United States District Court for the Norther District of Georgia

Bridget Guthrie SIHARATH, Plaintiff,
v.
SANDOZ PHARMACEUTICALS CORPORATION, Defendant

Bonnie Joyce Rider and Walter Anthony Rider, Plaintiffs,
v.
Sandoz Pharmaceuticals Corporation, a Delaware Corporation, Sandoz Ltd., a Swiss Corporation, and Sandoz Pharma Ltd., a Swiss Corporation, Defendants

Nos. CIV.A.195-CV-965TWT, CIV.A.195-CV-3068TWT

Decided March 1, 2001.

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ORDER

THRASH, District Judge.

Siharath v. Sandoz. Pharms. Corp., 131 F.Supp. 2d 1347

These are two complex products liability actions. In each case, a postpartum woman suffered a stroke after taking a prescription drug manufactured by the Defendant. In its simplest form, the question presented is did the drug cause the strokes? Or, is the temporal association of taking the drug and a subsequent stroke merely coincidental? To begin to answer those questions, the Court must address the recurring issue of what is the quantity and quality of scientific evidence that a plaintiff must present on the issue of medical causation in a world of imperfect scientific knowledge.

Although the cases have not been consolidated, the motions and documentary evidence filed, the expert testimony, and the issues raised are identical in both cases. Consequently, the Court addresses the pendingmotions of both cases in this single Order. Siharath v. Sandoz Pharmaceuticals Corporation, No. 1 :95-CV-965-TWT, ("Siharath") is before the Court on Defendant's Motion to Exclude and for Summary Judgment on Issues of Medical Causation Under Daubert v. Merrell Dow Pharmaceuticals, Inc. [Doc. 68]. Rider v. Sandoz Pharmaceuticals Corporation, No. 1 :95-CV-3068-TWT, ("Rider") is likewise before the Court on Defendant's Motion to Exclude and for Summary Judgment on Issues of Medical Causation Under Daubert v. Merrell Dow Pharmaceuticals, Inc. [Doc. 116].

I. BACKGROUND

Parlodel(r) is manufactured by Defendant Sandoz Pharmaceuticals Corporation--now Novartis Pharmaceuticals Corporation. [FN1] In 1980, the drug was approved for use to suppress postpartum lactation. Approximately 9 million women in the United States have taken the drug to suppress postpartum lactation. On September 20, 1989, Plaintiff Bridget Guthrie

Siharath gave birth by Caesarean section to her second child. At the time, she was 17 years-old. She was unable to breast feed the child because she had taken pain medication. To suppress lactation, her doctor prescribed Parlodel(r). Ms. Siharath took regular doses of Parlodel(r) from the evening of September 20, 1989, until the morning of September 25, 1989. Later in the day on September 25, Ms. Siharath suffered three seizures and a subarachnoid hemorrhagic stroke. Her treating physicians were unable to diagnose the cause of the seizures or the stroke. No unusual trauma resulted from the Caesarean section. There was no indication that she suffered from eclampsia, a toxic blood condition associated with pregnancy that causes seizures and sometimes coma. Ms. Siharath did not smoke. Although she did have a history of suffering migraine headaches, no evidence existed that her migraine history was related to the stroke. Her treating physicians also could not say that Ms. Siharath's stroke was caused by the spasm or constriction of the arteries and veins ("vasospasm" and "vasoconstriction" respectively). While taking Parlodel(r), Ms. Siharath regularly ingested pseudoephedrine, a nasal decongestant. It is possible that pseudoephedrine can react with ergot alkaloids, the class of drugs of which Parlodel(r) is a member. Pseudoephedrine taken at minimal doses, however, is unlikely alone to cause hemorrhagic strokes. Ms. Siharath was hospitalized from September 25 to October 7, 1989. On March 10, 1995, she filed this pharmaceutical products liability action in negligence and strict liability, alleging that Parlodel(r) caused her seizures and stroke. She seeks compensatory and punitive damages. [FN2]

Plaintiff Bonnie Joyce Rider gave birth to a daughter on December 2, 1993. The child was delivered by Caesarean section. At the time, Ms. Rider was 39 years old. On December 5, she was prescribed Parlodel(r) to suppress lactation. She took the medicine from then until December 8, 1993. On December 9, 1993, Ms. Rider began having difficulty moving her right leg and arm. She was admitted to the hospital with complaints of abrupt onset of headache and weakness of the right leg and arm. During her hospitalization, Ms. Rider intermittently complained of involuntary jerking movements of the right leg. Ms. Rider was given a computerized tomography ("CT") scan, which revealed that she had suffered an acute intracranial hemorrhagic stroke. A magnetic resonance imaging ("MRI") performed the following day confirmed that she had suffered a left parietal hemorrhage. No unusual trauma occurred as a result of the Caesarean section, and there was no indication that Ms. Rider suffered from eclampsia. Ms. Rider had smoked at various times, but no evidence suggested that smoking alone had caused the stroke. Her doctor concluded that her stroke was caused by vasospasm. On November 28, 1995, she and her husband, Walter Anthony Rider, filed this pharmaceutical products liability action in negligence and strict liability, alleging that Parlodel(r) caused her seizures and stroke. The Riders seek compensatory and punitive damages. [FN3]

After a preliminary review of the voluminous record, the Court held a status conference on August 2, 2000, and at that time granted Defendant's request for an evidentiary hearing on its Daubert objections to Plaintiffs' expert testimony on medical causation. Each side was given five hours for direct and cross examination of witnesses and one hour for argument. [FN4] The Court on December 18-20, 2000, held a three-day Daubert hearing at which it heard evidence and argument from both sides regarding medical causation. At the hearing, Plaintiffs presented testimony from two of their experts, Dr. Maurice N.G. Dukes and Dr. Kenneth Kulig. Defendant presented testimony from three of its experts, Dr. James Martin, Dr. Karl Engelman and Dr. David Buchholz. Both sides took full advantage of the opportunity to cross examine the other side's experts. In addition to the Daubert hearing, the Court has reviewed the massive volume of documentary evidence (in all, about 575 exhibits, depositions and affidavits) that relates to Plaintiffs' expert testimony on medical causation. The Court's ruling is based on both the testimony from the Daubert hearing and the substantial documentary evidence in the record.

II. SUMMARY JUDGMENT STANDARD

Summary judgment is appropriate only when the pleadings, depositions, and affidavits submitted by the parties show that no genuine issue of material fact exists and that the movant is entitled to judgment as a matter of law. Fed.R.Civ.P. 56(c). The court should view the evidence and any inferences that may be drawn in light most favorable to the nonmovant. Adickes v. S.H. Kress and Co., 398 U.S. 144, 158-159, 90 S.Ct. 1598, 26 L.Ed.2d 142 (1970). The party seeking summary judgment must first identify grounds that show the absence of a genuine issue of material fact. Celotex Corp. v. Catrett, 477 U.S. 317, 323-24, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). The burden then shifts to the nonmovant, who must go beyond the pleadings and present affirmative evidence to show that a genuine issue of material fact does exist. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 257, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

III. DISCUSSION

A. INTRODUCTION

Defendant contends that Plaintiffs' experts must be excluded from testifying in this case on the grounds that their expert testimony on medical causation is inadmissible. Expert testimony is admissible only if it satisfies the standards that the United States Supreme Court articulated in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993); accord General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997); Kumho Tire Co. v. Carmichael, 526 U.S. 137, 141, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999). The Supreme Court in Daubert explained that Federal Rule of Evidence 702 allows the admission of expert testimony only if: (1) the expert is competent and qualified to testify regarding the matters that he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable; and (3) the expert, through scientific, technical or specialized expertise, provides testimony that assists the trier of fact to understand the evidence or determine a fact in issue. Daubert, 509 U.S. at 590-91, 113 S.Ct. 2786; accord Allison v. McGhan Med. Corp., 184 F.3d 1300, 1309 (11th Cir.1999); City of Tuscaloosa v. Harcros Chemicals, Inc., 158 F.3d 548, 562 (11th Cir.1998).

The first element is competence. The expert must be qualified in his field of expertise. The proponent of expert testimony bears the burden of establishing its admissibility. Wells v. Ortho Pharm. Corp., 615 F.Supp. 262, 295 (N.D.Ga.1985), aff'd, mod. in part, and remanded on other grounds, 788 F.2d 741, 747-48 (11th Cir. 1986). "The burden of laying the proper foundation for the admission of the expert testimony is on the party offering the expert, and admissibility must be shown by a preponderance of the evidence." Allison, 184 F.3d at 1306. Where the burden has not been satisfied, Federal Rule of Evidence 702 precludes expert testimony. See United States v. Paul, 175 F.3d 906, 912 (11th Cir.1999) (witness' review of literature in area outside his field "did not make him any more qualified to testify as an expert ... than a lay person who read the same articles"); City of Tuscaloosa, 158 F.3d at 563 ("[P]ortions of [plaintiffs' expert's] testimony lie outside of his competence as a statistician ..., thus requiring the exclusion of those portions of [his] data and testimony ....").

The second element of admissibility is reliability. To be considered reliable, expert testimony on scientific issues must be supported by "scientific knowledge." "The adjective 'scientific' implies a grounding in the methods and procedure of science. Similarly the word 'knowledge' connotes more than subjective belief or unsupported speculation." Daubert, 509 U.S. at 590, 113 S.Ct. 2786. The Supreme Court in Daubert identified four factors to assist courts in determining whether testimony meets the standard of reliable scientific knowledge: (1) whether the expert's theory can and has been tested; (2) whether it has been subjected to peer review; (3) the known or expected rate of error; and (4) whether the theory or methodology employed is generally accepted in the relevant scientific community. Daubert, 509 U.S. at 593, 113 S.Ct. 2786. These factors, however, are not exhaustive. At its core, the "scientific knowledge" inquiry seeks to determine whether there is "some objective, independent validation of the expert's methodology." Moore v. Ashland Chem., Inc., 151 F.3d 269, 276 (5th Cir. 1998); accord Michigan Millers Mut. Ins. Corp. v. Benfield, 140 F.3d 915, 921 (11th Cir. 1998). "Thus, the proponent of the testimony does not have the burden of proving that it is scientifically correct, but that by a preponderance of the evidence, it is reliable." Allison v. McGhan Med. Corp., 184 F.3d 1300, 1312 (11th Cir.1999).

The final element of admissibility, set forth in Daubert, is an appropriate relevance, or "fit," between the expert's opinion and the facts of the case. Daubert, 509 U.S. at 591, 113 S.Ct. 2786; United States v. Gilliard, 133 F.3d 809, 812 (11th Cir.1998); United States v. Smith, 122 F.3d 1355, 1358-59 (11th Cir.1997). Scientific testimony does not assist the trier of fact unless the testimony has a valid scientific connection to the pertinent inquiry. Daubert, 509 U.S. at 591, 113 S.Ct. 2786. There is no "fit" where there is "simply too great an analytical gap between the data and the opinion offered," as when an expert offers animal studies showing one type of cancer in laboratory mice to support causation of another type of cancer in humans. General Elec. Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997).

In this case, Plaintiffs seek to admit the testimony of five medical experts to support their prima facie requirement of establishing medical causation. To survive Defendant's Motions for Summary Judgment, Plaintiffs must produce evidence that would allow a reasonable jury to find to a reasonable degree of medical certainty that Parlodel(r) is (1) capable of causing stroke and (2) that Parlodel(r) did in fact cause their strokes. See, e.g., Joiner v. General Elec. Co., 864 F.Supp. 1310, 1319 (N.D.Ga. 1994) ("When medical causation is at issue, plaintiffs must prove causation to a 'reasonable

degree of medical certainty.' "), rev'd on other grounds, 78 F.3d 524, 534 (11th Cir.1996), rev'd on other grounds, 522 U.S. 136, 146-47, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997); accord Parrott v. Chatham County Hosp. Auth., 145 Ga.App. 113, 115, 243 S.E.2d 269 (1978). The first element has been termed "general causation" while the second element has been termed "specific causation." Wheat v. Sofamor, S.N.C., 46 F.Supp.2d 1351, 1357 (N.D.Ga.1999). "General causation is the capacity of a product to cause injury; specific causation is proof that the product in question caused the injury of which the plaintiff complains." Id.

Defendant contends that three of Plaintiffs' five experts are not qualified to testify. Defendant also contends that the testimony of all five of Plaintiffs' experts is inadmissible because their testimony is neither scientifically reliable nor relevant. Defendant contends that Plaintiffs' experts' testimony fails to meet the Daubert standards for admissibility because Plaintiffs' experts (1) have failed to provide any evidence, either published or unpublished, that Parlodel(r) increases one's risk of stroke; (2) rely on uncontrolled and unreliable spontaneous reports and anecdotal case reports as the basis for their opinions; and (3) cannot show that their opinions have an acceptable error rate or are otherwise generally accepted.

Plaintiffs' five experts are as follows. Dr. Kenneth Kulig is a physician who is board certified in toxicology and emergency medicine. He is licensed to practice medicine in Colorado. A practicing physician for more than 20 years, Dr. Kulig received his undergraduate degree from Michigan State in 1972, followed by a M.D. degree from Wayne State Medical School in Detroit in 1978. He completed an internship in internal medicine and a residency in emergency medicine. He then obtained a two-year fellowship in clinical toxicology at the University of Colorado. Thereafter, he became affiliated with both Denver General Hospital and the Rocky Mountain Poison Center. In 1991, he joined Porter Adventist Hospital in Denver where he established a private practice, served as Chairman of its Department of Medicine, and remains to this day as both Chairman of the Pharmacy and Therapeutics Committee and Director of the Porter Regional Toxicology Center. Dr. Kulig also is an associate clinical professor in the Division of Emergency Medicine and Trauma at the University of Colorado Health Sciences Center. Dr. Kulig's affidavit states that he has published almost 150 journal articles, including one article related to Parlodel(r). Defendant in its briefs does not contest Dr. Kulig's qualifications in the field of toxicology. It contests only the reliability and relevance of his proposed testimony.

Dr. Dennis Petro is a board-certified neurologist. He received his M.D. degree at Pennsylvania State University. He completed a residency in neurology at Hershey Medical Center in Hershey, Pennsylvania. He became employed by the Food and Drug Administration ("FDA") in Rockville, Maryland, in 1977. While at the FDA, Dr. Petro reviewed drug applications relevant to neurologic disorders, specifically analgesics and drugs of abuse. At the time Dr. Petro began his employment with the FDA, Parlodel(r) was an investigative drug. After leaving the FDA, Dr. Petro became employed by the New York State Department of Health, but still continued part-time employment with the FDA as a consultant. Later he worked on the development of neurologic drugs while employed by Wyeth Laboratories and then Pfizer Pharmaceuticals. Thereafter, Dr. Petro joined the Nassau County Medical Center on Long Island, New York, to run its Neurologic Department Research Program. From there, he joined Fidia Pharmaceutical Corporation in Washington, D.C. Dr. Petro eventually left Fidia and became a consultant in new drug development. Since 1980, he has served as a member of the American Heart Association's Stroke Council. He also has published at least 16 medical articles in peer-reviewed journals. Defendant does not contest Dr. Petro's qualifications in the field of neurology.

It contests only the reliability and relevance of his proposed testimony.

Dr. Subir Roy is a reproductive endocrinologist who serves as a professor in the Department of Obstetrics and Gynecology at the University of Southern California ("USC") School of Medicine. He received his M.D. degree at the University of North Carolina at Chapel Hill. He completed both an internship and residency in obstetrics and gynecology at the Los Angeles County-University of Southern California Medical Center in Los Angeles, California. He then obtained a fellowship in gynecologic endocrinology and infertility from USC and has remained with USC ever since. Dr. Roy served on the FDA's Fertility and Maternal Health Drugs Advisory Committee when it considered the safety of Parlodel(r) in 1989. In October 1998, he was appointed to a four-year term on the FDA's OB/GYN Devices Advisory Committee. He is board certified by the American Board of Obstetrics and Gynecology. He has been a consultant to such publications as the American Journal of Obstetrics and Gynecology, The Journal of Reproductive Medicine, Obstetrics and Gynecology, and the Journal of the American Medical Association. He himself has

published more than 60 peer- reviewed articles. Nevertheless, Defendant contends that Dr. Roy is not qualified by education or experience to render an expert opinion in this case. It also contests the reliability and relevance of his proposed testimony.

Dr. Anthony Guarino is a pharmacologist and toxicologist. He received his Ph.D. in pharmacology in 1966 from the University of Rhode Island. From 1972 to 1980, Dr. Guarino served as the Chief of the Laboratory of Toxicology at the National Cancer Institute in Bethesda, Maryland. From March 1980 to August 1984, he served as a review scientist for the FDA, where he conducted pharmacology and animal toxicology reviews of drugs being offered for clinical investigation and FDA approval. He was responsible for determining, primarily on the basis of animal study data that pharmaceutical manufacturers submitted, whether drugs could be introduced to humans safely and ultimately whether they should be approved for widespread commercial marketing and use. Since 1985, Dr. Guarino has been an adjunct professor of pharmacology at the University of South Alabama College of Medicine in Mobile, Alabama. He also has consulted in the field of drug development in recent years. He has served on the editorial boards of three professional journals, including Regulatory Toxicology and Pharmacology. He has reviewed manuscripts for another 15 medical, chemical and environmental publications and has himself published more than 100 articles in his field. Nevertheless, Defendant contends that Dr. Guarino is not qualified by education or experience to render an expert opinion in this case. It also contests the reliability and relevance of his proposed testimony.

Dr. Maurice N.G. Dukes considers himself to be an adverse drug reaction scientist. No board certification exists for this discipline. Dr. Dukes received his medical degree from St. John's College in England in 1956 and a law degree from Cambridge University in 1957. Following graduation in 1957, Dr. Dukes accepted employment with Richardson-Merrell Pharmaceuticals in its Netherlands office. From 1961 to 1972, he worked at Organon Pharmaceuticals International, eventually obtaining the positions of research manager and assistant research director. In 1972, he became Vice Chairman of the Netherlands National Drug Regulatory Commission, that country's functional equivalent of the FDA. He remained in that position until 1982. Between 1978 and 1982, Dr. Dukes also served as Deputy Member of the European Economic Community's ("EEC") Committee for Proprietary Medicinal Products. In 1982, he left those positions to head the pharmaceuticals program for the World Health Organization's ("WHO") European Regional Office. He left that position in 1991 but continues to consult with the WHO and the World Bank on drug policy. Additionally, Dr. Dukes served between 1985 and 1997 as a professor of drug policy studies at the University of Groningen in the Netherlands. He now serves as an adviser in drug policy studies at the University of Oslo in Oslo, Norway. For years, Dr. Dukes has edited the two internationally recognized standard treatises on drug side effects. Since 1975, he has been the editor- in-chief of Meyler's Side Effects of Drugs. From 1977 to 1996, he served as editorin-chief of the Meyler's complement, Side Effects of Drugs Annual. He is also the editor-in-chief of the International Journal of Risk and Safety in Medicine and has authored such books as The Effects of Drug Regulation (1985) and Responsibility for Drug-Induced Injury (1988 & 2d ed.1998). He also has authored some 240 papers and journal articles on such issues as pharmaceutical products, drug policy, adverse reactions and drug economics. He remains active in the development and establishment of adverse reaction monitoring systems, particularly in Central and Eastern Europe, Africa, and Southeast Asia. Dr. Dukes has never been a licensed, practicing physician in the United States or any other country. Principally, for that reason, Defendant contends that Dr. Dukes is not qualified by education or experience to render an expert opinion in this case. It also contests the reliability and relevance of his proposed testimony.

Having reviewed the depositions, affidavits, other documentary evidence, and, in the cases of Dr. Kulig and Dr. Dukes, having observed and considered their testimony at the Daubert hearing, the Court concludes that Drs. Kulig, Petro, Roy, Guarino, and Dukes are all well qualified by education and experience to provide an opinion on medical causation in this case. Indeed, Dr. Dukes--whom Defendant most strenuously challenges--is an exceptionally qualified expert on the issue of adverse drug reactions. The fact that he has chosen to spend his professional life in the world of public policy and academics instead of clinical practice in no way reduces his expertise in the field of adverse drug reaction science. Defendant's argument to the contrary minimizes the contributions made to medical science by those who accept the call of public service and selflessly remain in that service throughout the duration of their careers.

The opinion of Plaintiffs' experts regarding medical causation in these cases is that Parlodel(r) caused Plaintiffs' seizures and hemorrhagic strokes.

The argument underlying their conclusion of medical causation is the following causal chain: (1) Parlodel(r)'s active ingredient, bromocriptine, prevents lactation from occurring by blocking thehormone that causes it. (2) Bromocriptine is a member of the ergot alkaloid class of drugs. (3) With respect to circulation, ergot alkaloids can cause vasoconstriction (narrowing of the blood vessels) and hypertension (high blood pressure). (4) Vasoconstriction can lead to seizures and even ischemic stroke (strokes caused by decreased blood flow to the brain). (5) If vasoconstriction can lead to ischemic strokes, it also likely causes hemorrhagic strokes (strokes caused by a rupture to the vessel). (6) Paroldel(r), therefore, caused Plaintiffs' hemorrhagic strokes.

Plaintiffs' experts admit that bromocriptine does not always act as a vasoconstrictor. They contend that bromocriptine can cause two seemingly anomalous circulation effects, depending on one's "vascular tone." If one's arterial resistance is low, Plaintiffs' experts admit that bromocriptine can cause vasodilation (widening of the blood vessels) and hypotension (low blood pressure). Vasodilation and hypotension are admittedly inconsistent with their theory of causation. If, however, one's arterial resistance is high, Plaintiffs' experts contend that bromocriptine, like other ergot alkaloids, can cause vasoconstriction and hypertension, which can lead to seizures and stroke. The "vascular tone" of Plaintiffs' cerebral arteries at the time of their strokes is completely unknown.

In short, the chain of Plaintiffs' argument is that Parlodel(r)'s active ingredient is bromocriptine, which is an ergot alkaloid. Ergot alkaloids are a class of drugs that can cause hypertension, seizures and ischemic strokes and, therefore, likely cause hemorrhagic strokes, also. The question before the Court is whether their methodology in constructing this causal chain is based on scientific knowledge that is sufficiently relevant and reliable to assist the trier of fact; or whether Plaintiffs' causal chain instead includes "leaps of faith" and is no more than a hypothesis not adequately supported by the scientific method. See In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 745 (3d Cir.1994) ("Daubert 's requirement that the expert testify to scientific knowledge--conclusions supported for good grounds for each step of the analysis--means that any step that renders the analysis unreliable under the Daubert factors renders the expert's testimony unreliable.") (emphasis in original); Allison v. McGhan Med. Corp., 184 F.3d 1300, 1314 (11th Cir.1999) ("Daubert decisions in other courts warn against leaping from an accepted scientific premise to an unsupported one.").

In Daubert, the Supreme Court "listed four noninclusive factors courts should consider in determining reliability under Rule 702:(1) whether the theory or technique can be tested; (2) whether it has been subjected to peer review; (3) whether the technique has a high known or potential rate of error; and (4) whether the theory has attained general acceptance within the scientific community." Allison, 184 F.3d at 1312 (citing Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 593-94, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993)). Sorting through the mass of material submitted in this case, a few things are clear. The theory of the Plaintiffs' experts has not been validated by testing except to the limited extent that the animal studies and epidemiological studies discussed below are considered tests. The theory has not been subjected to peer review except to the limited extent discussed below with respect to statements in medical treatises. The rate of error is unknown. The theory has not attained general acceptance within the scientific community unless the removal of the indication for suppression of lactation by the Food and Drug Administration ("FDA") discussed below constitutes such acceptance. Applying the Daubert criteria literally, the testimony of Plaintiffs' experts should be excluded as unreliable and irrelevant. Nevertheless, given that the Daubert criteria are noninclusive, the Court must go forward and address the issue of whether there is other data relied upon by Plaintiffs' experts that satisfies the necessity for reliable and relevant scientific knowledge.

B. EPIDEMIOLOGICAL STUDIES

The central question in this pharmaceutical products liability case, just as in Daubert, is the issue of medical causation. The starting point of the Daubert analysis must be consideration of the factors identified by the Supreme Court in that case to determine reliability and relevance. The first of these is whether the theory of causation has been tested. Epidemiology is the medical science devoted to determining the cause of disease in human beings. Epidemiologists employ cohort studies, case-control studies, and ecological studies to determine whether individuals exposed to an agent have a greater risk of developing the disease in question. Bailey, et al., "Reference Guide on Epidemiology," Reference Manual on Scientific Evidence 340- 45(2000). In epidemiological terms, the difference in risk of getting the disease is the "relative risk." A relative risk of 1.0 means that the agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other

background causes. A relative risk of 2.0 implies a 50 percent likelihood that an exposed individual's disease was caused by the agent in question. See, e.g., Hall v. Baxter Healthcare Corp., 947 F.Supp. 1387, 1403 (D.Or.1996); Reference Manual at 348-49. Thus, in the world of epidemiology, the threshold for concluding that an agent was more likely than not the cause of a disease is a relative risk greater than 2.0.

The existence of relevant epidemiological studies can be a significant factor in proving general causation in toxic tort cases. Hall, at 947 F.Supp. at 1403. Indeed, epidemiological studies provide "the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or disease." Conde v. Velsicol Chem. Corp., 804 F.Supp. 972, 1025-26 (S.D.Ohio 1992), aff'd, 24 F.3d 809, 814 (6th Cir.1994). Plaintiffs do not dispute this point. (Transcript of Daubert Hearing, at 192) (recounting statement previously made by Dr. Kulig that epidemiological studies are the most important source for establishing causation).

Four epidemiological studies have been conducted to investigate a possible association between Parlodel(r) and stroke. The first study at issue is Kenneth Rothman, An Epidemiologic Evaluation of the Possible Relation Between Bromocriptine, Puerperal Seizures and Strokes (Epidemiologic Resources, Inc. Sept. 30, 1988) (Defendant's Motion to Exclude and for Summary Judgment, Siharath v. Sandoz Pharms. Corp., Ex. 10.) [Doc. 68]; (Defendant's Motion to Exclude and for Summary Judgment, Rider v. Sandoz Pharms. Corp., Ex. 10.) [Doc. 116]. In the hearing, this was referred to as the ERI study. The ERI study, commissioned by Defendant, is the only epidemiologic study using case controls and cohorts that has sought to determine whether a causal relationship exists between Parlodel(r) and stroke. This study reviewed hospital records of 280,096 postpartum women. Out of a total of ten postpartum strokes in this population, only one occurred in a woman who had taken Parlodel(r). Of the 77 controls, only one had been exposed to Parlodel(r). The resulting relative risk calculation, at 8.4, was deemed not statistically reliable by the study's investigators. Even Dr. Kulig admitted, "I'm not going to say that this shows the drug causes stroke." (Transcript of Daubert Hearing, at 177.)

Realizing this limitation of the ERI study, Plaintiffs' experts emphasize instead their opinion that the study shows that Parlodel(r) does cause "late-occurring seizures"--seizures occurring more than 72 hours after delivery. Plaintiffs allege that the relative risk factor of Parlodel(r) for late-occurring seizures is 2.86. This allegation, however, ignores the fact that there were only three cases of late-occurring seizure in the study where the patient took bromocriptine. And in two of those cases, the patients also had been given ergonovine, which neither Plaintiff in this case ingested. Indeed, the study concluded that although there is a positive association between bromocriptine and seizures among those who also received ergonovine, there is "a weak negative association among those who did not receive ergonovine." Rothman, An Epidemiologic Evaluation, at 23 (emphasis added). Dr. Kulig may be correct when he says that the ERI study was not well-conducted and does not unequivocally establish that Parlodel(r) is not dangerous for postpartum women. (Transcript of Daubert Hearing, at 178.) But the conclusion cannot be drawn from the ERI study that Parlodel(r) causes hemorrhagic stroke in postpartum women. Consequently, the Court must agree with Defendant that the ERI study is inadequate to advance Plaintiffs' theory of causation.

The second study is HCIA Inc., Postpartum Complications and Parlodel(r) (October 1995). (Defendant's Motion to Exclude and for Summary Judgment, Siharath v. Sandoz Pharms. Corp., Ex. 12.) [Doc. 68]; (Defendant's Motion to Exclude and for Summary Judgment, Rider v. Sandoz Pharms. Corp., Ex. 12.) [Doc. 116]. This study, also commissioned by Defendant, is commonly referred to as the HCIA study. The study analyzed 533,816 delivery records from 128 hospitals. It tracked postpartum complications and correlated complications with Parlodel(r) use. The estimated relative risk for stroke associated with bromocriptine use was 1.088, with a confidence interval ("CI") from 0.448 to 2.643. Similarly, the estimated relative risk for seizures associated with bromocriptine use was 1.071, with a CI from 0.406 to 2.829. See Reference Manual at 360 ("A confidence interval is a range of values calculated from the results of a study, within which the true value is likely to fall; the width of the interval reflects random error.") For both preexisting and non- preexisting hypertensive women, the study concluded that there existed a negative association between bromocriptine (0.956 and 0.675 relative risks respectively) and hypertension. As Plaintiffs contend and Defendant admits, the HCIA study may possess methodological flaws that prevent a court from determining that Parlodel(r) definitely does not causeseizures and stroke, but the study certainly does not support Plaintiffs' theory of causation that Parlodel(r) does cause seizures and hemorrhagic stroke.

The third study is R.M.C. Herings and B.H.C. Stricker, Bromocriptne and Suppression of Postpartum Lactation, Pharmacy World & Sci. 17:133-37 (1995). (Defendant's Motion to Exclude and for Summary Judgment, Siharath v. Sandoz Pharms. Corp., Ex. 13.) [Doc. 68]; (Defendant's Motion to Exclude and for Summary Judgment, Rider v. Sandoz Pharms. Corp., Ex. 13.) [Doc. 116]. This study is often referred to as the Herings-Stricker study. In this study, investigators compared hospital admission and drug use of 2,130 women to identify the existence of ischemic heart disease, hypertension, and cerebrovascular events such as stroke before, during and after use of Parlodel(r) for postpartum lactation. The study found that no women whatsoever were admitted to hospitals for any of these conditions during the presumed exposure period or in the following two months. Plaintiffs question the methodology of this study on a number of grounds, including that the sample size was too small for an accurate epidemiological study. That may be, but the study also does not support Plaintiffs' theory that Parlodel(r) causes hemorrhagic stroke and seizures.

The fourth study is Andrea D. Witlin, et al., Postpartum Stroke: A Twenty-Year Experience. (Defendant's Motion to Exclude and for Summary Judgment, Siharath v. Sandoz Pharms. Corp., Ex. 11.) [Doc. 68]; (Defendant's Motion to Exclude and for Summary Judgment, Rider v. Sandoz Pharms. Corp., Ex. 11.) [Doc. 116]. This study was accepted for publication by the American Journal of Obstetrics and Gynecology but the offer was later withdrawn. The study, however, has been subjected to some peer review. It concluded that postpartum women who take bromocriptine are less likely to experience stroke than patients who are exposed to the drug. Indeed, the study concluded that, with a relative risk of 0.12, they are eight times less likely to suffer postpartum stroke. One of the study's authors, however, conceded in a deposition for the Rider case that "[t]his study was not designed to address whether bromocriptine causes stroke or not." (Deposition of Dr. Baha M. Sibai, at 146.)

In short, neither the ERI study, the HCIA study, nor the Herings-Stricker study shows any statistically significant relationship between Parlodel(r) and stroke. The unpublished Witlin study found that bromocriptine was negatively associated with postpartum stroke, but it is unpublished and questions surround its actual intended purpose. As Dr. Kulig stated, "there is no good epidemiology on the subject." (Transcript of Daubert Hearing, at 281.) Plaintiffs' experts concede that no epidemiological study shows a statistically significant association between Parlodel(r) and stroke. The epidemiological studies either show no relationship or a negative relationship between the drug and stroke. Unable to rely upon the epidemiological studies as support for their causation opinions, Plaintiffs' experts predictably are critical of the conclusion that the studies prove Parlodel(r) is safe for postpartum women. None of the epidemiological studies are perfect; all have their flaws. It is important to recall, however, that the burden is on Plaintiffs to show that well-conducted epidemiological studies do show a statistically significant relationship between Parlodel(r) and seizures and stroke. It is not Defendant's burden to show the lack of such relationship.

Plaintiffs' well-taken criticisms of the epidemiological studies does not satisfy their burden of proof. See Glastetterv. Novartis Pharmaceutials Corp., 107 F.Supp.2d 1015, 1044 (E.D.Mo.2000) ("In the absence of their own epidemiological evidence supporting the conclusions of their experts that Parlodel(r) can cause an ICH [intracranial hemmorrhage], the best plaintiffs can do is attack defendant's studies."); Brumbaugh v. Sandoz Pharmaceutical Corp., 77 F.Supp.2d 1153, 1156 (D.Mont. 1999) ("The plaintiff criticizes certain aspects of these studies, but she produced no epidemiological study, or other reliable scientific proof that does make the causal link between Parlodel and her condition, or any related condition. Plaintiff's lawyers attack on defendant's studies does not meet the law's requirements. She must come forward with reliable scientific evidence of her own to defeat a summary judgment motion when her case is based on the expert's proof."). No evidence has been offered of an increase in postpartum strokes after the drug was approved for suppression of lactation; no evidence has been offered of a decrease in postpartum strokes after the approval for suppression of lactation was withdrawn. Reference Manual at 345 ("Another epidemiologic approach is to compare disease rates before and after a point in time when some event of interest took place.") The absence of epidemiological support raises the question of whether the causation opinions of Plaintiffs' experts are merely speculative and not based on scientific knowledge.

The lack of epidemiological studies supporting Plaintiffs' claims creates a high bar for Plaintiffs to surmount with respect to the reliability requirement, but it is not automatically fatal to Plaintiffs case. If other reliable scientific knowledge exists, Plaintiffs may overcome this evidentiary gap in their case. Epidemiological evidence is not the only legally sufficient proof for establishing a prima facie case of

medical causation. In a pre-Daubert case, the Eleventh Circuit stated that:

[A] cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. As long as the basic methodology employed to reach such a conclusion is sound, such as use of tissue samples, standard tests, and patient examination, products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical.

Wells v. Ortho Pharm. Corp., 788 F.2d 741, 745 (11th Cir.1986) (quoting Ferebee v. Chevron Chemical Corp., 736 F.2d 1529, 1535-36 (D.C.Cir.1984)). Additionally, in Allison v. McGhan Medical Corporation, 184 F.3d 1300, 1316 (11th Cir. 1999), a post-Daubert case, the Eleventh Circuit analyzed all other proffered evidence even after it concluded that the plaintiff had not presented adequate epidemiological studies.

Epidemiology often is difficult to conduct. Additionally, ethical issues abound. "[O]ne cannot ethically experiment on human beings, exposing them to near certainty of some number of deaths, simply to satisfy some evidentiary standard." Globetti v. Sandoz Pharms. Corp., 111 F.Supp.2d 1174, 1180 (N.D.Ala.2000). Consequently, this Court looks not only to the existence of epidemiology but also the other forms of causation evidence that Plaintiffs offer in totality to support their case. As the Eleventh Circuit has stated, although an individual item of evidence alone may not suffice to establish causation, it may serve as one component, that when added to others, does prove causation:

Opinions of any kind are derived from individual pieces of evidence, each of which by itself might not be conclusive, but when reviewed in its entirety are the building blocks of a perfectly reasonable conclusion, one reliable enough to be submitted to a jury along with the tests and criticisms cross-examination and contrary evidence would supply.

Joiner v. General Elec. Corp., 78 F.3d 524, 531 (11th Cir.1996), rev'd on other grounds, 522 U.S. 136, 146-47, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997).

C. CASE REPORTS

In paragraph 36 of his affidavit, Dr. Dukes

In the absence of statistically significant epidemiological studies to support their general causation theories, Plaintiffs' experts rely most heavily on case reports. Case reports are a form of anecdotal evidence where one event is reported as following another. Reference Manual at 91. Defendant's response to the reliance upon case reports is twofold. First, it contends that the specific case reports relied upon by Plaintiffs are not cases where Parlodel(r) caused hemorrhagic stroke in postpartum women. Second, it contends that case reports in general do not satisfy the requirements of the scientific method sufficient to establish general causation. Following much thought and careful review of the case reports, relevant case law, and numerous scholarly articles, the Court agrees on both counts.

Dr. Dukes, Plaintiffs' principal adverse drug reactions expert, emphasized in his affidavit a number of Sandoz case reports as evidence for his opinion that Parlodel(r) causes strokes:

The most damning answer of all to Defendant's argument lies in the fact which I have detailed already, namely that Sandoz (both in Switzerland and the U.S.A.) had over a long period made use of precisely the evidence and methods which I have [been] using and had relied on them. From the records, one can see precisely what the general conclusions of Sandoz['s] own adverse reaction staff regarding Parlodel were when they had made use of these methods to examine specific reports. They were quite clear. Having examined the specific facts and circumstances implicated in individual reports of bromocriptine-associated adverse experiences, and without any references whatsoever to or reliance upon evidence from formal epidemiological studies, the DMC [Sandoz's Drug Monitoring Centre] at Basel concluded that * 1360 several adverse reactions--including, but not limited to, strokes, hypertensive crises, seizures, and myocardial infarctions--were probably caused by use of Parlodel (bromocriptine mesylate). When one turns back to the original DER's [drug experience reports] received by Sandoz which had led them to this conclusion one can see how firmly founded the conclusion was.

(Affidavit of M.N.G. Dukes, M.D., M.A., L.L.M., at § § 36-37 (emphasis in original).) After looking at the adverse reaction reports themselves, the Court must conclude that this is a considerable overstatement of the case. This should be apparent from a brief examination of the reports relied upon by Dr. Dukes.

states that Sandoz concluded that bromocriptine had probably caused an ischemic stroke in a woman five days after she began taking the drug. This woman, however, (1) was 62 years old; (2) was not postpartum; (3) had suffered from hypertension for 12 years; (4) suffered from acromegaly, a life-threatening pituitary disease that Dr. Dukes admits can lead to stroke; (5) was taking bromocriptine to reduce the size of a tumor (an approved indication); and (6) was also taking cortisone. (Plaintiffs' Ex. 125.) The case report emphasizes that her stroke was "[p]robably due to hypotension," not hypertension. The initial adverse drug report states only that it was possible, not probable, that the adverse event was due to Parlodel(r). A subsequent, more detailed analysis in the case report likewise states that causality "is difficult to ascertain" and that it is only "possible" that Parlodel(r) "may be related to ischaemic cerebral infarction." Additionally, even if it can be said that bromocriptine probably caused this woman's stroke, it should be noted that this is the only stroke that Sandoz's Drug Monitoring Centre has ever concluded as "probably" having been caused by bromocriptine. Dr. Dukes has written that "[s]ometimes an adverse development may be a complication of the primary disease which is being treated rather than a complication of drug therapy." M.N.G. Dukes, et al., Responsibility for Drug-Induced Injury: A Reference Book for Lawyers, the Health Professions and Manufacturers 43 (2d ed. 1998). This case report may be a good example of this process.

Dr. Dukes refers in paragraph 37 of his affidavit to a 23 year old German woman who took Parlodel(r) for three months and suffered from hypertension and cerebellar incoordination. As Defendant's counsel elicited from Dr. Dukes on cross-examination at the Daubert hearing, however, this patient was not postpartum; was taking Parlodel(r) to treat a pituitary adenoma, which itself can lead to hypertension and incoordination; and suffered from multiple sclerosis, a condition for which cerebellar incoordination is a classic symptom. (Plaintiffs' Ex. 57.) Also, the adverse event report stated only that it was "possible" that Paroldel(r) was causally related to her hypertension and incoordination. Mere possibility does not establish medical causation. Although an adverse case report is not required to "rule out" every other possibility to have some reliability, it should do more than just fail to rule out the alleged cause. It should provide a source for "ruling in" the alleged cause. A finding that Parlodel(r) "probably" caused a particular adverse event may add needed evidence to a causation theory. A finding that it only "possibly" caused the adverse event does not.

Dr. Dukes refers next in paragraph 37 of his affidavit to a 22 year old French woman who took Parlodel(r) to suppress postpartum lactation. She later developed hypertension and convulsions. (Plaintiffs' Ex. 60.) Dr. Dukes, however, fails to mention in his affidavit that the patient was hypertensive before delivery; that her hypertension decreased after taking Parlodel(r); and that she suffered from postpartum eclampsia, which can lead to seizures and stroke. See generally Steven J. Kittner, et al., Pregnancy and the Risk of Stroke, New Eng. J. Med. 768-74 (1996) (discussing 28.3 relative risk of stroke for pregnant women compared with non-pregnant women).

Dr. Dukes also refers to a 20 year old Arkansas woman who took Parlodel(r) to suppress postpartum lactation and later developed hypertension. Dr. Dukes says that her symptoms improved after being taken off the drug, but the case report notes that she continued to suffer from hypertension for another four to five days. (Plaintiffs' Ex. 61.) This fact raises questions about the dechallenge (stopping use of the drug by the patient) aspect of this report, which is what Dr. Dukes emphasizes. Dr. Dukes discussed additional case reports in his affidavit. Defense counsel effectively discredited these additional case reports as evidence of a relationship between Parlodel(r) and postpartum stroke. See Transcript of Daubert Hearing, at 108-19 (referring to Plaintiffs' Exs. 126, 127, 25 & 168). Thus, Defendant has raised serious questions about Dr. Dukes' analysis of these case reports.

Additionally, Dr. Dukes stated during the Daubert hearing that the value of adverse drug reports varies greatly, depending on the quantity, nature and content of the reports. (Transcript of Daubert Hearing, at 20.) He explained that in determining whether a sufficient quantity exists, one should ask how many reports have been received. In determining the nature of the reports, one should ask whether the reactions are what one might expect of the drug, the drug type and the dosage. In determining whether the content of the reports is sufficient, Dr. Dukes provided a chart at the hearing listing four questions that can assist in this analysis:

(1) Are at least some of the events described in full detail?
(2) Is the time course of the reaction credible?
(3) If the time reaction is reversible, did it disappear when the drug was stopped, or "dechallenged"? If it was ethical to repeat the treatment ("rechallenge"), did the effect reappear?
(4) Are more obvious alternative causes present?

The adverse drug reports in this case lack the requisite quantity, nature and content. From 1980 to 1994, millions of women took Parlodel(r). The modest number of case reports associating the drug with stroke or even postpartum hypertension is not what would be expected if there was a significant increased risk. Only one report exists that links Parlodel(r) to a stroke, and in that case the patient suffered from an underlying condition that itself can cause stroke. No other patient in any case reports suffered any form of stroke. The other patients instead suffered non-cerebral effects such as hypertension and myocardial infarction. Many of the case reports cited involved patients who were not

postpartum. One case report involved a patient who was dechallenged but continued to suffer from hypertension for another four to five days. In short, Plaintiffs'

have not pointed to a single case report involving a postpartum woman who suffered a hemorrhagic stroke. Accordingly, even if case reports could be used to establish general causation, the Court would have to conclude that they are insufficient to do so in this case. The case reports simply lack the quantity, nature and content that Dr. Dukes himself claims is necessary for case reports to provide reliable scientific information about causation.

The fact of the matter is that even if relevant case reports existed, they cannot establish general causation:

[C]ase reports are not reliable scientific evidence of causation, because they simply describe[ ] reported phenomena without comparison to the rate at which the phenomena occur in the general population or in a defined control group; do not isolate and exclude

potentially alternative causes; and do not investigate or explain the mechanism of causation.

Casey v. Ohio Medical Products, 877 F.Supp. 1380, 1385 (1995); see also Glastetter v. Novartis Pharms. Corp., 107 F.Supp.2d 1015, (E.D.Mo.2000) (concluding in Parlodel(r) products liability case that case reports did not support the reliability of plaintiffs' expert testimony); Hollander v. Sandoz Pharms. Corp., 95 F. Supp.2d 1230, 1235-38 (W.D.Okla.2000) (noting that "case reports have been repeatedly rejected as a scientific basis for a

conclusion regarding causation"); Brumbaugh v. Sandoz Pharm. Corp., 77 F.Supp.2d 1153, 1157 (D.Mont.1999) (concluding that testimony in Parlodel(r) case was inadmissible because the expert was relying only on case reports of possible adverse drug reactions); In re Breast Implant Litig., 11 F.Supp.2d 1217, 1228 (D.Colo.1998) ("To the extent there are case or anecdotal reports noting various symptoms or signs in breast implanted women, without controls, these suggest only a potential, untested hypothesis that breast implants may be their cause."); Willert v. Ortho Pharm. Corp., 995 F.Supp. 979, 981 (D.Minn. 1998) (concluding that case reports are not sufficient evidence of causation because they do not exclude other alternative explanations); Pick v. American Med. Sys., 958 F.Supp. 1151, 1161-62 (E.D.La. 1997) (noting that "courts have frequently rejected case studies as an insufficient basis to decide causation when they lack control groups" and that "the individual reports cited must be shown to be independently reliable under Daubert before they can be admitted"); Hall v. Baxter Healthcare, 947 F.Supp. 1387, 1411 (D.Or.1996) ("[C]ase reports and case studies are universally regarded as an insufficient scientific basis for a conclusion regarding causation because case reports lack controls."); Haggerty v. Upjohn Co., 950 F.Supp. 1160, 1165 (S.D.Fla.1996) ("[W]hile case reports may provide anecdotal support, they are not a substitute for scientifically designed and conducted inquiry."), aff'd, 158 F.3d 588 (11th Cir.1998); Muzzey v. Kerr-McGee Chem. Corp.,

921 F.Supp. 511, 519 (N.D.Ill.1996) (stating that anecdotal reports may be an incentive for more careful investigation, but are not reliable bases to form a scientific opinion about a causal link); Wade-Greaux v. Whitehall Labs., 874 F.Supp. 1441, 1453 (D.Vi.1994) ("[Case] reports record nothing more than a temporal association between an exposure and a particular occurrence. Because of individual confounding factors, one cannot draw causation conclusions from such anecdotal data. Epidemiologists use their population studies to eliminate the chance associations and confounding factors, which inherently affect anecdotal reports, to determine whether a statistically significant positive association exists.")

Adverse reaction reports and other case reports are generated by the clinical process of "differential diagnosis." Differential diagnosis is a patient-specific process of elimination that medical practitioners use in an attempt to identify the "most likely" cause of a set of signs and symptoms from a list of possible causes. Differential diagnosis, however, does not by itself unequivocally prove the cause, even for the particular patient. Nor can the process establish general causation. In re Breast Implant Litig., 11 F.Supp.2d 1217, 1230-31 (D.Colo. 1998); see generally Michael B. Kent, Jr., Daubert, Doctors and Differential Diagnosis: Treating Medical Causation Testimony as Evidence, 66 Def. Couns. J. 525, 532 (1999) (discussing differential diagnosis and general causation). Indeed, differential diagnosis assumes that general causation has been

proven for the entire list of possible causes that are eliminated one-by-one:

The process of differential diagnosis is undoubtedly important to the question of "specific causation." If other possible causes of an injury cannot be ruled out, or at least the possibility of their contribution to causation minimized, then the "more likely than not" threshold for proving causation may not be met. But it is also important to recognize that a fundamental assumption underlying this method is that the final, suspected "cause" remaining after this process of elimination must actually be capable of causing the injury. That is, the expert must "rule in" the other suspected cause as well as "rule out" other possible causes. And, of course, expert opinion on this issue of "general causation" must be derived from scientifically valid methodology.

Hall v. Baxter Healthcare Corp., 947 F.Supp. 1387, 1413 (D.Or. 1996) (quoting Cavallo v. Star Enterprise, 892 F.Supp. 756, 771 (E.D.Va. 1995),rev'd on other grounds, 100 F.3d 1150, 1157-59 (4th Cir.1996) (emphasis in Hall)). With respect to general causation, the relevant scientific field is epidemiology or toxicology and not clinical medicine.

Both of Plaintiffs' experts who testified at the Daubert hearing recognize the severe limitations of case reports and differential diagnosis in establishing general causation. Dr. Kulig admitted the limitations in the following exchange:

Q: As a matter of scientific methodology, Dr. Kulig, case reports do not establish general causation and you would never attempt to do so, true?

A: True.

Q: And as a matter of scientific methodology, Dr. Kulig, case series do not establish general causation and you would never attempt to do so, true?

A: True.

Q: And as a matter of scientific methodology, Dr. Kulig, differential diagnosis as applied to a specific patient cannot establish general causation?

A: In and of itself, I wouldn't establish it, but now you're getting closer.

(Transcript of Daubert Hearing, at 193.) Case reports can establish only specific causation. Testimony regarding specific causation, however, is irrelevant unless general causation is established. Hall, 947 F.Supp. at 1413. Accordingly, given the limits of case reports in establishing general causation, as recognized by Plaintiffs' experts, the Court must conclude that Plaintiffs' reliance upon case reports as a substitute for epidemiology cannot withstand the scrutiny that Daubert requires.

The court in Globetti v. Sandoz Pharmaceuticals Corporation, 111 F.Supp.2d 1174 (N.D.Ala.2000) gave considerable weight to case reports and the differential diagnosis process in overruling a Daubert objection. A couple of comments are in order. First, that case involved an allegation that Parlodel(r) caused an acute myocardial infarction. A case can be made that the medical community in general accepts the theory that Parlodel(r) is a risk factor for acute myocardial infarction in the postpartum period. This alone may be sufficient to satisfy the Daubert standard. Second, there is a much greater leap of faith from accepting that bromocriptine is a vasoconstrictor to the conclusion that it causes hemorrhagic strokes than to the conclusion that it can cause arterial spasm. Finally, the Court believes that the weight given to case reports in this Order is more consistent with the weight of authority in general and in Parlodel(r) stroke cases specifically. To the extent that Globetti holds that case reports are sufficient to show that Parlodel(r) causes stroke, this Court finds it unpersuasive, particularly given the strong epidemiological evidence that pregnancy itself is a strong risk factor for stroke. See generally Steven J. Kittner, et al., Pregnancy and the Risk of Stroke, New Eng. J. Med. 768-74 (1996) (discussing 28.3 relative risk of stroke for pregnant women compared with non-pregnant women).

D. EFFECTS OF OTHER ERGOT ALKALOIDS

Plaintiffs' experts also rely on adverse effects of drugs other than bromocriptine, but within the same class, to support their hypothesis that Parlodel(r) causes seizures and stroke. They allege that the effects of bromocriptine are similar to those of other ergot alkaloids, a family of naturally occurring and semi-synthetic compounds. Defendant contends that this reliance raises serious questions of "fit." The Court agrees. In general, "[t]estimony extending general conclusions about similar drugs does not meet Daubert 's requirements of reliability." Brumbaugh v. Sandoz Pharm. Corp., 77 F.Supp.2d 1153, 1157 (D.Mont.1999); accord * 1 364Schudel v. General Elec. Co., 120 F.3d 991, 996-97 (9th Cir. 1 997);see generally Daniel J. Capra, The Daubert Puzzle, 32 Ga. L.Rev. 699, 715 (1998) ("One example of improper extrapolation is an expert's use of structure analysis."). Small differences in molecular structure often have significant consequences. Schudel, 120 F.3d at 996-97. Each ergot alkaloid has distinctive pharmacological properties, and bromocriptine differs physically from the other ergot

alkaloids in several respects, most notably the addition of a bromine atom.

The chemical diversity of ergot alkaloids corresponds to the diversity of the biological activities of these
compounds. It is probably correct to state that there are few chemical groups which comprise substances with such diversified actions .... Many ergot compounds show a considerable spectrum of pharmacologic actions and, if the doses necessary to obtain a specific effect are taken into account, exhibit a high degree of specificity (selectivity).

B. Berde & H.O. Schild, Ergot Alkaloids and Related Compounds 2 (emphasis in original).

In Mitchell v. Gencorp, Inc., 165 F.3d 778, 782 (10th Cir. 1999), the plaintiffs' experts sought to testify that exposure to the defendant's chemicals caused the decedent to develop chronic myelogenous leukemia. The plaintiffs' experts attempted to support their conclusion with various published works that link exposure to benzene and certain types of leukemia. The plaintiffs' experts, however, did not possess any information suggesting that the decedent had ever been exposed to benzene. Consequently, the plaintiffs' experts attempted to show the following relationship: (1) the defendant's products were chemically similar to benzene; (2) because the defendant's products and benzene are chemically similar, they should affect the body in similar ways; (3) benzene exposure causes certain types of leukemia; (4) because benzene exposure causes other types of leukemia, it is logical that it could cause chronic myelogenous leukemia as well; (5) the decedent's exposure to the defendant's products caused him to develop chronic myelogenous leukemia. The district court found thatthe plaintiffs' experts' opinions lacked sufficient scientific validation to withstand the demands of Daubert. The Tenth Circuit affirmed:

In analyzing the experts' opinions, we begin by noting that the record contains some testimony about the similarities between benzene and Defendant's products. Missing from this evidence is additional testimony explaining exactly what these similarities are and how the similarities cause the human body to respond to Defendant's chemicals in a manner similar to benzene. Nor does the literature Plaintiffs presented support the notion that chemicals similar to benzene will affect the body in a manner similar enough to cause the same response as benzene.

Id.

Likewise, Plaintiffs' experts in this case cannot show that bromocriptine, the active ingredient in Parlodel(r), affects the body in a manner similar to other ergot alkaloids. Plaintiffs' argument in this regard is as follows: Parlodel(r)'s active ingredient is bromocriptine. Bromocriptine is a semi- synthetic ergot alkaloid. Ergot alkaloids are a class of drugs that can cause vasoconstriction. Vasoconstriction can lead to hypertension, seizures and ischemic strokes. Hemorrhages are another type of stroke, so it is possible that they also are caused by Parlodel(r). As in Mitchell, this argument suffers from a number of flaws. As mentioned above, bromocriptine cannot be assumed to cause the same effects as other ergot alkaloids. Bromocriptine differs physically from the other ergot alkaloids in several respects, most notably the addition of a bromine atom. It is accepted in the scientific and medical community that bromocriptine is not always a vasoconstrictor. It can be a vasodilator depending upon vascular tone. No evidence exists that other ergot alkaloids cause such peculiar effects. This scientific fact supports both the finding that small differences in chemical structure often have significant consequences and the conclusion that testimony about similar drugs often does not meet Daubert 's requirements of reliability.

Additionally, even if scientific support did exist for the Plaintiffs' conclusion that bromocriptine acts like other ergot alkaloids, Plaintiffs have presented no evidence that ergot alkaloids cause hemorrhagic strokes. There is evidence only that they may cause ischemic strokes. See, e.g., Goldfrank's Toxicologic Emergencies 754 (6th ed. 1998) ("In more serious cases, severe peripheral vasoconstriction may produce ischemic changes including angina, myocardial infacrction, cerebral ischemia, and mesenteric ischemia."). Dr. Kulig states that in his clinical experience drugs that cause ischemia can also cause hemorrhage, but he cites as examples only cocaine and methamphetamine, two highly dangerous drugs that no expert has claimed are similar to bromocriptine

or any other ergot alkaloid. (Transcript of Daubert Hearing, at 166.) Furthermore, no epidemiology or even learned treatises link ergot alkaloids to hemorrhagic strokes. (Transcript of Daubert Hearing, at 212). Significant physiological distinctions exist between ischemic and hemorrhagic strokes. Ischemic strokes are caused by lack of blood flow to the brain. Hemorrhagic strokes are caused by the rupture of a blood vessel in the brain. The treatises list only cerebrovascular ischemia among the cerebral risk factors for ergot alkaloids. For all of the above reasons, Plaintiffs' experts' argument that bromocriptine is akin to other ergot alkaloids has not been supported by sufficient reliable scientific evidence

Plaintiffs next contend that Food and Drug Administration findings and conclusions support their experts' causation opinions. On August 24, 1994, the FDA issued the following statement:

> Since approval of bromocriptine for use in preventing physiological lactation, FDA has received a number of reports of serious and life-threatening adverse experiences (hypertension, seizures, and CVA's [cardiovascular accidents]) associated with the use of bromocriptine for this indication. FDA believes that the number of women experiencing such adverse experiences may well be greater than those reported to the FDA. The above evidence, in aggregate, calls into question bromocriptine's safety for use in postpartum women given that bromocriptine may be responsible for hypertension, seizures, and CVA's in a small but significant number of patients. Moreover, bromocriptine may be an additional risk factor in patients who are already at risk for seizures and stroke. In addition, a possible mode of action exists for these adverse events. In the general population, a risk factor for hypertensive crises and spasms is exposure to ergot alkaloids. Bromocriptine is a semi-synthetic ergot alkaloid.
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> * * * * * *
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> FDA now has new information suggesting that therapeutic use of bromocriptine for the prevention of physiological lactation may lead to serious adverse experiences, including death and paralysis, in a small but significant number of patients. Patients at high risk of experiencing these serious adverse experiences cannot be adequately predetermined. In light of the limited benefit of using bromocriptine for the prevention of lactation, and the effectiveness and lack of serious adverse effects of conservative treatments such as breast binding with or without mild analgesics, the risk that bromocriptine may cause a serious adverse effect in a postpartum woman is unacceptable. Accordingly, the Director concludes 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. 43347, 43351 (Aug. 24, 1994).

Plaintiffs contend that this statement by the The methodology employed by a government agency "results from the preventive perspective that the agencies adopt in order to reduce public exposure to harmful substances. The agencies' threshold of proof is reasonably lower than that appropriate in tort law, which traditionally makes more particularized inquiries into cause and effect and requires a plaintiff to prove that it is more likely than not that another individual has caused him or her harm."

Mitchell v. Gencorp, Inc., 165 F.3d 778, 783 n. 3 (10th Cir.1999) (quoting Allen v. Pennsylvania Eng'g Corp., 102 F.3d 194, 198 (5th Cir.1996)). In this case, the lower standard is reflected in the FDA's August 24, 1994, order itself. The August 24 order fails to state affirmatively that a connection exists between bromocriptine and the type of injuries suffered in these cases. Instead it states that the evidence received by the FDA only "calls into question bromocriptine's safety," that bromocriptine "may be an additional risk factor in patients who are already at risk for seizures and stroke," and that the FDA had obtained new evidence "suggesting that therapeutic use of bromocriptine for the prevention of physiological lactation may lead to serious adverse experiences ...." 59 Fed.Reg. 43348, 43351 (Aug. 24, 1994) (emphasis added). This language does not suggest that the FDA concluded that bromocriptine causes seizures and stroke. It merely indicates that in light of the limited social utility of bromocriptine for suppression of lactation, the availability of alternative therapy, and reports of possible adverse effects, the drug should no longer be used for that indication. As the federal districts courts in Hollander v. Sandoz Pharmaceuticals Corp., 95 F.Supp.2d 1230, 1234 n. 9 (W.D.Okla.2000), and Glastetter v. Novartis Pharmaceuticals Corp., 107 F.Supp.2d 1015, 1036 (E.D.Mo.2000) noted, the FDA's decision was motivated not simply by concerns with bromocriptine, but also by the relative risks and benefits of available alternatives. Accordingly, Plaintiffs' reliance on this FDA action to show reliability is insufficient to satisfy the requirements of Daubert.

F. ANIMAL STUDIES

Plaintiffs' experts also rely on animal studies to support their causation opinions. Defendant questions the reliability, or "fit," of these studies. Extrapolations

from animal studies to human beings generally are not considered reliable in the absence of a credible scientific explanation of why such extrapolation is warranted. Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1410 (D.Or.1996); see also Turpin v. Merrell Dow Pharmaceuticals, Inc., 959 F.2d 1349, 1360 (6th Cir. 1992) (excluding testimony where the record failed to make clear how animal studies were sufficient to show that Bendectin causes birth defects); Richardson v. Richardson-Merrell, Inc., 857 F.2d 823, 830 (D.C.Cir. 1988) (excluding animal studies of Bendectin because of the overwhelming body of contrary epidemiological evidence and the admissions of the expert that animal studies merely raise a suspicion of causation in humans); Lynch v. Merrell-National Labs., 830 F.2d 1190, 1194 (1st Cir.1987) (excluding animal studies of Bendectin in the absence of significant confirmatory epidemiological data); Viterbo v. Dow Chemical Co., 826 F.2d 420, 424 (5th Cir.1987) (excluding evidence where there was only a single animal study and it showed a link to a disease completely different than plaintiff's diseases). The use of animal studies to prove causation in human beings has two distinct disadvantages. Reference Manual at 346. First, extrapolating from animals to humans is difficult because "differences in absorption, metabolism, and other factors may result in interspecies variation in responses." Id.; (Transcript of Daubert Hearing, at 19 (recounting Dr. Dukes' statement that with animal studies "you don't really know what that means in the living subject")). Second, "the high doses customarily used in animal studies requires consideration of the dose-response relationship and whether a threshold no-effect dose exists." Reference Manual, at 346; (Transcript of Daubert Hearing, at 255-57 (stating Dr. Kulig's agreement that these two disadvantages exist and limit the reliability of animal studies)). To ensure that the expert's conclusion based on animal studies is reliable, there must exist "a scientifically valid link between the sources or studies consulted and the conclusion reached." Cavallo v. Star Enterprise, 892 F.Supp. 756, 762 (E.D.Va.1995), aff'd in part, rev'd in part on other grounds, 100 F.3d 1150, (4th Cir.1996).

A few courts have been more amenable to the use of animal studies in proving causation, at least pre-Daubert. See In re Paoli R.R. Yard PCB Litig., 916 F.2d 829, 853-54 (3d Cir.1990) (questioning exclusion of animal studies by district court); Villari v. Terminix Int'l, Inc., 692 F.Supp. 568, 571 (E.D.Pa.1988) (allowing testimony based on animal studies because "a substantial portion of the scientific community relies on animal studies of this type in assessing health risks to humans"); Marder v. G.D. Searle & Co., 630 F.Supp. 1087, 1094 (D.Md. 1986) ("There is a range of scientific methods for investigating questions of causation--for example, toxicology and animal studies, clinical research, and epidemiology--which all have distinct advantages and disadvantages."), aff'd, Wheelahan v. G.D. Searle & Co., 814 F.2d 655 (4th Cir.1987). Nevertheless, the basic requirement remains: there must exist a reliable scientific explanation of why such extrapolation is warranted. Summarizing, as Judge Nangle has written:

> Although some courts have recognized the relevance of animal studies, in some toxic tort cases, they have tended to view such studies with suspicion, and several courts have specifically held that animal studies alone cannot prove causation in humans. "[Animal studies], singly or in combination, do not have the capability of proving causation in human beings in the absence of any confirmatory epidemiological data." One court has gone so far as to hold that animal studies "are of so little probative force and are so potentially misleading as to be inadmissible. They cannot be the predicate for an opinion under Rule 703." Nothing in the record persuades this Court to depart from the precedent set in Georgia federal district courts as well as in other circuits by viewing animal studies favorably.
>
> Bell v. Swift Adhesives, Inc., 804 F.Supp. 1577, 1579-80 (S.D.Ga. 1992) (citations omitted). After careful review of the animal studies at issue in this case, the Court concludes that Plaintiffs have not met the necessary standard for reliability.

There are basically three animal studies relied upon by Plaintiffs as evidentiary support for their theory that Parlodel(r) causes hemorrhagic strokes. These studies are (1) a Sandoz study conducted on the hind limb of a dog to determine bromocriptine's vasoconstrictive properties (Plaintiffs' Ex. 113); (2) a Sandoz study that assessed the effect of bromocriptine on the carotid artery of three mongrel dogs (Plaintiffs' Ex. 191); and (3) a group of Sandoz studies performed on pithed animals (Plaintiffs' Exs. 18, 19, 20, 21 & 210). As shown below, however, none of these studies establish that Parlodel(r) causes stroke in humans--or even in animals, for that matter. Even Dr. Kulig stated that he "wouldn't make the leap to stroke." (Transcript of Daubert Hearing, at 254 (emphasis added)). Furthermore, all of these animal studies have methodological flaws that prevent any conclusion that they "fit" with Plaintiffs' causation theory.

The Bertholet and Sutter study of the "hind-limb" of a dog (Plaintiffs' Ex. 113) attempted to determine, by injecting bromocriptine into the hind limb

of a dog, whether bromocriptine acts as a vasoconstrictor and, if so, at what point vasoconstriction takes place. Some of the experts in this case refer to this study as the "inversion point study" since it sought to determine at what vascular resistance bromocriptine changes, or "inverts," from a vasodilator to a vasoconstrictor. Plaintiffs contend that the study shows that Parlodel(r) is a vasoconstrictor. They admit, though, that the study does not demonstrate that Parlodel(r) causes stroke. (Transcript of Daubert Hearing, at 259.) The study also suffers from numerous other methodological flaws that raise serious questions about its reliability. First, the study did not attempt to measure any effects in the dog's cerebral blood vessels. Second, while not dispositive,

it is noteworthy that the drug caused vasoconstriction at 1,250 times the human dosage of bromocriptine. One could not possibly achieve this blood level in a human. (Transcript of Daubert Hearing, at 342.) Third, Plaintiffs' experts admit that they "do not know how the dog's hind limb artery resistance compares to a human's hind limb artery resistance." (Transcript of Daubert Hearing, at 260.) Fourth, Plaintiffs cannot say whether dogs and humans have similar inversion points or even whether humans have inversion points at all. (Transcript of Daubert Hearing, at 261.) Consequently, the Court must conclude that this study is not sufficiently reliable to make up for the absence of epidemiological studies.

The "carotid artery" study (Plaintiffs' Ex. 191) attempted to determine the effects of bromocriptine on the carotid artery of a dog. Plaintiffs emphasize that the study concluded that bromocriptine is capable of increasing vascular resistance by 177 percent. (Transcript of Daubert Hearing, at 157-58.) Plaintiffs contend that this fact clearly establishes that bromocriptine is a vasoconstrictor. Plaintiffs' experts, however, admit that this study does not demonstrate that bromocriptine causes stroke. (Transcript of Daubert Hearing, at 262.) The most they can say is that

a drug that can cause vasoconstriction of the carotid artery should be "high on the suspicious drug list" for causing stroke. (Transcript of Daubert Hearing, at 262.) Suspicion, however, does not constitute the reasonable degree of medical certainty required to establish prima facie causation. Additionally, Defendant has provided a very persuasive argument that this study is of limited significance. According to Defendant, the study shows only that vascular resistance increased, not that blood vessels constricted or dilated. Any number of other factors could have caused the change in blood flow. Simply put, a change in resistance may occur regardless of a change in the artery. Analogizing to decreased pressure that one might experience in the shower when additional water faucets are turned on, Defendant's expert Dr. Engelman explained how in the carotid artery study the dog's cardiac output already was rapid, blood pressure dropped, and consequently the flow into the carotid artery dropped, resulting in an increase in resistance. Dr. Engelman convincingly explained that Plaintiffs' experts' simply conclude that the increase in resistance was caused by vasoconstriction, but that was not necessarily the case at all. All anyone really knows is that there was an increase in resistance in the study. The reason is unknown. That vasoconstriction occurred is simply a hypothesis, not an actual scientific finding.

Furthermore, Defendant noted that the flow probe in the study was placed only at the common carotid artery before it branches, with one branch going to the brain and the other going to the rest of the head. Consequently, there was no way for the researchers to measure the flow in either of these two branches. Dr. Engelman explained that typically when blood pressure falls, the body seeks to preserve blood flow to the heart and the brain. One, therefore, would have expected in this study for the carotid artery branch to the rest of the head to have contracted to preserve blood flow to the brain via the other branch. Because of the manner in which the carotid artery study was conducted, there is no way to determine whether vasoconstriction occurred whatsoever in the branch to the brain. (Transcript of Daubert Hearing, at 335-41.) In short, the carotid artery study appears so flawed that it cannot be said to provide scientific knowledge on the effect of blood flow to the brain in dogs, much less humans.

Plaintiffs also contend that a number of studies conducted on pithed animals (Plaintiffs' Exs. 18, 19, 20, 21 & 210) show that bromocriptine can cause severe vasoconstriction. Pithed animals have had their central nervous system obliterated. The pithed animal studies at issue include rats, mice, dogs, cats and rabbits. Plaintiffs argue that vasoconstriction in these experiments was so severe that the tails of rats and mice became deprived of blood and fell off, as did the ear margins of dogs. Nevertheless, Plaintiffs' experts admit that they do not know whether these tests are predictive of human outcomes. (Transcript of Daubert Hearing, at 265.) It also is true that pithing an animal causes dramatic effects that otherwise would not be seen. As Defendant's expert, Dr. Engelman, testified, a pithed animal is one in which the brainstem is destroyed by inserting a probe or needle into the foramen magnum (the hole at the back, lower portion of the skull)

and then moving the probe back and forth and up and down until the lower portion of the brain has been destroyed. This portion of the brainstem is the area where regulatory reflexes control the body's

cardiovascular system. Consequently, destroying this regulatory mechanism renders an animal extremely sensitive to any change in blood pressure. Any drug that might affect blood pressure, whether to increase or decrease it, will thus magnify that change tremendously. (Transcript of Daubert Hearing, at 334.) Plaintiffs' expert, Dr. Dukes, has written that "[a]nimal studies can sometimes prove embarrasingly [sic] misleading, even where matters as serious as effects on pregnancy ... are concerned." M.N.G. Dukes et al., Responsibility for Drug-Induced Injury: A Reference Book for Lawyers, the Health Professions and Manufacturers 38 (2d ed. 1998). The methodology of using pithed animals to determine cardiovascular effects such as blood pressure seems less than reliable. Given the possible magnifying effects of pithing on blood pressure, the pithed animal studies are of limited, if any, utility. Because causation must be based on scientific knowledge allowing for a reasonable degree of medical certainty rather than mere "leaps of faith," the Court must conclude that the animal studies do not assist Plaintiffs in satisfying the requirements of Daubert.

G. LEARNED TREATISES

Plaintiffs also rely on a number of medical treatises that they contend support their causation theory. Plaintiffs cite medical treatises stating the following:

(1) "In the Physician's Desk Reference ... there is well-documented evidence of strokes in women receiving bromocriptine for postpartum breast milk suppression ...." M.D.B. Stephens, ed., Detection of New Adverse Drug Reactions 383.

(2) "Drug interactions and use after pregnancy can induce life-threatening responses," "[s]evere HT [hypertension] with stroke has been reported after use for suppression of lactation," and "[a] possible early identifying symptom in patients who are at risk for severe reaction to bromocriptine in the postpartum period is headache, which may occur hours to days before the development of hypertension, seizures, stroke, or myocardial infarction." Williams & Wilkins Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning 26 tbl. 1-34, 867 & 868.

(3) "Adverse effects [for bromocriptine] which occur more rarely, but which are serious ... include unusual and continuing headache, vision changes, seizures, or strokes." USP, Material Safety Data Sheet (1995).

(4) "Many postpartum patients who developed stroke and/or seizures in association with bromocriptine therapy complained of constant and often progressively severe headaches hours to days prior to the acute event." American Hospital Formulary Service Drug Information 2560 (1995).

These excerpts from the treatises, however, do not provide sufficient support for Plaintiffs' causation theory. The statements in the treatises are clearly based on case reports and, therefore, provide no more support than the case reports themselves. See Glastetter v. Novartis Pharms. Corp., 107 F.Supp.2d 1015, 1034 n. 18 (E.D.Mo.2000) ("Indeed, as defendant notes, all the texts, treatises, and journals cited by plaintiffs appear based upon the accumulated case reports or individual case reports. The Court does not believe that texts and treatises that draw an 'association' between Parlodel and vasoconstriction based upon case reports make such texts and treatises any more reliable than the case reports on which they rely."). They do not add any additional scientific knowledge. For example, the statement in Ellenhorn's Medical Toxicology that bromocriptine use after pregnancy can cause "life threatening responses" cites as authority a journal article authored by Dr. Kulig, Bromocriptine-associated headache: Possible life-threatening sympathomimetic interaction, 78 Obstetrics and Gynecology 941-43 (1991) (Plaintiffs' Ex. 516). This article is nothing more than a case report. Additionally, the Court notes that one of the treatises that discusses bromocriptine but fails to state that the drug causes stroke is Meyler's Side Effects of Drugs, which is edited by Plaintiffs' expert Dr. Dukes. In any event, the Court concludes that Plaintiffs' reliance on learned treatises is insufficient to make up for the lack of reliable epidemiological studies. To the extent that the court reached a different conclusion in Globetti v. Sandoz Pharmaceuticals Corporation, 111 F.Supp.2d 1174 (N.D.Ala.2000), this Court finds it unpersuasive and contrary to the weight of authority.

H. TOTALITY OF THE EVIDENCE

Plaintiffs have produced an enormous mass of evidence about Parlodel(r). Prior to Daubert, the Court in all likelihood would have said that it is the function of the jury to evaluate the relevance and reliability of Plaintiffs' expert testimony. The command of Daubert, however, is that scientific testimony must be based upon scientific methodology. In concluding that Parlodel(r) causes seizures and hemorrhagic strokes, Plaintiffs' experts have not relied upon reliable scientific methodology. This would be a different case if there was at least some support for the causal hypothesis in the peer-reviewed epidemiological literature, a predictable chemical mechanism, general acceptance in learned treatises and other scientific literature of a causal relationship, a plausible animal model, and dozens of well-documented case reports involving postpartum

women with no other risk factors for stroke. In such a case, the totality of the evidence would be enough to satisfy the demands of Daubert. In this case, no epidemiological studies support Plaintiffs' causation theory. Plaintiffs have not established that all ergot alkaloids cause vasoconstriction and strokes. Although the FDA has removed its indication of Parlodel(r) for postpartum lactation, this decision was based upon a risk-utility analysis rather than a finding using scientific methodology that Parlodel(r) causes strokes. The standard by which the FDA deems a drug harmful is much lower than is required in a court of law. The FDA's lesser standard is necessitated by its prophylactic role in reducing the public's exposure to potentially harmful substances. The animal studies that Plaintiffs rely on do not "fit" because the reliability of extrapolating them to the human situation has been forcefully and effectively challenged by Defendant. The excerpts from learned treatises that Plaintiffs cite are merely based on case reports and, therefore, provide no more assistance than the case reports themselves. The case reports do not establish that Parlodel(r) causes hemorrhagic stroke in postpartum women. Additionally, case reports do not establish general causation. In short, none of the types of evidence that Plaintiffs offer- - individually or collectively--establish a prima facie case that Parlodel(r) causes stroke. Cf. Wells v. Ortho Pharm. Corp., 788 F.2d 741, 744 (11th Cir.1986) ("Plaintiffs presented several epidemiological studies that indicated an association between spermicide use and deleterious effects on the fetus."). As Plaintiffs' expert, Dr. Dukes, has written, one cannot lump together lots of hollow evidence in an attempt to determine what caused a medical harm. (Transcript of Daubert Hearing, at 67 (recounting statement in Dr. Dukes' book Responsibility for Drug-Induced Injury)). Dr. Dukes has also stated that the "culmination of elements of evidence will clearly only lead to a valid result if the various elements of proof which are brought together each have some individual validity in and among themselves." Id.

Plaintiffs' causal chain also is seriously flawed. The chain of Plaintiffs' argument is that Parlodel(r)'s active ingredient is bromocriptine, which is an ergot alkaloid, and ergot alkaloids are a class of drugs that can cause hypertension, seizures and ischemic strokes and, therefore, likely cause hemorrhagic strokes. Three scientifically unwarranted "leaps of faith" exist in this causal chain. First, a serious question exists whether bromocriptine is like other ergot alkaloids since it generally causes hypotension rather than hypertension. Second, even if Parlodel(r) can occasionally cause hypertension, Plaintiffs have not established that it can cause hypertension so severe as to cause seizures and stroke in humans. Third, even if Parlodel(r) can cause hypertension severe enough to cause stroke in humans, Plaintiffs have not shown that it causes hemorrhagic stroke. Plaintiffs have identified no epidemiological or animal studies, or even case reports, where Parlodel(r) was deemed to have caused a hemorrhagic stroke. Additionally, all medical evidence presented in this case on other ergot alkaloids establishes only that they may cause ischemic stroke. As discussed, ischemic strokes and hemorrhagic strokes are distinct and have different modi operandi. Ischemic strokes are caused by a reduction in blood flow to the brain. Hemorrhagic strokes are caused by a rupture to a blood vessel in the brain. Perhaps there is a reasonable extrapolation of ischemic strokes to hemorrhagic strokes, but Plaintiffs never fully explained it on their own or even when the Court raised the issue during the Daubert hearing.(Transcript of Daubert Hearing, at 39, 85, 165-66.) As Judge Becker of the Third Circuit has explained, expert testimony must be supported by "good grounds" at each step of the causal chain; and any step that renders their analysis unreliable also renders the testimony inadmissible. In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 745 (3d Cir.1994). In this case, "there is simply too great an analytical gap between the data and the opinion proffered." General Electric Co. v. Joiner, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997).

In short, Plaintiffs' case is not based on reasonable medical certainty, or "probabilities." It instead is based merely on "possibilities." This fact is vividly shown by the following exchange:

Q: Is it your opinion to a reasonable probability that Parlodel caused seizures in the case of Ms. Siharath?
A: No, I [Dr. Kulig] just said it was a possibility. I didn't want to rule it out.
(Transcript of Daubert Hearing, at 267.)

The inability of Dr. Kulig--as well as Plaintiffs' other experts--to answer this question in the affirmative requires this Court to exclude the experts' testimony and grant summary judgment in favor of Defendant. Experts must do something more than just "rule out" other possible causes. They must explain how they were able to "rule in" the product in question. If all an expert does is rule out other possible causes, he or she may fail to account for other potential (and sometimes unknown or unthought of) causes. When an expert only rules out causes, the trier of fact knows only what did not cause the harm. This does not necessarily aid the trier of fact in determining what did cause the harm-- and that is what the law requires in tort cases, especially those

that involve allegedly toxic products.

As Defendant's expert, Dr. Buchholz explained at the Daubert hearing, doctors every day seek to determine causes of injury and illness and make patients healthier. In their eternal quest for "the answer," however, doctors sometimes believe that they have found a cause when they have not necessarily done so. Doctors in their day-to-day practices stumble upon coincidental occurrences and random events and often follow human nature, which is to confuse association and causation. They are programmed by human nature and the rigors and necessities of their clinical practices to conclude that temporal association equals causation, or at least that it provides an adequate proxy in the chaotic and sometimes inconclusive world of medicine. This shortcut aids doctors in their clinical practices because their most important objective day-to-day is to help their patients and "first, do no harm," as their Hippocratic oath requires. Consequently, "[t]hey make a leap of faith. And then in retrospect they build a bridge constructed of other anecdotal evidence, in some cases totally unrelated about heart attacks in older men and things like that and animal data, a bridge to help lead others across the chasm." (Transcript of Daubert Hearing, at 429.) The Court does not question Dr. Kulig's honest conviction that Parlodel(r) causes stroke or think that he is deliberately peddling "junk science." The Court also does not question that the methodology Dr. Kulig discussed at the Daubert hearing serves him well every day in the clinical practice of medicine. Dr. Kulig obviously is an exceptionally qualified practitioner, and the Court found him to be a very credible witness in this regard. Unfortunately, his clinical impression is not the sort of scientific methodology that Daubert demands.

Basically, Plaintiffs seek to survive Defendant's Motions to Exclude and for Summary Judgmentby emphasizing that they have employed the same methodology as is applied by doctors throughout the world in their clinical practices. Plaintiffs argue that they have used the best methodology available for this case. That may be so, but their methodology does not satisfy the requirements of Daubert. They have not provided sufficient, reliable scientific evidence to support a jury finding of legal causation. As Dr. Bucchholz explained:

I make clinical decisions all the time in the practice of medicine, Your Honor. I'm forced to because I have to take care of patients who are sick, and I have to decide what I think is going on, which most of the time I can't do based on scientific evidence because it doesn't exist or epidemiologic data because they don't exist.

So I make a judgment, a clinical decision about causation based on what's the background incidence of what just happened? Because if it's more than negligible, then any association may well be by chance. What's the plausible mechanism? It helps to have a mechanism. The more detailed and specific, the better. What's the quality of the case reports or clinical experience, not just the quantity, but the quality in terms of how specific is the association? How consistent is the association?

Does the--do the individual cases suggest that this mechanism that I might postulate has actually played out? Is there evidence of mechanism working along the way? And then finally, you have to do a differential diagnosis. What are the other possible explanations realizing in that differential that there is a large number of situations like stroke where you are going to wind up with an indeterminate diagnosis.

That is clinical decision making that I go through on a routine basis, but it is not scientific methodology.
Scientific methodology involves formulating a question or hypothesis and then testing it in such a way as to minimize bias in its founding, enabling a statistical analysis, publishing that if you can get it published through peer review, others replicating or refuting it. That's the type of process, that's not what I do as a doctor in formulating conclusions on causation in a daily basis.

(Transcript of Daubert Hearing, at 396-97 (emphasis added).)

Plaintiffs' counsel and their expert witnesses have done the best they could with the data available from the scientific literature and the Defendant's internal studies. If Daubert established a "best efforts" test, they unquestionably would have passed that test. Nevertheless, it appears that their "testimony is based more on personal opinion than on scientific knowledge." Allison v. McGhan Med. Corp., 184 F.3d 1300, 1319 (11th Cir. 1999). To steal a phrase from Judge Jones, their opinions are "educated guesses dressed up in evening clothes." Hall v. Baxter Healthcare Corp., 947 F.Supp. 1387, 1407 (D.Or.1996). To the extent that the court in Globetti v. Sandoz Pharmaceuticals Corporation, 111 F.Supp.2d 1174, 1179 (N.D.Ala.2000) held that Daubert is satisfied by presenting the "best scientific evidence available as a practical matter," this Court must respectfully disagree. Daubert demands reliable and relevant scientific opinion based upon reliable scientific methodology rather than mere "subjective belief or unsupported speculation." Allison,

184 F.3d at 1319, n. 23. The ultimate conclusion of the Court is that no expert can express such an opinion given the current state of scientific knowledge about Parlodel(r) and stroke.

Finally, the Court should not be too eager to make leaps of faith from a pharmaceutical manufacturer's basic research. Defendant continually researched whether an association exists between Parlodel(r) and hypertension, seizures, myocardial infarctions, and strokes. It attempted to determine whether the correlation of these conditions and Parlodel(r) use was a causal occurrence or rather only a chance occurrence. They never were able to establish causation. If this Court were to lower the Daubert standard based on anecdotal, temporal evidence obtained from Sandoz case reports, unfounded extrapolations, and leaps of faith, the Court would create an unintended disincentive for pharmaceuticals companies to engage in ongoing research as to their products' safety and efficacy. Such an "ostrich in the sand" approach would in the long run make pharmaceutical products more risky, not safer.

In an attempt to prohibit the presentation of "junk science" to the trier of fact, perhaps Daubert has raised the bar for admissibility of expert testimony too high. Maybe there should be a middle ground between the Daubert standard and a standard that would allow sympathetic plaintiffs with catastrophic injuries to recover against pharmaceutical manufacturers based upon nothing more than speculation and conjecture. It is not, however, for this Court to seek that middle ground. This Court's duty is to apply the law as it exists today. And Daubert requires reliable science to support scientific opinion. "Striking the appropriate balance may sometimes be a difficult task." Allison, 184 F.3d at 1321. In some cases, no reliable science exists. Unfortunately for Plaintiffs, it appears to the Court that this is one of those cases. As Judge Posner has written, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996). A court cannot determine causation in a case such as this one until science has done so. "Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly." See Allison, 184 F.3d at 1322 (11th Cir.1999) (quoting Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 597, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993)). That Parlodel(r) can and did cause the Plaintiffs' strokes "is not a natural inference that a juror could make through human experience." Allison, 184 F.3d at 1320. "Thus, medical expert testimony was essential to prove causation in this case." Id. Consequently, the Court must grant Defendant's Motions to Exclude and for Summary Judgment as to the Plaintiffs' negligence and strict liability claims.

IV. CONCLUSION

For the reasons set forth above, the Court in Siharath GRANTS Defendant's Motion to Exclude and for Summary Judgment on Issues of Medical Causation Under Daubert v. Merrell Dow Pharmaceuticals, Inc. [Doc. 68], DENIES AS MOOT Defendant's Motion for Partial Summary Judgment on Warning Claims [Doc. 69-1], DENIES AS MOOT Defendant's Motion for Partial Summary Judgment on Fraud and Negligent Misrepresentation [Doc. 69-2], DENIES AS MOOT Defendant's Renewed Motion for Summary Judgment on the Statute of Limitations [Doc. 69-2], DENIES AS MOOT Defendant's Motion for Oral Argument on its Renewed Motion for Summary Judgment on the Statute of Limitations [Doc. 126], DENIES AS MOOT Defendant's Motion for Leave to Amend its Answer to Plead Federal Preemption [Doc. 133-1], DENIES AS MOOT Defendant's Motion for a Briefing Schedule [Doc. 133-2], and DENIES AS MOOT Defendant's Motion for Oral Argument on its Federal Preemption Defense [Doc. 133-3]. The Clerk is directed to enter judgment for the Defendant.

Similarly, the Court in Rider GRANTS Defendant's Motion to Exclude and for Summary Judgment on Issues of Medical Causation Under Daubert v. Merrell Dow Pharmaceuticals, Inc. [Doc. 116], DENIES AS MOOT Defendant's Motion for Partial Summary Judgment on Warning Claims [Doc. 117-1], DENIES AS MOOT Defendant's Motion for Partial Summary Judgment on Fraud and Negligent Misrepresentation [Doc. 117-2], DENIES AS MOOT Defendant's Motion for Leave to Amend its Answer to Plead Federal Preemption [Doc. 177-1], DENIES AS MOOT Defendant's Motion for a Briefing Schedule [Doc. 177-2], and DENIES AS MOOT Defendant's Motion for Oral Argument on its Federal Preemption Defense [Doc. 177-3]. The Clerk is directed to enter judgment for the Defendants.

Opinion Footnotes:

FN1. For convenience, the company and its subsidiaries named in Rider will be referred to as "Defendant."

FN2. The case was assigned to the undersigned on May 19, 2000.

FN3. This action also was assigned to the undersigned on May 19, 2000.

FN4. Without reasonable time limits, the hearing would have been completely unmanageable due to the volume of documents and potential testimony. The time limits focused the experts and the attorneys upon what was important. The Court is convinced that it has as good (if not a better) understanding of the issues after three intense days than it would have if the hearing had lasted three months. The time allocated for the hearing was used efficiently because no evidentiary objections were allowed. See Federal Rules of Evidence 104(a) ("Preliminary questions concerning the qualification of a person to be a witness ... shall be determined by the court, subject to the provisions of subsection (b). In making its determination it is not bound by the rules of evidence except those with respect to privileges.").

Siharath v. Sandoz. Pharms. Corp., 131 F.Supp. 2d 1347