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Effective Therapies for Post-partum Depression—What choices do women have?

Anzule Navarrete
University of the Pacific, anzule_n@hotmail.com

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By

Anzule Navarrete

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INTRODUCTION and BACKGROUND

A CDC study shows that one out of nine women in the United States experience symptoms of postpartum depression. These numbers also vary by age, race and ethnicity. In addition, rates of postpartum depression vary by state, making it as high as 1 in 5 women with this disorder.[1] Postpartum depression (PPD) is a common illness that threatens the mental and emotional health of not only a new mother but also the entire family. Nonetheless, this disorder has not received the attention it deserves from the healthcare community. A mother should not be suffering by herself. She should have the resources and support from the healthcare system so that she can successfully overcome the painful emotions associated with PPD. As Richard J. Codey said, "Postpartum depression is a very real and very serious problem for many mothers. It can happen to a first-time mom or a veteran mother. It can occur a few days…or a few months after childbirth".[2]

Awareness of this disorder is necessary for solving this system deficiency. Diagnosing it is foremost. PPD is defined by the DSM-V[i] as depressive symptoms that must occur within 12 months following parturition. Sadly, many women might not reach out to their providers but coverup their symptoms, because of the stigma of depression, their feelings of failure as mothers, and their guilt over these negative feelings.[3] Screening for PPD in these patients is vital. Once this condition is diagnosed, a better understanding of the different therapeutic approaches to post-partum depression will aid clinicians and patients in selecting an option that is both effective and acceptable to the

patient. Treatment for PPD is not a one-size-fits-all. Understanding the features of PPD can explain the need for individualizing therapy and provide guidance for treatment choices. Clinicians and patients need to work together to surmount this challenging disorder.

While PPD is a common complication, its prevalence varies depending upon the report. However, most studies agree that the prevalence ranges between 10% to 16%.[4] Multiple risk factors predispose a mother to PPD. Among those risks are; marital conflicts, poor social and financial support during the puerperium, ages < 25 years, single-parenting, multiparity, family history of depression or mental illnesses, and unintended or unwanted pregnancy. Of all these risk factors, the greatest is a previous diagnosis or history of depression in the mother.[4,2]

The onset of PPD can vary. Besides, more than 50% will develop symptoms of depression before or during pregnancy, whereas over 40% will develop definite PDD within the first few months post-delivery. Of the women with PPD, 54% had onset within the first month, 40% between 2-4 months, and only 6% from 5 to 12 months.[4,3]

The potential consequences of postpartum depression are significant because they affect not just the patient, but also the patient's family, including her developing child, her spouse or partner, her other children, and others in the immediate family. Mothers suffering from PPD do not play, read stories, or develop a deep bond with their babies. Consequently, the bond between a mother and her baby is impacted.[3] Other findings in PPD include decreases in breastfeeding, attention to their baby's sleep hygiene and safe positioning, and in vaccination compliance, therefore increasing these

infants' risks for illnesses and injuries. PPD also strains the marriage and other relationships. Lastly, although women with PPD have the lowest incidence of suicide or infanticide, even one death is a frightening number for any family and society.[4] Therefore, early recognition and treatment of this disorder is critical to avoiding these complications.

Thus, after the diagnosis of PPD, treatment becomes a priority. The clinician and patient need to work as a team to choose a therapy that is appropriate for the severity of the symptoms and acceptable to the patient. Among current approaches to the treatment of PPD are non-pharmacologic treatments and pharmacologic treatments. Non-pharmacologic treatments consist of cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), nondirective counseling, psychodynamic psychotherapy, electroconvulsive therapy (ECT), exercise, acupuncture, and bright-light therapy. Pharmacotherapy consists of antidepressants, ketamine, and brexanolone. Antidepressants used are primarily the selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline. Recommended initial treatment for mild to moderate postpartum depression is psychotherapy, but often antidepressants such as SSRIs or SNRIs (serotonin-norepinephrine reuptake inhibitors) are used in addition or if the patient prefers them. In women suffering from moderate to severe PPD, the recommended treatment is pharmacotherapy with antidepressants, SSRIs, SNRIs, or mirtazapine, all of which are considered safe for pregnant and lactating women.[3,2] However, most clinicians simply prescribe SSRIs because of their safety and because it is a common practice.[4,1] Furthermore, most providers do not separate PPD into categories by degree of severity, which omission does not individualize therapy.[3,2]

Many factors influence treatment success, especially treatment adherence. Adhering to any therapy is challenging for a new mother because her time and attention are devoted to taking care of her newborn around the clock, thus leaving little reserve for taking care of her own needs. However, clinicians must remind patients that a successful mother must first care for herself. This factor highlights the importance of individualizing therapy and involving the patient in treatment decisions in order to optimize adherence.

In addition to recognizing the integral role of patient adherence, successful therapy requires a knowledge of the efficacies of various PPD treatments and a familiarity with their potential adverse effects and harmful aspects. The elements of treatment options, including non-pharmacologic and pharmacologic therapies, will be examined in order to provide clinicians with relevant evidence for medical decision-making.

DISCUSSION

Available research on PPD treatments includes randomized controlled trials (RCTs), systematic reviews, meta-analyses, and some case studies. Results varied depending on not only the treatment employed, but also the patient's history of previous episodes of major depression, and prior treatments, if any, along with the severity of depression, the patient's compliance with therapy, and her support network.

Nonpharmacologic Therapies:

Psychotherapeutic interventions have been championed because abnormal behaviors typically result from distorted cognition, which is the basis for CBT. In addition, psychotherapy is not burdened by potential adverse effects that antidepressants have on either the mother or her breastfeeding infant (via drug concentration in breast milk). Experts propose that CBT is beneficial in improving the symptoms of postpartum depression.

A systematic review and meta-analysis by Stephens et al. examined results of 10 RCTs involving 1324 new mothers in England with PPD. Psychological therapy was shown to be effective. Findings were significant, and no significant differences were noted among the different types of psychological treatments. Furthermore, in some of the RCTs, psychological therapy in combination with antidepressants was more effective than antidepressants alone.[5,2] The authors examined psychological interventions in primary care, hence were the first to provide evidence that such treatment is viable in that setting. Results of this research were strengthened by the inclusion of a sensitivity analysis that removed low quality studies.[5,3] Some of the weaknesses of this research were that many of the studies had small sample sizes, high attrition, and allowed concomitant use of antidepressant medication. Thus, these methodologic limitations weakened the conclusions and might have introduced bias.[5,3]

Exercise is another, potentially safe treatment option. A systematic review and meta-analysis by Pritchett et al. examining 13 RCTs with 1734 participants provided evidence that aerobic exercise does improve PDD. These findings were significant and comparable to the improvements seen with antidepressant therapy and with low intensity psychological interventions, such as CBT and usual care for PPD. This study

also highlighted that many women who have PPD had time constraints to exercise. Nonetheless, it can be extrapolated that those who have a robust support system could benefit from taking a few hours daily for themselves.

A study by Dowlati et al. examined another non-pharmaceutical therapy, dietary supplementation for improving postpartum blues (PPB). PPB are believed to be the prodromal state of postpartum depression and this prodromal state is more prevalent on postpartum day five. This dietary supplementation was created to target neurobiological changes[ii] in the prodromal state prior to PPD.[6] In this double blinded RCT, one group of participants (n=21) received the dietary supplement composed of 2 g of tryptophan, 10 g of tyrosine, and blueberry juice with blueberry extract. The control group (n=20) did not receive supplements. The dietary supplement group experienced resolution of intense post-partum blues. The large effect size of 2.9 (ten times greater improvement as compared with placebo and other interventions) was this study's strength. Its low-cost solution was also favorable. However, subjects were assigned based on protocol availability instead of an actual randomized double-blind placebo-controlled trial, which limits the quality of evidence by introducing bias.[6,3] Nonetheless, dietary supplementation might be augmented with exercise and psychotherapy.

Additional nonpharmacologic treatments for PDD and other reproductive conditions, such as menstruation and pregnancy, were examined in several studies. Therapies included acupuncture, electroconvulsive therapy, bright light treatment, and psychological interventions. A double blind RCT explored twice-weekly sessions of traditional and sham electro-acupuncture[iii] for treating PPD in 20 women who had been diagnosed with PPD. Even though the sample size was small, participants' symptoms

improved 50 and 44 percent for traditional versus sham electro-acupuncture, respectively. Despite participants' reduction in their symptoms, final results lacked statistical significance.[3,4]

Bright Light Treatment (BLT) was studied in women who met criteria for PPD. For several weeks, the treatment group of ten women received BLT daily while the placebo group of five women received a lower intensity light therapy daily, each session lasting thirty minutes in each group. Both groups had significant improvements in symptoms evidenced by a 49% reduction in SIGH-SAD[iv] scores in each group. Neither study found statistically significant differences and this limitation derives from inconsistencies in the methodology and also small sample sizes in both groups, hence the evidence was inconclusive.[3,3]

Postpartum electroconvulsive therapy (ECT) is a therapeutic option for severe PDD. The evidence from a systematic review revealed a more rapid improvement of depressive symptoms with ECT when compared with the usual antidepressants. Within two weeks, 5-7 treatments significantly reduced the severity of depression.[7] In a case study, a female with severe PPD and a suicide attempt at 38 weeks gestation was subsequently admitted to the hospital postpartum with her infant for ECT of her previously refractory PPD.[7,1] She experienced significant benefits that improved her quality of life and bonding with her baby. Notwithstanding the favorable results with ECT, its relapse rate exceeds 50% and thus, requires repeated administration for relapses. ECT's adverse effects also need to be considered, and include complications such as disorientation after each session, anterograde amnesia for recently learned

information, and retrograde amnesia for previously learned information all of these are most often transient.[7,3]

Pharmacologic Therapies:

Research has suggested the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in treating antidepressant-naïve patients with PPD who were unresponsive to CBT or other psychotherapies. Compared to any other class of antidepressants, SSRIs have been used more frequently during pregnancy and in postpartum women; they have also been studied in breastfeeding women. SSRIs are used in ninety percent of women suffering from postpartum depression. Among SSRIs, paroxetine or sertraline are most commonly used since adverse effects on infants appear to be low and they are not detectable in breastmilk.[8] Patients on SSRIs compared with those on placebo had a 40% improvement in depression symptoms compared with 20% in the placebo group.[8,1] Other antidepressants that have been safe and effective include the serotonin norepinephrine reuptake inhibitors (SNRIs)**,** mirtazapine and the tricyclic antidepressant (TCA), nortriptyline. PPD symptom improvements are similar for SSRIs and SNRIs therapies.[8,2] These findings are supported by a few head to head RCTs that compared those antidepressants for treating PPD and improvement in patients' depressive symptoms was equivalent among these antidepressants.[8,4]

Recently, the prophylactic use of ketamine for preventing postpartum depression in Chinese women undergoing Cesarean section was examined. Ketamine is a general anesthetic that also increases serotonin and melatonin, which effects are generally

beneficial. In this RCT, a total of 654 women were followed, some with antenatal depression and some without it. The treatment and control groups were well-matched. The treatment group was given a 0.5 mg/kg dose of ketamine ten minutes after Cesarean section, whereas the control group only received standard postpartum care. A significant reduction of PPD occurred in the group that received ketamine post-delivery. This therapy also decreased PPD in participants who had antenatal depressive syndrome and anxiety during pregnancy, both of which are risk factors for PPD. Adverse effects, were minor and transient.[9] The large group of participants and the single-administration of treatment (ensuring compliance) were study strengths. Nonetheless, the findings in this study have yet to be reproduced by other investigators. Furthermore, ketamine's mechanism of action for treatment of depression is not fully understood.

Another drug, brexanolone, was approved in 2018 by the FDA for treatment of postpartum depression and is considered one of the most effective treatments available for moderate to severe PPD. A review article by Powell et al of phase II and III trials reported rapid beneficial effects within 72 hours post infusion. However, durability of these effects beyond thirty days was questionable.[10] Nonetheless, brexanolone was efficacious in women with PPD who had moderate to severe symptoms. Some of the adverse effects reported were dizziness, somnolence, and headache.[10,2] Other less common side effects were nausea, rash, postural dizziness, dry mouth and hot flashes. Brexanolone has an FDA black box warning for central nervous system depression and loss of consciousness. Therefore**,** it requires administration in a specialized care facility as well as enrollment in REMS.[v]

Non-pharmacologic approaches vs pharmacologic approaches and their respective outcomes:

A study compared Interpersonal Therapy (IPT), sertraline-Clinical Management (CM) and placebo-CM in the acute treatment of PPD over 12 weeks. In this study, 162 women who met DSM-IV criteria for postpartum depression and met inclusion criteria were enrolled in the randomized treatment phase. Findings did not show significant differences between the IPT group and the medication groups. However, active interventions with or without pharmacotherapy delivered for a period greater than twelve weeks led to significant improvement in depressive symptoms and improved social adjustment in these women suffering from PPD. More importantly**,** this research confirmed that a woman's treatment preference should be honored whenever possible since patient-selected therapy was the major determinant for treatment adherence. It also validated the need for well-trained clinicians capable of applying evidence-based IPT as well as evidence-based pharmacotherapy for women suffering from PPD.[11] The double-blind, placebo-controlled trial design was a strength. In addition, the diversity among participants was conducive to generalizability even though the sample size was relatively small. Some participants dropped-out, creating a selection bias, probably because they could not enroll in the treatment they desired.

In summary, effective treatments for PPD include the following:

II. Data supporting non-pharmacologic therapies

- The effect of exercise was favorable compared to low intensity psychological interventions Such as online CBT and casual care for

depression in the general population. These effects are also compared to antidepressants [12]

- Psychological interventions are valid and should be tried in women who suffer from PPD and do not want to take antidepressant medications.[5]
- CBT in short-term and long-term follow up was associated with a better Edinburgh Postnatal Depression Scale (EPDS) than no CBT control.[13]
- A combination of tryptophan, tyrosine and blueberry extract/juice almost completely eliminated the vulnerability to depressed mood during the peak period of PPD with an effect size of at least 10-fold greater than the effect size reported for other interventions.[6]
- Traditional and sham acupuncture both improved symptoms of PPD with remission rates of 50% and 44%**,** respectively.[3]
- Response to electroconvulsive therapy was high, especially in patients with severe PPD. However, it is not recommended for patients with mild depression.[14] Significant adverse effects can occur.

III. Data supporting pharmacologic therapy

- SSRIs and SNRIs remain the safest choice for patients who fail CBT or other psychotherapies. These antidepressants are also safe for women who are breastfeeding.[10]
- Sertraline CM induced improvements in PDD more quickly (within eight to twelve weeks) than IPT and placebo pill.[5]
- Ketamine, when administered before a C-section compared with no ketamine, had a prophylactic effect against PPD.[12]

- Brexanolone is effective for the treatment of moderate to severe PPD and rapidly reduces PPD symptoms. However, clinicians must be aware of its side effects.[10]

Choosing the best treatment for each case—these are essential questions to ask:

1. Does the patient have a history of depression, anxiety, or any other mental illness?
2. Was she treated with CBT, antidepressants, or another approach?
3. If treated in the past, what was the outcome of treatment?
4. What is the severity of her depression at the time of assessment?
5. Were or are any suicidal ideations present?

CONCLUSION

The efficacy and safety of various non-pharmacologic and pharmacological measures for treating postpartum depression were examined. No singular treatment can be considered appropriate for all patients suffering from postpartum depression. However, psychological interventions are generally the safest because they have few clinical side effects. Low to moderate-intensity exercise, which is generally safe, was found to be effective and even superior to low intensity psychological approaches (such as online CBT and usual care for depression) and antidepressants. Medications, in particular SSRIs, SNRIs and brexanolone, are effective treatments. Ketamine also shows promise for prevention of PPD. In addition, an array of other treatments has been shown to be effective and provide alternatives for patients. Overall, psychological intervention is a validated treatment choice in primary care and is an excellent

alternative for women who do not want pharmacotherapy. Treatment must be carefully selected based on each woman's preference, her current level of depression, and her prior history of depressive disorders. Now clinicians can offer their patients a variety of treatments for the treatment of PPD, both pharmacologic and non-pharmacologic. Therapies available for this disorder are effective and should be individualized.

Areas for future research include long term follow up to assess the durability of treatments, exploring the relationship between Adverse Childhood Events as a risk factor for PPD, examining the role of support systems in the development and treatment of PPD, and considering the potentially harmful effects of PPD medications on breast-fed infants. Future investigations also need to determine whether antidepressants when given during pregnancy or post-partum have harmful effects on women's brains or children's development, and whether early screening identifies patients at risk of developing PPD, thereby affording opportunities to prevent it.

Notwithstanding the need, research in pregnant and post-partum women has challenges. Concern about how therapies may affect the infant as well as the mother may discourage participants. The fatigue and time constraints in this population of women make commitment to a study undesirable. Nonetheless, clinicians should champion research in this vulnerable population in order to improve women's health and that of their children and families.

REFERENCES

1. Depression Among Women. Centers for Disease Control and Prevention. https://www.cdc.gov/reproductivehealth/depression/index.htm#how. Published December 5, 2019. Accessed February 8, 2020.

2. Owner Pby MC, Owner MC, by nikzanta P, Nikzanta. Richard J. Codey said (Quotes 1). MottoCosmos.com. https://www.mottocosmos.com/quotes/richard-j-codey-said-quotes-1/. Published November 29, 2019. Accessed March 4, 2020.

3. Brandon AR, Crowley SK, Gordon JL, Girdler SS. Nonpharmacologic Treatments for Depression Related to Reproductive Events. *Current Psychiatry Reports*. 2014;16(12). doi:10.1007/s11920-014-0526-0

4. https://www-uptodate-com.pacificpa.idm.oclc.org/contents/postpartum-unipolar-major-depression-epidemiology-clinical-features-assessment-and-diagnosis?search=postpartum depression&source=search_result&selectedTitle=1~121&usage_type=default&display_rank=1. Accessed February 8, 2020. *12*

5. Stephens S, Ford E, Paudyal P, Smith H. Effectiveness of Psychological Interventions for Postnatal Depression in Primary Care: A Meta-Analysis. *The Annals of Family Medicine*. 2016;14(5):463-472. doi:10.1370/afm.1967

6. Dowlati Y, Ravindran AV, Segal ZV, Stewart DE, Steiner M, Meyer JH. Selective dietary supplementation in early postpartum is associated with high resilience against depressed mood. *Proceedings of the National Academy of Sciences*. 2017;114(13):3509-3514. doi:10.1073/pnas.1611965114

7. Gressier F, Rotenberg S, Cazas O, Hardy P. Postpartum electroconvulsive therapy: a systematic review and case report. *General Hospital Psychiatry*. 2015;37(4):310-314. doi:10.1016/j.genhosppsych.2015.04.009

8. https://www-uptodate-com.pacificpa.idm.oclc.org/contents/severe-postpartum-unipolar-major-depression-choosing-treatment?search=SSRIs for postpartum depression&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H1656261266. Accessed February 10, 2020.

9. Ma, Jia-Hui, et al. “Prophylactic Use of Ketamine Reduces Postpartum Depression in Chinese Women Undergoing Cesarean Section☆.” *Psychiatry Research*, vol. 279, 16 Mar. 2019, pp. 252–258., doi:10.1016/j.psychres.2019.03.026.

10. Powell, Jason G, et al. “Brexanolone (Zulresso): Finally, an FDA-Approved Treatment for Postpartum Depression.” *Annals of Pharmacotherapy*, Mar. 2019, p. 106002801987332., doi:10.1177/1060028019873320.

11. Ohara MW, Pearlstein T, Stuart S, Long JD, Mills JA, Zlotnick C. A placebo-controlled treatment trial of sertraline and interpersonal psychotherapy for postpartum depression. *Journal of Affective Disorders*. 2018;245:524-532.doi:10.1016/j.jad.2018.10.361

12. Pritchett RV, Daley AJ, Jolly K. Does aerobic exercise reduce postpartum depressive symptoms? a systematic review and meta-analysis. *British Journal of General Practice*. 2017;67(663). doi:10.3399/bjgp17x692525

13. Huang L, Zhao Y, Qiang C, Fan B. Is cognitive behavioral therapy a better choice for women with postnatal depression? A systematic review and meta-analysis. *Plos One*. 2018;13(10). doi:10.1371/journal.pone.0205243

14. Rundgren S, Brus O, Båve U, et al. Improvement of postpartum depression and psychosis after electroconvulsive therapy: A population-based study with a matched comparison group. *Journal of Affective Disorders*. 2018;235:258-264. doi:10.1016/j.jad.2018.04.043

[i] DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition

[ii] Neurobiological changes consist of low mood, emotional lability which are associated with fatigue, insomnia, poor appetite, and anxiety.

[iii] Sham electro-acupuncture: Small **electric** current is passed between pairs of **acupuncture** needles.

[iv] SIGH-SAD: The standard measure of winter seasonal affective disorder (**SAD**) severity

[v] REMS: Risk Evaluation and Mitigation Strategy