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<https://reachmd.com/programs/cme/optimizing-ppd-diagnosis-and-treatment-the-role-of-neuroactive-steroids-and-multidisciplinary-care/26913/>

Released: 12/10/2024

Valid until: 12/10/2025

Time needed to complete: 45 minutes

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Optimizing PPD Diagnosis and Treatment: The Role of Neuroactive Steroids and Multidisciplinary Care

Announcer:

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Dr. Payne:

Welcome to our program today. We'll be talking about optimizing postpartum depression diagnosis and treatment and focus on the role of neuroactive steroids and multidisciplinary care.

I'm Dr. Jennifer Payne. I'm professor and vice chair of research at the Department of Psychiatry and Neurobehavioral Sciences at the University of Virginia. And joining me is Dr. Christina Deligiannidis, who's the director of women's behavioral health at Zucker Hillside Hospital at Northwell Health. She is a professor of psychiatry, molecular medicine, and obstetrics and gynecology at the Donald and Barbara Zucker School of Medicine at Hofstra Northwell.

These are our disclosures.

And next, these are our objectives.

Today, I'll get us started by talking about from delayed diagnosis to early detection, improving postpartum depression screening practices.

So first, I'd like to talk about, how do we define postpartum depression? There are a number of postpartum psychiatric illnesses. I've highlighted 2 of them here; the first is postpartum blues, and the second is postpartum depression. But I would be remiss if I didn't mention that there are a host of other postpartum psychiatric illnesses, including postpartum psychosis, postpartum anxiety, postpartum obsessive-compulsive disorder, and postpartum post-traumatic stress disorder.

Postpartum blues is really a normal phenomenon. It's described as having mood lability, often accompanied by crying spells, some anxiety, some trouble sleeping. Postpartum blues usually start within 2 to 3 days of delivery and typically last maybe a few days and certainly last less than 2 weeks. There's no significant impact on functioning. There are no suicidal thoughts. And about 80% of women experience the blues, and they are thought to be secondary to the dramatic hormonal shifts that women undergo after delivering a baby.

In contrast, postpartum depression meets full DSM criteria for a major depressive episode. The symptoms are present for most of the day, every day for 2 weeks or longer, and the symptoms are severe enough that they cause functional impairment. So a woman with postpartum depression will not function in one or more areas of her life. Postpartum depression can also include severe symptoms, including suicidal ideation or even thoughts of infanticide. And most patients with postpartum depression experience anhedonia and anxiety. Symptoms of postpartum depression can start during pregnancy and then continue postpartum, but they can also start in the immediate postpartum time period.

The DSM-IV used the term postpartum to describe a depression that began either during pregnancy or within the first 4 weeks postpartum. The DSM-5 has now moved to using the term peripartum. And this really acknowledges the fact that about 50% of cases of postpartum depression actually begin during pregnancy.

So postpartum depression is even more common in women with preexisting mood disorders. So if we look at women with a preexisting diagnosis of major depression or bipolar disorder, about 20% to 30% of them will develop a postpartum depression that begins in the immediate postpartum time period. If we include cases that begin during pregnancy, about 50% of them will develop postpartum depression.

So what are the risk factors for postpartum depression? Well, perhaps this is obvious from what I just said, but having a history of major depression or bipolar disorder increases the risk for the development of postpartum depression. In addition, we know that postpartum depressions actually run in families with major depression and bipolar disorder. So having a family member with a history of postpartum depression increases an individual's risk as well. In addition, once you've had a history of postpartum depression, you are at increased risk for experiencing postpartum depression with subsequent pregnancies. Finally, probably one of the biggest risk factors is being depressed during pregnancy. Being depressed during pregnancy almost guarantees that a woman will be depressed during the postpartum time period.

There are a number of psychosocial risk factors that also increase the risk for postpartum depression, so any sort of stress, so financial stressors, partner dissatisfaction, a lack of social support, a history of or current physical or sexual abuse, and a history of adverse childhood experiences also increase the risk for postpartum depression.

And then finally, having a history of significant premenstrual mood symptoms is also associated with an increased risk of postpartum depression, because that's really a marker for being sensitive to times of reproductive hormonal change.

It is important to note that there's no evidence that the risk for major depression increases during pregnancy, but that a number of large studies have shown that the postpartum time period has an increased risk for the development of major depression. I've listed one there in the slides. There was a study by Vesga-Lopez in 2002 called the National Epidemiologic Survey on Alcohol and Related Conditions. And they actually interviewed over 14,000 women with a pregnancy in the past year, and they found that there was really no increased risk for major depression during pregnancy compared to nonpregnant females. However, the postpartum time period carried an elevated risk with an odds ratio of 1.52. So we know the postpartum time period is an increased risk period for the development of a major depressive episode.

Why do we think postpartum time period increases the risk for psychiatric illness? Well, I think there are a number of reasons. One is simply sleep deprivation. When a woman is not sleeping well, she may be at risk for developing a depressive episode, anxiety, and other psychiatric illness. In addition, although it's wonderful, it is stressful to become a parent and to care for a newborn. And then finally, many women discontinue their medications for pregnancy if they have a previous history of major depression or bipolar disorder, and this significantly increases the risk that they will become ill with their preexisting mood disorder, either during pregnancy or during the postpartum time period.

In addition, we know that there are significant hormonal changes associated with pregnancy and childbirth. So in the slide before you, you can see that estrogen and progesterone increase really dramatically during the course of pregnancy. And then after delivery, they plummet. There's just a clear drop-off of estrogen and progesterone hormone levels. And in women with a sensitive central nervous system, this can trigger psychiatric illness.

This was really elegantly demonstrated by Bloch et al in an elegant study in 2000, in which he took women who had a history of postpartum depression and women who had a history of a pregnancy but no postpartum depression, and really exposed them to hormonal changes that mimicked what women go through, through pregnancy, and then in the postpartum time period. And they found that only women with a history of postpartum depression developed mood symptoms. The women who'd had a previous pregnancy but no postpartum depression did not develop mood symptoms when they underwent these hormonal changes in a blinded fashion.

So what is the impact of postpartum depression? Well, it's actually very significant. In the United States, the maternal mortality rate is high and it continues to rise. And what you can see here is data from the CDC and the US and data comparing the United States maternal mortality rates to other countries. And you can see that the United States has double the rate of maternal mortality of other developed countries. And that almost becomes triple compared to Japan and Germany. In addition, the US maternal mortality rates are really high and are continuing to increase in minoritized populations in the United States. And you can see that the highest rates are found in the non-Hispanic Black population in the United States.

In addition, mental health conditions are the leading cause of maternal mortality in the United States. So maternal suicide is a major

cause of death in pregnancy and accounts for about 20% of all postpartum deaths. And psychiatric disorders are the leading cause of indirect maternal deaths. Even though suicide is a rare event during pregnancy and is generally lower than the rate in the general population, it is one of the leading causes of maternal mortality and is preventable. And it is really striking that mental health conditions are the leading cause of maternal mortality in the United States.

We know that postpartum depression causes a significant economic cost. So in 2017, one study estimated the cost to be \$14 billion in the United States alone. And there's really a myth that women should tolerate being depressed during pregnancy and postpartum for the sake of the baby. And the fact is, the literature is quite clear that being depressed during pregnancy and in the postpartum time period has significant negative impacts, not only on the woman, but the exposed child as well.

So we know that when Mom is depressed during pregnancy, is experiencing antenatal depression, that that is strongly associated with preterm birth, low birth weight, gestational diabetes, preeclampsia, and a higher rate of C-section. And all of those negative consequences for the pregnancy actually have long-term health consequences for the child. We know that when a child is born prematurely that they have a higher rate of cardiovascular disease in their 40s and 50s than when babies are born on time, for example. And so being depressed during pregnancy is not benign and is really considered an exposure for the developing child.

Mothers with postpartum depression talk less to their babies, and that can result in the slower language development that we see for children exposed to postpartum depression. When moms have postpartum depression, they're less likely to use their car seat and are less likely to adhere to healthcare recommendations for their children.

So we know that mothers being depressed during pregnancy and during a postpartum time period have a whole host of negative consequences for exposed children.

How do we identify postpartum depression? Well, postpartum depression really requires a diagnosis of major depression in the postpartum time period. So symptoms meet criteria for a major depressive episode. It's important to remember that symptoms can begin during pregnancy and that the DSM-5 now uses the term peripartum depression in order to acknowledge that depression can start during pregnancy and not just during the postpartum time period. I've listed the criteria here for you, but essentially, women must have 5 or more of nine symptoms, including the first one, which is a depressed mood and decreased interest or pleasure. There are generally changes in weight and appetite, changes in sleep, patients can appear to be psychomotor retarded or agitated. They generally have decreased energy and feelings of being worthless or guilt, decreased concentration, and they can have thoughts of death or suicide. In addition, the symptoms must be significant enough that it causes significant distress and impairment in functioning, and the symptoms cannot be better explained by a substance use disorder, other medical conditions, bipolar disorder, and is not explained by other psychiatric diagnoses.

There are a number of screening tools that can be used. So the Edinburgh Postnatal Depression Scale is a scale that was specifically developed for use during pregnancy and the postpartum time period. The Patient Health Questionnaire-9 is frequently used in healthcare settings and meets criteria for a diagnosis of major depression. And then the Mood Disorder Questionnaire helps physicians assess for bipolar disorder, and I'll talk about each of these in turn.

This is the EPDS, or the Edinburgh Postnatal Depression Scale. As I mentioned, it's specific to pregnant and postpartum women. A score of greater than 10 is 90% sensitive in picking up a diagnosis of major depression, and a score of 13 or higher is extremely strongly correlated with meeting criteria for a major depressive episode. Take note of question 10. Question 10 asks about suicidal thoughts, and so if you're using the scale in a clinic, it is important that someone always check question 10 and ask the woman about those kinds of thoughts and determine whether she's safe.

This is the PHQ-9, which is used in many healthcare settings to screen for major depressive disorder. The amount of the score really correlates with the severity of symptoms of major depression. So a score of 1 to 4 is minimal symptoms of depression, a score of 5 to 9 is considered mild depressive symptoms, a score of 10 to 14 is moderate, 15 to 19 moderately severe, and then any score over 20 is correlated with severe depression.

This is the Mood Disorders Questionnaire which really screens for bipolar disorder. The reason to screen for bipolar disorder in someone who's experiencing a major depressive episode is that if someone actually has bipolar disorder, starting an antidepressant for that particular patient may be dangerous and may trigger a hypomania or a manic episode. And the first item is very long. It really lists manic symptoms, and then items 2 through 5 address symptom overlap, the amount of problems in terms of functioning that someone may have had, and questions whether there's a family history or prior diagnosis of bipolar disorder. Bipolar disorder is strongly genetic, so asking about a family history of bipolar disorder can be helpful in determining if someone is at risk for bipolar disorder. If there's a positive screen on this scale, it's important to have a comprehensive evaluation for bipolar disorder, and I would refer any patient who screens positive on this to a mental health professional for further care.

So what is the conventional approach to treatment for postpartum depression? And is there room for improvement? So the standard treatment options for postpartum depression are really the standard treatment options for major depression. So we recommend that anybody who's diagnosed with major depression, whether it's postpartum or not, that they seek out psychotherapy, including certain therapy, such as cognitive behavioral therapy or interpersonal therapy, if at all possible. Studies have repeatedly shown that including psychotherapy in the treatment of major depression leads to improved outcomes. And I always say it's like if you have surgery, you really need to have physical therapy afterwards. Just doing the surgery rarely results in great outcomes without rehabilitating someone postsurgically with physical therapy. Standard antidepressant medications are used for postpartum depression, and I'll talk more about that in just a minute. But you can also use light box therapy, there's transcranial magnetic stimulation, and electroconvulsive therapy are all treatments that can be used, particularly for more severe forms of the illness.

In terms of antidepressant therapies for postpartum depression, in patients who had previously been diagnosed with major depression and they've been successfully treated with a particular antidepressant, if they develop postpartum depression, use the antidepressant that got them well previously. If they've never had a major depressive episode before and they develop postpartum depression, we generally recommend starting with a selective serotonin reuptake inhibitor. We know that those medications are fairly well tolerated, and there's evidence that they are useful for postpartum depression. If a patient has tried and failed several different antidepressants, try to use a different class of medication. So if a patient with postpartum depression has failed 2 or 3 SSRIs previously, it would be very reasonable to switch to a different class of medication, such as the SNRIs.

And I just want to remind you that an adequate trial is defined as 8 weeks at a therapeutic dosage. And there is a scale that rates whether someone has had adequate trials of antidepressants in the past, and that's called the ATRQ, and they require at least 6 weeks. But in general, we try to define an adequate trial as 8 weeks or longer at a therapeutic dosage.

There are a number of limitations with the current standard of care antidepressant therapy. The first, and maybe the foremost, is the onset of action. It really takes time to respond to the standard antidepressant treatment. With current oral antidepressants, on average, it takes 6 to 8 weeks for patients to achieve a response or remission to that antidepressant. And that can be a very long time, particularly for someone who's caring for a newborn.

In addition, efficacy is an issue. Not everybody responds to our standard antidepressant treatment. There are low rates of remission and substantial relapse rates, and those remain challenges in managing major depression and postpartum depression. So about 50% of patients given a standard antidepressant will have a response to the antidepressant, and about 25% to 30% will achieve remission. So we are not looking at high rates of efficacy.

In addition, improvements in functioning and quality of life tend to lag behind symptomatic relief. If you're a psychiatrist, you generally can recognize when someone is starting to turn the corner and get better from their depression, but the improvement in their own functioning and quality of life tends to take a longer time than that initial response.

In addition, current therapies are associated with significant side effects, which can interfere with adherence. I cannot tell you how many patients I've treated who have stopped their antidepressant treatment once they get better because of side effects. We know that adverse events are greatest with selective serotonin reuptake inhibitors, but we see them with all antidepressant treatments, and about 90% of patients experience at least one adverse event with antidepressant therapy. The common ones are weight gain, sexual dysfunction, insomnia, GI disturbances, and emotional blunting. And these side effects often lead to discontinuation and noncompliance with treatment.

So to conclude this section of our talks today, postpartum depression is common, serious, and has deleterious effects on maternal pregnancy and child outcomes. The increased risk of psychiatric illness during the postpartum time period is likely due to a combination of factors including genetics, hormonal change, stress, and sleep deprivation. Standardized screening for postpartum depression is easy and inexpensive with self-rating scales. And conventional antidepressants such as SSRIs can be used to treat postpartum depression, but really take weeks to work and have several common side effects.

So now I'd like to turn it over to Dr. Deligiannidis, who will be talking about advancing postpartum depression treatment, including pathophysiology of postpartum depression, current postpartum depression therapeutic strategies, and clinical implementation of neuroactive steroid. Dr. Deligiannidis.

Dr. Deligiannidis:

Thank you so much, Dr. Payne. So let's start a little bit about pathophysiology of peripartum or perinatal depression. Dr. Payne mentioned the importance of several of these mechanisms, and I wanted to even increase the number of mechanisms that are being researched in peripartum depression.

And so while the precise mechanism right now is unknown, there are several pathophysiological mechanisms or theories for perinatal depression pathophysiology, and those include several of these here. So as Dr. Payne mentioned, endocrine mechanisms, but also epigenetic and synaptic transmission mechanisms have been investigated. Neural network as well. Inflammatory mechanisms are proving to be very important to perinatal depression pathophysiology, as well as neurosteroid and stress mechanisms. And as I noted, the evidence to date really supports a multifactorial or multifactor mechanism of disease hypothesis. So it's rather the integration of many psychosocial and biological risk factors that we believe go into that risk for developing peripartum depression.

A leading hypothesis within this field is that women who are susceptible to developing peripartum depression may have a higher sensitivity of stress during pregnancy and after delivery, especially when these neuroactive steroid levels are changing, when these endocrine levels are changing. And there's some research that suggests that this sensitivity may correspond to an interaction between a neuroactive steroid called allopregnanolone and a very particular type of the GABA-A receptor in the hypothalamus, which is part of that stress circuit. So we'll talk a little bit about that, because much of this research really led to the development of this new category of antidepressants for postpartum depression. Then, obviously, there are other patient-level individuals. So whether a patient has risk factors that are genetic or epigenetic risk factors can affect whether she develops peripartum depression or not, but it also depends on her current levels of stressors and also supportive or resilience factors. So it is complex as the slide states, but we see these as really integrated and not just one mechanism.

I do want to talk about a little bit of exactly what are neuroactive steroids and how do they work on the brain. And so here you can see a cartoon figure of an astrocyte, which is a supportive cell in the brain, adjacent to a neuron. And within the astrocyte, you see that within the mitochondria, the brain itself, from cholesterol, manufactures neuroactive steroids. These neuroactive steroids are made in astrocytes and a few neurons in the brain, but they're also made outside of the brain as well. They're made by the ovaries and the adrenal glands and the placenta, for example. For these brain-based neurosteroids, they're made in the astrocytes, and then they interact with the postsynaptic membrane receptors. So here you see in blue, a picture of a GABA-A receptor, and you can see that the neurosteroid allopregnanolone interacts with that receptor. And so the classic definition is of a neuroactive steroid is a natural or synthetic steroid that act on the brain by either serving as with transcription factors for the regulation of gene expression, which is not depicted here, or by interacting with membrane-bound neurotransmitter receptors, which you see here.

And many of these neuroactive steroids are what are called positive allosteric modulators of the GABA-A receptor. So what that means is that when allopregnanolone binds to the GABA-A receptor in the presence of GABA, it causes the channel to open, and chloride flows into the postsynaptic neuron. And we have a lot of preclinical research that has really, over decades, shown us how important these neuroactive steroids are in both acute and chronic stress conditions and controlling stress in the brain.

Here's just a deeper dive into this, just to say that there are actually 2 main types of GABA-A receptors, synaptic and extrasynaptic, which you see depicted here on the left and on the right. And due to their configuration in the brain and in the receptor, the type of receptor it is, they have different effects on the postsynaptic neuron. And there's only certain subtypes of the GABA-A receptors that are sensitive to neuroactive steroid binding. So neuroactive steroids don't bind to every GABA-A receptor that they see, it's only a select subset of those GABA-A receptors that are sensitive to those neurosteroids.

And this is really important, because we've seen that perinatal depression is associated with neural network dysfunction. And the way we understand this is that the neuroactive steroids, via interacting with those GABA-A receptors, are regulating sort of the balance of inhibition and excitation in these brain networks. Because, as you know, GABA is the main inhibitory chemical in the brain, versus glutamate. So we believe that these neurosteroids are really sort of tweaking that network connectivity or that brain connections during this time. There's research that has shown that perinatal depression has been associated with misalignment or miscommunication in brain networks that are really important for emotion regulation in the brain, and those networks are listed here. We've also seen that this network disconnection or changes in the brain connectivity are associated with the blood levels of allopregnanolone in postpartum depressed individuals, which is correlated to the severity of their depression.

And so really, I think of it as all these different risk factors, these biological and social risk factors and psychosocial risk factors, sort of, at the very end of the day, are really manifesting themselves in this brain connectivity with these neurosteroids really having a central role in modulating this.

And just as I earlier noted, there are several underlying mechanisms of perinatal depression. I listed some of those in the leftmost column of this slide. But research indicates also that the neuroactive steroids that have been developed to treat postpartum depression may work to treat depression using very similar mechanisms. For example, ameliorating GABAergic dysfunction or hypothalamic pituitary adrenal axis dysfunction, neurosteroid deficits. So what we're seeing is that there's research both on what causes postpartum depression and then also how is it that these novel therapeutics, these FDA-approved neuroactive steroids actually have antidepressant effects for postpartum depression. We're seeing some of those mechanisms line up.

So where is this within treatment? So Dr. Payne beautifully outlined some of our current modalities that we have available or prior modalities that we've had evidence for. I'm just going to very briefly go over a couple of additional items and then introduce the novel FDA-approved medications for postpartum depression.

And so, as was noted, psychotherapy is very important. There's a strong evidence base for a variety of psychotherapies in the treatment of peripartum or perinatal depression, if I can use those interchangeably. And they're really indicated for mild/moderate peripartum or perinatal depression, can also be used in severe but definitely to start out with.

As Dr. Payne noted, the conventional antidepressants have been tested for moderate/severe postpartum depression. Although not FDA-approved for postpartum depression, they have been tested in clinical trials. And there was a nice meta-analysis that was done just a couple years back showing that there may be a benefit of SSRIs over placebo. But not everybody responds. Really, not everyone responds to everything, right? So it really is thinking personalized approach for each patient.

As noted, the treatment approach is one that does take time, that it requires titration until efficacy or tolerability, right, with recurrent checks on that to treat that acute episode. And then once reaching euthymia, so an absence of depressive symptoms not meeting criteria for major depressive episode any longer. Then we continue treatment called the continuation phase, to prevent relapse. As noted, we may often have to try 1, 2, or more medications to find the right fit.

And one important point for this patient population is that most of these conventional antidepressants are compatible with breastfeeding. I will say one of the databases most of us in this field uses an NIH database called LactMed. And the resources here get updated continually, so it's a web-based resource from the National Library of Medicine. And many authorities have said that relative infant doses less than 10% of the maternal dose may be compatible or acceptable for breastfeeding. And so there are a couple different caveats, but that's often a number that's quoted. And this is just a wonderful resource for clinical practice, because you can look up every FDA-approved medication, over the counter, under the counter, anything, herbal treatment. You can look to see what is known about its effects on breast milk and lactation and breastfeeding.

So to talk about the 2 FDA-approved medications, brexanolone was the first FDA-approved medication for the treatment of PPD in adults. It is an IV-administered exogenous version of allopregnanolone. So I told you, allopregnanolone is made naturally in the brain and some other places in the body. This is a synthetic version of that molecule, which is depicted on the right. And it is a positive allosteric modulator of both subtypes of the GABA-A receptor, the neurosteroid-sensitive ones. And the dose is typically 90 mcg/kg/hour. It can be reduced to 60 mcg/kg/hour if there's intolerance, but it's a 60-hour acute treatment.

There have been some breastfeeding studies. Those are in that database, LactMed, at the National Library of Medicine, and the relative infant doses is about 1.3%, so very similar to many, but not all, of the SSRI antidepressants. And there's more information at the dailymed.nlm.nih.gov. I love the DailyMed resource because it has all the labeling for the medicine.

So very quick 2 slides on the data from the clinical trials that supported FDA approval. This was a trial that we participated in. There was a couple of studies that were placebo-controlled RCTs of brexanolone, and so adult females with peripartum-onset major depression with moderate or severe symptoms entered the study, and they were randomized to a couple different options, so placebo or one of 2 doses of brexanolone, again, 60-hour infusion. And then the primary outcome was at 60 hours, so when the pump was turned off, that's when we looked at the change from baseline. How did the depression score change from before the pump was turned on to when it was turned off? And then we followed participants at day 7 and at day 30.

And what we reported and we published was that on the y-axis here you see the least squares mean change from baseline in that depression score. And on the x-axis, you see time in days. So you see a very rapid decline in depressive symptoms. And after 60 hours of infusion, participants treated with brexanolone had a statistically significant improvement of 17 points in their depression score versus 12.8 with significant reductions seen throughout with like a maintenance of effect through day 30.

And then what was really important about this finding was that we saw that it was very quick, right? It was a rapid onset. And also the amount of the effect, the effect size, was noteworthy as well. When you look at sort of what we call the drug effect, the change in the depression score from an investigational product versus placebo, it was 4.2 points here, which is really remarkable. The average that we saw from when you looked at all the FDA analyses of RCTs, of trials for depression, monotherapy for major depression, really, for the past several decades, this was a Stone et al 2022 study, they said the average drug effect was 1.82 in adults. So this was a greater than expected finding for the drug effect.

Now, adverse events associated with brexanolone, the most common are listed here and are sedation and somnolence. This is consistent with it working through GABAergic mechanisms, but also dizziness, presyncope, and vertigo. Loss of consciousness occurred in 3% to 5% of participants. And because of this, there's a boxed warning for excessive sedation and sudden loss of consciousness.

What does this look like? Sleepiness, falling asleep, and not responding because they're asleep.

So the data indicate that that loss of consciousness or altered state of consciousness is in about 4% of patients compared to 0% on placebo and that the participants who had that occur did recover when the pump was turned off, the dose was interrupted, they fully recovered within 15 to 60 minutes. But it is because of this risk that the FDA, when they approve the medication, that it's only prescribed through a Risk Evaluation Mitigation Strategy, or REMS, safety program. It's interesting, there was a recent data that looked at the rates of loss of consciousness since the medication was approved, and there have been no loss of consciousness reported in postmarketing surveillance, because they're monitoring this through the REMS.

And then zuranolone. So zuranolone is the second FDA-approved treatment for postpartum depression. It's not identical to allopregnanolone; it's a synthetic analog. And it's because there's this one addition of a cyano-pyrazole ring that's attached to the allopregnanolone structure. So it's not oral brexanolone; it's a different molecule, but it is a neuroactive steroid, and as I said, the backbone is allopregnanolone plus this group.

I joke that I'm not a chemist, but brexanolone has to be given as an effusion, because it's a very short half-life. Zuranolone is given as a once-daily treatment, an oral treatment. And so there must be something about that extra molecule that the group that's added that increases the oral bioavailability and makes it suitable for once-daily dosing. This was approved in 2023. And the breast milk studies to date have shown that the mean relative dose is less than 1% for zuranolone.

And briefly, the trials that supported FDA approval of zuranolone for postpartum depression. This was the first one called the ROBIN study, very similar study in adult females with severe peripartum depression, so in gestation with the first 4 weeks after delivery. They were randomized to placebos around 30 mg, they had a 14-day outpatient treatment course, and then we evaluated the change in depression score at day 15 and then again at follow-up at day 45. And you can see that after 2 weeks of outpatient treatment, patients treated with zuranolone had a statistically significant improvement of 17.8 points in their depression score, that HAMD-17, compared to 13.6 for placebo, with statistically significant maintenance of effect through the 4-week follow-up, day 45. And again, the drug effect was identical to brexanolone, a 4.2 difference in the HAMD.

And then we replicated that study but at 50 mg, and so very similar inclusion criteria, similar population, but again, a 14-day dose, but 50 mg versus placebo, and very similar data. So here, statistically significant improvement of 15.6 versus 11.6 at day 15. So that's the next morning after the last evening dose. Also to note here was that there was statistical significance of separation from placebo. You can see further on the left on day 3, so just after 2 doses. And it's a similar drug effect as brexanolone and zuranolone, just a different time frame.

And then side effects too, again, we see sort of a similar theme, so somnolence, dizziness, but also diarrhea and fatigue. No loss of consciousness was observed in either the trials, and there was no signal for increased suicidal ideation or suicidal behavior. There is a boxed warning, though, because this is a CNS depressant, for the impaired ability to drive or engage in hazardous activities. So patients should not drive or operate heavy machinery for at least 12 hours after taking the dose. And it is dosed in the evening usually around 8 pm.

A couple of clinical pointers before we close on this section, just to say that because it is a CNS depressant, we have to look at the whole patient, right? We want to avoid concomitant alcohol use, benzodiazepine use, opioid use, or other medicines that could increase impairment. Also zuranolone has not been tested in pregnant patients, and so these are postpartum treatments. It could have adverse fetal effects. So patients should, of reproductive potential, use effective contraception during treatment and for 1 week after the final dose. It can be taken as monotherapy or added to another antidepressant. Taken with fat-containing foods such as whole milk, full-fat yogurts, avocados, seeds, nuts, nut butters, things like that, or with a late dinner, helps with absorption. And again, this is a single acute treatment course of 50 mg for 14 days, but we usually check in around day 3 to see if there's any intolerable side effects. If that's the case, we would drop it down to 40 mg.

And within this field of neuroactive steroid investigation, there's at least one investigational product which is under investigation in clinical trials. This is an oral prodrug which is hydrolyzed to brexanolone, and this is in current phase 2 clinical trials. So more to come on new agents.

So in conclusion, the pathophysiology is definitely multifactorial, but I think the really important piece of that puzzle is the research on neuroactive steroids and their interaction with the GABAergic system. And as we noted, there are evidence-based treatments for peripartum depression, including psychotherapies, conventional antidepressants, and the novel FDA-approved neurosteroid-based antidepressant. And especially for this patient population of importance, we know that most conventional antidepressants, there are some outliers, so always check LactMed to get the data for each medicine, but also brexanolone and zuranolone are considered compatible with breastfeeding in most situations, as the relative infant doses are low, but obviously to take into consideration the age of

the infant, the health of the infant, the health of the mother, and any other medications that the breastfeeding patient might be taking.

So I will now turn it back over to Dr. Payne to discuss a unified approach for effective postpartum depression treatment.

Dr. Payne:

Thank you, Dr. Deligiannidis. That was a wonderful talk, and I'm looking forward to bringing us home. And I will be talking about that treatment of postpartum depression is really a team sport, and if you're the mental health professional, you are the quarterback. I think it's really important to communicate well with other members of the team and to make sure that everybody understands what the plan is for the treatment of a woman with postpartum depression.

So who is involved in a multidisciplinary team for treating postpartum depression? Well, I think really, there are 3 providers who are definitely required to be involved, and they include the mental health provider or team, the obstetrician-gynecologist provider or team, and the pediatrics provider or team. And the reason they are required is because they are all actively managing a woman who has postpartum depression. And it's really important that they're communicating so that they are all on the same page in terms of what the treatment plan is, why they're doing that particular treatment plan, and what the potential effects could be on the exposed child. I think one of the things that happens when the providers are not communicating well is that a woman who is in treatment for postpartum depression may get mixed messages, and it is important, therefore, that all providers are talking to each other.

It's also important to include the individual therapist if a woman is doing psychotherapy, which I think we've mentioned several times now is really a key part of treatment of postpartum depression. And if the woman is breastfeeding, a lactation consultant can be very helpful and, again, should understand what the treatment plan is, the reasons for that treatment plan, so that the lactation consultant doesn't inadvertently give misinformation to the patient.

There are many others that can be involved as well. If a family is not doing well or coping well with a new infant, a family therapist might need to be involved. Some places have dyad therapists, so therapists who specialize in treating mom and the baby together so that they are interacting more normally, even though a mom is suffering from postpartum depression. Social work sometimes can be involved and may need to be involved in the setting of certain psychosocial stressors, such as financial issues or household physical abuse, for example. Child development services and sometimes physical therapists can also be involved.

So how does a multidisciplinary team contribute to effective management of postpartum depression? Well, it's essential that the mental health, the ob-gyn, and pediatric providers and teams communicate and, quote, be on the same page regarding the plan of treatment in order to best support the patient and eliminate mixed messages. So, for example, if the mental health provider prescribes an antidepressant that the ob-gyn or the pediatrician is not familiar with, they may be reluctant to support that plan unless they've talked to the mental health provider and understand why that particular medication was chosen and the safety record of that medication during lactation.

In addition, a multidisciplinary team provides comprehensive assessment, ideally of the entire family, leading to a holistic approach and customized treatment. A team approach also reduces stigma, provides support that increases compliance, and allows for early intervention when problems arise. So one of the issues about treating mental health problems is that there's a lot of stigma associated with the treatment of mental health disorders. And making sure that all the providers are communicating can decrease that stigma and really increase support for that particular patient and for the treatment that's being provided, and in turn, that really can lead to increased compliance with the treatment.

Psychotherapy in addition to medication management has repeatedly been shown to be superior to psychotherapy or medication management alone in the treatment of depressive episodes, and so including the therapist in the team approach is really appropriate and very important. Psychotherapy increases insight into illness and reduces stigma and, again, increases long-term compliance with care.

And it's really important to not forget that the family is part of the team. So first and foremost, the family can provide moral support and can also provide physical support and help care for the baby and the household. And if the family understands the treatment plan and the reasons for the plan and the decisions that were made in terms of coming up with that plan, they can provide consistent messaging to the patient that really supports compliance with treatment. And also family understanding of the illness reduces stigma and also increases compliance. You are really running an uphill battle if a patient's partner does not understand why a particular medication is being used to treat postpartum depression and if they happen to have stigma about the treatment of mental health conditions. So educating every member of the family that you can reach can really help improve outcomes of the treatment of postpartum depression.

And what does effective team coordination look like? Well, it's communication, communication, communication. It's important that the team has regular check-ins with the patient and the family, as well as regular check-ins with the team. And a team approach can really

provide a holistic approach and evaluation and then decide if other professionals need to be brought in. So, for example, a mother who's breastfeeding but struggling with breastfeeding, as well as postpartum depression, might need a lactation consultant. And if the providers are checking in with the patient regularly, checking in with each other, that need can be identified earlier and addressed earlier to improve outcomes.

So in conclusion for this section, ideally, the management of postpartum depression is a team sport. And a multidisciplinary team approach allows for consistent communication and messaging and a holistic approach that takes into account the entire family's functioning. A multidisciplinary team approach also allows for enhanced support and early intervention if and when there are problems. And then finally, a multidisciplinary team approach also decreases stigma and increases compliance with care through education and consistent communication.

Thank you so much for joining us today. I hope you enjoyed our presentation. And I want to thank Dr. Deligiannidis for joining me in presenting to you today.

Dr. Deligiannidis:

Thanks so much for having me.

Announcer:

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