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Development and Management of Depression During and After Pregnancy

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Objectives

After completion of this program, the reader should be able to:

1. List the signs of depression in pregnancy.
2. Outline appropriate pharmacologic and nonpharmacologic treatment regimens for pregnant women who are diagnosed with depression as well as for women with postpartum depression during breastfeeding.
3. State the pharmacist's role in the management of depression in women who are pregnant and those experiencing postpartum depression.
4. Explain when antidepressants start to relieve symptoms and how long they take to reach their full effect.
5. Explain the role of exercise physiology in managing depression during pregnancy.

Abstract

Depression during pregnancy is common, whether it is a new onset of the disease or emerging symptoms of the already existent disease. Due to patient and prescriber concerns with antidepressant use during pregnancy, approximately three-quarters of those diagnosed with depression remain untreated. Furthermore, up to half of pregnant women with depression remain undiagnosed due to lack of recognition. As a result, both mother and fetus are at risk for negative health outcomes including substance abuse, functional impairment, increased risk of postnatal depression and poor pregnancy outcomes. Benefits must be balanced against the risks when considering pharmacologic treatment options to manage depression during pregnancy. Health care professionals must also consider the secondary effects of unmanaged depression during pregnancy such as the physical health of the patient. Nonpharmacologic options such as a balanced physical activity regimen and nutritional health may be considered to help improve the well-being of the patient. Therefore, it is important for health care professionals to be educated on the treatment and management of depression in pregnancy to help patients achieve optimal outcomes not only for maternal mental and physical health but also for the health of the fetus.

Key Terms

Antidepressive Agents; Depression; Postpartum Period; Depressive Disorder; Exercise; Female; Fetus; Mothers; Pregnancy; Pregnancy Outcome

Introduction

Depression can occur in pregnancy both as new-onset disease and as an exacerbation of existing disease. While the pathophysiology of depression remains unclear, it affects about 20 percent of women during pregnancy and has negative effects on pregnancy outcomes such as birth weight of the infant and preterm delivery.[1] Antidepressant therapy while pregnant or breastfeeding is controversial as many of the drugs commonly used in depression have a lack of evidence for use during pregnancy and breastfeeding. This results in both provider and patient reluctance to initiate new drug therapy during pregnancy or while breastfeeding. However, there are other, nonpharmacologic methods of treating depression including interpersonal therapy (IPT), psychotherapy, acupuncture and exercise. A risk-versus-benefit analysis should always be conducted when determining which therapy is appropriate for a given patient. It is also important to consider the risks of untreated depression during pregnancy including postpartum depression, decreased safety of the child and increased infantile colic. Pharmacists have the ability to provide a crucial role in evaluating a patient's depression, helping to select proper treatment, evaluating treatment progress and educating the patient. An interdisciplinary health care team can collaborate to help individualize the patient's treatment with maximal benefit.

Overview of Depression: Pathology, Symptoms, Diagnosis and Treatment

Although the pathophysiology of depression is unclear, one hypothesis points to a dysfunction in neurotransmitter signaling which includes the availability and concentration of neurotransmitters, receptor activation and response in the neuron.[2] Neurotransmitter imbalance is commonly thought to be the cause of depression. Neurotransmitters that are affected include serotonin (5-HT), norepinephrine (NE), dopamine (DA), glutamate and brain-derived neurotrophic factor (BDNF). Depression is caused by a decreased concentration of these neurotransmitters, a lack of effective activation of their receptors or a combination of both.

The site of 5-HT synthesis in the brain is the dorsal raphe nucleus where the reaction catalyzed by tryptophan hydroxylase is the rate-limiting step.[3] Tryptophan hydroxylase is an enzyme involved in the hydroxylation of the essential amino acid L-tryptophan to form 5-hydroxytryptophan, which is the precursor for 5-HT. The removal of 5-HT from the synapse is

completed either through degradation by the enzyme monoamine oxidase (MAO) or its removal from the synapse through the serotonin-reuptake transporter located on the presynaptic neuron.[2]

The other significant neurotransmitters involved with the pathology of depression are NE and DA. Both of these neurotransmitters are synthesized in the mesocortical and mesolimbic regions of the ventral tegmental area of the brain. The rate-limiting step in the synthesis of both DA and NE is the action of the tyrosine hydroxylase, which catalyzes the hydroxylation of the amino acid L-tyrosine to L-dihydroxyphenylalanine (L-DOPA), which is converted to DA and then to NE. The removal of NE and DA is either accomplished by MAO or catechol-o-methyltransferase (COMT) metabolism or reuptake into the presynaptic cleft by either the norepinephrine reuptake transporter or the dopamine reuptake transporter, respectively.[2] Because these medications work at the receptor level, it takes time for the full effectiveness of the medication to be seen. It takes about two weeks for most antidepressants to start to relieve some depression symptoms, and it takes about six to eight weeks to reach its full effect from the initiation of therapy.[4]

The signs and symptoms of depression vary in degree from patient to patient. In pregnant patients, the onset of depression can vary from the start of pregnancy to development postpartum.[5] Pregnancy is associated with increased hormone levels; it was found that pregnant patients have 30 times higher estrogen levels compared to women who are not pregnant. Pregnant patients also have increased cortisol levels comparable to those in patients with major depressive disorders. The associated symptoms of depression in pregnancy found in a study by Castro and colleagues include depressed mood, feeling worse in the morning, decreased energy, lack of concentration, sensitivity to criticism and feelings of heavy limbs. The authors noted these symptoms were experienced to a higher degree at the beginning and end of pregnancy than in the middle.

The diagnosis of depression is based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria.[6] A patient is diagnosed with depression if the patient exhibits symptoms of depressed mood or anhedonia, along with at least four other symptoms.[7] These other symptoms include the following: change in weight or appetite, insomnia, fatigue, feelings of worthlessness or inappropriate guilt, indecisiveness, recurrent thoughts of death or recurrent suicidal ideation, and psychomotor agitation or retardation. These symptoms must be present nearly every day during the same two week period and must represent a change from the patient's previous functioning.

Several different depression rating scales can be used to evaluate if a person has depression as well as to monitor the patient's progress throughout treatment. A few common scales include the Hamilton Rating Scale for Depression (HAM-D), Structured Clinical Interview mood module for depression and the Clinical Global Impressions Scale.[7] The HAM-D is commonly seen in drug studies and is considered the standard for comparison of other depression rating scales. The HAM-D is used for screening, determination of disease severity and assessment of outcomes. It is important to note that none of these scales are specific for evaluating depression in pregnant women.

In general, pharmacologic treatment of depression includes the first generation antidepressants (tricyclic antidepressants (TCAs) and MAO inhibitors) and the second generation antidepressants which include the newer, more favorable treatment classes (serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)).[8] Many health care professionals are reluctant to use these drugs during pregnancy, leading to the undertreatment of this disease in pregnant women. The appropriate use of pharmacologic medications in pregnancy to treat depression as well as nonpharmacologic treatment of depression will be further elaborated on in this article.

Epidemiology and the Impact of Depression in Pregnancy

The incidence of depression in pregnant women varies according to many contributing factors.[9] These factors include the age of the mother, whether the pregnancy was intended or unintended, marital status, socioeconomic status, history of domestic violence and comorbid diseases. It is estimated that 10 percent of pregnant mothers deal with depression, either as a result of the pregnancy or a relapse of pre-existing depression during pregnancy. Depression that is diagnosed before pregnancy must still be monitored prior to and after conception for the optimization of outcomes for both mother and child. Depression during pregnancy is characterized by a relatively high frequency of somatic symptoms, which can present as a lack of energy or suicidal thoughts. Consequences of depression in pregnancy include medical complications such as preeclampsia, inadequate prenatal care such as an imbalanced diet or use of tobacco, alcohol or illicit drugs.

Depression during pregnancy can cause stress on the mother which has been linked to preterm birth.[10] Smith and colleagues completed a study of 4,672 women from 2009 to 2011 to investigate the rate of depression in pregnancy. A total of 4,123 women were evaluated after excluding those with unknown marital status, unknown smoking status, unknown use or use of alcohol, those who developed gestational diabetes and women under 18 years of age or over 40 years of age. Of the 4,123 women, 8.05 percent (n=4,123) were told that they had depression at some point during their pregnancy. Compared to women who were not told they had depression while pregnant, those who were told they had depression while pregnant had statistically significantly increased odds of preterm birth with the reported odds ratio (OR) of 1.51 at a 95 percent confidence interval (CI) of 1.07 to 2.12. When adjusted for appropriate number of prenatal visits, the OR dropped to 1.29 and was no longer statistically significant (95 percent CI 0.9, 1.85). The self-reporting of depression in this study and the observational design limit the interpretation of this data.

Management of Depression During Pregnancy

Major depressive disorder in pregnancy is diagnosed using DSM-V guidelines.[6] The DSM-V guidelines define major depressive disorder with postpartum onset as a major depressive episode with onset within four weeks of delivery.[7] According to the major depressive disorder guidelines, prescribers should always evaluate the risks and benefits of pharmacotherapy during pregnancy and breastfeeding including the risks of untreated mood disorder and the lack of knowledge regarding the safety of drug therapy. Dose requirements may change during pregnancy due to changes in volume of distribution, metabolism and gastrointestinal absorption. While there is little controlled, long-term research, psychotherapies appear to be efficacious for depression during pregnancy and postpartum depression. The American Psychiatric Association and American College of Obstetricians and Gynecologists recommend psychotherapy as the first-line option for those who are not currently prescribed an antidepressant.[11]

Nonpharmacologic Treatment

Nonpharmacologic options are abundant for treating depression and are first-line options for women who are pregnant. One of these first-line nonpharmacologic options is interpersonal therapy (IPT) which may be useful for women who have never been prescribed an antidepressant.[12] If medication therapy must be considered, the patient should still continue the psychotherapy throughout the treatment process. Other nonpharmacologic options include peer or partner support, massage therapy, bright light therapy, acupuncture, nutrition, weight management, childbirth education and prenatal care.

Manber and colleagues conducted a study in which a total of 150 pregnant women who met the criteria for major depressive disorder were randomized to either treatment with acupuncture specific for depression or one of two active controls: control acupuncture or massage.[13] The junior acupuncturists were blinded, and treatments lasted eight weeks. The primary outcome of this study was the HAM-D score administered by the acupuncturists at baseline and after four and eight weeks of treatment. Women who received acupuncture specific for depression had a greater decrease in symptoms ($p<0.05$, CI 0.01-0.92) when compared to the controls. Those receiving acupuncture also had a greater response rate (defined as a 50 percent reduction in the HAM-D score from baseline) compared to the combined controls ($p<0.05$, CI 2.2-75.0). This study demonstrates that acupuncture may be a viable treatment option for depression in pregnancy.

Pharmacologic Treatment

As stated, SSRIs are one of the favored drug classes for the treatment of depression. The SSRIs work to improve serotonergic functioning by inhibiting the reuptake of serotonin from the synapse through the reuptake transporters on the presynaptic neuron.[4] Examples of SSRIs include fluoxetine, paroxetine, citalopram, escitalopram and sertraline. If a pregnant patient fails therapy with nonpharmacologic options, an SSRI may be the next option that is considered. The American Psychiatric Association guidelines for major depressive disorder do not specify one SSRI as being superior to others for use during pregnancy, but there are some suggestions stated in the guidelines as shown in Table 1.[7,14-17] Specific guidelines related to use of psychiatric medications in the pregnant patient warn against the use of paroxetine due to potential fetal harm.[18] Health care providers must assess the individual patient when beginning pharmacologic therapy and weigh the benefits against the potential adverse effects. In 2006, the U.S. Food and Drug Administration (FDA) issued a warning that the use of SSRIs in pregnancy has been associated with persistent pulmonary hypertension of the newborn (PPHN). However, in 2011, the FDA stated there was not enough evidence to link PPHN to SSRI use.[19] There is concern that 30 percent of infants born to mothers taking SSRIs in the third trimester have exhibited symptoms of withdrawal including jitteriness, hypoglycemia, rapid breathing, irritability, weak cry and seizures.

Depression has also been associated with an irregularity of omega-3 polyunsaturated fatty acids.[20] Therefore, it is hypothesized that taking omega-3 fatty acid supplements may help relieve symptoms caused by low levels. In an eight week, double-blind, placebo-controlled trial conducted in pregnant women with major depressive disorder, Su and colleagues evaluated the efficacy of omega-3 fatty acid supplementation as monotherapy in the treatment of depression during pregnancy in 24 pregnant women. As a measure of efficacy, individual HAM-D scores were recorded every other week. Response rate was characterized as a 50 percent improvement in HAM-D score compared to baseline. Compared to the placebo group, those taking omega-3 supplements had significantly lower HAM-D scores at weeks six and eight ($p=0.001$, 0.019, respectively), a higher response rate ($p=0.03$) and, while not statistically significant ($p=0.28$), a higher remission rate. In conclusion, omega-3 fatty acid supplements may have benefits for treating depression during pregnancy, but evaluation may need to be repeated in studies with a larger sample size.

Modification of Pharmacologic Therapy Prior to Conception

Women who have been diagnosed with depression prior to conception must be evaluated by a psychiatrist before making changes to their medication.[14] Women who are being actively treated for depression and are trying to become pregnant should consider speaking with their psychiatrist about the continuation or discontinuation of their therapy based on their depression management. The psychiatrist must evaluate the patient's risks, relapse history, suicide history and severity of depression before considering discontinuation or decrease in dose of the medication prior to pregnancy. If the patient has been symptom free for six months or greater, tapering off the antidepressant prior to conception may be a worthwhile consideration. However, discontinuation may not be appropriate in those with a history of suicide attempts or episodes of psychosis.

Table 1: A Review of Antidepressant Drugs for use in Pregnancy.[7,14-16]

Medication	FDA Pregnancy Category*	Potential Adverse Event in Pregnancy and/or Breastfeeding
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Paroxetine	D	Cardiac malformations
Fluoxetine	C	Minor physical abnormalities, lower birth weight, lower maternal weight gain, longer half-life than other SSRIs Breastfeeding: decreased feeding, irritability, watery stools and crying
Sertraline	C	Lower cord blood levels, but unknown significance to the fetus
Citalopram	C	Breastfeeding: decreased feeding, irritability, watery stools and crying
Escitalopram	C	No confirmed evidence of birth defects when used in the first trimester; risk of SSRI withdrawal syndrome when used in the third trimester
Tricyclic Antidepressants		
Desipramine, Imipramine, Nortriptyline	Inconclusive data	Congenital abnormalities have been reported in humans, but a causal relationship has not been established.
Other Antidepressant Agents		
Bupropion	C	The benefit for smoking cessation may make it preferred for women who are pregnant with Major Depressive Disorder and wish to quit smoking.
Venlafaxine	C	Limited data suggests there may be an increase in birth defects and spontaneous abortion.
Duloxetine	C	In animal studies, nonteratogenic effects in the newborn following third trimester exposure include respiratory distress, jitteriness, irritability, crying and tremor.
Mirtazapine	C	Limited data available; no confirmed evidence of birth defects when used in the first trimester.

* The use of the pregnancy category will be eliminated over the next few years per the U.S. Food and Drug Administration's new labeling requirements.[17]

Cohen and colleagues looked at relapse rates of depression during pregnancy, comparing mothers who chose to stay on their medication to mothers who chose to discontinue therapy.[21] Of the 201 mothers included in the trial, 86 women experienced a relapse in depression during pregnancy. Of mothers who continued their medication, only 26 percent (n=21) relapsed. The mothers who discontinued their medication experienced a significantly higher rate of relapse, 67.7 percent (n=44, p<0.001). This study demonstrates that medication can help reduce the rate of relapse, but even pregnant women who are being treated with medications are still at risk for experiencing a relapse of their depression.

Exercise Benefits

Exercise is another type of therapy that can be used in place of or in addition to pharmacologic agents for women who have depression or who are at a greater risk of experiencing depression during pregnancy. A study done by El-Rafie and colleagues found that exercise during pregnancy reduced depression symptoms.[22] This study examined 100 different females who completed the 20-item, Center for Epidemiologic Studies Depression Scale (CES-D). Aerobic exercise totaling 60 minutes a week was prescribed for 50 patients, while the other 50 patients did not perform any exercise. There was no significant difference in the CES-D score at baseline between

the groups. The results showed a significant reduction of depressive symptoms in the exercise group. After three months, the mean CES-D score decreased from 20.2 to 14.8 in the exercise group while the mean CES-D score was 20 in the control group at both baseline and three months ($p<0.001$).

New patterns, such as a new exercise routine, that are embraced during pregnancy could potentially affect a woman's health throughout her lifespan.[23] The American College of Obstetricians and Gynecologists and the American College of Sports Medicine recommend an accumulation of 30 minutes or more of moderate intensity exercise preferably seven days a week. An activity with an energy requirement of three to five metabolic equivalents (METS) is considered moderate activity. For example, a brisk walk at about three to four miles per hour is considered moderate activity. There are some contraindications to exercise for some pregnant women based on underlying conditions, so it is recommended that women interested in pursuing exercise during pregnancy should talk with their physician first to establish a safe exercise program.

Exercise for pregnant women should include aerobic exercise that uses large muscle groups in a continuous rhythmic contraction.[23] Activities such as walking, jogging, running, dancing and swimming, which are easily monitored for intensity, would be useful. Before prescribing modes of exercise with excessive joint stress, women should be aware that due to the increased weight gain during pregnancy, they will experience an increase in forces at the joints during weight bearing exercise, including more joint discomfort. The prescriber should carefully balance weight bearing versus non weight bearing activities. In addition to aerobic training, low weight resistance training and flexibility exercises should be incorporated into the exercise plan. Isometric or heavy resistance weight lifting should be completely avoided during pregnancy as such activities may result in vasoconstrictive effects.

If the pregnant woman has not engaged in physical activity before, the proper exercise intensity should be at about 50 to 60 percent of the woman's maximum oxygen uptake.[23] Women who were active before pregnancy may exercise at 60 to 85 percent of their maximum oxygen uptake. An easier way to track exercise intensity is to use ratings of perceived exertion on the six to 20 scale. A score of 12 to 14 is considered to be moderate intensity exercise.

Women participating in any type of exercise need to review proper hydration and nutrition.[23] Pregnant women have an average core body temperature that is 1.5 degrees Celsius warmer than that of nonpregnant women. Because of this increase in temperature, pregnant women will sweat more during exercise and will need to drink more water than they were used to drinking before pregnancy. In addition to drinking more water, pregnant women should exercise in a controlled environment with air conditioning. Following the above suggestions with physician approval, pregnant women with an increased likelihood of having depression during pregnancy can participate in moderate intensity exercise.

Risks Associated With Untreated Depression During Pregnancy

It is known that evaluating the risks versus the benefits of pharmacologic treatment of depression during pregnancy is imperative. However, there are also health risks if the patient refuses pharmacologic treatment and is unstable with psychotherapy alone. Left untreated, depression during pregnancy is one of the greatest risk factors for developing postpartum depression.[14] Associated outcomes with unmanaged depression postpartum include increased rates of maternal suicide as well as infanticide. Mothers experiencing postpartum depression have been associated with harsher parenting behavior compared to those not experiencing postpartum depression, resulting in decreased safety and development of the child. Additionally, higher rates of infantile colic have been noted in this population as well as decreased mother-infant bonding.

Identification and Management of Postpartum Depression

Identification

Prenatal focus on psychological well-being may help to identify women at risk of postpartum depression. Forman and colleagues conducted a prospective follow-up study based on questionnaires at an antenatal care clinic and delivery ward at Aarhus University Hospital located in Denmark.[24] The researchers evaluated psychiatric disease, distress and social support during pregnancy as well as four months postpartum using the Edinburgh Postnatal Depression Scale. Forman and colleagues enrolled 5,091 women giving birth between January 1994 and December 1995 who completed the questionnaires. It was found that 5.5 percent (n=281) of these women were suffering from postpartum depression (defined as a score of 13 or higher on the Edinburgh Postnatal Depression Scale). In a multivariate regression analysis, the researchers determined several risk factors were highly linked to postpartum depression. The greatest association of risk for postpartum depression was psychological distress in late pregnancy with an OR of 6.3 (95 percent CI 4.4-9.1)), followed by social isolation during pregnancy (OR 3.6 (95 percent CI 1.9-7.01)) and a positive history of prepregnant psychiatric disease (OR 2.1 (95 percent CI 1.4-3.21)). The authors estimated one out of three women with both psychological distress and social isolation late in pregnancy will develop postpartum depression. Complications during pregnancy and delivery were not associated with development of postpartum depression. This study shows the importance of focusing on women during their pregnancy to help identify those at risk of developing postpartum depression.

Management

Nonpharmacologic options have also been found to help treat postpartum depression. Psychotherapy is recommended as first-line treatment for patients with mild to moderate depression and no previous history of depression.[19] O'Hara and colleagues looked specifically at IPT as a way to treat

postpartum depression.[25] A total of 99 postpartum women with major depression were assigned to either receive IPT or were put on a waiting list. Interpersonal psychotherapy was administered in 12 one hour long individual sessions during a 12 week period. Self-reports, such as HAM-D, were given every four weeks to evaluate depressive symptoms and social adjustments. The HAM-D scores in those receiving IPT dropped from 19.4 to 8.3, which was significantly greater than those in the waiting list group in which patients' scores declined from 19.8 to 16.8 ($p=0.003$). Furthermore, O'Hara and colleagues noted the patients' Beck Depression Inventory Score (BDI). The BDI score for women receiving IPT declined from 23.6 to 10.6 over 12 weeks, which was another significant difference from the waiting list group whose scores went from 23.0 to 19.2 ($p<0.001$). Women receiving IPT also had a significant improvement on the Postpartum Adjustment Questionnaire and the Social Adjustment Scale ($p<0.001$). These results suggest that IPT is as efficacious in the treatment of postpartum depression as it is for depression during pregnancy.

Exercise Benefits

Some women may use exercise as a nonpharmacologic treatment for postpartum depression. In a study conducted by Songoygard and colleagues, it was found that women who were not physically active before pregnancy, but exercised during pregnancy, had a lower rate of postpartum depression.[26] According to the Guidelines by the American College of Obstetricians and Gynecologists, women who delivered without complication should resume their exercise gradually and with approval of a physician.[23] The exercise program should be individualized and light intensity at first. Some women can start light intensity exercise days after delivery; however, that is not the case for all mothers. Many morphological and physiological changes are still occurring in a woman's body four to six weeks after delivery, and exercise may not be recommended for some women until after this time. While exercise can be beneficial for women, women should always consult their physicians to make sure exercise is safe to resume postpartum.

Pharmacologic Considerations

Antidepressants are indicated for patients with moderate to severe postpartum depression or if they have responded to antidepressant therapy in the past.[19] The major concern with initiation of antidepressant therapy is the question of safety with breastfeeding. The U.S. National Library of Medicine maintains a database on the effects of drugs and chemicals on breastfed infants called LactMed. LactMed is a subset of the toxicology data network TOXNET.[27] A summary of the recommendations from this group with regard to the safety of antidepressant use during breastfeeding is shown in Table 2. A number of authoritative reviews have been written on this subject and all suggest mothers should continue to breastfeed if antidepressant therapy is initiated.[28-33] Sertraline or paroxetine should be suggested to mothers first, as these two medications are shown to be excreted in breast milk in negligible amounts and have not been detected in serum of the infant. Although there is some concern shown in those taking fluoxetine, citalopram or venlafaxine, due to low levels detected in breast milk, it should not be advised to switch to a "safer" alternative if the mother has been treated with one of these medications previously. In all cases, if an antidepressant is initiated in a mother who is breastfeeding, the infant should be monitored closely for excessive sedation, irritability, poor feeding or poor weight gain.[34]

The Role of Health Care Professionals in Depression Education and Management

The American Psychiatric Association's Committee on Research on Psychiatric Treatments has identified the treatment of major depression during pregnancy as a leading area for improvement in clinical management which should be a priority.[34] A model was created to give psychiatrists power to structure the problem through diagnostics and identification of treatment options for depression. Reproductive toxicity, the depression itself and how it could compromise health during pregnancy, the patient's willingness to participate and treatment outcomes should all be considered. The patient's loved ones, obstetrical physician and other health care professionals such as doctors and pharmacists should be involved in this ongoing process, as treatment response and progress should also be monitored. By applying this model, it ensures that clinicians look at critical aspects of the risks and benefits and include those considerations in their care of pregnant women with depression.

Pharmacist's Role

As part of an interdisciplinary team, pharmacists, along with other health care professionals, must use a collaborative approach to optimize the treatment outcomes for the patient; steps for appropriate collaborative treatment include the following:[14]

1. Individualize the treatment based on the mother's illness.
2. Educate the mother on the risks and benefits of pharmacologic treatment compared to nonpharmacologic treatment.
3. Provide firm clarity in recommendations, being careful not to send "mixed-signals" to the mother.
4. Implement a universal screening method when evaluating the mother.
5. Eliminate the stigma that is associated with depression and minimize the fears of the unknown by educating the mother on the dynamics of the disease.
6. Prioritize the mental and physical health of the mother and baby.

It is imperative that patients receive medication counseling from a pharmacist to achieve the best outcomes for their depression. A pharmacist can help patients manage depression during pregnancy through education, monitoring and assistance with adherence. It is important to support the mother's treatment decisions, whether she chooses pharmacologic or nonpharmacologic treatment. Pharmacists can monitor patients by asking the mother how she is doing on the medication, how she is feeling in regard to mood control, what signs and symptoms of depression she feels need addressed and if

Table 2. Safety of Antidepressant Medications During Breastfeeding.[27]

Drug	Concerns	Recommendation
Selective Serotonin Reuptake Inhibitors (SSRI)		
Sertraline	Negligible levels of sertraline found in breastmilk , but low levels detected of active metabolite; In preterm infants, potential for accumulation of drug and possible neonatal abstinence symptoms; Potential to impair lactation (class effect)	Considered one of the preferred antidepressants during breastfeeding
Paroxetine	Negligible levels of paroxetine found in breastmilk. Symptoms consistent with neonatal abstinence have been reported such as insomnia, restlessness and increased crying. Potential to impair lactation (class effect)	Considered one of the preferred antidepressants during breastfeeding
Fluvoxamine	Low levels detected in breastmilk, although not expected to cause adverse effects. Potential to impair lactation (class effect)	No adverse effects have been reported; can be considered an option
Fluoxetine	Compared to other SSRIs, has higher average amount of drug and active metabolite detectable in breast milk; Serum levels of the metabolite are detectable in infants less than 2 months of age; Some reports of adverse effects including increased crying, irritability, decreased sleep, reduced growth. Potential to impair lactation (class effect)	Not considered first choice in lactating women; can be used in conjunction with breastfeeding if mother was maintained effectively on this during pregnancy, or if other options are ineffective in managing the depression.
Citalopram	Levels detected in breastmilk and in serum of infants. Reports of minor behavioral side effects such as drowsiness and fussiness; no adverse effects on development noted in one year follow-up. Potential to impair lactation (class effect)	Not considered first choice in lactating women; can be used in conjunction with breastfeeding if mother was maintained effectively on this during pregnancy, or if other options are ineffective in managing the depression.
Escitalopram	Levels detected in breastmilk and in serum of infants. One report of necrotizing enterocolits in breastfed newborn whose mother was treated with escitalopram, although causality not confirmed. Potential to impair lactation (class effect)	Lower levels detected in breastmilk as compared to citalopram so may be preferable choice between these two agents.

Table 2 *(continued)*. Safety of Antidepressant Medications During Breastfeeding.[27]

Drug	Concerns	Recommendation
Serotonin Norepinephrine Reuptake Inhibitors (SNRI)		
Venlafaxine	Levels of venlafaxine and its metabolite desvenlafaxine are noted in breastmilk and in plasma of breastfed infants. Potential to impair lactation (class effect)	Not considered first choice in lactating women due to higher levels noted in breastmilk and infant's serum; can be used in conjunction with breastfeeding if mother was maintained effectively on this during pregnancy, or if other options are ineffective in managing the depression. No adverse effects in infants reported, but infants should be monitored closely due to potential drug exposure.
Desvenlafaxine	Levels of desvenlafaxine are detected in breastmilk and in plasma of breastfed infants, although total drug exposure is about half of that noted with venlafaxine. Potential to impair lactation (class effect)	Not considered first choice, but may be preferable to venlafaxine if an SNRI is desired. No adverse effects in infants reported, but infants should be monitored closely due to potential drug exposure.
Tricyclic Antidepressants (TCA)		
Nortriptyline	Low levels detected in breastmilk, generally not detected in serum of the infant.	Considered one of the preferred antidepressants during breastfeeding if appropriate for the mother. No adverse effects in infants reported.
Imipramine	Low levels detected in breastmilk, generally not detected in serum of the infant.	Considered one of the preferred antidepressants during breastfeeding if appropriate for the mother. No adverse effects in infants reported.
Desipramine	Low levels detected in breastmilk, generally not detected in serum of the infant.	Not expected to cause any adverse effects although limited information available.
Miscellaneous		
Bupropion	Low levels detected in breastmilk and minimal serum levels noted in infants. Two case reports of infant seizures possibly related to bupropion; In both cases, infants were exposed after six months of age.	Not considered first choice in lactating women; can be used in conjunction with breastfeeding if mother was maintained effectively on this during pregnancy, or if other options are ineffective in managing the depression.
Maprotiline	Low levels detected in breastmilk; no information on serum levels in infants.	No reports of adverse effects, although information is very limited to make a strong recommendation for safe use.
Duloxetine	Low levels detected in breastmilk; no reports of measureable serum levels in infants. Potential to impair lactation (class effect)	No reports of adverse effects, although information is very limited to make a strong recommendation for safe use.
Mirtazapine	Low levels detected in breastmilk; negligible levels detected in serum of infants. Unclear if any effects on lactation.	No reports of adverse effects, although information is very limited to make a strong recommendation for safe use.

she has any questions about her medication and pregnancy. A pharmacist can counsel on both antidepressant use during pregnancy as well as the effects of untreated depression during pregnancy to help the mother make the most informed choice of whether to continue or discontinue her chosen therapy. The pharmacist can also review the diagnosis and severity of depression and help to identify any comorbidities that may complicate treatment.

Pharmacists can continue to help to manage depression during the postpartum period. For example, a pharmacist can explain the benefits that breastfeeding has to the newborn and any associated risks with medications and breastfeeding. The pharmacist can help the mother make the most informed decision about whether to continue therapy and breastfeed, continue therapy and bottle feed or postpone therapy to breastfeed based on the risks versus benefits of the medication.

Follow-up with the patient is another key aspect of care in which pharmacists can participate. Pharmacists can follow up with the patient via outreach phone calls and counseling appointments to ensure that the patient is benefitting from the therapy. The pharmacist should emphasize the importance of adherence to antidepressant medications, as it takes time for some antidepressants to take full effect. The pharmacist should discuss side effects and best practices for taking the medications for the best chance for improvement.

Exercise Physiologist's Role

In order for prescribed exercise treatment to work well, it is crucial to have the patient follow up consistently with an exercise physiologist.[23] The exercise physiologist will monitor well-being and any complications and report them back to the physician and pharmacist. An integrated system between physician, pharmacist and exercise physiologist is needed to assure the patient's depression is treated properly. The exercise physiologist will make any changes deemed necessary or beneficial to the patient after careful discussion with the pharmacist and physician.

Conclusion

With more evidence of depression in pregnancy and postpartum depression getting more attention in the media, it is becoming critical that health care professionals are aware of related treatment considerations, risks, benefits and potential side effects. In addition, an interdisciplinary team of health care providers is instrumental in helping patients treat and manage depression prior to, during and after pregnancy. Health care professionals can be prepared to answer patient questions, give advice and collectively formulate an individualized treatment plan for the patient. Health care providers should be aware of risk factors for depression as well as the many options that can be used to treat depression in pregnancy. Providing both pharmacologic and non-pharmacologic therapies to treat expectant mothers and women postpartum with a diagnosis of depression will benefit not only the new mother but also the health of the infant.

References

1. Bennett, HA, Einarson A, Taddio A, Koren G, Einarson TR. Depression during pregnancy. Clin Drug Investig. 2004;24(3):157-79.
2. Halverson J. Medscape [Internet]. New York (NY): Medscape; c1994-2017. Depression; [updated 2016 Apr 29; cited 2017 Feb1]; [about 11 screens]. Available from: emedicine.medscape.com/article/286759-overview#a1.
3. Pubchem Open Chemistry Database [Internet]. Bethesda (MD): National Center for Biotechnology Information, U.S. National Library of Medicine. CID: 5202, Serotonin; 2004 Sep 16 [updated 2017 May 6; cited 2017 May 9]. Available from: pubchem.ncbi.nlm.nih.gov/compound/5202.
4. Teter CJ, Kando JC, Wells BG. Major depressive disorder. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L editors. Pharmacotherapy: A Pathophysiologic Approach [Internet]. 10th ed. New York (NY): McGraw-Hill. 2017 [cited 2017 Apr 28]. Available from: 0-accesspharmacy.mhmedical.com.polar.onu.edu/content.aspx?bookid=1861&sectionid=146064868.
5. Castro RTA, Anderman CP, Glover V, O'Connor TG, Ehler U, Kammerer M. Associated symptoms of depression: patterns of change during pregnancy. Arch Womens Ment Health. 2017;20:123-8.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
7. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. JAMA Psychiatry. 2010 Oct:1-152.
8. Bondy B. Pathophysiology of depression and mechanisms of treatment. Dialogues Clin Neurosci. 2002;4(1):7-20.
9. Gentile S. Untreated depression during pregnancy: short- and long-term effects in offspring: a systematic review. Neuroscience. 2017 Feb 7;342:154-66.
10. Smith KF, Brunner Huber LR, Issel LM, Warren-Findlow J. The association between maternal depression during pregnancy and adverse birth outcomes: a retrospective cohort study of PRAMS participants. J Community Health. 2015;40:984-92.
11. Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Obstet Gynecol. 2009 Sep;114(3):703-13.
12. Pearlstein T. Perinatal depression: treatment options and dilemmas. J Psychiatry Neurosci. 2008;33(4):302-18.
13. Manber R, Schnyer RN, Lyell D, Chambers AS, Caughey AB, Druzin M, et al. Acupuncture for depression during pregnancy: a randomized controlled trial. Obstet Gynecol. 2010 March;115(3):511-20.
14. Payne JL, Meltzer-Brody S. Antidepressant use during pregnancy: current controversies and treatment strategies. Clin Obstet Gynecol. 2009 Sep;52(3):469-2.
15. Lexicomp [Internet]. Hudson (OH): Lexi-Comp, Inc. c1978-2016. [cited 2017 Mar 20]. Available from: online.lexi.com/lco/action/home.
16. Drugdex [Internet]. Greenwood Village (CO): Thomson Reuters, Inc. c1974-2010 [cited 2017 Mar 20]. Available from: www.micromedex.com/products/drugdex/.
17. Pregnancy and Lactation Labeling (Drugs) Final Rule. US Food and Drug Administration 2014 Dec 14. [cited 2017 Jul 19] Available from: www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.
18. American College of Obstetricians and Gynecologists (ACOG). Use of psychiatric medications during pregnancy and lactation. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Apr. 20 p. (ACOG practice bulletin; no. 92).
19. Becker M, Weinberger T, Chandy A, Schmukler S. Depression during pregnancy and postpartum. Curr Psychiatry Rep [Internet]. 2016 [cited 2017 Jul 19];18:[9 p.] Available from: www.researchgate.net/profile/Ann_Chandy/publication/294729896_Depression_During_Pregnancy_and_Postpartum/links/5747068f08ae707fe21e348e/Depression-During-Pregnancy-and-Postpartum.pdf.
20. Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2008 Apr;69(4):644-51.
21. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006 Feb

1;295(5):499-507.
22. El-Rafie MM, Khafagy GM, Gamal MG. Effect of aerobic exercise during pregnancy on antenatal depression. Int J Womens Health. 2016 Feb 24;8:53-7.
23. Artal R, O'Toole M. Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period. Br J Sports Med. 2003;37:6-12.
24. Forman DN, Videbech P, Hedegaard M, Salvig JD, Secher NJ. Postpartum depression: identification of women at risk. Br J Obstet Gynaecol. 2000 Oct;107:1210-7.
25. O'Hara MW, Stuart S, Gorman LL, Wenzel A. Efficacy of interpersonal psychotherapy for postpartum depression. Arch Gen Psychiatry. 2000 Nov;57:1039-45.
26. Songoygard KM, Stafne SN, Evensen KAI, Salvesen KA, Vik T, Morkved S. Does exercise during pregnancy prevent postnatal depression? Acta Obstet Gynecol Scand. 2012;91:62-7.
27. LactMed [Internet]. Bethesda (MD): National Library of Medicine. 2017. [cited 2017 Jul 19]; Available from: toxnet.nlm.nih.gov/newtoxnet/lactmed.htm.
28. Weissman AM, Levy BT, Hartz AJ et al. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am J Psychiatry. 2004;161:1066-78.
29. The Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #18: use of antidepressants in nursing mothers. Breastfeed Med. 2008;3:44-52.
30. Lanza di Scalea T, Wisner KL. Antidepressant medication use during breastfeeding. Clin Obstet Gynecol. 2009;52:483-97.
31. Berle JO, Spigset O. Antidepressant use during breastfeeding. Curr Women's Health Rev. 2011;7:28-34.
32. Orsolini L, Bellantuono C. Serotonin reuptake inhibitors and breastfeeding: A systematic review. Hum Psychopharmacol. 2015;30:4-20.
33. Berle JO, Steen VM, Aamo TO et al. Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes. J Clin Psychiatry. 2004;65:1228-34.
34. Bobo WV, Yawn BP, Concise review for physicians and other clinicians: postpartum depression. Mayo Clin Proc. 2014;89(6):835-44.
35. Wisner KL, Zarin DA, Holmboe ES, Appelbaum PS, Gelenberg AJ, Leonard HL, et al. Risk-benefit decision making for treatment of depression during pregnancy. Am J Psychiatry. 2000 Dec;157(12):1933-40.

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Assessment Questions

1. Which of the following is not a typical symptom of depression in pregnancy?
    A. Decreased energy
    B. Lack of concentration
    C. Sensitivity to criticism
    D. Feeling worse in the evening

2. DSM-V criteria for depression includes all of the following EXCEPT:
    A. Depressed mood or anhedonia
    B. Weight and appetite changes
    C. Insomnia, fatigue, feelings of worthlessness
    D. Metabolic changes such as dyslipidemia

3. The first-line treatment option for treating a new onset of depression during pregnancy is:
    A. SSRI
    B. Nonpharmacologic therapy
    C. SNRI
    D. TCA

4. Which of the following SSRIs is not correctly paired with its associated adverse event profile?
    A. Paroxetine: fetal cardiac malformations
    B. Citalopram: spontaneous abortions
    C. Escitalopram: risk of withdrawal symptoms when used during the third trimester
    D. Nortriptyline: congenital abnormalities

5. It takes about _____ for most antidepressants to start to relieve some depression symptoms, and it takes about _____ to reach the full antidepressive effect.
    A. 1 week, 4 weeks
    B. 2 weeks, 4 weeks
    C. 2 weeks, 6-8 weeks
    D. 4 weeks, 6-8 weeks

6. Which is not a role of the pharmacist in the treatment of depression during pregnancy?
    A. Explain the benefits of breastfeeding and its associated risk
    B. Help the mother make an informed decision about continuing therapy
    C. Follow up with the patient, emphasizing the importance of medication adherence
    D. Choose a treatment option for her, without her input

7. What is the type of exercise recommended in the treatment of depression during pregnancy?
    A. Anaerobic, high velocity, continuous contractions involving small muscle groups
    B. Anaerobic, low velocity, continuous contractions involving large muscle groups
    C. Aerobic, continuous, rhythmic contractions involving large muscle groups
    D. Aerobic, noncontinuous, rhythmic contractions involving large muscle groups

8. All of the following are appropriate approaches for depression management in a female patient with depression who is trying to conceive EXCEPT:
    A. Immediately discontinue the use of antidepressant medications before conception
    B. Consider decreasing the dose of antidepressants if depression is controlled prior to conception
    C. Consider discontinuing the antidepressant by tapering down if depression is controlled prior to conception
    D. Consider switching the patient to the safest antidepressant drug therapy if not currently prescribed

9. If deemed an appropriate option for treatment, what is a viable first-line nonpharmacologic option for depression during pregnancy?
    A. Interpersonal therapy (IPT)
    B. Massage therapy
    C. Yoga
    D. Meditation

10. Which antidepressant has been shown to be excreted in breast milk in an amount undetectable in an infant?
    A. Venlafaxine
    B. Sertraline
    C. Citalopram
    D. Fluoxetine

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