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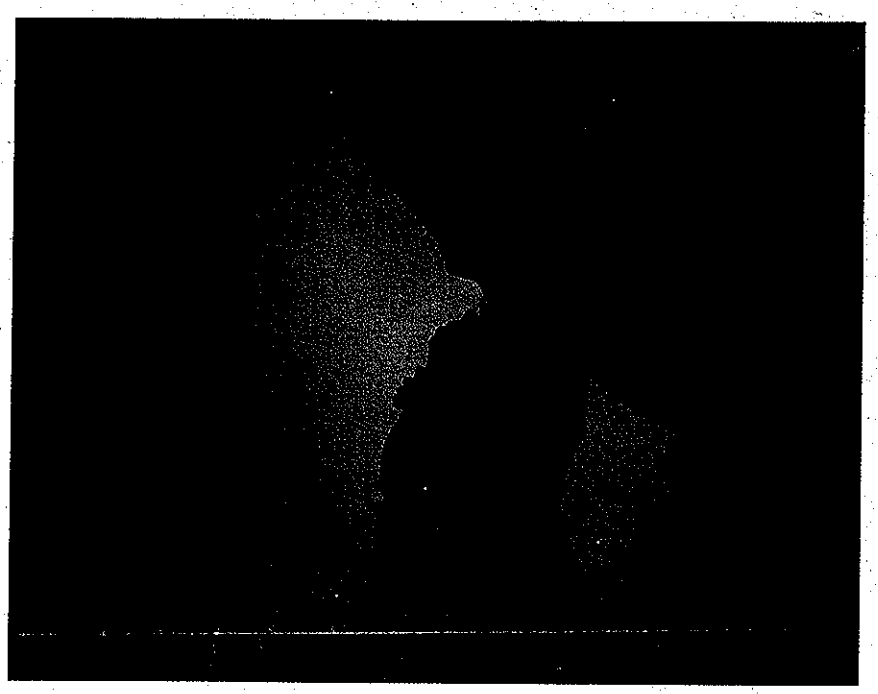
Antidepressants and Pregnancy

by Arline Kaplan

The extent to which antidepressant use during pregnancy is associated with increased risks of postnatal adaptation syndrome (PNAS), persistent pulmonary hypertension in the newborn (PPHN), first-trimester teratogenicity, stillbirth, and infant mortality is explored in 2 recent studies.[1,2]

In a recent interview, lead author Nancy Byatt, DO, MBA, a perinatal psychiatrist and Assistant Professor of Psychiatry and OB-GYN at the University of Massachusetts Medical School, said that depression and anxiety are very common during pregnancy and the postpartum period. Approximately 18.4% of women suffer from antenatal depression, and as many as 19.2% experience postpartum depression. In the third trimester, 1 of 5 women (21.7%) experiences anxiety disorders, and in the first 3 postpartum months, 11.1% have an anxiety disorder.[1]



In economically developed countries, the prevalence for depression during pregnancy ranges between 7% and 19%, according to obstetrician and epidemiologist Olof Stephansson, MD, PhD, of the Karolinska University Hospital Solna in Stockholm, who is also lead investigator on a recent study that assessed the relative risks of stillbirth and infant mortality associated with SSRI use during pregnancy.[2]

Byatt told *Psychiatric Times* that conflicting data have led to major controversies regarding antidepressant use during pregnancy. To help providers "understand the risks and benefits of using antidepressants during pregnancy and apply that knowledge to enhance clinical care," she and colleagues conducted an extensive review of the literature between 1966 and 2012.

Antidepressants considered in the review included SSRIs, SNRIs, and norepinephrine reuptake inhibitors. According to Byatt, the review focused on outcomes that "have the most controversy surrounding them." These are congenital malformations, PNAS, and PPHN.

Results

"The current evidence for malformations is limited because of inconsistent findings and limited methodology of the published studies," the review authors wrote. "Few studies

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Psychiatric Liability: A French Psychiatrist Sentenced After a Murder Committed by Her Patient

by Carol Jonas, MD, JD
and Nidal Nabhan Abou, MD

On December 18, 2012, French psychiatrist Daniele Canarelli, age 58, received a 1-year suspended prison sentence by the Criminal Court of Marseille. Dr Canarelli had been found guilty of multiple practitioner failures and misconducts after one of her patients—Joel Gaillard—killed 80-year-old Germain Trabuc on March 9, 2004. The court also sentenced Dr Canarelli to pay 7500 euros and 1000 euros, respectively, to each of Mr Trabuc's sons.

French psychiatrists rarely face lawsuits.[1] In cases involving harm by a patient to a third party, a hospital or insurance company usually assumes liability and pays for damages. Legal cases that result in prison sentences for psychiatrists remain exceedingly rare. That is precisely why this case has caused such a stir in Europe.

Some background on this case: Joel Gaillard had been Dr Canarelli's patient for nearly 4 years, between 2000 and 2004. During that time, Gaillard was repeatedly and mandatorily hospital-

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have controlled for maternal illness, and therefore do not take into account whether reproductive outcomes are due to maternal illness or antidepressant exposure."

"There are some individual studies that show a risk between specific SSRIs and birth defects, but if you look at the overall evidence, it has not been consistently observed, which is very reassuring," Byatt said. "There has not been any single malformation that has been consistently observed across studies with any commonly used antidepressant." The investigators concluded that PNAS occurs in up to 30% of neonates who are exposed to antidepressants in late pregnancy. But, it is a transient syndrome that typically resolves in days and in rare cases, a few weeks.

"The PPHN literature is limited by small and/or uncontrolled studies," according to Byatt and her group. In addition, "there are other reported risk factors, including race, method of delivery, obesity, asthma, and diabetes that many studies do not take into account." The evidence regarding the risk of PPHN because of in utero antidepressant exposure remains inconclusive. Some studies suggest a small association, and other studies suggest no association.

Byatt pointed to changes in drug safety advisories on SSRIs and PPHN over the years. In 2006, the FDA issued a Public Health Advisory warning of a possible link between SSRI antidepressant use during pregnancy and reports of PPHN. However, in 2011, the FDA, in a Drug Safety Communications, said that given conflicting results from different studies, it is "premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN."

"Overall, we do not recommend discontinuing SSRIs in pregnant women because of the risk of PPHN," Byatt said. The literature and her communications with other experts in the women's mental

on antidepressant use in pregnancy was published, an article by Nulman and associates[3] appeared on the neurodevelopment of children following prenatal exposure to venlafaxine (Effexor), SSRIs, or untreated maternal depression. Those investigators concluded that factors other than antidepressant exposure during pregnancy predicted children's intellect and behavior and that children of depressed mothers may be at risk for future psychopathology.

"You can extrapolate from the study that if you can help mom go into the postpartum period well and healthy with her symptoms in remission as much as possible, you can set the stage for mom to be in a position to care for the baby in such a way that would mitigate the child's risk of having his or her own future mental health symptoms," Byatt said.

Byatt was somewhat critical of a review that discussed the impact of SSRIs on fertility, pregnancy, and neonatal health.[4] Domar and colleagues[4] contended that there is evidence of risk with the use of SSRI antidepressants by pregnant women, that there is no evidence of improved pregnancy outcomes with SSRIs, and that pregnant women, providers, and the public should be advised of this. Byatt said that rather than conducting a systematic review of all the available evidence and coming to a nonbiased conclusion, Domar and colleagues cited a "few articles that support their conclusions," which can worsen the stigma and confusion surrounding depression treatment during pregnancy.

SSRIs and infant death

Byatt described the recent population-based cohort study by Stephansson and colleagues[2] as a "well done and very reassuring study." Analyzing data from Denmark, Finland, Iceland, Norway, and Sweden, Stephansson and colleagues looked at the use of SSRIs during pregnancy and the risk of stillbirth and infant mortality. The large size (more than 1.6 million births) facilitated the study of rare pregnancy outcomes, such as stillbirth, neonatal death, and postneonatal death, Stephansson told *Psychiatric Times*.

For the study funded by the Swedish Pharmacy Company and the authors' affiliations, the researchers obtained information on maternal use of SSRIs from prescription registries. Exposure was defined as 1 or more filled prescriptions for an SSRI from 3 months before the start of pregnancy until birth. The researchers also gathered information on maternal characteristics, pregnancy, and neonatal outcomes from patient and medical birth regis-

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of a possible link between SSRI antidepressant use during pregnancy and reports of PPHN. However, in 2011, the FDA, in a Drug Safety Communications, said that given conflicting results from different studies, it is "premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN."

"Overall, we do not recommend discontinuing SSRIs in pregnant women because of the risk of PPHN," Byatt said. The literature and her communications with other experts in the women's mental health field indicate that "the overall data on SSRI use in pregnancies is reassuring. SSRIs are considered to be relatively safe for use during pregnancy and the postpartum period." There are limited data regarding other classes of antidepressants. "The available studies are reassuring, but not definitive," she said.

Risks of untreated depression/anxiety

Understandably, providers may worry about the medication risks for the pregnant woman and her fetus/child, Byatt said, but equally important are the risks of untreated depression and anxiety. "Prenatal depression and anxiety can lead to missed obstetrical appointments, poor nutrition, poor sleep, and substance abuse," she said. "Depression also has been associated with poor birth outcomes, including preterm birth, preeclampsia and an increased risk for delivery of a low birth weight infant."

To assist clinicians in working with their pregnant patients, Byatt and colleagues included a Table of treatment recommendations in their article. These include using the lowest medication dose possible while avoiding undertreatment; avoiding polypharmacy; and maximizing nonmedication, evidence-based treatments.

At about the same time their literature review

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tries. They then estimated relative risks of stillbirth, neonatal death, and postneonatal death associated with SSRI use during pregnancy, taking into account maternal characteristics and previous psychiatric hospitalizations.

Among 1,633,877 singleton births in the study from 1996 to 2007, there were 6054 stillbirths, 3609 neonatal deaths, and 1578 postneonatal deaths. A total of 29,228 mothers (1.79%) had filled a prescription for an SSRI during pregnancy.

"Women taking SSRIs had slightly increased rates of stillbirth and postneonatal death," said Stephansson, Associate Professor at Karolinska University's Clinical Epidemiology Unit. Women exposed to an SSRI had higher rates of stillbirth (4.62 vs 3.69 per 1000) and postneonatal death (1.38 vs 0.96 per 1000) than those who did not. The rate of neonatal death was similar between groups (2.54 vs 2.21 per 1000).

However, when the researchers considered maternal factors, there was no association with SSRIs and stillbirth or infant death rates, Stephansson said. Such factors included a history of the severity of the psychiatric disorder among women taking SSRI drugs during pregnancy, their older age, the tendency for them to be smokers, and the greater incidence of diabetes and high blood pressure.

The researchers acknowledged that they might have overestimated the actual use of antidepressants, because having a drug prescribed doesn't always equate with using it. Stephansson noted that the study findings need confirmation by other studies in different settings. He added that the Nordic team of researchers has been looking at various issues involving SSRI use and pregnancy. Last year, in a large, multinational cohort study, Kieler and colleagues[5] found the risk of PPHN "after exposure to any SSRI in late pregnancy was more than doubled."

The results indicate that out of 11,014 mothers who used antidepressants in late pregnancy (later than gestational week 20), 33 babies (0.2%) were

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ized at the request of his family or the regional government's social services.

On the day that Gaillard murdered Trabuc, he was on probation and being treated as an outpatient. As such, Gaillard was the legal responsibility of the psychiatric hospital. Twenty days before the murder, Dr Canarelli had ordered the re-hospitalization of her patient, but the patient escaped during a consultation.

The jury found numerous and repeated lapses in judgment and actions on Dr Canarelli's part. At the start of the trial, the court pointed out that the "law does not require from the physician an obligation of result" and that "predictability and zero risk do not exist." The court also reassured psychiatric professionals by declaring that the case did not pertain to the entire profession. It was said at the trial that "the court is not judging psychiatry here, but rather a very specific case with a specific misbehavior of the treating doctor."[2]

Several acts of negligence were brought against Dr Canarelli. Charges outlined in the judgment text stated that under her supervision, the 4 years of therapy were marked "beyond any doubt" with "a succession of failures" and her attitude "resembled blindness." These charges were based on the following:

Despite "an escalation of acts of aggression, of increasing severity" perpetrated by the patient while he was in treatment, "Dr Canarelli remained stubbornly attached to her treatment approach and ignored such obvious alarm signals. She did not question her methodology or change her approach, thus creating or helping to create the situation that led to the realization of the crime."

The doctor also failed to "establish the correct diagnosis." This assertion may be debatable, but her reports concerning the patient revealed that she sometimes ruled out psychosis, which was noted by all the other doctors who examined the she received, and didn't put it to proper use during her counseling appointment of February 19, 2004, with the patient."

Dr Canarelli justified the non-use of coercive measures during therapy by "the need to establish and maintain a trusting relationship with the patient." The court did not share this reasoning and argued that while therapeutic alliance is of "major importance," the relationship of trust "is not an end in itself but only a means for patient adherence for the best outcome."

Dr Canarelli's conviction was mainly based on the principles of Article 121-3 of the Penal Code (**Box**). According to the court, a series of faults or acts of negligence occurred that justified her 1-year suspended prison sentence.

This case has spread a feeling of anxiety among French psychiatrists, who are now bound to manage the "dangerousness" of their patients—as if they are able to predict and neutralize any possible dangerous acts that their patients might commit. The case also led to the creation of law 2011-803, on July 5, 2011. The objective of that law is to ensure that "dangerous" psychiatric patients are monitored and attended to.[3-5]

In particular, this law replaced the "exit test" with "ambulatory care without consent." In principle, the law enables greater intervention by psychiatric teams. However, it also increases the responsibility of doctors by requiring more transparency (methodology, location where the treatment is administered, frequency of visits or consultations, etc) and obligates them to notify authorities if the patient does not adequately follow the therapeutic program. In this new, legally binding context, French psychiatrists now justifiably believe that lawsuits against them will become more frequent.

French Penal Code Article 121-3: When a Psychiatrist's Patient Harms Someone

Nordic team of researchers has been looking at various issues involving SSRI use and pregnancy. Last year, in a large, multinational cohort study, Kieler and colleagues[5] found the risk of PPHN "after exposure to any SSRI in late pregnancy was more than doubled."

The results indicate that out of 11,014 mothers who used antidepressants in late pregnancy (later than gestational week 20), 33 babies (0.2%) were born with PPHN (absolute risk, 3 per 1000 liveborn infants compared with the background incidence of 1.2 per 1000). With regard to SSRI use in early pregnancy, the results indicated that risk for PPHN was "slightly increased." Specific SSRIs had similar increased risks of PPHN, suggesting a class effect.

Currently, the Nordic collaboration team, according to Stephansson, is investigating spontaneous abortions and congenital malformations and their possible association with antidepressant exposure.

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ignored such obvious alarm signals. She did not question her methodology or change her approach, thus creating or helping to create the situation that led to the realization of the crime."

The doctor also failed to "establish the correct diagnosis." This assertion may be debatable, but her reports concerning the patient revealed that she sometimes ruled out psychosis, which was noted by all the other doctors who examined the patient as well as by the expert who was appointed to the court after the murder.

The court found a clear discrepancy between the mental disorder meticulously described by the doctors who recommended "hospitalization without consent," and the therapeutic approach adopted by Dr Canarelli. The patient had repeatedly objected to his hospitalization, as unanimously stated by experts who examined him on those occasions.

Dr Canarelli continued with the same therapeutic approach and prescribed successively longer "exit test" periods outside of the hospital, especially from October 2003 onward—despite several "alarming incidents and alerts" of which she had been aware.

Dr Canarelli was also accused of failing to take into consideration the experts' recommendation in 2001 to transfer her patient to a specialized facility (at that time there were 4 such facilities in France where extreme cases were admitted). Nor did she consider the experts' request to transfer the patient for treatment by another therapeutic team.

In January and February of 2004, Dr Canarelli had received alerts from the mental health center and the patient's family. But "she did not make any concrete conclusion out of the information

authorities if the patient does not adequately follow the therapeutic program. In this new, legally binding context, French psychiatrists now justifiably believe that lawsuits against them will become more frequent.

French Penal Code Article 121-3. When a Psychiatrist's Patient Harms Someone . . .

There is [. . .] transgression of the law, in cases of recklessness, negligence or breach of duty in terms of providing adequate care or safety, as stated by law or regulation, if it is established that the perpetrator has not completed the normal due diligence given, with regard to the nature of their duties, functions, skills and means put at their disposal.

Based on the above, **individuals who did not directly cause any damage**, but who created or helped to create the situation that led to the occurrence of the damage or **who have not taken appropriate measures to prevent it**, are criminally liable if it is determined that they have either manifestly violated, in a deliberate manner, their duty of providing care or safety as stated by law or regulation, or **exposed others to serious risk that they could not ignore, through their own misconduct** *[emphasis provided by the authors].*

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