Lay Summary (Provided by the Dana Foundation):

Premenstrual Dysphoric Disorder (PMDD), a severe form of Premenstrual Disorder, is both physically and emotionally debilitating, significantly impacting women’s lives and relationships. Yet our current treatment methods are ineffective for up to 40% of women, leaving a pressing need for additional research and treatment development. Further, negative stereotypes surrounding PMDD and PMS often leave women suffering in silence and without treatment.

PMDD has been thought to occur from low levels of serotonin, a neurotransmitter which may play a key role in regulating mood. However, the standard treatment of PMDD with drugs that increase serotonin levels in the brain (called SSRI’s) have not been effective in many people with PMDD. Recent research suggests that the symptoms in PMDD might be due to low levels of another brain chemical called oxytocin, which has been found to regulate serotonin levels. The proposed study posits a novel treatment of PMDD with oxytocin. Oxytocin administered through a nasal spray would go directly to the brain and affect levels of serotonin, potentially offering an alternative to women who don’t respond to traditional SSRI treatments. Administering oxytocin with a nasal spray is a safe, reliable and convenient method with no known side-effects.
Oxytocin as a Treatment for Premenstrual Dysphoric Disorder (PMDD)

Introduction

Purpose

Roughly 3 to 8 percent of menstruating women have Premenstrual Dysphoric Disorder (PMDD) in the United States—based on estimates calculated from information published by the United States Census Bureau on age and sex, anywhere from about 1,900 to 5,000 women are affected within the United States alone (United States Census Bureau). PMDD, sometimes called “severe premenstrual syndrome (PMS)” affects females’ moods (similar to depression) and bodies (like PMS), but characteristically only during the luteal phase of the menstrual cycle (MC). Yet, while this emotionally and physically debilitating disorder affects these women’s lives, personal relationships, and even careers, it has been paid relatively little attention. As such, it was only first included in the appendix for further study in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and recognized as a true disorder just recently in 2013, with the following edition of the manual, DSM-5.

While PMDD is surrounded by lots of political and scientific controversy as a disorder, a significant subset of individuals has been suffering greatly in the meantime. Only slightly more than half of PMDD patients (60%) respond to Selective Serotonin Reuptake Inhibitors (SSRIs) as a treatment for their symptoms. The other 40% still have no relief from their symptoms or suffer from serious side effects.

Hypothesis: Intranasal oxytocin (IN OXT) can be used effectively as a treatment for the physiological symptoms of Premenstrual Dysphoric Disorder (PMDD) in humans.

Background

PMDD has both mental, affective symptoms as well as physical, somatic symptoms. The DSM-5 determines that a female PMDD diagnosis requires that five of more PMDD symptoms be present, have heavily detrimental effects in their lives, and last at least two cycles. The possible PMDD symptoms are as follows: depressed mood, anxiety/tension, affective lability, anger and irritability, decreased interest in life and activities, difficulty in concentration, change in appetite, difficulties with sleep, feeling overwhelmed, and physical symptoms. Physical symptoms include breast tenderness and/or swelling, headaches, joint or muscle pain, bloating, and weight gain. As already mentioned, a key characteristic of PMDD is its presence only before menses, in the luteal phase.

Both PMDD and Major Depressive Disorder (MDD) are conventionally treated with SSRIs that elevate serotonin (5-HT) levels in the synapse. MDD patients have a similar response rate to these SSRIs, and oxytocin (OXT) has been researched as a potential alternative treatment. Studies have shown significant decreases in OXT levels in depressed females (Ozsoy, Esel, & Kula, 2009) as well as negative correlations between plasma OXT levels and depressive symptoms (Scantamburlo et al., 2007).

Recently, connections have been found between the OXT and 5-HT pathways that suggest that OXT plays a significant role in the effects of 5-HT, which include mood, a symptom of both MDD and PMDD. Specifically, the effects of intranasal (IN) OXT specifically have been linked to 5-HT signaling in the brain (Mottolese, Redouté, Costes, Le Bars, & Sirigu, 2014). The study found increased 5-HT activity in the amygdala and the subgenual frontal cortex after IN OXT, and both of these brain regions have been implicated in MDD. This serves as a potential piece of the pathway through which OXT may positively affect 5-HT and thus work as a treatment for depressive and mood disorders (MDD) as well as related disorders such as PMDD.

The effects of OXT on MDD and the pathways related to MDD are only relevant to PMDD because of the recorded correlational relationship between the two, as well as their very similar symptoms relating to mood in humans. Research has found significant relationships between the two disorders, especially with PMDD as a risk factor for MDD and vice versa (Accortt, Kogan, & Allen, 2013).

Because the complete mechanisms for PMDD and MDD are unknown but linked, OXT offers a clear treatment possibility for PMDD patients—both for the research in the already-addressed similar disorders, as well as its safety and relative lack of side effects.
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Experimental Design

Methodology

Females with PMDD are recruited from a women’s clinic to participate in paid research that could potentially alleviate their symptoms. In order to qualify to participate, females must be diagnosed with PMDD either before or during screening. They must also be ages 18-46, have a regular (24-35 days) menstrual cycle, not have been pregnant for six months or more, be otherwise healthy, and not be on any medication, including SSRIs and other antidepressants commonly used to treat PMDD clinically, as well as hormonal contraception. These criteria are based off of the precedents set by Deveci et al. as well as guidelines set by DSM-5 on the diagnosis of PMDD (See Figure 1, Deveci et al., 2014).

This study spans a total of six months, but only the last three will be recorded for this experiment. The initial screening of participants occurs based on their descriptions of their own symptoms. However, while some participants may have been diagnosed with PMDD prior to the screening, many more are suspected to be diagnosed over the course of the study due to the relative unfamiliarity of the public with this disorder. Thus, the prescreening of their symptoms will be two months, as is required for a PMDD diagnosis in the DSM-5 criteria. At the end of this pilot portion of the study, any participants whose recorded symptoms or cycles do not fit the inclusion criteria will be eliminated.

In addition, monitoring time is necessary to also determine each participant’s luteal phase so that the OXT can be administered correctly. Participants will measure morning body temperature daily, as there is a significant increase in body temperature between the follicular and luteal phases. They will also take the daily tests in order to obtain baseline values that can later be compared to their results in the experimental phase. The three tests used to gauge mood and the physiological symptoms of PMDD in this study are the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Daily Record of Severity of Problems (DRSP), and Premenstrual Tension Syndrome - Multiple Visual Analogue Scale (PMTS-VAS). The first two tests provide well-supported quantitative measures of mood (Endicott, Nee, & Harrison, 2006; Schechter, Endicott, & Nee, 2007), while PMTS-VAS has been created to deal specifically with PMDD physical symptoms (Steiner & Streiner, 2005). While the long form of the Q-LES-Q shows more thorough data, the general activities section alone (called the Q-LES-Q-Short Form; Q-LES-Q-SF) has been shown to be highly correlated with the overall results, is more adaptable to various lifestyles, and has more often been used in similar studies (Schechter et al., 2007). All references to Q-LES-Q from this point on signify Q-LES-Q-SF questions 1 – 14. Both Q-LES-Q and DRSP are used here because having both tests can secure against the common difficulties with quantifying mood reliably.

Participants will use a mobile/desktop application to track their menses, store this information, and take these tests. They will also receive alerts and reminders from this application to input their information during the monitoring phase as well as take their daily IN OXT dosage during the experimental phase.

After the 3 months total of monitoring, the participants begin their treatments of placebo, 20 IU once-daily, or 40 IU once-daily of IN OXT during luteal phases. IN OXT is used in this study not only because it is the principal mode of administration in previous OXT studies but also because IN OXT is the only way shown reliably to cross the blood-brain barrier through repeated studies for over 25 years (Macdonald & Feifel, 2013). The only other possibility that has been researched is intravenous OXT, which is both inconvenient for daily administration and has not always shown consistent results.

During this time, in addition to continuing their records of body temperature and menses as well as their daily responses to the three tests, they are also required to come in to the lab twice per luteal phase (six times total) to have their blood checked to measure plasma OXT levels. These measurements will be done via an immunocytochemistry technique,
using the enzyme-linked immunosorbent assay for OXT previously used in many other studies and described in depth in Szeto et al. (2011). Figure 2 shows the general breakdown of all four phases (approximately six months) of this study.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Methods</th>
<th>Duration (# MCs)</th>
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<tbody>
<tr>
<td>1. Initial Screening</td>
<td>• Select qualified participants using criteria. Eliminate all who do not qualify.</td>
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<tr>
<td>2. Monitoring, Pilot</td>
<td>• Participants record morning body temperature, menses, answer Q-LES-Q, DRSP, PMTS-VAS. • At end, participants eliminated if eligibility is questioned with data collected during pilot</td>
<td>2</td>
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<tr>
<td>3. Continued Monitoring</td>
<td>• Participants record morning body temperature, menses, answer Q-LES-Q, DRSP, PMTS-VAS.</td>
<td>1</td>
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<tr>
<td>4. Experimental</td>
<td>• IN OXT (20 or 40 IU) or placebo administered to participants daily. • Participants record morning body temperature, menses, answer Q-LES-Q, DRSP, PMTS-VAS. • Participants must come into the lab 2 times per luteal cycle to have blood checked for plasma OXT levels using ELISA technique.</td>
<td>3</td>
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Figure 2. Overview of All Experimental Phases in this Study. This figure shows the different phases with relevant description and durations, in view of the entire study, chronologically from top to bottom. Abbreviations in figure—MC: Menstrual Cycle; Q-LES-Q: Quality of Life Enjoyment and Satisfaction—Short Form; DRSP: Daily Report of Severity of Problems; PMTS-VAS: Premenstrual Tension Syndrome—Visual Analogue Scale.

Results

Overall, mood symptoms measured by the Q-LES-Q and DRSP are hypothesized to improve significantly in the 20 and 40 IU IN OXT groups compared to placebo without much variation due to dosage or time span. This IN OXT treatment is not hypothesized to have any overt effects on the non-mood symptoms of PMDD, but its physical effects (premenstrual tension syndrome) will be monitored through the aforementioned PMTS-VAS. The placebo, 20 IU OXT, and 40 IU OXT are not hypothesized to have significant variations in physical symptoms, so no graph is shown here for the results of the PMTS-VAS test.

Figure 3 shows similar results in the pertinent mood and symptom participant tests, based on previous studies (Yonkers & Foegh, 2004). In this figure, luteal phases are counted from the very beginning of the study, with luteal phase 1 as the first luteal phase in the monitoring phase. Because the Q-LES-Q is a measurement of the quality of life, lessened symptoms would be shown with an upward trend in Q-LES-Q results.
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Figure 3. Percent of Maximum Possible Q-LES-Q-SF Raw Scores Across Time by Experimental Group. The total raw score ranges from 14 to 70, so 0% is equivalent to 14 raw points and 100% is equivalent to 70 raw points. Percentages calculated by (raw score – 14)/56. This figure presents the average Q-LES-Q-SF calculated score for participants in each experimental group (placebo, 20 or 40 IU IN OXT) across all six luteal phases tracked in this study.

Conclusion

PMDD affects 1,900 to 5,000 biological females in the US, and is in need of further research for treatments catered specifically to the disorder and its physiological effects, both emotional as well as physical. This proposed study would attempt to find a solution for those suffering from PMDD who have not or cannot be treated successfully with SSRIs, as well as an alternate solution for women who are uncomfortable with the many side effects of SSRIs. For each of these women, such developments would vastly improve their quality of life, relationships, and careers. MDD is highly comparable to MDD, Post-Traumatic Stress Disorder, and PMS, so any new information about PMDD through this study could greatly contribute to the understanding of these different disorders and syndromes as well.

In addition, with more thorough understanding of the processes underlying the disorder, the stigma that currently surrounds premenstrual disorders and more generally, female MCs, can be lessened. PMDD research can validate the experiences of women who have PMDD, and also identifying that only the women who do have this disorder—not all women—have these emotional and psychological effects. By doing so, this scientific research can contribute to gender equality by showing that women without the disorder are emotionally stable and are able to lead.

If this study does not produce viable results with IN OXT, it will be instead used as a study on the effects of Agomelatine, a melatonin agonist, on PMDD. Agomelatine, like OXT, has been used successfully to treat MDD with considerably fewer side effects than traditional SSRIs (Srinivasan, Zakaria, Othman, Lauterbach, & Acuña-Castroviejo, 2012). Because luteal phase PMDD symptoms include insomnia and other troubles with the sleep-wake cycle, it has been suggested that melatonin and its related hormones be further researched in PMDD (Shechter, Lesperance, Ng Ying Kin, & Boivin, 2012). The alternate study will have a similar setup to this proposed study, but with two different groups in the experimental phase—placebo and one tablet (25 mg) of Agomelatine. The drug, which is available as a commercial product (under the trade name Valdoxan) for the treatment of MDD, has been tested and approved for administration in humans.
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Bibliography


