

Update on Reproductive Safety of Psychotropic Medications Part II of an Interview with Lee S. Cohen, M.D.

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Currents: Dr. Cohen, are benzodiazepines teratogenic?

Cohen: Early reports suggested that benzodiazepines, specifically diazepam, were associated with higher risk of cleft lip and/or cleft palate in children exposed during the first trimester, but several subsequent reports did not replicate that finding. Over the next decade or so, a number of investigators studied effects of individual benzodiazepines and benzodiazepines as a class, but the methodologic problems in their studies were considerable: their patients came from very different settings, had been exposed to different benzodiazepines at different dosages, and often had taken other psychiatric medications or illicit substances. It is therefore difficult to decide which studies are most appropriate for inclusion in a meta-analysis of benzodiazepine exposure. Lori Altshuler and I published a paper in 1996, which included a meta-analysis of benzodiazepines as a class (including diazepam, alprazolam, clonazepam, and other benzodiazepines). We looked specifically at risk for cleft lip and/or cleft palate, because there has been little concern about other malformations associated with benzodiazepines. When we included studies that had great variability with respect to methodologic rigor, we noted a small, but nonetheless increased, risk for oral clefts associated with first-trimester benzodiazepine exposure on the order of 0.6 percent. That is a ten-fold increased risk relative to the general population, where the risk of oral clefts is six in ten thousand.

An even larger meta-analysis was published in the **British Medical Journal** several years ago which examined the risk of malformations, and specifically oral clefts, across all benzodiazepines--and again, the results were mixed. In that study, the risk of oral clefts was increased, but not to the degree that we found in 1996. The increase in relative risk was more modest and differences were more discernible in the case-control than in the cohort studies. In fact, if one excluded from that meta-analysis the most profoundly flawed study (Laegrid et al), the risk estimate would be even smaller for clefts.

I think we can summarize what we know about teratogenic risk of benzodiazepines this way: if there is a risk for clefts, it is probably very small. Accordingly, we do not consider benzodiazepines contraindicated during pregnancy, because, as with depression, the literature suggests an association between untreated anxiety during pregnancy and higher rates of perinatal complications--children with lower APGAR scores and higher rates of pre-term labor, for example. We even noted (and published several years ago) a case of placental abruption in a woman whose panic attacks at term were associated with lability of blood pressure. A short time before that, she had quickly tapered and discontinued treatment with anti-panic therapy, after which she had suffered severe recurrent symptoms. So again, consideration of risks and benefits suggests that benzodiazepines need not be uniformly avoided during pregnancy.

Currents: Even during the first trimester?

Cohen: Even during the first trimester. The two meta-analyses I mentioned that were published over the last five years highlight the limitations of meta-analytic approaches for assessing reproductive safety. In those meta-analyses, investigators practiced what we call "class-action teratology," lumping different compounds into one treatment category to get a sample size large enough for good statistical power. In so doing, they not only lumped studies that differed dramatically with respect to rigor, but also considered studies that included women treated with many different benzodiazepines. Historically, we know that medicines in the same family may vary greatly with respect to teratogenic potential. Glutethimide (Doriden) is an example. Glutethimide was marketed in the 1970's as a sedative-hypnotic. It is not teratogenic, but if you change one methyl group, it becomes thalidomide. It's probably not appropriate to generalize about teratogenic potential of drugs that are considered to belong to the same class by virtue of their therapeutic action (SSRI's or anxiolytics, for example), when differences in their chemical structures may convey clinically significant differences in teratogenic risk.

Currents: What about variability of teratogenic risk among the SSRI's?

Cohen: We have the most data about fluoxetine, less for citalopram, and even less for sertraline and paroxetine. A recent study by Ericsson and colleagues from Scandinavia found no increased risk of major malformations in 365 pregnancies with first-trimester exposure to citalopram. One might have expected a larger sample size, since citalopram has been used outside the U.S. for many years, but there had been no registry of pregnancies established by the manufacturer of citalopram, as had been the case with fluoxetine. Instead, the data for their analysis derived from a birth registry within Scandinavia.

It is difficult to assess the reproductive safety of paroxetine and sertraline at this point, and it is even more difficult to assess the reproductive safety of other antidepressants such as venlafaxine, nefazodone, mirtazapine, or bupropion, since we have even less data about them.

Currents: Why, then, is bupropion a category B compound while the SSRI's are category C compounds? Doesn't that imply that bupropion is safer during pregnancy?

Cohen: The category labeling system, originally set up by the FDA to assign risk, includes categories A, B, C, D, and X: a drug is included in category A if controlled studies have demonstrated no risk; for drugs in category B, there is no evidence of risk in humans and the chance of fetal harm is remote; for the many drugs in category C, risk cannot be ruled out, either because of incomplete controlled human studies or because animal studies have shown some risk to the fetus; for drugs in category D, there has been positive evidence of risk; drugs in category X are contraindicated during pregnancy because of reports in animals or humans (either investigational post-marketing studies or post-marketing reports) describing positive evidence of fetal abnormalities.

The FDA's category labeling system is flawed, because drugs for which there are no adverse data and very limited other data can be given a category label that implies safety. In fact, the category label in those cases really indicates that data are unavailable or incomplete. The best example of that in psychiatry is the one you mention--the difference in classifying bupropion and SSRI's. Bupropion is a category B compound

because of absent animal data and very limited human data. There was no bupropion (as Wellbutrin) registry, and now there is a bupropion (as Zyban) registry that has yielded very little data at this point. The category B label of bupropion derives from a dearth of data. We have more data about fluoxetine, citalopram, and other SSRI's, which, as you point out, are in category C. We have a good deal of data with fluoxetine, and an evolving database with citalopram, that support the safety of first trimester exposure. However, because studies of rats given ten- to eighteen-times the maximum recommended dosages of fluoxetine or citalopram had smaller litters, FDA assigned a category C to SSRI's. Therefore, if a clinician looks for guidance in the PDR or the Briggs and Freeman text, which is widely cited in teratology, he or she would conclude, incorrectly, from the category label alone, that bupropion is safer than fluoxetine or citalopram, and that conclusion would be wrong. The good news is that the FDA recently has convened several advisory panels to re-examine category labeling, and I suspect that over the next five years we will see the category labeling supplemented by reproductive safety data in the package insert. At that point, clinicians will be informed not with an arbitrary category label alone, but with a category label complemented by data. You have no idea how many patients we see on our consultation service who come in after being counseled by their obstetrician or primary care physician to switch to another antidepressant with supposedly better reproductive safety based solely on category labeling.

Currents: What about sertraline? There is more data now than there was five years ago.

Cohen: Unfortunately, the manufacturer of sertraline decided against establishing a registry, despite the prevalence of sertraline use and the prevalence of unplanned pregnancies in this country and elsewhere. The number of reports of patients exposed to sertraline during pregnancy therefore remains small.

Currents: Haven't several hundred cases of sertraline-exposed pregnancies been reported?

Cohen: There must be adequate numbers of drug exposures to demonstrate teratogenic risk. For example, you need five- to six-hundred cases of first-trimester exposure to demonstrate even a two-fold increased risk of overall major malformations, compared to non-exposed controls, and that assumes a background risk of two to four percent of major congenital malformations in the general population. You can imagine how many cases of exposure you would need if you wanted to determine risk of a far less common specific anomaly. You would need many more exposures to have enough statistical confidence that, in fact, a medicine was not teratogenic.

Currents: How many cases did we know about when we began to think about fluoxetine as being acceptably safe during pregnancy?

Cohen: There are now approximately 2400 fluoxetine exposures documented in the literature. Once we get 500 to 600 cases, we can begin to feel more comfortable that a compound does not increase the risk of overall congenital malformations, compared with non-exposed samples. But again, you need many, many more cases of exposure when looking for an anomaly (such as oral clefts or Ebstein's anomaly) whose background risk in the non-exposed population is much smaller. As I mentioned, if the background risk in

the general population is two to four percent, you need about 600 cases for enough statistical power to see a two-fold increase in relative risk.

Currents: In practical terms, suppose your patient is a tricyclic nonresponder who has done well on sertraline and either does not respond to or does not tolerate fluoxetine. Based on what you know about sertraline at this point, and also what you know about desipramine or nortriptyline, do you have her "tough it out" on desipramine or nortriptyline or do you say, "Okay. Continue to take sertraline during your pregnancy."?

Cohen: That is one of the most common scenarios we see--the case of the patient who has exquisitely responded to a medicine for which we have less adequate reproductive safety data than we do for, say, fluoxetine or nortriptyline. We do not want the patient to suffer or "tough it out," because depression during pregnancy is associated with compromised neonatal outcome. We would have her continue the medication she was responding to and tolerating, as long as she did so in an informed fashion. I would extend your question to the more common case of the woman who has responded well to venlafaxine or bupropion (and has not responded to medicines for which we have better data supporting reproductive safety) and who inadvertently conceives. Do we have that patient switch to a different medicine for which we have better reproductive safety data, or do we have her stay on the medicine to which she has responded? At our center and other centers, such as Zach Stowe's at Emory, the practice is to leave the patient on the medicine she has responded to and to inform her about what we do and do not know about the medicine. The rationale driving that recommendation is the concern, particularly in a more refractory patient, that switching her to a medicine to which she had either not responded or responded to partially would put her at risk of suffering from depression during pregnancy. That would open the door to a second risky exposure--untreated depression--and could therefore represent a failure in the risk/benefit decision process.

Currents: Would you monitor her any differently than you would a fluoxetine-treated patient during pregnancy?

Cohen: No.

Currents: Incidentally, do you still recommend sonography in lithium-treated patients?

Cohen: In 1994, we reported the more modest risk estimate of 0.5 percent for Ebstein's anomaly associated with first-trimester lithium exposure, and that drove our recommendation that recurrently ill bipolar women stay on lithium during the first trimester. Despite the low risk of cardiovascular malformations from first trimester lithium exposure, we uniformly recommend a Level 2, targeted fetal cardiac ultrasound to document the integrity of the fetal cardiac anatomy. The results are reassuring to parents when it is negative. We have not seen Ebstein's anomaly associated with first-trimester exposure to lithium, but if, at 16 weeks gestation, when we typically recommend that patients get the ultrasound, the results were positive, the patient would have an opportunity to make what might be a very difficult choice to terminate a pregnancy or to plan for appropriate interventions at the time of delivery. It's important to keep in mind that, while we talk about Ebstein's anomaly as a uniform malformation, it really is not. It is a heterogeneous anomaly, one that occurs with varying levels of severity. In its most severe form, it is associated with mortality rates as high as fifty percent. However,

children born with milder forms of Ebstein's anomaly can do very well over a long term with current pediatric cardiothoracic interventions.

Currents: What do we know at this point about neurodevelopmental effects of SSRI's and other psychotropic medications?

Cohen: While we have gotten much more data over the last decade about risk of organ malformations associated with psychiatric medications, we still have little data about longterm neurobehavioral sequelae of prenatal exposure to psychiatric medications. We also have little data regarding longterm neurobehavioral sequelae of untreated psychiatric disorder during pregnancy. We should keep that in mind, at least theoretically, because animal studies show that hypercortisolemia during pregnancy is associated with loss of hippocampal cell volume in the offspring. I don't know of similar studies in humans, but we do know that depression may be associated with hypercortisolemia, and I wonder whether babies born to mothers with untreated depression may be at similar risk.

Of the limited data available, most concern effects of antidepressants. Gideon Koren's group studied seven-year-old children who had been exposed during gestation to fluoxetine, tricyclic antidepressants, or no psychotropic medication. Using a variety of widely used neurobehavioral and neuropsychological measures, they found no differences across the three groups. I find that reassuring. Even more striking are data recently presented by the same group, suggesting that in children exposed to tricyclic antidepressants, fluoxetine, or no prenatal medication, the strongest predictor of neurocognitive development was maternal history of depression. We do not have good data about longterm outcome in children exposed during gestation to benzodiazepines or antipsychotics.

With respect to mood-stabilizers, we have almost no data since 1976, when Schou reported in a relatively famous paper called, "Whatever Happened to the Lithium Babies?", a very preliminary and crude assessment of children who had been exposed to lithium. I say "crude" because its findings were based only on chart review and reports from pediatricians. No studies have been reported since, and so we are now conducting a study in which we are using a variety of neuropsychological and neurobehavioral indices for longterm follow-up of children who had been exposed to lithium *in utero*.

I am most concerned about potential longterm sequelae of fetal exposure to anticonvulsants, given their wider use in treating bipolar disorder. Some data suggest an association between *in utero* exposure to phenobarbital and lower IQ, but that has not been reported across anticonvulsants. But again, few studies have looked at this, and we need better data about longterm sequelae of anticonvulsant exposure, particularly since there is some concern in the teratology community about potential effects of anticonvulsants on longer term neurobehavioral function.

Currents: Have there been animal studies of *in utero* anticonvulsant exposure?

Cohen: There have, but their relevance to humans is unclear.

Currents: Does that apply as well to animal studies of SSRI's and other psychiatric medications?

Cohen: Yes. We know that prenatal exposure to psychiatric medications in animal models results in changes in multiple neuromodulating systems, but how that translates to

humans, let alone to the types of neurobehavioral or neuropsychological outcomes we would be interested in or could systematically measure, is speculative at best at this point.

Currents: What about reproductive safety of St. John's wort or other herbals?

Cohen: We get many questions about the potential wisdom of switching from antidepressants to St. John's wort during pregnancy, and that concerns me. We have seen many women who had finally found an antidepressant that was effective for them after several unsuccessful trials with other antidepressants, who then switched to St. John's wort because they assumed it was safer during pregnancy; some went on to relapse. People tend to assume that "natural" substances are safer. Yet, there are many compounds derived from plants that one would not necessarily recommend for women who are pregnant. It is an enormous and incorrect intuitive leap to conclude *a priori* that treatment with an herbal is safer than treatment with a prescription antidepressant medicine, particularly when we have some reproductive safety data for the prescribed antidepressant that supports absent or low risk.

Currents: Lack of data about adverse effects does not imply reproductive safety.

Cohen: Yes, and that is a critically important point. Analogously, the absence of data showing that an herbal is not effective for a given indication does not imply that it is. You mentioned St. John's wort, but if S-adenosylmethionine (SAME) or omega-3 fatty acids were convincingly shown to be effective for depression, a stronger case could be made for their reproductive safety than for that of St. John's wort. SAME and omega-3 fatty acids are naturally occurring compounds that are essential in a spectrum of human metabolic processes, whereas St. John's wort is not. I would feel more comfortable prescribing either of them than I would an herbal that may have components that confer risk to the fetus during prenatal exposure. Even so, teratology is an area where there is no perfect solution, obliging us to consider relative levels of comfort and relative levels of risk against some hopefully quantifiable benefit.

Currents: Does folic acid have protective effects against drug-induced teratogenicity?

Cohen: The issue of folate supplementation has come up primarily with respect to risk for neural tube defects associated with valproic acid exposure. The recommendation to coadminister folic acid (4 mg/day) to women taking sodium valproate during pregnancy derived from the finding that folate supplementation modulated the background risk for neural tube defects in the offspring of women in the general population. The recommendation did not derive from samples of women who had had babies with neural tube defects associated with exposure to valproic acid. That is an important distinction, because naturally occurring neural tube defects and valproate-related neural tube defects may result from different mechanisms. Yet, because it is hypothesized that there may be a shared mechanism with respect to etiology, the use of folate is probably appropriate in valproate-dependent women with bipolar disorder. Even so, some animal models suggest that valproic acid exerts a direct neurotoxic effect on neural crest cells and may thereby contribute to risk for neural tube defects. Nevertheless, it has become standard practice, at least at our center, to initiate folic acid three months before attempts to conceive in bipolar women who are going to remain on valproic acid during the first trimester. However, given the teratogenicity of valproate (five-percent risk of neural tube defects),

we do not consider it a first-line treatment for bipolar women during their reproductive years, particularly since the rate of unplanned pregnancy in the U.S. is approximately 50 percent.

Currents: Are there outcome data on folate prophylaxis in valproic acid-treated women?

Cohen: We don't have outcome data on the capacity of folate to modulate risk of neural tube defects specifically in women who took valproic acid.

Currents: Let's talk now about psychotropic drugs and breastfeeding. Are there any convincing reports of adverse effects in infants nursed by women taking SSRI's?

Cohen: There are a few case reports, and unfortunately, a few case reports frequently affect clinical practice. For example, an old case report of a child who was noted to be colicky while being nursed by a fluoxetine-treated mother has driven review article after review article recommending avoidance of fluoxetine during breastfeeding. A few reports of adverse effects also have been reported in children nursed by citalopram-treated mothers, and they too have affected clinical practice. The good news is that over the last five years or so, we have seen a growing number of rigorously conducted studies that have attempted to quantify serum concentrations in nursing newborns whose mothers are taking SSRI's, particularly sertraline, paroxetine, and fluoxetine. Those studies have not described toxicity in nursing infants, nor have they demonstrated exposure to medication beyond what most would consider a trace amount.

Currents: Does it seem feasible, from what you know about antidepressant concentrations in breast milk and antidepressant concentrations in infant plasma, that infants could ingest enough drug to cause adverse effects?

Cohen: Some infants may be vulnerable to effects of even trace amounts of medicine, but I believe that they are rare and must be considered in the context of medical and emotional benefits of breastfeeding.

Currents: What is the best available information about breast milk and infant plasma concentrations of SSRI's and other antidepressants?

Cohen: Over the last four to five years, multiple series have been published describing mothers treated with sertraline, fluoxetine, paroxetine, and tricyclics, and the data indicate that they all are secreted into breast milk. In fact, if the medication is absent in breast milk (even using a crude, relatively non-sensitive commercial laboratory assay), the mother is probably not taking the medicine.

It is useful to look at drug plasma concentrations in nursing infants to help quantify their exposure to maternal medication, and a lot of effort has gone into refining laboratory assays so that they can detect very low concentrations. Those assays have shown that it is not unusual to find trace amounts of fluoxetine or sertraline (or their metabolites) in plasma of nursing infants. Zachary Stowe and I have submitted for publication a study of maternal and infant serum fluoxetine and norfluoxetine concentrations in 49 (fluoxetine-treated-)mother-infant pairs; we noted a linear relationship between infant and maternal serum concentrations of fluoxetine and norfluoxetine, suggesting non-accumulation of the medicine.

As I mentioned, it is not uncommon to find trace amounts of both sertraline and desmethylsertraline in infant serum. Paroxetine may differ. Zachary Stowe and I published a study in the **American Journal of Psychiatry** about a year and a half ago in which we found paroxetine in every sample of breast milk in a group of 16 paroxetine-treated mothers, but were unable to find paroxetine in their infants' plasma. It was clearly there, but in concentrations smaller than we could detect with even the sensitive laboratory assay we used (which could detect 1 ng/ml).

Currents: Given the rare nursing infant vulnerable to SSRI adverse effects and the not uncommon finding of some SSRI's in serum of nursing infants, what do you tell your SSRI-treated patients who are breastfeeding?

Cohen: What we tell them at our center is that there is no "safest" antidepressant to take during lactation, and that the antidepressant used for postpartum psychiatric illness should not be guided by whether a woman is going to breast feed, but rather by how she responds to the antidepressant. As I mentioned earlier, we have seen patients who have been switched to medicines that were presumed "safer" after they had not responded to them in the past, and had responded robustly to an antidepressant for which we had less data regarding safety in breastfeeding. Switching patients under those circumstances is a failure in the risk-benefit decision, because it may put them at increased risk for postpartum psychiatric illness.

With respect to possible risk to nursing infants, we tell patients what we know and what we don't know. We do the same thing that I mentioned before when we were talking about teratology. For example, we may know a lot about organ malformations, but we don't know as much about neurobehavioral follow-up of children. So, what we tell patients who ask about breastfeeding is that if a mother uses a medicine (regardless of the type of medicine), the infant is exposed. We qualify that by telling them that the level of exposure, at least insofar as we can quantify it from the infant's plasma, is extremely small, but that we don't know the precise long-term effects of exposure to even trace amounts of an SSRI in that setting. We are very clear that there have not been long-term neurobehavioral studies in children whose mothers have used SSRI's where we have quantified

exposure with assay of infant blood concentrations and then looked at those children at follow-up. We do share, however, the growing experience with SSRI's as a class during lactation, and the absence of at least readily observable treatment-emergent adverse effects in children.

Presented with that information, women do different things. Some women say, "If the baby is going to be exposed, then I'd just as soon bottle feed." Other women will say, "If no serious problems have been seen with SSRI's in children, then I am going to breastfeed, because I feel very strongly that breastfeeding is best, both medically and emotionally." Whatever decision they make, it should be made with the best available information.

Currents: Do you recommend infant serum monitoring?

Cohen: Not routinely, but we do monitor infant serum when there are risk factors. For example, we might be more inclined to monitor the serum of a particularly small baby or a baby born slightly prematurely, because those babies are more likely to have immature

hepatic metabolism. Babies with hyperbilirubinemia, for example, may have reduced capacity to clear even trace amounts of some medicines. In our fluoxetine study, we found that the age and weight of nursing infants strongly predicted whether fluoxetine would be found in their serum. We were more likely to find even trace amounts in the serum of smaller and younger-aged babies--not particularly high amounts, just any amount.

We might also monitor infant serum when there is some type of clinical correlate that concerns the mother or pediatrician. It could be something as nonspecific as jitteriness, a change in sleep pattern, or increased irritability. A change in the infant's behavior while Mom is using a medicine and breastfeeding would prompt us to think more seriously about assaying the infant's plasma. In addition, factors such as low weight at birth, prematurity, and evidence of immature hepatic metabolism all increase the likelihood of being able to detect even small amounts of medication in the infant's plasma. In these situations, our threshold for monitoring the infant's plasma would be lower.

Currents: And how would you interpret the results of the assay?

Cohen: Given our current level of information, we can interpret it only in binary fashion: the drug is there or it is not there. Parents (frequently in consultation with the pediatrician) ultimately decide whether finding it there is going to influence their decision about breastfeeding. If finding the drug in plasma will not change what they are going to do, we don't do the assay. On the other hand, we see mothers who request assay of their babies' serum because they have decided that even if we find only trace amounts of the medicine (even with a highly sensitive, research-quality assay), they will not breastfeed. They know that we are not sure of the short- or long-term significance of finding even trace amounts of the drug, and for them, finding any drug in the baby's blood is enough to induce them to bottle feed.

Our experience has been that parental requests for assaying their infant's plasma do not derive from observable, behavioral changes. I have never been asked by a Mom to assay her baby's plasma because the baby was jittery or not sleeping, for example. It just has never happened in our experience with this population. The issue of infant blood monitoring comes up because a mother is appropriately vigilant or concerned about the possibility that her baby may be the unusual case where there is particularly rich secretion of medicine or reduced capacity to metabolize even trace amounts of medicine. She wants to be reassured that the drug either is not detectable or is detectable in a very small amount in her baby's blood.

Currents: What about breastfeeding by mothers taking mood stabilizers?

Cohen: The data are sparse. Over the last several years, there has been a series of reports regarding the use of sodium valproate. One case report described severe, hepatocellular injury in a child whose mother was using sodium valproate during lactation. Again, that was a single case report, but nonetheless the potential adverse effect was very severe. There is an even sparser literature about using lithium during breastfeeding. We used to recommend that women defer breastfeeding if they were taking lithium. That was because lithium is richly secreted into breast milk, and there had been a small number of

case reports describing lethargy or hypotonia in children whose mothers had been using lithium during breastfeeding.

We recently have been looking more closely at lithium treatment during breastfeeding, and between our center, the Emory center, and one of the centers in Toronto, we have put together a small case series of children whose mothers insisted on breastfeeding while using lithium. So far, we have only a small series of about a dozen patients, but we have not observed adverse effects. More importantly, the amount of lithium that we have been observed in the infants' plasma either has been undetectable or has been present in very low concentrations (on the order of 0.1 meq/L). Our thinking about the use of lithium during breastfeeding is beginning to change. At our center, we no longer consider lithium an absolute contraindication to breastfeeding for women who will be taking lithium postpartum, which is a common scenario, given the vulnerability of bipolar women to relapse in the postpartum period. However, we usually assay the infant's plasma at about four weeks postpartum to evaluate the serum lithium concentration, and we may do it sooner if there are potential adverse effects.

Currents: Do risks of adverse effects differ in infants nursed by lithium-treated and valproic acid-treated mothers?

Cohen: Some women switch from valproic acid to lithium during pregnancy because of teratogenic concerns, but when they have responded to valproic acid before pregnancy, they may switch back to it during breastfeeding, given the greater experience with valproic acid during breastfeeding. However, if as we look at this question more critically, we find that the kinds of adverse effects that occur in infants nursed by valproate-treated mothers are more severe than those that occur in infants nursed by lithium-treated mothers, we may think more seriously about having women who have responded to lithium during pregnancy continue lithium postpartum.

The issue of breastfeeding and mood stabilizers also should be considered in the context of bipolar disorder. We sometimes discourage bipolar women from breastfeeding because breastfeeding can disrupt sleep. The risk of relapse is high in the postpartum period and we don't want to drive the risk even higher with sleep deprivation associated with breastfeeding. Bottle feeding allows multiple caretakers to feed the baby so that Mom's sleep can be protected. The importance of protecting the sleep of the bipolar mom cannot be overestimated.

Currents: What is the consensus among neurologists in your area with respect to safety of breastfeeding by valproate-treated women?

Cohen: They do not consider valproate contraindicated.

Currents: Do we know anything about safety of breastfeeding during treatment with lamotrigine or gabapentin?

Cohen: I'm not aware of any data on either yet, but the issue of breastfeeding during treatment with lamotrigine came up in our clinic recently, when we saw a woman with bipolar disorder who was lamotrigine-dependent. She had not responded to anything except lamotrigine, and she needed lamotrigine, given her bipolar diathesis and risk for relapse. Given the relative contraindication of using lamotrigine in children (who are

more vulnerable to Stevens-Johnson syndrome), we view the use of lamotrigine during breastfeeding as being absolutely contraindicated.

Currents: What about safety of breastfeeding during maternal treatment with antipsychotics?

Cohen: The data on antipsychotics, and also benzodiazepines, is limited to small case series and anecdotal reports over decades of use. We have many patients who use benzodiazepines during the postpartum period because of the significant incidence of postpartum anxiety disorders and the extent to which postpartum anxiety may complicate postpartum depression. We also have many patients who breastfeed while taking antipsychotics. There is very little data about the atypical antipsychotics during breastfeeding (only a few case reports).

Currents: Does risperidone, with its propensity to induce robust hyperprolactinemia, affect breastfeeding?

Cohen: I have not seen a single report about it. One might hypothesize that it would potentially increase amount of milk flow, but we don't know.

Currents: A case series published by an Australian clinician reported reduced milk flow in women taking sertraline. Have you seen that?

Cohen: That surprises me, because sertraline has been extensively studied and is widely used clinically in nursing women. In fact, it was an SSRI of choice for nursing women in the most recent Expert Consensus Guidelines published last March. If reduced milk flow associated with use of SSRI's by nursing women were common, I suspect that we would have seen it or heard about it.

Currents: Do you consider psychotropic drugs other than lamotrigine absolutely contraindicated during breastfeeding?

Cohen: It's not so much an absolute contraindication as a relative concern, but we would hesitate to prescribe clozapine during breastfeeding because that would oblige us to follow hematologic parameters in the newborn, which would be cumbersome and difficult for mother and infant. We would try to use a different atypical antipsychotic because of that. We have seen clozapine used during the postpartum period in refractory bipolar patients who only responded to clozapine, but nonetheless, it was cumbersome because of the need to follow the infant's hematologic parameters

Currents: What about effects of marijuana or other illicit drugs during breastfeeding?

Cohen: It doesn't come up much in our clinic (perhaps because women are reluctant to share that information), and I'm not aware of any data about it. We can assume, though, that across all of those compounds, there is no breast-child barrier. Regardless of whether someone is ingesting alcohol, caffeine, nicotine, herbals, prescribed medication, or illicit drugs, one can reasonably assume that those substances will be secreted into breast milk and that secretion will be highly variable.