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Premenstrual Dysmorphic Disorder/Premenstrual Syndrome Luteal Phase Treatment

Shelby Gawarecki
University of North Dakota

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Shelby Gawarecki, PA-S
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

Abstract

- PMS/PMDD symptoms affect many women's emotional and physical well-being.
- SSRIs, progesterone, and sepranolone are luteal phase treatment options.
- Studies were all peer-reviewed, including randomized control trials or a meta-analysis.
- SSRIs are a consistent primary treatment for symptom alleviation especially cognitive symptoms. SSRIs are the current mainstay, recommended for luteal phase treatment of PMS/PMDD.
- SSRIs, including citalopram, sertraline, escitalopram, and fluoxetine, were examined to determine their efficacy in relieving mood-related symptoms such as irritability, anxiety, and depression during the luteal phase.
- Data on progesterone treatment in the luteal phase is inconclusive.
- Allopregnanolone levels and sepranolone treatment research are currently delivering a new understanding of hormonal mechanisms in PMS/PMDD.
- Sepranolone remains in trial and is not yet available for clinical use.

- *Keyword Search:* Premenstrual Dysphoric Disorder, Selective Serotonin Reuptake Inhibitors, Progesterone, Fluoxetine, Premenstrual Syndrome, Sepranolone, Allopregnanolone, Luteal Phase, or Premenstrual.

Introduction

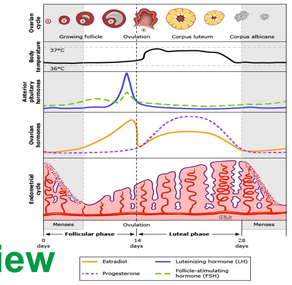
- Premenstrual dysphoric disorder (PMDD) affects up to 10% of women more severely than premenstrual syndrome (PMS).
- The literature review focuses on the luteal phase of the menstrual cycle to identify treatments for the symptoms of PMDD/PMS.
- PMDD diagnosis is based on criteria outlined in the DSM-5 including symptoms interfering with daily life for at least two cycles.
- The pathophysiology involves complex hormonal fluctuations.
- Some research has suggested that when progesterone levels drop, CNS changes in gamma-aminobutyric acid (GABA) and progesterone metabolites affect the GABA-A receptor complex, so symptomatic women may have a different response than non-symptomatic women.
- Allopregnanolone, a progesterone metabolite which influences the GABA-A receptor complex, fluctuates during the menstrual cycle, potentially contributing to PMDD symptoms.
- Neurotransmitters, specifically serotonin, play a critical role in PMDD/PMS.
- Selective serotonin reuptake inhibitors (SSRIs) are being used to boost serotonin levels and relieve symptoms of PMS/PMDD.
- Symptomatic women have a greater sensitivity to the fluctuation of an additional excitatory neurotransmitter, Glutamate, than non-symptomatic women, research shows.
- Studies have shown abnormalities in the hypothalamic-pituitary-gonadal axis in PMDD/PMS with lower levels of cortisol and beta-endorphins leading to hypothalamic-pituitary-adrenal axis dysregulation.
- Factors, such as genetics, neurotransmitters, environment, and hormones, make this a complex subject (Mishra et al., 2023).

Statement of the Problem

Management of PMS/PMDD is complex, and the pathophysiology is not fully understood. This literature review aims to look for alternative therapies targeted at the luteal phase of a woman's menstrual cycle that would more fully resolve the physical and mental symptoms of PMS/PMDD.

Research Question

Among women diagnosed with premenstrual dysphoric disorder (PMDD) or premenstrual syndrome (PMS), what is the efficacy of various luteal phase pharmacologic treatment options, including luteal phase SSRIs, luteal phase progesterone and luteal phase sepranolone in reducing symptoms of PMDD/PMS?



Literature Review

SSRI Treatment:

- Wikander et al. (1998) looked at the effects of using citalopram, an SSRI, at different dosages and duration throughout three complete menstrual cycles in women who experienced severe irritability and or depression in the luteal phase of their menstrual cycle. Overall, this study found that intermittent citalopram was an effective treatment for those who experience severe irritability during the luteal phase of menstruation.
- Yonkers et al. (2015) suggest that continuous or luteal phase SSRI treatment is beneficial in reducing symptoms of PMDD; they sought to investigate further if starting SSRI treatment in the luteal phase during PMDD symptom onset would be as beneficial. In conclusion, Yonkers et al. (2015) determined that symptom-onset SSRI treatment with a primary assessment based on DRSP scores was ineffective. However, they found that SSRI treatment did help improve symptoms of anger/irritability, and there was no significant interference with withdrawal symptoms.
- Steinberg et al. (2012) studied the effects of fluoxetine in women who were diagnosed with PMDD according to the DSM-5 criteria. In this study, Steinberg et al. (2012) found that most women in the fluoxetine group experienced symptom improvement 48 hours after medication initiation.
- Ericksson et al. (2008) in this study looked at the luteal phase administration of escitalopram for those who had a diagnosis of PMDD. This study found that both the 10 mg and 20 mg treatment with escitalopram compared to placebo were beneficial. Overall, when comparing 20 mg to 10 mg, the 20 mg treatment was statically significant and more efficacious in treating PMDD (p<.05).
- Freeman et al. (2004) looked at treating PMDD or severe PMS with sertraline using continuous or intermittent dosing. For those who finished the study, significant improvement was analyzed via an ANOVA based on DRPS scores across all groups (p<0.01). Additionally, when comparing continuous sertraline treatments to placebo, symptoms were significantly improved based on the DRPS (p=0.02). There was also a significant improvement in symptoms based on DRPS when looking at luteal phase sertraline versus placebo (p=0.009). The study also compared continuous versus luteal phase treatment with sertraline and did not find a significant difference between the two (p=.76) (Freeman et al., 2004).
- Wu et al. (2008) looked at the treatment of PMDD and compared continuous versus intermittent administration of paroxetine. There was an improvement in mood (p<0.005), behavior (p<0.010), pain (p<0.010), and food cravings (p=0.003) with intermittent paroxetine administration. When continuous treatment was used, there was only statistically significant improvement in mood (p=0.024) and behavior (p=0.002).

Progesterone Treatment:

- A study by Kimball et al. (2020) looked at ten healthy premenopausal females compared to 24 postmenopausal females throughout the premenopausal female's menstrual cycle. They looked at allopregnanolone levels at three different times: follicular phase (d 1–7), mid-cycle phase (d 13–16), and luteal phase (d 20–23). Kimball et al, (2020) found that levels of allopregnanolone increased from the follicular to luteal phase p = 0.02. Levels of progesterone also rose across the menstrual cycle p < 0.0001. When looking at premenopausal vs. postmenopausal women, postmenopausal women had lower levels of progesterone and allopregnanolone in all phases of the menstrual cycle.
- Ford et al. (2012) conducted the most up-to-date meta-analysis to see if progesterone hormone replacement is effective for those with premenstrual syndrome. In one study, both the progesterone and placebo groups showed symptom improvement, but there was no statistical significance (p>.05). In the other study, those who received progesterone showed improvement in symptoms in the first cycle, but compared to the placebo, it was not statistically significant (p>.05).
- Hilgers, MD (2010), shares that progesterone therapy must be properly timed within the menstrual cycle when using progesterone therapy to relieve PMS symptoms. Overall, this study showed that timed HCG or progesterone treatment was the most beneficial for women with PMS.
- Freeman et al. (1995) studied the effects of oral micronized progesterone and alprazolam versus placebo during the luteal phase for women with severe PMS. Based on statistical analysis with an ANOVA test at the end of three months, it was noted that there was a significant improvement in those who took alprazolam versus placebo or progesterone (p<.05).

Ongoing Research on Allopregnanolone:

- Bixo et al. (2017) investigated if sepranolone could be an effective medication for PMDD treatment. Bixo et al. (2017) used data from 106 participants and found significant treatment effects when using DRSP scores and borderline significance for the negative mood scores compared to placebo. In those who received sepranolone treatment, their DRSP score was reduced by 61.1% compared to placebo, which was reduced by 50.4% (p=0.041). When looking at negative mood scores, those with treatment had a reduction in symptoms by 66% compared to 53.8% in the placebo group (p=.051).
- Bäckström et al. (2021) conducted a parallel, double-blind, randomized controlled trial design study examining the efficacy and safety of sepranolone in women with PMDD. It is the second study of its kind to investigate this medication. During their study, Bäckström et al. (2021) found that overall treatment of symptoms improved with 10 mg (p=0.008) compared to the placebo but did not see improvement compared to placebo with 16 mg.

Discussion

SSRI Treatment:

- Literature suggests that SSRI treatment during the luteal phase consistently improves cognitive symptoms of PMDD/PMS.
- Various SSRIs, including citalopram, sertraline, escitalopram, and fluoxetine, have shown effectiveness.
- Correct dosage during the luteal phase significantly improves mood-related symptoms like irritability, anxiety, and depression.

Progesterone Treatment:

- Mixed results for progesterone treatment in the luteal phase.
- Ford et al. (2012) meta-analysis found improvement in some studies but not statistically significant.
- Freeman et al. (1995) study with oral progesterone showed no statistically significant improvement.
- Hilgers, MD (2010) suggests an individualized approach to treatment, emphasizing the importance of tracking ovulation with oral progesterone showing improvement if properly timed (administered from peak +3 through peak +12, corresponding to ovulation).

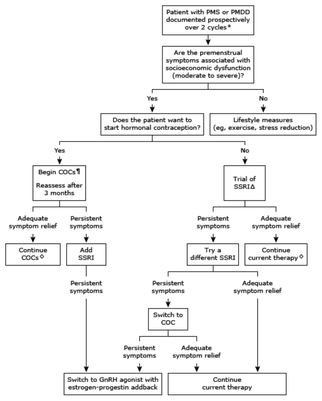
Ongoing Research on Allopregnanolone:

- Allopregnanolone levels are linked to mental health in the luteal phase.
- Sepranolone studies by Bixo et al. (2017) and Bäckström et al. (2021) show promising results for improving mental health symptoms in PMS/PMDD.
- There is a need for continued investigation into sepranolone as a treatment option.

Summary & Future Research

- SSRI treatment remains the mainstay due to statistically significant symptom reduction.
- There are challenges and complexities in progesterone replacement therapy.
- Sepranolone has promising potential and is still in clinical trials.
- Ongoing exploration of allopregnanolone levels provides insights into hormonal mechanisms.
- Future research should explore medications addressing the physical and mental aspects of PMDD/PMS and consider the individualized timing of ovulation in treatment approaches.

Application to Clinical Practice



This literature review of luteal phase treatment for PMS/PMDD is a good foundational review of treatment options. At this time, SSRI therapy remains the most efficacious when treating symptoms of this complex diagnosis. Providers can also consider using progesterone therapy with women who opt to practice Natural Family Planning and have a good understanding of how to track ovulation. Finally, with advancements in research, providers can continue to check on the updates of sepranolone, which provides promising outlooks in treating PMS/PMDD in the future.

References

•Bäckström, T., Ekberg, K., Hirschberg, A. L., Bixo, M., Epperson, C. N., Briggs, P., Panay, N., & O'Brien, S. (2021). A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder. *Psychoneuroendocrinology*, *133*, 105426. https://doi.org/10.1016/j.psyneuen.2021.105426
•Bixo, M., Ekberg, K., Poromaa, I. S., Hirschberg, A. L., Jonasson, A. F., Andréen, L., Timby, E., Wulff, M., Ehrenborg, A., & Bäckström, T. (2017). Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010)-A randomized controlled trial. *Psychoneuroendocrinology*, *80*, 46–55. https://doi.org/10.1016/j.psyneuen.2017.02.031
•Eriksson, E., Ekman, A., Sinclair, S., Sörvik, K., Ysander, C., Mattson, U.-B., & Nissbrandt, H. (2008). Escitalopram Administered in the Luteal Phase Exerts a Marked and Dose-Dependent Effect in Premenstrual Dysphoric Disorder. *Journal of Clinical Psychopharmacology*, *28*(2), 195. https://doi.org/10.1097/JCP.0b013e3181678a28
•Ford, O., Lethaby, A., Roberts, H., & Mol, B. W. J. (2012). Progesterone for premenstrual syndrome. *Cochrane Database of Systematic Reviews*, *3*. https://doi.org/10.1002/14651858.CD003415.pub4
•Freeman, E. W., Rickels, K., Sondheimer, S. J., & Polansky, M. (1995). A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA*, *274*(1), 51–57.
•Freeman, E. W., Rickels, K., Sondheimer, S. J., Polansky, M., & Xiao, S. (2004). Continuous or Intermittent Dosing With Sertraline for Patients With Severe Premenstrual Syndrome or Premenstrual Dysphoric Disorder. *American Journal of Psychiatry*, *161*(2), 343–351. https://doi.org/10.1176/appi.ajp.161.2.343
•Hilgers, MD, T. W. (2010). *The NaProTECHNOLOGY Revolution Unleashing the Power in a Woman's Cycle*. Beaufort Books.
•Kimball, A., Dichtel, L. E., Nyer, M. B., Mischoulon, D., Fisher, L. B., Cusin, C., Dording, C. M., Trinh, N.-H., Yeung, A., Haines, M. S., Sung, J. C., Pinna, G., Rasmusson, A. M., Carpenter, L. L., Fava, M., Klibanski, A., & Miller, K. K. (2020). The allopregnanolone to progesterone ratio across the menstrual cycle and in menopause. *Psychoneuroendocrinology*, *112*, 104512. https://doi.org/10.1016/j.psyneuen.2019.104512
•Mishra, S., Elliott, H., & Marwaha, R. (2023). Premenstrual Dysphoric Disorder. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK532307/
•Steinberg, E. M., Cardoso, G. M. P., Martinez, P. E., Rubinow, D. R., & Schmidt, P. J. (2012). Rapid Response to Fluoxetine in Women with Premenstrual Dysphoric Disorder. *Depression and Anxiety*, *29*(6), 531–540. https://doi.org/10.1002/da.21959
•Wikander, I., Sundblad, C., Andersch, B., Dagnell, I., Zylberstein, D., Bengtsson, F., & Eriksson, E. (1998). Citalopram in Premenstrual Dysphoria: Is Intermittent Treatment During Luteal Phases More Effective Than Continuous Medication Throughout the Menstrual Cycle? *Journal of Clinical Psychopharmacology*, *18*(5), 390.
•Wu, K.-Y., Liu, C.-Y., & Hsiao, M.-C. (2008). Six-month paroxetine treatment of premenstrual dysphoric disorder: Continuous versus intermittent treatment protocols. *Psychiatry and Clinical Neurosciences*, *62*(1), 109–114. https://doi.org/10.1111/j.1440-1819.2007.01785.x
•Yonkers, K. A., Kornstein, S. G., Gueorguieva, R., Merry, B., Van Steenburgh, K., & Altemus, M. (2015). Symptom-Onset Dosing of Sertraline for the Treatment of Premenstrual Dysphoric Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *72*(10), 1037–1044. https://doi.org/10.1001/jamapsychiatry.2015.1472

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