Title:	Intranasal oxytocin to promote weight loss in children, adolescents and adults with brain tumors and hypothalamic obesity syndrome
NCT:	NCT02849743
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This document describes our plans and rationale for analysis of the intranasal oxytocin (OXT) weight loss trial data (NCT02849743). This document has been generated before un-blinding. Specifically, we review the a priori defined primary and secondary outcomes, and provide the preplanned analysis including sensitivity analyses to support the findings reported in the main text. We offer these details to further the goals of reproducible research. Analyses were performed with RStudio (v.1.4.1103).

1.0. Definition of the Endpoints

1.1. The primary endpoint will be the change in body weight over 8 weeks during OXT versus placebo treatment.

1.2. Secondary endpoints will include the following:

- Cognitive restraint (stop-signal task) after monitored dose of OXT versus placebo
- Calories consumed (as a percentage of calories offered) during a test meal after a monitored dose of OXT versus after a monitored dose of placebo
- The change in arm circumference, over 8 weeks during OXT versus placebo
- The change in waist circumference, over 8 weeks during OXT versus placebo
- The change in hyperphagia (Hyperphagia Questionnaire), hunger, disinhibition of eating, cognitive restraint (Eating Inventory), mental/emotional health and quality of life (Neuro-QOL), family function (FAD-GRS) over 8 weeks during OXT versus placebo
- Fat mass, lean mass, and % body fat (DXA) at the conclusion of 8 weeks OXT versus 8 weeks of placebo
- Resting energy expenditure (REE) at the conclusion of 8 weeks OXT versus 8 weeks of placebo
- Respiratory quotient (RQ) at the conclusion of 8 weeks OXT versus 8 weeks of placebo
- Usual energy intake (calories/day via self-reported 3-day diet record) at the conclusion of 8 weeks OXT versus 8 weeks of placebo
- Change in self-reported physical activity (via BMDCS-PA questionnaire) during 8 weeks of OXT versus 8 weeks of placebo
- OXT pulse profiling after exogenous OXT vs placebo
- Safety and tolerability of OXT based on AEs

2.0 Statistical Analysis

2.1. Primary Analysis:

For the primary outcome, i.e., the change in body weight during each treatment block, linear mixed-effects modeling will be performed to assess the effect of OXT on the outcome as compared to placebo. The primary model will include the treatment (i.e., OXT vs. PBO), the randomization sequence (OXT-PBO vs. PBO-OXT), and the starting body weight in each treatment block as a time-varying covariate. We will test for a carryover effect by including the interaction of treatment by sequence in the model. This interaction term will NOT be included in the primary model if it is not significant (i.e., $p > 0.05$). (**Table 4**)

2.2. Secondary Analysis:

Similar modeling approaches will be applied to the secondary outcomes that are continuous and measured in both Blocks as in the Primary Analysis (**Supplementary Table**).

2.2.1. Descriptive Analyses

Standard descriptive statistics will be used to summarize the demographics and baseline clinical characteristics of the participants (**Table 1**), and also to summarize primary and key secondary outcomes

related to OXT vs. PBO (**Table 2**). We will describe the retention during the study and adherence to OXT or PBO. Waterfall plots will be provided to display the change in body weight for each participant, stratified by the treatment (OXT vs. PBO). Additionally, spaghetti plots of the body weight measured at each visit will be made to inform the trajectory of body weight change over time during each treatment block. Similar plots will be produced for other outcomes of interest.

2.2.2. Adverse Events (AE)

Treatment-related AEs in each treatment period (OXT vs. PBO) will be summarized and reported as count (and %) in tables (**Table 3**). In this Table, we will include any AE that is at least possibly related to study drug, and either occurs in at least 2 participants (with any CTCAE grade for severity) and/or occurs in at least 1 participant (with CTCAE Grade 2 or higher). McNemar test will be performed to compare the prevalence of the AEs of interest between OXT and PBO. We will describe changes in ECG parameters and in sodium levels/DDAVP use, since cardiovascular and fluid balance considerations are special AEs of interest.

2.3. Additional Sensitivity Analyses

We will test the effect of sequentially adding age, gender, as well as the adherence to treatment to the primary model as sensitivity analyses to understand the extent to which these may influence the main result. Adherence is defined in two ways that capture different dimensions of likely effect: first, the average % of doses consumed as compared to prescribed during each treatment block, and second, the % of days during each block with complete adherence. In exploratory analyses, we will also test the extent to which hypothalamic damage (as reflected by the presence or absence of diabetes insipidus, and by centralized MRI-based assessment of hypothalamic damage) impacts response to treatment.

2.4. Power Calculations

We will perform power calculation based on our current sample size and observed standard deviation (SD) of the within-subject difference in the weight loss between OXT and PBO. Specifically, we will calculate the detectable effect size (and 95% CI) of the weight loss difference between OXT and PBO to reach 80% power at significance level of 0.05. We then compare this effect size with the observed effect size. Since we did not reach the original recruitment goal due to the COVID19 pandemic and new considerations regarding risk for QTc interval prolongation, we will do similar calculations and comparisons assuming the originally planned sample size.