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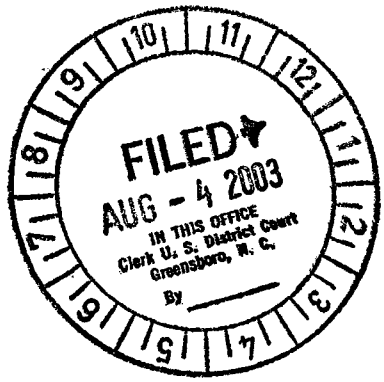
IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA

SHAREN AND RANDY LEE DUNN)
)
Plaintiffs,)
)
v.) 1:98CV00912
)
SANDOZ PHARMACEUTICALS)
CORPORATION)
)
Defendants.)



JUDGMENT

TILLEY, Chief Judge.

For the reasons set forth in a contemporaneously filed Memorandum Opinion, Defendant's Motion in Limine and Motion for Summary Judgment on the Issue of Medical Causation [Doc. # 75] is GRANTED, Defendant's Motion for a Daubert Hearing on Medical Causation [Doc. # 77] is DENIED, Defendant's Motion for Summary Judgment [Doc. # 79] is GRANTED. The remaining motions [Docs. # 98, 104, 112, 115, 116, 122, 124, 126, 135, 147, and 148]] are DENIED as MOOT.

This, the 5 day of August, 2003.

United States District Judge

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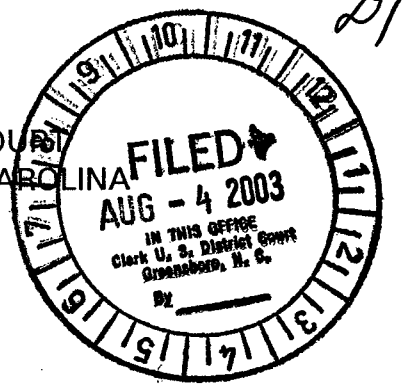

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MEMORANDUM OPINION

TILLEY, Chief Judge

The following motions are currently pending before the Court: Defendant's Motion in Limine and Motion for Summary Judgment on the Issue of Medical Causation [Doc. # 75], Defendant's Motion for a Daubert Hearing on Medical Causation [Doc. # 77], Defendant's Motion for Summary Judgment [Doc. # 79], Plaintiff's Motion for Leave to File a Surreply [Doc. # 98], Plaintiff's Motion to Strike Response to Suggestion of Subsequently Decided Authority [Doc. # 104], Plaintiff's Motion to Strike Subsequently Decided Authority [Doc. #112], Defendant's Motion to Supplement the Daubert Record [Doc. # 115], Plaintiff's Motion to Strike Suggestion of Subsequently Decided Authority [Doc. # 116], Defendant's Motion for Leave to File Summary Judgment Motion [Doc. # 122], Plaintiff's Motion to Strike Suggestion of Subsequently Decided Authority [Doc. # 124], Plaintiff's Motion for a Hearing on Defendant's Motion for Leave to File an Additional Summary Judgment Motion [Doc. # 126], Plaintiff's Motion to Strike

Defendant's Response to Submissions of Subsequent Decisions [Doc. # 135], Plaintiff's Motion for Order to Supplement the Summary Judgment Record [Docs. # 147 and 148].

For the reasons set forth below, Defendant's Motion in Limine and Motion for Summary Judgment on the Issue of Medical Causation [Doc. # 75] is GRANTED, Defendant's Motion for a Daubert Hearing on Medical Causation [Doc. # 77] is DENIED, Defendant's Motion for Summary Judgment [Doc. # 79] is GRANTED. The remaining motions [Docs. # 98, 104, 112, 115, 116, 122, 124, 126, 135, 147, and 148] are DENIED as MOOT.

I.

On April 6, 1994, by Cesarean section, Ms. Dunn gave birth to her second child. Ms. Dunn was discharged from the hospital on April 9,1994 and prescribed Parlodel to suppress lactation. On April 11, she called her obstetrician complaining of a severe headache. She was told to go to the hospital for evaluation. Ms. Dunn was admitted to Moses Cone Hospital on April 11, 1994. Following treatment with Demerol, Staydol, Toridal and Fiorinal, Ms. Dunn's headaches resolved, and she was discharged on April 13. Ms. Dunn was readmitted to the hospital on April 13 after returning to the emergency room with a severe headache. She was treated and discharged from the hospital on April 16.

On April 18, Ms. Dunn contacted her doctor and complained that the right side of her body was numb and tingling. On April 20, Ms. Dunn had an MRI that

showed she had suffered a stroke. On April 22, Ms. Dunn underwent a four vessel cerebral arteriogram that revealed cerebral vasculitis.

Ms. Dunn filed suit against Sandoz Pharmaceuticals, the manufacturer of Parlodel, alleging that Parlodel caused her strokes and seeking damages. Sandoz asserts that Ms. Dunn does not have sufficiently reliable evidence to support her contention that Parlodel causes stroke. Sandoz has filed a motion in limine to exclude Ms. Dunn's medical causation expert[1] on the grounds that the expert's methods do not satisfy the reliability standards for expert witnesses established by the Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). Sandoz further asserts that if the motion to exclude Ms. Dunn's experts is granted that it will be entitled to summary judgment because Ms. Dunn will be unable to prove causation.

II.

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[1] Ms. Dunn has provided expert reports by a number of doctors to establish both general causation and specific causation. See discussion in section III infra. The court's opinion refers only to Dr. Kenneth Kulig, who is Ms. Dunn's primary general causation expert for the following reasons.

Ms. Dunn has also retained Dr. George Macones, an epidemiologist, to "review the extremely limited epidemiology literature that exists retaining to Parlodel." Macones Aff. ¶ 3. Dr. Macones does not opine that there is epidemiological evidence to support a causal relationship between Parlodel and stroke in postpartum women, and Dr. Macones does not offer an opinion that Parlodel may cause stroke.

Furthermore, because the court has decided that Dr. Kulig's testimony is not sufficiently reliable to satisfy the Daubert standard on the issue of general causation, it is unnecessary to consider Ms. Dunn's specific causation experts. See Raynor v. Merrell Pharmaceuticals Inc., 104 F.3d 1371, 1376 (D.C. Cir. 1997).

The introduction of expert opinion testimony is governed by Federal Rule of Evidence 702.[2] Under Rule 702, trial judges act as gatekeepers to "ensure that any and all scientific testimony . . . is not only relevant, but reliable." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). In conducting a Daubert determination, the trial court must ask two questions: (1) whether the proffered scientific evidence is valid and reliable and (2) whether the testimony will aid the trier of fact in deciding the ultimate issues in the case. United States v. Barnette, 211 F.3d 803, 815 (4th Cir.2000).

As with all other admissible evidence, expert testimony is subject to being tested by "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof." Daubert, 509 U.S. at 596. Thus, the Daubert inquiry does not require consideration of whether the proffered testimony is correct or whether the proffered evidence is sufficient to allow a verdict in favor of the proponent. Instead, the focus must be on whether the testimony is reliable and can aid the ultimate trier of fact. As the Fourth Circuit has explained, "courts must recognize that due to the difficulty of evaluating their testimony, expert witnesses have the potential to be both powerful and quite misleading." Westberry

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[2] "If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert . . . may testify thereto in the form of an opinion or otherwise. Expert testimony is admissible under Rule 702, then, if it concerns (1) scientific, technical, or other specialized knowledge that (2) will aid the jury or other trier of fact to understand or resolve a fact at issue." Fed. R. Evi. 702 (West Supp. 2003).

v. Gislaved Gummi AB, 178 F.3d 257, 261 (4th Cir.1999) (quoting Daubert, 509 U.S. at 595) (internal quotation marks omitted). Thus, because expert testimony, particularly scientific expert testimony, can be very powerful before a jury, it is essential to ensure that only scientifically reliable methods are used to generate the opinions offered to a jury.

Sandoz has moved to have a Daubert hearing. Ms. Dunn, however, has opposed this motion asserting that a hearing is not necessary. Dr. Kulig has testified about his causation opinions involving Parlodel before several courts in Daubert hearings. The parties have provided transcripts of these hearings. Dr. Kulig has also given more than 150 hours of deposition testimony in the Parlodel cases. He has provided a written report and an affidavit that describe in detail his position on causation. The parties have also extensively briefed this issue. Because Ms. Dunn, who has the burden of proving that Dr. Kulig satisfies the Daubert standard, believes that the written material before the Court is sufficient to make a Daubert determination, Sandoz' motion for Daubert hearings is DENIED.

III.

In cases that require medical evidence to establish causation, courts have typically drawn a distinction between "general causation" and "specific causation." Reference Manual on Scientific Evidence 444 (2d. ed. 2000). General causation "is established by demonstrating . . . that exposure to a substance can cause a particular disease." Id. Specific, "or individual, causation, however is established

by demonstrating that a given exposure is the cause" of a particular individual's disease. Id. If an plaintiff is not able to establish general causation, it is unnecessary to consider whether the plaintiff can establish specific causation. See Raynor v. Merrell Pharmaceuticals Inc., 104 F.3d 1371, 1376 (D.C. Cir. 1997).

Ms. Dunn's primary general causation expert is Dr. Kenneth Kulig, a medical toxicologist and emergency physician. Dr. Kulig has been the designated expert on general causation in numerous Parlodel product liability actions. The cases on which he has served as the general causation expert were filed in federal district court in New Jersey and consolidated for discovery purposes in New Jersey. Following discovery, the district court denied the plaintiffs' motion to consolidate the cases for trial, and the individual cases were transferred to the home districts of each plaintiff. In re Consolidated Parlodel Litigation, 22 F. Supp. 2d 320 (D.N.J. 1998). In most of these in which the trial court conducted a Daubert determination and issued a reported opinion, Dr. Kulig was not allowed to testify at trial because the courts held that his opinions did not satisfy the reliability prong of Daubert.[3] On at least two occasions, however, Dr. Kulig's testimony has been admitted.[4]

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[3] Rider v. Sandoz Pharmaceuticals Corp., 295 F.3d 1194 (11th Cir. 2002), Hollander v. Sandoz Pharmaceuticals Corp., 289 F.3d 1193 (10th Cir. 2002), Glastetter v. Novartis Pharmaceuticals Corp., 252 F.3d 986 (8th Cir. 2001), Soldo v. Sandoz Pharmaceuticals Corp., 244 F. Supp.2d 434 (W.D. Pa. 2003), Caraker v. Sandoz Pharmaceuticals Corp., 188 F. Supp.2d 1026 (S.D. Ill.2001).

[4] Brasher v. Sandoz Pharmaceuticals Corp., 160 F. Supp.2d 1291 (N.D. Ala. 2001) (Mag. J. Putnam); Globetti v. Sandoz Pharmaceuticals Corp., 111 F.

As a general causation expert in Parlodel litigation, Dr. Kulig has opined that Parlodel may cause strokes, seizures, hypertension, and myocardial infarction. Dr. Kulig believes that vasospasm or vasoconstriction is likely the mechanism by which Parlodel may cause these events. Dr. Kulig has explained that "the scientific methodology that I use to assess causation is derived from the Bradford Hill[5] Criteria." Kulig Aff. ¶ 12. Dr. Kulig asserts that the Bradford Hill criteria may be used to establish causation when a scientist has identified an association between two variables. Dr. Kulig states that he has identified an association between Parlodel and stroke based on the pharmacological properties of bromocriptine, epidemiology, clinical studies, case reports, and animal studies. As Dr. Kulig has described his methodology:

> [Y]ou attribute an appropriate weight to the various components of the medical evidence. The medical evidence could include, involving the drug Parlodel, is Parlodel a vasoconstrictor? Does Parlodel cause vasospasm? Has Parlodel been associated with stroke in human beings? Is there animal evidence that Parlodel is a vasospastic agent? Do the pharmacokinetics of the drug lend themselves to saying it makes sense, that it's plausible the drug was the cause? And again, I'm not saying that any of these components individually leads one to draw that conclusion, but in compilation of all of the evidence involving all of these components, one might be able to reach a conclusion.
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> Many scientists and physicians end right there, Your Honor. They say, I've seen enough. I'm willing to say that in Patient X, the

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Supp.2d 1174 (N.D. Ala. 2000)(Mag. J. Putnam).

[5] Bradford Hill, The Environment and Disease: Association or Causation, 58 Proc. Royal Soc'y Med. 295, 295-300 (1965). The Bradford Hill factors are strength of relationship, consistency, specificity, temporality, dose response, biologic plausibility, coherence, experimental evidence, and analogy.

drug caused the adverse drug reaction. I've taken it even one step further and I use the Bradford-Hill criteria, which is outlined in detail in my affidavit. It's my representation that the Bradford-Hill criteria are generally accepted criteria for analyzing causation, both for drugs and for nondrugs such as chemicals.

The toxicologic community, my peers, use Bradford-Hill extensively. When a paper is presented at our scientific meeting, it is not uncommon for people to say, I believe causation exists because I've applied the Bradford-Hill criteria and here's what my analysis shows.

. . . But what I'm saying, Your Honor, is that it is appropriate to use an outline, a construct, a logical construct to say, *I believe cause and effect exists because of all of this, but in addition, I've taken the extra step and applied a published, generally accepted criteria to the analysis.* You may not agree with everything I have to say about that analysis, you may interpret the evidence differently, but at least I'm willing to lay it on the line and say, Here is my thought process, here is the evidence I've looked at and why I believe cause and effect exists. And the Bradford-Hill criteria, in my opinion, it's a generally accepted scientific methodology for the analysis of adverse drug reactions.

Vol. I: 77-79 (Kulig at Glastetter Hearing) (March 20, 2000) (emphasis added). In the motion in opposition to Daubert hearings, Ms. Dunn asserted that the Court could rely on previous Daubert hearings in making the determination in this case. Plaint. Memo. in Opp. [Doc. # 89] at 3. There is no evidence to suggest that Dr. Kulig's methodology has changed since his testimony in the Glastetter case.

Sandoz asserts that Dr. Kulig has improperly applied the Bradford Hill criteria. According to Sandoz, the Bradford Hill criteria are applied to analyze whether an epidemiological study that has demonstrated an "association" between two variables can be taken a step further and said to establish "causation" between those two variables. See Darwin R. Labarthe, M.D., Ph.D. Aff. ¶ 7 ("Before

applying the Hill considerations, one must make a preliminary assessment whether an association or apparent connection between exposure and outcome has been established through epidemiological evidence."). Essentially, Sandoz asserts that (1) the Bradford Hill criteria cannot be used to establish causation absent an epidemiological study that demonstrates an association between two variables; (2) Dr. Kulig does not have an epidemiological study that demonstrates an association between Parlodel and stroke; thus (3) Dr. Kulig improperly applied the Bradford Hill criteria to form his opinion that Parlodel causes stroke.

Dr. Kulig asserts that it is not necessary to have an epidemiological study that demonstrates an association as a prerequisite for applying the Bradford Hill criteria. Rather, Dr. Kulig asserts the pharmacological properties of bromocriptine, statistically insignificant epidemiological studies, clinical studies, case reports, and animal studies are sufficient to establish an association and that the application and satisfaction of the Bradford Hill criteria can establish causation.

The greater weight of authority supports Sandoz' assertion that the Bradford Hill criteria is a method for determining whether the results of an epidemiological study can be said to demonstrate causation and not a method for testing an unproven hypothesis. Sir Bradford Hill identified the starting point of his criteria as "an association between two variables" that is "perfectly clear-cut and beyond what we would care to attribute to the play of chance." Bradford Hill, The Environment and Disease: Association or Causation, 58 Proc. Royal Soc'y Med.

295, 295-300 (1965). An untested hypothesis has not ruled out chance.

In addition, the small number of reported cases in which the Bradford Hill criteria have been used by experts describe the Bradford Hill criteria as a tool for determining whether an epidemiological study establishes causation. See Amorgianos v. National Railroad Passenger Corp., 137 F. Supp. 2d 147 (E.D.N.Y. 2001) ("Even when an *appropriately designed study yields evidence of a statistical association* between a given substance and a given health outcome, epidemiologists generally do not accept such an association by itself as proof of a causal relationship between the exposure and the outcome. Epidemiologists generally look to several additional criteria to determine whether a statistical association is indeed causal. These criteria are sometimes referred to as the Bradford Hill criteria, after the author of a leading statement of the principles.")(internal citations omitted) (emphasis added); In re Breast Implant Litigation, 11 F. Supp.2d 1217, 1234 n.5 (D. Colo.1998) ("The Bradford-Hill criteria *start with an association demonstrated by epidemiology* and then apply such criteria as the temporal sequence of events, the strength of the association, the consistency of the observed association, the dose-response relationship, and the biologic plausibility of the observed association.") (emphasis added); Missouri Pacific R. Co. v. Navarro , 90 S.W.3d 747, 753 (Tex. App. 2002) ("Dr. Dayal testified that if an epidemiological study finds a relationship between an exposure and a disease, you still must apply the Bradford Hill nine-step criteria.").

The Federal Judicial Center's Manual on Scientific Evidence also contains a description of the Bradford Hill criteria. Reference Manual on Scientific Evidence 336-37 (2d ed. 2000). The first step in the causation analysis pursuant to Bradford Hill is an epidemiological study that has identified an association between two variables. Once a study has shown that there is an association, the next step is to determine whether the "association identified in an epidemiologic study may or not be causal." Id. The toxicology section of the Manual does not include the Bradford Hill criteria as a method for determining causation between a drug and disease.

Other than the testimony of Dr. Kulig, Ms. Dunn has not provided any other evidence that Dr. Kulig's application of the Bradford Hill criteria to prove a hypothesis, as opposed to using the factors to evaluate whether an association shown by a study establishes a causal relation, is generally accepted in the medical community or reasonably relied upon by other toxicologists in reaching an opinion on causation. As the Supreme Court has explained, "nothing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." General Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997). See also Moore v. Ashland Chemical Inc., 151 F.3d 269, 276 (5th Cir. 1998) (explaining that expert testimony must be based on "some objective, independent validation of the expert's methodology. The expert's assurances that he has utilized generally accepted

scientific methodology is insufficient").

Dr. Kulig has not performed a study, the results of which show that bromocriptine causes vasoconstriction that results in stroke in postpartum women, and he is not applying the Bradford Hill criteria to determine whether his study demonstrates causation. Rather, Dr. Kulig has developed a hypothesis and has attempted to use the Bradford Hill criteria to prove that assertion. Dr. Kulig has not demonstrated the utilization of a reliable scientific methodology and his application of the Bradford Hill criteria does not satisfy the reliability prong of Daubert. See Soldo v. Sandoz Pharmaceuticals Corp., 244 F. Supp. 2d 434, 461 (W.D. Pa. 2003) (concluding that "Dr. Kulig improperly used the Bradford-Hill criteria to attempt to support his opinion that Parlodel ® can cause [stroke]"); Caraker v. Sandoz Pharmaceuticals Corp., 172 F. Supp.2d 1046, 1049 n.5 (S.D. Ill.2001) ("Dr. Kulig's application of the Bradford Hill criteria was unimpressive. The plaintiffs did not expound much on it at the hearing, many of the affidavit paragraphs are curt conclusions making vast assumptions, and Dr. Kulig's application of the Bradford Hill methodology seems more like an afterthought, inasmuch as it appears that he had already came [sic] to a conclusion using a differential diagnosis and later 'came to the same conclusion' using the Bradford Hill criteria. Justifying a conclusion after the fact by applying a methodology does not generally lead to reliable scientific knowledge.").

Finally, it must be noted that by requiring an epidemiological study as a

starting point for application of the Bradford Hill criteria, the court is not requiring Ms. Dunn to provide an epidemiological study in order to establish causation.[6] The Fourth Circuit has clearly held that epidemiological studies are not required to establish causation. See Benedi v. McNeil-P.P.C., Inc., 66 F.3d 1378, 1384 (4th Cir.1995) ("Under the Daubert standard, epidemiological studies are not necessarily required to prove causation, as long as the methodology employed by the expert in reaching his or her conclusion is sound."). Requiring Dr. Kulig to have a statistically significant epidemiological study as the beginning point for application of the Bradford Hill criteria does not require Dr. Kulig to have a statistically significant study in order to prove causation. Dr. Kulig's opinion that Parlodel may cause stroke based on the application of the Bradford Hill factors does not satisfy the reliability prong of Daubert and that opinion is excluded.

IV.

Apart from the Bradford Hill methodology, Dr. Kulig has identified a number of factors that he believes support his opinion that Parlodel may cause stroke in postpartum women through the mechanism of vasoconstriction. Each of these factors will be considered to determine whether Ms. Dunn can establish general causation independent of the Bradford Hill criteria.

A. Epidemiology

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[6] This argument was asserted in Ms. Dunn's sur-reply brief, which was attached to her Motion to file a Sur-reply Brief. Generally, sur-reply briefs are not allowed. The arguments contained in Ms. Dunn's brief have been considered.

Both parties agree that there are no scientific tests that are controlled, blinded, and statistically valid that prove or disprove the hypothesis that Parlodel causes stroke. There is, however, one epidemiological study, the ERI study, involving Parlodel and postpartum women. While the parties agree that the study is not statistically significant, both parties cite various aspects of the study as supportive of their position.

Sandoz commissioned a study to be performed by Epidemiologic Resources, Inc. Kenneth Rothman, An Epidemiologic Evaluation of the Possible Relation Between Bromocriptine, Puerperal Seizures and Strokes, (Sept. 30, 1988) ("ERI Study"). The study included data from over 280,000 deliveries. According to Sandoz, the important aspect of the study is that of the more than 280,000 women in the study, only 10 women had postpartum strokes and only 1 of those 10 women had been prescribed Parlodel for the suppression of postpartum lactation. Dr. Kulig places emphasis on the resulting relative risk[7] calculation of 8.4. However, the authors of the study found that this calculation was not statistically-significant, and the study was deemed "not informative." ERI Study at 2. Sandoz explains that the relative risk calculation was based on the fact that only one of the 77 control group patients had taken Parlodel and also notes that the

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[7] Relative risk is "the ratio of the incidence rate of disease in exposed individuals to the incident rate in unexposed individuals." Reference Manual on Scientific Evidence 348 (2d ed. 2000). A relative risk that is less than 1.0 means that exposure is associated with the absence of disease, and a relative risk that is greater than 1.0 means that exposure is associated with disease.

confidence interval for risk of stroke due to Parlodel ranged between 0.4 to 162.[8]

The parties agree that the study itself is statistically insignificant and inconclusive on causation due in part to a sample size that was inadequate to appropriately address whether Parlodel causes stroke in postpartum women. Statistically insignificant results do not constitute proof that Parlodel causes stroke. Wheelahan v. G D Searle & Co. , available at 1987 WL 267679, *3 (4th Cir. Mar. 16, 1987) ("The court cannot properly draw any conclusions about the increased risk when that increase is not statistically significant.").

B. Pharmacological Properties of Bromocriptine

Dr. Kulig asserts that Parlodel is an ergot alkaloid, and ergots are known vasoconstrictors. Ergots are a class of drugs with similar molecular structures and common properties. One of the common properties of ergots is that they are known to cause vasospasm. Bromocriptine, the active ingredient is Parlodel, is an ergot alkaloid. Essentially, Dr. Kulig asserts a simple syllogism that (1)

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[8] Sandoz also cites two other studies: The HCIA Study analyzed 533,816 delivery records from 128 hospitals, tracked postpartum complications, and attempted to correlate these complications with Parlodel use. HCIA, "Postpartum Complications and Parlodel" (October 1995). The study found a relative risk for stroke of 1.088 with a confidence interval of .448 - 2.643. This study did not find any statistically significant association between Parlodel and stroke.

The Herrings and Stricker study was performed among postpartum women who were treated with a course of bromocriptine. The investigators found: "None of the 2,130 women were hospitalized for ischemic heart disease, hypertension or cerebral vascular events during the index period or the two month period after discontinuance of bromocriptine use." Herrings and Stricker, "Bromocriptine and Suppression of Postpartum Lactation," Pharmacy World & Sci. 17(4): 133-37 (1995).

bromocriptine is an ergot alkaloid and (2) ergots cause vasospasm, thus (3) bromocriptine may cause vasospasm. Although this syllogism is the basic structure of his opinion, Dr. Kulig acknowledges that a difference between bromocriptine and the other ergot alkaloids makes the conclusion more difficult than a simple syllogism.

Bromocriptine differs from the other ergot alkaloids in that the bromocriptine "molecule has a bromine atom attached to the second carbon of the basic ergot ring." Kenneth Kulig, M.D., Bromocriptine and Adverse Drug Reactions: Report on Casualty Assessment (hereinafter "Kulig Report"). The bromine atom typically makes bromocriptine a vasodilator, the opposite of a vasoconstrictor. Dr. Kulig asserts that "it is misleading and inaccurate to suggest that the drug can never cause vasoconstriction or hypertension in any person." (Kulig Report at 3).

Dr. Kulig does not assert definitively that bromocriptine causes vasoconstriction: "it is not argued here that just because bromocriptine is an ergot, it must cause vasoconstriction. It is being argued that because the drug is an ergot, one should not be surprised that it possesses the vasoconstrictive properties of the other ergots, but the other evidence including epidemiology and adverse drug reaction reports must be examined to determine that it is." Kulig Report at 3.

Dr. Kulig's assertion that because bromocriptine is an ergot alkaloid and *may* behave like other ergot alkaloids and cause vasoconstriction simply does not support the proposition that Parlodel causes stroke in postpartum women.

Opinions merely expressing "possibilities" do not suffice to support the admissibility of expert testimony. See Saldana v. Kmart Corp., 260 F.3d 228, 234 (3d Cir.2001) ("the mere possibility that something occurred in a particular way is not enough, as a matter of law, for a jury to find it probably happened that way")

C. Clinical Studies

As additional evidence of his opinion that bromocriptine causes vasoconstriction, Dr. Kulig cites to several clinical studies. The first study he cites involved Parlodel and hypertension. Study No. 60, commissioned by Sandoz, examined women who received Parlodel for amenorrhea-galactorrhea syndrome.[9] Dr. Kulig asserts that in the "second limb" of this study, 11 of 57 patients "demonstrated increases of their blood pressure, either systolic, diastolic, or both." Kulig Rep. at 6. Assuming that the rise in blood pressure for each of these patients could be attributed to bromocriptine, Dr. Kulig has not explained how bromocriptine's effect on women with amennorrhea-galactorrhea syndrome could be extrapolated to conclude that Parlodel would have the same effect on women who took the drug to suppress postpartum lactation.

The Watson study demonstrated that women with pregnancy induced hypertension who are given bromocriptine have a higher incidence of postpartum hypertension than women not taking bromocriptine. While this study may be

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[9] This syndrome is characterized by the production of breast milk (lactation) not associated with nursing and the absence of menstrual periods (amenorrhea).

some evidence that bromocriptine causes hypertension in patients who were already hypertensive, it is not evidence that bromocriptine causes hypertension in patients who were not hypertensive prior to taking bromocriptine.

D. Case Reports

In addition to the clinical studies on bromocriptine and hypertension, Dr. Kulig cites case reports as evidence of his hypothesis that bromocriptine causes stroke through vasospasm. Adverse drug reactions are a type of case report compiled by drug manufacturers for submission to the FDA and describe "any adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 314.80(a). Dr. Kulig lists the adverse drug reaction reports for Parlodel between 1978-1994 as follows: 23 deaths, 101 cases of hypertension, 88 seizures, 36 strokes, and 17 myocardial infarctions. Kulig Aff. ¶ 30.4

Dr. Kulig acknowledges that adverse drug reaction case reports are of limited value in determining causation. Dr. Kulig has written that "case reports are traditionally viewed as the least vigorous form of proof of a hypothesis or validation of a therapy." Soldo v. Sandoz Pharmaceuticals Corp., 244 F. Supp.2d 434, 463 (W.D. Pa. 2003) (citing Brent, Kulig and Rumack, "Analysis of the Types of Papers Presented at the Annual Toxicology Meetings," 32 Vet. Hum. Toxicol. (April 1990)).

Case reports are an " account of a particular patient's reaction to a drug or

other stimulus" and "make little attempt to screen out alternative causes for a patient's condition," and "frequently lack analysis." Glastetter v. Novartis Pharmaceuticals Corp., 252 F.3d 986, (8th Cir. 2001). Case reports are not controlled studies, and they cannot be verified through peer review. Case reports often do not include information about the patient's medical history, family medical history, use of other medications or drugs, or other information that would be necessary to determine whether causation between the use of the drug and the reported adverse effect can be established. Case reports are not scientific proof of causation. See Rider v. Sandoz Pharmaceuticals Corp., 295 F.3d 1194 (11th Cir. 2002) (explaining that "while they may support other proof of causation, case reports alone ordinarily cannot prove causation").

Dechallenge and rechallenge reports are another kind of case report. Dechallenge occurs "when a drug that is suspected of causing a certain reaction is withheld to see if the reaction dissipates." Rider v. Sandoz Pharmaceutical Corp., 295 F.3d 1194, 1199 (11th Cir. 2002). Rechallenge occurs when a doctor re-exposes a patient to a drug believed to have caused an earlier adverse reaction; dechallenge removes that exposure.

Dr. Kulig cites 1984 FDA reports in which seven patients who were taking bromocriptine and were hypertensive were dechallenged. Six of the seven dechallenged patients had normal blood pressure. Two of the dechallenged patients were then rechallenged with bromocriptine. One of the two rechallenged

patients had a recurrence of hypertension.

While dechallenge and rechallenge reports are more valuable to demonstrating causation because they measure the patient's reaction to a drug, the value of the information gained from rechallenge and dechallenge tests for purposes of establishing general causation is limited because they involve only individual patients rather than groups. Although the dechallenge and rechallenge data are more probative of causation than case reports, the small number of dechallenge/rechallenge patients do not constitute a reliable basis to support a conclusion that Parlodel may cause stroke in postpartum women generally.

E. Animal Studies

Dr. Kulig cites various animal studies that he asserts demonstrate that bromocriptine is a vasoconstrictor. In his affidavit, Dr. Kulig asserts that bromocriptine "caused constriction of the basilar and carotid arteries in dogs," "caused vasoconstriction of blood vessels in the tail of rats such that they necrose and fall off," "caused vasoconstriction and tail necrosis in mice," "caused necrotic ear margins in canines." Kulig Aff. ¶¶ 27.8-27.11 Based on the these studies, Dr. Kulig concludes in his affidavit that bromocriptine causes "digital, cerebral, coronary, and peripheral vasoconstriction in humans." Kulig Aff. ¶¶ 27.13.

Neither in his affidavit nor in his report, however, does Dr. Kulig address how these animal studies can be used as a basis to conclude that bromocriptine causes vasoconstriction in humans. In the silicone breast implant litigation, Dr. Kulig

testified that "[t]here are many problems in trying to apply that data [from animal studies] to the human situation, particularly, in rodents . . . . " In re Breast Implant Litigation Hearing Tran. at 862-65. See also Reference Manual On Scientific Evidence 346 (2d ed. 2000) (explaining the difficulty in extrapolating the results in animal studies to human beings due to "differences in absorption, metabolism, and other factors [that] may result in interspecies variation in responses"). An additional difficulty in using animal studies in an attempt to establish causation in human beings is "that the high doses customarily used in animal studies" make extrapolating the effect on much lower doses in humans very difficult to determine. Reference Manual on Scientific Evidence 346 (2d ed. 2000). Animal studies do not demonstrate causation between Parlodel and stroke in postpartum women.

F. FDA Regulatory Action

Finally, Dr. Kulig cites FDA action with respect to the postpartum lactation indication for Parlodel. In 1994, the FDA published a Notice of Opportunity for a Hearing on a proposal to withdraw approval of the postpartum lactation suppression indication for Parlodel.[10] As with the adverse drug reaction reports, Dr. Kulig does not appear to rely upon FDA action as a basis for his opinion that Parlodel may cause stroke. Rather he asserts that "[w]hat is important regarding the FDA's analysis of bromocriptine when used for postpartum lactation is that the logic and causation analysis employed by that agency . . . in determining that

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[10] Sandoz voluntarily withdrew the indication.

bromocriptine may cause hypertension, strokes, seizures, myocardial infarctions and death is exactly the same as the log consistently used by myself."

The FDA evaluated the medical literature and concluded that Parlodel might cause seizures or strokes in women already susceptible to disease. The FDA decided that "the potential risks associated with the use of bromocriptine for the prevention of physiological lactation outweigh its limited benefits and bromocriptine is no longer shown to be safe for use in preventing physiological lactation." 59 Fed. Reg. at 43351. The FDA is concerned with safety and risk benefit analysis: if the risks outweigh the benefits, the FDA may take regulatory action. The FDA balanced Parlodel's possible harm against its limited beneficial use. The FDA's balancing does not demonstrate that Parlodel may cause stroke in postpartum women.

IV.

As the Fourth Circuit has explained, a "reliable expert opinion must be based on scientific, technical, or other specialized knowledge and not on belief or speculation, and inferences must be derived using scientific or other valid methods." Oglesby v. General Motors Corp., 190 F.3d 244, 250 (4th Cir. 1999). Even when viewed in compilation, each of the factors Dr. Kulig has observed do not satisfy the reliability prong of Daubert. See e.g. Glastetter v. Novartis Pharmaceuticals Corp., 252 F.3d 986 (8th Cir. 2001) (explaining that "we do not believe that the aggregate of this evidence presents a stronger scientific basis for [the plaintiff's] proposition that Parlodel can cause [stroke]"); Caraker v. Sandoz