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Review Article

Pharmacotherapy of postpartum depression: An update

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ABSTRACT

Postpartum depression (PPD) is a mood disorder with depressive symptoms during perinatal period. It negatively impacts women, child, family, and society and hence must be promptly diagnosed and adequately treated. Etiopathogenesis of postpartum depression is not known but is hypothesized to be a complex interplay among various maternal, biological, psychosocial, and genetic factors. Maternal factors encompass high or tender age at pregnancy, while the biological factors include fluctuation of hormones like estrogen and progesterone during perinatal period and dysfunction of HPA-axis. Recognized psychosocial factors are history of depression, symptoms of depression or anxiety during pregnancy, stressful life events and postpartum blue symptoms, single status, lower educational level, multiple offsprings, poor marital relationship and low socioeconomic status. Genetic variations in hemicentin-1 (HMCN1) gene have been found to have increased susceptibility to PPD. Women with PPD presents with fatigue, sadness anhedonia, impaired concentration, irritability, guilt, psychomotor agitation, sleep disturbances and changes in appetite and weight. Management of PPD is a multidisciplinary approach and encompasses complementary health practices, psychological interventions, pharmacotherapy, and somatic therapy. Complementary health practices are educating women about self-care and about growing treatment-seeking behaviour. Cognitive behavioral therapy (CBT) and Interpersonal psychotherapy (IPT) are specifically adapted and well-studied psychological interventions for PPD. Many drugs like antidepressants, estrogen and progesterone have been used for long time for treatment of PPD but their use has not been approved by any regulatory authorities. The First drug approved by U.S. Food and Drug Administration (US FDA) for PPD was brexanolone which is an injectable. Zuranolone is recent addition to this approved category and is an oral one. Both brexanolone and zuranolone are indicated for severe PPD where psychological interventions and antidepressants are usually ineffective.

1. Introduction

Women may experience depressive symptoms during postpartum period. The symptoms range from mild postpartum blue to major mood disorders such as postpartum depression and postpartum psychosis. Postpartum depression (PPD) must be differentiated from postpartum blue and postpartum psychosis.[1] Postpartum blue is relatively common with trivial mood symptoms like feeling stressful, anxious, lonely, or weepy during initial two weeks or so following baby's birth. It is usually self-limiting and does not require any specific treatment.[2] Postpartum psychosis on the other hand, is severe mood disturbance with psychotic symptoms which most often require specific treatment.[3]

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Postpartum depression (PPD) is a non-psychotic depressive disorder that usually begin in perinatal period and extends into post-natal period for a varied time-period.[4] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) defines postpartum depression as a major depressive episode (MDE) with peripartum onset when onset occurs within pregnancy or up to 4 weeks postpartum.[5] The World Health Organization (WHO) defines the postpartum period as up to 1 year after delivery.[6] PPD negatively impact the women, child, family, and society.[7] Prevalence of PPD varies considerably across and within the countries ranging from 4 to 25%.[8–10] The variability is substantially influenced by marital status, education status, social and financial supports, spouse care, violence from intimate partner, gestational age, breast feeding, life stress, smoking and alcohol intake, and living conditions.[11] Post-partum depression is not promptly diagnosed.[12] If diagnosed, there is lack strong evidences regarding treatment modality.[13] RCTs assessing therapeutic efficacy of various drugs in PPD have conflicting results, therefore clinicians find difficulty to decide drug therapy.[14,15] Until recently, there was no approved drug for PPD therefore drug therapy was mainly based on drugs used for depression. It was March 2019 in which for the first time a drug for PPD was approved by U.S. Food and Drug Administration. This article presents an updated review of drugs used for PPD aiming psychiatrists, obstetricians, pharmacologists, general practitioners, and psychologist/psychotherapist as target audiences.

2. Risk Factors

Maternal factors: High (≥ 35years) or tender maternal age (adolescence), shorter gestational age, and gestational diabetes have been found to be associated with increased risk of PPD.[16]

Psychosocial factors: Risk has also been found to be high in women with low self-esteem, history of depression, symptoms of depression or anxiety during pregnancy, stressful life events and postpartum blue symptoms.[17]

African-American race, single status, lower educational level, low occupational prestige, multiple offsprings, poor marital relationship, intimate partner violence, poor social support, low socioeconomic status, and unplanned/unwanted pregnancy are the other recognized risk factors.[18,19]

3. Etiopathogenesis

The etiopathogenesis of PPD is not well understood. It assumed to be a complex interplay among biological, maternal, psychosocial, genetic factors. We have already discussed linkage of various maternal factors and psychosocial factors with maternal mental health and development of PPD. Other factors which need further elaboration are-

3.1. Biological factors

1. Decline in estrogen and progesterone: Plasma level of estrogen and progesterone are raised during pregnancy and decline following delivery.[20,21] Although, plasma level of estrogen fluctuates during pregnancy and after child birth, but estrogen treatment has not been found successful on long-term basis.[22] In this context, role of low progesterone in causation of PPD has been more explored and substantiated.[23] Level of allopregnanolone (ALLO) a metabolite of progesterone gradually rises during gestation and sharply decline after delivery. An association of level of ALLO and severity of PPD has been established.[24]
2. Dysregulation of HPA axis: The Hypothalamic-Pituitary-Adrenal (HPA) axis hormones which have been most extensively investigated for their role in etiopathogenesis of PPD are corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol.[25] The placenta starts secreting placental CRH (pCRH) at around 8 week of gestation. This leads to progressive rise in CRH, ACTH and Cortisol level over the course of gestation. The cortisol gives negative feedback to hypothalamic CRH but positive feedback to pCRH. This positive feedback loop of cortisol to pCRH serve as biological timer which ends with parturition.[26] The pCRH, by stimulating ACTH release and increasing cortisol level, is assumed to initiate labour process and facilitate parturition.[27] Normalization of these HPA axis hormones starts within few days of delivery and may take up to 12 weeks. Failure of HPA axis hormones to get normalized within expected time limit is postulated to be responsible for pathogenesis of PPD.[28] A systematic review including perinatal women as well as rodents found no clear association between maternal plasma cortisol and perinatal depression.[29]
3. Low oxytocin level: In normal pregnant women, oxytocin level remains raised from 35 week of gestation till 6 months postpartum. However, in women with PPD, level decline from 38^{th} of gestation to two days postpartum. Therefore, lower serum oxytocin level has been assumed to be associated with an increased risk of PPD.[30] However, a recent metanalysis found this association controversial.[31]
4. Thyroid dysfunction: Auto-immune thyroid dysfunction has been linked to the physiological changes that occur in the women after child birth.[32] Presence of thyroid peroxidase antibody (TPOAb) antibody during pregnancy has been linked to development of PPD and may serve as a biomarker and as well as potential target for pharmacotherapy.[33]

3.2. Genetic factors

Evidences suggests clustering of PPD cases in family and twin pregnancy.[34] Certain genetic variations such those involving chromosome 1q21.3-q32.1, 9p24-p22.3 and hemicentin-1 (HMCN-1) gene have been recognized as genetic basis of susceptibility to PPD. Some these have binding sites for estrogen, suggesting a possible of role of estrogen in pathogenesis of PPD through genetic mechanism.[35]

3.3. Role of immune function

Role of immune system in etiopathogenesis of PPD is yet to be delineated. Certain anti-inflammatory cytokines having their role in immunosuppression have been found elevated during pregnancy and assumed to be protective for foetus. But soon after parturition the immune system turns pro-inflammatory and remain so for many weeks. Many immunologic parameters such as regulatory T cells, CXCR1, CCR2, MNP1, CD11a, and neopterin have been investigated for role in pathogenesis of PPD. An increase in regulatory T cells, decrease in CXCR1, and elevated neopterin level during perinatal period in mother with symptoms of PPD are important findings. These immunologic parameters are thus being further investigated as potential immune biomarker for PPD.[36]

4. Signs and Symptoms

Many symptoms of PPD are common with those of major depressive disorder (MDD). Women with PPD presents with fatigue, sadness anhedonia, impaired concentration, irritability, guilt, psychomotor agitation, sleep disturbances and changes in appetite and weight.[37] In severe PPD, the women may develop suicidal thoughts[38] and the child may be exposed to a risk of child abuse[39] or even infanticide.[40] Postpartum depression significantly increases maternal suicide and risk is further increased by other co-morbidities.[41]

5. Screening

Studies reveals PPD is still under-detected and hence under-treated.[42] There is paucity of robust national screening programs particularly in developing nations.[43] Various society, committee, association, and organisation associated with postpartum depression recommends screening, early detection, and prompt treatment.[44] The American College of Obstetrician and Gynecologists recommends use of Edinburgh Postnatal Depression Scale (EPDS) for screening of PPD which is the most extensively and highly validated screening tool for PPD.[45] Other commonly used scales are the Patient Health Questionnaire-9[46] and the Beck Depression Inventory.[47]

6. Treatment

Management of PPD often requires a multidisciplinary approach. Various treatment strategies include-

6.1. Complementary health practices

Educating the women about self-care and about growing treatment-seeking behaviour as soon as symptom develops, is the basic health practice.[48] Sleep protection is an act of ensuring maternal sleep. Infant behavioral sleep intervention increases amount of maternal sleep and may improve symptom, if the cause of depressed mood is sleep-deprivation resulting from infant care.[49] Many evidences support benefit of aerobic exercise in improvement of PPD symptoms.[50,51] Identification and alleviation of social stressor are the key steps and should never be missed. Psychosocial supports such as peer support and counselling from a professional are the other health practices that should be given to the women. These health practices unequivocally benefit all women with mild PPD and are accepted by most women, particularly the pregnant ones.[52] Therefore, these practices must be applied to all cases of mild to moderate PPD before stepping up to next treatment modality.

6.2. Psychological interventions

Several psychological interventions have been evaluated for effectiveness in postpartum depression. Among these, Cognitive Behavioral Therapy (CBT)[53] and Interpersonal Psychotherapy (IPT)[54] have been most extensively evaluated and widely used. These interventions are next level approaches and have of demonstrated proven benefit in PPD both on short-term and long-term basis. Another type of psychological intervention, dynamic therapy has also been found effective.[55]

6.3. Pharmacotherapy

6.3.1. Drugs not approved by regulatory authorities (Evidence-based)

Until recently there was no approved treatment for PPD. Therefore, traditionally the treatment of PPD was adapted from that of major depressive disorder (MDD). Following classes of drugs have been used-

6.3.1.1. Antidepressant drugs.

1. Selective Serotonin Reuptake Inhibitors (SSRIs): SSRIs are the most thoroughly studied antidepressants.[56] Highest evidences are in the favour of sertraline and fluoxetine.58,59 Others like paroxetine,[57] fluvoxamine,[58] and escitalopram[59] have also been supported by RCTs. SSRIs have also been found to be safe for infants; highest evidence is with sertraline and hence, has been used in nursing mothers

with PPD.[60]

2. Selective Norepinephrine Reuptake Inhibitors (SNRIs): Use of SNRIs in PPD has not been supported by any RCT.[61]
3. Tricyclic Antidepressants (TCAs): An RCT demonstrated efficacy of nortriptyline in PPD and was found safe also for infant.[62]

Although many RCTs evaluated effectiveness of antidepressant in PPD, findings have been equivocal. A meta-analysis of eleven RCTs analysing efficacy and safety of antidepressants versus any other treatments or placebo in women with depression in the first 12 months postpartum concluded SSRIs to be beneficial in compared with placebo but not significantly better than other treatments.[63] A systematic review of six RCTs analysing efficacy of antidepressants in comparison with other treatments or placebo found SSRIs to be superior to placebo but not to other treatments.[64] A meta-analysis incorporating same studies concluded that although efficacy of SSRIs was superior to placebo but the quality of evidences was low and insufficient to support their use for PPD.[65] Despite ambiguous findings, there has been a consensus supporting antidepressant use in treatment of mild to moderate cases of PPD.

6.3.1.2. Hormonal therapy.

1. Estrogen: Current evidences on the use of estrogen in PPD is limited. In a double-blind, placebo-controlled trial, women receiving transdermal estradiol showed a greater and rapid improvement in depressive symptoms over 1^{st} month of treatment, but none of the two groups achieved complete remission.[66] In another RCT comparing transdermal estradiol with placebo, an inference could not be made because study was stopped prematurely owing to serum estrogen level not reaching expected level.[22] More powered RCTs are needed to generate evidences for the use of estrogen in PPD.
2. Progestins: A double-blind randomized placebo-controlled trial found norethisterone enanthate injected within 48 hours of delivery was associated with an increased risk of developing postpartum depression.[67] Another RCT evaluating risk of PPD associated with postnatal contraceptive depot medroxyprogesterone acetate (DMPA) in comparison intrauterine device (IUD) injected or implanted within 48 hours of parturition found DMPA to have an increased risk of PPD in comparison with IUD.[68] A metanalysis of two RCTs analysing effects of estrogen and progestins in comparison with placebo or usual care to prevent or to treat PPD concluded that synthetic progestin like norethisterone enanthate is associated with an increased risk of PPD and should be used cautiously as contraceptive in postpartum period.[69]

6.3.2. Drugs approved by US FDA

6.3.2.1. Brexanolone. Indication: Brexanolone was approved by the U.S. Food and Drug Administration on March 19, 2019 for the treatment of postpartum depression in adult women. It was the first drug approved by U.S. FDA specifically for postpartum depression. Because of promising response during clinical trial, the FDA has given brexanolone a 'Priority Review' and 'Breakthrough Therapy Designation' for the treatment of PPD.[70]

Dose and route: Brexanolone is administered as a continuous IV infusion over a total of 60 hours. The recommended dosing schedule is as follows-

0-4 hours: Initiate infusion at 30 mcg/kg/hour.

4-24 hours: Increase infusion rate to 60 mcg/kg/hour.

24-52 hours: Increase infusion rate to 90 mcg/kg/hour.

52-56 hours: Decrease infusion rate to 60 mcg/kg/hour.

56-60 hours: Decrease infusion rate to 30 mcg/kg/hour.

However, a reduction to 60 mcg/kg/hour may be considered for patients who do not tolerate 90 mcg/kg/hour.

Efficacy: The efficacy of brexanolone was demonstrated by three placebo-controlled trials. The trials included participants with moderate to severe postpartum depression who received 60-hour continuous infusion of brexanolone or placebo. Also, the participants were followed for four weeks. The primary efficacy outcome was the mean change from baseline in depressive symptoms as measured by a reduction in Hamilton Depression Rating Scale (HAM-D) scores. In all the studies, brexanolone demonstrated superiority to placebo in improving depressive symptoms at completion of first infusion. The superiority of brexanolone to placebo was also observed at the end of follow-up period.[71]

Mechanism of action: Brexanolone is an aqueous formulation of allopregnanolone. Allopregnanolone is a major metabolite of progesterone metabolism produced by the brain corpus luteum and placenta during pregnancy. Reduced level of allopregnanolone in the peripheral blood or cerebrospinal fluid has been found to be associated with increased risk of anxiety and depression and elevated serum level is assumed to lower the risk. Plasma allopregnanolone level keeps on increasing during pregnancy peaking around delivery and falls precipitously after delivery. Downregulation of $GABA_A$ receptors in response to falling hormone level is believed to contribute to symptoms of PPD. Thus, allopregnanolone is thought to underlie the pathogenesis of PPD.[72] Allopregnanolone is an inhibitory neuroactive steroid (neurosteroid) that act as positive allosteric modulator on GABAA-receptor and causes net inhibitory effect. Allopregnanolone has activity on all GABAA-receptor isoforms, but has greatest potentiation of those containing δ-subunit. Although not fully understood, brexanolone is assumed to modulate GABAA-receptors and enhance GABAergic activity.[73] Animal studies have shown that female mice with decreased δ-subunit-containing

GABAA-receptors developed depression-like behaviours and were deficit in maternal care which closely mimic PPD.[74] Another animal study demonstrated improved PPD behaviours following the administration of drugs which potentiate GABAA-receptors.[75]

Pharmacokinetics: Oral bioavailability of brexanolone is less than 5% and therefore, administered intravenously. Its volume of distribution is approximately 3L/kg. and plasma protein binding is >99%. The half-life is approximately 9 hours. The drug is mainly metabolized by non-CYP enzymes via 3 reactions- ketoreduction, glucuronidation and sulfation and none of the metabolites are pharmacologically active. No studies have specifically evaluated the interaction of other drugs with it.[76]

Safety: Serious side effects were reported by trial participants which include excessive sedation, sleepiness, sudden loss of consciousness, dry mouth and facial flushing. Patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. The need for these steps is addressed in a Boxed Warning in the drug's prescribing information. Patients should be advised not to drive, operate heavy machinery, or do other dangerous activities until the drowsiness has completely vanished. It is recommended for health care providers to consider changing the therapeutic regimen, including discontinuing brexanolone in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviours. Because of this safety concern, brexanolone has been approved with a "Risk Evaluation and Mitigation Strategy (REMS)" and is only available to patients through a restricted distribution program at certified health care facilities where the health care providers can monitor the patients.[77] Nothing is known about the safety of the brexanolone for unborn baby and the drug is secreted in milk. Therefore, treatment with brexanolone during pregnancy or lactation should be considered when benefit outweighs the risk.[78]

6.3.2.2. Zuranolone. Indication: The U.S. Food and Drug Administration approved zuranolone (Zurzuvae®), the oral medication to treat PPD. The efficacy of brexanolone for treatment PPD has been demonstrated in two randomized, double-blind, placebo-controlled, multicentre trails. In one trial, women with major depressive symptoms received 50mg of zuranolone or placebo once daily in the evening for 14 days[79] while in another trial the trial participants received 30 mg of zuranolone or placebo for 14 days.[80] Patients in both studies were monitored for at least four weeks after the 14-day treatment. Patients in zuranolone groups showed significantly more improvement in their symptoms compared to those in the placebo groups. Treatment effect was maintained at Day 42-four weeks after the last dose of zuranolone.

Mechanism of action: Zuranolone is a positive allosteric modulator of synaptic and extra-synaptic $GABA_A$ receptors.[81]

Dose: 50 mg; once daily in the evening for 14 days with fatty meal.

Adverse effects: The most common side effects include drowsiness, dizziness, diarrhea, fatigue, nosopharyngitis and UTI. Other important side effects are suicidal thoughts.

Caution: The label contains warning that zuranolone can impair a person's ability to drive and perform other potentially hazardous activities. So, patient should not drive or operate heavy machinery for at least 12 hours of taking zuranolone.

6.3.3. Somatic therapy

Candidates for somatic therapy are those with moderate to severe depression in whom psychotherapy and/or antidepressants fail to induce remission or are contra-indicted. It can be administered as a stand-alone treatment or combined with psychotherapy and/or psychopharmacotherapy. Various techniques of somatic therapy are- seizure therapies which include electroconvulsive therapy (ECT) and magnetic seizure therapy; non-invasive techniques which encompasses focal brain stimulation therapies such as repetitive transcranial direct current stimulation, and cranial electric stimulation; and surgical approaches which include vagus nerve stimulation, epidural electrical stimulation, and deep brain stimulation. Electroconvulsive therapy (ECT) becomes one of the most effective tools for women with severe depressive symptoms including suicidal thoughts and psychotic symptoms and being safe in pregnancy, is particularly useful during antenatal period. Requirement of general anaesthesia and some side effects like memory impairment limits usefulness of ECT in PPD and should be chosen as the last resort.[82] Management algorithm for PPD (Figure 1).

7. Summary

Many drugs have been evaluated for their efficacy in PPD. Antidepressants and hormones have been more extensively investigated. Among these, although not approved by any regulatory authorities, antidepressants are still being used for mild to moderate cases who fail to respond to psychosocial and psychological psychotherapy. Somatic therapies such as electroconvulsive therapy are used of severe depressive symptoms. SSRIs followed by SNRIs are the first line drugs. U.S. FDA has approved brexanolone, an injectable and zuranolone, an oral drug for their use in severe PPD. Somatic therapies such as electroconvulsive therapy are used for women with severe depressive symptoms.

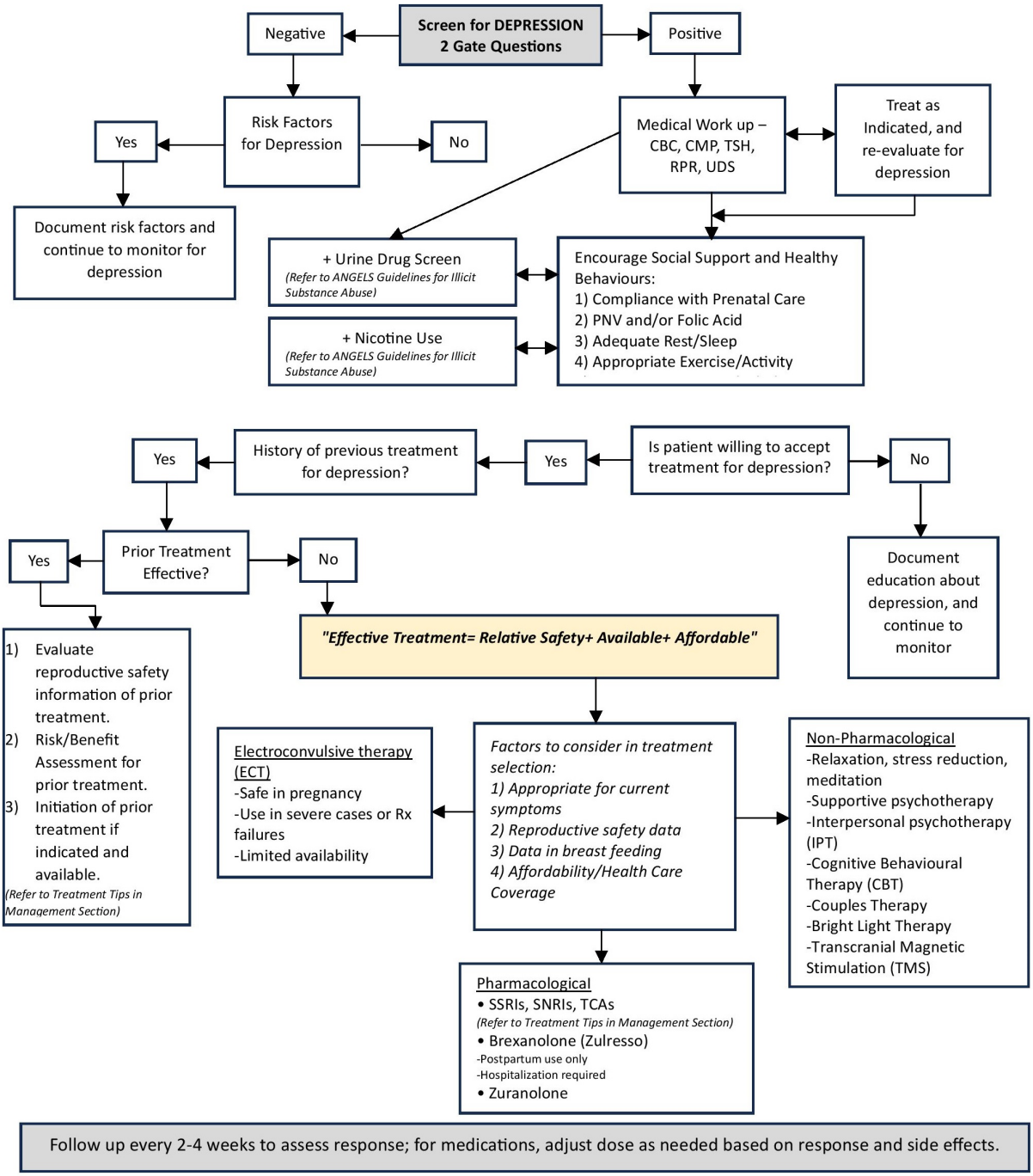

Figure 1: Guidelines for evaluation and treatment of women with depression during perinatal period. (Adapted from The Antenatal and Neonatal Guidelines, Education and Learning System (ANGELS). Management of depression during perinatal period. www.angelsguidelines.com.) (Abbreviations: CBC: Complete blood count; CMP: Comprehensive metabolic panel; TSH: Thyroid stimulating hormone; RPR: Rapid plasma regain; UDS: Urine drug screen, PNV: Prenatal vitamin; SSRI: Selective serotonin re-uptake inhibitors; SNRI: Serotonin/norepinephrinere-uptake inhibitors.)

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9. Conflict of Interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

1. No financial relationship at present or within the previous three years with any organizations that might have an interest in submitted work.
2. No other relationships or activities that could appear to have influenced the submitted work.

References

1. Florio AD, Forty L, Gordon-Smith K, Heron J, Jones L, Craddock N. Perinatal episodes across the mood disorder spectrum. *JAMA Psychiatry*. 2013;70(2):168–75.
2. Seyfried LS, Marcus SM. Postpartum mood disorders. *Int Rev Psychiatry*. 2003;15(3):231–42.
3. Friedman SH, Reed E, Ross NE. Postpartum Psychosis. *Curr Psychiatry Rep*. 2023;25(2):65–72.
4. Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J. Non-psychotic mental disorders in the perinatal period. *Lancet*. 2014;384(9956):1775–88.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Publishing; 2013. doi:10.1176/appi.books.9780890425596.
6. Robertson E, Grace S, Wallington T, Stewart DE. Antenatal risk factors for postpartum depression: a synthesis of recent literature. *Gen Hosp Psychiatry*. 2004;26(4):289–95.
7. Bauman BL, Ko JY, Cox S, Cox S, Mph DD, Warner L, et al. Vital Signs: Postpartum Depressive Symptoms and Provider Discussions About Perinatal Depression - United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2020;69(19):575–81.
8. Hahn-Holbrook J, Cornwell-Hinrichs T, Anaya I. Economic and Health Predictors of National Postpartum Depression Prevalence: A Systematic Review, Meta-analysis, and Meta-Regression of 291 Studies from 56 Countries. *Front Psychiatry*. 2018;8:248.
9. Takehara K, Tachibana Y, Yoshida K, Mori R, Kakee N, Kubo T. Prevalence trends of pre- and postnatal depression in Japanese women: A population-based longitudinal study. *J Affect Disord*. 2017;225:389–94.
10. Anokye R, Acheampong E, Budu-Ainooson A, Obeng EI, Akwasi AG. Prevalence of postpartum depression and interventions utilized for its management. *Ann Gen Psychiatry*. 2009;17(18). doi:10.1186/s12991-018-0188-0.
11. Kroska EB, Stowe ZN. Postpartum Depression: Identification and Treatment in the Clinic Setting. *Obstet Gynecol Clin North Am*. 2020;47(3):409–19.
12. Cox EQ, Sowa NA, Meltzer-Brody SE, Gaynes BN. The Perinatal Depression Treatment Cascade: Baby Steps Toward Improving Outcomes. *J Clin Psychiatry*. 2016;77(9):1189–1200.
13. Molyneaux E, Telesia LA, Henshaw C, Boath E, Bradley E, Howard LM. Antidepressants for preventing postnatal depression. *Cochrane Database Syst Rev*. 2018;4(4):CD004363.
14. Walton GD, Ross LE, Stewart DE, Grigoriadis S, Dennis CL, Vigod S, et al. Decisional conflict among women considering antidepressant medication use in pregnancy. *Arch Womens Ment Health*. 2009;17(6):493–501.
15. Frieder A, Fersh M, Hainline R, Deligiannidis KM. Pharmacotherapy of Postpartum Depression: Current Approaches and Novel Drug Development. *CNS Drugs*. 2019;33(3):265–82.
16. Azami M, Badfar G, Soleymani A, Rahmati S. The association between gestational diabetes and postpartum depression: A systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2019;149:147–55.
17. Beck CT. Predictors of postpartum depression: an update. *Nurs Res*. 2001;50(5):275–85.
18. Earls MF. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. *Pediatrics*. 2010;126(5):1032–9.
19. ACOG Committee Opinion No. 757: Screening for Perinatal Depression. *Obstet Gynecol*. 2018;132(5):208–12.
20. Moses-Kolko EL, Berga SL, Kalro B, Sit DKY, Wisner KL. Transdermal estradiol for postpartum depression: a promising treatment option. *Clin Obstet Gynecol*. 2009;52(3):516–29.
21. Tal R, Taylor HS. Endocrinology of Pregnancy. In: Feingold KR, Anawalt B, Blackman MR, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc; 2000.
22. Wisner KL, Sit DKY, Moses-Kolko EL, Driscoll KE, Prairie BA, Stika CS, et al. Transdermal Estradiol Treatment for Postpartum Depression: A Pilot, Randomized Trial. *J Clin Psychopharmacol*. 2015;35(4):389–95.
23. Reddy DS. Neuroendocrine insights into neurosteroid therapy for postpartum depression. *Trends Mol Med*. 2023;29(12):979–82.
24. Etyemez S, Miller KN, Voegtline KM, Özdemir İ, Standeven LR, Santovito LS, et al. Metabolites of progesterone in pregnancy: Associations with perinatal anxiety. *Psychoneuroendocrinology*. 2023;156:106327.
25. Payne JL, Maguire J. Pathophysiological mechanisms implicated in postpartum depression. *Front Neuroendocrinol*. 2018;52:165–80.
26. Chai Y, Li Q, Wang Y, Tao E, Asakawa T. The Value of HPA Axis Hormones as Biomarkers for Screening and Early Diagnosis of Postpartum Depression: Updated Information About Methodology. *Front Endocrinol (Lausanne)*. 2022;13:916611.
27. Thomson M. The physiological roles of placental corticotropin releasing hormone in pregnancy and childbirth. *J Physiol Biochem*. 2012;69(3):559–73.
28. Laurent H, Goodman SH, Stowe ZN, Halperin M, Khan F, Wright D, et al. Course of ante- and postnatal depressive symptoms related to mothers' HPA axis regulation. *J Abnorm Psychol*. 2018;127(4):404–16.
29. Schalla MA, Stengel A. The role of stress in perinatal depression and anxiety - A systematic review. *Front Neuroendocrinol*. 2024;72:101117.
30. Jobst A, Krause D, Maiwald C, Härtl K, Myint AM, Kästner R, et al. Oxytocin course over pregnancy and postpartum period and the association with postpartum depressive symptoms. *Arch Womens Ment Health*. 2016;19(4):571–9.
31. Zhu J, Jin J, Tang J. Oxytocin and Women Postpartum Depression: A Systematic Review of Randomized Controlled Trials. *Neuropsychiatr Dis Treat*. 2023;19:939–47.
32. Donne ML, Settineri S, Benvenga S. Early pospartum alexithymia and risk for depression: relationship with serum thyrotropin, free thyroid hormones and thyroid autoantibodies. *Psychoneuroendocrinology*. 2011;37(4):519–33.
33. Wesseloo R, Kamperman AM, Bergink V, Pop VJM. Thyroid peroxidase antibodies during early gestation and the subsequent risk of first-onset postpartum depression: A prospective cohort study. *J Affect Disord*. 2017;225:399–403.
34. Forty L, Jones L, Macgregor S, Caesar S, Cooper C, Hough A, et al. Familiality of postpartum depression in unipolar disorder: results of a family study. *Am J Psychiatry*. 2006;163(9):1549–53.
35. Mahon PB, Payne JL, MacKinnon DF, Mondimore FM, Goes FS, Schweizer B, et al. Genome-wide linkage and follow-up association study of postpartum mood symptoms. *Am J Psychiatry*. 2009;166(11):1229–37.
36. Krause D, Jobst A, Kirchberg F, Kieper S, Härtl K, Kästner R, et al. Prenatal immunologic predictors of postpartum depressive symptoms: a prospective study for potential diagnostic markers. *Eur Arch Psychiatry Clin Neurosci*. 2014;264(7):615–24.

37. Tebeka S, Gauld C, Belzeaux R, Peyre H, Dubertret C. Major depressive episode and postpartum depression: A network analysis comparison on the IGEDEPP cohort. *Eur Psychiatry*. 2023;66(1):51.
38. Pope CJ, Xie B, Sharma V, Campbell MK. A prospective study of thoughts of self-harm and suicidal ideation during the postpartum period in women with mood disorders. *Arch Womens Ment Health*. 2013;16(6):483–8.
39. Plant DT, Pariante CM, Sharp D, Pawlby S. Maternal depression during pregnancy and offspring depression in adulthood: role of child maltreatment. *Br J Psychiatry*. 2015;207(3):213–20.
40. Spinelli MG. Maternal infanticide associated with mental illness: prevention and the promise of saved lives. *Am J Psychiatry*. 2004;161(9):1548–57.
41. Lee YL, Tien Y, Bai YS, Lin CK, Yin C, Chung CH, et al. Association of Postpartum Depression with Maternal Suicide: A Nationwide Population-Based Study. *Int J Environ Res Public Health*. 2022;19(9):5118.
42. Sharma V, Khan M, Corpse C, Sharma P. Missed bipolarity and psychiatric comorbidity in women with postpartum depression. *Bipolar Disord*. 2008;10(6):742–7.
43. Upadhyay RP, Chowdhury R, Salehi A, Sarkar K, Singh SK, Sinha B, et al. Postpartum depression in India: a systematic review and meta-analysis. *Bull World Health Organ*. 2017;95(10):706–17.
44. Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315(4):380–7.
45. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150:782–6.
46. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–13.
47. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev*. 1988;8(1):77–100.
48. Dennis CL, Chung-Lee L. Postpartum depression help-seeking barriers and maternal treatment preferences: a qualitative systematic review. *Birth*. 2006;33(4):323–3.
49. Kempler L, Sharpe L, Miller CB, Bartlett DJ. Do psychosocial sleep interventions improve infant sleep or maternal mood in the postnatal period? A systematic review and meta-analysis of randomised controlled trials. *Sleep Med Rev*. 2015;29:15–22.
50. Pritchett RV, Daley AJ, Jolly K. Does aerobic exercise reduce postpartum depressive symptoms? a systematic review and meta-analysis. *Br J Gen Pract*. 2017;67(663):684–91.
51. Mccurdy AP, Boulé NG, Sivak A, Davenport MH. Effects of Exercise on Mild-to-Moderate Depressive Symptoms in the Postpartum Period: A Meta-analysis. *Obstet Gynecol*. 2017;129(6):1087–97.
52. Goodman JH. Women's attitudes, preferences, and perceived barriers to treatment for perinatal depression. *Birth*. 2009;36(1):60–9.
53. 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):e0205243.
54. O'Hara M, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. *Arch Gen Psychiatry*. 2000;57(11):1039–45.
55. Stephens S, Ford E, Paudyal P, Smith H. Effectiveness of Psychological Interventions for Postnatal Depression in Primary Care: A Meta-Analysis. *Ann Fam Med*. 2016;14(5):463–72.
56. Kimmel MC, Cox E, Schiller C, Gettes E, Meltzer-Brody S. Pharmacologic Treatment of Perinatal Depression. *Obstet Gynecol Clin North Am*. 2018;45(3):419–40.
57. Yonkers KA, Lin H, Howell HB, Heath AC, Cohen LS. Pharmacologic treatment of postpartum women with new-onset major depressive disorder: a randomized controlled trial with paroxetine. *J Clin Psychiatry*. 2008;69(4):659–65.
58. Suri R, Burt VK, Altshuler LL, Zuckerbrow-Miller J, Fairbanks L. Fluvoxamine for postpartum depression. *Am J Psychiatry*. 2001;158(10):1739–40.
59. Misri S, Abizadeh J, Albert G, Carter D, Ryan D. Restoration of functionality in postpartum depressed mothers: an open-label study with escitalopram. *J Clin Psychopharmacol*. 2012;32(5):729–32.
60. Davanzo R, Copertino M, Cunto AD, Minen F, Amaddeo A. Antidepressant drugs and breastfeeding: a review of the literature. *Breastfeed Med*. 2010;6(2):89–98.
61. Cohen LS, Viguera AC, Bouffard SM, Nonacs RM, Morabito C, Collins MH, et al. Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry*. 2001;62(8):592–6.
62. Wisner KL, Hanusa BH, Perel JM, Peindl KS, Piontek CM, Sit DKY, et al. Postpartum depression: a randomized trial of sertraline versus nortriptyline. *J Clin Psychopharmacol*. 2006;26(4):353–60.
63. Brown JVE, Wilson CA, Ayre K, Robertson L, South E, Molyneaux E, et al. Antidepressant treatment for postnatal depression. *Cochrane Database Syst Rev*. 2021;2(2):CD013560.
64. Molyneaux E, Howard LM, Mcgeown HR, Karia AM, Trevillion K. Antidepressant treatment for postnatal depression. *Cochrane Database Syst Rev*. 2014;2014(9):CD002018.
65. Molyneaux E, Howard LM, Mcgeown HR, Karia AM, Trevillion K. Antidepressant Treatment for Postnatal Depression. *Issues Ment Health Nurs*. 2016;38(2):188–90.
66. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet*. 1996;347(9006):930–3.
67. Lawrie TA, Hofmeyr GJ, Jager MD, Berk M, Paiker M, Viljoen E. A double-blind randomised placebo controlled trial of postnatal norethisterone enanthate: the effect on postnatal depression and serum hormones. *Br J Obstet Gynaecol*. 1998;105(10):1082–90.
68. Singata-Madliki M, Hofmeyr GJ, Lawrie TA. The effect of depot medroxyprogesterone acetate on postnatal depression: a randomised controlled trial. *J Fam Plann Reprod Health Care*. 2016;42(3):171–6.
69. Dennis CL, Ross LE, Herxheimer A. Oestrogens and progestins for preventing and treating postpartum depression. *Cochrane Database Syst Rev*. 2008;2008(4):CD001690.
70. Azhar Y, Din AU. Brexanolone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; [Updated 2023 Jun 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541054/.
71. Morrison KE, Cole AB, Thompson SM, Bale TL. Brexanolone for the treatment of patients with postpartum depression. *Drugs Today (Barc)*. 2019;55(9):537–44.
72. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol*. 2013;113:79–87.
73. Nik AM, Pressly B, Singh V, Antrobus S, Hulsizer S, Rogawski MA, et al. Rapid throughput analysis of GABAA receptor subtype modulators and blockers using DiSBAC1(3) membrane potential red dye. *Mol Pharmacol*. 2017;92(1):88–99.
74. Melón L, Hammond R, Lewis M, Maguire J. A Novel, Synthetic, Neuroactive Steroid Is Effective at Decreasing Depression-Like Behaviors and Improving Maternal Care in Preclinical Models of Postpartum Depression. *Front Endocrinol (Lausanne)*. 2018;9:703.
75. Maguire J, Mody I. GABA(A) R plasticity during pregnancy: relevance to postpartum depression. *Neuron*. 2008;59(2):207–13.
76. Scott LJ. Brexanolone: First Global Approval. *Drugs*. 2019;79(7):779–83.
77. Cornett EM, Rando L, Labbé AM, Perkins W, Kaye AM, Kaye AD, et al. Brexanolone to Treat Postpartum Depression in Adult Women. *Psychopharmacol Bull*. 2021;51(2):115–30.
78. Edinoff AN, Odisho AS, Lewis K, Kaskas A, Hunt G, Cornett EM, et al. Brexanolone, a GABAA Modulator, in the Treatment of Postpartum Depression in Adults: A Comprehensive Review. *Front Psychiatry*. 2021;12:699740.
79. Clayton AH, Lasser R, Parikh SV, Iosifescu DV, Jung J, Kotecha M, et al. Zuranolone for the Treatment of Adults With Major Depressive Disorder: A Randomized, Placebo-Controlled Phase 3 Trial. *Am J Psychiatry*. 2023;180(9):676–84.
80. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, Doherty J, Jonas J, Li S, et al. Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2021;78(9):951–9.

81. Althaus AL, Ackley MA, Belfort GM, Gee SM, Dai J, Nguyen DP, et al. Preclinical characterization of zuranolone (SAGE-217), a selective neuroactive steroid GABAA receptor positive allosteric modulator. *Neuropharmacology*. 2020;181:108333.
82. Mughal S, Azhar Y, Siddiqui W. Postpartum Depression. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; [Updated 2022 Oct 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519070/.

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