LEADER (U.S.)

DRUG INTERACTIONS

Financial Ties to Industry Cloud Major Depression Study

At Issue: Whether It's Safe For Pregnant Women To Stay on Medication

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Updated July 11, 2006 12:01 a.m. ET

For pregnant women considering whether to continue taking antidepressant drugs, a study in a February issue of the Journal of the American Medical Association, or JAMA, contained a sobering warning: Stopping the medication greatly increases the risk of relapsing into depression.

The study authors -- most of them leading psychiatrists at Massachusetts General Hospital, the University of California Los Angeles and Emory University -- said their results challenged a common assumption that hormonal changes during pregnancy protected expectant mothers against depression. In their article, they predicted the findings would prompt some women to stay on their depression medication through pregnancy. That was good news for the makers of big-selling antidepressants, who have recently faced growing questions about the safety of their medications when used during pregnancy.

But the study, and resulting television and newspaper reports of the research, failed to note that most of the 13 authors are paid as consultants or lecturers by the makers of antidepressants. The lead author -- Lee S. Cohen, a Harvard Medical School professor and director of the perinatal and reproductive psychiatry research program at Massachusetts General Hospital -- is a longtime consultant to three antidepressant makers, a paid speaker for seven of them and has his research work funded by four drug makers. None of his financial ties were reported in the study. In total, the authors failed to disclose more than 60 different financial relationships with drug companies.

Dr. Cohen and some of his coauthors subsequently hit the lecture circuit, telling physicians about their findings while also spotlighting flaws in other recent studies that have found increased risks to babies born to mothers who use antidepressants.

The work of these academic researchers highlights the role of "opinion" or "thought" leaders coveted by drug companies because of their ability to influence not only the practice of doctors, but popular opinion as well. In the case of antidepressant use during pregnancies, the industry-paid opinion leaders have become dominant authorities in the field. They help establish clinical guidelines, sit on editorial boards of medical journals, advise government agencies evaluating antidepressants and teach courses on the subject to other doctors. In some cases, the financial ties between industry and these leading researchers are not

disclosed.

The researchers, including Dr. Cohen, maintain that their financial links have no bearing on their research work or what they say about antidepressant use during pregnancy in interviews or lectures. The pharmaceutical companies say the academic researchers they work with provide important expertise that benefits patients. "It is important to remember that this is a partnership with the mutual goal of advancing science and enhancing patient care," says a Pfizer spokeswoman.

But such ties are prompting a growing debate in the medical community. Some physicians say they worry that it's hard to get unbiased information about treatment options for depressed pregnant women and that safety concerns about the use of antidepressants during pregnancy are being wrongly discounted.

"Whether or not to keep taking an antidepressant during pregnancy is a critical question for pregnant women suffering from depression," says Adam Urato, a Bradenton, Fla., obstetrician and perinatologist who publicly questioned Dr. Cohen and colleagues about their industry relationships during a recent online training session. "What these pregnant women and the providers who care for them need is expert advice that is free from pharmaceutical industry influence or the suggestion of bias that results when these experts are being paid by so many antidepressant manufacturers."

JAMA says its policies require that authors of studies disclose financial ties to the medical industry. JAMA's editor-in-chief, Catherine D. DeAngelis, says the journal wasn't aware of the relationships Dr. Cohen and some co-authors of the February article had to drug companies. "As soon as JAMA found out that they didn't disclose, we contacted the corresponding author, Dr. Cohen, and asked for his explanation," she says. "We have one and it will be published very soon in an upcoming issue of JAMA."

Dr. Cohen said his industry relationships have no influence on his research work or public comments on the issue. He added that the drug companies "tend to pick people who are expert in this area." He declined to specify what he does in his consulting role for the companies or how much he is paid, other than to say "we are not talking about megabucks."

Dr. Cohen said "it didn't seem relevant" for him and several of his co-authors to disclose their industry relationships in the JAMA paper in part because the study was funded by the government, not drug makers.

Big Ramifications

Whether or not pregnant women continue or stop the use of antidepressants has big ramifications for makers of those drugs. Women are twice as likely to suffer from depression as men and have a 25% risk of developing depression during their lifetime, according to U.S. government estimates, with that risk peaking during childbearing years. The American Medical Association estimates that over 1% of pregnant women in the U.S., or more than 40,000, are taking antidepressants. Sales of antidepressant drugs in the U.S. last year exceeded $12.5 billion, according to IMS Health, which tracks prescription-drug sales.

Recently, new concerns have been raised about the safety of antidepressants during pregnancy, mostly among the large class of drugs known as selective serotonin re-uptake inhibitors, or SSRI's. Eli Lilly & Co.'s Prozac, Pfizer Inc. 's Zoloft and Glaxo SmithKline PLC's Paxil are all SSRI's. Some studies have found an increased risk of a potentially fatal breathing disorder and an increased risk of seizures and fetal death among infants born to mothers using a broad spectrum of SSRI's, including these drugs. And two studies have found an increased risk in cardiac malformations in babies born to Paxil users.

Drug makers say patients need to decide with their physician if taking an antidepressant during pregnancy is the right thing to do. "It is obviously a weighing of benefits and risks between the patient and their physician," says GlaxoSmithKline spokeswoman Mary Anne Rhyne. "We try to be as transparent as possible in providing information to factor into that analysis." Most antidepressants carry warning labels that explain the potential risks to the unborn baby.

For physicians, it is becoming increasingly complicated to balance the risks posed by antidepressant use by expectant mothers against the dangers associated with depression during pregnancy. Several studies have linked depression to premature birth and developmental delays. Depression during pregnancy is also associated with an increased risk of postpartum depression, which some researchers believe affects parenting and can result in developmental delays and behavioral problems for children.

The Cohen study was published around the same time that another study appeared in the New England Journal of Medicine warning of an alarming increase in a dangerous breathing problem among babies born to mothers using antidepressants.

The study of 1,213 women, led by Christina Chambers, a pediatric researcher at the University of California San Diego, found a sixfold increase in the rate of persistent pulmonary hypertension of the newborn, or PPHN, among babies born to mothers who used SSRI's late in their pregnancy. About 10% to 20% of babies born with the condition do not survive. The condition, which is marked by severe respiratory failure, normally occurs in about one or two infants per 1,000 births. For babies exposed to antidepressants late in pregnancy, the rate of occurrence rose to six to 12 births per 1,000, according to the study.

Dr. Chambers and another author receive research funding from several generic drug makers to study the safety of drugs taken during pregnancy to treat rheumatoid arthritis and other auto-immune diseases. The study itself was funded by government grants.

In an accompanying editorial, James Mills, a senior biomedical research scientist at the National Institute of Child Health and Human Development, wrote that the association between SSRI use and the breathing problem was "very unlikely to be due to chance" and that women considering whether to use antidepressants during pregnancy should take the new findings into consideration.

After the study, Dr. Chambers says she heard from women across the country who took antidepressants and had babies born with the condition. Alexis McLaughlin of Dayton, Ohio, says she took 20 milligrams of Paxil daily during her pregnancy with her fourth child. She didn't take an antidepressant when pregnant with her other children. Mrs. McLaughlin says her depression began after the birth of her third child. "I couldn't stop crying," she says. "I couldn't sleep. I looked like I was falling apart." The Paxil was effective in treating her depression, she says.

She says her daughter started to experience difficulty breathing soon after coming home from the hospital. Within days, the baby was back in the hospital in the critical care unit, where she needed a respirator to breathe. After several days, the baby was diagnosed with PPHN and transferred to the children's hospital in Cincinnati. After treatment there, the baby began to get better and eventually recovered.

The results of Dr. Chambers's study are being questioned by industry-paid experts in the field. In a recent online symposium for doctors, Adele C. Viguera, the associate director of the Massachusetts General perinatal psychiatry program and professor at Harvard Medical School, said of the Chambers study: "We were very surprised by those findings because it really didn't jibe with our clinical experience." She went on to say that Mass General "informally surveyed" colleagues across the country and that none of them had

ever seen the problem identified by Dr. Chambers. "So I think it really underscores this point that we can't let one study dictate our clinical care."

Dr. Viguera is a member of the GlaxoSmithKline speaker's bureau. Dr. Viguera says she is paid to talk about Lamictal, another Glaxo drug that is used to treat bipolar disorder. She says she does about a half dozen of those talks a year and is paid $2,000 for each.

Her comments came during a May 17 lecture sponsored by the Massachusetts General Hospital Psychiatry Academy. The event carried the stamp of the Harvard Medical School and bore the slogan "CME you can trust." The initials stand for continuing medical education -- a certain amount of which is required of doctors annually by state medical-licensing boards. Doctors received CME credit for the May 17 event.

The panel of experts for the session on "Psychotropic Drug Use During Pregnancy" was comprised entirely of psychiatrists with financial ties to drug makers. The Mass General psychiatry academy itself is funded by six drug makers, including two antidepressant makers. These relationships were disclosed.

During the hour-long Web broadcast of the panel session, Dr. Chambers appeared in a 90-second videotaped clip to explain her findings and respond to some of the criticisms from the panel.

Warning Labels

The panelists were also critical of a recent action by the Food and Drug Administration to add new warnings about potential birth defects to the Paxil label. In December, the FDA issued a health advisory saying it determined exposure to Paxil in the first trimester of pregnancy may increase the risk of congenital malformations. The advisory said an as-yet-unpublished Swedish study of 6,896 women found a doubling of cardiac defects among infants born to mothers who use Paxil, compared with those in the general population. Most of the cardiac defects involved the failure of the wall between the left and right sides of the heart to completely develop.

Panelist Zachary Stowe, who directs the women's mental health center at Emory, described the recent FDA decision to change the warning label for Paxil as "driven by a single set of data that is unpublished, non-peer reviewed, and somehow this trumps the very nicely done prospective investigations that have really failed to find this risk." Dr. Stowe has served as an adviser and speaker for several antidepressant makers.

To further make that point, a videotaped interview with Gideon Koren, the director of the Motherisk Program at the University of Toronto, was played.

Dr. Koren said the data identifying a risk of cardiac malformation were "very low quality" and that regulatory agencies were "just throwing us statements, mostly for medical-legal reasons." Dr. Koren is currently conducting a study funded by drug maker Wyeth looking at the development of children exposed to the company's Effexor, a non-SSRI antidepressant. That relationship was not disclosed.

Beginning this fall, the Mass General psychiatry academy plans to conduct CME symposiums in a dozen cities across the country. Dr. Cohen is overseeing a segment on treating psychiatric disorders during pregnancy, according to material promoting the events.

Robert Birnbaum, the medical director for postgraduate medical education in the psychiatry department at Massachusetts General, said the panelists were chosen because they are nationally recognized leaders in

their field. He said the academy curriculum is supported by a consortium of pharmaceutical companies, but that the drug makers have no input into the selection of faculty or program content.

Experts with industry ties were also heavily represented at a U.S. government-sponsored conference in Florida last month. The conference, sponsored by the National Institute of Mental Health, a government agency, drew hundreds of researchers from academia, industry and government.

A panel titled "Use of SSRIs and Mood Stabilizers During Pregnancy: Weighing the Risks" included Drs. Cohen and Viguera, as well as Alan J. Gelenberg, the head of the psychiatry department at the University of Arizona and the editor of the Journal of Clinical Psychiatry. The lone panelist without industry ties was Kathleen Uhl, the director of the FDA's Office of Women's Health. Her talk was largely a general discussion about how the FDA decides to assign various warning labels to drugs.

While the speakers made no mention of their industry affiliations during their presentations, conference attendees were provided a booklet when they registered that listed speakers and their financial relationships.

Dr. Gelenberg said at the conference "probably there has been an overreaction" to recent concerns about heart defects linked to Paxil use during pregnancy. Dr. Gelenberg reports numerous consulting and speaking arrangements with several antidepressant makers. In an interview, Dr. Gelenberg said less than 5% of his income comes from pharmaceutical company consulting work and that he no longer owns stock of antidepressant makers. He said he knows of academic colleagues earning six-figure incomes from those companies. "The problem is if you want an expert on antidepressants in pregnancy, most of us have taken some industry money," he said. The solution, he adds, is more independent or government funding of research work.

Nada Stotland, a professor of psychiatry and obstetrics at Rush Medical College in Chicago, says there is a lack of good studies looking at the use of antidepressants in pregnancy. She says one problem is that pharmaceutical companies have the resources to do the studies that are needed, but "only do what they are required to do" by the FDA. She also says few studies look at non-drug alternatives to treating depression in pregnancy, such as psychotherapy.

Citing the conflicting and often confusing research on antidepressant use during pregnancy, the American Medical Association House of Delegates last month passed a measure directing the association to come up with guidelines concerning the treatment of depression during pregnancy.

The JAMA study by Dr. Cohen and others was the first major paper to establish a risk of relapse for pregnant women who stop antidepressant treatment. For many years, doctors were taught that pregnancy is a time of emotional well-being that protects women from getting depressed. The study was widely covered by print and television.

Wide Publicity

Headlines warned of the danger of stopping antidepressants during pregnancy, and many local television news stations broadcast, unedited, a "video news release" put out by JAMA reporting on the study. That release featured Dr. Cohen and one of his patients, Lisa Kirshenbaum of Cranston, R.I., who was a part of the study. Ms. Kirschebaum experienced a miscarriage when she went off her antidepressants, according to the video. When she became pregnant again, she took her medication and delivered a healthy baby, according to the release. The actual study, however, did not examine whether mothers delivered healthy or sick babies. It tracked only whether they suffered from depression.

The study reported financial relationships with antidepressant makers for two of the 13 authors of the study, Emory's Drs. Stowe and Jeffrey Newport. But at least seven others have relationships that were not disclosed. Among the most significant of the missing disclosures are those of the second listed author -- Lori Altshuler, director of the Mood Disorders Research Program at UCLA. She is a speaker or consultant to at least five antidepressant makers. An assistant says she is on sabbatical and unavailable for comment. Two of her colleagues -- Vivien Burt and Victoria Hendrick -- were also authors who didn't report financial relationships they have with antidepressant makers. Dr. Burt, in an interview, said "we all regret not having" disclosed those relationships and are "all genuinely interested in doing the right thing at all times." Attempts to contact Dr. Hendrick were unsuccessful. Dr. Cohen says JAMA has imposed an embargo on his letter until the journal publishes it, so he can't discuss the contents.

Dr. Viguera of Mass General was another author, and did not disclose her speaking relationship with GlaxoSmithKline. She said the study was designed in such a way that "I don't see how any kind of relationship we have with a pharmaceutical company plays a role in that. ...I don't believe there is a conflict of interest."

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