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Comparative Research of Effective Treatment Measures for Postpartum Depression

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by

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Abstract

Postpartum depression is a mood disorder that includes depressive symptoms during the time period following childbirth. There are various possibilities for what may cause this disorder, but the drastic change in hormones after delivery can play a role. With the chance this disorder may be fatal to both the mother and child, an appropriate, effective, and safe treatment is necessary to control depressive symptoms. The standard, first-line pharmacotherapeutic option is a selective serotonin reuptake inhibitor (SSRI) antidepressant. SSRI antidepressants are well understood, but these medications may take time to become effective. Knowing this, medical professionals can find a more rapid option that would be appropriate; thus, hormone replacement therapy is an alternative. In this review, numerous scientific databases were evaluated, including PubMed, Cochrane, and DynaMed. Keywords and mesh terms were searched to obtain a total of 384 studies. After various exclusion criteria were evaluated, a final total of 19 research articles were included. The results of this literature review showed that both treatment options of SSRI antidepressants and hormone replacement therapy are effective, and various side effects, risks, and contraindications are present with both therapy options. Currently, Brexanolone, an endogenous hormone, is the only FDA-approved indicated medication for postpartum depression. Clinically, psychotherapy and SSRIs are used as first-line options. Further research is necessary to evaluate the effectiveness and possible adverse effects with all options of antidepressants, hormone replacement therapy, and the possibility of a bridge therapy to decrease depressive symptoms.

Keywords: Postpartum depression, drug therapy, physiopathology, hormone replacement therapy, SSRIs, Brexanolone, safety, contraindications, and adverse events.

Comparative Research of Effective Treatment Measures for Postpartum Depression

Introduction

Postpartum depression is a mood disorder that includes depressive symptoms during the postpartum period following childbirth. This disorder affects about 6.5%-20% of all postpartum women and can be quite dangerous if unnoticed or untreated (Warren, Fedorowicz, & Ehrlich, 2018). The exact cause of this illness is unknown and may vary per woman and pregnancy. It is thought that hormone changes may impact this disorder; these changes include a decline in estrogen and progesterone following childbirth (Warren et al., 2018). The typical treatment for postpartum depression includes psychotherapy or counseling and first-line, pharmacotherapy of a selective serotonin reuptake inhibitor (SSRI) antidepressant. Due to such hormone changes that occur, it may be appropriate to use reproductive hormone replacement therapy as an alternative treatment. Therefore, the purpose of this study is to compare the use of typical SSRI antidepressant medication and hormone replacement therapy safety, efficiency, and efficacy on postpartum depression symptoms to promote a healthier and happier experience for the mother, child, and family.

Statement of the Problem

For new-onset, moderate-to-severe postpartum depression, SSRIs are the typical first-line therapy. According to Cooper, Kilvert, Hodgkins, Roskell, and Eldar-Lissai (2019), "current pharmacological treatments, including SSRIs, are associated with a slow rate of improvement (6-12 weeks), and there is a lack of reliable evidence to support the onset of efficacy occurring within the first week" (p. 2). Knowing that this standard treatment option can take time, it is necessary to find a quicker alternative such as hormone replacement therapy. This alternative is "well suited for postpartum depression because it occurs after 100-fold decreases in estradiol

between late pregnancy and 48 hours postpartum" (Moses-Kolko, Berga, Kalro, Sit, & Wisner, 2009, p. 3). Further usage of hormone replacement therapy could include estrogen, progesterone, and even a new medication, Brexanolone, an FDA-approved endogenous hormone treatment for postpartum depression. Researching the different treatment options can help medical professionals understand what causes postpartum depression, leading to a more effective therapy regimen.

Research Question

In postpartum females, does the use of hormone replacement therapy compared to medication therapy using SSRI antidepressants decrease postpartum depression symptoms more effectively?

In postpartum females, does the use of hormone replacement therapy compared to the use of SSRI antidepressants decrease or increase morbidity and mortality in the short and long-term therapy for postpartum depression?

In postpartum females, does bridge treatment using hormone replacement until SSRI becomes clinically efficacious compared to a standardized treatment with either hormone replacement therapy or SSRIs improve safety and recovery speed of postpartum depression?

Research Methods

A variety of literature was searched using scientific databases, including PubMed, DynaMed, Clinical Key, Cochrane Library, and Access Medicine. Keywords and mesh terms were searched to obtain relevant research, which included: postpartum depression, drug therapy, physiopathology, hormone replacement therapy, SSRIs, Brexanolone, safety, contraindications, and adverse events. The search was limited to articles within the last 10 years. This search included approximately 384 studies. Articles were then excluded if they did not pertain to SSRI

antidepressants and hormone replacement therapy. Further exclusion criteria were used due to minimal discussion of efficacy, efficiency, and safety of these options. Following evaluation and exclusion, 32 articles remained, but to obtain more information about treatment measures and etiology, the articles' time period was extended to be within 15 years. Conducting the literature review, further exclusion was executed due to insufficient data and evidence following the articles' summarization. There were 19 articles remaining that were then used in this literature review.

Literature Review

Reviewing the literature and research conducted on the treatment options for postpartum depression shows variable efficiency, efficacy, and safety in both SSRIs and hormone replacement therapies to decrease postpartum depression symptoms. This review shows that one treatment option may be more efficient and effective than the other in treating postpartum depression and its symptoms. The research is completed keeping the mother and child's safety in mind for each of these options.

Hormonal Changes in Postpartum Depression

It is known that postpartum depression is a multifactorial disease that can present in many different ways. For one to treat certain disorders, it is essential to understand how they occur. To begin with this understanding, Deems and Leuner (2020) compiled a comprehensive literature review to evaluate changes in the female body that can lead to various brain diseases and diminished health, including postpartum depression. This research was completed with a final total of 356 articles ranging in years from 1998 to 2019. As Deems and Leuner explain, with depression being a complex disease, it is believed that hormones have been a significant contributor to the cause of postpartum depression in some women. A study included in their

review explained that estrogen and progesterone withdrawal increased depression symptoms. Knowing that there are some drastic changes in hormones following childbirth, this could be a possible etiology to lead to potential treatment options.

The major limitation and weakness presented in Deems and Leuner (2020) would be that it is not statistically written and does not include studies to provide evidence; instead, it compiles results from a wide assortment of research for information purposes on etiology. The review's strengths include a wide variety of articles compiled to show the physiological processes present in numerous neurological and psychiatric disorders. Deems and Leuner highlight the leading causes that can result in postpartum depression, including changes in reproductive hormones that can essentially lead to an appropriate treatment option for women and a way to decrease depressive symptoms.

For further evaluation of possible etiologies, Schiller, Brody-Meltzer, and Rubinow (2014) conducted a review to examine fluctuations in reproductive hormone levels during pregnancy and the postpartum period that may trigger postpartum depression in susceptible women. The methods included evaluating medical databases to achieve a final total of 157 articles ranging from 1980 to 2014. Schiller et al. researched a reproductive hormone model that discusses why reproductive hormone changes may play a role in developing postpartum depression. As stated in their review, reproductive hormones play a significant role in various neurologic functions, including emotion and motivation (Schiller et al., 2014). To be specific, “in the forebrain and hippocampus, ovariectomy decreases and estradiol increases brain-derived neurotrophic factor (BDNF) levels, which are decreased by depression and stress and increased by antidepressants" (Schiller et al., 2014, p. 4). Because postpartum depression is a multifactorial disease, reproductive hormones have been thought to impact many other parts of the body as

well, including "thyroid function, lactogenic function, hypothalamic-pituitary-adrenal (HPA) axis, and the immune system" (Schiller et al., 2014, p. 5). With all of these changes and their effect on the body, the possible cause of postpartum depression can be identified.

Schiller et al. (2014) review's main limitation and weakness include minimal statistical information with the studies completed. Their review was more about providing information regarding the causes of postpartum depression rather than statistical analyses. Further research should be conducted to understand the cause of these depressive symptoms per woman and how to treat these differences. The strength of their literature review includes a discussion of many neuroendocrine effects that can cause postpartum depression. Based on this research, clinical decisions for the most effective and appropriate treatment option for treating women with postpartum depression can be determined.

Similar to the articles above, Warren et al. (2018) wrote a systematic review for *DynaMed* to discuss postpartum depression in its entirety. Completing this review allows for the background knowledge of postpartum depression, including evaluation, management, etiology, risk factors, and much more information regarding postpartum depression. The methods of this included a general reference list evaluation of a total of five articles ranging from 2015 to 2018. Warren et al. found that the direct cause of postpartum depression is unknown at this time due to it being a complex disorder. Their review includes an understanding of the possible neuroendocrine causes of postpartum depression, including significant hormonal changes that characterize the transition to the postpartum period. These include third-trimester hormone levels of high estrogen and progesterone. Following childbirth and the transition to the postpartum period, both estrogen and progesterone have a rapid decline (Warren et al., 2018). According to Warren et al., in a woman's body, these "reproductive hormones are involved in emotion

processing, arousal, cognition, motivation, regulation of biological systems implicated by significant depression, and modulation of neurocircuitry in normal and abnormal affective states" (para. 13). Understanding these various changes and how they can affect the body leads medical professionals to a greater knowledge of postpartum depression and its possible treatment options.

The key strength of Warren et al. (2018) includes that it is all-encompassing of postpartum depression; from the prevalence to the side effects, their review contains the essential information to understand what postpartum depression is, how it may occur, and how it can be treated. On the contrary, limitations and weaknesses present include minimal statistical data about the causes of postpartum depression and its possible etiologies, including hormone changes. When looking at etiologies, it would be helpful to have further research completed to evaluate the direct causes of postpartum depression, its symptoms, and how these differences can vary per woman and pregnancy.

SSRI Treatment Effectiveness for Postpartum Depression

Postpartum depression is a multifactorial disorder that can be difficult to gather research on, and with its complexity, it may be challenging to determine the best possible treatment. Based on postpartum depression symptoms, SSRIs are the typical first-line option clinically prescribed for women experiencing these symptoms. For further evaluation, the following articles highlight the option of treating postpartum depression symptoms with SSRI antidepressant therapy. Evaluating this drug class's effectiveness first is shown in a comprehensive overview from Clinical Key (2020). A final total of 59 articles were assessed throughout this review ranging from 1987 to 2017. Clinical Key showed that SSRIs are an appropriate clinical treatment option for postpartum depression. More specifically, for classification of depression ranging from mild to severe, SSRIs can be used as a backup to

psychological strategies for some and is a first-line pharmacotherapy option for others. However, antidepressant medications are found therapeutic after some time, so rapid recovery is not typically present with this option. For the patient to respond to these SSRI medications, “effects are noticeable after two to three weeks, and then this medication option is continued for six months to one year” (Clinical Key, 2020, para. 17). Understanding this, it may be challenging to obtain a quick recovery for these postpartum women.

Within Clinical Key (2020), various limitations and weaknesses are present with the information provided, including minimal statistical data on SSRIs' effectiveness in treating postpartum depression. Further research can and should be conducted to evaluate these medications' effectiveness in postpartum women and if treatment can be done in a timely and safe manner. Their overview's strength includes an in-depth overview of postpartum depression itself; from clinical presentation to prevention, most information about this disorder can be found within Clinical Key. With this information, SSRI antidepressants are a first-line pharmacotherapy option and an appropriate treatment alternative for postpartum women.

The next article, Frieder, Fersh, Hainline, and Deligiannidis (2019), examined various pharmacotherapy options to treat postpartum depression, including SSRIs. The authors’ goal was to evaluate numerous SSRI antidepressants to obtain statistical research and data. This was completed by examining four open-label postpartum clinical studies and eight randomized control trials that have evaluated SSRI use with postpartum depression. Beginning with the first study of Frieder et al., a 12-week trial of 35 women evaluated the medication paroxetine versus a combination of cognitive behavioral therapy and paroxetine. These results showed that the paroxetine monotherapy group and paroxetine plus cognitive behavioral therapy (CBT) group were both effective treatments. However, there was no additional significance from the added

CBT. Further research on paroxetine included an eight-week trial of 70 women comparing paroxetine versus placebo. Results of this Frieder et al. study found that paroxetine showed significantly higher remission rates compared to the placebo (37% compared to 15%), but the paroxetine group did not show significantly higher response rates (43% compared to 31%).

The next evaluation in Frieder et al. (2019) was an 18-week trial of 254 women at four weeks postpartum taking various antidepressants, mainly SSRIs, and compared these medications to supportive counseling. The results showed that these participants receiving antidepressants showed significant symptom resolution. However, at 18 weeks postpartum, there was no significant difference between those receiving antidepressants and those receiving supportive counseling (Frieder et al., 2019).

The final study evaluated was a 12-weel trial of 45 women comparing sertraline and cognitive behavioral therapy. The results of Frieder et al. (2019) found that the specialized CBT program for postpartum depression was superior as monotherapy when compared with sertraline alone. A final understanding from Frieder et al. explains that SSRIs are shown to be effective medication options alone and in conjunction with cognitive behavioral therapy.

With the numerous amounts of data presented throughout Frieder et al. (2019), the weaknesses include a slight conflict of interest with one of the authors receiving a grant from a sponsor, small sample sizes, and minimal statistical values included in the evaluation. The strength of their review consists of the direct comparisons of various SSRI antidepressants, placebo, and cognitive behavioral therapy to achieve the best possible outcome for the patients in the various treatment options.

The next review of Warren et al. (2018), a systematic review for *DynaMed*, is similar to the previous review by Frieder et al. (2019), as there were various studies compiled to gain data and research for the use of SSRIs in postpartum depression. Warren et al. explains postpartum depression in its entirety; this information includes diagnostics, etiologies, treatment options, and much more information about this disease. The first study of their review evaluated if SSRIs can increase remission in women with postpartum depression (Warren et al., 2018). There were six randomized trials of antidepressants in 596 women with postpartum depression evaluated. When comparing SSRIs (sertraline and paroxetine) to placebo, Warren et al. found that SSRIs are associated with increased treatment response (risk ratio 1.43, 95% Cl (1.01-2.03), number needed to treat [NNT] 3-278 with treatment response in 36% of the placebo group). There was also an increased remission (risk ratio of 1.79, [Cl] (1.08-2.98), NNT 2-48, with remission in 26% of the placebo group).

Further research in their review compared fluoxetine and cognitive behavioral therapy (Warren et al., 2019). This study had 87 women with postpartum depression (Edinburgh Postnatal Depression Scale [EPDS] score >10) randomized to one of four treatment groups, including: fluoxetine plus one CBT, fluoxetine plus six CBT, placebo plus one CBT, and placebo plus six CBT. Depression scores were then assessed at one, four, and 12 weeks. The results of this study in Warren et al. (2019) showed that both fluoxetine and cognitive behavioral therapy were associated with improvements in postpartum depression scores, but the effects were not additive. There was no significant difference in mean score reduction between fluoxetine and cognitive behavioral therapy.

The final study of Warren et al. (2018) looked at if antidepressants can improve depression symptoms more than supportive care in women with postpartum depression. This

study was based on a randomized trial without blinding of 254 women with major depression (EPDS score >13) diagnosed in the first six months postpartum. These women were randomized to antidepressant treatment (mostly SSRIs) plus supportive care or placebo plus supportive care for four weeks; these women were further evaluated at 18 weeks as well. At four weeks, the results showed symptoms were improved by 45% with antidepressant therapy and 20% for the placebo ($p<0.001$, NNT 4). At 18 weeks, there was an improvement in 62% of the antidepressant group and 51% of the placebo with significant treatment crossover (Warren et al., 2018). The crossover of treatments at 18 weeks included 59% of women randomized to antidepressants were receiving counseling, and 34% randomized to supportive care were taking antidepressants (Warren et al., 2018).

When further evaluating this review, Warren et al. (2018) contained two limitations and weaknesses. These included significant crossover of treatments in the final study, and one trial was conducted without blinding, which could have altered the final results. Their review's main strength includes strong evidence and statistical data showing the use of SSRIs as an effective treatment option for postpartum depression.

Hormone Replacement Therapy Effectiveness for Postpartum Depression

Knowing that SSRIs are the typical first-line treatment based on the articles previously discussed, there is a need for further treatment alternatives that work as effectively and rapidly. According to the previous reviews explaining the various hormone changes present during the postpartum period, hormone replacement could be an effective therapy option. To evaluate this possible treatment, Dennis, Ross, and Herxheimer (2008) conducted a Cochrane review of the literature to explain the hormonal background of postpartum depression and the possible use of estrogens, progestins, and other compounds as different therapy options. Two evaluations were

completed throughout their review, including the self-reported Edinburgh Postnatal Depression Scale (EPDS) and the clinical-rated measure of the Montgomery-Asberg Depression Rating Scale (MADRS). The first study of Dennis et al. looked at the effect of synthetic progestogen administered within 48 hours of delivery among South African women. Depressive symptoms were evaluated at six weeks and 12 weeks postpartum. At six weeks, women who received a single dose of the synthetic progestogen were significantly more likely to report depressive symptoms using either self-reported (EPDS >11, relative risk (RR) 1.75, 95% confidence interval (CI), 1.12 to 2.72) or clinician-rated measures (MADRS >9, RR 1.74, [CI] (1.08 to 2.81)). This effect was consistent when mean scores were examined (EPDS, weighted mean difference (WMD) 3.10, [CI] (1.02 to 5.18); MADRS, WMD 3.40, [CI] (0.72 to 6.08)) (Dennis et al., 2008). At 12 weeks postpartum, there was no significant difference in depressive symptoms using either self-reported (EPDS>11; RR 1.09, [CI] (0.69 to 1.71)) or clinician-rated measures (MADRS>9, RR 0.97, [CI] (0.60 to 1.58)). These results of the mean scores were found insignificant (EPDS, WMD 0.80, [CI] (-1.28 to 2.88): MADRS, WMD 0.50, [CI] (-2.14 to 3.14)) (Dennis et al., 2008).

Further evaluation in the second study of Dennis et al. (2008) was conducted to determine the effectiveness of a different hormone replacement option. This looked into transdermal estrogen therapy to treat postpartum depression among United Kingdom women experiencing major depression within 12 weeks postpartum. Depressive symptoms were evaluated at four weeks and 12 weeks postpartum, as previously done in their other study. The results showed a significant decrease in mean EPDS scores among women in the estrogen group at four weeks postpartum compared to those who received a placebo (WMD -3.20, 95% CI (-5.97 to -0.43)). However, there was no significant difference in the proportion of women

scoring greater than 13 on the EPDS, indicating worsened postpartum depression (RR 0.68, [CI] (0.45 to 1.01)) (Dennis et al., 2008). At 12 weeks post-treatment, significantly more women who received the placebo had an EPDS score greater than 13, showing persistently worsened postpartum depression (RR 0.30, [CI] (0.14 to 0.66)) (Dennis et al., 2008).

Dennis et al. (2008) article's main strength is found with the various statistical analyses in which provided evidence behind or against the included trials of hormone treatments. This data was collected over two periods to show a different outlook on the included results. There are numerous limitations and weaknesses present within their review, and bias was found in both studies; these include small sample sizes evaluated, the blinding of the first study was compromised due to an adverse effect, and many women in the placebo group missed the scheduled follow up (10/27 estrogen group versus 6/34 in the placebo); all of which may have influenced the final results.

Slightly differing from Dennis et al. (2008), English, Goodwin, Dickinson, and Rey (2019) wrote an article for the *Journal for Managed Care and Formulary Management* explaining the use of the new medication, Brexanolone, as a treatment option for women experiencing postpartum depression symptoms. This article aimed to explain a new treatment option that has shown promising outcomes for postpartum depression, including efficacy, safety, and general information about the drug. This was done by evaluating three double-blind, randomized, placebo-controlled trials labeled 202A, 202B, and 202C. In all three trials of English et al., study participants were randomly assigned to the recommended 60-hour continuous IV infusion of Brexanolone or placebo. Based on three trials, 35 patients were randomized to Brexanolone 60mcg (BRX60), 94 to Brexanolone 90mcg (BRX90), and 105 to placebo. Each study of English et al. demonstrated statistically significant mean reductions in

baseline Hamilton Depression Rating Score (HAM-D) at hour 60 for the BRX90 treatment arm compared to the placebo. Specifically, results showed mean differences between BRX90 and the placebo treatment to be -12.2 (p=0.008), -3.7 (p=0.02) and -2.5 (p=0.02). Study participants had variable responses to placebo treatments, with mean HAM-D reductions of -8.8, -14.0, and -12.1 (English et al., 2019).

BRX60 treatment was also evaluated in English et al. (2019), examining a change in Brexanolone dosage during the continuous IV infusion to 60mcg versus placebo. The results showed the BRX60 treatment arm demonstrated statistically significant reductions in mean HAM-D scores compared to placebo, with a mean difference of -5.5 (p=0.001). The mean difference between the two treatment arms was 11.9 (p=0.01) for 202A, -3.8 (p=0.048) for 202B, and 0.5 for 202C, although this was not a significant finding for 202C (p=0.67) (English et al., 2019).

Understanding the new and only FDA approved treatment for postpartum depression is a significant strength of English et al. (2019). Including information about safety, efficacy, and all other aspects shows that Brexanolone is a quick and effective medication option to decrease depressive symptoms. The main limitation and weakness include examining only three trials with small sample sizes to evaluate Brexanolone treatment. Further research would help gauge this new medication's effectiveness, safety, and patient outcomes to clinically make the best possible treatment choice. As this medication is an endogenous hormone, looking at alternative reproductive hormones besides Brexanolone would be appropriate to determine their effectiveness in postpartum depression treatment.

To evaluate the possible use of transdermal and sublingual estradiol, a literature review by Moses-Kolko et al. (2009) in Clinical Obstetrics and Gynecology included two published

trials evaluating treatment with estradiol. These two trials in Moses-Kolko et al. suggest that postpartum depression treatment response to estradiol (~80%) exceeds standard antidepressants (50.1%± 9.0%). In the first evaluation, 61 non-breastfeeding women presented within 18 months of delivery (Moses-Kolko et al., 2009). Subjects had severe depressive symptoms, with a mean EPDS score of 21.6 ± 3.0, and were then randomized to six months of treatment with placebo or high-dose transdermal 17β-estradiol. When evaluating transdermal estradiol, the results of Moses-Kolko et al. showed that EPDS scores of the estradiol-treated group within one month of treatment were four points lower on average compared to the placebo-treated group. At three months of treatment, 80% of the estradiol group had EPDS scores <14, whereas only 31% of the placebo group had scores <14 (Moses-Kolko et al., 2009).

The second trial in Moses-Kolko et al. (2009) treated 23 postpartum, severely depressed women (mean MADRS= 40) who presented within 12 months following childbirth. They were treated with sublingual 17β-estradiol for eight weeks. The results showed that 21 of 23 subjects had 50% symptom MADRS score reductions within one week of treatment, and by two weeks, 19 of 23 (83%) subjects achieved remission (MADRS score ≤7) (Moses-Kolko et al., 2008).

With some crossover treatment (47% and 37% in the estradiol and placebo arms) and various side effects and risks present for these women not explained in Moses-Kolko et al. (2008), limitations and weaknesses were present in the trials completed. However, the strengths include elaborated differences of the hormone replacement therapies, possible side effects for the mother, and the efficacy and safety of these medication options. Further research would be essential to understand the effectiveness and potential use of hormone replacement therapy to decrease postpartum depression symptoms.

As previously discussed, Schiller et al. (2014) examined fluctuations in reproductive hormones levels during pregnancy and the postpartum period that may trigger postpartum depression in susceptible women. Various studies were conducted to evaluate hormone replacement therapy being used in the treatment of postpartum depression. The first trial included in Schiller et al. was a pilot study of 11 women with a history of postpartum depression who were prophylactically administered oral Premarin immediately following delivery to prevent estrogen withdrawal. The final results showed that 10 of the 11 women remained well during the postpartum period and the first year following delivery (Schiller et al., 2014).

The next study was a double-blind, placebo-controlled study of 61 women with postpartum depression that began within three months of delivery (Schiller et al., 2014). Of the 61 women, Schiller et al. (2014) showed that women treated with transdermal estradiol (n=34) improved significantly more than women who received a placebo (n=27).

The final study of Schiller et al. (2014) examined the effects of sublingual estradiol treatment for eight weeks on a group of 23 women with severe postpartum depression, many that had attempted treatment with antidepressants or psychotherapy without further improvement. The results showed that after the first week, depressive symptoms significantly decreased. By the end of eight weeks, all patients had achieved depressive symptoms scores consistent with clinical recovery (Schiller et al., 2014).

The limitations and weaknesses present in Schiller et al. (2014) include minimal statistical data on the different trials, and small sample sizes were evaluated to gather results. One of the study's selection criteria was to assess women who were more vulnerable to perinatal changes in reproductive hormones, which may have been challenging to differentiate and possibly skewed the results. The strengths include evaluating different groups of women with

various estradiol treatments, including oral and transdermal options. Essentially, the results of Schiller et al. showed significant findings of these therapies; the use of hormone replacement therapy following failed use of psychotherapy and antidepressants shows hormone replacement as a useful option when others are not as effective.

To obtain direct information and opinions about hormone therapy's effectiveness, Studd (2014) completed an email survey of patients for *Post Reproductive Health*. This was done by data collection from a bulk email sent out to all the patients seen at the London PMS and Menopause Centre over the past five years inviting them to return a questionnaire if depression had been a significant symptom shown. This survey had 238 out of 1,305 with depression as a presenting symptom; these women were treated with transdermal estrogen. This survey began by asking, “has hormone therapy cured your depression?”. From this, 33.5% explained they were cured, 55.7% stated hormone therapy helped significantly, 7.1% stated hormone therapy helped a little, and 3.7% stated there was no improvement (Studd, 2014, p. 133). The next question asked, “has hormone therapy been life-changing for you?”. For this question, 225 women answered yes, while 13 women answered no. None of the patients included said that the treatment was life-changing for the worse (Studd, 2014, p. 133). Of the 163 patients who had received antidepressants, 147 (90%) women responded better to hormone replacement therapy than to antidepressants, one woman was worse, and 15 were about the same for both (Studd, 2014, p. 133).

With this evaluation being completed by an email survey compared to controlled trials is the main limitation and weakness in Studd (2014). This can put the results at risk of variability regarding the patient's experience or how effective the medications were. However, the strength includes provided percentages and numbers of the women in the study, those affected, possible

side effects, and the outcomes following survey results that can influence how effective hormone replacement therapy was on a personal level with the patients.

For further evaluation of estrogen use in treating depression, Studd and Panay (2009) completed a literature review for *Best Practice & Research Clinical Obstetrics and Gynecology*. The results began by showing two different trials evaluated; the first study of Studd and Panay was a double-blind, placebo-controlled trial of 60 women with major depression, which began within three months of childbirth and persisted up to 18 months. Participants were given either placebo patches or transdermal estradiol patches daily for three months without any added progestogen. After three months, a progesterone adjunct was added. The women were assessed monthly by EPDS evaluation and a clinical psychiatric interview. During the first month of therapy, the results of Studd and Panay showed that the women who received estrogen improved rapidly and to a greater extent than the control group. The percentage with EPDS scores >14 (diagnostic of postpartum depression) was reduced by 50% at one month and 90% at five months; this was much better than the placebo response (Studd & Panay, 2009).

The second study included was an uncontrolled study using sublingual estradiol in 23 women with major postpartum depression (Studd and Panay, 2009). The results showed improvement in 12 of the 23 patients at one week and 19 of the 23 patients at two weeks. The mean MADRS was 40.7 before treatment, 11 at one week, and two at eight weeks after treatment. At the end of the second week of treatment, the MADRS scores showed clinical recovery in 19 of the 23 patients (Studd and Panay, 2009)

The strength present with Studd and Panay (2009) includes two studies that showed improvement with estradiol treatment in postpartum depression symptoms in specific periods; this allows another treatment option for women with postpartum depression symptoms. The

limitations and weaknesses include interpreting an uncontrolled study conducted in Studd and Panay's second review. There were also small sample sizes evaluated with both studies that do not provide high-quality results but do provide an idea for further research.

As previously stated above, Warren et al. (2018) completed a systematic review for *DynaMed* to discuss postpartum depression in its entirety. The first study evaluated whether Brexanolone might reduce depression in women with moderate-to-severe postpartum depression (Warren et al., 2018). This was based on two randomized trials that included 138 adult women less than 45 years old with depression less than six months postpartum and were randomized to one of three IV infusions over 60 hours. The results of Warren et al. showed a mean reduction in HAM-D scores at 60 hours of 17.7 points reduced in the BRX90 (95% CI (-0.5 to -6.9)). For BRX60, there was a 19.5 point reduction ([CI] (-2.2 to -8.8)). Both of these treatments were found to have significant reductions. The placebo showed a decrease of 14 points (Warren et al., 2018). The rates of remission (HAM-D score <7 points) include 32% with BRX90, 51% with BRX60 (p=0.0011 versus placebo, NNT 3), and 16% with the placebo. There were no significant changes in remission rates at 30 days (Warren et al., 2018).

The next study in Warren et al. (2018) evaluated 108 women with depression greater than six months postpartum and who were randomized to BRX90 infusion versus placebo for 60 hours. The results showed a mean reduction in HAM-D scores of 14.6 points versus 12.1 points at 60 hours (95% CI (-0.5 to -4.5)); this was a significant finding. Remission at 60 hours was found in 61% for BRX90 versus 38% for placebo (p=0.0033, NNT 5) (Warren et al., 2018). However, at 30 days, the mean reduction in HAM-D scores was 14.7 points versus 15.2 points, which was not a significant finding (Warren et al., 2018).

The final study evaluated if estrogen therapy may reduce major depression symptoms after 12 weeks in women with severe postpartum depression (Warren et al., 2018). This review was a randomized control trial of 61 women with major postpartum depression being treated with transdermal estrogen. Warren et al. (2018) results showed transdermal estrogen therapy use was associated with a significant reduction in mean EPDS scores, but there was no reduction in women with EPDS scores >13 (indicating major depression) at four weeks. However, there was a significant reduction in the proportion of women with EPDS scores >13 at 12 weeks.

Warren et al. (2018) review's limitations and weaknesses include small sample sizes evaluated and minimal statistical data to provide evidence of these results. The strengths include various studies on hormone replacement therapy options, including transdermal estrogen and the newer option, Brexanolone, to show that hormone replacement can be a useful option for women with postpartum depression.

Safety in SSRI Antidepressant Treatment for Postpartum Depression

After understanding the possible causes of postpartum depression described above, the next step would be to evaluate the various treatment options to control or change the possible etiologies. When deciding the correct therapy for postpartum women, medical professionals need to understand the possible contraindications and adverse effects of these medications. With the evaluation of safety in SSRIs, Heimberg and Ehrlich (2018) completed a review for *DynaMed* to explain the adverse effects that can occur when taking antidepressants in the general population. Their study examined two articles ranging from 2010 to 2015. Similar to all other antidepressants, there is a black box warning for increased risk of suicidality. When looking at possible adverse effects explained in Heimberg and Ehrlich of two similar classes of antidepressants, SSRIs and SNRIs, these effects include neurological changes of dementia or

cognitive impairment, hepatotoxicity, and a possibility of developing a dangerous arrhythmia. Looking at SSRIs specifically, further symptoms may include various gastrointestinal effects, mood changes, sleep disturbances, sexual side effects, discontinuation syndrome, and serotonin syndrome, which can be a life-threatening disorder (Heimberg & Ehrlich, 2018).

There is minimal statistical data presented about SSRIs' adverse effects, which is the main limitation and weakness of Heimberg and Ehrlich (2018). The above review does not directly explain the risks of women taking these medications during pregnancy and the postpartum period. However, the strength and purpose is to explain all the various adverse effects and risks of taking an SSRI antidepressant for the general population. Knowing and understanding the information Heimberg and Ehrlich provide is essential.

To further elaborate on the previous article by Heimberg and Ehrlich (2018), Kramer, Jolanda van Zuuren, and Ehrlich (2018) completed a review for *DynaMed* to explain the adverse effects of antidepressant therapy during pregnancy and the postpartum period associated with lactation. The evaluation was done by examining two articles ranging from 2008 to 2014. The data of antidepressant use during pregnancy and after is limited to observational studies, but it has been noted that discontinuation of these medications can cause a relapse of depressive symptoms. When looking at safety while breastfeeding, Kramer et al. examined 57 observational studies evaluating breastmilk and the use of SSRIs. Based on the infant's safety, “it was determined infant plasma level >10% of the mother's plasma level to be of potential clinical significance” (Kramer et al., 2018, para 23). With the closer evaluation of specific medications, most SSRIs typically produce undetectable infant levels. On the contrary, fluoxetine produces the highest infant levels. When examining the lactation risk assessment of medications, antidepressants categorized as low lactation risk include sertraline, paroxetine, and nortriptyline.

Moderately safe lactation risk include fluoxetine, citalopram, venlafaxine, and escitalopram (Kramer et al., 2018).

Possible limitations and weaknesses present with the review by Kramer et al. (2018) include only having observational studies for the associated risks of taking SSRIs due to the risk to the population being examined. There was also minimal information regarding the effects and harm during the postpartum period, outside of lactation risk. The strength present in their review includes stating various risks and effects present when pregnant and when in the postpartum period while breastfeeding. With this understanding, one can make a clinical decision during pregnancy and after to keep both the mother and child safe.

Molyneaux, Telesia, Henshaw, Boath, Bradley, and Howard (2018) completed a systematic review for the *Cochrane Database of Systematic Reviews* to analyze antidepressant studies on postpartum depression symptoms and possible adverse effects that may have occurred. Molyneaux et al. evaluated two small trials, one of which was excluded due to the medication class being a tricyclic antidepressant rather than an SSRI. In a small study of 25 women, the antidepressant sertraline was given prophylactically and evaluated for its effectiveness and safety. The results of Molyneaux et al. showed that one of the 14 women developed postpartum depression compared with four of the eight taking placebo. One woman taking sertraline experienced a hypomanic episode; also, dizziness and drowsiness were more common among women taking sertraline compared to women taking the placebo. Molyneaux et al. further evaluated children's safety and found possible exposure to these medications across the placenta or through breastfeeding. However, exposure to antidepressants in breastfed infants is "five to ten times lower than exposure in utero" (Molyneaux et al., 2018, para. 4). More broadly, there is limited data on the safety of antidepressants during breastfeeding, particularly for longer-term

outcomes. However, the findings to date suggest that the benefits of taking antidepressants may outweigh the risks in breastfeeding women who need treatment for their depression.

The small sample sizes and inconsistent findings throughout Molyneaux et al. (2018) are the main limitations and weaknesses noted; the quality of the evidence presented was low. The main strength would include showing specific side effects that occurred while taking these medications, resulting in discontinuation for the mother and explaining the baby's possible risks. Both the strengths and weaknesses allow for strong clinical evidence for and against SSRI antidepressants' safety in pregnancy and postpartum women.

Safety in Hormone Replacement Therapy Treatment for Postpartum Depression

With hormone replacement therapy not being the standard treatment option, understanding the risks associated with these medications is an important step in the clinical treatment of postpartum depression. Beginning the evaluation of safety in the use of hormone replacement therapy, English et al. (2019) completed a study for the *Journal for Managed Care and Formulary Management* explaining the new medication, Brexanolone, as a treatment option for women experiencing postpartum depression symptoms. When examining this medication's safety, English et al. evaluated a population that includes 140 patients who received Brexanolone and 107 patients who received a placebo. The incidence of adverse effects was quite similar between the two treatment options (Brexanolone 50.0%; placebo 50.5%). Adverse effects found in English et al. found that two patients (1.4%) receiving Brexanolone experienced serious adverse events such as suicidal ideation, syncope, and loss of consciousness. Sedation-related effects occurred more frequently in the Brexanolone group (27.1%) compared to those who received the placebo (14.0%). These various effects included sedation (15%), dizziness (13.6%), fatigue (3.6%), loss of consciousness (4.3%), and amnesia (0.7%) (English et al., 2018, p. 734).

Brexanolone does have a black box warning for excessive sedation and sudden loss of consciousness. Similar to other antidepressants, Brexanolone may also have a black box warning for increased risk of suicidal thoughts and behaviors, even though this medication has not been specifically evaluated for this risk (English et al., 2018, p. 734).

There is minimal statistical evidence behind the risks associated with this new medication, Brexanolone, which is the main limitation and weakness with English et al. (2018) in evaluating Brexanolone safety. Furthermore, there is only one trial evaluated and included in this review, so continued research should be conducted on this medication's safety in the short and long term to assess possible effects that can occur. The main strength of English et al. is a full review of Brexanolone, including safety, efficacy, and much more helpful information about this new drug. Though not all the long-term effects are noted due to minimal studies and Brexanolone being a newer medication, the short-term effects and possible black box warnings are laid out. These effects can be evaluated with each patient to determine the best possible treatment option.

Similar to the article by English et al. (2019) in explaining Brexanolone, Moses-Kolko et al. (2009) completed a literature review for *Clinical Obstetrics and Gynecology* to discuss the use of transdermal estradiol and the possible effects that may occur for the treatment of postpartum depression. The methods include evaluating a total of 90 articles ranging from 1972 to 2009 from various databases. The most common side effects and risks present with estrogen use include hypertension, various gastrointestinal effects, migraines, edema, breast tenderness, hair loss, and changes in vaginal secretions, including spotting or bleeding (Moses-Kolko et al., 2009). Like other types of hormones, there is an increased risk of developing cancer, especially in endometrial and breast tissue. Moses-Kolko et al. evaluated various medical risk factors that

require more careful monitoring, including smoking, thromboembolic events, and various family history disorders. The reason for closer monitoring and possible restrictions would be the increased risk of clotting events that can occur when taking hormone replacement. During the postpartum period and breastfeeding, estrogens have also been found to affect breast milk production. If taking these medications before well-established lactation (around six to eight weeks postpartum), breast milk production can be diminished, which is critical to discuss with each patient as well (Moses-Kolko et al., 2009).

With some crossover treatment in the included studies (47% and 37% in the estradiol and placebo arms) and possible side effects or risks present in some women that were not included in the review, limitations and weaknesses were present in Moses-Kolko et al. (2009). However, their review's strengths show elaborated differences of hormone replacement therapies, including oral and transdermal estradiol, possible effects for the mother ranging from minor bloating to as severe as cancer, and the efficacy and safety of this medication option.

Comparison of SSRI Antidepressants and Hormone Replacement Therapy: Preference of Treatment Options for Postpartum Depression

Thus far, throughout this review, the evaluation was conducted separately of the two treatment options, SSRI antidepressants and hormone replacement therapy. To fully understand which of these therapies would be most effective and safe in treating postpartum depression, it would be best to have direct comparative research. When looking at the comparisons of the two treatment options, Cohen, Wang, Nonacs, Viguera, Lemon, and Freeman (2010) completed a literature review for *Psychiatric Clinics of North America*. This review was completed by evaluating 139 articles ranging from 1941 to 2009. Their review found that various antidepressants have shown great efficacy in treating postpartum depression and have been well

tolerated (Cohen et al., 2010). Knowing that there is a change in hormones present during the postpartum period, hormone replacement therapy can be of benefit. According to Cohen et al., two studies have described the benefit of estrogen therapy, either alone or in combination with antidepressant treatment in women with postpartum depression. Although these studies suggest a role for estrogen in treating women with postpartum depression, these treatments are relatively understudied. There is always a risk associated with estrogen therapy, including changes in breastmilk production and the risk of thromboembolic events. Cohen et al. found that antidepressants are safe, well-tolerated, and highly effective; these medications should remain the first choice for women with moderate to severe postpartum depression.

The main limitation and weakness present in Cohen et al. (2010) include minimal statistical data within the studies completed. Strengths present in their review include various research conducted on the typical usage of SSRIs as well as the newer, understudied treatment of hormone replacement therapy. With the evidence provided, an SSRI is an acceptable and safer first-line therapy option compared to hormone replacement therapy in decreasing depressive symptoms for postpartum women.

Showing similarities with Cohen et al. (2010) in explaining and comparing the two treatment options, Cooper et al. (2019) completed a meta-analysis for *Central Nervous System Drugs* to compare and contrast the medication therapy options of Brexanolone and SSRIs for treating postpartum depression. This review was conducted by 26 studies that were identified in a systematic literature review evaluating therapy in postpartum depression. For Cooper et al., two evaluation measures, HAM-D and EPDS outcomes, were used to evaluate the difference between Brexanolone and SSRIs. Further evaluation and analysis were completed using matching-adjusted indirect comparisons (MAICs), adjusted Bucher indirect treatment comparison (ITCs),

and network meta-analysis (NMA) between Brexanolone, placebo, and SSRI treatments at three different time points: day three, week four, and final observation (time varies).

Results of Cooper et al. (2019) show that in both analyses, for day three, the change from baseline in the HAM-D and EPDS for BRX90 was more significant than that for SSRIs (HAM-D: 12.79, [95% CI] (8.04–17.53) and 13.47, [CI] (9.84–17.10); EPDS: 7.98, [CI] (5.32–10.64) and 7.97, [CI] (5.39–10.54)). These differences were found to be significant (Cooper et al., 2019). At week four, SSRIs were found to have significantly smaller reductions in EPDS scores compared with BRX90 (Bucher ITC: 6.35, [CI] (3.13–9.57); NMA: 6.86, [CI] (3.75–9.97)). In the evaluation of the HAM-D scores, the Bucher ITC showed that SSRIs still had smaller reductions compared with BRX90, and this was considered nonsignificant (5.87, [CI] (-1.62 to 13.37)). The NMA for the HAM-D scores at the same time gave a significantly greater difference for BRX90 compared with SSRIs (8.41, [CI] (2.94–13.88)) (Cooper et al., 2019). The final time point evaluated (EPDS: weeks 4–18; HAM-D: week four to six months) should be when SSRIs have reached maximum effect. Both analyses showed that SSRIs had smaller reductions in the EPDS and HAM-D compared with BRX90 (HAM-D: 0.97, [CI] (-6.35 to 8.30) [Bucher ITC] and 2.02, [CI] (-3.18 to 7.22) [NMA]; EPDS: 4.05, [CI] (0.79–7.31) [Bucher ITC] and 3.76, [CI] (0.62–6.90) [NMA]). However, the differences between BRX90 and SSRIs were the smallest and were no longer significant at this time point compared with the previous time points evaluated (Cooper et al., 2019). Essentially, the final results and understanding from Cooper et al. suggest a greater efficacy with BRX90 compared to SSRIs for both patient-reported (EPDS) and clinician-reported (HAM-D) measures at all time points included.

There are strong statistical analyses presented in the comparison of BRX90 and SSRIs in decreasing depressive symptoms; these provide solid evidence for the use of Brexanolone over

SSRIs for treating postpartum depression. Cooper et al. (2019) review's limitations and weaknesses include an unadjusted analysis that showed occasional non-significance for the studies evaluated. Another limitation is seen with using EPDS scores as they are secondary outcomes and are self-rated by the patient, thus changing the results' reliability.

To further understand Brexanolone as previously discussed, English et al. (2019) wrote an article for the *Journal for Managed Care and Formulary Management* explaining the use of Brexanolone as a treatment option for women experiencing postpartum depression and included a researched comparison to SSRI antidepressants. This review was done by evaluating 13 articles ranging from 2008 to 2019. For the treatment of postpartum depression, SSRIs have been the standard pharmacotherapy option. Though not indicated for this use, SSRIs are safe and effective in decreasing depressive symptoms and are a less expensive option for postpartum depression. The onset of action in SSRIs is much slower compared to other treatments, including Brexanolone, a new, FDA approved medication for postpartum depression (English et al., 2019). Brexanolone provides clinically significant short-term symptom improvement with a rapid onset of actions, which is necessary to treat postpartum depression.

In English et al. (2019), there is minimal statistical data about the comparison of Brexanolone versus SSRIs in which is the main limitation and weakness in their review. As previously noted, the main strength includes a comprehensive analysis of this new medication treatment and a comparison to the past standard option of SSRI antidepressants. The final understanding is that SSRIs are not as adequate in efficacy compared to Brexanolone.

In the evaluation of various SSRIs and other hormonal supplement therapies, Kim, Epperson, Weiss, and Wisner (2014) completed a review for *Expert Opinion on Pharmacotherapy* to explain these possible treatment options for postpartum depression. There

are currently eight open-label studies and eight randomized control trials looking at the efficacy of antidepressants and hormonal supplements in treating postpartum depression. The results of Kim et al. show that sertraline is an efficacious option, finding between 50% to 67% of women respond to treatment at around six to eight weeks. According to general depression guidelines, women should be continued on antidepressants for at least nine to 12 months once symptoms have subsided. Per this review, hormonal supplements are used much less often (Kim et al., 2014). There were no recent estradiol treatment studies and no new prevention studies conducted. The risk of short-term estrogen therapy is generally low; however, there are contraindications, including tobacco use, significant cardiovascular disease, a personal or family history of breast cancer, or a history of clotting disorders (Kim et al., 2014). Therefore, based on the current evidence, there is no recommendation for using any form of estradiol in the treatment of postpartum depression.

A significant limitation and weakness of Kim et al. (2014) would be the minimal information regarding hormone replacement therapy timelines and efficacy compared to SSRIs, and also a lack of information about other possible hormone therapies. The main strength includes various studies about the use of SSRIs in the treatment of postpartum depression and briefly explaining the use of hormone replacement therapy. This review evaluates the effectiveness, efficacy, and safety of these different therapy options. There is always a need for further research to help clinically determine the best possible treatment option for postpartum depression symptoms.

To further look at these options, Ng, Hirata, Yeung, Haller, and Finley (2010) looked at the comparison of various antidepressants and different hormone replacement therapies by completing a systematic review for *Pharmacotherapy* to explain possible treatment options for

postpartum depression, including efficacy and adverse effects following treatment. For the evaluation of antidepressants, 14 articles examined the effectiveness, nine were included in the analysis, and seven looked at SSRIs' effectiveness. For SSRIs, response rates ranged from 43-87%, and remission rates varied from 27-48%. There were no significant differences reported between treatments, and combinations did not provide an additive effect (Ng et al., 2010).

When examining a hormone treatment alternative, Ng et al. (2010) had 11 articles that examined the effects of sex hormones for postpartum depression, and only two were included in this review. This first study included a randomized, placebo-controlled trial using two transdermal estradiol patches administered twice a week compared with placebo patches for six months. After three months of this therapy, a progestin treatment was added to the regimen (Ng et al., 2010). The results of Ng et al. showed a significant therapeutic effect with the hormones as early as one month, and this was maintained for the study's entire duration. Adverse effects did not differ between study groups, but one subject in the active treatment group committed suicide shortly after starting progestin.

The other investigation of hormones included was a short, eight week, open-label trial of 23 subjects receiving sublingual estrogen (Ng et al., 2010). After one week of treatment, 21 of 23 subjects exhibited a therapeutic response when looking at the second study, and nearly 40% had achieved remission after the study. The final understanding of Ng et al. (2010) showed that estrogen supplementation through transdermal patches or sublingual preparations produced rapid and significant decreases in depression severity, with occasional adverse reactions. For SSRIs, the response and remission rates were quite variable and not shown to be as effective.

The major strength of Ng et al. (2010) includes a numerous amount of studies conducted, evaluated, and compared on the use of SSRI antidepressants and hormone replacement therapy.

When looking at the limitations and weaknesses present, small sample sizes were evaluated, and a possible selection bias occurred during this study. This bias excludes women experiencing depression symptoms during pregnancy, which is commonly found among postpartum women and could hinder the final results.

Bridge Therapy Option for the Treatment of Postpartum Depression

It has been previously stated that SSRIs take time to become effective and are associated with a slow rate of improvement (6-12 weeks) for people that take these medications (Cooper et al., 2019). Research stated above that hormone replacement can be a more rapid alternative. With postpartum depression being complex and a dangerous disorder, bridge therapy may be an option for these women. Though this is a new concept and there is limited research, Joffe and Cohen (1998) completed a review for *Biological Psychiatry* to discuss a relationship between estrogen and serotonin on mood treatments, including postpartum depression. This review was done by examining two studies that had a total of 41 patients; the two studies evaluated the effect of adding estrogen therapy to imipramine, a tricyclic antidepressant. The first study evaluated imipramine with estrogen, imipramine monotherapy, and a placebo group (Joffe & Cohen, 1998). The results showed that both imipramine-treated groups showed improvement over placebo, but there was no difference between imipramine, with and without estrogen.

The second study of Joffe and Cohen (1998) evaluated the addition of estrogen after two weeks of imipramine treatment to 11 women previously unresponsive to antidepressants. Overall, no significant improvement in Hamilton Depression Rating Scale (HDRS) scores were seen four weeks after the addition of estrogen, with only one subject showing significant improvement (Joffe & Cohen, 1998).

There are numerous limitations and weaknesses present in Joffe and Cohen (1998), including small sample sizes, lack of randomly assigned control groups, evaluation of a tricyclic antidepressant rather than an SSRI, and different hormone replacement administration compared to clinical application. There is minimal research regarding bridge therapy of hormones and SSRIs in the treatment of postpartum depression. However, the strengths of their review include a description of the effects estrogen has on the central nervous system and how this relates to serotonin as well. Few studies have been conducted on the coadministration of hormones and antidepressants for depression treatment, which could be the start of further research.

Like the previous article examining hormone and antidepressant co-therapy, Newport, Hostetter, Arnold, and Stowe (2002) completed a literature review for *The Journal of Clinical Psychiatry* to explain other treatment options for postpartum women. This review was done by an evaluation of 135 total articles ranging from 1943 to 2001. Hormone replacement therapy, such as sublingual and transdermal estrogen, has been tested in postpartum depression treatment and showed success, but with only modest symptom relief. Explained in Newport et al., estrogen was co-administered with an antidepressant. Findings of their review concluded that this treatment option should not be a first-line recommendation due to the limited benefit and lack of safety data regarding the postpartum use of estrogen supplementation.

Newport et al. (2002) review's main limitation and weakness include minimal information regarding co-treatment bridge therapy of hormone replacement therapy and SSRI antidepressants as there was no direct evidence behind this option or statistical data to support this therapy. The strength includes one possible study that was completed looking at an antidepressant and estrogen co-therapy option, even though this treatment was not further elaborated throughout their review. Medical professionals should remember that SSRIs may take

time to become effective. Depending on the patient risks, hormone replacement therapy may be a possible starting option during this time to provide more significant relief.

Discussion

From the initial understanding that postpartum depression is a multifactorial disorder that affects many women following childbirth, there is a need to understand why this disease occurs and how postpartum depression can be treated safely. Though every woman and pregnancy are different, the treatment options can vary to treat these depressive symptoms appropriately. Understanding the various hormone changes following childbirth being a possible etiology to postpartum depression is an important concept to recognize. Warren et al. (2018) explained that there is an increase in hormones during the third trimester and a drastic decline following childbirth into the postpartum period. Schiller et al. (2014) completed a neuroendocrine, reproductive hormone model of postpartum depression that details specifically the effects that occur throughout the body and how these depressive symptoms arise. To try lead to the most effective treatment option, medical professionals are hopeful to gain insight into hormone changes being a possible etiology to developing postpartum depression.

There are various treatment options for major depressive disorder itself, and these options are similar in treating postpartum depression. Initial treatment begins with psychotherapy or counseling for some women and antidepressant treatment for others (Clinical Key, 2020). The most common, first-line pharmacotherapy option for postpartum depression are SSRI antidepressants. The effectiveness of this therapy is highlighted through Frieder et al. (2019) by examining several antidepressants compared to placebo and psychotherapy options. Similarly, Warren et al. (2018) evaluated numerous SSRI studies compared to placebo and cognitive behavioral therapy, thus increasing the evidence behind the effectiveness of SSRIs in treating

postpartum depression. Given this understanding, SSRIs are an appropriate option for treating these depressive symptoms, although their effects can take time (Clinical Key, 2020).

To maximize treatment effectiveness and recovery, a quicker therapy option is necessary for treating postpartum depression. This can be achieved with hormone replacement therapy. As explained by English et al. (2019) and Warren et al. (2018), Brexanolone is a new and FDA approved medication for postpartum depression treatment that has been found to significantly reduce depressive symptoms. When evaluating other hormone replacement therapies, numerous studies included showed that estrogen treatment significantly reduced postpartum depression symptoms based on statistical analyses (Moses-Kolko et al., 2009; Schiller et al., 2014; Dennis et al., 2008; Studd & Panay 2009). However, Dennis et al. (2008) found that progesterone therapy showed an increase in depressive symptoms following administration, providing weak evidence behind this alternative. In the studies included, to have the appropriate treatment in place, it is essential to understand the effectiveness of treatments and possible contraindications, risks, and adverse effects.

To adequately treat postpartum depression with the available options, these medications' safety needs to be understood. The treatment options above and the articles included explain that various adverse effects can occur with both hormone replacement therapy and SSRI antidepressants. These range from minor symptoms of nausea and vomiting to significant adverse reactions such as loss of consciousness (Heimberg & Ehrlich, 2018; English et al., 2019). With SSRIs, there can be some passage of these medications to infants from breastfeeding that can cause adverse reactions to both the infant and mother (Kramer et al., 2018). When examining contraindications and increased risks with SSRIs, there is a known black box warning for all antidepressant medications for an increased risk of suicidality (Heimberg & Ehrlich,

2018). There are further contraindications to hormone replacement therapy for increased risk of clotting disorders, thromboembolic events, and trouble with breastfeeding as it can decrease milk production (Moses-Kolko et al., 2009). It is essential to understand these various adverse effects and discuss the woman's lifestyle, history, and preference to provide the most effective and safe treatment.

Conflicting results showed that both treatment options are effective therapies at times and ineffective in others. Each has its own benefit, consequence, and possible risk associated. Looking at a direct comparison of these two treatments, Cohen et al. (2010) and Kim et al. (2014) explained that SSRI antidepressants are the superior therapy treating postpartum depression. Antidepressant medications are safe and effective compared to estrogen and other hormone replacement therapies since these medications have increased contraindications and risks. On the contrary, Cooper et al. (2019) includes direct statistical analyses showing that Brexanolone hormone replacement is quicker, safer, and more effective over SSRIs. The remaining articles included agree that both of these medication options are effective therapies for postpartum depression. There are variable results, adverse effects, and opinions on which option is best for decreasing depressive symptoms.

With such variability present, further research can be conducted on a possible combination or bridge therapy, including both treatment options. When examining the co-treatment of both therapies, Joffe and Cohen (1998) found no additional improvement of symptoms with the addition of estrogen to antidepressant therapy. Further research found limited safety and benefit with co-treatment (Newport et al., 2002). With SSRIs taking time to become therapeutic, initial treatment with hormone replacement therapy and coadministration of antidepressants could be an effective option pending further research.

Conclusion

Postpartum depression is a disease that is quite common, often underdiagnosed, and hard to evaluate the direct etiology. It is known that hormones fluctuate during and after pregnancy, but whether these changes are the leading cause of such depressive symptoms is unknown. This population of women is at a higher risk of complications when conducting research and considering their child's health when determining effective medications. SSRIs are medications that take time to become clinically therapeutic in many people and there are various risks associated with these. However, risks are even more prevalent with hormone replacement therapy. With this understanding, both treatment options would be reasonable and appropriate to treat certain women for postpartum depression, pending contraindications, risks, and concerns for their child. Further research is necessary to confirm a plan to treat postpartum women and to evaluate the possibility of a bridge therapy regimen.

Applicability to Clinical Practice

With the information provided in the literature review, medical providers can prescribe the most effective, efficient, and safe medication option to decrease postpartum depression symptoms based on medical research evidence and statistical analyses. This research would allow physician assistants and other medical professionals to understand postpartum depression, the possible etiology following childbirth, and adequate treatment options. For now, Brexanolone is the only FDA approved medication indicated for postpartum depression, but psychotherapy and antidepressants are often used clinically. Until further research is conducted, these options should be utilized, understood, and explained to the patients to make the best possible clinical decision for both mother and child.

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