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A randomized controlled trial of GLP-1 receptor agonist dulaglutide
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Conflict of interest statement
The authors have declared that no conflict of interest exists.
Abstract

Background Primary polydipsia, characterized by excessive fluid intake, carries the risk of water intoxication and hyponatremia, but treatment options are scarce. Glucagon-like peptide-1 (GLP-1) reduces appetite and food intake. In experimental models, they also play a role in thirst and drinking behavior. The aim of this trial was to investigate whether GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia.

Methods In this randomized, double-blind, placebo-controlled, 3-week crossover-trial, 34 patients with primary polydipsia received weekly dulaglutide (Trulicity®) 1.5mg and placebo (0.9% sodium chloride). During the last treatment week, patients attended an 8-hour evaluation visit with free water access. The primary endpoint was total fluid intake during the evaluation visits. Treatment effects were estimated using linear mixed-effects models. In a subset of 15 patients and additional 15 matched controls, thirst perception and neuronal activity in response to beverage pictures were assessed by functional MRI.

Findings Patients on dulaglutide reduced fluid intake by 490ml [95%-CI -780, -199], p=0.002, from 2950ml [95% CI 2435, 3465] on placebo to 2460ml [95% CI 1946, 2475] on dulaglutide (model estimates), corresponding to a relative reduction of 17%. 24-hour urinary output was reduced by -943ml [95%-CI -1473, -413], p=0.001. Thirst perception in response to beverage pictures was higher in patients with primary polydipsia versus controls and lower on dulaglutide versus placebo, but functional activity was similar between groups and treatments.

Interpretation GLP-1 receptor agonists reduce fluid intake and thirst perception in patients with primary polydipsia and could therefore be a treatment option for these patients.

Trial registration: Clinicaltrials.gov NCT02770885

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INTRODUCTION

Primary polydipsia is characterized by exaggerated thirst perception and excessive drinking (1, 2). This syndrome has most often been described in psychiatric patients (3) but seems increasingly prevalent in health conscious people who voluntarily change their drinking habits with the aim to improve their well-being (4). However, high fluid intake is not always healthy or harmless. In fact, it may lead to life-threatening water intoxication, hyponatremia and cerebral edema (1). In the light of these consequences, primary polydipsia merits careful evaluation and appropriate treatment. Unfortunately, few treatment options exist (5). Behavioral therapy is often ineffective because of the compulsive component of this disorder and the persistent thirst perception (6, 7). In psychiatric patients, medications such as clozapine, risperidone or lithium have been proposed in case reports or case series and may modulate drinking behavior by controlling psychotic symptoms (8, 9). However, the unfavorable side effects, such as weight gain and diabetes mellitus, render these medication unsuitable outside of the acute psychiatric setting(10). So far there are no published randomized controlled trials investigating pharmacological treatment options on fluid intake in primary polydipsia.

The hormone glucagon-like peptide-1 (GLP-1) is released in response to food intake (11, 12) and is involved in central regulation of appetite and energy intake (13, 14). GLP-1 receptor agonists (GLP-1 RA) are widely used to treat diabetes mellitus and obesity.(15) Emerging evidence suggest that the satiating properties of GLP-1 are not limited to food intake, but may also have an impact on thirst and drinking behavior (16-19). In fact, neurons of the lamina terminalis – a key brain structure for sensing thirst and regulating water balance (20, 21) – express GLP-1 receptors and are believed to confer satiety of thirst during fluid ingestion (22). In rats, McKay et al. observed a reduction of fluid intake on GLP-1 RA treatment, which was independent of food intake (23). In humans, we have recently shown that the GLP-1 RA dulaglutide tends to reduce fluid intake and lowers 24-hour urinary output in healthy volunteers (24).
GLP-1 may regulate not only homeostatic thirst, but might also have a role in hedonic control and the pathophysiology of addiction (25, 26). The compulsive or addictive components of primary polydipsia may, therefore, be targeted by GLP-1 RA.

The aim of this trial was to investigate whether GLP-1 RA as compared to placebo reduce fluid intake in patients with primary polydipsia. Secondly, we aimed to explore the effect of dulaglutide as compared to placebo on thirst perception, brain activity and resting-state functional connectivity.
RESULTS

Baseline characteristics

Between 2016 and 2019 a total of 35 patients were enrolled in the trial and randomly assigned (figure 1). One patient withdrew informed consent after the first study drug injection because of adverse events, i.e., recurrent vomiting (unblinding showed that the patient had received dulaglutide). The other 34 patients, who all received the intended treatment and were analyzed, were predominantly female (67.6%) and had a median [IQR] age of 29.5 years [26.0, 38.8]. Fourteen (41.2%) patients had psychiatric comorbidities and were labeled as “psychogenic polydipsia” whereas the remaining 20 patients were labeled as “habitual polydipsia”. At baseline, median [IQR] reported fluid intake was 4500 ml per day [3600, 5000]. Baseline characteristics are shown in table 1. Baseline characteristics before placebo treatment according to treatment sequence, i.e., placebo or dulaglutide first, was similar between the two groups. The only apparent difference was an increased diastolic blood pressure before the beginning of placebo in patients who received dulaglutide first. However, this patient group also had a higher diastolic blood pressure as compared to the other randomized patient group at the beginning of the first treatment, see table S1.

Fluid intake and 24-hour urinary output

The estimated total fluid intake under placebo was 2950 ml [95% CI 2435, 3465] versus 2460 ml [95% CI 1946, 2475] on dulaglutide. Hence, patients on dulaglutide had an estimated reduction in fluid intake of -490 ml [95%-CI: -780, -199] ml, p=0.002, as compared to placebo (figure 2A). This corresponds to a relative reduction of 17%. Two thirds of patients drank less on dulaglutide as compared to placebo (figure 2B). These findings were consistent in the per-protocol analysis (estimated mean difference [95% CI] dulaglutide versus placebo -492 ml [-811, -173]) and in the sensitivity analyses adjusting for adverse effects at beginning of the evaluation visit (-474 ml [-812, -136]) or anytime during the evaluation visit (-428 ml [-850, -6]).
Estimated 24-hour urinary output on dulaglutide was lower as compared to placebo: 3591 ml [95%CI 2922, 4260] vs 4534 ml [95%CI 3865, 5203]; estimated mean difference -943 ml [95%CI -1473, -413], p=0.001.

We found no evidence for a difference between patients with psychogenic versus habitual polydipsia regarding total fluid intake or 24-hour urinary output (post-hoc analyses, data not shown). Body weight, median [IQR], remained stable during the study period (65.8kg [55.3-77.5] and 65.3kg [56.5-78.5] on dulaglutide and placebo, respectively).

**Thirst and drinking behavior**

Acute thirst perception at different time points of the evaluation visit was lower on dulaglutide versus placebo (supplementary figure S1). Reported thirst perception of the preceding weeks remained constant during treatment with dulaglutide and increased slightly on placebo.

Reported daily fluid intake decreased on dulaglutide from median [IQR], 4500 [3625, 5000] ml to 3000 [2500, 3875] ml, while it remained constant on placebo: from 4000 [4000, 5000] ml to 4000 [3500, 5000] ml. The estimated, baseline adjusted, difference during the week preceding the evaluation visit between dulaglutide and placebo was -1257 ml [95%CI -1751, -764], p-value < 0.001 (figure 3A).

Self-reported daytime voiding frequency, median [IQR], decreased on dulaglutide from 9.5 [6.0, 12.0] to 7.5 [6.0, 9.0] while we observed no obvious decrease on placebo: from 10.0 [6.5, 12.0] to 9.5 [7.0, 11] (figure 3B). The proportion of patients reporting drinking at night did not change, but nocturia decreased on dulaglutide, while it slightly increased on placebo (figure 3C). Nocturia resolved in 7/19 patients on dulaglutide and in 1/16 patients on placebo.

**Serum and urinary electrolytes**

At the beginning of the evaluation visit, patients' serum sodium levels were in the normal range and did not differ between dulaglutide and placebo (median [IQR]: 140 mmol/l [138; 141] versus 140 mmol/l [138; 141]). 24-hour urinary electrolytes were similar on dulaglutide versus placebo. Particularly, our data provided no evidence of a difference in urinary sodium excretion.
between the treatment arm (estimated mean difference [95%-CI]: -8.67 mmol/l [-19.37, 1.82]), p=0.12, see supplementary table S2.

Looking at individual differences in sodium or urine osmolality changes during the evaluation visit while patients were freely drinking, a less pronounced decreased of these parameters was observed for most patients on dulaglutide versus placebo if, see supplementary figure S2 and S3.

Quality of life

At baseline, i.e. before both treatment phases, patients indicated a moderate reduction in quality of life due to symptoms of polyuria-polydipsia (numerous rating scale; median [IQR]: 3.00 [0.25, 4.75] for dulaglutide and 3.0 [1.25, 5.00] for placebo). This decreased on both treatments, slightly stronger on dulaglutide as compared to placebo; baseline-adjusted estimated mean difference [95%CI]: -0.9 [-1.9, 0.1] p=0.019.

Results of the SF-12 quality of life questionnaire did not show a clear change on dulaglutide or placebo treatment, see supplementary appendix.

Adverse effects

Gastrointestinal side effects were more prevalent on dulaglutide versus placebo and peaked during the first treatment week. In the morning of the evaluation visit the number of patients reporting nausea was balanced between the treatment arm (two each). See table S3 and supplementary figure S4.

Two patients developed mild hyponatremia during both evaluation visits. In the first patient (female, 56 years, on multiple medications inclusive low dose quetiapine), minimum plasma sodium on dulaglutide was 133 mmol/l and on placebo 131 mmol/l. In the second patient (healthy female, 24 years) minimum plasma sodium on dulaglutide was 132 mmol/l and on placebo 133 mmol/l. Both patients had chronic profound primary polydipsia (reported daily fluid intake of 5000 ml and 6000 ml and collected 24-hour urinary output of 6000 ml per day at baseline). The first patient showed a reduction of fluid intake (during the evaluation visit) from
6500 ml to 4400 ml on dulaglutide, while the second patient did not respond to dulaglutide (fluid intake of 6700 ml and 7400 ml on dulaglutide and placebo, respectively). A few other adverse effects were recorded during the study drug intervention, e.g., fatigue, headache and mild upper respiratory tract infections. They were similar between the treatment arms and were considered as unrelated to the trial drug (data not shown).

**fMRI results**

Baseline characteristics of 15 primary polydipsia patients from the mother study (11 females, median [IQR] age 32 years [25, 39.5], 2 left-handed) and additional 15 matched controls enrolled in the fMRI sub-study are shown in supplementary table S4. Plasma sodium concentrations at the time point of the fMRI sessions were in the mid-normal range and similar for patients on dulaglutide as well as placebo and for controls (data not shown).

Thirst ratings in patients were highest on placebo treatment while exposed to beverage pictures (numerous rating scale; median [IQR] 6, 6-6). Dulaglutide reduced thirst ratings both while viewing beverage pictures (numerous rating scale; median [IQR] 6, 4.5-6), p=0.0017, and control pictures (numerous rating scale; median [IQR] 5 [3-5] vs 3 [2-5], p=0.0016). In matched controls, thirst ratings were higher while exposed to beverage versus control pictures, but both ratings were lower as compared to patients with primary polydipsia, see figure 4.

The whole-brain analysis did not reveal any treatment: stimuli interaction effect in patients. The analysis of the main effect of treatment across both stimuli did not reveal any significant difference (supplementary figure S5 A and B). The analysis of the main effect of stimuli did not reveal any specific activation of regions linked to thirst regulation or motivation while exposed to beverage pictures, not even in the subgroup of participants with a high thirsting state, supplementary figures S6 A and B.

When comparing controls and patients on placebo there was no treatment: stimuli interaction effect, supplementary figure S7.
Resting-state functional connectivity in the reward network or the hypothalamus did not differ between dulaglutide and placebo, nor between patients as compared to controls.
DISCUSSION

Our results provide evidence that GLP-1 RA have hypodipsic properties and lead to a reduction in fluid intake and thirst perception in patients with primary polydipsia, offering a pharmaceutical treatment option in these patients.

The hypodipsic effect of dulaglutide was independent of food intake and was not a consequence of altered body weight on dulaglutide treatment, which is in line with data from rodents and healthy volunteers (23, 24).

Dulaglutide decreased fluid intake on the evaluation visit by 17% which was more than the expected 13% reduction. Although we are not able to compare the efficacy of dulaglutide to other pharmacological treatments due to lack of data (5), we judge the hypodipsic effect of dulaglutide to be clinically relevant. Given the short observation period of 8 hours and the artificial setting with limited choice of beverages, the obtained effect size of 17% reduction may even underestimate the therapeutic impact of dulaglutide in the real-life setting. In fact, self-reported average daily fluid intake decreased by more than 30% (mean difference of -1600 ml per day) on dulaglutide which is in line with the assessed mean 24-hour urinary output reduction of 1000 ml per day. As a consequence, daytime voiding frequency and nocturia decreased on dulaglutide and polydipsic patients felt less constrained by polyuria-polydipsia symptoms. Additionally, serum sodium and urinary osmolality showed a lesser decline throughout the day in most patients receiving dulaglutide, supporting the clinically relevant impact of reduced fluid intake on dulaglutide.

In a healthy individual, the regulation of thirst and drinking integrates both homeostatic and behavioral signals (21, 22, 27), i.e. fluid intake is calibrated according to physiological need before osmolality and blood volume effectively change (28, 29), GLP-1 seems to have a direct role in this regulatory circuit (30) as enriched GLP-1 receptor expression has been found in thirst-inhibitory neurons of the lamina terminalis (22) – a key brain structure for water homeostasis (20). In rats, a polydipsic overdrinking phenotype was observed after ablation of these GLP-1 receptor expressing thirst inhibitory neurons (22). In our trial, dulaglutide had an important impact on thirst perception. Acute thirst ratings during the evaluation visit as well as
during the thirst craving task in the fMRI session were clearly lower on dulaglutide as compared to placebo – although we were not able to detect associated changes in functional brain activity. As expression of an exaggerated thirst perception, patients (on placebo) versus matched controls scored higher thirst ratings irrespective of beverage or control pictures. Dulaglutide reduced patients’ thirst ratings while exposed to control pictures into the range of matched controls. Importantly, polydipsic patients never reached thirst satiation, not even in the presence of free water access. Sodium levels of participants were in the mid-normal range and did not differ between treatment arms or patients and matched controls. Based on our results, the exaggerated thirst perception or desire for drinking in primary polydipsia seems uncoupled from osmolality and homeostatic factors.

Besides homeostatic aspects, drinking behavior is also influenced by psychological factors such as motivation and learning. The compulsive component of fluid intake in primary polydipsia shares similar features with other addictive behaviors such as excessive eating or drug intake (25, 31). Interestingly, growing literature imply that GLP-1 is also involved in reward regulation and the pathophysiology of addiction (25) as GLP-1 receptors are expressed in brain areas related to reward processing (32-34). Peripheral GLP-1 administration in humans has been shown to modulate functional brain activity in regions such as amygdala, insula, caudate, putamen and orbitofrontal cortex - supporting this hypothesis (35, 36). Therefore, we assume that hypodipsic properties of dulaglutide in primary polydipsia may also be explained by modulation of addictive components of this condition. With our exploratory fMRI sub-study, we were not able to reinforce this hypothesis. Specifically, we did not observe altered resting state functional connectivity between homeostatic and reward-related brain areas on GLP-1 RA, as previously showed in healthy volunteers by Meyer-Gerspach et al. (37).

The most important complication of primary polydipsia is water intoxication and hyponatremia (38). In our trial, two patients experienced mild hyponatremia during the evaluation visits, both receiving placebo and dulaglutide. In primary polydipsia, hyponatremia occurs when fluid intake exceeds urinary and insensible losses (38). Thus, the risk of hyponatremia increases in profound polydipsia and if the renal capacity to excrete water is
impaired (39, 40), e.g., due to stimulation of the antidiuretic hormone. This may be triggered by medication, acute infection, stress or by low solute intake in malnutrition/anorexia. The two patients experiencing hyponatremia suffered from profound polydipsia characterized by a baseline 24-hour urinary output of more than 6 l/d. One patient received quetiapine, an antipsychotic drug known to predispose for hyponatremia. The second patient had no other risk factor but did not respond to dulaglutide.

Guidelines for managing primary polydipsia are lacking (5). To avoid complications, it seems sensible to minimize factors impairing the renal capacity to excrete water on one hand, while addressing the compulsive drinking behavior on the other. A combination of pharmaceutical treatment (e.g. dulaglutide) and cognitive behavioral therapy might be a reasonable approach, but more research is needed in this area.

This trial has limitations: First, the treatment period of three weeks was short and we are unable to make conclusions about long-term effects of dulaglutide in primary polydipsia. Second, gastrointestinal symptoms, known and frequent side effects of GLP-1 RA at the beginning of treatment, may have interfered with the obtained results. Reassuringly, during the evaluation visit and assessment of the primary endpoint, gastrointestinal symptoms were similar in the two treatment arms and hypodipsic properties were also confirmed after adjusting for gastrointestinal adverse effects and accounting for treatment sequence.

In terms of blinding, it is likely that gastrointestinal symptoms at treatment start with dulaglutide had compromised the blinding in this study. This has to be kept in mind while interpreting patient-reported secondary outcomes that are particularly prone to be affected by the knowledge of the assigned intervention.

Third, we did not assess the primary outcome “total fluid intake” at baseline which lowers the confidence in the observed treatment effect.

Forth, dulaglutide is one of the larger GLP-1 RA molecules (>50-60 kilo Dalton) with possibly impaired blood brain barrier permeability (41). Our results are, therefore, not directly transferrable to other GLP-1 RAs. However, smaller molecules with enhanced access to the central nervous system (e.g. liraglutide, semaglutide or lixisenatide) (42) may be even more
potent in reducing fluid intake in primary polydipsia. Fifth, the fMRI sub-study did not detect changes in functional brain activity despite clinically meaningful changes in the behavioral data. This is likely explained by the limited number and probably also by the non-thirsting state of participants. Becker et al. (43), who used the same thirst craving task in healthy controls, observed increased neural responses to beverage versus control pictures in a thirsting state (no drinking for 7 hours), but not in the no-thirst session.

The strength of our work is the prospective, double-blind, placebo-controlled trial design and the reasonably large cohort of patients with primary polydipsia. Due to the high prevalence of psychiatric comorbidities, undertaking randomized controlled trials in primary polydipsia patients is difficult which is also mirrored by the lack of research in this field (5).

In summary, our data show that a 3-week treatment with the GLP-1 RA dulaglutide reduces fluid intake, thirst perception and voiding frequency in patients with primary polydipsia. This proof of concept study is a first approach to provide a pharmaceutical treatment option for patients with primary polydipsia, where currently no effective treatment options exist.
MATERIALS AND METHODS

Study design and participants

This is a single-center, randomized, double-blind, placebo-controlled, 3-week crossover-trial, conducted at the University Hospital Basel, Switzerland. 50 participants (35 patients with primary polydipsia and 15 controls) were enrolled. Inclusion criteria for patients were age 18 to 65 years, and a diagnosis of primary polydipsia based on polydipsia of >3000ml per day and polyuria >50 ml/kg body weight per day. Exclusion criteria were central or nephrogenic diabetes insipidus (excluded by water deprivation test or hypertonic saline test), secondary polyuria (e.g., diabetes mellitus, hypokalemia, hypercalcemia), inability to follow the study procedures e.g. due to unstable psychiatric conditions, history of pancreatitis and treatment with GLP-1 RA within the last 3 months.

An exploratory functional magnetic resonance imaging (fMRI) case-control sub-study was conducted in a subset of 15 patients and 15 matched controls. Exclusion criteria for patients to participate in the fMRI sub-study were any medical condition affecting the brain (e.g., stroke, epilepsy, multiple sclerosis), any ferromagnetic non-removable device and claustrophobia. Controls were matched for age, sex, nicotine consumption, psychiatric comorbidities and handedness. Matched controls underwent one fMRI session only and did not receive the study drug.

The trial protocol and drug were approved by the Ethical Committee North-West and Central Switzerland (EKNZ, Basel) and the national agency for the authorization and supervision of therapeutic products (Swissmedic, Berne). Written informed consent was obtained from each participant after full explanation of the purpose and nature of all procedures used. The trial was registered on ClinicalTrials.gov (NCT02770885).

Trial objective and outcomes

The objective of this trial was to explore whether a 3-week treatment with the GLP-1 RA dulaglutide as compared to placebo reduces fluid intake in patients with primary polydipsia. The primary outcome was total fluid intake (in ml) during an 8-hour evaluation visit.
Further outcomes were thirst perception during the preceding weeks and during the evaluation visit, 24-hour urinary output, day and nighttime voiding frequency, quality of life, serum and urine electrolytes and osmolality and adverse effects, e.g., gastrointestinal symptoms.

The objective of the exploratory fMRI sub-study was to assess whether dulaglutide as compared to placebo alters behavioral aspects (thirst rating) and neuronal activity of patients while exposed to desirable beverage and control pictures. Further, we aimed to explore the effect of dulaglutide on resting state functional connectivity of homeostatic and reward-related brain regions.

**Trial procedures**

The trial procedures and timeline are schematically displayed in figure S8 of the supplementary data. Allocation to treatment sequence was randomized 1:1 based on a prefabricated randomization list of the Clinical Trial Unit Basel integrated in the electronic data capture system. Patients, investigators and study nurses were blinded except one unblinded study nurse who injected the trial medication. Patients received a 3-week treatment with dulaglutide (Trulicity®) 1.5 mg or placebo (0.9% sodium chloride) subcutaneously once weekly and attended an 8-hour evaluation visit during the last treatment week. After a wash-out period of at least 3 weeks, patients received the complementary intervention. For the fMRI sub-study, patients attended two additional visits and underwent an fMRI session during the last treatment week in each treatment phase.

**Assessment of fluid intake and urinary output during the evaluation visit**

Patients arrived at 8.00 am at the trial site after an overnight fast (no food and beverages) for 12 hours. On arrival, patients were requested to void their bladders and a 24-hours urine collection was started. Clinical parameters and symptoms were assessed at 8.00 am, noon and 4.00 pm. A water dispenser with a content of 10 liters was provided and refilled if necessary. Patients were invited to drink freely from the provided water, but they were blinded to the amount of water in the dispenser. At 8.30 am and at noon standardized, savory meals
were provided (consisting of 116 g carbohydrates, 60 g fat, 25 g proteins, 12 g fibers and 5.7
g salt, in total 1284 kcal). To standardize for food intake, patients were requested to consume
the entire meals, irrespective of their appetite. Besides the provided water and meals no other
beverages or food were allowed. At 4.00 pm, patients were asked to void their bladders and
instructed to collect their urine until 8.00 am of the following day.

Assessment of thirst perception, drinking behavior and electrolytes

Thirst perception was assessed in three different ways: first, we assessed average thirst
perception of the preceding week at the weekly study visit using a 10-point numerous rating
scale (0 = no thirst, 10 = extreme thirst). Second, during the evaluation visit, patients were
asked at 8.00 am, 9.00 am, noon, 1.00 pm and 4.00 pm to indicate their current thirst
perception on the 10-point numerous rating scale. Third, during the fMRI examination, thirst
was rated while exposed to desirable beverage pictures as described below on a 7-point
numerous rating scale.

Drinking behavior was assessed at the weekly study visits: reported average daily fluid intake
and average daytime voiding frequency as well as drinking at night and nocturia (yes/no) of
the preceding week.

Electrolytes, glucose and osmolality were assessed in plasma and urine at the screening visit
as well as during the evaluation visits. Urinary electrolytes were also measured in the collected
24-hour urine.

Assessment of quality of life

We assessed quality of life in two ways at each weekly study visit and at the evaluation visit
(relating to the timespan of the preceding week): First, patients were asked whether and how
symptoms of polyuria and polydipsia (e.g., constant thirst, daytime voiding frequency, nocturia)
had affected their quality of life on a 10-point numerous rating scale (i.e., 0 = quality of life not
reduced, 10 = quality of life maximally reduced). Second, patients responded to the
standardized short form 12 (SF-12) questionnaire, a standardized questionnaire to assess quality of life. Higher scores indicate a better health state.

Assessment of adverse effects
At the weekly visit and during the evaluation visit, gastrointestinal symptoms, i.e. nausea and abdominal pain, were assessed on a 10-point numerical rating scale (e.g., 0 = no nausea, 10 = unbearable nausea). Other adverse effects were recorded in free text.

Functional MRI
Detailed information about the fMRI session methodology are given in the supplementary appendix. In brief, fMRI sessions consisted of a high-resolution structural image (T1) and two functional tasks (thirst rating task, resting state). The fMRI paradigm showed pictures of beverages (n = 24) and chairs (n = 24) on uniform gray-colored background. Pictures were pseudorandomized in 10 sets (5 sets of chair and 5 sets of beverage) of 10 pictures, each picture shown for 2 seconds without interruption. After each set, patients had 4 seconds to rate their perceived thirst on a 7-point numerical rating scale. For standardization, patients abstained from drinking, eating and smoking for at least 3 hours before the fMRI examination. Serum sodium concentration was measured prior to the scan.

Sample size estimation
Sample size was estimated to show, with a power of 80%, a 13% stronger decrease in the primary endpoint under dulaglutide as compared to placebo. Based on own data, we assumed a mean (sd) fluid intake of 4630ml (1710ml) before start of treatment. We expected a decrease of 7% under placebo and 20% under dulaglutide. We used a random sampling procedure and examined sample sizes ranging from 20 to 120 patients by drawing 999 times each from a bivariate normal distribution with assumed mean (sd) of 4.3l (1.7l) after placebo and 3.7l (1.7l) after dulaglutide with a within-subject correlation of 0.8. Using a Wilcoxon signed rank test, the Null hypothesis was rejected if the resulting p-value was lower than 0.05.
Accounting for a dropout rate of 15%, a total of 35 patients should be recruited in order to have 29 evaluable patients.

**Statistical analysis**

Statistical analyses were pre-planned in a statistical report and analysis plan prior to data base closure. The primary endpoint, and – unless indicated otherwise – all continuous secondary endpoints, were analyzed for a treatment effect (dulaglutide - placebo) using linear mixed-effect models (LMM). First, treatment sequence and interaction term between trial arm and sequence were included to account for carry-over effect of the study drug. These analyses did not indicate a main effect of treatment sequence or an interaction effect of treatment. Therefore, the overall treatment effect was estimated. Detailed statistical methodology is described in the supplementary appendix. Estimated treatment means and the mean difference are reported with 95% confidence interval. The main analysis of the primary endpoint was performed as intention-to-treat analysis including all patients (full analysis set). Further, a per-protocol analysis was performed based on 31 patients who received all three injections in each trial phase. In addition, we performed sensitivity analyses, including adverse effects at the beginning and at any time-point during the evaluation visit as additional covariates with interaction term in the statistical model.

No missing values occurred for the primary endpoint. All secondary analyses were performed on complete cases of the full analysis set. Missing values were rare. We report the number of available measurements for each endpoint.

Analyses were performed using the statistic program R, Versions 3.6.0 and 4.0.2 (46). Linear mixed-effects models were fitted using the R package lme4, p-values was derived using the R package lmerTest. P-values and widths of confidence intervals are not adjusted for multiplicity.

**fMRI sub-study analyses:**

No missing values occurred for the fMRI data. In patients, brain activation was compared between treatment (dulaglutide vs placebo) and stimuli (chair vs beverage) by means of an
interaction analysis (treatment: stimuli). The hypothesis was that dulaglutide diminishes the activation of thirst-related areas during the presentation of beverage stimuli. Similarly, brain activation was compared between group (patients on placebo vs controls) and stimuli (chair vs beverage) by means of an interaction analysis (group: stimuli). We assumed that patients would have a higher activation than controls in thirst-related areas such as cingulate cortex, insular cortex or the amygdala while exposed to beverage pictures.

In a subgroup analysis, only participants in a high thirst state were analyzed (14 patients on placebo and 10 controls reporting a median thirst rating of 5 or more), assuming a higher activation of thirst-related areas during the presentation of beverage stimuli, as compared to chairs (43).

Functional connectivity of three key regions of the reward network (left accumbens, right accumbens, midbrain) and the hypothalamus (see supplementary figure S9) with the rest of the brain was assessed during the resting-state session (37). In patients, the main effect of treatment on functional connectivity values was tested with the hypothesis that functional connectivity between those core regions and other regions of the reward network would be altered on dulaglutide, as compared to placebo (37). Similarly, functional connectivity of those regions was compared between patients under placebo and controls.

Details of the statistical analyses of the fMRI data are described in the supplementary appendix. Raw, unthresholded statistical maps will be made publicly available on NeuroVault (https://neurovault.org; https://identifiers.org/neurovault.collection:8995).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report. The first and the last authors had access to all the data and had final responsibility for the decision to submit for publication.
AUTHOR CONTRIBUTIONS

BW designed the study and wrote the protocol, collected, analyzed and interpreted the data, did the literature search and wrote the manuscript. COS was involved in the study design, collected, analyzed and interpreted the data, did the literature search and wrote the manuscript. Within the first-author position, BW is named first as she initiated and designed the study. DC analyzed and interpreted the fMRI data, contributed to the manuscript. DZ was involved in the study design and the set-up of fMRI data acquisition. DRV planned, performed and interpreted the statistical analyses and contributed to the manuscript. SU and JR contributed to data collection. MCC designed the study, interpreted data and supervised all steps of the conduct of the study. All authors edited and approved the final manuscript.

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References


The reconstructed CONSORT diagram for the randomized controlled trial.
Figures 2A and 2B: Observed total fluid intake during the evaluation visit on dulaglutide or placebo.

A: Thick line indicates the median; box indicates the interquartile range (IQR); whiskers include all points within the range of 1.5x the IQR; dots represent all points outside 1.5x the IQR. Please note that the figure shows descriptive summary statistics of data (“raw data”), while we report estimated means and mean difference from statistical models in the results (linear mixed-effect model with trial arm as single fixed effect and patient as random effect).

B: Within-patient differences in total fluid/water intake (within 8 hours) during the evaluation visit between treatment with dulaglutide versus placebo. Differences are calculated as the value on dulaglutide minus on placebo, hence, negative differences indicate a reduced fluid/water intake on dulaglutide, while positive values indicate an increased or unaltered fluid/water intake on dulaglutide.
Figures 3A, 3B, 3C: Time course of self-reported average daily fluid intake, daytime voiding frequency and nocturia.

A: Self-reported average daily fluid intake during the preceding week for each study injection visit and both treatment arms.

B: Daytime voiding frequency per day during the preceding weeks for each study injection visit and both treatment arms.

C: Patients reporting nocturia during the preceding week for each study injection visit and both treatment arms.

Thick line indicates the median; box indicates the interquartile range (IQR); whiskers include all points within the range of 1.5x the IQR; dots represent all points outside 1.5x the IQR.
Figure 4: Thirst perception during the functional paradigm of the MRI visit

Self-reported thirst perception on a 7-point numerous rating scale (NRS) of matched controls, patients on dulaglutide or placebo during the functional paradigm of the MRI visit. Thick line indicates the median; box indicates the interquartile range (IQR); whiskers include all points within the range of 1.5x the IQR; dots represent all points outside 1.5x the IQR.
<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>34</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>29.5 (26.0, 38.8)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>34 (100%)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>23.1 (20.7, 25.5)</td>
</tr>
<tr>
<td>Psychogenic polydipsia, n (%)</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Habitual polydipsia, n (%)</td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>Other comorbidities, n (%)</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>14 (41.2)</td>
</tr>
<tr>
<td><strong>Polydipsic characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Reported daily fluid intake (ml), median (IQR)</td>
<td>4500 (3600, 5000)</td>
</tr>
<tr>
<td>24h urine output (ml), median (IQR)</td>
<td>4700 (3900, 5600)</td>
</tr>
<tr>
<td>Daytime voiding frequency, median (IQR)</td>
<td>10 (8, 12)</td>
</tr>
<tr>
<td>Drinking at night, n (%)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Nocturia, n (%)</td>
<td>19 (56)</td>
</tr>
</tbody>
</table>

Abbreviations: n = number, BMI = body mass index; IQR = interquartile range.