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www.reachmd.com
info@reachmd.com
(866) 423-7849

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# Let's Discuss Postpartum Depression: Screening, Diagnosis, and Management

**Announcer:**
Welcome to CME on ReachMD. This activity entitled "Let's Discuss Postpartum Depression: Screening, Diagnosis, and Management" was presented during Omnia Education's Women's Health 2022: Beyond the Annual Visit.

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**Dr. Payne:**
All right, thank you and welcome to Women's Health 2022: Beyond the Annual Visit. Today we'll be discussing, Let's Discuss Postpartum Depression: Screening, Diagnosis, and Management. Your speakers today are Dr. Anita Clayton, who is the Davidson C. Wilson Professor and Chair in the Department of Psychiatry and Neurobehavioral Sciences at the University of Virginia in Charlottesville, Virginia, as well as myself, Dr. Jennifer Payne, who is Professor and Vice Chair of Research, also in the Department of Psychiatry at the University of Virginia.

Strategies for earlier recognition of postpartum depression. This slide is a representation of a unified theory of depression. Depression, I think we know at this point is really multifactorial in terms of understanding the underlying causes of postpartum depression. There's definitely a genetic susceptibility to postpartum depression. And postpartum depression appears to run in families with mood disorders, either major depression or bipolar disorder. And this indicates that there's likely an underlying genetic vulnerability to the development of postpartum depression.

But in addition to a biological susceptibility, there are many environmental triggers that have been associated with the development of postpartum depression. These include being of low so - socioeconomic status, various stressors, having adverse childhood events, etcetera. All of these can predispose to the development of postpartum depression.

In addition, my work and others have indicated that there are epigenetic changes that occur at various genes that may predispose to postpartum depression. And what we know is that all of these kind of work together to lead to the changes that are described here, including HPA axis hyperactivity, reduced neuroplasticity, inflammatory mechanisms, and neural network dysfunction, along with decreases in the monoamine neurotransmitters, decreases in GABA, which is the major inhibitory system in the nervous system, and increases in glutamate, as well as changes in neuroactive steroid mechanisms that lead to the clinical condition that we call major depression.

Postpartum depression is really a major depressive episode that occurs in the immediate postpartum time period. And it's thought that some of the biological and hormonal changes that women go through at the time of delivery may trigger a major depressive episode in susceptible women.

Perinatal depression is incredibly common; it's actually considered the most common complication of childbirth. And women with perinatal and major depression occurring prior to pregnancy are much more likely to relapse during pregnancy than postpartum with a major depressive episode. So it's really important to monitor women with a pre-existing mood disorder, such as major depression or a pre-existing postpartum depression throughout pregnancy, especially when women stop their antidepressants for pregnancy.

About 40% of episodes begin immediate postpartum time period, about 33% of start during pregnancy, and about 27% begin before pregnancy. Overall, the highest rates for major depression in women occurred during the major reproductive years, between the ages of 25 and 44 years of age. And about 10 to 16% of pregnant women have a diagnosis of major depression.

After the first trimester, major depression is two times the rate in the general population. And it is often associated with a prior history of depression, specifically reproductive-related mood disorders such as premenstrual dysphoric disorder, or depression during or after a prior pregnancy. And when antidepressant medication is discontinued, either prior to pregnancy or with the onset of pregnancy, about 70% of women relapse with major depression, either during pregnancy or in the immediate postpartum time period. The relapse rate is significantly higher for populations with severe or recurrent depression with a relative risk of 2.3.

It's also important to note that having a psychiatric history really strongly associated with the risk for perinatal depression. And you can see here that if the risk and the general population is a little bit over 10% in women with a history of major depression, the risk increases to about 25%. And if a woman has depressive symptoms during pregnancy, this increases the risk of perinatal depression up to about 30%. And if a woman has a previous history of a postpartum depression, her risk is about 50% in the postpartum time period.

So let's differentiate postpartum depression from the baby blues. The baby blues appears to affect almost all women. So about 80% of women will report having symptoms of a brief period, usually just a couple of days and certainly less than two weeks, of mild worry unhappiness, emotional lability, crying, and fatigue in the immediate postpartum time period. And the baby blues are really thought to be a function of the fluctuations in hormones that are going on after delivery. Many women describe it as just being really more emotional. So they may be crying, but they may be crying because they're happy and not just sad. So really, it's about mood lability.

In contrast, postpartum depression is a major depressive episode that begins within the first four weeks of childbirth. And some clinicians have observed that there may be later onset after weaning and breastfeeding women. But technically, postpartum depression really has to have onset in those first four weeks after delivery. It appears to be related to a rapid drop from extremely high levels of estrogen and progesterone during pregnancy to prepregnancy levels. And that may really be about the brain not being able to adapt to those rapidly changing hormone levels.

We really see this in women who are particularly sensitive to normal hormonal changes. So many women will have a history of being sensitive to times of hormonal change and can report a history of having premenstrual mood symptoms or mood symptoms in the setting of starting, for example, hormonal contraception.

Postpartum depression is seen in about 10 to 15% of women from the general population, and is much more common in women with a pre-existing mood disorder. So about 25 to 40% of women with a pre-existing mood disorder will experience postpartum depression, even if they're taking psychiatric medications during pregnancy.

So how do we screen for postpartum depression? Well, there is a scale called the Edinburgh Postnatal Depression Scale. It's a self-rated scale, very easy to use. It can be used in clinics when women are waiting to be seen by their doctors, for example.

And this is a study that was completed by Kathy Wisner in 2019. And they actually screened 10,000 women four to six weeks in the postpartum time period. And they found that about 14% screened positive with a score of greater than or equal to 10. And they found that 40% of those postpartum depression episodes began in the immediate postpartum time period, and about a third began during pregnancy, and about another third began prior to the onset of pregnancy; 70% of those that screened positive were diagnosed with major depression, but two-thirds of them had a comorbid anxiety disorder, and almost one-fourth had bipolar disorder and almost 20% had self-harm ideation. And drug-related deaths and overdose and suicide are the major contributors to maternal death in the 12 months after delivery. So screening with the EPDS or the Edinburgh Postnatal Depression Scale, is really important in the postpartum time period to identify those for at risk of psychiatric illness, suicidal thoughts, and even substance abuse, and potential maternal death.

This is a picture of the Edinburgh Postnatal Depression Scale, and you'll see that it has 10 items. And the last one is particularly important, number 10, which is the thought of harming myself has occurred to me. And basically, a woman can go through the symptoms and rate how frequently she's been having these types of symptoms.

Now, I don't want to leave you with the idea that the EPDS is the only scale available to screen for postpartum depression. There are many others. We've listed them here. These include the Patient Health Questionnaire-9, or PHQ-9, the CDC Pregnancy Risk Assessment Questions, or the PRAMS, the Hamilton Rating Scale for Depression, or the HAMD-17, the Beck Depression Inventory, and the Generalized Anxiety Disorder 7 items, GAD-7, can all be used to screen for postpartum depression as well as anxiety.

So here's some clinical pearls for treatment during pregnancy. We recommend utilizing the EPDS for screening and early detection to follow through pregnancy and beyond, and also using the EPDS to monitor our treatment response and outcomes. If a woman stops an antidepressant because of pregnancy and depression recurs, we recommend restarting previously effective medication. In this case,

past history guides treatment. So if a woman, for example, was taking fluoxetine prior to pregnancy and was successfully treated, if she stops the medication for pregnancy and becomes ill, it is perfectly reasonable and appropriate to return to fluoxetine. If a woman's never been treated before, the most data is available for the use of fluoxetine during pregnancy, and really, any of the SSRIs can be used. Sertraline can also be used. So both fluoxetine and sertraline have been around for long periods of time. We have good data on their relative safety during pregnancy, and they can be used both during pregnancy.

It's also important to not undertreat. I think doctors and patients alike have an instinct that if I take less of a medication, then that will be safer for the baby. And the reality is that if you're undertreating a woman, if she has both depression symptoms as well as taking an antidepressant, you're really exposing the baby to two risk factors, and one is the antidepressant exposure, but you're also exposing the baby to depression during that pregnancy. And depression during pregnancy is associated with a lot of bad outcomes both for the pregnancy and for the exposed infant. These include low birth weight, preterm birth, a higher rate of C section, more likely to develop gestational diabetes. And a mom who's depressed during pregnancy has an extremely high chance of being depressed during the postpartum time period. And postpartum depression has been associated with lower IQ and slower language development, and more behavioral problems in exposed infants. So it's actually important to treat mom to wellness in order to limit the number of exposures for that baby.

It's important if we're going to be treating to really maximize the use of one medication during pregnancy as opposed to polypharmacy. But again, use polypharmacy if necessary to get a woman well. It's also important to note that as a woman's pregnancy progresses, she is gaining weight, her metabolism is revved up, and her blood volume doubles during, uh, pregnancy. And so you may need to increase the dose of an antidepressant during pregnancy because of those biological changes.

Finally, I will re-emphasize, please avoid exposure to both drug and continued depression, we know that this is really associated with worse fetal outcomes. And so if you're going to be using a medication during pregnancy, use it effectively and get Mom well.

And here are some clinical pearls for the postpartum time period. So plan in advance if a woman has a history of a prior postpartum depression, if she's not depressed during the pregnancy, and wants to avoid any symptoms of postpartum depression, simply start an antidepressant after delivery and try to prevent the onset of a new postpartum depression. If a woman first develops postpartum depression, and the symptoms are mild to moderate according to the EPDS, start an oral antidepressant or initiate psychotherapy. So for example, cognitive behavioral therapy has been shown to be very effective for postpartum depression if the symptoms are mild to moderate.

You can utilize an SSRI and SNRI, bupropion or mirtazapine. Any of those medications are appropriate to start for postpartum depression. And you want to titrate to a therapeutic dose and continue for at least six to eight weeks to ensure an adequate treatment trial. And then if a woman's not responding, please change to another medication.

If a woman has a history of major depression, and she then experiences an onset of a major depressive episode or postpartum depression in the immediate postpartum time period, please use a medication that was previously effective and do not withhold treatment due to breastfeeding. Exposure is much lower than in utero, and self-tapering will occur with weaning. So don't be afraid to treat if a woman is lactating and actively breastfeeding.

If postpartum depression is moderate to severe, and especially if a rapid response is desirable, it is appropriate to treat with brexanolone, which Dr. Clayton will go into in more detail in the next set of lectures.

And now I'll turn it over to Dr. Clayton, who will be talking about current and emerging therapeutic strategies for postpartum depression. Dr. Clayton.

**Dr. Clayton:**
Hi, I'm the David C. Wilson Professor and Chair of the Department of Psychiatry and Neurobehavioral Sciences at the University of Virginia School of Medicine in Charlottesville, Virginia. And I'm excited to talk both about current and available treatments for postpartum depression and emerging therapeutic strategies.

I'd like to get you to think back about that united theory of depression. And we know that decreased monoamines essentially have some effect in some people in terms of contributing to depression. So standard oral antidepressants act on the neurotransmitters like serotonin, dopamine, and norepinephrine, usually as reuptake inhibitors. And this then boosts the neurotransmitter activity, or makes the activity longer in the synapse, because the actual neurotransmitter is there for longer. This is all going to improve neurotransmission. And we know there are downstream effects as the result of changes in neurotransmitters in the brain.

So our standard oral antidepressants are going to be those that we're going to sort of think about which of these neurotransmitters are impacting on women, and they've never been tried before. We're going to try to tailor that to the individual woman. As you heard, if

they've already been on it before, something - we're going to try that and restart it.

More exciting to be right now are neuroactive steroids. These have been evaluated in postpartum depression because they bind to the gamma aminobutyric acid, or GABA type A positive allosteric modulators or PAMs. And remember what the nature of the GABA receptor is; remember, it is five subunits that are around an ionic channel. And when you bind it certain areas, particularly on the synaptic areas, like GABA binds there and benzodiazepines bind there, this leads to rapid, but very brief phasic effects. So that's why giving someone a benzodiazepine may, in fact, open up that channel, but it only stays open briefly. And so that could be something we can use occasionally, or when something is critical to treat in terms of relief of anxiety or something like that. But it's not going to have a long-lasting effect or an impact on depression. It's the extra synaptic receptors. So those that are not at the synapse, but they are generally around the membrane. Because remember, this is a transmembrane ion channel, and they are the site where positive allosteric modulators bind, the progesterone metabolite like allopregnanolone. And we also know that brexanolone, and potentially the oral neuroactive steroid, zuranolone, leads to rapid and sustained or tonic effects. And these are what we're striving for, because that way, we might get a rapid impact on the women's symptoms, but we also hope to see it sustain, and the duration of the treatment is brief.

So brexanolone is a neuroactive steroid, GABAA receptor positive allosteric modulator, administered in a 60-hour inpatient I.V. infusion, followed by a 12-hour observation period. Women who were six months or less postpartum who had postpartum depression and were willing to temporarily stop breastfeeding were enrolled.

You can see that in study 1, women had HAMD-17 scores consistent with severe postpartum depression. And in study 2, they had scores consistent with moderate to severe postpartum depression. Over 100 women were enrolled in each of the studies. In study number 1, patients could receive 60 micrograms per kilogram per hour of brexanolone, or 90 micrograms per kilogram per hour of brexanolone or placebo. In study 2, it was only 60 micrograms per kilogram per hour of brexanolone or placebo that patients were randomized to.

The results are really pretty impressive. This is at the conclusion of the infusion, patients who received 60 micrograms per kilogram per hour of brexanolone had a drop in their HAMD score of 19.5. And this was significant versus placebo. At the 90 micrograms per kilogram per hour dose, the drop was 17.7 on the HAMD-17, and the P value was also significant. That placebo drop was 14. And the only really serious adverse event in the study was suicidal ideation and an overdose in the patient, not during the infusion, but later in the follow-up. In study 2, 60 micrograms per kilogram per hour of brexanolone led to a drop of 14.6 points on the HAMD-17 And this was significant versus placebo, which the drop was 12.1 points on the HAMD-17. One serious adverse event occurred with altered mental status and syncope in one patient. There was really no difference in the adverse events from placebo with brexanolone, the most common being headache, dizziness, and somnolence. And if you think about it, it makes sense for where this is binding to a GABAA receptor that then is going to potentially lead to sleepiness or somnolence.

This is the data from the first phi - phase 2 trial of brexanolone versus placebo. There were 11 placebo subjects, and 10 women received brexanolone. And you can see this is pretty impressive. The drop is occurring very quickly. Within the first 24 hours, there's a significant difference between brexanolone and the placebo. And this continues at every time point measured, including at the end of the infusion, and the 12 hours afterwards, and also out at 14 days and 30 days. The HAMD effect size is huge. It's 1.2. And similar results were seen for the and the CGI, that women who received brexanolone, 70% of them had remission from their depressive symptoms, versus only 9% in the women who received placebo. And you can see here the difference at 24 hours was significant, at 60 hours was significant, and at the 30-day follow-up as well.

So brexanolone was FDA approved for postpartum depression. It's given, as I mentioned, as a 60-hour I.V. infusion, titrated up though; it begins at 30 micrograms per kilogram per hour for 4 hours up to 60 micrograms per kilogram per hour, and then further to 90 if you're going to use that dose, and then later titrated down in the last 4 hours of the infusion to the 30 micrograms per kilogram per hour before discontinuation. And you can see the rates of adverse events with brexanolone include somnolence, which was the largest over 12%, headache about 9%, dizziness nearly 8%, tract infection, and that was in the period following the administration, and diarrhea, sedation, and nausea. So in women with postpartum depression, they had both a rapid effect, you saw the significant difference at 24 hours. And so that's a phasic effect. But you also see the sustained or tonic effects out through the infusion, and to day 30 seen with brexanolone.

So the Advisory Committee for the FDA recommended approval, but they left the decision of dosing either 60 or 90 micrograms per kilogram per hour up to the FDA. And they have recommended that 90 There is a REMS, however, and the administration must occur in medically supervised settings, including with a pulse oximeter, and monitoring for 12 hours after the infusion, and monitoring both for the drop in oxygen and potential sedation and loss of consciousness. So because of this evaluation needed for excessive sedation, it needs to be done every 2 hours during the planned non-sleep period. Patients don't need to be awakened for this.

And they need to be monitored, as I said, for the 12 hours after infusion, and for any adverse events.

If they're having their baby boarding in or visiting during the infusion time period, someone else must be present in case the mom is overly sedated and they will care for the baby then. And the suggestion to pause breastfeeding during the infusion and for 36 hours after the completion of the in – infusion is recommended.

Now, zuranolone is an oral neuroactive steroid GABAA receptor positive allosteric modulator that is in development. And two of the studies for that have been done in postpartum depression. There have been other studies in major depression alone. Uh, the evaluation also looked at change in from baseline in the HAMD-17 Total score. And in the ROBIN study, and this is part of the NEST program. So you can see that the names of birds being used here, zuranolone was given at 30 milligrams versus placebo PO once daily in the evening for 14 days. And the women who received zuranolone, there were 76 of them, and placebo 74, had similar baseline demographics and characteristics. About 20% in both groups were on a baseline antidepressant therapy that they had been on before, obviously had not responded significantly to that, but they were continued on that through the treatment and out to the follow-up at day 45.

So zuranolone met its primary endpoint, which was changed from baseline in depressive symptoms using the HAMD-17 Total score at day 15. So the women were taking oral zuranolone every evening for 14 evenings. And so the following day, they were assessed, and that was the primary endpoint. You can see here though, that the other endpoints at day 3, at day 8, and subsequent to the primary endpoint at day 21 and day 45 were all statistically significant in terms of separating from placebo. And you can see it the day 15, the drop with zuranolone in the HAMD score was nearly 18, and was over 13 for placebo. And this was statistically significant.

Recently completed is the SKYLARK study. And I only have the data from a presentation at ECMP just last month. And what you can see here is very similar outcomes related to the ROBIN study. So women also had statistically significant differences at the primary endpoint at day 15. And they also had significant differences at day 3, day 28, and day 45. So significance in every measured time point.

And it's important to think about, these are pretty frequent measures, and then having an evaluation at day 3, 8, and 15, as being potentially likely to stimulate a placebo response. But you can see it's still separated. So the response was rapid, and it was sustained out to day 45, and significant improvements were seen at every time point.

So I'd like to bring Dr. Payne back into our conversation. And maybe you'd like to start talking about additional screening tips in women potentially for depression during pregnancy and postpartum.

**Dr. Payne:**
Sure. So I actually think one of the crucial questions to ask a woman while she's pregnant is not only about her own history, so, 'Do you have a history of depression or being treated for depression? Do you have a history of anxiety?' But it's really crucial to ask about a family history of postpartum depression. And I think a lot of clinicians don't think about that. But there's clearly a genetic basis for being susceptible to postpartum depression. And so saying, 'Did your mom or did any of your aunts have a history of postpartum depression?' can alert you to the fact that a woman is at higher risk. Similarly, if she has a history of being sensitive to hormonal changes, she's also going to be at higher risk. So asking about premenstrual symptoms or hormonal treatments that she may have undergone, and whether she had mood symptoms in that setting, can really give you a clue that a woman's at higher risk for the development of postpartum depression.

**Dr. Clayton:**
So we did talk a bit about untreated depression on babies, because frequently the woman who's pregnant, her partner, her primary care provider, or OB/GYN, may be concerned about taking medications during pregnancy. And we certainly have some that we don't utilize in pregnancy at all, or stop if people find themselves pregnant. But they worry about the dose, they want to be only on a low dose if they're going to be treated, but they also worry about what it might do to the baby.

We know though, that there are not significant to teratogenic effects with SSRIs or SNRIs, except potentially paroxetine compared to other antidepressants. But women often don't think about the impact if they don't get treated, if they just suffer through it with depression. And I think it's really critical to help them understand those things. Are they concerned - maybe they have twins even and they're concerned about a preterm birth, this is going to be more likely if they have depression during the pregnancy. And the babies are born at low birth weight, and they are slow to gain weight after delivery. That woman may be at risk of gestational diabetes and a preeclampsia, all of which can complicate the delivery, can impact on the baby, and certainly can have an effect on the woman.

And so I think it's really important that we help them understand that I wouldn't withhold treatment while they're pregnant. And I wouldn't withhold treatment if they are choosing to breastfeed their baby. And I encourage breastfeeding. It's great for babies and for moms. And there's no reason to hold that back just because a mom is breastfeeding her baby. In fact, the exposure is about eight times greater when the baby's in utero than in breast milk.

**Dr. Payne:**

That's right. And we often think about risk-benefit discussions. And really here we're talking about a risk-risk discussion. So there's a risk of using a medication during pregnancy. And even though those risks, over time, there have been better and better studies done that are well controlled and really show that the risks are minimal, but there's this robust literature that the risks are not minimal for untreated depression during pregnancy. And so, I always sit women down, I say, 'Well, let's have a risk-risk discussion. Here's the risks that we know, and they are small with antidepressant exposure, and here's the risk that we know with untreated depression and pregnancy. And they're not minimal.' So when you weigh those risks versus risks, the odds usually come down on the side. Of course, depending on the case, on treatment during pregnancy,

**Dr. Clayton:**
I will say one other thing is, it's frequently the partner who's saying, 'No, I don't want the baby exposed to medications in utero.' But it's the woman, especially if she's previously had depressive symptoms, who knows how bad it can be for her and knows what she's feeling right now. And so, I usually try to involve the partner as well in these discussions and help them understand that it's also not dose related. So if we're going to up the dose – we're going to start somebody on an antidepressant and then we're going to up the dose, because of these increases in metabolism and fluid retention and things like that, then I want them to understand it's not a dose-related phenomena. And as Dr. Payne discussed, we need to treat her fully to remission if we can accomplish that.

**Dr. Payne:**
Yes, I think bringing the partner in is key. I also sometimes have patients bring anybody who is saying anything to them about whether they should take a medication during pregnancy. So mothers, mother-in-law's can be part of that conversation. I teach residents that it's important as the psychiatrist to be the communicator and to reach out to the OB/GYN and explain what the plan is and why we are planning a certain approach. So it's really key to identify women who are at elevated risk and to treat both during pregnancy and during breastfeeding, if appropriate.

**Dr. Clayton:**
And I think that's when we really start to need to think about individualizing the care of the mother and potentially exposure of the baby in breast milk in a woman with postpartum depression. So if she has moderate or mild depressive symptoms, she had previously responded to a treatment, I wouldn't necessarily start on sertraline during the pregnancy because she's going to breastfeed if she previously responded to escitalopram. But it's important for us to be thinking about what she's already taken before, what's worked for her, because we don't have time to mess around finding out if something else will work.

I think if she has severe depression, then there are other factors we really have to think about in the postpartum period. Severe depression means a lot of times severe functional impairment. And if a mom already has children at home, then they're also going to suffer with mom's depression. We also may need to have a rapid turnaround. In the past, we've used ECT often, but now we have an infusion that doesn't do that, people can be in to visit while a woman's having an infusion with brexanolone, and that effect is sustained. So especially for a woman who may have had prior tolerability issues with antidepressants, this may be beneficial because she doesn't have to continue on the brexanolone daily for a year like we might treat with other antidepressants.

And I think zuranolone, I'm looking forward to that treatment coming because of convenience. A woman doesn't need to be hospitalized with that, it has not quite as rapid an effect, not in 60 hours. But it does have an effect in 24 hours initially, and then significant effect and achieving of remission and many women by day 15 after she's taken the medications. If she's already on an antidepressant during the pregnancy, she can still be started on brexanolone or potentially, if approved, zuranolone. And we could see rapid improvements in functional impairment as well. And that's going to be great for both mom, baby, and the rest of the family.

**Dr. Payne:**
Completely agree. I think that there are a couple of things to touch on here. One is that a lot of times treatment providers will try to strategize by taking a medication that is – does not go into breast milk as much as another medication. And so they'll think that they should use one medication in pregnancy and another in lactation. And actually, that makes no sense; the baby's already exposed in pregnancy and if a medication is working, that same medication should be continued during lactation.

Another common scenario that I see a lot of is a woman might be on a newer antidepressant that we know less about in terms of safety for pregnancy, and she's doing fine, she's on a newer medication and she gets pregnant. Fifty percent of pregnancies are still unplanned in the United States today. And so then she'll wonder well maybe I should switch to a medication that we have more data. And actually that doesn't make sense because, A, the medication's working, B, the baby's already exposed and if you switch to another medication, you may then expose the baby to two antidepressants and potential for relapse in the mother. And so, we really tried to make medication changes prior to pregnancy unless mom is not doing well during pregnancy.

And - and I think your comments on brexanolone and the upcoming zuranolone are spot on. When a mom is severely depressed, suicidal, not functioning, and we really need a quick turnaround, quick hospitalization for essentially three days, it's really phenomenal

that we're able to do that at this point. And because hospitalizations usually last on average about two weeks or even longer for severe cases of postpartum depression. And I'm really looking forward to zuranolone as well. I

think it's going to revolutionize how we think about treating these illnesses. And a lot of patients are going to be very happy that they don't have to stay on the medication forever. So looking forward to that.

And I think you really have to think about every case as a unique case when designing a treatment approach for postpartum depression.

**Dr. Clayton:**
So thank you. And I just want to go over the conclusions I hope you can take away from our presentations and discussion.

Some women are sensitive to normal hormonal changes. And so, these women may be at higher risk for depressive episodes during times of changes of hormones. And we need to monitor for mood changes in depressive symptoms during risk periods like pregnancy, postpartum, the perimenopause, etcetera.

We know that medications acting on serotonin, GABA, and dopamine or monoamine oxidase inhibitor have a bidirectional relationship with sex steroids, and they appear more effective for hormonally-mediated mood disorders. So we need to keep that in mind. For mild to moderate postpartum depression, the standard of care oral antidepressants are effective and well tolerated. And if they had a prior response to a specific antidepressant, that's the one we should be using.

And for moderate to severe postpartum depression, the neuroactive steroid GABAA receptor positive allosteric modulators, brexanolone and hopefully in the future, zuranolone, have both phasic that is rapid, and tonic that is sustained effects that enhance inhibition of a hyperactive hypothalamic pituitary adrenal axis, and restored neural network functioning; so therefore, rapidly relieves symptoms of postpartum depression.

Other interventions such as lifestyle modifications, dietary changes, stress management, psychotherapy, phototherapy, they can all be combined with pharmacotherapy and individualized to the specific woman to provide the best possible outcome for her and her baby. Thank you very much.

**Dr. Payne:**
Thank you.

**Announcer:**
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