Promising effects of oxytocin on social and food-related behaviour in young children with Prader–Willi syndrome: a randomized, double-blind, controlled crossover trial

R.J. Kuppens*†, S.H. Donze*† and A.C.S. Hokken-Koelegra*†

*Dutch Growth Research Foundation, and †Erasmus University Medical Center-Sophia Children’s Hospital, Subdivision of Endocrinology, Department of Pediatrics, Rotterdam, The Netherlands

Summary

Background Prader–Willi syndrome (PWS) is known for hyperphagia with impaired satiety and a specific behavioural phenotype with stubbornness, temper tantrums, manipulative and controlling behaviour and obsessive–compulsive features. PWS is associated with hypothalamic and oxytocinergic dysfunction. In humans without PWS, intranasal oxytocin administration had positive effects on social and eating behaviour, and weight balance.

Objective and hypotheses To evaluate the effects of intranasal oxytocin compared to placebo administration on social behaviour and hyperphagia in children with PWS.

Design Randomized, double-blind, placebo-controlled, crossover study in a PWS Reference Center in the Netherlands.

Method Crossover intervention with twice daily intranasal oxytocin (dose range 24-48 IU/day) and placebo administration, both during 4 weeks, in 25 children with PWS (aged 6 to 14 years).

Results In the total group, no significant effects of oxytocin on social behaviour or hyperphagia were found, but in the 17 children younger than 11 years, parents reported significantly less anger (P = 0.001), sadness (P = 0.005), conflicts (P = 0.010) and food-related behaviour (P = 0.011), and improvement of social behaviour (P = 0.018) during oxytocin treatment compared with placebo. In the eight children older than 11 years, the items happiness (P = 0.039), anger (P = 0.042) and sadness (P = 0.042) were negatively influenced by oxytocin treatment compared to placebo. There were no side effects or adverse events.

Conclusions This randomized, double-blind, placebo-controlled study suggests that intranasal oxytocin administration has beneficial effects on social behaviour and food-related behaviour in children with PWS younger than 11 years of age, but not in those older than 11 years of age.

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Introduction

Prader–Willi syndrome (PWS) is characterized by neonatal hypotonia with sucking problems, early onset of hyperphagia with impaired satiety, endocrine disturbances and a specific behavioural phenotype with stubbornness, temper tantrums, manipulative and controlling behaviour, obsessive–compulsive features and difficulties in changing routines.1–3 This results from the absence of expression of the paternally derived genes located on chromosome 15 at the locus q11-2-13, caused by a paternal deletion, maternal uniparental disomy, imprinting centre disorder or paternal chromosomal translocation.1 One of the nonexpressed genes in this region is MAGEL2.

MAGEL2-deficient mice have a major reduction of oxytocin in the hypothalamus and an altered onset of suckling activity resulting in impaired feeding and 50% mortality.4 Injection of a specific oxytocin receptor antagonist in wild-type mouse pups resulted in a similar feeding deficiency as seen in MAGEL2 mutants.4 Administration of oxytocin to MAGEL2-deficient mouse pups 3–5 h after birth normalized sucking and feeding behaviour and rescued all of them.4 Human newborns with PWS show similar sucking problems as found in the MAGEL2-deficient mice, which suggests that the lack of MAGEL2 gene might play a role in the sucking deficit seen in PWS newborns.

In adult patients with PWS, the number of oxytocin-expressing neurons in the hypothalamus was significantly decreased by 42% and plasma levels of oxytocin were relatively low in relation to their obesity.5,6 However, in 23 children with PWS between 5 and 11 years of age, high plasma levels of oxytocin were reported.7 Altogether, the oxytocin system in patients with PWS appears to be dysfunctional.

Oxytocin is known to be involved in food intake,8,9 body weight10,11 and social skills,12 all of which are seriously affected
in patients with PWS. The majority of patients with PWS have hyperphagia with impaired satiety, and they are severely at risk to become obese. They show symptoms of autistic spectrum disorder (ASD) and 36% of them fulfil the criteria of ASD.13 Social cognitive functioning is markedly reduced, which has major consequences for the family and surrounding and for the approach of patients with PWS.14,15 Currently, there are no treatment options for the hyperphagia and social behavioural problems of patients with PWS, but the oxytocin system is a promising target. Studies on intranasal oxytocin administration showed that oxytocin reduced body weight of obese non-PWS patients.10 Also, a single oxytocin gift improved emotion recognition in healthy and autistic adults16,17 and reduced repetitive behaviours in those with ASD.18

Only two studies have investigated the effects of oxytocin treatment in PWS. Tauber et al administered a single gift of 24 IU intranasal oxytocin to 24 adults with PWS. After two days, they showed increased trust in others and decreased sadness tendencies with less disruptive behaviour.19 In the placebo-controlled crossover study by Einfeld et al., 22 individuals with PWS aged 12–30 years received 18–40 IU intranasal oxytocin twice daily during 8 weeks, but they showed no benefit in the target behaviours or weight.20

Given the possible dysfunction of the oxytocin system in PWS and the involvement of oxytocin in social skills, food intake and body weight, we hypothesized that oxytocin supplementation in children with PWS would improve social behaviour and hyperphagia. We therefore investigated the effects of intranasal oxytocin administration on social behaviour, food intake and satiety in children with PWS in a randomized, double-blind, placebo-controlled, crossover study.

Methods

Subjects

To be eligible to participate in this study, subjects (1) had a genetically confirmed diagnosis of PWS, (2) were aged 6 to 14 years, (3) had social behavioural problems and/or a preoccupation with food, (4) were naïve for oxytocin treatment at time of enrolment and (5) used growth hormone therapy for at least 1 year and were still receiving it. Exclusion criteria were (1) severe psychiatric problems such as psychosis, serious illness or cardiac abnormalities; (2) allergic reactions or hypersensitivity to oxytocin; (3) medication to reduce weight (fat) other than GH; and (4) noncooperative behaviour resulting in inability to comply with intranasal administration and/or hospital visits.

Forty-two children with PWS were eligible. Parents of 17 children refused to participate; ten due to too large burden, five due to practical issues and two because the children themselves did not want to participate. The study group consisted of 25 children (14 boys, 11 girls) with PWS, aged 6–14 years. GH therapy was prescribed at an initial dose of 1 mg/m2/day, and dose was lowered in case of high IGF-1 levels. One child used levothyroxine and another used citalopram and aripiprazole.
food. Therefore, the Oxytocin Study Questionnaire was developed by three physicians and a psychologist, all very experienced in PWS. The questionnaire unravels (changes in) emotions, social and eating behaviour and possible side effects. Parents were asked to fill in the applicable change from −3 (much less frequently) to +3 (much more frequently), in which 0 was ‘no difference’. An example of a question is ‘In the last 4 weeks, my child was...sad’. Comparable questions were asked regarding being angry, being happy, showing food-seeking behaviour, having conflicts with others, etc.

**Assays**

All blood samples were determined in the same laboratory according to a standardized procedure. Levels of serum creatinine, hepatic enzymes and glucose were measured with COBAS 8000 systems of Roche, and thyroid function was measured with Vitros ECIQ immunoanalyzer system of Ortho Clinical Diagnostics. Oxytocin levels in blood samples were measured in duplo with an oxytocin ELISA kit (Enzo Life Sciences). To assure the content of the vials, one puff per child per phase was measured by the same oxytocin ELISA kit. In summary, all children had one vial with and one vial without oxytocin, which confirmed perfect execution of the randomization.

**Statistics**

Statistical analysis was performed by SPSS version 23.0. Calculation of the sample size was based on the Oxytocin Study Questionnaire. Parents answer questions about changes in eating behaviour and social behaviour, from −3 (much less frequently) to +3 (much more frequently), in which 0 was ‘no difference’. A decrease of four points was considered clinically relevant. Based on an SD of four, a power of 0.9 and significance level of 0.05, a total of 24 patients had to enter the two-treatment crossover study. Data were not normally distributed; therefore, nonparametric tests were used and data are expressed as median (interquartile range [IQR]) unless otherwise stated. Statistical analysis appropriate for crossover trials was used, taking into account any carry-over or treatment-period effect, calculated by Wilcoxon signed rank test and Mann–Whitney U-tests, but these were not found. Depending on the data, results of the visit (i.e. questions about changes) or differences (Δ) between visit one and two, and between visit two and three (i.e. Δweight) were used. The effect of oxytocin vs placebo was assessed by Wilcoxon tests in case of continuous data and McNemar tests in case of binary data. Correlations between effect of oxytocin or oxytocin levels and other parameters were assessed using Spearman’s rho. Differences were considered significant if P-value was <0.05.

**Study approval**

Written informed consent was obtained from parents and from children older than 12 years; assent was obtained in children younger than 12 years. The study protocol was approved by the Medical Ethics Committee of Erasmus University Medical Center, the Netherlands, and registered at Nederlands Trial Register NTR4950 (www.trialregister.nl).

**Results**

**Baseline characteristics**

Table 1 shows the baseline characteristics of the 25 children with PWS who were included between January and September 2015. Median age was 9.3 (range 6.0–13.7) years, and BMI was 2.4 (0.7–4.3) SDS. Thirteen (52%) patients had a deletion and 12 (48%) an mUPD. All received GH treatment with a median dose of 0.8 (0.6–1.0) mg/m2/day (≈0.024 mg/kg/day), started at a median age of 1.3 (1.0–2.2) years, with a median duration of GH treatment of 8.0 (5.7–9.2) years. The median dose of oxytocin was 16 IU (range 12–24) twice daily. All 25 children completed the study.

**Effects on social behaviour, food intake and satiety**

In the total group of 25 children with PWS between 6 and 14 years of age, no effects of oxytocin vs placebo treatment were found on social behaviour, food intake and satiety. In contrast to these nonsignificant effects of oxytocin in the total group, correlation analyses showed that a younger age was strongly associated with beneficial effects of oxytocin treatment on social and eating behaviour (P=−0.553, P=0.004 and P=−0.485, P=0.014, resp.), and therefore, subanalyses were performed. In line with the stratification, we divided the total group in 17 patients younger than 11 years and eight patients older than 11 years.

**Subanalysis in the younger children**

**Effects on social behaviour.** Parents filled out questionnaires about their child. The items anger, sadness and conflicts improved significantly during oxytocin treatment compared to placebo (P=0.001, P=0.005 and P=0.010, resp.) (Table 2, Fig. 1). The total Oxytocin Study Questionnaire score showed a significant improvement of −4 (−7.5 to −1) points during oxytocin treatment compared to placebo (P=0.001). Ten of 17 (58.8%) parents reported an improvement in social behaviour during oxytocin treatment, while four (23.5%) parents reported improvement during placebo (P=0.059).

**Effects on eating behaviour.** The 17 younger children showed a significant improvement in food-related behaviour during oxytocin treatment (P=0.011). During 4 weeks of oxytocin treatment, food-seeking behaviour and satiety remained similar (P=0.429 and P=0.713, resp.); however, at baseline, food-seeking behaviour was only reported by six (35.3%) of the 17 parents, and in three of them, food-seeking behaviour was seen a few times per year. In both phases, almost all children finished their standardized breakfast meal. Only three children left pancakes (median 95, range 70–140 gram) during oxytocin...


Table 1. Baseline characteristics of total group and per treatment schedule

<table>
<thead>
<tr>
<th></th>
<th>PWS (n = 25)</th>
<th>Oxytocin / Placebo (n = 11)</th>
<th>Placebo / Oxytocin (n = 14)</th>
<th>P*</th>
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<tbody>
<tr>
<td>Gender</td>
<td>14 boys, 11 girls</td>
<td>6 boys, 5 girls</td>
<td>8 boys, 6 girls</td>
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<tr>
<td>Genetic subtype (DEL/mUPD)</td>
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<td>6 / 5</td>
<td>7 / 7</td>
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<tr>
<td>Age (yrs)</td>
<td>9-3 (6-9 to 11-9)</td>
<td>9-0 (6-4 to 11-2)</td>
<td>10-3 (7-0 to 12-5)</td>
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<td>Height for age (SDS)</td>
<td>0-8 (0-2 to 1-6)</td>
<td>1-2 (0-4 to 1-7)</td>
<td>0-5 (0-0 to 1-1)</td>
<td>0.222</td>
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<tr>
<td>Weight for height (SDS)</td>
<td>2-0 (0-6 to 4-1)</td>
<td>2-3 (0-3 to 6-1)</td>
<td>1-9 (1-0 to 4-1)</td>
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<td>BMI for age (SDS)</td>
<td>2-4 (0-7 to 4-3)</td>
<td>2-4 (–0-1 to 6-3)</td>
<td>2-2 (1-2 to 3-9)</td>
<td>1.000</td>
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<tr>
<td>Age at start GH treatment (yrs)</td>
<td>1-3 (1-0 to 2-2)</td>
<td>1-3 (0-9 to 2-2)</td>
<td>1-5 (1-0 to 2-6)</td>
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<tr>
<td>Duration of GH treatment (yrs)</td>
<td>8-0 (5-7 to 9-2)</td>
<td>7-3 (5-3 to 9-0)</td>
<td>8-2 (5-9 to 9-3)</td>
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<tr>
<td>GH dosage (mg/m²/day)</td>
<td>0-8 (0-6 to 1-0)</td>
<td>0-8 (0-5 to 1-0)</td>
<td>0-8 (0-6 to 1-0)</td>
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<tr>
<td>Prepubertal/pubertal</td>
<td>16 / 9</td>
<td>7 / 4</td>
<td>9 / 5</td>
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Patients of 6 to 11 years

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<tr>
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<th>PWS (n = 17)</th>
<th>Oxytocin / Placebo (n = 8)</th>
<th>Placebo / Oxytocin (n = 9)</th>
<th>P*</th>
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<tbody>
<tr>
<td>Gender</td>
<td>9 boys, 8 girls</td>
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<tr>
<td>Genetic subtype (DEL/mUPD)</td>
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<td>4 / 4</td>
<td>5 / 4</td>
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<tr>
<td>Age (yrs)</td>
<td>7-3 (6-4 to 9-7)</td>
<td>7-8 (6-1 to 9-3)</td>
<td>7-3 (6-7 to 10-3)</td>
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</tr>
<tr>
<td>Height for age (SDS)</td>
<td>0-5 (0-0 to 1-3)</td>
<td>1-2 (0-0 to 1-6)</td>
<td>0-3 (–0-2 to 0-8)</td>
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<td>Weight for height (SDS)</td>
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<td>1-7 (0-4 to 5-3)</td>
<td>1-7 (0-9 to 3-9)</td>
<td>0.743</td>
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<tr>
<td>BMI for age (SDS)</td>
<td>1-9 (0-6 to 3-9)</td>
<td>2-1 (0-0 to 5-7)</td>
<td>1-8 (1-0 to 3-6)</td>
<td>0.963</td>
</tr>
<tr>
<td>Age at start GH treatment (yrs)</td>
<td>1-3 (0-9 to 1-7)</td>
<td>1-3 (0-8 to 2-0)</td>
<td>1-2 (0-9 to 1-5)</td>
<td>0.743</td>
</tr>
<tr>
<td>Duration of GH treatment (yrs)</td>
<td>6-3 (5-3 to 8-4)</td>
<td>6-3 (5-2 to 8-2)</td>
<td>6-3 (5-5 to 8-8)</td>
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<tr>
<td>GH dosage (mg/m²/day)</td>
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<td>0-7 (0-5 to 1-0)</td>
<td>0-7 (0-5 to 1-0)</td>
<td>0.963</td>
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<tr>
<td>Prepubertal/pubertal</td>
<td>14 / 3</td>
<td>6 / 2</td>
<td>8 / 1</td>
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Patients of 11 to 14 years

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<th>Placebo / Oxytocin (n = 5)</th>
<th>P*</th>
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<tbody>
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<td>3 boys, 2 girls</td>
<td></td>
</tr>
<tr>
<td>Genetic subtype (DEL/mUPD)</td>
<td>4 / 4</td>
<td>2 / 1</td>
<td>2 / 3</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>12-5 (11-6 to 13-7)</td>
<td>12-3 (11-8 to 13-0)</td>
<td>12-6 (11-9 to 13-7)</td>
<td>0.393</td>
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<tr>
<td>Height for age (SDS)</td>
<td>1-2 (0-6 to 1-6)</td>
<td>1-6 (1-1 to 1-8)</td>
<td>1-0 (0-2 to 1-6)</td>
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<tr>
<td>Weight for height (SDS)</td>
<td>2-2 (0-9 to 4-3)</td>
<td>2-3 (0-4 to 4-6)</td>
<td>2-0 (0-8 to 4-3)</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI for age (SDS)</td>
<td>2-8 (0-9 to 5-6)</td>
<td>3-2 (1-3 to 5-5)</td>
<td>2-5 (1-2 to 5-4)</td>
<td>1.000</td>
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<tr>
<td>Age at start GH treatment (yrs)</td>
<td>2-7 (1-8 to 4-3)</td>
<td>2-2 (1-6 to 2-9)</td>
<td>2-9 (2-1 to 4-9)</td>
<td>0.393</td>
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<tr>
<td>Duration of GH treatment (yrs)</td>
<td>9-5 (8-5 to 11-1)</td>
<td>9-9 (9-5 to 10-6)</td>
<td>8-5 (8-2 to 11-0)</td>
<td>0.393</td>
</tr>
<tr>
<td>GH dosage (mg/m²/day)</td>
<td>1-0 (0-7 to 1-0)</td>
<td>0-9 (0-8 to 1-0)</td>
<td>1-0 (0-7 to 1-0)</td>
<td>0.786</td>
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<tr>
<td>Prepubertal/pubertal</td>
<td>2 / 6</td>
<td>1 / 2</td>
<td>1 / 4</td>
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</tr>
</tbody>
</table>

*P-value at baseline between the two-treatment schedules.

Data expressed as median with interquartile range.

Subanalyses in the older children

Effects on social behaviour. We did not find beneficial effects of oxytocin in the eight children older than 11 years (Table 2). The items happiness, anger and sadness were negatively influenced by oxytocin treatment compared to placebo (P = 0.039, P = 0.042 and P = 0.042, resp.). The Oxytocin Study Questionnaire showed an unfavourable score of +1.5 (0.3–5) points during oxytocin treatment compared to placebo.
Effects on eating behaviour. During oxytocin treatment, food-related behaviour, food-seeking behaviour and satiety remained similar ($P = 0.066$, $P = 0.102$ and $P = 0.317$, resp.) in the children older than 11 years. In both treatment phases, all

(P = 0.027). Three (37.5%) parents reported a deterioration of social behaviour during oxytocin treatment, while four (50%) parents reported an improvement during placebo treatment ($P = 0.038$).
children finished their standardized breakfast meal, while the rate and duration of eating was similar during oxytocin and placebo treatment (23.8 vs 24.5 gram/min, \( P = 0.779 \) and 12.0 vs 11.6 min, \( P = 0.889 \)) (Table 2). 

### Associations

There were no significant differences in oxytocin vs placebo effects between boys and girls, between children with a deletion or mUPD, or between children with or without serious behavioural problems. The effects of oxytocin treatment were not associated with baseline BMI or BMI SDS. In the total group, the association between age and social and eating behaviour during oxytocin treatment was stronger than the association between pubertal stage and these outcomes \( (p = 0.533, P = 0.004 \) and \( p = 0.485, P = 0.014 \) vs \( p = 0.452, P = 0.023 \) and \( p = 0.396, P = 0.050 \), resp.).

### Oxytocin levels in blood

Serum oxytocin levels before and during study were determined to further unravel the different effects in younger and older children (Fig. 2). At baseline, children younger than 11 years had a median fasting oxytocin level of 3156 (1864–5325) pg/ml, and 12–14 h after the last oxytocin dose after 4 weeks of treatment it was 4685 (2809–9490) pg/ml \( (P = 0.134) \). Children older than 11 years had a baseline fasting oxytocin level of 2692 (1737–3754) pg/ml, and 4750 (1976–7831) pg/ml after oxytocin treatment \( (P = 0.327) \).

In the younger children, lower oxytocin levels after 4 weeks of oxytocin treatment were associated with positive effects on social behaviour \( (p = 0.540, P = 0.027) \). This association was not found in older children. Baseline oxytocin levels or change in oxytocin levels during treatment was not associated with positive effects.

![Fig. 2](image1.png)

**Fig. 2** Fasting serum oxytocin levels at baseline in pg/ml per age. ● represents a patient with positive effect of oxytocin treatment. ○ represents a patient without effect of oxytocin treatment. x represents a patient with negative effect of oxytocin treatment. The grey line indicates the age of 11 years.

Only one patient older than 11 years had benefit from oxytocin treatment. Remarkably, this patient had the highest baseline oxytocin level of patients older than 11 years, which decreased considerably to the lowest level of 1126 pg/ml during oxytocin treatment (Fig. 2). The other older patients without benefit had lower baseline oxytocin levels (Fig. 2), which increased or only slightly decreased during oxytocin treatment.

### Dosing

The oxytocin/placebo dose was based on body surface (see Methods). In the total group, median dose was 16 IU \( (12–20 \) twice daily, which was 12.3 \( (12.0–13.3 \) IU/m\(^2\) and 0.39 \( (0.34–0.44 \) per kilogram body weight (IU/kg). Given the different effects of oxytocin in the younger and older group of patients, the correlation between dosage and age was investigated. The dose in IU/m\(^2\) did not correlate with age, but the given dose recalculated as IU/kg correlated inversely with age \( (p = 0.663, P < 0.001) \), meaning that older patients received a lower dose when recalculated in IU/kg (Fig. 3). The median dose was 0.42 \( (0.37–0.45 \) IU/kg in the children younger than 11 years and 0.34 \( (0.30–0.37 \) IU/kg in the older children \( P = 0.002 \). Remarkably, the only patient older than 11 years, who had benefit from oxytocin treatment, had one of the lowest recalculated doses in IU/kg of the older patients and the lowest dose in IU/kg of all patients with beneficial effects of oxytocin.

### Safety parameters

The intranasal administration of oxytocin was very well tolerated, and there were no side effects. Renal function, hepatic
enzymes, thyroid function and glucose remained stable and normal for all patients, as did the systolic blood pressure. Diastolic blood pressure was lower during oxytocin treatment (median 64 vs 73 mmHg, \( P = 0.008 \)), but within normal limits. Similar results were found in patients younger or older than 11 years.

**Discussion**

Our randomized, double-blind, placebo-controlled, crossover study is the first oxytocin study in children with PWS aged between 6 and 14 years. Although there were no effects in the group as a whole, subanalyses demonstrated that children with PWS between 6 and 11 years had beneficial effects of intranasal oxytocin administration on social behaviour and hyperphagia. Their parents reported significantly less anger, sadness, conflicts and food-related behaviour, and improvement of social behaviour during oxytocin treatment compared with placebo. In children with PWS, older than 11 years were the beneficial effects of oxytocin on social behaviour and hyperphagia not found. We did not find side effects or adverse events.

Until now, there have been no effective treatment options for behaviour and food-related problems in PWS. Our study suggests that intranasal oxytocin administration is a novel and promising treatment for young children with PWS. Children with PWS have a specific behavioural phenotype with stubbornness, temper tantrums, manipulative and controlling behaviour, obsessive-compulsive features and difficulties in changing routines.\(^1\)–\(^3\) The social behavioural problems and hyperphagia seriously affect the quality of life of the children and their parents and caretakers.

Nowadays, most parents of children with PWS have made all kind of adjustments in everyday life to limit access to food, such as locks on the fridge.\(^24\) This explains why, prior to the study, children had a low prevalence of food-seeking behaviour. It is therefore not surprising that we found no effects of oxytocin on food-seeking behaviour. However, the baseline food-related behaviour scores show that these children are still pre-occupied with food, characterized by talking about food, asking for food, playing that they are cooking, etc., despite all the adjustments to control hyperphagia. Oxytocin treatment decreased this food-related behaviour, which argues that oxytocin has an inhibiting effect on the hyperphagia, despite the lack of effects on food-seeking behaviour and satiety. Studies on the long-term effects of 4 weeks treatment and also long-term oxytocin treatment trials are warranted to confirm our findings on efficacy and safety.

In contrast to the beneficial effects of oxytocin in the younger children, no positive effects were found in children with PWS older than 11 years. Some parents of the older subgroup even reported negative effects of oxytocin on social behaviour, especially regarding happiness, anger and sadness, in contrast to none of the parents of younger children. These findings are in line with the results of an 8-week oxytocin trial in 22 individuals with PWS between 12 and 29 years,\(^20\) in which no benefits in target behaviours or weight were found. The only significant difference found in that study was an increase in temper outbursts when the oxytocin dose was increased. Tauber et al. reported positive effects of oxytocin on social behaviour in adults with PWS, but comparison is difficult because they investigated a single dose of intranasal administration.\(^19\)

We measured plasma oxytocin levels prior and during the oxytocin trial. At baseline, oxytocin levels in children with PWS younger than 11 years showed high interindividual variability, in line with findings in children with PWS of similar age by Johnson et al.,\(^7\) and there was no relation between baseline oxytocin levels and positive effects during treatment. In contrast, a lower oxytocin level after 4 weeks of oxytocin treatment was associated with stronger positive effects on social behaviour, suggesting that it is beneficial for young children to have a lower plasma oxytocin level during oxytocin treatment. Those older than 11 years had, however, lower and less widespread baseline oxytocin levels and their levels increased during oxytocin treatment. The only older boy with beneficial effects of oxytocin treatment had a declining oxytocin level during treatment, like most of the younger children.

Why did the oxytocin treatment work in the younger, but not in the older children? One explanation could be that mistakes had been made in the preparation or delivery of the intranasal sprays in the older children. For that reason, an independent laboratory measured the content of the vials and was able to reject that explanation. Second, it could be that the sample size of the older subgroup was too small to show significant changes, but that argument is unlikely as several significant negative effects of oxytocin administration were found in the older subgroup. Third, there could have been a dosing issue. We calculated the oxytocin doses according to body surface, a common way of hormone dosing in children, which resulted in a relatively lower dose in IU/kg in children older than 11 years. However, an inappropriately low dose is also an unlikely explanation, as the only older boy with positive effects of oxytocin had the second lowest dose of all children in IU/kg. Besides, Einfeld et al. reported adverse effects of higher oxytocin doses in older patients.\(^20\) A fourth explanation could be that the behaviour and coping style of older patients with PWS are more embedded in their personality and are therefore not easy to change. A treatment period of 4 weeks is not short, but it could be that a longer period than four or 8 weeks of oxytocin treatment might be needed to induce beneficial effects in older children.

Another, more pathophysiological explanation might be that older children with PWS have developed an unresponsive oxytocin system over the years, with a lower number of oxytocin receptors and neurons in the hypothalamus. Adults with PWS have a 42% decrease in oxytocin neurons in the hypothalamus and relatively low plasma levels of oxytocin in relation to their obesity.\(^5,6\) One of the nonexpressed genes in the PWS region on chromosome 15 is MAGEL2. This gene is known to be expressed in mouse hypothalamus during development and their knockout alters the number and/or function of oxytocin neurons.\(^25\) MAGEL2–knockout pups were not hypotonic, but had an altered onset of sucking activity resulting in impaired feeding and 50% mortality,\(^4\) while the survivors had deficits in social recognition and social interaction on the long term.\(^26\) These sucking problems in infancy and social problems later on are similar to children with PWS, suggesting that this gene might play a role in the abnormalities seen in children with PWS.
suckling and behavioural problems in PWS. Adult MAGEL2–
knockout mice expressed a significantly reduced number of oxy-
tocin receptors in several regions of the brain. Children with
PWS, who are MAGEL2 deficient, could therefore be less or non-
responsive to oxytocin treatment when they become older,
because their oxytocin system deteriorated over time. In contrast,
it was shown that daily administration of oxytocin in the first
postnatal week prevents the deficits in social behaviour in the
adult mutant mice and partly restore a normal oxytocin system
in the brain. This suggests that the postnatal period is a critical per-
iod for the oxytocin system in which social behaviour is pro-
grammed. Nevertheless, our study shows that oxytocin treatment
has beneficial effects in children with PWS until the age of
approximately 11 years, thus also beyond the postnatal period.

It is remarkable that the changeover in oxytocin effects occurred
around the age of 11 years, the time of puberty onset. We previ-
ously demonstrated that GH-treated children with PWS have a
normal age at onset of puberty, but that the majority shows a dete-
rrioration in pubertal development after Tanner stage 2–3 with a
decline in gonadal function in boys. It might be that the reac-
tivation of the GnRH axis just before the onset of puberty together
with the lack of expression of MAGEL2 and other yet unknown
genes, not only result in a rapid gonadal failure after the onset of
puberty but also in an enhanced deterioration of the oxytocin sys-
tem in patients with PWS. We acknowledge that our supposition
is very hypothetical, but we consider it noteworthy to mention
that these processes seem to occur in the same timeframes. Studies
are warranted to further unravel the pathophysiology and to
determine whether others also find the 11-year cut-off for benefit
of oxytocin treatment.

Present study was a placebo-controlled study in which we cal-
culated the dose according to body surface, based on doses used
in other trials. We did not perform a dose-finding study, and no washout period was included to limit the number of
hospital visits. We found no differences in food intake during
the breakfast meal test between the oxytocin and placebo phase.
This might be due to the lack of a satiety level in PWS or that
their satiety level was much higher than the maximum amount
of food that we offered, but we considered it unethical to pre-
sent an unlimited amount of food as patients with PWS feel
never satiated and have an increased risk of gastric rupture.

In conclusion, administration of intranasal oxytocin appears
to have beneficial effects on social behaviour and food-related
behaviour in children with PWS younger than 11 years of age
without side effects or adverse events. Parents reported signifi-
cantly less anger, sadness, conflicts and food-related behaviour,
and improvement of social behaviour during oxytocin treatment
compared with placebo. In contrast to the younger children with
PWS, those older than 11 years of age did not benefit from
oxytocin treatment.

**Author contributions**

RJK substantially contributed to conception and design of study,
aquisition of data, analysis and interpretation of data and
drafting the manuscript. SHD substantially contributed to acqui-
sition of data, interpretation of data and critical revision of the
manuscript. AKH substantially contributed to conception and
design of study, analysis and interpretation of data and critical
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**Declaration of interest and Financial disclosure**

The authors have nothing to disclose.

**Key points**

- Prader–Willi syndrome (PWS) is known for hyperphagia
with impaired satiety and a specific behavioural phenotype with
stubbornness, manipulative and controlling behaviour and
obsessive–compulsive features. PWS is associated with hypotha-
lamic and oxytocinergic dysfunction.
- In humans without PWS, intranasal oxytocin administra-

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