



Letter to the Editor

Serotonin reuptake inhibitors and heart defects[☆]

The paper by Bérard et al. [1] ostensibly is a review of epidemiology methods. It is also a platform for Dr. Bérard to advance the opinions to which she has testified in birth defect lawsuits against manufacturers of serotonin reuptake inhibitors. These opinions are not generally accepted; neither are they acceptable. The authors begin their paper using serotonin reuptake inhibitors as an example of medications associated with an increase in risk for congenital heart and other defects, acknowledging that not all studies showed a statistically significant increase in risk. They dismiss the lack of statistical significance in most of these studies by referring to the limited power of those studies that are consistent with the null.

The dismissal of studies that fail to support Dr. Bérard's litigation opinion begs the question of how the literature would look if serotonin reuptake inhibitors did not increase the risk of congenital malformations. A large literature evaluating a large number of end points would be expected to include some studies reporting an increased risk estimate and some studies not reporting an increased risk estimate. The literature on paroxetine, for example, includes large studies that are reasonably precise and consistent with the null (e.g., [2–7]). Dr. Bérard might argue that among these studies, there are few exposed affected children, but of course, that is the point. Reassurance comes from the relatively large number of exposed unaffected children in these studies. The studies suggesting an increase in some malformations do not show a consistent group of malformations, and as noted in an editorial by Dr. Chambers, a Bérard coauthor, “lack of consistency across these studies with respect to specific malformations and specific drugs makes it difficult to translate the findings into clinical practice” [8].

Moreover, there are now studies showing the importance of confounding by indication in studies of serotonin reuptake inhibitors. In a large study involving all pregnancies in Denmark between 1997 and 2009, there was an increase in congenital heart defects among children whose mothers had filled a prescription for a serotonin reuptake inhibitor, but the risk did not differ based on whether the mother filled the prescription during pregnancy or only months before and after the pregnancy [7]. Other studies show an attenuation of risk estimates toward the null with analytic consideration for the underlying disease state or with the use of sibling controls [9,10].

Of particular concern is the justification by Bérard et al. of a conflation of different malformations based on findings for a lumped group of malformations. They write, “findings for an organ system group (for example – heart defects overall) can be extrapolated to specific defects within the group if they occur at the same embry-

ological stage.” This opinion has no foundation. Thalidomide, for example, causes longitudinal but not transverse or a variety of other limb defects [11]. The development of these defects within the same embryological stage does not mitigate the differences in pathogenesis among them.

The heart, a highly complex organ, has a number of different developmental events occurring at the same time, but no evidence demonstrates that diverse heart defects must therefore have a common cause. The ventricular septum forms in a manner different from the atrioventricular valves, even though both are forming at around the same time. Within the ventricular septum, defects have different origins, depending on which part of the septum is affected. The classification system of the National Birth Defects Prevention Study is among the most widely accepted for etiologic studies [12]. These authors wrote, “Classification and analysis of congenital heart defects (CHD) in etiologic studies is particularly challenging because of diversity of cardiac phenotypes and underlying developmental mechanisms.” Since the appearance of that paper, there have been additional advances in embryology of the heart, further demonstrating the need for specificity in etiology studies. For example, tetralogy of Fallot, once considered a conotruncal defect associated with impaired neural crest cell migration, is now understood to originate in discrete portions of the secondary heart field [13].

The assertion that the broad category of “heart defects” stands for each individual defect cannot be supported given our understanding of the development of individual heart defects. The occasional studies involving serotonin reuptake inhibitors that identify a statistically significant increase in “heart defects” and also evaluate types of heart defects show us that the heart defect findings often are due to septal defects or right ventricular outflow obstruction, two broad categories of defects that are the most prone to biased ascertainment based on possible increased use of echocardiography in the children of anxious mothers or in children with serotonin-reuptake inhibitor transition difficulties [14–16]. Given the possibility of biased ascertainment and the demonstrated confounding by indication, the statements of Bérard et al. about serotonin reuptake inhibitors and the use of “heart defects” to stand for individual defects are unreliable.

Conflict of interest

The author has testified for the defense in litigation involving paroxetine and birth defects.

References

- [1] A. Bérard, K.L. Wisner, S. Hultzsich, C. Chambers, Field studies versus database studies on the risks and benefits of medication use during pregnancy: distinct pieces of the same puzzle, *Reprod. Toxicol.* (2016), <http://dx.doi.org/10.1016/j.reprotox.2016.02.002>.

[☆] Editors's Note: Dr. Berard declined the opportunity to respond in print to Dr. Scialli's letter to the editor.

- [2] C. Louik, A.E. Lin, M.M. Werler, S. Hernández-Díaz, A.A. Mitchell, First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects, *N. Engl. J. Med.* 356 (26) (2007) 2675–2683.
- [3] A. Einarson, A. Pistelli, M. DeSantis, H. Malm, W.D. Paulus, A. Panchaud, D. Kennedy, T.R. Einarson, G. Koren, Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy, *Am. J. Psychiatry* 165 (2008) 749–752.
- [4] L.H. Pedersen, T.B. Henriksen, M. Vestergaard, J. Olsen, B.H. Bech, Selective serotonin inhibitors in pregnancy and congenital malformations: population based cohort study, *BMJ* 339 (2009) b3569, <http://dx.doi.org/10.1136/bmj.b3569>.
- [5] J.B. Kornum, R.B. Nielsen, L. Pedersen, P.B. Mortensen, M. Nørgaard, Use of selective serotonin reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis, *Clin. Epidemiol.* 2 (2010) 29–36.
- [6] H. Malm, M. Artama, M. Gissler, A. Ritvanen, Selective serotonin reuptake inhibitors and risk for major congenital anomalies, *Obstet. Gynecol.* 118 (1) (2011) 111–120.
- [7] E. Jimenez-Solem, J.T. Andersen, M. Petersen, K. Broedbaek, J.K. Jensen, S. Afzal, G.H. Gislason, C. Torp-Pedersen, H.E. Poulsen, Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study, *BMJ Open* (2012) 2e001148, <http://dx.doi.org/10.1136/bmjopen-2012-001148>.
- [8] C. Chambers, Selective serotonin reuptake inhibitors and congenital malformations, *BMJ* 339 (2009) b3525.
- [9] K.F. Huybrechts, K. Palmsten, J. Avorn, L.S. Cohen, L.B. Holmes, J.M. Franklin, H. Mogun, R. Levin, M. Kowal, S. Setoguchi, S. Hernández-Díaz, Antidepressant use in pregnancy and the risk of cardiac defects, *N. Engl. J. Med.* 370 (2014) 2397–2407.
- [10] K. Furu, H. Kieler, B. Haglund, A. Engeland, R. Selmer, O. Stephansson, U.A. Valdimarsdottir, H. Zoega, M. Artama, M. Gissler, H. Malm, M. Nørgaard, Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design, *BMJ* 350 (2015) h1798, <http://dx.doi.org/10.1136/bmj.h7198>.
- [11] C.G.H. Newman, Teratology update: clinical aspects of thalidomide embryopathy—a continuing preoccupation, *Teratology* 32 (1985) 133–144.
- [12] L.D. Botto, A.E. Lin, T. Riehle-Colarusso, S. Malik, A. Correa, The National Birth Defects Prevention Study, Seeking causes: classifying and evaluating congenital heart defects in etiologic studies, *Birth Defects Res. (Part A)* 79 (2007) 714–727.
- [13] P. Parisot, K. Mesbah, M. Théveniau-Ruissy, R.G. Kelly, *Tbx1*, subpulmonary myocardium and conotruncal congenital heart defects, *Birth Defects Res. (Part SA)* 91 (2011) 477–484.
- [14] N. Roguin, Z.-D. Du, M. Barak, N. Nasser, S. Hershkowitz, E. Milgram, High prevalence of muscular ventricular septal defect in neonates, *J. Am. Coll. Cardiol.* 26 (1995) 1545–1548.
- [15] C. Wren, S. Richmond, L. Donaldson, Temporal variability in birth prevalence of cardiovascular malformations, *Heart* 83 (2000) 414–419.
- [16] A. Correa, J.D. Cragan, J.E. Kucik, C.J. Alverson, S.M. Gilboa, R. Balakrishnan, M.J. Strickland, C.W. Duke, L.A. O’Leary, T. Riehle-Colarusso, C. Siffel, D. Gambrell, D. Thompson, M. Atkinson, J. Chitra, Metropolitan Atlanta congenital defects program 40th anniversary edition surveillance report. Appendix A, *Birth Defects Res. (A)* 79 (2007) 94–177.

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24 March 2016

27 May 2016

Available online 7 June 2016