NON-PRECEDENTIAL DECISION - SEE SUPERIOR COURT I.O.P. 65.37

ROBERT AND KATHERINE PORTER, INDIVIDUALLY, AND AS PARENTS AND NATURAL GUARDIANS OF ROBERT T. "BO" PORTER, A MINOR

Appellants

v.

SMITHKLINE BEECHAM CORPORATION, PFIZER, INC. AND WOLTERS KLUWER HEALTH, INC.

IN THE SUPERIOR COURT OF PENNSYLVANIA

No. 3516 EDA 2015

Appeal from the Order Entered October 8, 2015
in the Court of Common Pleas of Philadelphia County Civil Division
at No(s): September Term, 2007 No. 03275

BEFORE: BENDER, P.J.E., DUBOW, J., and FITZGERALD, J.*

MEMORANDUM BY FITZGERALD, J.: **FILED MAY 08, 2017**

Appellants, Robert and Katherine Porter, individually, and as parents and natural guardians of Robert T. "Bo" Porter, a minor, appeal from the order entered in the Philadelphia County Court of Common Pleas granting the motion of Appellee, Pfizer, Inc., for summary judgment.[1] Appellants

* Former Justice specially assigned to the Superior Court.

[1] On September 29, 2014, the trial court granted GlaxoSmithKlein, LLC's renewed motion to dismiss and ordered the claims against them be dismissed with prejudice. ***See*** R.R. at 21a. Appellants had settled with Wolters Kluwer Health, Inc. prior to trial. ***See id.*** at 96a. Therefore, this appeal is properly before this Court. ***See*** Pa.R.A.P. 341(b)(1). For the parties' convenience, we refer to the reproduced record where applicable.

contend the trial court erred in precluding the testimony of their expert witness based upon ***Frye v. United States***, 293 F. 1013 (D.C. Cir. 1923). We affirm.

The trial court summarized the facts and procedural posture of this case as follows:

> On June 15, 2012 [Appellants] filed an Amended Complaint against [Appellee] Pfizer alleging that the ingestion of Zoloft[2] by [Appellant] Mrs. Porter during her pregnancy caused Minor [Appellant] to be born with the serious birth defect omphalocele.[3] On August 14, 2015 [Appellee] filed ***Frye*** Motions seeking to preclude the Expert Testimony of Dr. [Michael] Freedman [M.D., Ph.D.] and [Robert M.] Cabrera[, Ph.D].[4] On August 26, 2015 [Appellants] filed a Response. A two day hearing was held on September 16 and September 17, 2015. At that hearing the court heard from Dr. Freeman and [Appellee's expert, Dr. Stephen Edward Kimmel M.D.] and received into evidence numerous documents including the written report of Dr. Cabrera. On September 30, 2015 Appellee's Motion was Granted as to Dr. Freeman and he was not permitted to testify at trial. On October 5, 2015 [Appellee's] Motion was Granted as to Dr. Cabrera and he

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[2] Zoloft is a sertraline.

> Sertraline is a medication used to treat depression, obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder. A brand name for sertraline is Zoloft. Zoloft belongs to the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs).

R.R. at 906a.

[3] "An omphalocele is a midline abdominal wall birth defect. This defect occurs when the intestines and potentially other visceral organs protrude outside the body through the umbilical opening." R.R. at 959a.

[4] ***See*** R.R. at 247a.

> was not permitted to testify at trial. . . . On September 15, 2015[, Appellee] filed a Motion for Summary Judgment. On October 8, 2015[, Appellant] filed a Response to [Appellee's] Motion for Summary Judgment. On October 8, 2015[, Appellee's] Motion for Summary Judgment was Granted.

Trial Ct. Op., 2/10/16, at 1-2 (footnotes omitted). This timely appeal followed. Appellants filed a Pa.R.A.P. 1925(b) statement of errors complained of on appeal and the trial court filed a responsive opinion.

Appellants raise the following issue for our review: "Did the trial court improperly preclude Dr. Cabrera from testifying on ***Frye*** grounds?" Appellants' Brief at 3. Dr. Cabrera was offered as an expert "on general and specific causation." ***Id.*** Appellants contend the trial court "overlooked the general acceptance of Dr. Cabrera's methodological tools, and inserted [itself] as an independent assessor of Dr. Cabrera's credibility and persuasiveness." ***Id.*** at 22. Appellants argue:

> Dr. Cabrera described the foundational principles of the modern study of teratology as expressed by James Wilson, the co-founder of the Teratology Society and founder of the field. The principles include the so-called "dose response" principle restated in the context of teratology: "Manifestations of deviant development increase in frequency and degree as dosage increased from the No Observable Adverse Effect Level to a dose producing 100% Lethality." The central point made by Dr. Cabrera is that low doses "may exert no or very little toxicity or teratogenicity, while higher doses are expected to increase the incidence and severity of the observed malformations."
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> Dr. Cabrera explained the importance of animal studies in rabbits and rats as a vehicle for testing whether a compound is a human teratogen.
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> Dr. Cabrera then discussed numerous animal studies that affirmatively suggest that Zoloft is a teratogen that **causes** birth defects.
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> At the same time, Dr. Cabrera identified shortcomings with the studies that he found reduced their statistical power. He ultimately concluded that "while the reported data provided indications of the presence of cranial, kidney, and heart defects due to [Zoloft] exposure, the studies lacked any detailed pathology that might have allowed the investigators to draw more reasoned conclusions."
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> For present purposes, the key point is that animal studies represent a generally accepted tool for building an assessment about the teratogenicity of a pharmaceutical compound.
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> [H]e focuses on the 2007 Louik study[5] . . . . The Louik study was a peer reviewed, case-controlled study reflecting a strong, statistically significant positive correlation between first trimester Zoloft exposure and omphalocele. The study found that maternal use of Zoloft during the first trimester was associated with a nearly *six times greater risk* of the infant developing an omphalocele.
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[5] Louik C., A. E. Lin, et al. (2007). "First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects." N. Engl. J. Med. 2007, Vol. 356(26): 2675-2683. R.R. at 624a.

> Of course, Dr. Cabrera did not limit his inquiry to the Louik study. . . . Concededly, some of these studies did not involve enough subjects to show a "statistically significant" association between Zoloft taken during pregnancy and omphalocele.
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> Dr. Cabrera also discussed studies by Reefhuis[6] and Furu[7] that, although they did not show a statistically significant association between omphalocele and Zoloft in particular, did show statistically significant associations between omphalocele and other SSRIs exhibiting the same mechanism of action as Zoloft.
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> Dr. Cabrera made careful and appropriate use of the Bradford-Hill criteria[8] in further developing his **causation analysis**.
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[6] Reefhuis J., S. M. Gilboa, et al. (2015). "The national birth defects prevention study: A review of the methods." Birth Defects Res A Clin Mol Teratol. R.R. at 630a.

[7] Furu, K., H. Kieler, et al. (2015). "Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design." BMJ 350: h 1798. R.R. at 628a.

[8] "The Bradford-Hill criteria were developed as a mean[s] of interpreting an established association based on a body of epidemiologic research for the purpose of trying to judge whether the observed association reflects a causal relation between an exposure and disease." ***Soldo v. Sandoz Pharms. Corp.***, 244 F.Supp.2d 434, 514 (W.D.Pa. 2003). "While we recognize federal district court cases are not binding on this court, Pennsylvania appellate courts may utilize the analysis in those cases to the extent we find them persuasive." ***Stephens v. Paris Cleaners, Inc.***, 885 A.2d 59, 68 (Pa. Super. 2005) (citations omitted).

> It is conceded that Dr. Cabrera's analysis has limitations based on the limitations of the available scientific evidence, which in turn is based on the impossibility of directly conducting studies on pregnant women.
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> In other words, Dr. Cabrera explained, after finding a general causal relationship between drug and disorder, the researcher identifies and rules out other potential causes to determine whether the drug **caused** the disorder in that specific instance. **That is the differential causation analysis that Dr. Cabrera performed here**.

Appellants' Brief at 26-27, 29-30, 33, 35, 38-39 (citations and footnote omitted) (emphasis added).

Dr. Cabrera opined:

> It is my opinion, within a reasonable degree of scientific certainty, that Zoloft (sertraline) is teratogen,[9] both in animals and in humans, when ingested during pregnancy. The teratogenicity of sertraline, has been amply demonstrated in animal studies, as well as in a number of human epidemiological and registry studies. There exists a biologically plausible mechanism of teratogenic action (MOA) based on the MOA of SSRIs. In general, it is my opinion, within a reasonable degree of scientific certainty, that alteration of serotonin signaling by sertraline, can impact embryonic development resulting in several different congenital malformations, involving various organ and body systems, including, but not limited to abdominal wall defects such as omphalocele. It is my opinion that Kathy Porter's ingestion of Zoloft while pregnant caused Bo Porter's omphalocele.

R.R. at 578a.

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[9] "Teratology is the study of abnormal embryonic development. The founding principles of the modern study of teratogens were initially articulated by Janes G. Wilson (Wilson 1973), co-founder of The Teratology Society, in his monograph, 'Environment and birth Defects.'" R.R. at 578a.

Although the order currently before this court awarded summary judgment, "an appeal of a final order subsumes challenges to previous interlocutory decisions," such as preclusion of expert testimony. ***Betz v. Pneumo Abex***, 44 A.3d 27, 54 (Pa. 2012). "Generally, the appropriate appellate standard of review is the one pertaining to the underlying ruling." ***Id.*** Instantly, the trial court granted summary judgment after precluding Appellant's expert testimony. "[The a]ppellant's issue[ ] on appeal, therefore, challenge[s] the court's preclusion of [her] expert testimony." ***Haney v. Pagnanelli***, 830 A.2d 978, 980 (Pa. Super. 2003)

Our review is governed by the following principles:

> [A]s to the standard of appellate review that applies to the ***Frye*** issue, we have stated that the admission of expert scientific testimony is an evidentiary matter for the trial court's discretion and should not be disturbed on appeal unless the trial court abuses its discretion. An abuse of discretion may not be found merely because an appellate court might have reached a different conclusion, but requires a result of manifest unreasonableness, or partiality, prejudice, bias, or ill-will, or such lack of support so as to be clearly erroneous.

Grady v. Frito-Lay, Inc., 839 A.2d 1038, 1046 (Pa. 2003) (citations omitted).

Rule 702 of the Pennsylvania Rules of Evidence governs the admissibility of expert opinion. Rule 702 provides as follows:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:

> (a) the expert's scientific, technical, or other specialized knowledge is beyond that possessed by the average layperson;
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> (b) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; and
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> (c) **the expert's methodology is generally accepted in the relevant field**.

Pa.R.E. 702 (emphasis added).

"The ***Frye*** test . . . adopted in Pennsylvania in ***Commonwealth v. Topa***, [ ] 369 A.2d 1277 (Pa. 1977), is part of Rule 702." ***Grady***, 839 A.2d at 1043. "***Frye*** only applies when a party seeks to introduce **novel** scientific evidence." ***Trach v. Fellin***, 817 A.2d 1102, 1109 (Pa. Super. 2003) (*en banc*). In ***Betz***, our Supreme Court opined that "a reasonably broad meaning should be ascribed to the term novel." ***Id.*** 44 A.3d at 53.

However, "***Frye*** only applies to determine if the relevant scientific community has generally accepted the principles and methodology the scientist employs, **not** the conclusions the scientist reaches, before the court may allow the expert to testify." ***Trach***, 817 A.2d at 1112. In ***Trach***, this Court noted that

> the scientific method is a method of research in which a problem is identified, relevant data are gathered, a hypothesis is formulated from these data, and the hypothesis is empirically tested. Within the meaning of the definition of the scientific method, empirical means provable or verifiable by experience or experiment. Key aspects of the scientific method include the ability to test or verify a scientific experiment by a parallel experiment or

> other standard of comparison (control) and to replicate the experiment to expose or reduce error.

Id. at 1113 (citations and quotation marks omitted).

Our Pennsylvania Supreme Court in ***Grady*** "emphasize[d] that the proponent of expert scientific evidence bears the burden of establishing all of the elements for its admission under Pa.R.E. 702, which includes showing that the ***Frye*** rule is satisfied." ***Grady***, 839 A.2d at 1045. Pennsylvania law does not permit "experts to evade a reasoned ***Frye*** inquiry merely by making references to accepted methods in the abstract." ***Betz***, 44 A.3d at 58.

In the case *sub judice*, the trial court opined:

> [Appellants] seek[ ] to have [Dr. Cabrera] testify as to general and specific causation of the birth defects of this case. Within Dr. Cabera's forty-seven page report,[10] are five pages devoted to his training, education, and experience and twelve pages devoted to animal studies concerning SSRIs, Zoloft, and birth defects. The most recent animal study referenced is a seventeen year old study from 1998. Animal studies can be instructive in determining the teratogenicity of a pharmaceutical and indeed in the absence of human studies may become the basis for a valid extrapolated scientific opinion. However, animal studies are of limited utility in determining teratogenicity where a significant body of human exposure studies exists in the published medical literature. Dr. Cabrera does not acknowledge these limitations.
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> Dr. Cabrera's opinions rely on a limited number of the peer review articles. Dr. Freeman relied on these same studies and formed a comparable analysis. Dr. Cabrera's

[10] ***See*** R.R. at 572a.

analysis suffers from many of the same methodological defects in Dr. Freeman's opinions. **The methodological defects identified as to Dr. Freeman's opinions are incorporated herein.**

Dr. Cabrera's report contains other methodology failings. Dr. Cabrera finds that the studies show that SSRIs significantly increase the risk of birth defects in human studies and opines that SSRIs are teratogenic. However, he does not specifically analyze SSRIs results which exclude the pharmaceutical Paxil.[11] This is a fatal methodological flaw because Paxil has been identified as having significantly different effects from Zoloft and other SSRIs. Paxil is a causal factor in birth defects. Dr. Cabrera's opinion, as reflected in his report, does not contain any adequate discussion of the differences between Paxil and Zoloft with respect to causation of birth defects.

Dr. Cabrera opines that the mechanism of action resulting in birth defects is that an "alteration of serotonin signaling by sertraline, can impact embryonic development resulting in several different congenital malformations."[12] This opinion is speculative and without scientific basis. Dr. Cabrera presents no information as to the baseline serotonin level in the developing fetus or the change caused by Zoloft. Without this data there can be no valid opinion as to whether the level of serotonin changes in positive or negative manner or has any outcome determinative effect at all. Likewise, Dr. Cabrera did not perform the dose response analysis necessary to draw a valid scientific conclusion that a medication causes a specific biological mechanism.

For the reasons precluding the testimony of Dr. Freeman and those herein Dr. Cabrera likewise was

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[11] "In 2005, Mrs. Porter's Paxil was prescribed by her primary care physician . . . . She was switched to Zoloft . . . by her obstetrician . . . in approximately the 7th week of her pregnancy." R.R. at 948a.

[12] ***See*** R.R. at 578a.

> properly precluded from offering causation opinions in this matter.

Trial Ct. Op. at 18-19 (footnotes omitted and emphasis added).

The trial court precluded Dr. Freeman from testifying on ***Frye*** grounds and opined:

> Dr. Freeman correctly concedes that the studies reveal precious little specific data on Zoloft and omphalocele. Dr. Freeman effectively solely relies on the Louik study as evidence of causation between Zoloft and the birth defect. The Louik study is the only study to report a statistically significant association between Zoloft and omphalocele. Reliance on this one study is questionable because of its limitations. Louik's confidence interval which ranges between 1.6 and 20.7 is exceptionally broad. Equally significant is the lack of power concerning the omphalocele results. The Louik study had only 3 exposed subjects who developed omphalocele thus limiting its statistical power. Studies that rely on a very small number of cases can present a random statistically unstable clustering pattern that may not replicate the reality of a larger population. The Louik authors were unable to rule out confounding or chance. The results have never been replicated concerning omphalocele. Dr. Freeman's testimony does not explain, or seemingly even consider these serious limitations.
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> [T]he Louik authors themselves expressed concern that they cannot distinguish true associations from random elevations of risk. The Louik authors were unable to rule out the possibility of chance:
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> > "The previously unreported associations we identified warrant particularly cautious interpretation. In the absence of preexisting hypotheses and the presence of multiple comparisons, distinguishing random variation from true elevation in risk is difficult. Despite the large size of our study overall, we had limited numbers to evaluate associations between rare outcomes and

> rare exposures. We included results based on small numbers of exposed subjects in order to allow other researchers to compare their observations with ours, but we caution that these estimates should not be interpreted as strong evidence of increased risks."[13]

Dr. Freeman ignores the issues specifically pointed out by the authors.

In addition to proper analysis of the appropriate literature, generally accepted methodology required that the epidemiologist consider the problem of confounding by indication. Women who are depressed and take SSRIs

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[13] The Louik study concluded:

> Our findings do not show that there are significantly increased risks of craniosynostosis, omphalocele, or heart defects associated with SSRI use overall. They suggest that individual SSRIs may confer increased risks for some specific defects, but it should be recognized that the specific defects implicated are rare and the absolute risks are small.

R.R. at 915a. Dr. Cabrera relied upon the Louik study in his expert report. He opined as follows:

> Louik and co-workers published on SRRI exposure and risk of birth defects in the New England Journal of Medicine (NEJM) in 2007. . . . In regard to study limitations, the authors report concerns for recall bias were minimized through multilevel structured questionnaire design. Recall bias will also not explain specific risk associated with individual SSRIs. Selection bias was also reported as unlikely, since mothers were invited to participate without knowledge of exposure. In regard to confounding by indication, the authors report, "the absence of significantly increased risk of various birth defects associated with the use of non-SSRI antidepressants suggests that depression itself is unlikely to be the cause of the defects studied."

R.R. at 605a-606a.

> have been more likely to smoke, be older, have less education, have poor nutrition, use other drugs, and have chronic diseases such a diabetes and hypertension, than women who do not use SSRIs. These factors have been linked to an increased risk of birth defects. Dr. Freeman does not properly analyze confounding.
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> In his report Dr. Freeman cites Jimene[z]-Solem,[14] Furu,[15] and Huybrechts as three studies that also found

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[14] Dr. Cabrera opined:

> Two additional studies that specifically report on SSRIs or sertraline exposure and risk of omphalocele merit mentioning. The first is a Danish cohort study on the teratogenicity of covering pregnancies from 1997-2009 [Jiminez-Solem, E., J. T. Andersen et al. (2012) "Exposure to selective serotonin reuptake inhibitors and the risk of congenital malformations: a nationwide cohort study." BMJ Open 2(3); e001148]. This study reported association with major congenital malformations and exposure to sertraline, adjusted [ ] and association between congenital malformations of the heart and exposure to sertraline, adjusted [ ]. However, they indicate, "**We found an association for exposure to an SSRI in the first trimester and craniosynostosis [ ] but not for omphalocele** or anencephaly."

R.R. at 608a (emphasis added), 629a.

[15] Dr. Cabrera opined:

> The latest study to report on omphalocele is a Nordic population based cohort study (Denmark, Finland, Iceland, Norway, and Sweden) conducted between the periods of 1996-2010 (Furu, Kieler *et al.* 2015). The study utilized national health registry data from each of the participating countries. It reported an odds ratio (OR) for SSRI exposure and omphalocele risk [ ], indicative of a significant increased risk for omphalocele amongst infants

> statistically significant increased risk of congenital malformation associated with SSRI exposure. All three of these studies acknowledged the problem of confounding, and discussed the problem in their analysis. Dr. Freeman does not address the authors' conclusions about confounding.
>
> Generally accepted methodology considers statistically significant replication of study results in different populations because apparent associations may reflect flaws in methodology. Dr. Freeman claims the Alwan[16]

> of mothers receiving SSRI treatment during pregnancy, **but no Zoloft–specific risk was reported**.
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> There are three additional studies that examined SSRI exposure and present general population rates of omphalocele, **but in each report the incidence is too low generally and in exposed population to perform statistical testing for risk of omphalocele**. These studies include reports from Danish [Pedersen, L. H., T. B. Henriksen et al. 2009). "Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study." BMJ.1 339:b3569.], Canadian [Berard, A., J. P. Zhao, et al. (2015) "Sertraline use during pregnancy and the risk of major malformations." Am J Obstet Gynecol 212(6): 795 e791-795 e712.] and European registries [Wemakor, A., K. Casson et al. (2015). "Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European register-based study." Eur J Epidemiol.]

R.R. at 609a-610a (emphases added), 625a, 627a, 631a.

[16] Alwan, S., J. Reefhuis, et al. (2007). "Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects." New England Journal of Medicine 356(26): 2684-2692. R.R. at 621a. The Alwan study concluded that

> [m]aternal use of SSRIs during early pregnancy was not associated with significantly increased risks of congenital heart defects or of most other categories of birth defects.

> and Reefhuis[17] studies demonstrate replication. However, the population Alwan studied is only a subset of the Reefhuis population and therefore they are effectively the same. More significantly neither Reefhuis nor Alwan reported statistically significant associations between Zoloft and omphalocele. . . .[18]

> Associations were observed between SSRI use and three types of birth defects, but the absolute risks were small, and these observations require confirmation by other studies.

R.R. at 2014a. The authors identified the three types of birth defects as anencephaly, craniosynostosis, and omphalocele. ***Id.*** at 2016a.

[17] Reefhhuis et al. "Specific SSRI's and birth defects: bayesian analysis to interpret new data in the context of previous reports." BMJ 2015; 350; h3190. R.R. at 839a. The study acknowledged its limitations, *inter alia*, as follows:

> This analysis does not address whether the birth defect associations we observed were caused by maternal SSRI treatment, underlying maternal disease, or some other factor. Since there was no specific question on depression and we cannot identify all participants with untreated depression, there is the possibility of confounding by indication.

R.R. at 935a.

[18] Dr. Cabrera opined:

> In 2007, Alwan also published on SSRI exposure and risk of birth defects in the NEJM. The study employed a case-control design using data from the US National Birth Defects Prevention Study (Alwan, Reefhuis *et al.* 2007). The study utilized maternal reporting of SSRI usage (fluoxetine, sertraline, and paroxetine). The study reported an odds ratio for SSRI exposure and anencephaly risk [ ], indicative of a significant increased risk for neural tube defects amongst infants of mothers receiving SSRI treatment during pregnancy, and a Zoloft-specific increased risk [ ]. For those birth defects previously

> Dr. Freeman agrees that he must, and claims he has, applied the Bradford-Hill Criteria to support his opinion. However, the starting procedure of any Bradford-Hill analysis is "an association between two variables" that is "perfectly clear-cut and beyond what we would care to attribute to the play of chance." Dr. Freeman testified that generally accepted methodology requires a determination, first, that there's evidence of an association and, second, whether chance, bias and confounding have been accounted for, before application of the Bradford-Hill criteria. Because no such association has been properly demonstrated, the Bradford-Hill criteria could not have been properly applied.[19]

> associated with SSRI use (anencephaly, craniosynostosis, and omphalocele) there was also an increased risk [ ] associated with reported maternal sertraline usage. There was a significant increased risk [ ] with any SSRI usage and omphalocele [ ] and a non-significant increased risk [ ] with sertraline exposure and omphalocele [ ]. Limitations reported by the authors in the study included the inability to separate the effect of maternal SSRI use from that of the underlying depression, under-reporting of other SSRI usage, potential for recall bias, and selection bias towards the null hypothesis.
>
> Reefhuis *et al.* utilized the data from 10 centers in the United States, as part of the National Birth Defects Prevention Study, to test SSRI exposure and risk of birth defects (Reefhuis, Gilboa *et al.* 2015). The study specifically reported an odds ratio [ ] for sertraline exposure and omphalocele risk [ ] **indicative of a non-significant increased risk for omphalocele amongst infants of mothers receiving SSRI treatment during pregnancy**. Limitations reported by the authors in the study included the inability to separate the effect of maternal SSRI use from that of the underlying depression, self-reporting, multiple testing, and small numbers for individual defects.

R.R. at 606a-607a (emphasis added).

[19] Dr. Cabrera stated:

* * *

> Dr. Freeman opines specifically that [Appellant] Bo Porter's giant omphalocele birth defect was caused by exposure to Zoloft in utero.

* * *

> The temporal relationship between the exposure and disease is also a factor which must be considered in assessing specific causation. For an exposure to be the cause of a disease the exposure must have occurred prior to the disease. Dr. Freeman fails to address the temporal failure of exposure between Mrs. Porter's use of Zoloft and minor plaintiff's giant omphalocele. A Giant Omphalocele is the result of an incomplete folding of the abdominal wall during the third to fifth weeks of pregnancy. During the third to fifth weeks of her pregnancy Mrs. Porter was taking Peroxetine (a generic version of the known teratogene Paxil). Mrs. Porter did not being taking Zoloft until her seventh week of pregnancy. While Dr. Freeman concedes this timing failure is an issue, he does not form any opinion of his own but instead claims to defer to other experts offering opinions which have not been revealed and therefore necessarily not subject to cross-examination.

* * *

> A review of the literature indicates that Zoloft is associated with teratogenicity. Association, however, does not alone prove causation and **further analysis is necessary**. Sir Bradford-Hill proposed a set of criteria to determine association between exposure and outcome. These criteria are accepted in the scientific community as a viable method of determining the potential existence of causality.

R.R. at 614a (emphasis added).

> Clinical differential diagnosis is a generally accepted methodology. Dr. Freeman is not a clinician and does not profess to perform a clinical differential diagnosis of cause. Dr. Freeman fails to properly rule out genetic causes.
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> Dr. Freeman does not discuss and fails to rule out maternal risk factors such as age, obesity, cigarette smoking, alcohol, maternal stress, and family history. Dr. Freeman fails to exclude Paxil (Peroxetine) as a risk factor.
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> * * *
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> Dr. Freeman's failure to analyze, discuss, and exclude other possible causes departs from generally accepted methodology.

Trial Ct. Op. at 8-10, 12, 13-15, 17 (footnotes in original omitted).

Stephen Edward Kimmel, M.D., Appellee's expert in epidemiology and a pharmacoepidemiology, testified at the ***Frye*** hearing, *inter alia*, as follows:

> [Appellee's counsel]: Did Dr. Freeman employ generally accepted methodology?
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> A: No.
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> Q: Did you identify a number of specific ways in which you believe that Dr. Freeman deviated from a generally accepted methodology?
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> A: Yes, I did.
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> Q: And is this—does this slide summarize the methodological flaws you identified with respect to Dr. Freeman's methodology?
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> A: Yes, it does.
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> Q: Would you please briefly describe what those flaws are?

A: Sure. So there are four groupings listed there. The first is ignoring chance, confounding and bias as a possible cause of false associations, essentially not applying any epidemiological principles to reviewing the results and ignoring the lack of replications . . .

.

Q: I'd just ask you to slow down a little bit, if you don't mind?

A: And ignoring the lack of replication. The second is improperly grouping all SSRIs as a class to draw conclusions about Zoloft. The third is improperly drawing conclusions about Zoloft and omphalocele based on findings from other unrelated congenital defects. And the forth is incorrectly reporting several findings from the literature.

* * *

Q: You're familiar with the Louik study?

A: Yes.

Q: The Louik study has a finding with respect to omphalocele, correct?

A: Correct.

* * *

Q: So when it says three exposed subjects, what does that mean?

A: That's only three Zoloft—three women used Zoloft had omphaloceles. So there's only three Zoloft—exposed women.

Q: In the Louik group, did they conduct multiple comparisons?

A: They did.

Q: How many comparisons did they do?

A: Just from the paper, 42 initial, 66 additional that they reported in the paper, so over a hundred comparisons.

Q: Did the authors recognize the limitations of doing a hundred plus comparisons?

A: Yes, they do. The quote here is that they state in the presence of multiple comparisons distinguishing random variation from two elevations in risk is difficult. Meaning, we can't tell whether these are true findings or false positives.

Q: So assuming the authors of the Louik study were aware of the concept of chance, right?

A: Yes.

Q: Is what they did improper by conducting a hundred and six comparisons?

A: No, it's not improper.

Q: Why would authors like the Louik authors do so many comparisons understanding the potential limitations that arise from concepts like chance?

A: Because they were doing it to generate hypothesis, not to answer or address hypothesis. As they state, in the absence of preexisting hypothesis. So it was to generate hypothesis that could then be tested later.

The Court: Could any scientific conclusion about omphalocele be made on the basis of the Louik paper?

The Witness: No.

The Court: Next question.

[Appellee's counsel]: And have subsequent studies looked at the issue of Zoloft and omphalocele?

A: Yes.

The Court: Can any scientific conclusion be drawn from about omphalocele from the Louik study and any other studies subsequent that examined it?

The Witness: Yes, when you put it all together you can.

[Appellee's counsel]: . . . Dr. Freeman lists four studies with respect to Zoloft and omphalocele, correct?

* * *

A: Correct.

* * *

Q: Does Alwan replicate the Louik finding with respect to omphalocele?

A: No, it does not.

Q: Why not?

A: Because the odds ratio of 1.5 . . . is consistent with the play of chance.

Q: And would it be fair and generally accepted and accurate to say that Alwan shows that a woman taking Zoloft had a 50 percent increased risks of having a child with omphalocele?

A: No.

The Court: Why is that improper to conclude?

The Witness: Because this is based on the results of this population-based study, they did not demonstrate a relationship overall between Zoloft and omphalocele that could be attributed to a real association. The relationship there is attributable to chance . . . .

[Appellee's counsel]: Dr. Freeman also cites this Jiminez-Solem finding as at least having a relationship between Zoloft and omphalocele, correct?

A: He does in his report.

Q: Is the odds ratio in what he cited here with respect to Jiminez-Solem and the confidence interval, are those correct?

A: No, they're not.

Q: You've had a chance to take a look at the Jiminez-Solem paper, right?

A: Yes, I have.

* * *

Q: But there is actually data that's reported or information reported in Jiminez-Solem about abdominal wall defects, right?

A: There was.

Q: And abdominal wall defects would be something that would, a category that would encompass omphalocele?

A: Yes, that's correct.

Q: And what were the findings with respect to abdominal wall defects?

A: So in this study there were no omphalocele defects among the women who took Zoloft.

* * *

Q: . . . And then Reefhuis also looked at Zoloft and omphalocele, right?

A: Yes.

Q: Do you remember who sponsored the Reefhuis study?

A: That was a study sponsored by the Centers For Disease Control.

Q: . . . Carol Louik is an author on this paper, right?

A: Correct.

Q: That's the same Carol Louik who actually wrote the Louik paper?

A: Correct.

Q: Dr. Freeman cites this CDC study as supporting his findings in his paper, right?

A: He does.

* * *

Q: And what do the authors say about their own data?

A: So the authors say this is just a quote from their paper—and I just want to clarify, they were doing this very specifically because they were trying to answer the question of does—can Zoloft be associated with omphalocele because of the prior literature. And what they found and what they said was it is reassuring that none of the five previously reported associations between Zoloft and birth defects, which includes omphaloceles were confirmed in this analysis.

* * *

Q: Now, did Reefhuis and . . . her colleagues employ a generally accepted methodology?

A: Yes, they did.

Q: Peer reviewed?

A: Yes, it is.

* * *

Q: Did Dr. Freeman use a generally accepted methodology in evaluating these papers that he relied on?

A: No, he did not.

Q: Why not?

A: So several reasons. First of all, there was no application of epidemiologic methods to determine the issues that we talked about before, chance, bias and confounding. There was no critical appraisal of these results. And there was—he did not account for or acknowledge the play of chance in these findings.

* * *

Q: Based on all the data, both the data on Dr. Freeman's chart and the other data that you evaluated, is there a consistent association between Zoloft and omphalocele?

A: No, there's none.

* * *

Q: Has the CDC also indicated whether SSRIs can be treated as a class with respect to birth defects generally and omphalocele specifically?

A: In the Reefhuis paper, yes, they did.

Q: What did the Reefhuis authors of the CDC paper say specifically about the class effect?

A: So they said, this is a quote, this analysis confirms the need to assess the association between specific SSRIs and specific birth defects rather than combining an entire drug class.

* * *

Q: So in viewing all the data regarding SSRIs and class effect, is it a generally accepted methodology to treat SSRIs as class with respect to causation when assessing birth defects, and in particular, when assessing something like omphalocele?

A: No, it's not.

Q: Did Dr. Freeman do that?

A: He did.

* * *

Q: Now, let's move to your third criticism of Dr. Freeman's methodology. And this deals again with drawing improper conclusions about omphalocele based on findings of unrelated birth defects.

Now, in his report Dr. Freeman grouped together various types of malformations into a single outcome, right?

A: Yes.

Q: Can you explain whether such grouping raises methodological issues?

A: It does.

Q: Can you explain why and how?

A: So, if you find a relationship between a drug and one type of defect, those data can't be used to say that that drug causes a different defect. . . .

* * *

Q: Do the authors of the CDC study also address generally accepted methods for evaluating specific birth defects?

A: Yes, they do.

Q: This is from the Reefhuis paper again?

A: Yes, it is.

Q: What do they say?

A: They say the analysis confirms the need to assess associations between specific birth defects rather than combining heterogeneous groups of birth defects.

* * *

> Q: Is it consistent with what you believe is generally accepted in the field of epidemiology?
>
> A: Yes.
>
> Q: Is it consistent with what Dr. Freeman did?
>
> A: No.

R.R. at 5039a, 5041a-5044a, 5046a-5047a.

Dr. Cabrera was deposed and testified, *inter alia*, as follows:

> Q: . . . The same type of birth defects that are at issue in this litigation can and do occur in children whose mothers have not taken Zoloft or any other SSRI during pregnancy, correct?
>
> A: That is correct.
>
> Q: Am I correct that there's no scientifically validated test, procedure or protocol that you could point me to in the medical literature, in a textbook that provides a method to determine whether or not a specific birth defect in an individual has been caused or contributed to by Zoloft; is that right?
>
> A: My understanding is that's something that a medical doctor would do for individual cases. As far as individual cases goes, I'm not aware, but I don't practice at—you know, at a case level for individuals, like a medical doctor.
>
> Q: And my question is directed to your knowledge. You're not aware, then, of any specific test that would identify whether or not a specific birth defect in an individual was caused or contributed to by Zoloft?
>
> A: We're actually developing tests for that, but they're not available right now.

R.R. at 3670a-3671a.

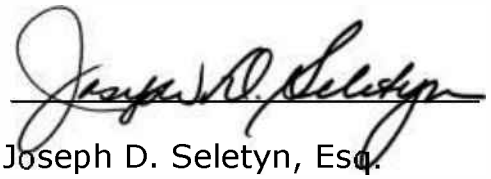
In sum, Dr. Cabrera's opinions rely upon peer review articles. ***See*** R.R. at 605a-610a. Dr. Cabrera relied upon the Louik study. ***See*** R.R. at 605a-606a. However, the Louik authors found that their analysis did not confirm an association between the use of SSRIs and omphalocele. ***Id.*** at 919a. Dr. Cabrera refers to the Alwan and Reefhuis studies. ***Id.*** at 606a-607a. The Alwan study concluded that confirmation by other studies was required. ***Id.*** at 2014a. The Reefhuis study stated that its "analysis does not address whether the birth defect associations we observed were caused by maternal SSRI treatment." ***Id.*** at 935a. Dr. Cabrera concedes that the Jiminez-Solem, Andersen study did not find an association for exposure to an SSRI and Omphalocele. ***See id.*** at 608a. Furthermore, he acknowledged that in the Furu, Kieler study, there was no Zoloft specific risk reported with mothers receiving SSRI treatment during pregnancy. ***See id.*** at 609a-610a. He refers to three other studies, viz., Pedersen, Henriksen, Berard, Zhao, and Wemakor, Cassib, which concluded that "the incidence is too low generally and in exposed population to perform statistical testing for risk of omphalocele" assocation with SSRI exposure. ***See id***. at 610. In his deposition, Dr. Cabrera conceded he was not aware of any tests that were available to determine whether Zoloft contributed to any birth defects. ***See id.*** at 3670a-3671a.

It was Appellant's burden to establish all of the elements of Rule 702 for the admission of Dr. Cabrera's expert report. ***See*** Pa.R.E. 702. Rule 702

includes the ***Frye*** test. ***See Grady***, 839 A.2d at 1043. The trial court found Dr. Cabrera's report contained methodological defects, for the reasons precluding the expert testimony of Dr. Freeman. ***See Betz***, 44 A.3d at 58. We agree that Appellants failed to prove the methodology Dr. Cabrerra employed was generally accepted in the relevant scientific community. ***See Trach***, 817 A.2d at 1112. Accordingly, we discern no abuse of discretion by the trial court in precluding Dr. Cabrera from testifying on ***Frye*** grounds. ***See Grady***, 839 A.2d at 1046.

Order affirmed.

Judgment Entered.



Joseph D. Seletyn, Esq.
Prothonotary

Date: 5/8/2017