical and psychiatric comorbidities and medication. Compared to patients with DI, polydiptic patients typically report a less acute onset and often deny nocturia and drinking during the night [24]. The next diagnostic step is to exclude other forms of polyuria (e.g., diabetes mellitus) and to measure plasma, urine osmolality and electrolytes. Low normal plasma sodium in the presence of a low urine osmolality is indicative of PP. The widely accepted gold standard for the differential diagnosis of PP is the indirect water deprivation test, introduced in 1964 [54]. The test indirectly assesses AVP activity by measurement of urinary osmolality, and thus the concentration capacity of the kidneys, during a prolonged dehydration period, and finishes by assessing the response (increase in urinary osmolality in %) to the administration of exogenous vasopressin (desmopressin) [55–57].

However, this procedure is limited by poor diagnostic accuracy of 70% overall and an especially poor diagnostic performance of only 41% for PP [2, 58]. Therefore, other methods have been studied. Direct measurement of AVP was used with initially promising results [59]. However, due to measuring difficulties and the instability of AVP, direct measurement of AVP has never entered everyday practice [60–62].

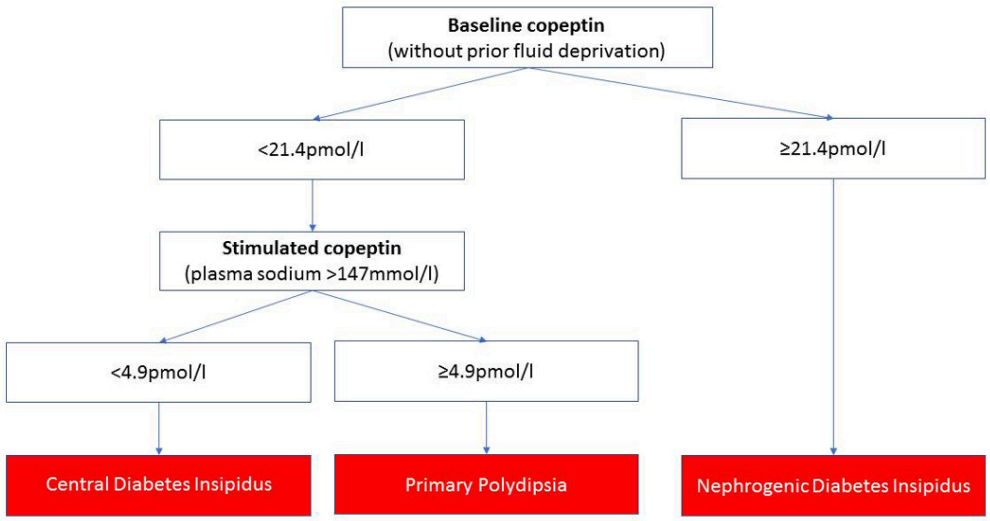
Copeptin, the c-terminal part of the AVP precursor peptide, was found to be a stable, sensitive and easily measured surrogate marker for AVP [61, 63, 64]. Copeptin has been shown to accurately discriminate between PP and DI [28, 64]. Without prior thirsting, a single basal copeptin value >21.4 pmol/l differentiates nephrogenic DI from other aetiologies with a high sensitivity and specificity. If the basal copeptin value is below this cut-off, an osmotic stimulation (plasma sodium >147 mmol/l) either by fluid restriction or the administration of a hypertonic saline infusion is necessary for differentiation between central DI and PP [28]. An osmotically stimulated copeptin value ≥4.9 pmol/l differentiates between patients with PP and central DI with high diagnostic accuracy (fig. 2).

Complications of PP

The most common and severe acute complication of PP is the development of hyponatraemia [10, 11, 30, 65]. Hyponatraemia in PP occurs when free fluid intake exceeds free fluid excretion [31, 60, 66]. The normal excretory capacity of the kidneys can compensate for liquid intake up to 15-18l/day (considering a maximum urine diluting capacity of 50mmol/l and an excretion of 900mmol/24h), but this system may be altered by several factors [66]. Beside chronic and acute ingestion of excessive quantities of fluids, conditions impairing urine dilution capacity predispose hyponatraemia - primarily increased AVP release [1, 10, 11, 31, 65–71]. Risk factors for hyponatraemia are displayed in table 2.

About 20% of patients with schizophrenia and PP develop hyponatraemia [4, 9, 11]. As AVP is known to be a stress hormone, an acute psychotic episode increases the activity of AVP, leading to water retention and potentially hyponatraemia, especially if polydiptic behaviour persists [9, 60, 72]. Similarly, somatic stress (e.g., acute diseases, pain) stimulates AVP secretion [73]. Recent case reports have

Figure 2: Diagnostic algorithm of copeptin in the differential diagnosis of patients with PP, central and nephrogenic DI. A basal copeptin value of ≥21.4 pmol/l confirms the diagnosis of nephrogenic DI. A basal copeptin value of <21.4 pmol/l needs an osmotic stimulation (water deprivation or hypertonic saline infusion) to differentiate between central DI and PP. An osmotically stimulated copeptin value ≥4.9 pmol/l differentiates between patients with central DI and PP with a high diagnostic accuracy [28].Adapted from Christ-Crain and Fenske (2016) [53].



shown an association between acute infection and hyponatraemia. Particularly in urinary tract infections when both the infection per se and stress-induced AVP release reduce the renal excretory capacity, a combined with medical advice to increase fluid intake, patients in general and especially with PP are at risk of the development of hyponatraemia [74–77].

Several medications may promote hyponatraemia by stimulating AVP release or increasing the sensitivity of the kidneys to AVP: thiazide diuretics, antipsychotic drugs, antidepressant drugs, antiepileptic drugs, and lithium [68, 70, 71, 78–81]. Furthermore, the anticholinergic side effects of antidepressant drugs may result in an elevated sensation of thirst and hence lead to increased drinking.

In patients with beer potomania, patients with PP and malnutrition or anorexia nervosa, low solute intake plays a major role in the development of hyponatraemia [30]. The amount of solute intake defines the maximum dilution capacity of the kidneys as free fluid without solutes cannot be excreted. Thus, if solute intake decreases, the kidneys' excretory capacity of water may decrease from around 15 l/d to 4 l/d, a threshold that is quickly passed in patients with chronic polydipsia and beer potomania [66].

Hyponatraemia may lead to several serious consequences. In the acute setting, if hyponatraemia treatment is delayed or inadequate, complications include brain oedema, seizures, falls and fractures as well as rhabdomyolysis and central pontine myelinolysis [11, 82–86]. In the long-term, hyponatraemia is associated with increased rehospitalisation rates, morbidity and mortality [12, 87].

Importantly, the risk of hyponatraemia seems to increase with duration of the underlying disease of PP [4]. It is speculated that excessive fluid intake over a long period may modulate drinking behaviour relative to actual water deficit and lead to a disturbance in the osmoregulation. Hence, over time, subjects declare thirst and keep drinking even in the presence of reduced serum osmolality [60, 88, 89]. Similarly, a downward resetting of the osmostat results in delayed or incomplete suppression of AVP and hence impairs water excretion.

Beside hyponatraemia, other complications of chronic excessive fluid consumption exist. Renal concentration capacity may diminish through a washout mechanism and downregulation of aquaporine-2 water channels, as shown in rodents [90]. Furthermore, malnutrition, gastrointestinal distress, bladder dilatation, hydronephrosis, renal failure, congestive heart failure, osteopenia and central nervous system dysfunction have been discussed [13, 16, 91, 92].

Table 2: Factors predisposing to hyponatraemia.

Acute fluid intake of high amount		
Impaired water excretion		
	Age	
	Renal failure	
	Low solute intake	
		Malnutrition
		Anorexia nervosa
		Beer potomania
	Concomitant stimulus	
		Medication (e.g., antidepressants, antipsychotics, diuretics)
		Acute infection (e.g., pneumonia, urogenital tract infection) or other acute diseases (e.g., stroke, myocardial infarction)
		Psychological stress (e.g., acute psychosis)

These data, however, mostly derive from case reports and retrospective studies and therefore provide low evidence.

Treating primary polydipsia and its complications

Treatment options for PP are scarce. Voluntary reduction of water intake would be the ideal therapy for PP, however, it often fails due to non-compliance of the polydiptic patient who suffers from thirst and compulsive drinking behaviour [88, 93–95]. Supportive measures to avoid hyponatraemia are the following: ingestion of a balanced diet, avoidance of drugs that may cause a dry mouth, hence increasing drinking, and frequent weighing to detect water retention. Studies have investigated behavioural therapy such as disease education, relaxation training using biofeedback, conditioning of desired behaviour, group therapy and others [15, 16, 92, 96] and have shown variable results. However, the feasibility of behavioural treatments, requiring substantial time and manpower, are limited in an outpatient setting [16].

Different medications have been suggested to improve polydiptic behaviour and prevent hyponatraemia. As PP has mainly been studied in acutely psychotic patients, it is not surprising that most drugs studied are antipsychotic drugs and mood stabilisers such as olanzapine, lithium, risperidone, aripiprazole and clozapine [15, 17, 19, 97–101]. The question however remains whether these drugs are treating the urge to drink, or if they are simply reducing acute psychosis and thus treat PP that might be a symptom of acute psychosis. Other medications that have been found to reduce polydiptic behaviour are phenytoin, bupropion, and propranolol [102–104]. All therapeutic options studied are considered low evidence, as these are descriptions of case reports, small case series or small case-control group studies. In conclusion, the wide spread of different medication used underlines the difficulty in treating this disorder and the need for better options.

Acute treatment of hyponatraemia in PP primarily consists of fluid restriction. In cases of profound and symptomatic hyponatraemia, a 3% saline infusion may be used. Overcorrection of hyponatraemia (increase of serum sodium >12 mmol/24h) has been described in patients with PP, fortunately without neurological complications [29, 84, 105]. Nevertheless, treating physicians should be aware of the risk of overcorrection and consequently pontine myelinolysis.

Conclusion

In conclusion, the pathophysiology of PP is complex and poorly understood. PP is associated with a wide spectrum of psychiatric comorbidities beyond schizophrenia. Moreover, habitual polydipsia appears to be increasing in prevalence in lifestyle conscious healthy people. Several factors impairing water excretion exist and may promote hyponatraemia in PP, a condition linked to substantial morbidity and mortality.

Fluid restriction is a successful measure to correct the complication of acute hyponatraemia, however, in the long run treatment options for this typically chronic condition are scarce. Studies elaborating novel therapeutic approaches would be desirable. But most importantly, educational

measures in the general population might be needed to rationalise the prevalent advice to “drink enough”.

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