Should Paroxetine Be Used to Treat Depression During Pregnancy?

TO THE EDITOR: In the June 2008 issue of the *Journal,* Adrienne Einarson, R.N. et al. (1) concluded that the existing evidence does not suggest an association between the use of paroxetine during pregnancy and congenital cardiovascular defects. Their conclusion was based on an observational study and five previous cohort studies. The authors stressed the need to treat depression during pregnancy and stated that if appropriate treatment includes paroxetine, the findings of their study "should reassure women and their health care providers" (1, p. 752). This endorsement is at odds with regulatory warnings (2).

The design and reporting of the study raise questions pertaining to claimed results. No data are provided regarding 1) baseline characteristics of exposed women and unexposed comparison women, 2) whether the analysis is intention-to-treat or per protocol, 3) loss to follow-up, or 4) proportion with evaluable outcomes. Both the exposure levels and procedures to select comparison women were unclear. Additionally, the outcome assessment was not blinded to exposure, and treatment for ambiguous diagnoses was unclear.

Einarson et al. included a secondary analysis of five cohort studies of paroxetine exposure during pregnancy. Although four of these studies included comparison groups and two reported significant increases in congenital malformation rates among exposed women (3, 4), these data were omitted. The authors reported a subset of available observational studies, and the selection criteria were unclear.

If harm from paroxetine use during pregnancy cannot be excluded based on the evidence provided, can benefit be assumed? To our knowledge, no randomized controlled trial has examined whether paroxetine treats depression during pregnancy more effectively than placebo, psychotherapy, or alternative treatment/therapy. Einarson et al. stated that randomized controlled trials cannot be conducted "for obvious reasons" (1, p. 751). We question the assumption that treatments should be offered to pregnant women with less evidence of benefit than those treatments offered to nonpregnant women. More, not less, caution is needed to ensure that potential benefit outweighs potential harm.

The authors also cited a study published in the *Journal of the American Medical Association* (*JAMA*) (5) reporting high rates of depression relapse after discontinuation of paroxetine during pregnancy. The study was not randomized, neither patients nor treating doctors were blinded, and patients were briefed about the "risk of depressive relapse associated with discontinuation of antidepressant therapy." Additionally, no attempts to distinguish relapse from drug discontinuation syndrome were described.

Neither the safety nor effectiveness of paroxetine treatment during pregnancy has been established. Since studies conducted in a range of settings have indicated potential harm, should we not adopt a cautious approach to further exposure, rather than requiring certainty about harm?

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Ms. Einarson Replies

TO THE EDITOR: We thank Drs. Mintzes and Jureidini for their interest in our study. They felt that the statement "appropriate treatment of depression during pregnancy is essential and if this includes taking paroxetine, this information should reassure women and their health care providers" was an endorsement, which is at odds with regulatory warnings. This is an incorrect assumption because we do not endorse any drugs used in pregnancy; we only examine safety. Critically, the regulatory warnings they reference (1, 2) are based on the results of preliminary findings, which have not been updated because new data, including our study, has been published, refuting these early findings (3, 4).

The design employed in our study is one that has been used over many years to examine the safety of numerous drugs in pregnancy (5). It is widely considered to be an optimal design in the absence of randomized control trials that cannot be ethically conducted among pregnant women. The study design was discussed in detail in our article, documenting that the maternal characteristics were similar in both the exposed group and the unexposed comparison group. We also detailed the limitations in the discussion section. The data Drs. Mintzes and Jureidini state were missing would have only been available if our study had been a randomized control trial. The results of the previously published data were included—since we documented that there was a 1.5% increased risk for heart defects as opposed to approximately 1% in the general population—both in the abstract and in the body of the article. As we discussed, 50% of all pregnancies are unplanned, and all the women who participated in our study were receiving paroxetine prior to becoming pregnant. We cited the *JAMA* study conducted by Cohen

et al., since it illustrated the importance of treating depression during pregnancy when appropriate.

The treatment of depression during pregnancy with antidepressants is a complicated decision for both the physician and the pregnant patient. Being "on the safe side" by not using these drugs during pregnancy because of unproven potential harm is not always an option, especially if a woman is already pregnant and receiving an antidepressant. Each case requires individual evaluation, and a risk/benefit assessment must be conducted in order to serve the best interest of both the pregnant mother and her unborn child.

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Neuroleptic Malignant Syndrome With the Addition of Aripiprazole to Olanzapine

TO THE EDITOR: Second-generation antipsychotics are thought to have less severe adverse effects than traditional agents (1). Although their safety profiles have been established as single agents, they are frequently used in combinations (1, 2). We describe the case of the occurrence of neuroleptic malignant syndrome in a vulnerable patient who was receiving a specific combination of second-generation antipsychotics.

"Mr. M" was a 33-year-old African American man with mild mental retardation who was brought to the emergency room by ambulance after he had become incoherent, incontinent, and tremulous. He had been prescribed olanzapine (10 mg daily) over a 9-month period for aggressive behaviors. Aripiprazole and benztropine were added 1 month prior to presentation for continuing irritability and insomnia. Approximately 2 weeks later, aripiprazole was increased from 5 mg to 10 mg daily. Shortly afterward, the patient's mother reported that he had stopped walking, refused to eat and drink, discontinued self-care, and developed generalized stiffness, weakness, pain, and cold sweats.

There was no prior history of movement disorders, illegal drug use, allergies, or falls. After standard emergency room evaluation of the patient's airway, breathing, and circulation, psychiatry and neurology consults recommended medications, neuroimaging, and intravenous hydration. On exam, Mr. M was alert, verbally incoherent, and had elevated temperature, diaphoresis, tachycardia, and muscular rigidity. Laboratory examinations revealed leukocytosis; mildly elevated levels of blood urea nitrogen; hypokalemia; and elevated levels of alanine aminotransferase, aspartate aminotransferase, and creatinine phosphokinase (peak=3,210 U/liter). A noncontrasted head computed tomography scan, chest X-ray, lumbar puncture, CSF, urine, and blood cultures were all negative. The patient was admitted to the medical intensive care unit and started on bromocriptine, lorazepam (intravenous), and antibiotics, which were discontinued after the cultures were evaluated.

After his symptoms improved and his creatinine phosphokinase levels were normalized, Mr. M was transferred to a medical unit where some fluctuation of blood pressure, sweating, rigidity, tremors, and confusion continued. Dantrolene (intravenous) was added to his treatment regimen. Approximately 5 weeks from the onset of neuroleptic malignant syndrome, most of his symptoms were resolved. However, his hospital course was prolonged by pneumonia and urinary tract and skin infections.

The present case describes the evolution of neuroleptic malignant syndrome following the addition of low-dose aripiprazole to olanzapine. Data are accumulating on the risk of neuroleptic malignant syndrome with second-generation antipsychotics (3, 4), including aripiprazole at therapeutic doses. Benztropine can contribute to delirium, and mental retardation is a risk factor for neuroleptic malignant syndrome (5). However, the addition of an agent with high dopamine receptor affinity (1) to existing second-generation antipsychotic treatment appears to have been a key factor in this case.

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