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CERHR
P.O. Box 12233
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RE: NTP-CERHR Report on Fluoxetine

By regular mail and electronic mail (shelby@niehs.nih.gov)

Dear Sirs:

The following comments are in follow-up to my testimony before the NTP-CERHR Expert Panel given on March 3, 2004. I am attaching a curriculum vitae which highlights my work in the area of reproductive psychiatry over the last 18 years. I am Director of the Perinatal and Reproductive Psychiatry Clinical Research Program at Massachusetts General Hospital and Associate Professor of Psychiatry at Harvard Medical School. I have sub-specialty training and longstanding clinical activity in the area of treatment of mood and anxiety disorders. This has been complemented by over fifteen years of dedicated work as a clinical researcher in the area of mood disorders in women and, specifically, the treatment of depression during pregnancy and the puerperium. As noted during my comments in Washington, I have also served as a consultant to Eli Lilly since the original launch of fluoxetine and have carefully followed and examined the accumulating data regarding the reproductive safety of the compound since it came to market in the United States.

The Program I direct at Massachusetts General Hospital is designed to help patients make decisions about the potential use of psychiatric medications, including antidepressants, during pregnancy. Our group consults on approximately 1000 women per year to review the relative risks of continuing pharmacotherapy during pregnancy versus the risks of depressive relapse and the impact of such relapse on maternal and fetal well-being. Our web-driven Perinatal Information Resource Center (see http://www.womensmentalhealth.org) receives approximately 17,000 visits per month, with the majority of queries focusing on the use of psychiatric medications during pregnancy.

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NTP-CERHR Expert Panel Report: Points of Concern

Introduction:

The conclusion of the NTP Expert Panel that fluoxetine is a "reproductive toxin," has the potential to dramatically affect the treatment of major depression in women of reproductive age. Major depression is a highly prevalent illness and clusters in women during the childbearing years. There is already stigma associated with depression and its treatment; treatment of depression during pregnancy is a particular concern for patients and lay literature and scientific reports are frequently conflicting or inconclusive. Much of the data referenced and reviewed by the Expert Panel, and on which conclusions have been made regarding the reproductive safety of fluoxetine, have clear flaws acknowledged by the original investigators in many cases.

Risk for Congenital Malformations:

While the Expert Panel did not conclude that fetal exposure to fluoxetine was associated with an increased risk for major congenital malformations, they did suggest that prenatal exposure *was* associated with increased risk for minor congenital anomalies. This is ironic since, while there was an increase in two and three minor anomalies in the exposed versus unexposed children, there was no apparent pattern of minor anomalies noted. Given the absence of a consistent pattern with respect to minor anomalies, the authors clearly acknowledge the inability to make a causal link between fetal exposure to fluoxetine and increased risk for minor anomalies. It is also noteworthy, that the dysmorphologic evaluation with respect to minor anomalies was conducted on only half the original sample, hence introducing a bias which is not acknowledged by the NTP Panel in the Expert report (see Cohen and Rosenbaum, 1994, NEJM for comment).

Poor "Neonatal Adaptation" Associated with Prenatal Exposure to Fluoxetine

The Expert Panel report also addresses the risk for "perinatal toxicity," which typically includes symptoms of jitteriness and autonomic reactivity in the newborn. Reports have accumulated over the last decade suggesting that prenatal exposure, particularly during the third trimester, to several selective serotonergic reputable blockers (SSRIs), including fluoxetine, may be associated with an increased risk of transient symptoms as noted above. Most reports have not associated such exposure with adverse longer-term sequelae. Fluoxetine is the only SSRI for which we have long-term neurobehavioral data, including follow-up of exposed children through ages 4-7. No differences in long-term neurobehavioral outcome between exposed and unexposed children were noted.

Another concern regarding conclusions made by the Expert Panel lies with the failure to acknowledge an important potential confound in the literature reviewed by the committee, namely, the extent to which untreated maternal mood may have adverse effect on fetal and neonatal outcome. Recent literature (see Orr and Miller, 2002) supports earlier preliminary concerns regarding the adverse effects of untreated maternal mood on fetal and neonatal well-being, with data suggesting higher rates of obstetrical and neonatal complications in offspring of mothers who suffer from depression during pregnancy. In our own work, we note that the threshold for patients' willingness to use antidepressant during pregnancy is frequently high. So greater duration of treatment during pregnancy, as noted in some of the studies reviewed by the

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NTP Expert Panel, really implies that the study population suffers from more severe depression compared for example, to a group exposed only "early in pregnancy" (see Chambers, 1996). It is my opinion that the failure to address the confound of untreated depression during pregnancy, and its potential effect on the observed outcome, constitutes a serious omission.
Our group has spent nearly twenty years counseling women about the relative risks of antidepressant use during pregnancy, including fluoxetine. Decisions are best made on a case-by-case basis since, when presented with the same information, patients make very different decisions as a function of wishes and individual perception of risk and benefit. These decisions are best made collaboratively between patient and physician around a specific clinical situation.

Fluoxetine is used to treat a serious illness; it is not a potential environmental toxin, such as those reviewed by other NTP panels. The compound in question is a therapeutic agent where safety is actually reviewed in an ongoing fashion by a separate governmental agency. The report does not indicate that decisions about whether to use fluoxetine during pregnancy are clinical choices made by patients in the context of some risk-benefit analysis made collaboratively between the patient, her family, and the physician.

My colleagues and I have described high rates of relapse in women with a history of recurrent major depression who discontinue antidepressants in pregnancy. Depression during pregnancy is associated with compromised fetal and neonatal outcomes, risks that are not reflected in the report. Discontinuation of antidepressant medication near the end of pregnancy also appears to increase the risk for postpartum depression.

The Expert Panel notes in the report that any risks of fluoxetine need to be weighed against the risks of untreated disease. But this brief statement, embedded in a lengthy document that describes fluoxetine as "a reproductive toxin," is inadequate. I am particularly concerned as to how this report will impact the decisions made by my patients, and patients of my colleagues, who use these therapeutic agents to treat a disease like major depression with its attendant morbidity and potential mortality.

Sincerely,

Lee S. Cohen, M.D.