JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eNeonatal Review
Podcast Issue
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by an Educational Grant from Ikaria and Abbott Nutrition

VOLUME 8 — ISSUE 12: TRANSCRIPT

Featured Cases: Neonatal Abstinence Syndrome

Our Guest Author is is Dr. Estelle Gauda, Professor of Pediatrics, and Dr. Tamorah Lewis, a fellow at the Johns Hopkins University School of Medicine in Baltimore.

After participating in this activity, the participant will demonstrate the ability to:

- Describe the different assessment tools used to determine whether pharmacological intervention is needed for an infant with prior prenatal exposure to opioids,
- Discuss the risk of sudden infant death syndrome in infants with prenatal exposure to opioids, and
- Discuss the effectiveness of buprenorphine and methadone for treating opioid addiction in pregnant women and the effect of these agents on the frequency and severity of neonatal abstinence syndrome in their infants.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to *Neonatal Abstinence Syndrome* in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 8, Issue 11 eNeonatal Review newsletter—Neonatal Abstinence Syndrome.

Unlabeled/Unapproved Uses: The author has indicated that this presentation will include discussions of currently unapproved uses clonidine and buprenorphine.

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Faculty Disclosure
Estelle Gauda, MD and Tamorah Lewis, MD have disclosed no relevant financial relationships with commercial supporters.

Release Date
June 7, 2011

Expiration Date
June 6, 2013

PROGRAM DIRECTORS

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MR. BOB BUSKER: Welcome to this *eNeonatal Review*™ Podcast.

eNeonatal Review is presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Ikaria and Abbott Nutrition.

Today's program is a companion piece to our Volume 8, Issue 11 eNeonatal Review newsletter: *NAS — Neonatal Abstinence Syndrome*.

Our guests are both authors of that issue: Dr. Estelle Gauda and Dr. Tamorah Lewis from Johns Hopkins.

This activity has been developed for physicians, nurses, and respiratory therapists caring for neonates. There are no fees or prerequisites for this activity.

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Learning objectives are, that after participating in this activity, participants will demonstrate the ability to:

- Describe the different assessment tools used to determine whether pharmacological intervention is needed for an infant with prior prenatal exposure to opioids,
- Discuss the risk of sudden infant death syndrome in infants with prenatal exposure to opioids, and
- Discuss the effectiveness of buprenorphine and methadone for treating opioid addiction in pregnant women and the effect of these agents on the frequency and severity of neonatal abstinence syndrome in their infants.

I'm **BOB BUSKER**, managing editor of eNeonatal Review. On the line we have with us Dr. Estelle Gauda, Professor of Pediatrics, and Dr. Tamorah Lewis, a fellow. Both clinicians are at The Johns Hopkins University School of Medicine in Baltimore.

Drs. Gauda and Lewis have no relevant relationships with commercial supporters to disclose, and their presentation today will include discussion of currently unapproved uses clonidine and buprenorphrine.

Dr. Gauda, Dr. Lewis — welcome to this eNeonatal review podcast.

DR. ESTELLE GUADA: Thank you, Bob, for inviting me.

DR. TAMORAH LEWIS: : It's my pleasure, thank you.

MR. BUSKER: Our objective today is to explore how the information discussed in your newsletter issue can be applied in actual patient practice. So if you would, Dr. Lewis, please present us with a patient scenario.

DR. LEWIS: BT is a 2.3 kg female term infant born to a 24-year-old caucasian female who is gravida 1, now para 1. Her pregnancy was complicated by heroin addiction. The mother has been enrolled in a methadone maintenance program since 23 weeks' gestation, and since that time has been taking 150 mg of methadone daily. She denies using alcohol or other illicit substances but does admit to smoking 10 to 12 cigarettes a day during the pregnancy.

At the time of the delivery, the mother's urine toxicology screen was negative for opioids, cocaine, and benzodiazepines. The infant was born via spontaneous vaginal delivery and had Apgar scores of 8 and 9. Other than being symmetrically small for gestational age, the infant has a normal physical exam. The infant rooms in with the mother, and the mother intends to breastfeed.

MR. BUSKER: Dr. Gauda, in the case just presented: as opposed to the routine type of monitoring that would be used for a nonexposed newborn, what additional monitoring will this infant need?

DR. LEWIS: And do you mind reviewing the different monitoring tools that can be used for a baby with neonatal abstinence syndrome?

DR. GUADA: One of the important things we need to do for this infant is monitor for signs and symptoms of neonatal abstinence syndrome. And similar to being able to look for vital signs, we gave tools that measure the severity of opiate dependency in infants who have been exposed to opiates prenatally.

I'm going to review a few of those and focus on the ones that are most commonly used and how they are used. Particularly, the one that we use here at Hopkins and the one that's most commonly used, probably, across the United States is the Finnegan neonatal abstinence scoring system. It was designed by Dr. Finnegan, and it's a 31-item scale that quantifies the severity of NAS and guides treatment.

You score the infant every four hours. The constellations of signs and symptoms include an increase in stools, irritability, increase in Moro response, increased crying, jitteriness; things that certainly are evident in the babies with neonatal abstinence syndrome.

We apply a numerical score between 1 and 5, and then you sum the scores. With a score greater than 8, you would most likely intervene with pharmacological therapy, in contrast to the standard things we do for babies.

We use a modified Finnegan score here at Hopkins in which some of the scoring items have been condensed into an 18-scoring algorithm versus a 31-item scale.

The other scoring system is the Lipsitz neonatal drug withdrawal scoring system. It's an 11-item scale, and each symptom is scored between 0 and 3, depending on the severity of the symptom. A score greater than 4 recommends that pharmacological therapy be done. This scale has been recommended by the American Academy of Pediatrics; however, it does provide somewhat subjective ratings of gross individual symptoms expressed by some infants, and some of the items are yes or no.

So it is our preference and my recommendation that the modified Finnegan score can be used, and actually example of this can be seen in the article that was published by Janssen in Opiate Management in 2009.

The other scores include the Austria score, which is a six-item, simple ranking score, the neonatal withdrawal inventory score, and the neonatal narcotic withdrawal index. These are used less commonly.

I want to point out that the goal of therapy is to reestablish homeostasis in the baby, so it is important to use these scoring tools because some of these symptoms are very subjective. If I can say that your tolerance to a baby who has increase in crying may be less tolerant than the nurse or the other physician. Because these scores can be subjective and because they can affect how effectively the treatment is done for these babies, I think it's really important that we try to be as objective as possible. I absolutely cannot emphasize more to your readers and to your listeners that, in fact, these scoring tools be used to help to guide therapy.

MR. BUSKER: Dr. Lewis? Your question?

DR. LEWIS: Dr. Gauda, what is the probability that an infant who is exposed to 150 mg of methadone daily will have signs of opiate dependence?

DR. GUADA: That's a good question, Dr. Lewis. You know, you point out that the baby has been exposed to 150 mg of methadone, and that is a high level. But believe it or not, the majority of studies do not show that there is a direct relationship between the amount of opiate that the mother is on and the severity of neonatal abstinence syndrome.

With that said, however, I do want to say that if you look at the numbers, that postnatally, about 94 percent of infants who are exposed to intrauterine opiates usually develop neonatal abstinence syndrome, and of those approximately 60 to 80 percent will need pharmacological treatment for neonatal abstinence syndrome. I want to point out again that there is not a direct relationship between how much the mother is getting and how severe the symptoms may be.

Earlier treatment programs have tried to taper the mother down off of her methadone to get a lower dose in the hope that the babies might, in fact, have less severe neonatal abstinence syndrome. That didn't turn out to be the case. What can happen under those circumstances is that the mother may be more likely to use heroin again, and that is not something that you want to happen. So, again, the treatment should be directed toward the mother to give her what she needs to control her drug craving so that she doesn't go back to use illicit substances.

DR. LEWIS: Dr. Gauda, if the baby in this case does require pharmacologic therapy for signs of NAS, what are the appropriate therapies to begin?

DR. GUADA: Although the mother is on methadone, the usual standard of treatment is to put the baby on a shorter-acting opiate, particularly morphine, a sulfate, or either morphine hydrochloride. Morphine sulfate

comes in a concentration of 0.4 mg/mL, and morphine hydrochloride comes in a concentration of 0.2 mg/mL.

We use a shorter acting opiate preparation because it's much easier to taper it and to titrate it down than methadone. We know more about the pharmacokinetics of morphine in babies than we know about methadone, but the pharmacokinetics are varied in older people as well as in children. For example, in adults who are coming off their methadone or someone who is going through detoxification, the recommendation is to wean it by 10 or no more than 20 percent every 14 days.

We don't do that in babies who might have been placed on methadone. We recommend that that weaning be done every two to three days. In contrast to babies who are on our shorter-acting morphine drug or opiate preparation, you can wean that infant every 24 hours. We recommend going down only about 0.02 mg of morphine during a 24-hour period, provided that the baby has modified Finnegan score of less than 9.

MR. BUSKER: A question on dosing, Dr. Gauda. In a circumstance where a baby does need morphine for NAS symptoms, do you dose the morphine according to the baby's symptoms or by the baby's weight?

DR. GUADA: There are two approaches. Many people base it on milligrams per kilo. However, I think the approach of basing it on symptoms and starting at a certain amount and increment up, depending on what the scoring system is, is another very reasonable approach.

And, in fact, that's the approach that we took in the clonidine study that is mentioned in the transcript. But let me explain that a little better for you.

MR. BUSKER: You mentioned that approach when you described the clonidine study in your newsletter issue. Would you expand on that a little more for us?

DR. GUADA: The symptom-based approach that Janssen also describes in her paper in Opioid Management in 20091 that, for example, if an infant has a score between 9 and 12, you would start the morphine sulfate at 0.04 mg. If the scoring is 13 to 16, you would start it at 0.08 mg. And if the score is 17 to 20, you would start morphine sulfate at 0.12 mg.

That is a symptom-based approach that works very well, and we have had a lot of good experience with it. It's actually how we do it here at one of the hospitals in the Hopkins system. Now, the other question is, is what do you do when you're trying to wean the baby off? I must emphasize to our readers that it's really important that the frequency of morphine dosing should be every three to four hours, because extended dosing intervals are associated with longer lengths of stay.

So it is important that you give the medication when the baby needs it. But also if the baby is stable for 48 hours without incrementing scores and has a score in the modified Finnegan scoring system of less than 9, then it is appropriate to use the scoring to then start to wean the baby and not to use our just gestalt on whether we think the baby is more irritable or not.

With this approach, you can be very successful in decreasing the length of stay. In fact, with this approach, we have a length of stay for some of our babies who have been exposed to opiates throughout gestation, and, in fact, their length of stay is somewhere between two and three weeks.

DR. LEWIS: Dr. Gauda, what if you can't control the NAS symptoms with just morphine or just methadone? When do you have to add a second drug, and if you add a second drug, which ones would you consider?

DR. GUADA: Occasionally we do have infants who are very difficult to manage, and those are often babies who have poly-drug exposure. Maybe concurrently with their opiate exposure, mother is on a benzodiazepine. Perhaps it's been nicotine. Nicotine is very important in enhancing the signs and symptoms of neonatal abstinence syndrome. So occasionally you do have to add another drug.

Two drugs are usually given, and I'll give you the reasons for using both. I'll speak about clonidine first, because it is my favorite and not because it is just the drug du jour per se but because it makes a lot of pharmacological, molecular, and cellular sense to use it.

Most of the signs and symptoms of withdrawal are associated with the release of norepinephrine from neurons that contain the mu opioid receptor. The mu opioid receptor, as you know, binds methadone or morphine and decreases the excitability of the neuron.

However, with continued exposure, that neuron sort of wants to reestablish excitation. What happens is upregulation of the norepinephrine within the cell, and when the morphine is released from the opiate receptor, which happens at birth, there is a large release of norepinephrine that is then associated with tremors, increase in blood pressure, jitteriness, excitability, tachycardia, increase in respiratory rate, all of these things that we know about the sympathetic nervous system.

Clonidine binds to the alpha-2 adrenergic receptor on norepinephrine-containing neurons. So it, too, decreases the cell's excitability. So the binding of clonidine to the alpha-2 adrenergic receptor, in addition to the concurrent binding of morphine to the mu opioid receptor, will decrease the excitability of that cell. And then as you then slowly reduce the doses of these medications, the cell is able to reestablish its normal level of norepinephrine.

Because the clonidine is targeting the norepinephrine-containing neurons, you can have withdrawal from nicotine, you can have withdrawal from opiates, you can have withdrawal from many different substances that all come to a common final pathway of that related to the norepinephrine-containing neuron.

So I'm an advocate of clonidine. But on the other hand, it is not recommended that it be started immediately in all babies. If you can do well with one single drug, then do so. However, occasionally a baby will need another. The indicator would be if the baby needs more than 0.2 mg of morphine equivalent every four hours, then we add clonidine in a dose of 1 mcg/kg Q4 hours.

Some of the pharmacokinetic data that we gathered on this population shows that after the second week of life, going up to 1.5 mcg/kg Q4 may also be appropriate, because it's renally excreted, and the blood flow to the kidney as well as renal function increases.

MR. BUSKER: Dr. Gauda, what about the use of phenobarbital?

DR. GUADA: Phenobarb is often used. Here are some indications for which phenobarb might be appropriate. I think phenobarb got most of its claim to fame, if I can use that expression, when an article came out in Pediatrics 2002 by Mary Coyle.2 What they reported was something that a lot of insurance companies picked up on.

They showed that if you add phenobarb to DTO versus DTO alone, you can significantly reduce the length of hospitalization by several weeks or so, which represented a marked increase in savings. However, the length of treatment for those babies was excessive. If I could just quote here, that paper basically showed that the babies who were discharged on phenobarbital remained on phenobarbital for two to nine months after discharge, with an average length of treatment being three and a half months.

So although these babies were discharged from the hospital, they were still treated for their neonatal abstinence syndrome for an extended period of time. We do know about some data from babies with seizures. Certainly the standard practice is now to get the baby off the phenobarb as soon as possible, to decrease the changing of the neurotransmitter profile that's going in the brains of these babies.

Phenobarbital is a sedative, and it works by increasing the inhibition of the GABA neurotransmitter system. GABA is the major inhibitory neurotransmitter in the brain, so although you are sedating the infant to get the decrease in neonatal abstinence syndrome, you're also decreasing neuronal activity of a very major neurotransmitter system.

So it is not my recommendation to use phenobarbital. However, circumstances in which I would use it would be in a baby who has seizures from neonatal abstinence syndrome. Although you must adequately treat that, until you know for sure that the infant's EEG is normal, you should start phenobarbital as well.

MR. BUSKER: A question, Dr. Gauda, about the safety of breastfeeding. This mother — who's going to continue to take oral methadone — wants to breastfeed her infant. How do you feel about that?

DR. GUADA: I strongly recommend breastfeeding. Breastfeeding is absolutely the thing that should be done to allow for bonding, and it's very relaxing for a baby to breastfeed. It's very relaxing for the mother as well. For a mother who has a history of opioid addiction, we should encourage as much normalization as possible. We need to normalize the infant, and we need to normalize the infant/mother bond. And to breastfeed is a wonderful thing.

You might say, okay, but the baby might be getting methadone. Well, the studies don't really show that. They may be getting a small amount, and I would say that they are, but we do know that the babies who are breastfed by mothers who are well controlled in methadone programs, those babies need less of an additional opiate, and they also have a shorter length of stay.

However, I must also say that when the amount of breast milk decreases, some of those babies may have enhanced symptoms of withdrawal that might have to come to the attention of a professional for additional treatment. So I would suggest that the baby be followed closely, but breastfeeding be strongly encouraged.

DR. LEWIS: Outside of the opiate exposure and the NAS that has now been treated, are there other things that the mother should be counseled about on discharge of this baby?

DR. GUADA: The mother is still smoking, and that's a problem. We do know that infants who have been previously exposed to opiates have a higher incidence of sudden infant death syndrome. Currently, the number one modifiable risk for sudden infant death syndrome, after turning babies on their back, is prenatal exposure to cigarette smoke. So this baby already has added increase in risk for dying of sudden infant death syndrome.

We really must be sure that we talk to the mother about back sleeping and stopping smoking because secondhand smoke also increases that risk. That's a hard conversation to have, but it has to be very much emphasized to the mother that the baby is still at risk.

The SIDS rate in opiate exposure has gone back and forth. I've been intrigued by some more recent data that has been published in the last several years looking at the co-association between HIV and opiate use during pregnancy. When you look at those babies of an NIH study just published that came out of Switzerland published in the Archives of Diseases in Childhood in 2007,3 it was amazing what the risk was.

If I could quote it here, they looked at 124 pregnancies and found that the relative risk of sudden infant death syndrome compared to the general population was 18 with a confidence interval of 9 to 38, or 95 percent confidence interval for all infants of HIV-infected mothers and 69 with a 95 percent confidence interval, 33 to 141, for those with intrauterine opiate exposure. That's an astonishingly increased incidence of sudden infant death, 14.9 per thousand live births.

With HIV plus opiate exposure, the incidence is 5 per thousand live births. Let me put that in perspective for you. In the United States the incidence of sudden infant death syndrome was 0.57 per thousand births.

So we know that HIV and prenatal opiate exposure commonly go together. And so this is an intriguing association that I think we need to pay more attention to and find out the mechanism of that.

MR. BUSKER: And we'll return in a moment with Dr. Estelle Gauda and Dr. Tamorah Lewis from Johns Hopkins.

DR. CHRISTOPH LEHMANN: Hello, I'm Dr. Chris Lehmann. I'm the Director for Clinical Information Technology at the Children's Medical and Surgical Center at Johns Hopkins and one of the Program Directors for eNeonatal Review.

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For more information on registration to receive eNeonatal Review without charge, or to look at archived issues, please go to www.eneonatalreview.org. Thank you.

MR. BUSKER: Welcome back to our eNeonatal Review podcast. I'm Bob Busker, managing editor of the program. Our topic is neonatal abstinence

syndrome. And our guests are Drs. Estelle Gauda and Tamorah Lewis from the Johns Hopkins University School of Medicine.

Before we continue, I want to remind our listeners that links to publications referred to in today's discussion can be found in the transcript version of this podcast.

And now, Dr. Lewis, please present us with another case scenario.

DR. LEWIS: TL is a 21-year-old African-American woman with sickle cell disease whose chronic pain from our sickle cell disease is managed with oral tramadol and a fentanyl transdermal patch. She has continued both of these analgesic medications during her pregnancy. She is currently admitted to the labor and delivery service in premature labor at 28 weeks' gestation.

You are the neonatologist on call and have been asked to discuss with the parents potential complications associated with premature delivery. During this interaction, the mother wants to know if her chronic pain medications have affected her baby and if the baby is addicted to the narcotics that she has been taking.

MR. BUSKER: Dr. Gauda, tell us about tramadol — what is it, and does it cross the placenta?

DR. GUADA: Yes, tramadol does cross the placenta, and it is a very weak opiate analgesic. It's used to treat moderate to severe pain. Tramadol is a synthetic codeine, and codeine, as you probably know, gets metabolized to morphine.

The other interesting thing, though, is that tramadol not only blocks opiate receptors, it also releases serotonin, and it inhibits the reuptake of norepinephrine, very similarly to SSRIs and the SNRIs that we're familiar with. It can also block NMDA receptors, similarly to methadone.

DR. LEWIS: In this baby who's been exposed to both tramadol and a transdermal fentanyl patch, what is the probability that she will require pharmacologic therapy for opioid withdrawal?

DR. GUADA: Well, similarly — you didn't ask me about fentanyl, but I'm sure you know — that fentanyl is a very, very potent opiate, about 100 times more potent than morphine. It also is very lipophilic, so it crosses the placenta easily as well, and in addition it gets into the breast milk.

Whether this baby will have withdrawal, I'm not sure, because the baby is only 28 weeks. The symptoms of neonatal abstinence syndrome in preterm babies are less commonly presented than those in a term infant , and there could be a variety of reasons why that is the case. It's possible that the baby may have some irritability, but whether the irritability would be sufficient that the baby might, in fact, need opiates for to decreasing that irritability is unclear. I think we'd have to follow the baby closely.

DR. LEWIS: This mom who has sickle cell disease will need continued treatment with analgesics after the delivery. She wants to breastfeed her infant but also continue to take the tramadol and the fentanyl. Do you think this is safe, as safe as it is for a mom who is taking methadone?

DR. GUADA: Let's talk about the fentanyl first, and then we can talk the tramadol next. Fentanyl, as I mentioned, will get in the breast milk. But I only know of one paper that's been published in the Journal of Human Lactation in 2009,4 in which they actually measured the fentanyl metabolites in an infant who was breastfeeding. That baby was term. Right after birth he did have neonatal abstinence syndrome that needed therapy. But then after discharge, the mother continued to breastfeed. And when they measured the fentanyl metabolites in the baby's bloodstream, they were very low.

So we don't have a large population here, but I would again encourage the mother if she was only on fentanyl to continue to breastfeed the baby.

What I'm more concerned about is the tramadol. As I mentioned, tramadol gets metabolized to codeine, and codeine then gets metabolized to morphine. It's known that there can be some ultra-fast metabolizing phenotypes that, in fact, will increase the metabolism of codeine to morphine much more rapidly, which results in a very high level of morphine in the breast milk that then ends up increasing the level of exposure to the baby. Several reports have addressed overdosing of babies with morphine from a mother on codeine.

I would be very cautious about this and follow the baby closely and then talk to the mother about the

signs and symptoms of sleepiness, not feeding well, those sorts of things.

MR. BUSKER: Dr. Lewis, a question about neurodevelopmental outcome?

DR. LEWIS: Does this baby who's been opiate-exposed have different neurodevelopmental outcomes than a typical 28-week preemie?

DR. GUADA: I wish I knew the answer to that, and I really don't. There aren't any studies. Most of the studies that have looked at neurodevelopmental outcome from preterm birth have not looked at preterm birth with the caveat of opiate exposure. The opiate exposure literature is looking at term infants in neurodevelopmental outcome.

So I would say that I don't think we know, but I would be very encouraging to the mother and then say some important things that it's about the environment that the baby goes home to, that he and she would be stimulating environment to work on sort of milestones, that sort of thing. So I would be encouraging with the mother.

MR. BUSKER: We've got time for one more case scenario — so if you would, Dr. Lewis.

DR. LEWIS: The third case is about MT, who's a 30-year-old white woman who's HIV-positive secondary to exposure to IV drug use. However, for the past 10 years the mother has been compliant in a methadone maintenance program. She is currently 14 weeks pregnant with her third child. Her two other children, ages six and three, are doing well. However, both children had moderate to severe neonatal abstinence syndrome and remained in the hospital for three weeks after birth. The mother is concerned that this will happen in her third pregnancy.

She's heard about buprenorphine and was told that infants exposed to buprenorphine do not have neonatal abstinence syndrome. She is seeking the opinion of the neonatologist about whether she should switch from methadone to buprenorphine during this pregnancy.

She's currently taking 100 mg of methadone per day, along with her typical HIV anti-retroviral medication.

MR. BUSKER: Before you discuss the case, Dr. Gauda, please brief us on buprenorphine and how it differs from methadone.

DR. GUADA: Buprenorphine is also an opiate, and it binds to the mu receptor, but it also binds to the kappa receptor and the delta opioid receptor. The interesting thing is that it's a partial agonist for the mu opioid receptor and a partial or FU agonist for the delta opioid receptor.

Of importance is its very high binding affinity for the mu receptor. This is really important because, since it binds so tightly, if an overdose were to happen, naloxone doesn't treat it as effectively as it would with a methadone or morphine overdose. However, it can, and naloxone is given as a continuous infusion with an opiate overdose from buprenorphine.

The other thing you should know is that the preparations that are being used for buprenorphine here in the United States do not contain naloxone at the current time. But some of them will, and in other countries it does, and I assume that it will certainly become more common in the United States for the preparation to contain naloxone and buprenorphine. That would be done because then it decreases the possibility that it can be abused by IV.

You must know that buprenorphine also is given sublingually. It can be given intravenously but is not taken orally because it rapidly gets metabolized or broken down in the stomach. So it has to be done sublingually, and that's important.

In contrast to methadone, buprenorphine has a ceiling effect. It has a ceiling effect on respiratory depression as well. If you give 32 mg of buprenorphine, that's what you get. If you give 40 or 50, there is no added effect. That's in contrast to methadone, with which you can continue to escalate the methadone and get the effect.

DR. LEWIS: Dr. Gauda, are there any adverse effects of buprenorphine on the developing fetus?

DR. GUADA: A few studies are looking at the effect of buprenorphine on the developing human fetus, but of the studies that do exist, there does not appear to be an increase risk of any teratogenic effects. We have much more experience, as you know, with exposure to methadone, which is a full agonist to the mu opioid receptor, and we have lots of babies that have been

exposed to methadone. Here we can say that the association with teratogenic effects is minimal to none.

Methadone also, if I can bring that up, in comparison to buprenorphine, does bind to the NMDA receptors, which is a major receptor that regulates glutamate transmission, and glutamate is the primary excitatory neurotransmitter in the brain. So whether this binding of methadone to the MDA receptors contributes to worse neurocognitive outcomes in infants prenatally exposed to methadone than in control infants is unclear. But I must say that buprenorphine doesn't have that effect. So maybe there's some advantages that we don't know about buprenorphine.

DR. LEWIS: Dr. Gauda, how would you respond to the mothers question whether or not she should switch from methadone to buprenorphine during this pregnancy to decrease the risk of NAS in the baby?

DR. GUADA: My overall recommendation would be that she not do it for the following reasons. Switching from buprenorphine to methadone is often difficult, even in people who are not pregnant. And the withdrawals can last for several days or more and are often encountered mostly when the methadone dose is higher than 30 mg a day. And as you know, this mother is on 100 mg a day.

The switching to buprenorphine at this higher dose can be uncomfortable, because you have to stop the methadone for a little while and then add the buprenorphine. So there could be some risk of the baby having some withdrawal.

A recent trial that was discussed in the newsletter and was published in the New England Journal of Medicine in 2010 noted that, although infants had significantly less neonatal abstinence syndrome in mothers who were on buprenorphine than in those who are on methadone, the severity of the NAS was less, but they still had neonatal abstinence syndrome. So I would suggest that this mother not change because of the risk of her having withdrawal during pregnancy.

And in addition, in that study, they showed that the percentage of mothers who were unable to stay on buprenorphine was higher than those who were on methadone. So that increases the chance of the mother actually getting involved in more illicit drugs on the street, and that is something that we don't want to happen.

DR. LEWIS: Dr. Gauda, my last question about this case is, the typical neonatal course for an infant prenatally exposed to buprenorphine, can you describe that briefly?

DR. GUADA: The incidence of neonatal abstinence syndrome appears to be the same between the methadone and buprenorphine-treated infants, but the severity of it is much less for the buprenorphines. And if I can give you some data that is outlined in the newsletter, in 131 neonates whose mothers were followed to the end of the pregnancy, with 58 exposed to buprenorphine versus 73 exposed to methadone, the buprenorphine group needed less morphine and had significantly shorter hospital stays. In fact, the babies on buprenorphine had 10 days of exposure in the hospital versus 17 days, and that's absolutely significant.

MR. BUSKER: Dr. Gauda, take the last word for us, please, to wrap up this discussion of NAS.

DR. GUADA: I think NAS is a problem of our newborns who have to be adequately treated, but I'm encouraged by the new research, particularly the work on buprenorphine, the clonidine work, other ways to give us more choices in the ways that we can adequately treat our babies. And then I just want to remind our listeners that, although we've talked a lot about pharmacology here, it's really important to note that teaching the mother how to bond with her baby, teaching her how to calm her baby without using drugs is also very, very important.

MR. BUSKER: Dr. Estelle Gauda, Dr. Tamorah Lewis — thank you for participating in this eNeonatal Review podcast.

DR. GUADA: Thank you, Bob. I enjoyed doing it, and thank you very much.

DR. LEWIS: I appreciate the invitation, and I really enjoyed it. Thank you.

MR. BUSKER: This podcast is presented in conjunction with the eNeonatal Review Newsletter, a peer-reviewed, CME/CE-accredited literature review e-mailed monthly to clinicians caring for neonates.

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eNeonatal Review is supported by an educational grant from Ikaria and Abbott Nutrition.

Thank you for listening.

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