Intranasal oxytocin administration improves mood in new mothers with moderate low mood but not in mothers with elevated symptoms of postnatal depression: A randomised controlled trial

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Accepted Manuscript

Citation: Lindley Baron-Cohen, K., Feldman, R., Fearon, P., & Fonagy, P. (2022). Intranasal oxytocin administration improves mood in new mothers with moderate low mood but not in mothers with elevated symptoms of postnatal depression: A randomised controlled trial. *Journal of Affective Disorders, 300,* 358-365. https://doi.org/10.1016/j.jad.2021.11.062

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Abstract

Background: Oxytocin (OT) is a neuropeptide hormone that has anxiolytic and antidepressant effects, and positive effects on social affiliation and behaviour, particularly in parenting and attachment relationships. In women with postnatal depression (PND), each of these are reduced. This study investigated if OT administration reduces low mood in new mothers with PND and across the low mood spectrum. **Design:** A double-blind, placebo-controlled, randomised controlled-trial, within-subjects, cross-over design was conducted. **Participants**: Mothers (N = 58) between 3-9 months postpartum. Participants were screened for traits of PND on the Edinburgh Postnatal Depression Scale (EPDS) and assigned into 2 groups: probable PND cases (N = 26, scoring ≥9) and controls (N = 32, scoring ≤9). **Method**: Participants rated their current mood on the Positive and Negative Affect Scale (PANAS) at Baseline (before nasal administration), Condition 1 (after first OT/Placebo administration) and Condition 2 (after second OT/Placebo administration). **Results:** OT administration did not affect mood in women with PND scores above the cut-off point but significantly reduced negative mood in those scoring below the cut-off point. To explore if a subgroup was driving this, we compared participants with mild, moderate and severe scores on the EPDS. OT administration significantly reduced negative mood in women with moderate low mood scores on the EPDS. **Limitations:** PND was assessed by the EPDS, rather than a clinical diagnosis. **Conclusion:** These results illustrate individual differences in response to OT administration and suggest that OT administration may offer treatment benefit to new mothers who report moderate sub-clinical levels of depression.

Keywords Oxytocin, postnatal depression, mood

1. Introduction

Postnatal depression (PND) has high clinical importance because it causes significant distress to new mothers, and in severe cases can lead to suicide (Boots Family Trust, 2013). PND is often underdiagnosed in community populations, and has continued to increase each decade (Granat et al., 2017). The most recent and largest global meta-analysis of prevalence, published in 2018, reported that the global pooled prevalence of PND in new mothers is 17.7% (Hahn-Holbrook et al., 2018). In addition, 50% of cases are not identified clinically and are only ascertained by community surveys, and therefore may not receive clinical support (NCT, 2017). Untreated PND is associated with longer-term maternal anxiety and depression beyond the postnatal period, as well relationship and social difficulties in these women (Slomian et al., 2019).

PND is also a concern for the infant, since infants of women with PND are at greater risk of psychosocial developmental difficulties and long-term mental health issues (Apter-Levy et al., 2013; Feldman et al., 2009; Priel et al., 2019a). PND disrupts the mother's regulatory behaviour, which mediates the impact of the mothers' depression on the child's emotional and executive functioning from infancy to late childhood (Priel et al., 2019b, 2019a). PND is also associated with reduced cognitive flexibility and abnormalities in the child's hypothalamic-pituitary-adrenal (HPA) axis stress management system (Apter-Levi et al., 2016). By age 6 years, 61% of children from chronically depressed mothers develop an Axis I psychiatric condition (e.g., anxiety, depression, or conduct disorder), compared to 15% of children from non-depressed mothers (Apter-Levy et al., 2013). By age 16 years, children of women that had PND are more than 40% likely to experience life-time depression (Murray et al., 2011). Altered stress reactivity has also been identified in the adult children of women who had PND (Barry et al., 2015). This suggests that exposure to early postnatal maternal depression has long-term negative effects on the infant through to adulthood, supporting 'sensitive period' models of early childhood for good long-term mental health (Feldman, 2015). It is therefore a clinical priority to intervene early, but despite this, there remains a lack of understanding about the condition and the treatments available.

Turning to the biology of this mother-infant dyadic system, the hormone oxytocin (OT) has attracted interest due to its role in regulating social and specific parenting behaviour, anxiolytic effects, as well as lactation during breastfeeding, each of which are areas that women with PND have difficulties (Jobst et al., 2016). PND is associated with reduced maternal plasma OT during pregnancy (Skrundz et al., 2011) and the postnatal period (Stuebe et al., 2013). In addition, OT has also been found to mediate the effects of maternal depression on child behavioural difficulties across the first decade of life (Priel et al., 2019a). Although it is still unclear whether disruption to the OT system is a cause or consequence of PND, dysregulation of the OT system may be an underlying mechanism impairing a woman's adaptation to motherhood, which is a risk factor for PND.

Regarding whether OT administration could be a potential treatment for PND, intranasal OT administration has been found to reduce stress and anxiety in adults (Heinrichs et al., 2003), and to reduce salivary cortisol levels (Ditzen et al., 2009). OT administration also activates brain areas involved in emotion regulation (Szymanska et al., 2017), and selectively increases trust (Van IJzendoorn and Bakermans-Kranenburg, 2012), emotion recognition (Marsh et al., 2010), facial communication (Pavarini et al., 2019) and eye contact (Auyeung et al., 2015). There is understandable reluctance to use ordinary antidepressants to treat PND as these have unwanted side effects, high relapse rate, and are not advised for women who are breastfeeding (Sockol et al., 2011). For these reasons, OT, being a natural hormone involved in breastfeeding and mother-infant bonding, is an important new candidate for treatment.

To date, as far as we are aware, there have been five randomised controlled-trials (RCTs) that have focused on OT nasal administration to treat PND specifically (De Cagna et al., 2019; Fortunata Donadon et al., 2020). Clarici et al (2015) evaluated symptoms of depression in new mothers after daily OT administration in combination with a 12 session weekly course of brief psychodynamic psychotherapy. Overall, there were no significant differences reported in low mood between OT and placebo (Clarici et al., 2015). However, this study was underpowered, with a total sample size of 16.

Three other studies were conducted by the Mah lab: In 2013, they found in a sample of 25 women with PND that OT administration improved the mother's perception of the relationship with her baby (Mah et al., 2013), although mood did not improve. In 2015, they reported that OT administration in 16 women with PND induced protective behaviours towards their infant, in the presence of a socially intrusive stranger (Mah et al., 2015). In 2017, they reported that OT administration led 25 women with PND to rate their infant's cry as having greater urgency (Mah et al., 2017). The most recent study, conducted by Fortunata Donadon et al (2020), measured negative thoughts as well as emotion recognition of infant facial expression in a sample of 20 women with PND and 35 controls. They reported a significant effect of OT on reducing negative thoughts in women with PND. OT was also associated with a maternal response bias to infant happy facial expressions in the PND group only, although it should be noted that in this sample there was no baseline group difference in accuracy of emotion recognition, which has been observed in other samples (Fortunata Donadon et al., 2020). Given that three out of five of these studies were from the same lab, with some overlap in the sample of participants, and only two of the studies reported measures of mood or negative thoughts, this makes the available RCT data specific to PND quite limited.

A separate RCT investigated the use of intranasal OT to treat low mood in males with major depressive disorder (MDD) (De Cagna et al., 2019). The results indicated no benefit from OT administration, which if anything appeared to increase anxiety (MacDonald et al., 2013). However, it is not clear how far results from clinical trials that include males can be generalised to females (Quintana et al., 2021), especially given that both testosterone and estrogen have important roles in OT regulation (Dumais and Veenema, 2016). New mothers with PND therefore require separate investigations given the significant sex steroid hormonal fluctuations that take place during the perinatal period and how this may moderate the effects of OT administration (Kim et al., 2014).

In light of the limited data available on OT effects in PND, our study aimed to test if, in principle, new mothers with PND benefit from intranasal OT administration. Given that a wide range of severity of PND has been included in previous studies, it is still not known if the effect of OT on mood will be the

same in all new mothers, regardless of severity of depression. The present study therefore investigated if OT administration has an effect on low mood in new mothers with PND and across the low mood spectrum.

1.1. Aims and hypotheses

Aim: The objective was to test for change in maternal mood after intranasal OT, relative to baseline and placebo. Hypothesis: We predicted that maternal low mood would improve after intranasal OT, relative to baseline and placebo, in new mothers with and without symptoms of PND, and with mild, moderate and severe symptoms of PND.

2. Materials and methods

2.1. Design

A double-blind, placebo-controlled, randomised controlled-trial (RCT), within-subjects, cross-over design was used.

2.2. Participants

Mothers (N = 58, mean age = 33.62 years, SD = 4.48) who were between 3-9 months postpartum (mean = 4.70, SD = 1.71) took part in the study. Details about the range of social demographic factors included in the sample are shown in Table 1. Statistical comparison tests found no significant difference between groups on any of the variables reported in Table 1 ($p > 0.05$). Participants were recruited in the community via an advert that was displayed in child development centers and online parenting support groups. All participants were provided with an information sheet explaining what participating in the study would involve, and all participants provided informed written consent before taking part. Exclusion criteria included if the mother was younger than 18 years old or post-menopausal, or pregnant.

Table 1

Participant demographic characteristics

Category		**Total Sample (N = 58) %**	**Probable PND cases (N = 26) %**	**Controls (N = 32) %**	**High EPDS Scorers (N = 19) %**	**Moderate EPDS Scorers (N = 22) %**	**Low EPDS Scorers (N = 17) %**
Marital status	Married	77.6	73.1	81.3	73.7	77.3	82.4
	Cohabiting	10.3	11.5	9.4	15.8	0.0	17.6
	Single	12.1	15.4	9.4	10.5	22.7	0.0
Sexual orientation	Heterosexual	93.1	84.6	100	84.2	95.5	100.0
	Bisexual	3.4	7.7	0.0	10.5	0.0	0.0
	Missing	3.4	7.7	0.0	5.3	4.5	0.0
Parent to other children	Yes	19.0	11.5	25.0	15.8	81.8	23.5
	No	81.0	88.5	75.0	84.2	18.2	76.5
Educational level	University	84.5	84.6	84.4	89.5	77.3	88.2
	College	1.7	0.0	3.1	0.0	0.0	5.9
	School	1.7	3.8	0.0	0.0	4.5	0.0
	Missing	12.1	11.5	12.5	10.5	18.2	5.9
Birth control	Non-hormonal	84.5	84.6	84.4	84.2	86.4	82.4
	Contraceptive pill	15.5	15.4	15.6	15.8	13.6	17.6
Menstruating at Baseline	No	96.6	96.2	96.9	94.7	95.5	100.0
	Yes	3.4	3.8	3.1	5.3	4.5	0.0
Menstruating at the time of Placebo administration	No	98.3	100.0	96.9	100.0	95.5	100.0
	Yes	1.7	0.0	3.1	0.0	4.5	0.0

Menstruating at the time of OT administration	No	98.3	100.0	96.9	100.0	100.00	94.1
	Yes	1.7	0.0	3.1	0.0	0.0	5.9
Breastfeeding	Exclusively	79.3	69.2	87.5	73.7	77.3	88.2
	In combination	20.7	30.8	12.5	26.4	22.6	11.8
	No	0.0	0.0	0.0	0.0	0.0	0.0
Recent self-reported diagnosis	Postnatal depression	20.7	38.5	6.3	36.8	18.2	5.9
	Postnatal anxiety	12.1	23.1	3.1	26.3	4.5	5.9
	Psychosis	0.0	0.0	0.0	0.0	0.0	0.0
	Post-traumatic stress disorder	1.7	3.8	0.0	5.3	0.0	0.0
	Borderline personality disorder	3.4	7.7	0.0	10.5	0.0	0.0
Mental health history	Depression	20.7	38.5	6.3	36.8	18.2	5.9
	Anxiety	12.1	23.1	3.1	26.3	4.5	5.9
	Psychosis	1.7	3.8	0.0	0.0	4.5	0.0
	Post-traumatic stress disorder	1.7	3.8	0.0	5.3	0.0	0.0
	Borderline personality disorder	3.4	7.7	0.0	10.5	0.0	0.0
Currently receiving mental health treatment	Talking therapy	12.1	26.9	0.0	36.8	0.0	0.0
	Antidepressant	3.4	3.8	3.1	0.0	4.5	5.9
	None	84.5	69.2	96.9	63.2	95.5	94.1

Previous mental health treatment	Talking therapy only	17.2	30.8	6.3	36.8	13.6	0.0
	Antidepressant only	1.7	0.0	3.1	0.0	0.0	5.9
	Talking therapy and antidepressant	6.9	11.5	3.1	10.5	9.1	0.0
	None	74.1	57.7	87.5	52.6	77.3	94.1
Pregnancy length	Full term	84.5	80.8	87.5	84.2	81.8	88.2
	Premature	13.8	15.4	12.5	15.8	13.6	11.8
	Missing	1.7	3.8	0.0	0.0	4.5	0.0
Birth delivery	Vaginal	65.5	73.1	59.4	73.7	50.0	76.5
	C-section	34.5	26.9	40.6	26.3	50.0	23.5
Birth delivery was induced	Yes	37.9	46.2	31.3	47.4	27.3	41.2
	No	60.3	53.8	65.6	52.6	68.2	58.8
	Missing	1.7	0.0	3.1	0.0	4.5	0.0
Epidural during delivery	Yes	56.9	53.8	59.4	52.6	54.5	64.7
	No	41.4	46.2	37.5	47.4	40.9	35.3
	Missing	1.7	0.0	3.1	0.0	4.5	0.0
Nationality	British	55.2	42.3	65.6	42.1	63.6	58.8
	Non-British	44.8	57.7	34.4	58.1	36.1	41.3
First language	English	75.9	73.1	78.1	73.7	77.3	76.5
	Other	24.1	26.9	21.9	26.5	22.5	23.6

All participants were screened for traits of PND on the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) and were assigned initially into 2 groups: probable PND cases (N = 26) and controls (N = 32). The range of scores on the EPDS was 0-24 (mean = 8.62, SD = 5.89). The clinical cut-off point used for inclusion into the PND group was equal to or greater than 9, as recommended for clinical

referral of PND and in research for cultures that have a low detection rate of PND in community populations (Cox et al., 1987; Martin and Redshaw, 2018).

2.3. Measures

2.3.1. OT and Placebo

The single 24IU OT (40.32µg, Syntocinon) dose was based on previous studies that used the same dose and reported OT alters social cognition compared with placebo (De Cagna et al., 2019). The placebo was made by the same pharmacy with the identical content excluding OT.

2.4. Primary outcome variable

2.4.1. Positive and Negative Affect Scale (PANAS)

The PANAS short form questionnaire (Watson et al., 1988) measures current mood. Participants are asked to rate on a series of 20 emotions how much they are feeling each emotion, at that precise moment, on a scale from 1-5. The scores on specific items are calculated to produce a total positive affect score and total negative affect score. These scores can range from 10-50, with higher scores representing greater positive or negative affect respectively. The PANAS questionnaire has been confirmed to show strong reliability and validity in general and depressed populations (Vera-Villarroel et al., 2019).

2.5. Protocol

All participants received intranasal OT or placebo on separate visits to the research centre, which were scheduled at the same time of day, approximately 1 week apart, to control for carry-over effects, in a balanced within-subjects design. Both active and placebo nasal sprays were dispensed by independent pharmacists in identical bottles and independently blinded as to the content. The order of the codes representing OT and placebo for each participant were randomised into a computer-generated list to ensure half of the participants received OT during the first visit and the other half received OT during the second visit.

At each visit, on arrival at the lab, participants completed the Positive and Negative Affect Scale (PANAS) short form questionnaire (Watson et al., 1988) about their current mood. A single dose of 24IU OT (40.32µg, Syntocinon) or placebo nasal spray was administered by 3 actuations to each nostril (4IU, 6.72µg each). Participants were then asked to rest for between 35-45 minutes to allow for the pharmacokinetics of OT to cross the blood-brain barrier (Mah et al., 2017; Quintana et al., 2021). To test for change in maternal mood, 35-45 minutes after the nasal administration, participants completed a new copy of the PANAS questionnaire about their current mood. Participants were asked to complete the questionnaire honestly about their mood at that moment, without reflecting on the answers they had provided before. The delay period between nasal administration and data collection is in line with the timeframe used in previous research that reported changes in behavioural and neural effects after OT administration compared to placebo (De Cagna et al., 2019).

2.6. Data analysis

The nasal spray codes were unblinded at the end of data collection to perform the statistical analyses, which were conducted using SPSS 26. Since the two condition sessions took place on different days, the baseline data was collected on the PANAS questionnaire at both sessions prior to nasal administration. A test of reliability to calculate the coefficients of consistency for each of the positive and negative affect scales was conducted. The baseline scores from each session were combined into one scale that comprised either positive or negative affect and represented the average baseline mood respectively. Each scale consisted of 20 items. Cronbach's alpha showed both the Positive Affect scale ($\alpha = 0.94$) and the Negative Affect scale ($\alpha = 0.87$) reached acceptable reliability for internal consistency. Repeated-measures ANOVAs were conducted to compare the effects of OT or placebo on maternal mood.

2.7. Statistical power

The sample size was based on a power calculation using R that showed with $N \geq 24$ per group and with an effect size of $d = 0.57$, there will be 80% power to detect a difference between groups, with 5% Type 1 error. Both groups were matched on infant and maternal age. The whole sample was then stratified

into 3 groups: N = 19 high scorers (>11), N = 22 moderate scorers (6-10) and N = 17 low scorers (<5) on the EPDS. Taking into account the different group sizes, a power calculation using Stata showed that with an alpha of 0.05 and a power of 0.8, the minimum sample size required was 17 per group, which is met. The estimated effect size was 0.45, and the estimated variance was 0.02.

3. Results

3.1. Background variables

The following variables were not associated with maternal mood outcomes on the EPDS or PANAS questionnaires: time of session, maternal age, educational level, marital status, postpartum duration, number of children, nationality, birth control use, menstrual cycle, duration of gestation, mode of delivery, or whether the mother was breastfeeding. Maternal mental health history of depression was significantly associated with EPDS score ($r_s = 0.40$, $p \leq 0.01$) and PANAS negative affect scale scores at baseline only ($r_s = 0.27$, $p \leq 0.04$). Maternal mental health history of anxiety ($r_s = 0.31$, $p \leq 0.02$) was significantly associated with EPDS, but not PANAS scores. Bisexual orientation ($r_s = 0.28$, $p \leq 0.04$) was significantly associated with EPDS, but not PANAS scores, although this was driven by two outliers from the clinical group. There was no significant group difference in sexual orientation between probable PND cases and controls.

3.2. PANAS

A three-way interaction was tested between the drug (OT and Placebo), maternal mood (PANAS score), and group (PND and controls). Three within-subject factor levels were used and the total PANAS score at baseline, OT and placebo conditions was included as within-subject variables.

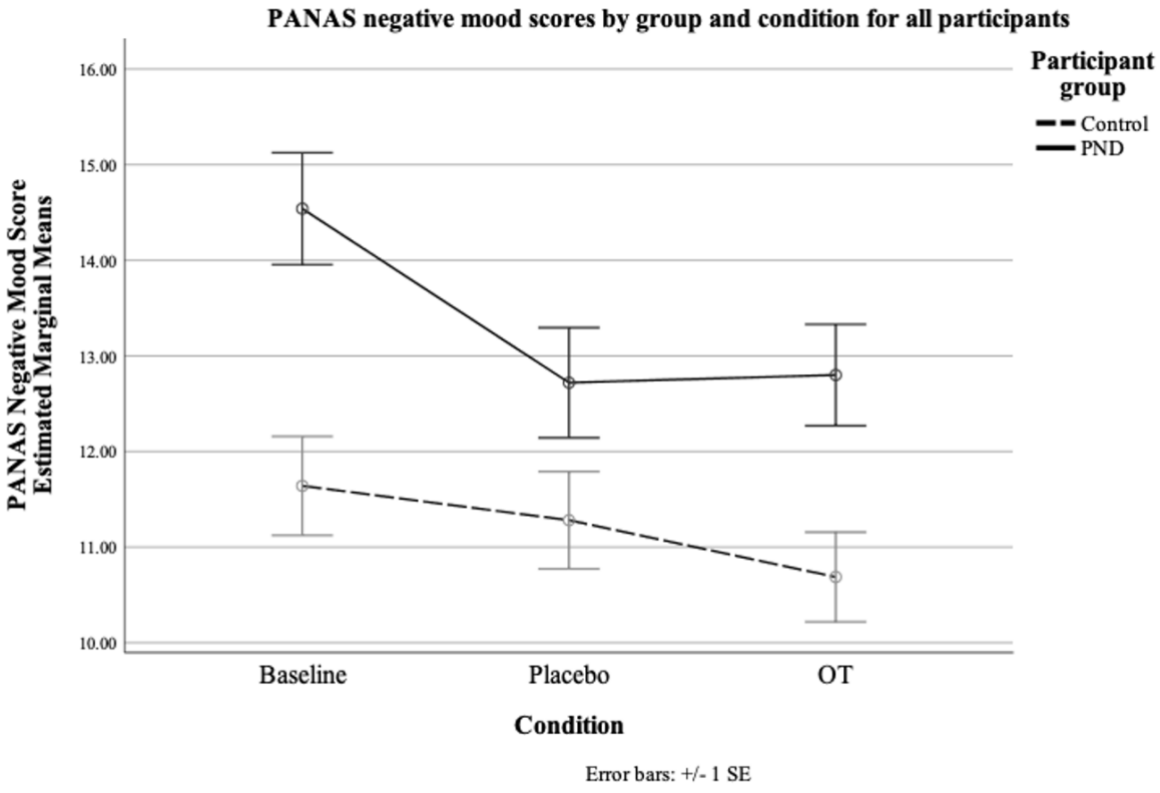
3.2.1. Negative affect scale

As would be expected, the PND group had significantly higher negative mood than controls ($F(1,55) = 10.40$, $p < 0.002$, partial-$\eta^2 = 0.16$). There was a clear significant effect of Condition (baseline, OT and placebo) ($F(2,110) = 11.14$, $p < 0.0001$, partial-$\eta^2 = 0.17$) and a marginally significant interaction effect

between Condition x Group ($F(2,110) = 2.91$, $p < 0.059$, partial-$\eta^2 = 0.05$). See Figure 1 for means (error bars represent 95% confidence intervals) and Table 2 for means and standard deviations of PANAS scores by group and condition. After excluding participants who were receiving antidepressant treatment at the time of the testing session (N = 2), the significant group difference remained ($F(1,53) = 10.03$, $p < 0.003$, partial-$\eta^2 = 0.16$). The significant effect of Condition also remained ($F(2,106) = 9.77$, $p < 0.0001$, partial-$\eta^2 = 0.16$), however the interaction effect between Condition x Group became slightly weaker ($F(2,106) = 2.85$, $p < 0.06$, partial-$\eta^2 = 0.05$).

Figure 1

PANAS negative mood scores by group and condition for all participants

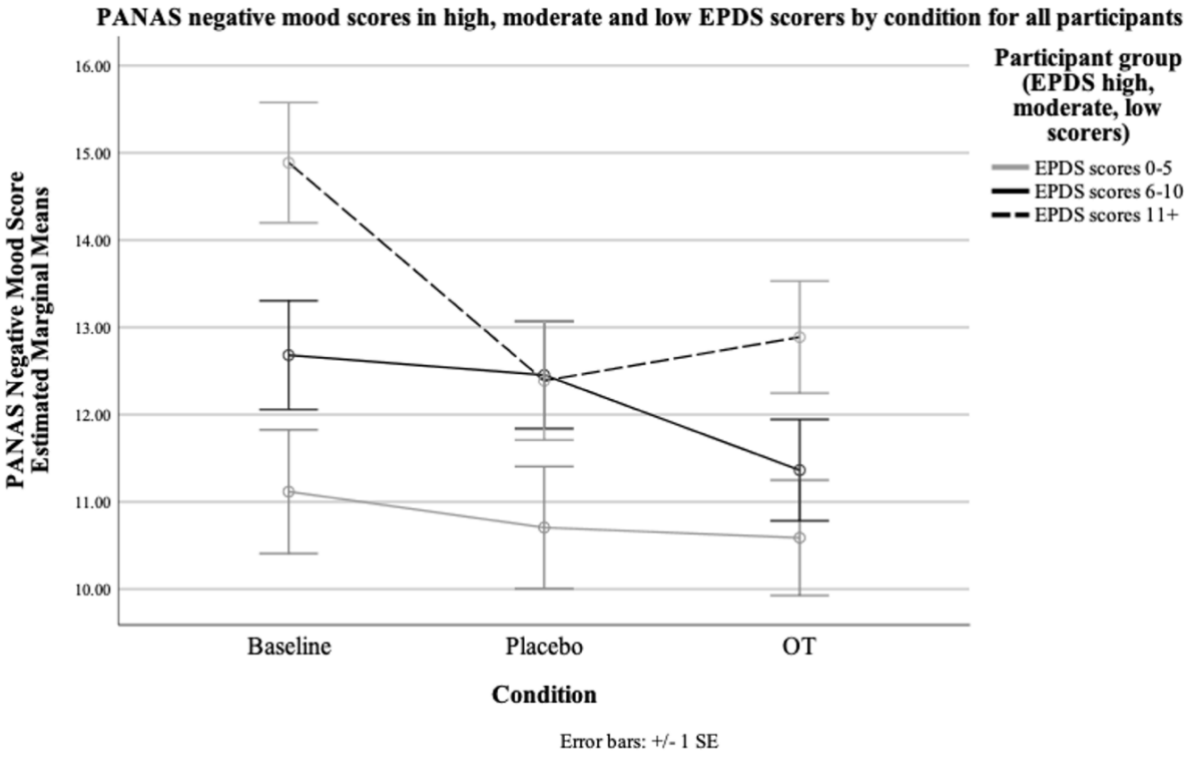


As can be seen from Figure 1, there was an OT effect on low mood, but only within controls. To understand whether the Group x Condition interaction was driven by a subgroup on the low mood spectrum, the whole sample was stratified into 3 groups: N = 19 high scorers (>11), N = 22 moderate scorers (6-10) and N = 17 low scorers (<5) on the EPDS. There was a clear significant effect of Group

($F(2,54) = 4.51$, $p < 0.02$, partial-$\eta^2 = 0.14$), Condition ($F(2,108) = 10.75$, $p < 0.0001$, partial-$\eta^2 = 0.17$), as well as a significant effect of the Group x Condition interaction ($F(4,108) = 3.56$, $p < 0.01$, partial-$\eta^2 = 0.12$). OT administration significantly reduced negative mood but only in moderate EPDS scorers. See Figure 2 for means (error bars represent 95% confidence intervals) and Table 2 for means and standard deviations of PANAS scores by group and condition. After excluding participants who were receiving antidepressant treatment at the time of the testing session (N = 2), the significant group difference remained ($F(2,52) = 4.15$, $p < 0.02$, partial-$\eta^2 = 0.14$), as did the significant effect of Condition ($F(2,104) = 9.25$, $p < 0.0001$, partial-$\eta^2 = 0.15$) and the Group x Condition interaction ($F(4,104) = 3.56$, $p < 0.01$, partial-$\eta^2 = 0.12$). A repeated measures ANOVA testing the effect of OT in moderate EPDS scorers only was strongly significant ($F(2,42) = 5.33$, $p < 0.01$, partial-$\eta^2 = 0.20$).

Figure 2

PANAS negative mood scores in high, moderate and low EPDS scorers by condition for all participants



3.2.2. Positive affect scale

The PND group had significantly lower positive mood than controls ($F(1,55) = 6.43$, $p < 0.01$, partial-$\eta^2 = 0.11$). There was no significant effect of OT by Condition ($F(2,110) = 1.38$, $p > 0.26$) or in the interaction between Condition x Group ($F(2,110) = 0.26$, $p > 0.77$). See Figure 3 for means (error bars represent 95% confidence intervals) and Table 2 for means and standard deviations of PANAS scores by group and condition.

Figure 3

PANAS positive mood scores in PND vs Controls, by condition

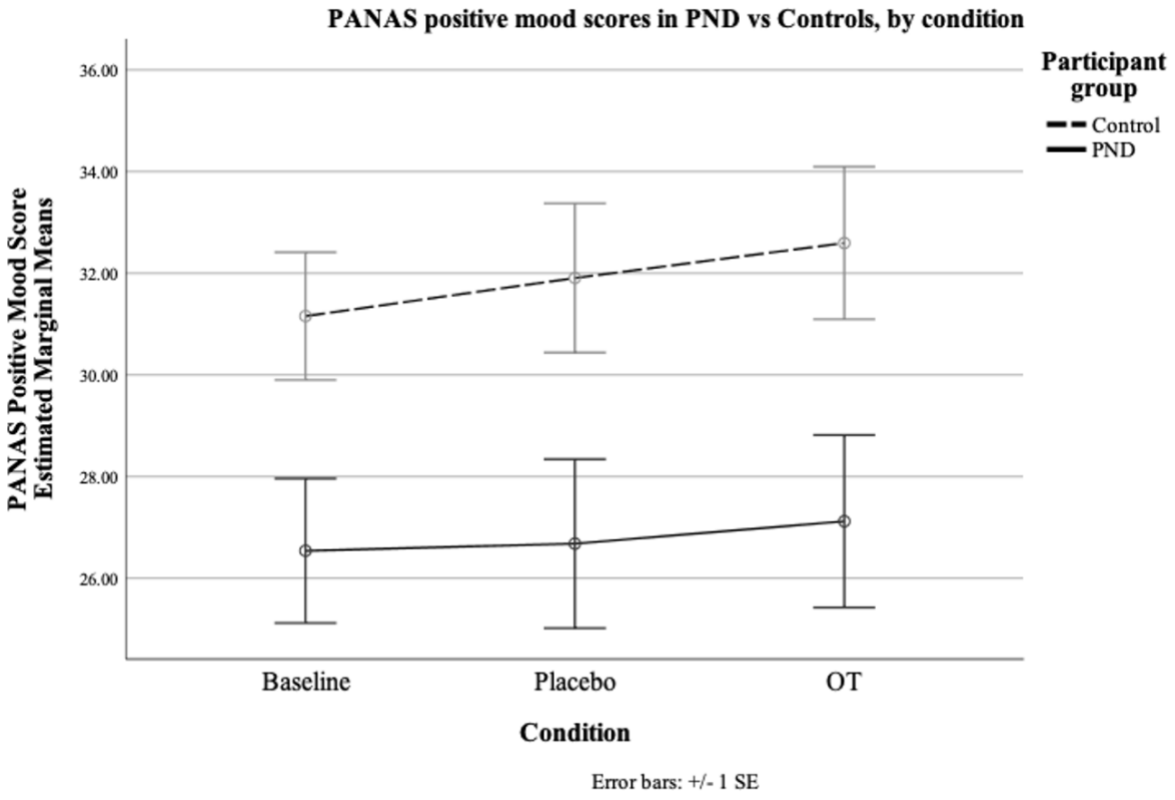


Table 2

Means and standard deviations of PANAS scores by group and condition

	Negative PANAS Score			Positive PANAS Score		
	Baseline *Mean (sd)*	Placebo *Mean (sd)*	OT *Mean (sd)*	Baseline *Mean (sd)*	Placebo *Mean (sd)*	OT *Mean (sd)*
Controls	11.64 (1.81)	11.28 (2.04)	10.69 (1.40)	31.16 (7.67)	31.91 (8.51)	32.59 (8.23)
Probable PND cases	14.54 (3.92)	12.72 (3.69)	12.80 (3.69)	26.54 (6.30)	26.68 (8.03)	27.12 (8.80)
High EPDS scorers	14.88 (4.12)	12.39 (2.38)	12.89 (3.51)			
Moderate EPDS scorers	12.68 (2.60)	12.45 (3.83)	11.36 (2.80)			
Low EPDS scorers	11.12 (1.41)	10.71 (1.69)	10.59 (1.28)			

4. Discussion

In this study we tested the effects of OT nasal administration in new mothers with traits of PND and in new mothers across the negative mood spectrum. We found that relative to placebo, and using a double-blind cross over RCT design, OT had an effect on low mood but only within controls. When the whole sample was stratified into 3 groups comprising participants who scored high, moderate and low on the EPDS for traits of PND to test if a subgroup was driving this, OT did not significantly reduce negative mood in women with clinical levels of PND but did reduce low mood significantly in those with moderate severity EPDS scores. These results illustrate individual differences in response to OT administration and suggest that OT administration as a single dose at 24 IU may offer treatment benefit to new mothers who report moderate sub-clinical levels of depression on the EPDS.

OT administration may not have affected negative mood in women with higher levels of PND for a number of reasons. First, the severity of depression presented by this group indicates either a stronger dose or prolonged administration of the intervention may be required to manifest an effect (De Cagna et al., 2019). Second, this group may have a reduced plasticity of the OT system (Feldman, 2021, 2020) and/or reduced OT receptor responsivity, which has been reported in patients with adverse early caregiving experiences which itself is a risk factor in patients with PND (Bakermans-Kranenburg and

Van IJzendoorn, 2013; Kim et al., 2014). If this is the case, the severe PND trait group may have had a reduced reaction to OT compared to the mild therapeutic effect found in the mild-moderate PND trait group. In either case, it may be that a stronger dose of OT, and/or repeat doses, is needed for OT to cause a change in negative mood in women with PND. This needs investigating further. A third possibility is that in women with PND, the effect of OT is harder to detect, perhaps due to a ceiling effect, but that this might be seen in a larger sample.

Other possibilities could be that in the high PND trait group, OT may affect other, more biological, indices of negative mood that are not measured by the PANAS questionnaire, such as cortisol or amygdala response (Ditzen et al., 2009; Koch et al., 2016). If this is the case, our findings may be related to alexithymia and difficulties in monitoring change of emotions in depression (Quirin et al., 2014). It is possible that OT could help women with PND not by reducing negative affect but in relation to other dimensions of negative mood, such as through better capacity to regulate or tolerate negative emotions, rather than the extent of experiencing them. Therefore, other measures that target negative affect more indirectly, such as through physiological response, behaviour or reaction time, may be more informative measures that can capture change not reported by a global instrument such as the PANAS questionnaire.

Our findings add to a growing evidence base addressing inconsistent effects of OT and demonstrating that the influence of intranasal OT may only be found in less severe cases and does not impact severe cases, as has also been demonstrated in relation to participants who experienced childhood emotional maltreatment and parental love withdrawal (Bhandari et al., 2014; Riem et al., 2013; Van Ijzendoorn et al., 2011). Nevertheless, the significant OT effect on low mood in new mothers with moderate levels of low mood is a potentially important finding, and further trials will be needed to test if this intervention has a clinically significant impact on mood. Even if this initial demonstration of an effect within this specific subgroup is replicated, further investigations will be needed to explore timing, dose-response and monitoring of unwanted side effects of synthetic OT before translating this finding into clinical practice. Previously, with other groups, clinical trials have used a relatively low dose (18–40 IU) and have reported minimal unwanted side effects (De Cagna et al., 2019; Erdozain and Peñagarikano, 2020;

Quintana et al., 2021). However, if stronger doses are to be used such safety issues will need to be carefully explored.

The existing evidence base suggests that OT administration may operate by reducing stress, and by enhancing parental sensitivity and maternal behaviour to benefit bonding with the infant (Szymanska et al., 2017). However, the present results highlight the person-dependent nature of OT. It remains unclear what the precise mechanisms are through which intranasal administration of OT affects brain and behaviour, although it is likely that these are the result of interactions between the OT system, the corticotropin-releasing hormone (CRH) stress regulator of the HPA axis, the serotonergic system, and the dopaminergic reward system. Given that these areas are altered in depressed populations, this has implications for the treatment of depression (De Cagna et al., 2019; Dölen et al., 2013; Li et al., 2020; Neumann and Landgraf, 2012). A recent review of the RCTs of intranasal OT to treat depression and anxiety highlights that OT could plausibly work in combination with other treatments (De Cagna et al., 2019; Horta et al., 2020). However, even for the subgroup of new mothers with moderate levels of low mood, who showed a treatment response to OT in this study, we should caution that we do not yet know how long such improvements last, and if the improvements might have been greater in combination with other treatments. Currently, the first line treatment for PND recommended by the NICE guidelines in the UK is Cognitive Behavioural Therapy (CBT), either delivered alone or in combination with SSRI antidepressant medication (NICE Guidance, 2014).

Although in our study we found no effect of OT on positive mood in our sample, despite observing a reduction of negative mood, this is in line with Fortunata Donadon et al's study that found no effect of OT on positive thoughts in women with PND nor controls, despite finding a reduction of negative thoughts in women with PND, as well as a positive-bias effect of OT on social judgement during an emotion recognition task in this group only (Fortunata Donadon et al., 2020). This is an interesting finding that supports previous research demonstrating that OT has a stress-buffering effect on brain activity (Ditzen et al., 2009; Kim et al., 2014; Koch et al., 2016) that has been argued to promote a desire for social contact, without fear, and enhance social affiliation, which supports the attachment

process (Carter, 2014; Feldman, 2015). However, it may also be the case that other measures of positive mood, as well as measures of social involvement and social salience, could have captured a dimension of change in positive mood that was not observed in our study. Given that Mah et al also reported differences in the effect of OT administration on maternal mood compared to maternal perception of the relationship with their infant in women with PND (Mah et al., 2013), further research is needed to determine the distinction found between the effects of OT on positive and negative mood, and social cognition, in women with PND. This may also be impacted by individual and contextual variables, such as breastfeeding rates of new mothers included in the samples which were higher in this study as well as in the report from Fortunata Donadon et al's 2020 study, compared to the rate reported in Mah et al 2013.

Finally, it is important to consider some limitations of the present study. First, both the EPDS and PANAS are self-report questionnaires, so there may be a risk of under- or over-reporting of mood. However, these are clinically validated scales which previous studies have shown correlate significantly with clinician assessments of mood (Díaz-García et al., 2020; Smith-Nielsen et al., 2018). Our findings are also in line Fortunata Donadon et al's recent OT administration study on negative thoughts in women with PND that included cases in their sample who were screened using both the Structured Clinical Interview on the DSM-5 as well as a cut-off point of ≥10 on the EPDS (Fortunata Donadon et al., 2020). Second, whilst our sample size is comparable to previously published studies, the effect size of OT influences in women with PND (the high scorers in this study) is small and so may only be detectable with larger sample sizes. Third, in this study, the cut-off points used to determine the high, moderate and low scorers on the EPDS were determined by the number of participants scoring in these ranges to establish the sample sizes required to detect a difference between groups. The cut-off points used should therefore be treated as provisional until the results are replicated. Fourth, as mentioned previously, other measures may be more informative to assess negative and positive emotions. Given that this study included a single outcome variable, we can only interpret the results through a narrow perspective. Fifth, the sample included a skew towards university educated participants, and mothers who were all, at least in part, breastfeeding their infant at the time of taking part in the research, and

given that breastfeeding is reduced in women with PND (Kim et al., 2014; Stuebe et al., 2013), these results are limited to a subgroup of women with traits of PND. Finally, although we did not find a significant group difference in sexual orientation in our sample, given that we found a significant association between bisexual orientation and EPDS traits, future research could explore sexual orientation as a potential moderating variable within the context of our study in a larger sample. Similarly, although we did not find any meaningful impact of breastfeeding status, mental health history and birth delivery in our sample, given that these factors have been reported in the general literature to have potentially clinically meaningful differences, these factors could also be explored as potential confounding variables in future research replicating the results in a larger sample.

Despite these caveats, we conclude that in this study we observed clear effects of a single dose of OT nasal administration on negative mood in new mothers with moderate scores of depression. We are aware that showing a short-term impact on mood only identifies OT as having a potential to alter mood in mild or moderate (sub-clinical) cases of PND. Future Phase I trials could consider extending the duration of OT administration to test for longer term effects of intranasal OT on mood as well (De Cagna et al., 2019; Horta et al., 2020).

Authors statement

The authors declare that they have no conflict of interest. The study is registered at https://www.clinicaltrials.gov (NCT04745494). This report is independent research supported by the National Institute for Health Research ARC North Thames. The views expressed in this publication are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care. Funding was provided by The Lord Leonard and Lady Estelle Wolfson Foundation, the Fund for Psychoanalytic Research through the American Psychoanalytic Association, International Psychoanalytical Association, Michael Samuel Charitable Trust, Denman Charitable Trust and Galvani Foundation.

Declarations of competing interests

None.

Acknowledgments

We would like to thank the mothers and infants who took part in this study and Cordelia Uys for her valuable help with recruitment.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.ejps.2020.105216.

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