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# Preventing Postpartum Depression with Intranasal Oxytocin

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DETAILED STUDY PROTOCOL

# Testing the Efficacy of Intranasal Oxytocin for the Prevention of Postpartum Depression and PTSD

Sponsor: National Institute of Health (NIH), Brain and Behavior Research Foundation (NARSAD), MGH Executive Committee on Research (ECOR)

Research Site: Massachusetts General Hospital

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## 1. BACKGROUND AND SIGNIFICANCE

1.1. Postpartum depression. [Note: Although postpartum depression is a time-honored diagnosis, the DSM-5 lists the diagnosis Peripartum Depression instead, in recognition of cases in which depression may have its onset even *prior to* parturition. However, because the focus of this proposal is the prevention of depressive symptoms *following* parturition, we will use the term postpartum depression (PPD) throughout this proposal.] PPD is a debilitating disorder. New mothers must struggle with the adverse consequences of depression and at the same time be responsible for parenting their child. PPD poses a threat to mother *and* infant health, which in extreme cases may involve maternal suicide and/or infanticide. An estimated 600,000 American women suffer from PPD annually, making it one of the most frequent complications of pregnancy. Available secondary preventive interventions often are ineffective, which calls for identifying novel approaches (O'Hara and McCabe, 2013).

Impaired infant-mother bonding is a hallmark of PPD (O'Higgins et al., 2013). Depressed mothers have more difficulties developing maternal feelings towards their infant and are less likely to provide sensitive caregiving, providing fewer opportunities for reciprocal engagement. In turn, bonding impairments may worsen the mother's depression, creating a vicious cycle. Resultant disruptions in the early mother–infant relationship may engender insecure attachment, with consequent lifelong disruptions in the child's socioemotional and cognitive development.

1.2. Postpartum posttraumatic stress disorder (PP-PTSD). Posttraumatic stress symptoms have also been described in mothers following a traumatic childbirth experience, and these may overlap with PPD (Söderquist et al., 2009), creating further maternal morbidity as well as

diminishing mother-infant bonding (Parfitt and Ayers, 2009). As our study and others show, women who develop PP-PTSD are also at risk for suffering from bonding impairment (Dekel et al., 2018) and interruption in the mother-infant bonding relationship in the sensitive postpartum period which can adversely modify the child's developmental trajectory.

1.3. Current treatment status. Antidepressant medication is the most common treatment for PPD and also for PP-PTSD, although there is no evidence that antidepressant perform better than placebo and women who breastfeed are ambivalent about taking the drug (O'Hara and McCabe, 2013). There is no treatment that specifically targets PP-PTSD (Olde et al., 2006). Moreover, antidepressant has not been found to help with bonding impairments. Antidepressants do not prevent PP-PTSD (Dekel et al., 2016). To date there are two direct interventions to promote bonding, viz., baby massage and coaching; both are partially effective at best. There is a need for a brief, inexpensive, feasible treatment to enhance bonding. Here we propose a novel intervention aimed at enhancing maternal bonding, and reducing PPD and posttraumatic symptom severity. We will test the heretofore uninvestigated clinical preventive potential of the posterior pituitary peptide hormone *oxytocin* (OXT), administered intranasally (IN), to mothers during the first postpartum days.

1.4. Theoretical basis for administering oxytocin. In addition to IN-OXT's putative anxiolytic and antidepressant properties (Bakermans-Kranenburg and van IJzendoorn, 2013), a large body of research supports OXT's role in the maintenance of maternal behavior across species. OXT knockout mice display deficits in maternal behavior, and exogenous administration of OXT enhances it. Recent evidence in postpartum mothers indicates that high peripartum OXT levels are associated with enhanced maternal behavior (Feldman et al., 2007), and low levels with depressive symptoms (Skrundz et al., 2011). Low OXT levels during bonding have been documented in depressed women (Stuebe et al., 2013), suggesting that OXT deficiency is an underlying mechanism of impaired bonding in PPD. Exogenous OXT administration has been found to enhance maternal brain responses in women (Riem et al., 2011), as well as to reduce the fear response in healthy humans (Acheson et al., 2013), suggesting it may also be a promising candidate for PP-PTSD. In a non-postpartum sample, IN OXT given to individuals at risk for PTSD following trauma exposure shows beneficial effects of the treatment in lowering non-postpartum PTSD (van Zuiden et al., 2017). Abnormalities in the biological stress response manifested in dysregulations in the hypothalamic-pituitary-adrenal (HPA) axis is a hallmark of PTSD. OXT deficiency may heighten the stress response in humans (Donadon et al., 2018) in part through failure to reestablish bodily homeostasis following exposure to the trauma. Low OXT after traumatic exposure has been documented in individuals with PTSD. OXT production peaks in labor (Fuchs et al., 2016), as is the norm, and has been associated with extinction of the memory for the traumatic nature of the birth experience (Brindle et al., 1991; Brett and Baxendale, 2001). This accords with OXT's specific role in reducing traumatic memory overconsolidation to protect against PTSD. Thus, increase of OXT in the immediate postpartum may protect women following a traumatic delivery.

1.5. Intranasal oxytocin and brain access. For exogenous OXT to enhance bonding it must exert effects on the central nervous system (CNS) through brain OXT receptors. IN administration of OXT has been found to produce significantly increased OXT levels in cerebrospinal fluid (CSF) after IN delivery (Striepens et al., 2013). Side effects were not

observed after the delivery of short-term 18 to 40 IU IN-OXT to humans (MacDonald et al., 2011), including postpartum women (Rupp et al., 2014). Of direct relevance to the proposed project, a study that investigated the role of sequential IN-OXT in promoting lactation at a dose of 4 IU in each nostril q 4h (total daily dose 48 IU), from as early as one day postpartum, found no safety concerns (e.g., Fewtrell et al., 2006). Administration of OXT was documented to reduce the fear response in healthy humans (Acheson et al., 2013). In an animal model, central OXT administration in the immediate post-stressor phase reduced PTSD-like behavior (Cohen et al., 2010). A few studies support of the use of OXT to facilitate fear extinction in the treatment of individuals suffering from PTSD (Koch et al., 2014; Koch et al., 2016). However, given the unpredictable nature of traumatic events, designing prospective studies to test OXT's protective role is challenging. A recent study of sequential IN-OXT administration *after* (day 12) an automobile accident shows some beneficial effects for PTSD reduction (van Zuiden et al., 2016). Along these lines, it is suggested that there might be a "window of opportunity" for a preventive intervention in the *first days* following traumatic exposure, viz, before the trauma memory is consolidated and symptoms arise (Zohar et al., 2011).

1.6. Significance of the study. Our study will attempt to fill the current gap in effective preventive interventions for pregnant mothers at risk. No study has yet examined the therapeutic effects of OXT on maternal bonding as well as on early PPD and PP-PTSD symptoms. If we succeed in establishing the effectiveness of this highly feasible preventive intervention, it could become a stand-alone treatment for bonding impairment. Our intervention may also offer hope for women at risk for the aversive complications of childbirth-related psychopathology. Strengthening the important process of mother-infant bonding from the very beginning of the child's life may also have long-lasting positive implications of the child's psychological development. We further expect that our findings will advance the scientific knowledge concerning the major role of OXT in social interaction, and its anti-anxiety and anti-depressive properties in humans. Research on the clinical potential of IN-OXT for treating mental illness, although promising, is in its infancy, and our study may provide knowledge concerning issues of dosage and timing in order to achieve sustained central nervous system effects. Lastly, our findings may revise central concepts in postpartum psychopathology. Obtaining data that attribute PPD to a bonding impairment, and the prevention of PPD by enhancing bonding, may challenge the current psychiatric conceptualization of PPD as merely a subtype of depression. Implication of posttraumatic stress symptoms in PPD may shift the focus of postpartum mental health to include traumatic stress responses. Evidence of sustained OXT effects on bonding may provide empirical support in favor of a sensitive period for mother-infant bonding in the early postpartum period, which would have important health care implications.

## 2. SPECIFIC AIM

2.1. The primary hypothesis is that administration of a course of four days of IN-OXT at a dose of 4 IU in each nostril q 4h (total daily dose 48 IU), from as early as one day postpartum, initiated immediately following delivery, in comparison to placebo (PLA), will: 1) enhance mother-infant bonding, and 2) reduce PPD and PP-PTSD symptoms, at 5 days and again at two months postpartum, in mothers at risk for bonding failure and PPD.

2.2. We further hypothesize that bonding level will mediate the hypothesized beneficial effect of IN-OXT on depressive symptoms. Secondarily, we also hypothesize that IN-OXT will have positive effects on breastfeeding, and that improved breastfeeding will improve depression.

## 3. SUBJECT SELECTION

For Oxytocin study

3.1. Inclusion Criteria. 1) Third-trimester pregnant women being followed at the MGH Obstetrics Program who are at risk of PPD as indicated by their scoring >9 on a prenatal administration of the Edinburgh Postnatal Depression Scale (EPDS). (Note: Although the adjective "Postnatal" refers to the use of the EPDS during the *post*partum period, this instrument is also used as a *pre*partum screening instrument for PPD risk.) Additionally, we will enroll women with score of >21 on the Peritraumatic Distress Inventory (PDI) who might also be at risk for bonding impairment from PPD and PP-PTSD.

3.2. Exclusion criteria. 1) Age <18 or >50; 2) Failure to participate in regular prenatal check-ups; 3) Current diagnosis of psychosis; 4) Obstetric complication (e.g., preeclampsia, excessive hemorrhaging, gestational diabetes insipidus, emergency Caesarian section resulting in the newborn being admitted to the NICU). Note that planned Caesarian section will not serve as an exclusion criterion because immediate contact with the newborn occurs after the procedure.); 5) Use of potentially confounding or interacting medications (e.g. antidiuretic hormone, steroids); 6) Complicating pediatric medical condition in the newborn.; 7) suicidality (candidates indicating 2+ on EPDS item 10 will be further assessed by PI, a licensed clinical psychologist); 8) current substance abuse.

3.3. Recruitment methods. 3596 women delivered a baby at Massachusetts General Hospital (MGH) in 2012. During proposed five-year project period, we plan to recruit 110 subjects (Sbjs) (who satisfy the inclusion and exclusion criteria) and expect a drop-out rate of 20% between assessments, resulting in an anticipated final sample of 56 women. Additionally, we plan to recruit and study 88 partners (starting at day 1 postpartum, taking into account women's drop-out rate between pre-partum and day 1 postpartum assessments), also expecting a drop-out rate of 20% between assessments, resulting in a final sample of 56 partners.

## 4. SUBJECT ENROLLMENT

Study candidates will be primarily enrolled through social workers, medical assistants and nurses at MGH OB/GYN. After administering and scoring the EPDS, the social workers, medical assistants, and nurses will introduce the study and obtain permission from the study candidate to be contacted by study staff. We will also identify potential study candidates through their EPDS score in their medical records. We will then approach physicians of qualified candidates to obtain permission that their patient will participate in the study and permission that study staff contact candidate, if not approached through other OB staff. Physicians will not take part in the study recruitment. Candidates will secondarily be enrolled via study flyers and by study announcement in the hospital's websites.

## 5. STUDY PROCEDURES

### 5.1. Design.

Phase I: Screening (two stages).
First, study candidates (third trimester of pregnancy) will undergo screening via self-report questionnaire, the EPDS, to identify women at risk for PPD. Next, study candidates will be further screened over the telephone or in person at the OB by a study staff. For exclusion criteria, use of potentially confounding or interacting medications (e.g. antidiuretic hormone, steroids), and current mental disorders assessed by the mini Structural Clinical Interview for DSM (mini SCID). The treating obstetrician will be asked regarding contraindicating medical conditions (e.g., preeclampsia). Also, candidates' medical records will be reviewed for exclusion criteria. For those who will be enrolled from the Mothers Wellbeing Study, we will enroll them based on their PDI score obtained as part of the Mothers Wellbeing Study. Medical records will be reviewed for exclusion.

Phase II: Assessment. i) At *approximately 32 weeks of pregnancy*, study Sbj will complete additional self-report questionnaires and 40 mL of blood will be collected from Sbj, if she agrees. ii) *Postpartum (PP) Day 1*, Sbj will complete further self-report questionnaires. *Starting 8 hours after delivery with modification in the start time up to 12 hours postpartum if needed*, Sbj will self-administer the first dose of study medication in the hospital. In cases of delays due to medical procedures (e.g., emergency C-section) medication start time will be extended to up to 24 hours post-delivery. iii) *PP Days 1-4,* Sbj will continue to self-administer the medication in the hospital and then at home. iv) *Approximately PP Day 5,* Sbj will complete additional self-report questionnaires. v) *2 months, but with modification up to approximately 3 months PP,* Sbj will complete the same self-report measures and participate in a short video-clip with her infant. 40 mL of blood will be collected from Sbj, if she agrees. Following this, PI will answer any questions Sbj may have and make mental health treatment referral, if indicated and desired. Women enrolled through the Mothers Wellbeing Study will begin this study at PP Day 1.

5.1.1. Assessment # 1 (after approximately 32 weeks pregnancy). At MGH, Sbj will provide written informed consent after a full explanation of the procedures. Alternatively, for the convenience of the Sbj given their condition as well as to adhere to their visits to the OB, Sbj will be consented by the study physician over the phone in the presence of the PI or Research Fellow. If the consenting process occurs via telephone, the PI will first meet with the candidate and give her the written consent for her to review. She will then review the Consent Form with the study physician over the phone. The PI will be able to address any questions that may arise after the phone call. At this time, Sbj will be asked for her permission for study staff to contact her partner. Sbj will be provided with the "Partner Study Introduction Letter" to give to her partner, which invites the partner to participate in the study. Her decision on this matter will not affect her enrollment in the study. Next, study staff will email a copy of the consent form to the Sbj. The study doctor will sign the document upon receipt from Sbj. Next, study staff and the PI will administer assessment to Sbj via self-report questionnaires (60 minutes total) pertaining to demographics, medication usage (Medication Questionnaire [MED]), attachment (Maternal-Fetal Attachment Scale [MFAS]), mental health (Brief Symptom Inventory [BSI], PTSD CheckList for DSM-5 [PCL-5 1]), personality (Five Factory Inventory [NEO-FFI]), relationships and social support (Experiences in Close Relationships-Revised Questionnaire [ECR-R] and

Multidimensional Scale of Perceived Social Support [MSPSS]), trauma history (Life Events Checklist for DSM-5 [LEC-5], Childhood Trauma Questionnaire Short Form [CTQSF]), sleep (Bergen Insomnia Scale [BIS]), and expectations about delivery (Wijma Delivery Expectancy/Experience Questionnaire [W-DEQ 1]). All study questionnaires will be completed electronically, with the option to complete hard copies. If needed, self-report measures may be completed remotely. Following this, Sbj will be taught to self-administer the nasal spray containing either drug or placebo. Finally, if agreed by Sbj, 40 mL of blood will be collected from Sbj from venipuncture specimens performed for the purpose of this study and related studies. Samples will be later analyzed for hormone levels (e.g., oxytocin and cortisol) and DNA. Sbj (and her partner, if involved) will be contacted approximately 1 month after Assessment 1 as a reminder about her participation in the study.

5.1. 2. Assessment # 2 and initial study medication administration (approximately 8 hours after delivery). Study staff will receive epic notification indicating that Sbj has been admitted to the Labor and Delivery Unit (L&D). Sbj will complete questionnaires (25 minutes total) at MGH's postpartum unit targeting mental health (BSI), peritraumatic responses (Peritraumatic Dissociative Experiences Questionnaire [PDEQ], Peritraumatic Distress Inventory [PDI], [W-DEQ 2]), depressive symptoms [EPDS], maternal bonding (Mother-to-Infant Bonding Scale [MIBS], and medication (MED). Additionally, as prescribed in the physicians order sheet (OXT order sheet), Sbj will self-administer the study medication (Syntocinon 40 mg/ml or placebo nasal spray, per randomization schedule), 1 spray into each nostril, before feeding their baby if possible, q 4 hours, including nighttime.

5.1.3. Continued study medication administration (up to 4 days after delivery). Sbj will continue using the spray as instructed over 4 consecutive days. Sbj will complete a diary recording their use of the study medication over the 4-day period (10 minutes total). Drug diary will be completed electronically, with the option to complete a hard copy version. Sbj will be called after the assessment #2 to provide any assistance with the study medication or the diary, and to monitor responses to questionnaires. Sbj will also be called or texted as a reminder to use the spray over the 4 days, if desired. Further, as part of routine hospital care, Sbjs' vital signs are taken in the postpartum unit before medication administration and are consistently monitored by the nurses during the course of the Sbjs' hospital stay as part of routine hospital care.

5.1.4. Assessment # 3 (approximately 5 days after delivery). Sbj will complete self-report questionnaires (30 minutes total) pertaining to mental health (EPDS, PCL-5 2, BSI, PTGI), breastfeeding (Index of Breastfeeding Status [IBS]), maternal bonding and attachment (MIBS, Postpartum Bonding Questionnaire [PBQ], Maternal Attachment Inventory [MAI]), childbirth experience (W-DEQ 2), and medication (MED). Sbj will be called after assessment to monitor responses to questionnaires. Additionally, if Sbj's partner expressed interest in participating in the study, they will receive the "Partner Recruitment Letter" and, upon implied consent, will complete the EPDS (EPDS-P) and MIBS (MIBS-P) adapted for partners. Partners will complete all questionnaires electronically, with the option to complete hard copies.

5.1.5. Assessment # 4 (approximately 2 months after delivery). Sbj will complete (40 minutes total) concerning mental health (EPDS, PCL-5 2, BSI), bonding (MIBS, PBQ), breastfeeding (IBS), child development and temperament (Ages and Stages Questionnaire, 2 months [ASQ-3],

Infant Behavior Questionnaire [IBQ-R]), psychological growth (PTGI) and medication (MED), administered by PI and study staff research assistants. If needed, self-report measures may be completed remotely. Sbj will also participate in a short video-clip of free play with their infant (10 minutes total) obtained by research staff (see Video Completion Form), which will later be coded using Coding Interactive Behavior (CIB). Sbj is instructed to freely interact with baby. Assessment may be completed at Sbjs home, if desired. Child development will also be measured by the Bayley Scales of Infant Development (Bayley-III), relevant for the age group studied. The Bayley-III, which focuses on observational behavior, will be conducted by PI or by trained research staff, supervised by PI. Finally, if agreed by Sbj, 40 mL of blood will be collected from Sbj from venipuncture specimens performed for the purpose of this study and related studies. Samples will be later analyzed for hormone levels (e.g., oxytocin and cortisol) and DNA. After completion, a member of the study team will answer any questions Sbj may have about the study and provide mental health referral, as needed and desired. Additionally, partner's enrolled in the study will complete the EPDS-P and MIBS-P.

## 6. BIOSTATISTICAL ANALYSIS

6.1. Statistical analysis will be performed via a mixed model for repeated measures, with Drug (OXT vs. PLA) as a Class factor, psychometric scores as univariate and/or simultaneous multivariate dependent measures, additional covariates as appropriate, and Sbj as a random effect. Currently available mixed model analytic programs are able to handle missing data. Effect sizes will be employed in power analyses to calculate sample sizes for subsequent larger studies. Path analysis will be employed to test the role of bonding as a mediating factor of drug effect on depression outcome.

6.2. Power analysis. The major goal of this first study is to obtain measures of effect size that can be used to calculate sample size requirements for a subsequent, larger study, should the data from this study be promising. Thus, even if we are unable to meet the recruitment goals below, the study will still obtain useful and important data. That being said, we offer the following power analysis below, should recruitment go as well as hoped.

Because of the novelty of this project's hypothesis, no data are available regarding the potential protective effect of IN-OXT against the development of PPD, from which to estimate an effect size for the proposed study. However, a meta-analysis of studies of the effect of intranasal OXT in both healthy and clinical groups with implications for pharmacotherapy yielded an estimated effect size of d=0.32 (Bakermans-Kranenburg and van IJzendoorn, 2013), on which we will base our power analysis. With $\alpha$ set at 0.05, and 1-$\beta$ (i.e., power) set at 0.80, n=56 Sbjs (approximately 28 completed Sbjs in each of two groups) will be required to detect an effect size of d=0.32 in a simple t-test analysis comparing OXT and PLA subjects. Estimating dropouts at 20% between assessments, 70 and 88 Sbjs and partners will have to complete the second and first postpartum assessments, respectively, and 110 Sbjs will be required to complete the pre-partum assessment. Of all pre-partum women given psychometrics, an estimated 20% will be found to be at-risk, requiring the administration of psychometrics to 550 study candidates. To summarize:

550 administered psychometrics

110 women identified at risk, pass final screening, and complete pre-partum assessment
88 women randomized, and complete assessment #2; 88 partners complete assessment #1 at day 1 postpartum
70 women complete assessment #3; 70 partners complete assessment #2 at day 5 postpartum
56 women complete participation; 56 partners complete participation

6.3. Successful results.
As above, successful results will consist of our obtaining sufficient data that, if promising, will allow planning of a further, more definitive study of the effective role of IN-OXT in enhancing maternal bonding and/or preventing postpartum depressive and or posttraumatic symptoms, including calculating sample size requirements. Successful results also pertain to gaining knowledge about the potential positive effects of IN-OXT on mother at risk and knowledge about the feasibility of the intervention. Given the under-researched area of PP-PTSD, successful findings will include knowledge about the prevalence, course and risk factors of posttraumatic stress and its relations with depressive symptoms and mother-infant bonding.

## 7. RISKS AND DISCOMFORTS

7.1. Study Medication. OXT nasal spray has been previously administered to women following childbirth. There are reports of mild side effects at a dosage to promote lactation for as early as day 1 postpartum (e.g., Fewtrell et al., 2006; Ruis et al., 1981). Mild complaints may include: breast and nipple discomfort (13-20 out of 100) and uterine cramps (5 out of 100). However, such side effects were also reported by women receiving placebo (Stern, 1961). As indicated in the drug brochure, women experiencing painful uterine cramps should not drive or operate machinery. Other uncommon side effects include bleeding from the nose after using the drug (1 out of 48) (Huntingford, 1961), unfamiliar sensation in the nose (5 out of 100), and complaint about taste (1 out of 100) (Stern, 1961). Use of the drug by participants who experience postpartum depression was reported to transiently lower mood (Mah et al., 2013). A subsequent study, however, by the same group did not mention these outcomes (Mah et al., 2015), nor were these outcomes reported elsewhere (Clarici et al., 2015). A recent study by Mah and colleagues (2017), based on the 2013 sample, reports no effect of IN-OXT on maternal sensitive interaction with own baby but more negative care giving response to another's baby. The authors warrant further research on IN-OXT in depressed mothers. Other potential undesirable effects mentioned in the nasal spray package insert but not encountered in the literature include: headache, nausea, rash and allergic dermatitis (all rare).

7.2. Questionnaires and video recording. Sbj may experience emotional distress from answering questions concerning their mental health and childbirth experience. Interacting with their infant on camera may cause Sbj discomfort.

7.3. Blood drawn. Sbj may experience discomfort from having blood drawn. Side effects may include bruising, swelling at the injection site, dizziness and lightheadedness.

7.4. Unknown Risks. There may be other risks and side effects that are not known at this time. If any significant new findings develop during the course of this study that may affect the risk: benefit ratio for participants, appropriate institutional reporting protocol will be followed.

## 8. POTENTIAL BENEFITS

8.1. Potential benefits to participating individuals. First, women with PPD have an increased incidence of lactation problems (Assarian et al., 2014), and they are at risk for breastfeeding failure and cessation (see Figueiredo et al., 2013, for a review). This can be unfortunate, because breastfeeding helps to reduce PPD symptoms (Fairlie et al., 2009; Figueiredo et al., 2014; Ystrom, 2012). Therefore, it is reasonable to expect that a significant portion of our Sbjs (and their newborns) who receive active drug will benefit from the lactation-promoting effect of IN-OXT, with consequent benefit to infant nutrition and reduction in maternal anxiety. Second, in a recent study of women with PPD three months following delivery (Mah et al., 2015), IN-OXT was found to enhance the quality of mother-infant bonding and maternal protective behavior. Hence, our proposed active intervention may benefit the newborn as well. Third, women who receive active drug may be protected from developing PPD and bonding impairment. Other less substantive benefits include, if this turns out to be the case, the use of IN-OXT may reduce or obviate the need for antidepressant medication, with a reduction of possible transmission via secretion into maternal milk. Further, PPD is often accompanied by symptoms of anxiety and irritability (Righetti-Veltema et al., 2003). OXT has been shown to attenuate the neural response to arousing stimuli (Rupp et al., 2013) and to reduce amygdala activation in response to infant crying (Riem et al., 2011). Thus we have reason to expect that OXT may prevent to some degree PP-PTSD symptoms in women at risk.

8.2. Potential benefits to society. The information collected from this study may enable researchers to obtain knowledge on the effectiveness of oxytocin for enhancing bonding and preventing depressive and posttraumatic symptoms in postpartum women. If the findings are promising, this study may serve as a platform for larger-scale studies that may ultimately support a new drug indication for postpartum women at risk.

## 9. MONITORING AND QUALITY ASSURANCE

9.1. Administration of Protocol.
The protocol will be conducted in accordance with the protocol submitted to and approved by the Partners MGH IRB, as well as by NARSAD and ECOR. Sbjs will not be recruited until written notification of approval of the research project is issued by the IRB and NARSAD and ECOR are notified of the approval.

9.2. Data Monitoring. Given the reduced risk of this study, monitoring by the PI and Partners IRB should be sufficient. A physician investigator will review all laboratory/questionnaire results. The PI will closely monitor emotional dysregulation and concerning responses to questionnaire items that inquire about suicidality (BSI, question #9, responses of 2 or more; EPDS question #10, responses of “sometimes” or “yes, quite often”). Women who report suicidality in the screening and consent to the study will be monitored by the PI during their study participation. Likewise, the PI will monitor subjects who report suicidality in subsequent study assessments. If needed, the PI will conduct a suicidality assessment. Based on Sbj’s response, several actions will take place, including frequent contact with Sbj during study participation, suicide contract, referral for psychiatric consultation and treatment for medication,

if needed, and, in extreme cases, hospitalization. PI, who is a licensed clinical psychologist, will immediately evaluate subject suicide-related responses as data becomes available and will immediate attempt to contact subject for assessment and appropriate triage. The PI will review cases that are clinically significant and will notify the IRB in case of adverse events that may influence the IRB decision to continue or not the study trials, in accordance with IRB's policies. In the event possible serious or adverse effects of participation, Paul Cannistraro, M.D., an MGH psychiatrist who has served as a Medical Monitor on other studies conducted by the MGH PTSD group, and who is not an investigator on the present study, will be available to review the event and make recommendations to the PI and the IRB.

9.3. Communication between Principal Investigator and Sponsor. The PI will provide written reports about the study progress to NARSAD. Six months after the project start date, the PI will send an interim report followed by a second report one year later. A final report will be sent within 90 days of the grant termination. The final report will include a narrative pertaining to the main findings of the study and information about additional grants, if relevant. NARSAD will also obtain from the PI copies of relevant presentations and publications generated by the study. Additionally, annual and final progress report will be submitted to NIH. If any change is considered in the protocol, an amendment will first be sent to the IRB, and significant changes in the protocol will be sent to NARSAD for review and approval. We will notify the FDA of significant changes to the protocol and we will send a report to the FDA of adverse events that are serious, related, and unexpected within 90 days.

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