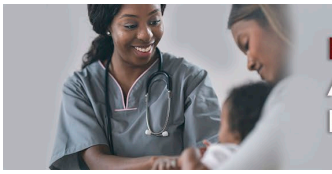

ELEVATING PATIENT CARE: EARLY DETECTION AND EVIDENCE-BASED PHARMACOTHERAPY FOR POSTPARTUM DEPRESSION IN PRIMARY CARE

Editor's Note: This is a transcript of a presentation on April 12, 2024. It has been edited and condensed for clarity.
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Module 1: Introduction and Recognition

Barbara Yawn, MD, MSc: We want to start by talking a little bit about what is perinatal depression, how we recognize it and what is the impact. Depression, during and after pregnancy, is very common. In the postpartum period, 10% to 15% of patients experience it during pregnancy, perhaps as high as 15%. It is a leading contributor to morbidity and mortality. It affects the mother, the child, the partner, and the family. It is a major concern.

Let's talk about the impact of postpartum depression on the mother and the babies. This includes compromised parental behavior in infant-mother bonding, lack of adherence to safety recommendations by the mother, potential substance misuse, relationship problems, and financial difficulties. For the child, delayed development and milestones, lower IQ, poor executive functioning, sleep difficulties, social-emotional difficulties, and psychiatric illnesses, including depression, may be seen. Also, we're not talking about the period of infancy only. We're talking about throughout that child's life.

Then, let's talk about the effects of unrecognized, untreated, or under-treated depression during pregnancy. This has the effect primarily on the mother, with inadequate nutrition and increased hospital admissions, but also on the infant with pregnancy complications, preterm delivery, and intrauterine growth retardation. These are all things that are very significant. Also, it's important to recognize that a major depressive episode can follow pregnancy loss too. The more severe the pregnancy loss, that is, the later in pregnancy, can result in a more severe depression.

The key takeaway is that depression, during and after pregnancy, is common and harmful if unrecognized, under-treated or untreated for the mother, the baby, and the family.

Module 2: Practical Screening Approaches

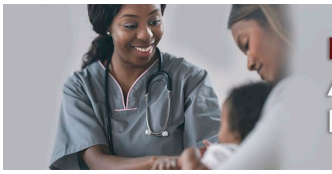
Barbara Yawn, MD, MSc: Knowing the importance of recognizing and treating postpartum and perinatal depression, we want to talk about how you identify it. This is one of the things for which screening is important. There are several recommendations from different organizations, including the United States Preventive Services Task Force (USPSTF), the American Psychiatric Association (APA), American College of Obstetricians and Gynecologists (ACOG), and American Academy of Pediatrics (AAP). The American Academy of Family Physicians (AAFP) doesn't have a specific recommendation, but they go with USPSTF recommendations, as well as other evidence-based recommendations. In summary, each organizations says you routinely screen every pregnant woman and in the postpartum period.

Let's go a little deeper into what the recommendations are. If we look at USPSTF, they say all adults, including those who are pregnant or postpartum, should be screened. They talk about not only screening, but providing intervention or referral for patients who screen positive for depression or are at high risk, using evidence-based care. This entails psychotherapy, pharmacotherapy, considering patients' preferences, benefits vs harm in treatment, and collaborative care. This is important. We're not just screening. We need to do something with those screening results.

The APA also has recommendations that suicidal thoughts and behaviors must be addressed. We also screen for bipolar affective disorders; if you have a woman that screens positive and you're considering starting an antidepressant, you don't want to do that until you make sure she doesn't have bipolar disorder. You could trigger a manic episode if you're not aware. She's going to need different therapy. Also, risk and evidence of other psychiatric disorders should be assessed, including generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD). These recommendations are more comprehensive than that of USPSTF.

It's important to recognize that we need to screen women repeatedly. The diagram suggests that about 27% of depression starts before pregnancy, about one-third will happen first during pregnancy and about 40% will start during the postpartum period.

In a study of 10,000 women, 14% screened positive for postpartum depression with Edinburgh Postnatal Depression Scale (EPDS) scores of 10 or greater, nearly 20% of those had self-harm Ideation—really emphasizing that you don't want to miss this—and almost 23% of screen-positive participants had bipolar disorder. At the onset of pregnancy or when planning a pregnancy, women may choose to stop their antidepressant. This is not recommended, and you need to look at that because women who've stopped their



antidepressant are at very high risk for perinatal depression, both during pregnancy and postpartum.

Let's talk about screening tools, including the EPDS and the Patient Health Questionnaire-9 (PHQ-9), endorsed by all the agencies we talked about. Both tools take about 4 minutes or less to complete. They only have 9 or 10 questions, and both assess suicidality in the final step. In the EPDS scale, each item is scored from zero to 3, with zero meaning there is not a problem. Total scores of 10 or greater suggest depression. Some of the items, like being able to laugh, looking forward to things, being anxious or worried, are scored in the forward direction. Then, there are some that are scored in the reverse direction, like blaming yourself, being panicky or scared, things getting on top of you, being so unhappy you can't sleep, feeling sad or miserable and being so unhappy that you've been crying. Then, let's pay attention to the final one about if the thought of harming myself has occurred to me. This is question 10 on the EPDS and anyone who checks anything other than "never" needs further assessment. It can be difficult for a woman to admit that she has had these ideas about harming herself, so she may put the lowest positive score, "well, hardly ever." But when you ask questions about this, like "Can you tell me what hardly ever means?" "How often is that?" "Have you had thoughts of how you'd harm yourself?" "Have you made plans?" Having very specific follow-up questions is important.

Also, screening goes beyond depression. In this group of women, 20% to 25% may have bipolar disorder, so you need to think about screening for that. You can use the Mood Disorder Questionnaire (MDQ) that we'll talk about; you can use the Composite International Diagnostic Interview (CIDI); for substance abuse disorders, the 4Ps and the National Institute on Drug Abuse (NIDA) Quick Screen; and the Generalized Anxiety Disorder-7 (GAD-7) for anxiety. All these are useful.

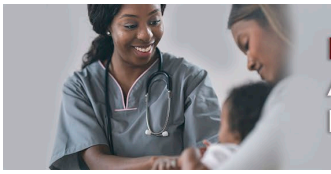
The mood disorder questionnaire is interesting. There are 3 sections. The first section asks about symptoms, like "I feel so good or hyper that I've been doing things beyond normal." "I am being irritable." "I'm much more self-confident." "I don't have to sleep as much as usual," and "I'm spending money that got my family or me into trouble." All those items are important, and if a woman has more than 1 of those, you want to pay special attention. Then, the next question asks, "If you said yes to any of these, have they happened at the same period of time?" Then, the third is "How much of a problem were these things?" with answers ranging from "no problem" to "serious problem." This can help you decide what this woman's screening scores look like for mood disorder and does she likely have bipolar disorder.

When do you screen? You screen during pregnancy, at the hospital, well-child checks, postpartum visits, routine well-child checks, and within 1 year of delivery. Who should do the screening? Basically, anybody that deals with the woman and her family during this period. During pregnancy, anybody who's doing the maternity care can do it, but also, if you, the family physician, are seeing this woman during her pregnancy, but not doing the maternity care, you still should consider doing this screening. Office staff can be very helpful with this. Frequently, your medical assistants are young women who feel this is important. They or their family or their friends have had postpartum depression, and they may become the champion in your practice. The screening within a year of delivery is important for a couple of reasons. One, you may have missed it before, and 2, to make sure that the woman's symptoms have been treated to remission.

The diagnosis of postpartum depression or depression must go beyond an elevated screening score. We want to use the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for this. You need a major symptom and several minor symptoms. The major one includes either depressed mood or loss of interest, which are major questions in the PHQ-2. Then, you want to go beyond that—weight loss, fatigue, feeling worthless, recurrent thoughts of death, and suicidal ideation, plans or attempts. All these things are important to say, "Yes, this is depression and not just kind of feeling bad for a day or 2." They need to cause significant distress or impairment, and they're not attributable to some other cause.

Regarding the differential diagnosis, we can talk about baby blues, but baby blues are usually not as severe and resolve quickly, within 2 to 4 weeks. We also must think about bipolar affective disorder. Could it be postpartum psychosis? Are these women not just depressed, but also have psychotic symptoms, such as hallucinations? This is a psychiatric emergency. These women should not leave your office without help, such as referral directly to a psychiatrist or inpatient admission. These women that screen positive may also have anxiety disorders, obsessive-compulsive disorder (OCD), panic disorders, post-traumatic stress disorder (PTSD) or a medical condition. Thyroid dysfunction can masquerade as postpartum depression, and most of us have had that happen to us once or twice.

Risk factors that help you decide on screening and early intervention include history of depression, discontinuing their antidepressant for pregnancy, family history, personal



history of anxiety, complicated pregnancy or birth, ambivalence about this pregnancy, stressful life events like marital conflict, being a single mother, adolescent unplanned pregnancy, abuse history, substance use disorders, poor support, low socioeconomic status (because it usually is accompanied by many other stressors), and finally, one that is newer and some of us may miss, preexisting diabetes or gestational diabetes. Breastfeeding difficulties are also a risk factor. The question is, does postpartum depression cause difficulties or do the difficulties cause depression? It is probably yes to both ways.

We have multiple barriers to diagnosis and seeking help. Lack of time, stigma, and childcare issues are examples. That's why it's so important to talk to these women and say, "Look, you don't have depression because you're a bad mother. This doesn't make you a bad mother. This is not something you brought on. This is something that has to do with chemicals in your body and the brain, including hormones and changes, and these are not things you have control over happening, but you do have control over helping to make it better."

The reason you want to do this, among many others, is that women with postpartum depression that are untreated may still be depressed 3 to 5 years after delivery. Imagine living in a household with a depressed woman for the first 5 years of your life! This is obviously very problematic for the family and for the child. We also have greater acceptability of help when the mental health services are provided within the family medicine or obstetric clinic. We need to continually reduce the stigma. Also note, the postpartum depression, if untreated and still depressed 3 to 5 years later, especially happens if the woman has a mood disorder, gestational diabetes or a preterm delivery.

What are our takeaway messages for this section? Screen routinely for perinatal depression with validated instruments at multiple time points. You must follow up on elevated scores with further evaluation and management when warranted.

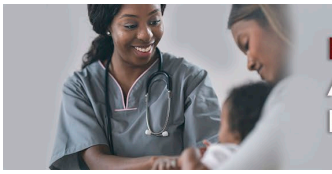
Module 3: Approaches to Treatment

Sarah Nagle-Yang, MD: Once you identify that your patient may be experiencing postpartum depression or another perinatal mental health condition, how do you even start to think about a plan for your patients? While we're going to primarily talk about pharmacotherapy today, we can't emphasize enough the role of psychotherapy. Psychotherapy alone can be used as a first-line treatment for mild to moderate postpartum depression. For more severe illness, combining medications with psychotherapy is more effective than medications alone. Additionally, the USPSTF recommends that patients are not only screened for current symptoms of perinatal depression, but also symptoms of or risk factors for postpartum depression. USPSTF also recommends that clinicians refer patients who are at risk for postpartum depression to evidence-based psychotherapy interventions. In that recommendation, they note that evidence-based psychotherapy interventions, which may include cognitive behavioral therapy or group therapy interventions, can decrease the development of postpartum depression for those at risk by 39%.

Once we get to treatment planning, it's important to consider a treatment plan that is comprehensive and tailored to each patient. For many patients, the acuity and severity of symptoms will guide the approach. For mild to moderate symptoms, we think about first-line intervention being psychotherapy and again, this could include various forms of evidence-based psychotherapy, such as cognitive behavioral therapy and interpersonal therapy, and/or medication. When we think about medications, the first question to ask is, "Has this patient experienced depression or depression and anxiety in the past, and if so, what has worked for them?" If they have not had previous medication trials, selective serotonin reuptake inhibitors (SSRIs) will be the first-line medication that we think about for many perinatal individuals. However, if somebody has been on a medication in the past and we know that that medication has worked for them, we consider that medication strongly. Other antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) or atypical antidepressants, like Wellbutrin or mirtazapine, have less data to inform their safety profile, but also have really reassuring data among the data that exists. Then, we think comprehensively about the role of psychotherapy and social or peer support. Peer support groups can be an effective intervention in the perinatal period, as well as programs to increase movement, social connectedness, etc.

When we have somebody presenting with moderate to severe symptoms, we must think strongly about the essential role of medication. Again, we might approach medication selection in a similar way. We think about the role of neurosteroid medications, as well, when we're thinking about moderate to severe symptoms.

One of the primary principles of forming a treatment plan in the perinatal period is thinking about balancing risk. If we have a mental health condition presenting either during pregnancy or after, we have some risk already. Then, we're weighing what is the risk of a potential medication or other



treatment option that we might be recommending vs the risk of not providing that treatment and the underlying condition either being untreated or under-treated. The goal is to minimize risk by improving the overall health of the individual. This also guides us to think about treatment to remission. We need to think about what strategies we can put together to improve the chances that this patient will achieve remission of their symptoms. What we don't want is to have some treatment on board and have a certain amount of risk associated with that, and at the same time, have the underlying illness not be fully addressed. That presents a situation where we have risk on both sides. We want to make sure that we're really addressing the risk of the underlying condition which also guides us in terms of our dose selections. When we're thinking about medications, of course we want to use the lowest dose that works for each individual patient—with an emphasis on what works. We also want to use a dose that's robust enough to get us to that state of remission.

Also, as we think about treatment, models of care are important. Identifying postpartum depression within a patient's obstetric home can be important to increasing access to care, and acceptability of that care, for our patients. Given how busy and in demand primary care providers can be, having the support of a team that's available for assistance and collaboration can be instrumental.

The collaborative care model has strong evidence to support that it can increase the capacity for primary care teams to address mental health conditions within a primary care setting in a cost-effective manner. There are resources to get a lot more in-depth information about collaborative care models, but the essentials of the model are that, 1, it is patient-centered. The team is circling around the patient rather than asking the patient to ping-pong between different provider types. The primary care provider is the leader of the care team and is supported by the behavioral health care manager, as well as the psychiatric consultant. Collaborative care is a population health model with all patients enrolled in the program tracked within a registry. This allows the behavioral health team to identify patients who might have fallen through the cracks or aren't improving with initial intervention and might need a stepped-up level of care. Collaborative care is associated with improved outcomes and high satisfaction among patients and providers. It's a culture shift in the way that medicine is generally practiced. Implementing collaborative care requires some attention to expectations from patients and providers alike and being transparent about the model and its reasons. Again, there are a lot of wonderful resources through the APA and other organizations, if you want more information.

Regarding key takeaways, a key treatment goal is to minimize risk, that is, the risk of untreated depression on both the mother and the fetus vs the risk of medications during pregnancy and lactation. Also, think about treatment to remission, as well as making purposeful decisions about a comprehensive and personalized care plan.

Module 4: Pharmacotherapy in Detail

Sarah Nagle-Yang, MD: Now that we've talked about the general guidelines of treatment for postpartum depression, we're going to dive in deeper to pharmacotherapy. Starting with effectiveness, we're going to start by talking about SSRIs. Then, Dr. Clayton is going to follow up on some newer and innovative treatments. But thinking about SSRIs, we're going to first talk about effectiveness and then safety.

There isn't a lot of effectiveness data specifically around SSRIs in postpartum depression. This meta-analysis and systematic review, which was published in 2021, included randomized, controlled trials that had women who were experiencing postpartum depression up to 12 months postpartum. They compared antidepressants, alone or in combination with other medications, vs any other treatments, placebo or treatment as usual. What they found was those individuals on SSRIs, which are the gold standard treatment for initial treatment of postpartum depression and major depressive disorder outside the postpartum period, were more likely to have a response, achieve remission and show a reduction in depressive symptoms. However, confidence intervals are spanning 1, and the overall effect size is not as robust as what we might hope. The summary of this meta-analysis and systematic review was that the evidence was insufficient to assess the efficacy of SSRIs vs other therapies and placebo. In addition, there's too much variation in the safety reporting among these different studies to make a conclusion about safety within the study. Additionally, the way this study was conducted didn't allow for an assessment of dosing. We know that perinatal women are more likely to be under-dosed in terms of treatment of their depression, and we couldn't factor that in in terms of what we were seeing in terms of efficacy outcomes. There's a critical need for more efficacy data surrounding SSRIs in the postpartum period.

Then, thinking about risk, we're going to go into these categories in more detail. We're going to talk about teratogenicity, obstetric complications, neonatal toxicity and long-term neurobehavioral effects and what we know about these potential concerns when it comes to SSRIs. Overall, the data supports that these are low-risk medications in pregnancy and the postpartum period. When they are used for a clear indication, like perinatal depression, the risks of these medications are outweighed by the need and the

underlying risk of depression or anxiety itself. These are the most common medications that are used in the perinatal period because of the high degree of comfort in terms of the safety profile.

There's been a lot of work around understanding if SSRIs increase the risk for teratogenic effects. Cumulatively, that data shows no consistent associated risk, with the exception of paroxetine. Starting in 2005, with some data from the manufacturer, there was a concern of cardiac malformations as an association, earning paroxetine a category D rating from the United States Food and Drug Administration (FDA). That's when we had those A, B, C, D, X pregnancy categories which have since been eliminated. There have been cohort studies and case-controlled studies as a follow-up, and we've had conflicting results. Four out of 5 meta-analyses that have been done since that time have showed no statistically significant increased risk of major malformations with any SSRI, inclusive of paroxetine. We also have a meta-analysis from 2015 which included 23 studies, concluding slightly increased risk. When we look at the odds ratio, you'll see that they're quite small, but there is a statistically significant increased risk for any major congenital malformation, cardiac malformations more specifically and more robustly for septal defects and right ventricular outflow tract defects. Therefore, while paroxetine isn't absolutely contraindicated, it can be an option for our patients, and certainly may be considered if a patient has had a strong response to paroxetine in the past and hasn't responded to other medications. It's not our first-line treatment, especially if somebody doesn't have that complicated treatment history.

What about some other pregnancy complications? We know that untreated or under-treated depression increases risk for preterm delivery. Essentially, the data would suggest that SSRIs have a risk that approximates that of untreated or under-treated depression. When we think about treatment of depression during pregnancy, the way that I talk to my patients about it is that this is probably a risk associated with having antenatal depression, and we want to treat the depression. Treating depression is not going to increase the risk any further.

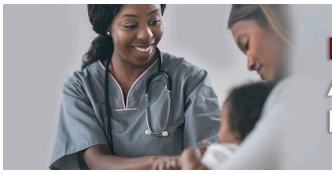
Regarding spontaneous abortion, there have been individual studies that have reported a small elevation in risk with SSRIs. However, when you look at the data, it supports that it's more likely to be the underlying depression that's associated with that risk rather than the medication.

There's been interest in if SSRIs affect gestational weight. What we see is that there's an absolute difference, but it's very small and probably not clinically meaningful when it comes to the overall treatment recommendations.

Starting in 2006 with a study published in the *New England Journal of Medicine*, there's been concern about whether SSRIs increase risk for persistent pulmonary hypertension of the newborn (PPHN). This study has shown an association. It suggested that infants with PPHN were 6 times more likely to have been exposed to SSRIs in the second half of gestation with 2 major caveats. One, the study had 14 infants who were exposed to SSRIs, so a very limited amount of information that we might be able to gain from the study. Also, the study didn't control for underlying depression. There have been many follow-up studies that have been much more sophisticated and larger. They have not shown this association over time. There was some potential interest in the late 2000s about discontinuing antidepressants in the third trimester. This newer data would suggest that that is not a recommended practice, potentially because it could also increase risk for postpartum depression.

Finally, there's the question of poor neonatal adaptation. This describes complications that may be associated with third trimester exposure to SSRIs. It may affect about 30% of infants exposed to SSRIs in the last part of pregnancy. Symptoms include jitteriness, irritability, increased muscle tone, feeding disruptions, respiratory distress that occurs in the first days of life and, for the most part, outside of multiple exposures and more complicated exposures, poor neonatal adaptation is thought to be self-limited and not requiring additional treatment. There are cases of severe symptoms; those are more likely to happen in combination with other exposures. What I talk to patients about, with respect to this finding, is that I note that yes, when we look at big groups of babies and we do very detailed neurobehavioral assessments, we find this small difference that usually resolves on its own. We know that each individual baby might have differences from others, and it's hard to know in the postpartum period if your individual baby might be a little fussy because of this exposure or because they're a baby and babies can go through periods like that.

Let's discuss some clinical pearls regarding poor neonatal adaptation. We know that untreated depression is associated with some differences in terms of regulation of infants in the immediate neonatal period, and importantly, we know that SSRIs in general are associated with relative infant doses under that 10% that we think of that's compatible with breastfeeding, and high enough to alleviate some symptoms of discontinuation syndrome. We think about weaning as a tapering of exposure and a potential way



to mitigate some of the risk for neonatal adaptation concerns.

That is some summary information about SSRIs during and after pregnancy. Dr. Anita Clayton will now talk about some newer medications available that are based on neuroactive steroids.

Anita H. Clayton, MD: Let's talk first about fluctuations in our endogenous hormones. We know there are specific cycles related to estrogen, progesterone and its metabolite, allopregnanolone, in our regular menstrual cycles. We also see a steep climb in estrogen, progesterone and allopregnanolone during pregnancy to birth. Then, we see a rapid drop-off, usually within about 3 days after delivery. That steep slope contributes to a significant discombobulation of the whole system. One thing to be mindful of is that during pregnancy, gamma-aminobutyric acid (GABA) receptors are reduced, so we have reduced inhibition of excitatory elements in the brain during pregnancy. Postpartum, those are restored, but it can take longer than those 3 days.

GABA is an ion channel that goes through the membrane. It's composed of 5 subunits and has both synaptic and extrasynaptic receptors. The synaptic receptors are the ones that act quickly but don't last very long. GABA binds to receptors separate from where benzodiazepines bind, and neuroactive steroids also bind to synaptic receptors. That's why you can see a rapid response to neuroactive steroids. On the other hand, extrasynaptic receptors modify the configuration of the GABA receptor and keep it open longer. Binding of neuroactive steroids to the extrasynaptic sites is going to lead to a sustained response. This is unique to these medications.

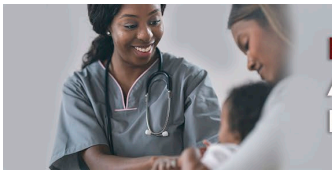
It's also important for us to think about hypothalamic-pituitary-axis (HPA) hyperactivity in both postpartum depression and major depressive disorder. With stress, we see a rise in action through that system, but for men, they tend to drop quickly back to normal. Women, however, sustain hyperactivity and have a long time after resolution of their stresses before they're going to see a resolution of their HPA hyperactivity. Low stress levels have a good balance between inhibitory effects, like with GABA and neuroactive steroids, and excitatory effects, such as with glutamate. When we start to experience stress, be it acute or subchronic stress, we see a reduction in inhibition activity and a marked increase in excitation. When we have chronic stress or defective GABA function, we see a reduction in both inhibitory and excitatory activities. This needs an additional element to get that back to normal. That's where allopregnanolone treatment in postpartum depression is significant in restoring both the inhibition and the excitation and moving people from a depressed state to a euthymic state.

The other thing that is critical for you to understand about neuroactive steroid therapy is that it's a completely new paradigm. You don't have to take this medication daily. In fact, it's not going to be available that way. You get a very short course of treatment and a very rapid onset of efficacy early in that treatment course. Yet, those effects are sustained long after that treatment course is completed whether or not you're taking any other kind of chronic antidepressant. It's similar in tolerability to our standard antidepressants, and its efficacy is greater than placebo.

The first medication I'm going to talk about is brexanolone. It's administered intravenously (IV), so it requires hospitalization. The Hummingbird program had 3 randomized, placebo-controlled clinical trials. In studies A and C, they were randomized 1:1 to 90 µg/kg/h, but they got there by starting at 30 µg/kg/h, then going to 60 µg/kg/h, then going to 90 µg/kg/h and then back down in a taper to discontinuation at 60 hours. The other study included both 90 µg/kg/h vs 60 µg/kg/h. This was a continuous 60-hour infusion, and we looked predominantly at an integrated efficacy analysis of the 90 µg/kg/day. Women had severe depression, as indicated by the Hamilton Rating Scale for Depression (HAMD-17). You can see it is significantly superior to placebo over that time period. You can see also that 60 µg/kg/h was at least as effective as 90 µg/kg/h—potentially more effective—and it also was better tolerated. In my practice, I would generally give the 60 µg/kg/h unless there was some other consideration.

There is a boxed warning about excessive sedation and sudden loss of consciousness. In general, when we look at the adverse effects related to brexanolone vs placebo, they're common to what we see with other central nervous system (CNS) active drugs, in particular antidepressants. You see dizziness, sedation, and somnolence. Sometimes other symptoms are involved like diarrhea or tachycardia. There is a risk evaluation and mitigation strategy (REMS) that requires continuous pulse oximetry monitoring during the infusion, which is not a big problem. Also, presence of a caregiver to take care of the infant when the infant is visiting the mom in case of maternal loss of consciousness is needed.

Zuranolone is an orally administered allopregnanolone analog, and in the ROBIN study, 30 mg of zuranolone was given. These women were also experiencing severe major depressive episodes. Patients received either placebo or zuranolone 30 mg for 14 days of treatment, generally administered in the evening or at night with food. The primary endpoint was measurement at day 15. After the 14-



day course, the next day they were evaluated. You see a significant difference between HAMD scores and their changes with zuranolone versus placebo. It's only 14 days of treatment, whether or not they're getting an ongoing SSRI.
The Skylark study looked at a dose of zuranolone 50 mg per day nightly for 14 days. These were also women with severe major depressive episodes. Day 15 was also the primary endpoint. You can see a significant difference between outcomes on the HAMD-17 with zuranolone vs placebo. The impressive thing is that you see a massive improvement after 2 doses of the drug. We saw these patients on days 3, 8, 15, 21, 28 and 45. Remember, their treatment course ended after the dose on day 14. We saw significant improvement in women treated with zuranolone vs placebo after 2 doses. This means we would be able to assess somebody on day 3 and know what their response is expected to be with this treatment.

The safety results are similar to those from the ROBIN trial. Again, somnolence, headache, dizziness, and sedation. No episodes of loss of consciousness, no increase in suicidal ideation or behavior (and this was tracked with the Columbia Suicide Rating Scale). The 1 warning is not to drive or operate heavy machinery within 12 hours of taking zuranolone, but if you take it at 8:00 PM, for example, and you might need to drive at 8:00 AM, you've gotten through that 12-hour warning period. When the woman is evaluated on day 3, after she has taken the 2 doses, this could be checked for sedation, including persistent sedation, in the AM.

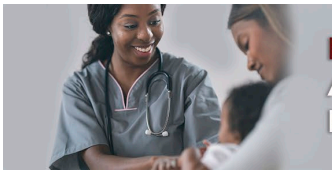
The key takeaways are that SSRIs, SNRIs and many of the atypical antidepressants are safe and efficacious for mild, moderate, and severe perinatal depression. We use these during pregnancy, and we would shoot for remission. Neuroactive steroids are not approved and have not been tested in pregnant women, so they are approved by the FDA for use in postpartum depression after delivery. They are safe and efficacious in those patients who have moderate or severe perinatal depression. A group that I would consider using this in are women who were on adequate doses where we could've anticipated a response during pregnancy, but they did not achieve remission. After delivery, especially if we see worsening of their depression, neuroactive steroid GABA-A positive allosteric modulators are the drugs to be thinking about.

Module 5: Personalizing Pharmacotherapy

Anita H. Clayton, MD: I've talked in general about using SSRIs, SNRIs and neuroactive steroids in the treatment of perinatal depression, but we need to personalize that treatment for each of our individual patients and some of that requires that we know our patient preferences. What are our considerations for treatment selection? Tolerability certainly. Sometimes it would be specific symptoms and probably more concerning should they have suicidal ideation. Various comorbidities. How rapid we need onset of efficacy, so if women have significant impairment in functioning, we need a more rapid response. Drug-drug interactions. Prior treatment response is key, especially during pregnancy, and ease of use is important. We can get some information from patient preferences, like not wanting sexual dysfunction or gain weight, and we can help temper their expectations. Cost may be an issue, and treatment history is important. If they previously responded to a treatment for a major depressive episode, especially for postpartum depression, we should have been anticipating that before delivery. Thoughts of death are also something we need to consider and act upon should they be significant.

During pregnancy, we need to use the lowest effective dose, but we need to treat to remission. Often, those are in conflict. Starting dose is rarely the effective dose for most women. We need to be willing to increase the dose. We especially need to be increasing it over the pregnancy and in the third trimester, if we're treating during pregnancy, because of increased volume of distribution and metabolism. Their effective dose or levels essentially are dropping during that time. Obviously, if they've already responded to a treatment, we don't want to waste time giving them something that's recommended in general when we know what works for them. Also, utilize a validated rating scale. We generally use the EPDS because it resonates better with women, but if they show a positive screen with that, we usually give the PHQ-9 also because it's directly linked to the DSM-5 diagnostic criteria, and we need to make a specific diagnosis of major depressive episode. In addition, we need to use those tools also to monitor their treatment response and outcomes. Also, we don't want to use drugs with a long half-life. Furthermore, it's better to prescribe the maximum dose of a single antidepressant than 2 antidepressants at inadequate and low doses.

Don't undertreat. I can't say this enough. We've already heard that the risks of medication exposure are not dose-related, and they are not enough to keep us from treating women with depression during pregnancy. Maximize 1 medication as opposed to polypharmacy. That's generally good practice. And I've already mentioned increasing the dose. Avoid exposure to both drug and continued depression by giving an inadequate dose of the antidepressant. That is critical. Please do not reduce the dose or stop it in the third trimester. We should be



increasing it. Most of my patients, at the end of their pregnancy, are on higher than standard doses of antidepressants. For example, 200 or 250 mg of sertraline if that's what we're using. That should be continued for some period after delivery at that dose. Finally, if the patient is unsure about their plan for breastfeeding, just assume that they will breastfeed when making decisions during the pregnancy.

What about after pregnancy? This is 1 thing that people don't talk about very much. The risk, if you have had a prior postpartum depression, of having one with a subsequent pregnancy is often quoted at 50%, but it's actually 70% to 90%. If a woman is not depressed during pregnancy but had a previous postpartum depression, start the previously effective antidepressant at delivery. I literally tell moms that when that baby pops out, you pop that first pill in, and they already have the prescription in hand. Then, we rapidly titrate to whatever the dose was that was required to reach remission in the prior postpartum depression. Also, don't withhold treatment due to breastfeeding. Exposure is so much lower than in utero and, as we heard before, self-tapering will occur with weaning.

We need to identify and overcome treatment barriers because there's no magic pill. It doesn't affect all the issues that may be impacting a woman in terms of her depression. Foster shared decision-making, and address patient preferences. Many patients who don't adhere to their treatment are doing so because they're experiencing exactly what they said they didn't want to experience. Check on their adherence at visits, looking at refills and any other visits that may occur. Monitor for treatment response, assessing it ongoing just as you would for medical conditions occurring during pregnancy and postpartum, and use validated tools. Make sure they had an adequate trial of a medication if they tell you it didn't work for them. They must have an adequate dose which is generally, in pregnancy and postpartum, higher than your standard dose.

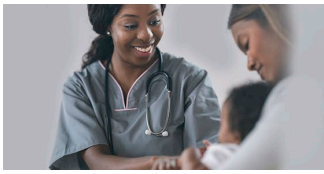
If they're not in remission, add something else. After 6 weeks, if they're not in remission, you should crank that dose up or add another treatment, like medication or psychotherapy. We would give psychotherapy for mild depression anyway. We can add it as an adjunct in severe depression.

Our key takeaway messages from this section—we want to individualize treatment and monitor treatment response using validated tools, and we treat to remission. We need to not be frightened to use adequate doses and, if somebody is not improved in 4 to 6 weeks on a normal or even a higher dose, then we talk about changing the therapy or adding something like psychotherapy.

Module 6: Case Studies

Barbara Yawn, MD, MSc: We've given you a lot of information. Let's see how we could use these different data points that you've learned in patient care. Let's talk about Christine. She's 30 years old. She is a gravida 1, para 0. She is now 24 weeks pregnant. She came in earlier, and at 20 weeks, she had an EPDS score of 12 when you screened her, but today she comes in because things are not going well with her at all. She says she's feeling moody, crying, no motivation, poor energy level, fatigue, and concentration difficulties. She's feeling guilty and worthless. Her EPDS is 22. That's how you started some of this discussion—by looking at the EPDS and the things that she chose to mark. When you continue to talk to her, you find that her medical history is significant for GAD, and she has had 1-on-1 psychotherapy, which you didn't notice at the first visit. She has stopped that psychotherapy because she's had no energy to continue it. She does have a lot of other social problems that we noticed. She's a preschool teacher, but she's recently been demoted because of this period of increased fatigue and not being interested or able to do anything, much worse than the first 12 weeks of pregnancy where many women feel fatigued. She says she attends regular marriage counseling. She and her husband have had a lot of struggles. He's had some infidelity, and now there are financial issues. He was recently diagnosed with manic depression and had been spending a lot of their finances. You let her talk to you a little bit about how this is affecting her. She tells you that there are lots of problems. "My boss keeps acting like I'm whiny because of my pregnancy. She had an easy one. She's not appreciating that this one for me is harder." "My husband says I'm irritable all the time." "I really don't want to see the scale. I don't want to get on it. It says 200 lb. I never wanted to see that happen." "I don't ever want to feel this way, and I don't want anybody else to ever have to feel this way again."

What is the next step? We know we have a high EPDS. We look at the last question number 10; it's a 1 which is hardly ever, but I don't assume that really means hardly ever. I assume that she was uncomfortable, and she chose the lowest positive score. I ask her, "Tell me what this 'hardly ever' means. Is that hardly more than once a day, more than once an hour, more than once a week? What kind of things are you thinking? What kind of self-harm have you thought about? Desiring to die? Have you made some plans?" All those kinds of things need to be assessed because they're going to decide what I'm going to do acutely with this woman and who may I ask for help. My first-line treatment approach? She hasn't been on treatment previously. She's just had psychotherapy. I certainly would want her to restart that, but I'm probably going to try an SSRI, and I'm going to monitor her treatment response by following the EPDS.



Because she has this elevation in EPDS number 10—the suicidal ideation—even if I don't think she's a big risk right now, I'm going to see her again in 4 weeks. I'm going to talk to this woman on the telephone in a couple of days and see her again in a week or 2 weeks. Alternately, maybe I do a hand-off to her counselor and have her have an appointment with the counselor in a week or 2, and we communicate in this collaborative care.

Sarah Nagle-Yang, MD: The second patient that we're going to talk about is Nitya. She is a 31-year-old G1P1 Indian American female who comes in at 6 weeks postpartum with her son, and this is her first time seeing you. She wants to establish care for herself and for her son. She reports that she feels overwhelming sadness, low energy, sluggishness, like she can't get motivated to do anything, having a hard time concentrating, feels like her appetite isn't what it used to be. She is also noticing pretty rapid weight loss, more than you would expect at 6 weeks postpartum. She also endorses passive suicidal ideation. Her EPDS score is 25, and she answers negative to the suicide question which is question number 10. However, when you ask her more about how she's feeling, she says, "You know, I don't want to kill myself, but I do have this picture that comes into my mind about being hit by a car. When I have that picture, it just feels like a relief, like I can be out of this situation." "Everyone says my son is beautiful, but I just don't feel anything. I feel guilty about the way that I'm feeling disconnected from my baby." "When I picture my future, I see darkness. I don't know how I can have a life like this, really a sense of hopelessness about the future." "I'm losing my pregnancy weight so fast. Everyone's complimenting me, but really, it's not a good thing. It's because I'm feeling like I just can't eat, like I'm just not hungry, like I'm just too sad to think about nourishing myself."

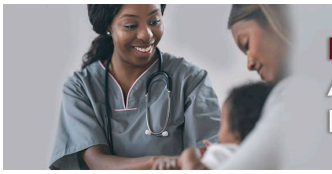
When you ask her more about her history, you learn that she has a 10-year history of OCD and major depressive disorder that has been moderate in course over the past 10 years and started when she was 24. Previously, she was on a combination of psychotherapy and fluoxetine at 80 mg a day, but during early pregnancy, she was feeling so nauseous and vomiting so much that it was too hard to take the medication. She stopped it and just hasn't resumed.

When I think about Nitya's presentation, it's striking to me the severity of her depressive symptoms. I'd be worried about the direction that this is going. She's only 6 weeks postpartum. She's taking care of a very young baby who needs her much of the time. Most likely her sleep has been disrupted. I'd want to follow up this conversation that I've had to understand better. She has a history of OCD. I'd want to know more about if OCD is coming into the picture now. We might be asking about depression because she's had a positive screen on the EPDS, and if she's having an exacerbation of her underlying OCD and we're not addressing that, then certainly it would work against us in terms of a treatment response or achieving remission of her depressive symptoms. I'd also want to know more about her support system. I'm not sure who is at home with her, who is helping her in terms of caring for her son, and what that means for sleep. I would be thinking about ways to support her in prioritizing sleep, in addition to the other things that we think about from a treatment perspective. In terms of first-line treatment approach, I would be thinking about fluoxetine. She presumably had a good response from fluoxetine in the past. She required 80 mg, which is not surprising at all, given the fact that her underlying diagnosis has been both depression and OCD. We know that we often need much higher doses in OCD, and 80 mg wouldn't be the highest dose that I would use in OCD. Getting her back to that dose as quickly as I can and as she can tolerate would be 1 thing that I would be thinking about. Certainly, making sure that she is engaged in psychotherapy again would be important and then thinking about follow-up that's attuned to the level that I'm worried. I am thinking about seeing her back in 2 weeks and following her at a pretty frequent cadence until I can see that she's starting to have a response and then continuing to follow her until she's achieved a full remission.

I'm curious, Dr. Yawn, if there are other treatment options that you would consider or add to that mix that I outlined.

Barbara Yawn, MD, MSc: I'd want to know what's surrounding her and at what point would we think about neuroactive steroids for this woman. When would we think about that, Dr. Clayton?

Anita H. Clayton, MD: I think that's a good question, especially with fluoxetine because it takes so long to reach steady state with fluoxetine and then you'd want to get up to 80 mg per day. I would be starting at 20 mg, but I would go to 40 mg after 10 days, 60 mg after 10 more days and 80 mg after 10 more days. We might start to see a benefit then. I would also check and see what type of therapy her provider was giving her because cognitive behavioral therapy is the most effective treatment for anxiety disorders in terms of therapy. I didn't speak to neuroactive steroids, but I would wait until we had her at 80 mg a day of fluoxetine because then she will have been on some fluoxetine, increasingly over the course of that time period. We could then make an assessment. She could get a



neuroactive steroid even at 80 mg of fluoxetine a day concomitantly.

Barbara Yawn, MD, MSc: Thanks. Well, let's go on to the next case. This is yours, Dr. Clayton.

Anita H. Clayton, MD: This is Ugochi. She's a 34-year-old G2P2 African American woman who presents to your clinic for her 6-week postpartum visit. She has her infant daughter with her, but they missed the daughter's 1-week, 2-week and 4-week well-child checks. She has a past medical history significant for postpartum depression with a previous pregnancy, and it was managed with 50 mg of sertraline. A low dose worked for her. However, she's got other things happening this time. She was pregnant with twins, and she suffered a late-term pregnancy loss of 1 twin at 35.5 weeks. Then, both twins were delivered quickly by C-section; 1 was a live birth, and 1 was stillborn. She was prescribed sertraline 50 mg per day on discharge from the hospital because that previously worked for her. Here's what she says in our evaluation. "I keep replaying the moment I found out that she didn't have a heartbeat, each time picturing it happening differently." She feels joy related to the daughter she has, but then feels guilty for feeling that way too, given the loss of her other child. She can't stop going over everything that she might have done wrong, so she's got inappropriate guilt and ruminations. Also, she feels like it must have been something done by her to cause this, and she just can't accept it. She keeps replaying it over and over. She wants to change it, and she hasn't really accepted that she cannot. She reports overwhelming sadness. Mood symptoms are a cardinal symptom. She also has frequent crying spells, excessive guilt, self-loathing, trouble concentrating, low energy, poor appetite and other things like stomachaches and frequent headaches. She's lost a lot of weight because of her appetite being low. Her EPDS is significant at 26, and her item 10 score is a 2. We're a bit worried about that.

What's the next step in evaluating this patient? One, I would be sure to make a diagnosis of major depressive episode. She has the cardinal symptom and 5 other symptoms, so she does meet those criteria. It is severe, so we need to act relatively quickly. The key thing that we must add into the mix and do quickly is trauma-based therapy. This was a significant trauma for her around the delivery and pregnancy. Despite the fact that she has a beautiful daughter, she doesn't have the second child. We really need to worry about trauma in that case. She has severe symptoms. She ruminates a lot, and this may be significantly impacting her function. I would talk to her about that. She's also really distressed.

What would you do about her score of 2 on the EPDS item number 10? I would do an in-depth suicide assessment. You need to know if she's safe for herself and whether her baby is safe because quite often, we see thoughts of self-harm and actual self-harm of moms and potentially of their baby in the first 10 weeks after delivery. We want to manage her. She's already 6 weeks out.

Then, what can we do to adjust her treatment regimen? I would rapidly increase the sertraline since that worked for her before, but we're going to have to go way beyond that 50 mg since she's already on it, and it hasn't worked after 6 weeks. We could consider adding zuranolone to her treatment, especially given the scoring on thoughts of self-harm.

Barbara Yawn, MD, MSc: I'd like to remind all of my primary care colleagues that these were 3 complex patients, and you shouldn't limit your screening to just this group of patients with all these risk factors. For one, I didn't know some of these risk factors until we got into it in depth. The other thing is that women with no obvious risk factors are also going to have mild or even moderate postpartum or perinatal depression. When we talk about screening, we need everybody who is pregnant and is postpartum.

Anita H. Clayton, MD: Our key concepts for this presentation is depression during and after pregnancy is common. It's harmful to the mother and the child if it's unrecognized, untreated, or even under-treated. We need to screen routinely for perinatal depression using a validated questionnaire. We need to use that to monitor outcomes, and we need to individualize treatment and consider women's preferences in their medication. If their appetite is reduced, they don't want something that's going to continue to reduce their appetite, for example. SSRIs and SNRIs appear safe and efficacious for mild, moderate, and severe perinatal depression and especially during pregnancy since

the risks of use during pregnancy of SSRIs and SNRIs is low. Neuroactive steroids, like allopregnanolone and its analogs, that are GABA-A receptor positive allosteric modulators have been FDA-approved for postpartum depression. They are safe and efficacious in moderate or severe perinatal depression and particularly should be considered in women who have been treated during pregnancy but have not achieved remission and are postpartum and depressed.

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