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June 16, 2004

CERHR
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RE: NTP-CERHR Report on Fluoxetine

Gentlemen:

I am responding to the most recent NTP-CERHR report on fluoxetine dated April 2004. I had previously reviewed the document published that was dated November 2003. I am specifically addressing the issues with regard to some aspects of developmental toxicity.

Background:

Received BA in 1948, M.D. with honor in 1953 and a Ph.D. in embryology and radiation biology in 1944 from the University of Rochester. First postdoctoral fellow of the March of Dimes in the area of birth defects 1953-54, Pediatric Residency at the Massachusetts General Hospital. I am a Board Certified pediatrician who was chairman of a large pediatric department for 30 yeas at the Jefferson Medical College with pediatric programs at the Thomas Jefferson University Hospital, the Methodist Hospital, Christiana Hospital and the duPont Hospital for Children. We have had a large neonatal program with intensive care nurseries in two of the hospitals and as many as 20,000 deliveries per year, all told, during some of our peak years. My own area of interest and research is in teratology, developmental toxicology and genetics. I had a NIH training program for many years and our trainees are heads of developmental biology programs at universities and in industry. I was funded continuously during my research career by the NIH and the DOE and have been consulted and continue to be consulted by the FDA, CDC, NIH, DOE, industry and the Attorney General's office of the United States. I have published 400 papers, six (6) books and numerous abstracts in my areas of expertise. I am a member of the IOM of the NAS, the NCRP, HESI, HPS, and a number of other research societies. One of the societies of which I am a charter member is the Teratology Society, having been elected president in 1966-67, as well as editor of the Journal, Teratology for three five-year terms. Although I no longer am chairman of the Pediatrics department, I still have a laboratory, teach medical students and residents and have students in our laboratory. I am presently a member of the Dental Institute's Dental Amalgam Committee and have just been appointed to a new committee of the NAS dealing with the

environmental toxicology. Other consultations include solving environmental toxicology issues concerning new drugs and chemicals that are quite similar to the issues raised in the fluoxetine report. My most recent publication is a supplement to the April issue of "Pediatrics," which is a series of 30 chapters dealing with environmental toxicology issues. I was the senior editor and Michael Weitzman was co-editor. The preface and four (4) chapters were written by the both of us and two chapters were authored solely by myself (Brent 2004). My present position is Distinguished Professor of Pediatrics, Pathology and Radiology.

Consultation with Lilly:

Before being consulted by Eli Lilly, I had an interest in this topic because my oldest son is Chairman of Child Psychiatry at the University of Pittsburgh and his field is childhood depression and suicide. He is involved in extensive research in treating depressed children and is involved with the evaluation of the impact of the controversial papers recently published dealing with the risks of SSRI's. Therefore, it is important that future publications contain conclusions that are supported by definitive data and not presumptions or hypotheses. Depressed adults and children need all the assistanee we can give them.

My general reaction to the report with regard to developmental toxicity is that the expert panel is required to follow past guidelines set forth by NTP CERHR with regard to drawing conclusions about developmental toxicity and are requested to respond with a yes or no answer (i.e. is the substance developmentally toxic or not). Having to follow this guideline places the expert panel in an untenable position of having to draw a firm conclusion when firm data is not available. It is like having to label and individual as a dangerous criminal because he has committed a crime, regardless of what the crime is (i.e. serious felony vs. minor traffic violation). It would be much better if the committee would describe what they consider to be the developmental findings that are of concern and the quality of the data on which the conclusion is based. Labeling an agent as a developmental toxicant on the basis of minimal or controversial data is not appropriate.

Congenital Malformations:

The animal studies and the epidemiological studies indicate that therapeutic doses of fluoxetine in the human and in animals at pharmacokinetically equivalent doses do not result in an increase in major birth defects. Although the expert panel is in agreement with the lack of data demonstrating an effect on major malformations, they state that fluoxetine exposure during early gestations may result in an increased incidence of minor anomalies. With regard to the issue of minor anomalies the expert committee focused on the paper by Chambers et al. published in the New England Journal of Medicine in October 1996. In that paper, the author's conclusions do not include any inference that the minor anomalies were an issue in their study. They reported a

decrease in the incidence of one minor anomaly in the exposed population compared to the controls, and an increase in two or three minor anomalies in the exposed population compared to the controls. All three of these comparisons were statistically significant. The authors felt that they could not conclude that this was a causal association because the spectrum of minor anomalies had no consistent pattern in the exposed group as compared to the controls. This is a very important principle in teratology that is utilized in evaluating major malformation syndromes as well as clusters of minor anomalies. Minor anomalies can be used in teratology studies in many ways. For instance repeated clusters of minor anomalies may be associated with an increase in major anomalies at a higher exposure. Minor anomalies may occur at lower exposures as sentinels of a teratogenic exposure. But if you do not have major malformations either clinically or in animal studies, then the occurrence of minor anomalies cannot be interpreted to be a definitive sign of teratogenicity. If a child was exposed to thalidomide but exhibited no major malformations but did have a band around the little finger and a small sacral dimple, the experienced dysmorphologist would know that these minor malformations were not the result of the thalidomide exposure, because those are not minor malformations that have been identified in the thalidomide syndrome.

The other issue with regard to the minor anomalies is that Dr. Kenneth Jones, who is a well-known authority on dysmorphology and an expert in examining patients with dysmorphology effects, did not examine all of the patients in the Chambers study. Approximately 50% of the patients were examined by him so that the incidence and statistics for major malformations were determined from the whole group of exposed population and the minor anomalies were only determined from a portion of the exposed population. The most important aspect of the Chambers et al. paper is that they themselves did not believe that the minor anomalies issue was a causal association. I called Dr. Chambers and spoke with her in detail about the minor anomalies and she was surprised that the expert committee would draw any conclusions abut the data on minor anomalies, since the authors themselves did not infer that there was a causal association based on their data. It might be worthwhile for the Committee to discuss the issue of minor anomalies with her directly. She is very approachable and very forthright.

Neonatal Adaptation:

Another issue that the expert committee dealt with was neonatal adaptation. As the committee pointed out, these were all transient signs that were present in the newborn nursery and at higher incidence in the fluoxetine-exposed mothers than in the controls. I would point out to the committee that this is an extremely difficult study to perform because there was no randomization of the patients being sent to the intensive care nursery versus those going to the regular nursery. Patients in the intensive care nursery or intermediate nurseries are more carefully monitored compared to the normal nursery. The intensive care nurseries have more

attendants and the babies are evaluated more closely. The physical and behavioral signs are recorded in more detail in these nurseries as compared to the regular newborn nurseries. It is more likely that a mother who has been depressed and on fluoxetine is going to have her baby sent to an intensive care nursery or intermediate care nursery for observation compared to the patients who would go to a normal nursery who are not depressed and on fluoxetine. As a result of the differences in patient care, you do not have a comparable control group for the exposed patients with regard to the intensity of observing these infants. Many normal newborn babies have these transient neonatal adaptive findings in the normal nurseries that are not recorded. An important point that the panel determined was that these adaptive findings were not permanent and that when the babies were examined weeks or months later all these newborns adaptive findings were gone.

Method of Evaluation:

In developmental biology, five important criteria are considered in the process of evaluating and concluding whether or not an agent causes developmental toxicity in humans. These five areas include: 1) Consistent findings in two or more high quality epidemiology studies, 2) Ecological or secular trend analysis, 3) Animal studies that include teratology and developmental biology studies, 4) Pharmacokinetic or toxicokinetic studies in the animal models that include the equivalent human exposures, 5) Biological principles, method of action studies, receptor studies, biological plausibility and the application of teratology and developmental biology principles.

Using the above methodology we can arrive at the following conclusions:

1) The human epidemiology studies and animal studies indicate that fluoxetine does not cause congenital malformations. In the area of minor anomalies, we do not have consistency of multiple epidemiology studies that describe a cluster of minor anomalies that is associated with fluoxetine exposure. The Chambers study is the only one that deals with minor anomalies and the authors conclude that their study was not a causal association.

2) Secular trend or ecological analysis cannot be utilized because fluoxetine is utilized in only a small percentage of pregnant women.

3) and 4) The animal studies and animal toxicology studies clearly indicate that fluoxetine is not a teratogen and that you do not get any developmental effects until you raise the exposures high enough to produce maternal toxicity. This also is an important finding that can be used in evaluating the clinical aspects of fluoxetine exposure in pregnant women.

5) The last area that is considered by developmental biologists in evaluating the clinical significance of drug and chemical exposures in pregnancy is biological plausibility. Since there is an absence of animal studies and human studies to indicate that fluoxetine produces major malformation, biologic plausibility is not utilized to evaluate the occurrence of major malformations, since it is mainly used to support the presence of a teratogenic or developmental effect. On the other hand, biological plausibility does not support the concept that fluoxetine would be causally related to the etiology of minor malformations, since we do not have teratogens that only produce minor malformations at low doses, but no severe major malformations at higher exposures.

Fetal Growth Retardation:

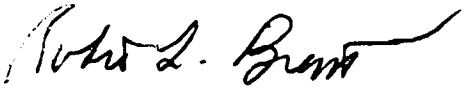
The expert panel concluded that they were concerned about the possibility that fluoxetine may have been responsible for growth retardation in one population of newborns exposed in utero (Chambers et al. 1999). Growth retardation is an important, sensitive developmental effect. Although it was reported that the fluoxetine-exposed fetuses were smaller than controls (3419 gms vs. 3711 gms), both groups were above the national average at birth. It is difficult to draw any conclusions about fluoxetine's effect on growth when the average weight of the fluoxetine-exposed newborns was above the national average in this study.

Conclusion:

The expert panel had three concerns, which in their opinion, was sufficient to label fluoxetine as a developmental toxicant. Such a labeling may seem appropriate to the panel as a precaution, but does the available data warrant such a label. As I indicated in my discussion, an essential characteristic of a causal or statistically associated effect is consistency of the finding in epidemiological studies, which is presently not available. The minor malformation data, the growth retardation data and the transient neurological data have yet to be confirmed as definitive positive findings. This group of drugs is important for the treatment of very serious and debilitating diseases and the committee has a responsibility to act on the basic definitive results of developmental toxicity studies that are not available at this time. It is appropriate to describe the "positive" findings and the quality of the data on which these findings are based. Reversible effects (neonatal adaptation) and inconsequential results (statistical growth retardation in groups of normal sized babies) need to be carefully evaluated before determining that they are causal effects or significantly detrimental.

If you have any questions about these comments, please feel free to contact me.

Sincerely,



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