IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF ILLINOIS

ALISA ANN CARAKER and
KEITH ALLEN CARAKER,

Plaintiffs,

v.

SANDOZ PHARMACEUTICALS CORP.
and SANDOZ AG,

Defendants

Case No. 96-CV-411-DRH

MEMORANDUM OPINION AND ORDER

Before this Court is Sandoz' motion *in limine* to exclude the testimony of the plaintiffs' experts, Drs. Kulig and Petro. (Doc. 212).

On September 12, 2001, following a two-day *Daubert* hearing, this Court issued a preliminary order granting Sandoz' motion to exclude the plaintiffs' experts' causation testimony [Doc. 316] Upon a full consideration of the testimony, exhibits and arguments of the parties, the Court hereby issues its final order. For the reasons discussed below, the defendant's motion to exclude the plaintiffs' expert causation testimony is granted.

BACKGROUND

This is a products liability case that involves the drug Parlodel. Parlodel is manufactured by Defendant Sandoz Pharmaceutical Corporation--now known as Novartis Pharmaceutical Corporation and Sandoz A G. ("Sandoz")

The active ingredient of Parlodel is bromocriptine mesylate ("bromocriptine"). Bromocriptine is derived from ergot, a naturally-occurring fungus that grows on the rye plant. Drugs derived from ergot are known as ergot alkaloids Bromocriptine differs structurally and physically from the other ergot alkaloids in that a bromine atom has also been added Bromocriptine prevents lactation from occurring by blocking the secretion of the hormone prolactin, which acts on the breasts to induce the secretion of milk

In 1980, the Food and Drug Administration ("FDA") approved Parlodel to be used to prevent postpartum lactation in women who could not or elected not to breast-feed. Fourteen years later, on August 18, 1994, the defendant withdrew the Parlodel indication for prevention of physiologic lactation after receiving notice that the FDA would be filing a notice of opportunity and hearing to withdraw Parlodel for that indication Parlodel remains approved for various other indications (e g , Parkinson's Disease, amenorrhea, and acromegaly). For the prevention of physiologic lactation ("PPL"), Parlodel was typically prescribed for fourteen days with a prescribed dosage of 5 mg per day, taken in two 2.5 mg. doses.[1]

On the evening of May 9, 1988, after an uneventful pregnancy, 24-year-old Alisa Caraker delivered her infant via a normal and uneventful cesarean section. The next day, May 10, Mrs Caraker began taking Parlodel, prescribed at 2.5 mg. twice per day for 14 days because she had elected not to breast feed On May 11, while still in the hospital, Mrs. Caraker reported developing headaches. During her hospitalization, she also experienced some transient (temporary, passing away with time) elevated blood pressure. On May 13, Mrs. Caraker was

[1]When this Court refers to Parlodel, it is simply referring to bromocriptine in its therapuetic dosage for the PPL indication.

discharged in good health, but, after returning home, Mrs. Caraker's headaches progressively became much worse

On May 15, six days postpartum, still on Parlodel, Mrs. Caraker returned to the Carbondale Hospital with a severe headache, hypertension, and neurologic symptoms. That day, a CT scan (a method of examining the body's soft tissues using X-rays) revealed a large, left-sided intracerebral hematoma ("ICH") due to intracerebral hemorrhaging. On May 16, 1998, Mrs. Caraker was transferred to St. Francis Medical Center where she underwent brain surgery to remove the hematoma blood clot and stop the bleeding

The plaintiffs filed their complaint on March, 25, 1996, claiming that Parlodel is an unreasonably dangerous and defective product. Specifically, they allege that (1) in May of 1988, Ms. Caraker took Parlodel PPL; (2) after taking Parlodel, Ms. Caraker suffered an ICH; and (3) Ms. Caraker's ingestion of Parlodel caused her stroke The Carakers claim damages for their resulting injuries.[2]

To show that Parlodel caused Mrs. Caraker's stroke, the plaintiffs rely on the testimony of Toxicologist Kenneth Kulig and Neurologist Denis Petro Together, they testify that a causal relationship exists between Mrs. Caraker's ingestion of Parlodel and her stroke.

The defendants moved to exclude the testimony of Drs Kulig and Petro on the grounds that it is not sufficiently reliable. This Court ordered the parties to file briefs, detailed witness affidavits and all the relevant exhibits. After reviewing this extensive amount of information, this Court conducted a two-day *Daubert* hearing, at which both sides had the opportunity to

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[2]Mr. Caraker has asserted a loss of consortium claim.

present their best streamlined case for or against admissibility. *See Sharath v. Sandoz Pharmaceuticals Corp*., 131 F.Supp 2d 1347, 1350 n.4 (N.D. Ga. 2001)

DISCUSSION

The admissibility of plaintiffs' expert evidence is governed by, *inter alia*, Federal Rule of Evidence 702 – as interpreted by *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 (1993), and its progeny.[3]

The plaintiffs had the burden of showing two things. First, they had the burden of showing that their experts' opinions were reliable. The hallmark of this reliability prong is the scientific method, *i.e.*, the generation of testable hypotheses that are then subjected to the real world crucible of experimentation, falsification/validation, and replication. *See Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579, 593 (1993). Second, they must show that their experts' opinions "fit" (*i.e.*, have a valid scientific connection to) the issues in this lawsuit so as to assist the fact-finder in understanding the evidence. *See Daubert*, 509 U.S. at 590-92 & n.9.

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[3] Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

"[T]he adjective 'scientific' implies a grounding in the methods and procedures of science," and "the word 'knowledge' connotes more than subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 589-90. Thus, the court must determine whether the evidence "is genuinely scientific, as distinct from being unscientific speculation offered by a genuine scientist." *Rosen v. Ciba-Geigy Corp*., 78 F.3d 316, 318 (7th Cir. 1996).

This requirement is not satisfied when there is "simply too great an analytical gap between the data and the opinion proffered." *General Elec. Co v Joiner*, 522 U S. 136, 138 (1997).

The district court is not required to simply "tak[e] the expert's word for it." *Advisory Committee Notes to 2000 Amendments to Rule 702* (citing *Daubert v Merrell Dow Pharmaceuticals, Inc.*, 43 F.3d 1311, 1319 (9th Cir. 1995)) Instead, district courts must rigorously scrutinize (1) the sufficiency of the data upon which the expert relies, (2) the reliability of the principles and methods the expert employs, and (3) the reliability of the expert's application of the principles and methods to the facts of the case. *See* Fed. R. Evid. 702.

Focusing on the three items enumerated in Rule 702, district courts must determine whether the expert's opinion "is genuinely scientific [or] unscientific speculation offered by a genuine scientist." *Rosen v. Ciba-Geigy Corp* , 78 F 3d 316, 318 (7th Cir. 1996) (noting that "an insightful, even an inspired, hunch" is insufficient). This so-called "gatekeeper" function requires that the district court separate "expert opinion evidence based on 'good grounds' from subjective speculation that masquerades as scientific knowledge." *Glastetter v Novartis Pharmaceuticals Corp* , 252 F.3d 986, 989 (8th Cir 2001)

In this case, Drs. Kulig and Petro testified that (1) Parlodel can cause ICH in general; and (2) Parlodel caused Ms Caraker's ICH specifically. To reach their opinions, they each rely on a differential diagnosis methodology, a methodology that involves "ruling in" potential causes to develop a potential-cause checklist and then "ruling out" potential causes one by one based on objective data and criteria. Causation is attributed to the last potential cause left on the list, or at least the most probable one if there are two left The methodology, in the abstract, has been

considered sound, *see Glastetter*, 252 F 3d at 989; *cf. Cooper v. Carl A Nelson & Co* , 211 F.3d 1008, 1019 (7th Cir. 2000), but when it is used in the practice of science (as opposed to its use by treating physicians in the practice of medicine out of necessity) it must *reliably* "rule in" a potential cause. *See Glastetter*, 252 F.3d at 989. Thus, if the "ruling in" step is based on too great an analytical leap (or several such leaps), the whole opinion is questionable. *See Advisory Committee Notes to 2000 Amendments to Rule 702* ("any step that renders the analysis unreliable . renders the expert's testimony inadmissible")

To "rule in" Parlodel on their differential diagnoses, the plaintiffs' experts postulate their theory: (1) Parlodel causes arteries to constrict (*i e* , vasoconstriction) either in general or when the patient has a low vascular tone specifically; (2) vasoconstriction can elevate blood pressure, (3) high blood pressure is a recognized risk factor for ICHs, (4) Parlodel causes (or can cause) ICH, especially in postpartum women who would expect to normally have low vascular tone immediately after delivery *Cf Glastetter*, 252 F 3d at 989 (outlining methodology of Drs Kulig and Petro); *Sharath v. Sandoz Pharmaceuticals Corp.*, 131 F.Supp 2d 1347, 1354-55 (N.D. Ga. 2001) (outlining methodology of plaintiffs' experts including Drs. Kulig and Petro).

In support of their premise that Parlodel causes vasoconstriction, the plaintiffs' experts point to several kinds of evidence: (1) epidemiological data, (2) case reports, (2) human dechallenge/rechallenge data, (3) animal studies, (4) an ergot-alkaloid inference, (5) medical texts, (6) Sandoz documents, and (7) FDA actions While admitting most of this data, individually, would not show that Parlodel causes ICH, they insist on being 90% certain that

Parlodel can cause ICH after putting the pieces of the puzzle together.[4]

Generally, the problem with the opinions of Drs. Kulig and Petro is that their "ruling in" decision requires too many extrapolations from dissimilar data, too many analytical leaps and involves a loose application of purportedly objective scientific causation standards. For these and other reasons, the data these experts used to extrapolate their conclusions is suspect, and their opinions are more like personal opinions than products of any scientific methodology rigorously applied.

A. EPIDEMIOLOGICAL STUDIES

Epidemiology is the study of disease patterns and risks in human populations. "Epidemiology focuses on the question of general causation (*i.e.*, is the agent capable of causing the disease?) rather than that of specific causation (*i.e.*, did the agent cause the disease in this particular individual?)." *Reference on Scientific Evidence* 335 (Fed. Judicial Ctr. 2000).

In a typical epidemiologic study, an epidemiologist compares the health of people exposed to a substance to that of persons not so exposed to determine whether the exposure to the substance is associated with an increased rate of disease. There are essentially three types of study designs used by epidemiologists in attempting to determine whether there is an association between exposure to an agent and development of a disease: (1) randomized trial or randomized clinical trial, (2) cohort studies, and (3) case-control studies

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[4]The 90% figure is suspect and implies a 10% error rate. How Dr. Kulig arrived at this percentage, however, is uncertain. When asked about his certainty/uncertainty rate at the *Daubert* hearing, Dr. Kulig admitted that he has "never been asked [that question] before today" and confessed that he was "very hesitant to give a percentage" (Hrg. I:181).

In any epidemiological study, the first question is whether an association exists; the second is whether that association is actually a true association and not an association due to some error. *Reference on Scientific Evidence* 387 (Fed Judicial Ctr. 2000). The second step is important, because, while a causal relationship is one possible explanation for an association, an association does not necessarily mean that there is a cause-effect relationship. *See generally, id* at 348 Epidemiology cannot objectively prove causation; rather, causation is a judgment for epidemiologists and others interpreting the epidemiological data

Epidemiologic studies typically provide an estimate of "relative risk" ("RR"),[5] which is the strength of an association between exposure and disease. Relative risk is the ration of the incidence of a disease in exposed individuals to the incidence in unexposed individuals A relative risk of 1.0 means that the incidence in the groups is the same; that is, the exposure has no association with the disease. If the study is properly performed, a relative risk below 1.0 means that the exposure is associated with the absence of the disease (a negative association), whereas a relative risk significantly above 1 0 means that exposure is associated with an increased risk of the disease (positive association).[6]

If an epidemiologist finds any association (either positive or negative), he then scrutinizes the results in his particular study to determine whether that association indicates a

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[5] "Relative risk" is defined as [Incidence Rate % in Exposed] / [Incidence Rate % in Unexposed] *Reference on Scientific Evidence* 348 (Fed. Judicial Ctr 2000).

[6] If the rate of subjects developing the disease in the exposed group was 0.4 (or 40%) and the rate of subjects developing the disease in the unexposed group was 0.10 (or 10%), then the relative of 4 0 (or 400%) indicates that the RR of disease in the exposed groups is four times as high as the risk in the unexposed group.

causal relationship or is due to chance, error or bias. Similarly, a study that does not find an association may be erroneous on the same grounds.

In this case, the plaintiffs' experts generally state that the potentially relevant epidemiological studies that do exist are "fundamentally flawed" and, therefore, do not show conclusively that Parlodel either does or does not cause stroke or that the postpartum period is a risk factor for ICH by itself. Nevertheless, Drs Kulig and Petro selectively use some data from the existing epidemiological studies in support of their opinions.

Two types of epidemiological studies are relevant to this case, namely (1) Parlodel studies (*e g.*, ERI Study, the HCIA Study, the Herrings and Stricker Study), and (2) studies indicating an increased risk of stroke in the post-partum period generally (*e g* , the Kittner study, the Lanska Studies, the Within Study).

1. Parlodel Studies

The ERI Study included data from over 200,000 deliveries However, the investigators identified a total of only ten cases of women who suffered stroke, only one of whom also had been prescribed Parlodel. The resulting stroke data was not statistically significant. Hrg. I:116-22 (Kulig). Plaintiffs' experts agree that the ERI Study is not a controlled study which reliably proves a causal association between Parlodel and strok. Hrg. I:117, 120 (Kulig).

Nevertheless, while Dr. Kulig is of the opinion that the study is "horribly flawed" and "inherently unreliable," he relies on the study as "critically important" proof of causation. *Id.* at 117-18. Dr. Kulig, however, fails to address the problem of statistical significance in regards to the favorable data that he plucks from the ERI study On the other hand, Dr Petro testified that

the ERI Study was simply a "failed study," and so would not rely on it at all. *Id.* at II:342.

The HCIA Study analyzed 533,816 delivery records from 128 hospitals and tracked postpartum complications, correlating these complications with Parlodel use. HCIA, "Postpartum Complications and Parlodel, January 1, 1991 - March 31, 1994" (October 1995). Dr Kulig does not rely on the HCIA Study because it did not find any statistically significant association between Parlodel and stroke. Hrg. I:123 (Kulig)

The plaintiffs' experts also criticize and do not rely on the Herings and Stricker Study In this study, investigators compared hospital admissions and drug use to identify women who experienced stroke, hypertension, or heart attacks before, during, and after Parlodel use for the prevention of physiological lactation Herrings and Stricker, "Bromocriptine and Suppression of Postpartum Lactation," Pharmacy World & Sci. 17(4): 133-37 (1995).

The study was performed among 2,130 women of 15-44 years of age who were treated with a course of bromocriptine (median 5 0 mg for 15 days post-partum)[7] in 1990-92, and found that none of these women were admitted to the hospital for cardiovascular or cerebrovascular events. The investigators found: "None of the 2,130 women were hospitalized for ischemic heart disease, hypertension or cerebral vascular events during the index period or the two month period after discontinuance of bromocriptine use" *Id.* The investigators concluded that "[a]dverse reactions or events may . . be wrongly associated with bromocriptine use as the occurrence of these reactions might be explained by the background risk of cardiovascular manifestations

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[7]The investigators assumed that women from 15-44 taking short course of bromocriptine were pregnant, inasmuch the other indications for prescribing bromocriptine normally occur in much older women (Parkinson's disease, acromegaly, prolactinoma).

among pregnant women" *Id.*

Dr Petro criticized this study for many of the same weaknesses pointed out by the study's authors: (1) it was underpowered; (2) five subjects initiating diuretic therapy while on Parlodel may have represented subjects with emergent hypertension due to Parlodel; (3) not all emergent events were detected (*e g* , death outside a hospital); (4) high-risk patients (*e g* , patients with cardiovascular symptoms) may not have been studied; and (5) patients who discontinued Parlodel therapy due to inefficacy or adverse events (dropouts) were not included in the analysis (Petro Aff , ¶ A7(c)) (*See* Doc. 212, Dfs ' Ex 42)

2. Studies Indicating Postpartum Period Is A Risk Factor For Stroke

The plaintiffs' experts discount several studies indicating that the postpartum period is itself a high risk factor for stroke

Most notable among this group of studies is the Kittner Study. The Kittner Study analyzed the hospital discharge records of over one million female patients aged 15 to 44. The study found that "the postpartum state . . was associated with an increased risk of cerebral infarction and, particularly, intracerebral hemorrhage" (Doc. 212, Dfs.' Ex 43, p. 774). Specifically, the study reported an increased relative risk of 28.3 for intracerebral hemorrhage in the six postpartum weeks.

Dr. Petro criticized the Kittner Study on two grounds. (Petro Aff., ¶ A8(b)) (*See* Doc. 212, Dfs.' Ex 43). First, he noted that, while the study found eight ICHs, it determined causes for five of them Therefore, Dr. Petro concludes, there were really only three ICHs with indeterminate causes that would lead to a substantially lower relative risk than the study found.

Second, he noted that 79% of the ICH cases occurred among non-white women even though the majority of study population were white women. He faults the study for not recognizing that different racial groups have different rates of stroke

In this case, Drs. Kulig and Petro have generally attacked the existing epidemiological studies as fundamentally flawed, while, at the same time, selectively using data (which they admit is not statistically significant) to support their opinions.

The absence of good epidemiological support is not fatal to the plaintiff's case. This Court imposes no absolute epidemiology requirement or any other requirement, except reliability and relevance. *See Glastetter*, 252 F.3d at 992 ("The absence of epidemiological evidence did not doom [plaintiff's] case, as the district court indicated ... Of course, epidemiological evidence might have assisted [plaintiff] in establishing causation, and thus its absence limited the available tools with which she could prove causation.").

This Court, however, rejects the plaintiffs' experts' opinions inasmuch as they rely on selective use of statistically insignificant data from epidemiological studies. *Accord Glastetter v Novartis Pharmaceuticals 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 can cause an ICH, the best plaintiffs can do is attack defendant's studies."), *aff'd*, 252 F.3d 986 (2001); *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.") (emphasis in original); *Siharath*, 131 F.Supp 2d at 1358

(criticizing the available epidemiological studies "does not satisfy [plaintiff's] burden of proof").

Moreover, Plaintiffs' experts' broad criticisms of the existing epidemiological evidence does not help them meet their burden Plaintiffs' burden is an affirmative one, not served by such attacks, Sandoz is not required to disprove a causal association in this case. *See, e g ,* *Sharath*, 131 F Supp. 2d at 1358, *Glastetter*, 107 F Supp. 2d at 1044, *Brumbaugh*, 77 F. Supp. 2d at 1156

B CASE REPORTS

The plaintiffs' experts primarily rely on case reports Case reports are "reports in medical journals describing clinical events in one or more individuals They report unusual or new disease presentations, treatments, manifestations, or suspected associations between two diseases, effects of medication, or external causes." *Reference Manual on Scientific Evidence* at 374 (Fed. Judicial Center 2000) In this case, the case reports do not provide a reliable foundation for a causation opinion.

Specifically, Dr. Petro relies on a June 1, 1988, Adverse Drug Event, in which a Sandoz doctor states that Parlodel was the "probable" cause of postpartum hypertension and eclampsia in an individual (Doc. 245, Pls Ex. 60). He relies on a February 5, 1984, Adverse Event assessment, in which a Sandoz doctor states that Parlodel was a "possible" cause of a migraine headache in an individual (Doc. 245, Pls.' Ex. 83). He also relies on a 1980 Maryland Department of Health Adverse Reaction Report, in which it was reported that an unknown female patient of unknown age experienced a numbness of the extremities while taking Parlodel

to treat her amenorrhea/galactorrea condition (Petro Aff., ¶ A13(a)) (*See* Doc. 245, Pls.' Ex. 313).

The plaintiffs' experts also rely on some published case reports that they claim indicate that bromocriptine induced peripheral vasospastic responses (Doc. 245, Pls.' Exs. 136, 189, 208). In one of those case reports, entitled "Raynaud's phenomenon in infertile women treated with bromocriptine," the author noted that he "observed two infertile women who developed Raynaud's phenomenon on low-dose (5.0 to 7 5 mg/day) Parlodel" (Doc. 245, Pls.' Ex. 136). The author stated that "[t]he cases are reported to alert clinicians to the potential relationship between Raynaud's phenomenon and low-dosage Parlodel usage in women using the drug for hyperprolactinemia [elevated levels of prolactin in the blood, which is a normal physiological reaction during lactation] or infertility indications" (*Id* at 3).

The plaintiffs' experts also rely on non-published internal case reports Sandoz submitted to the FDA as part of its Parlodel application for the PPL indication (Petro Aff., ¶ A13(a)) (*See* Doc 245, Pls ' Ex 40; Ex 41; Ex 268). For example, Dr. Petro relies on a 1974 case report in which Sandoz Dr David Archer recorded higher systolic and diastolic blood pressure for a patient after she started taking Parlodel (Doc. 245, Pls ' Ex 40). Dr. Petro relies on a 1974 case report in which Sandoz Dr. David Archer recorded a higher systolic and diastolic blood pressure for a patient after she started taking Parlodel (Doc 245, Pls.' Ex 41). Dr. Petro relies on an excerpt from a 1974 case report, indicating that one patient complained of numbness and tingling of the left arm and leg after ingesting Parlodel (Doc. 245, Pls ' Ex. 268).

These case reports upon which Drs Kulig and Petro rely make little attempt to isolate or

exclude possible alternative causes, lack adequate controls and analysis. Granted, an overwhelming amount of case reports of a temporal proximity between a very specific drug and a very specific adverse event might be enough to make a general causation conclusion sufficiently reliable.

In this case, however, plaintiffs' experts cite an array of case reports covering diverse effects such as digital vasospasm, Hr 1:217, and even effects allegedly secondary to *hypo*tension, Hrg. II:279-280, 312-313, in diverse patient populations with diverse confounding considerations There is not the volume of or specificity within these case reports to reliably show that Parlodel causes ICH

Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on these case reports. *Accord Glastetter*, 252 F.3d at 990-91 ("Case reports make little attempt to screen out alternative causes for a patient's condition. They frequently lack analysis. And they often omit relevant facts about the patient's condition Hence, causal attribution based on case studies must be regarded with caution ") (quotation and citation omitted); *Glastetter*, 107 F Supp.2d at 1031 (rejecting reliance on case reports "in light of the case law discussing case reports and the testimony of plaintiffs' experts" which downplayed their reliance on them in establishing general causation); *Hollander v Sandoz Pharmaceuticals Corp.*, 95 F Supp.2d at 1237 (same); *Siharath*, 131 F.Supp.2d at 1359 (similar); *Brumbaugh*, 77 F Supp.2d at 1156 (noting that the most significant analytical defect of case reports is that they "don't isolate and investigate the effects of alternative causation agents...[t]hey reflect reported data, not scientific methodology.").

C. HUMAN DECHALLENGE / RECHALLENGE REPORTS

Dr. Petro relies on rechallenge and dechallenge data (Petro Aff., ¶ A11(a)) (*See* Doc. 245, Pls.' Ex. 24, at pp 178, 251-53; Ex. 57; Ex. 126; Ex. 155; Ex. 156, at p. 2; Ex. 168). "Rechallenge occurs when a doctor re-exposes a patient to a drug believed to have caused an earlier adverse reaction, dechallenge removes that exposure." *Glastetter*, 252 F.2d at 990. This type of data is "substantially more valuable than run-of-the-mill case reports because a patient's reactions are measured against his own prior reactions." *Id.* Nevertheless, in this case, for the reasons stated below, the Court finds that the plaintiffs' rechallenge/dechallenge data is not reliable.

Dr. Petro relies on a May 5, 1984, letter from Sandoz Dr. Pierre Krupp to a Sandoz affiliate, in which Dr Krupp indicates that, after he reviewed two adverse migraine headache events, he determined that "[f]or the two cases in question a causal relationship has to be considered as the adverse effects occurred during Parlodel medication, subsided upon discontinuation of medication and reappeared after reexposition in one case." (Doc. 245, Pls.' Ex. 156)

Dr. Petro also relies on a May 16, 1988, letter from Sandoz Dr. Pierre Krupp, in which he sent Sandoz Dr. R. J. Ziance a list of "25 reports of psychotic reactions associated with the suppression of lactation under Parlodel treatment which have been brought to the attention of the [Sandoz] Drug Monitoring Center" (Doc. 245, Pls.' Ex 155). One case report indicated a positive dechallenge/rechallenge for hallucinations.

Dr. Petro also relies on a June 9, 1987, letter from Sandoz Drug Monitoring Dr. D. Hart

to Sandoz Dr. Majer. In that letter, Dr. Hart thanked Dr. Majer for informing him that a 23-old female with an abnormal pituitary tissue had symptoms of cerebellar incoordination during Parlodel therapy which stopped within three weeks after discontinuing Parlodel therapy (Doc. 245, Pls Ex. 57)

These "dechallenge/rechallenge" case reports suffer from the same reliability flaws as do the others. FOF 36-37; *Hollander*, 95 F. Supp. 2d at 1234-35 n.10 (rejecting plaintiffs' experts' reliance on dechallenge/rechallenge articles because, *inter alia*, there are "too few [such articles] for them to be consequential [and] they present the problems inherent in the other case studies or adverse drug reaction reports relied upon by the plaintiffs' experts"); *Glastetter*, 107 F. Supp. at 1031 & n 9; *Revels*, 1999 WL 644732, at *3-*5.[8] The adverse events involved in these reports are events other than ICH. Furthermore, the number of dechallenge/rechallenge reports is too scant to reliably screen out other causes or confounders

Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on human dechallenge/rechallenge reports. *Accord Glastetter*, 252 F.3d at 990-91 (holding that the district court did not abuse its discretion rejecting these human dechallenge/rechallenge reports); *Hollander v. Sandoz Pharmaceuticals Corp* , 95 F.Supp.2d 1230, 1235 n.10 (W.D. Okla. 2000) (rejecting experts' reliance on dechallenge/rechallenge reports because "not only are there too few rechallenge reports for them to be consequential, they present the problems inherent in the other case studies or adverse drug reaction reports relied upon by the plaintiffs' experts").

[8] Even the FDA, upon whose regulatory methodology plaintiffs' experts rely, concluded that a cause and-effect relationship could not be established after reviewing the Parlodel dechallenge/rechallenge data.

D ANIMAL STUDIES

The plaintiffs' experts rely on animal studies observing a connection between vasoconstriction and bromocriptine and other ergot alkaloids (Petro Aff., ¶ A12)

According to Dr Petro, various animal studies indicate that bromocriptine causes vasoconstriction sufficient to lead to necrosis in the ears of dogs (Pls.' Exs 17, 18), gangrene in the tails of rats (Pls ' Exs. 19, 20, 21), a greater blood flow resistance in dogs' necks (Pls.' Ex. 71), pressor activity[9] in "spinal cats" (Pls.' Ex 67, 200) and in pithed[10] rats (Ex. 68), and that ergotamine (*i e* , an ergot alkaloid used to manage migraine) caused vasoconstriction in the hind leg of a dogs that had low vascular resistance (Pls ' Ex. 113).[11]

In this case, none of the pertinent studies were designed to reveal whether bromocriptine could cause ICH, and none so concluded. Some studies involved almost poisonous doses; some involved animals that had a steel rod injected down their spinal cords so the animals had no intact nervous systems; some involved bromocriptine's reaction locally (*e.g.*, in a single isolated vein of an animal) as opposed to a systemic administration; and some were poorly documented.

Plaintiffs' experts cannot identify any animal study showing that Parlodel causes ICH or

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[9]Pressor activity results in producing increased blood pressure or denoting afferent (inflowing toward a center) nerve fibers that, when stimulated, excite vasoconstrictors, which increase peripheral resistance.

[10]To pith means to pierce the medulla of an animal with a sharp instrument introduced at the base on the skull. "[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 " *Stharath v. Sandoz Pharmaceuticals Corp.*, 131 F.Supp.2d 1347, 1369 (N D. Ga. 2001).

[11]At higher levels of vascular resistance, the bromocriptine caused vasodilation (widening the space within the interior of blood vessels).

any other stroke or hypertension or injury purportedly secondary to cerebral vasospasm. Hrg. II:340 (Petro). Moreover, when the animal studies conflict with his hypothesis, Dr. Kulig opines that the studies "ha[ve] nothing to do with the human situation where the dose may be different. It's a different species, it's a different indication, et cetera, et cetera." Hrg I 153-54

To the extent that the opinions of Drs Kulig and Petro are based on animal studies, this Court does not believe the "fit" requirement has been met in this case, because "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 (1997) (expert offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans). While researchers might reliably extrapolate from animal studies sometimes, *see Glastetter*, 252 F.3d at 991 n.5 ("We do not discount the value of animal studies *per se*. Rather, we find that the particular animal studies submitted in this case do not present scientifically compelling evidence of causation."), the type of extrapolations Drs. Kulig and Petro divine from these particular animal studies require giant analytical leaps between the data and the opinions proffered.

Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on animal studies. *Accord Glastetter*, 252 F.3d at 991 ("We are convinced that the animal studies relied on by [plaintiff's expert physicians are insufficient to prove that bromocriptine causes ICHs."); *Glastetter*, 107 F.Supp 2d at 1041 (same), *Stharath*, 131 F.Supp 2d at 1357 ("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."); *Hollander*, 95 F Supp 2d at 1238 ("The court also rejects the plaintiffs' experts' attempt to extrapolate from animal studies to show that

Parlodel causes strokes. The studies relied upon involved different drugs, did not test the systemic effect of the drug, some of the animals were anesthesitized, and they were neither pregnant nor post-partum . [T]he animal studies on which the plaintiffs' experts rely are too dissimilar to the facts presented in this litigation to be reliable ")

E EFFECTS OF OTHER ERGOT ALKALOIDS

The plaintiffs' experts rely on various data indicating that other ergot alkaloid derivatives have vasoconstrictive effects (Petro Aff., ¶ A10). They rely on the general notion that ergots can cause "ergotism." "Ergotism" is a term that has been used synonymously with vasospasm from ergots and the delirious effects that vasospasm cause (*e.g.*, hypertension, seizures, stroke, myocardial infarction, and ischemia in other parts of the body from decreased blood supply).

In this case, the plaintiffs' experts assert that bromocriptine is an ergot alkaloid and that some, even many, ergot alkaloids have been known to cause vasoconstriction/vasospasm. Drs. Kulig and Petro hypothesize that it is likely that bromocriptine, a member of the ergot alkaloid family, behaves like its chemical cousins.

However, using this "guilt by association" inference in their methodology is of questionable scientific reliability, inasmuch as (1) a structural difference between bromocriptine and other ergots is the addition of a bromine atom (Hrg. I:105); and (2) even small structural changes at the molecular level can radically change a particular substance's properties. BERDE, ERGOT ALKALOIDS AND RELATED COMPOUNDS (EX. D-14). Using this inference as part of their methodology of determining the complicated comparative molecular effects of two structurally

different substances is particularly questionable given Dr Kulig's inability to articulate how bromocriptine would operate differently (or how it operates at all) on a molecular level (Hrg. I: 105-08). The plaintiffs' experts' "generic assumption that bromocriptine behaves like other ergot alkaloids carries little scientific value." *See Glastetter*, 252 F 3d at 990

Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on the ergot alkaloid inference. *See id* (noting that even small structural changes at the molecular level "can radically change a particular substance's properties"); *Glastetter*, 107 F Supp.2d at 1034 ("Like the Court in *Hollander*, this Court does not find, based on all the evidence, that plaintiffs' experts, and plaintiffs' evidence, establishes that 'bromocriptine and the other ergots have sufficiently similar physiological effects to warrant comparison.'"); *Hollander*, 95 F.Supp.2d at 1238 ("The plaintiffs have failed to demonstrate that bromocriptine and the other ergots have sufficiently similar physiological effects to warrant comparison."); *Brumbaugh*, 77 F.Supp.2d at 1157 ("Testimony extending general conclusions about similar drugs does not meet *Daubert*'s requirement of reliability... [Plaintiff's expert's] unsupported suspicion may be correct but it is not a reliable scientific opinion based on the record before me."); *Sitharath*, 131 F.Supp 2d at 1363 (finding that plaintiffs' experts' reliance on the generalized ergot alkaloid inference "raises serious questions of 'fit'").

F MEDICAL TEXTS

The plaintiffs' experts cite clippings from various scientific literature First, Dr. Petro relies on two cardiac treatises, noting bromocriptine's potential ability to cause coronary

vasospasm and attendant myocardial infarction. The first, HURST'S THE HEART, states: "[t]hree newly recognized associations and/or causes of coronary spasm include general anesthesia, 'allergic angina' (histamine-induced), and postpartum bromocriptine usage. . . . In postpartum women receiving bromocriptine in the presence of pregnancy-induced hypertension acute myocardial infarction has occurred" (Doc. 245, Pls ' Ex. 1450, at p. 3). The second, BRAUNWALD'S HEART DISEASE, states:

> Peripartum AMI [acute myocardial infarction] is often associated with normal coronary angiographic findings; this suggests a decrease in coronary perfusion, possibly due to spasm or in situ thrombosis [clotting within a blood vessel which may cause infarction of tissues supplied by the vessel], as a relatively common etiological factor in this patient population. Although the cause of the spasm is not clear, it has often been associated with pregnancy-induced hypertension and in some instances with the use of ergot derivatives to suppress lactation.

(Doc. 245, Pls ' Ex. 2511, at p 2).

Second, Dr. Petro relies on a stroke treatise, in which Parlodel's potential ability to cause cerebral arterial vasoconstriction is noted. BARNETT'S STROKE: PATHOLOGY, DIAGNOSIS AND MANAGEMENT (1998) states: "The physiopathology and cause of reversible angiopathy is focal arterial vasoconstriction, which may be due to sympathomimetic [exhibiting a mutual relation between two organs, systems or parts of the body] drugs such as ergot derivatives, crack cocaine, methyl amphetamine, and phenylpropanolamine" (Doc. 245, Pls.' Ex. 2512, at pp 2-3).

Third, Dr Petro relies on Sandoz Medical Research Department Dr. Robert Griffith's 1978 contribution to the book, DOPAMINERGIC ERGOT DERIVATIVES AND MOTOR FUNCTION, in which he stated, under the heading "Bromocriptine Toxicity," that "[d]igital vasospasm in cold weather occurs with high doses [of bromocriptine], especially in patients who have previously

reported Raynaud's phenomenon" (Pls.' Ex. 219).

In this case, a fair reading of the majority of plaintiffs' medical texts indicates that there is an *association* between bromocriptine and vasospasm, which is quite different from drawing the conclusion of *causation* between therapeutic doses of bromocriptine and ICH. Moreover, the plaintiffs' experts would agree that medical texts provide no more support than the evidence upon which they rely.

Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on these medical texts *Accord Glastetter*, 252 F.3d at 990 (observing that "[s]ome of the texts referred to by plaintiffs' experts were "largely grounded upon case reports and other anecdotal information"); *Glastetter*, 107 F Supp.2d at 1034 n.18 (observing that "all the texts, treatises, and journals cited by plaintiffs appear based upon the accumulated case reports or individual case reports" and rejecting the argument "that texts and treaties 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").

G DEFENDANT'S INTERNAL DOCUMENTS

Dr Petro relies on statements extracted from internal Sandoz documents/correspondence (Petro Aff., ¶ A6) This Court, however, does not believe that Sandoz' statements, taken in context, actually "admit" that Parlodel can cause IHC. Rather, placed in context, these statements merely express a desire to perform further testing. *See Glastetter*, 252 F.3d at 990.

Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on

Sandoz documents and statements. *Accord Glastetter*, 252 F.3d at 990 ("Glastetter argues that [Sandoz'] internal documents admit that Parlodel causes hypertension and strokes. She points to three or four statements excerpted from company memoranda... Glastetter lifted these statements out of context from longer memoranda between Novartis doctors. Placed in proper context, it is apparent that Novartis doctors simply expressed a desire to perform further testing to determine whether Parlodel might be associated with certain types of seizures and strokes. These statements do not 'admit' that Parlodel can cause an ICH.")

H FDA's 1994 ACTION

Plaintiffs' experts also rely on the FDA's 1994 action that rescinded its earlier approval of Parlodel to suppress PPL. They argue that the FDA's action is evidence that Parlodel can cause ICH. 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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> * * * * * *
>
> 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) Notably, the Order does not state that the FDA has determined that there is a causal connection between bromocriptine and ICH. Rather, the Order merely indicates the FDA's conclusion that " the limited benefit of using bromocriptine" for the prevention of physiological lactation is outweighed by the "potential risks associated with the use of bromocriptine."

Plaintiffs' experts' contention that the FDA's order directly supports their opinions ignores the fact that the agency determination is based on risk-benefit analysis, a standard lower than the one this Court must now apply. *See Glastetter*, 252 F.3d at 991, *Sharath*, 131 F Supp 2d at 1336. Therefore, this Court rejects the plaintiffs' experts' opinions inasmuch as they rely on actions taken by the FDA.

I TOTALITY OF THE EVIDENCE

Each of plaintiffs' experts' bits of evidence in this case suffers from reliability and/or relevance deficiencies such that an opinion based on it fails *Daubert* And, plaintiffs' experts have not suggested that they would hold the same opinions (or hold them to the requisite degree of probability) if they were foreclosed from relying on one category of evidence, such as case

reports. Nevertheless, the Court has gone on to consider whether, in aggregate, the evidence cited supports an inference that would enable plaintiffs' experts to offer an admissible causation opinion. The Court concludes that it does not In this particular case, the data points pulled from each "type" of evidence are too limited, too disparate and too inconsistent. It amounts to a hollow whole of hollow parts. *See Siharath*, 131 F. Supp 2d at 1371.

CONCLUSION

Mrs. Caraker has plainly suffered a great loss, and will undoubtedly be forced to shoulder considerable suffering in the future, as a result of her traumatic ICH. This Court understands Mrs Caraker's belief that the timing in this case points a finger at Parlodel. As a matter of fact, Parlodel might have indeed been the cause of her injury. This Court, however, is not now in the position of a finder of fact, and this ruling makes no determination about the cause of Mrs. Caraker's injury

Rather, the only issue before the Court is whether the testimony of Drs. Kulig and Petro is reliable under the *Daubert* standard discussed above Under *Daubert*, the Courts are forbidden from allowing expert testimony that is scientifically unreliable, and this Court has attempted to faithfully apply that standard in this case. After careful consideration of the testimony, exhibits and arguments of the parties, the Court has concluded that the expert testimony of Drs. Kulig and Petro is scientifically unreliable

Therefore, for the reasons discussed above and in accordance with this Court's September 12, 2001, Order, IT IS ORDERED that the plaintiffs' experts' opinions are inadmissible in their

entirety and Sandoz' motion to exclude their testimony (Doc. 212) is GRANTED.

This shall serve as this Court's final ruling on this issue. This Court hereby GRANTS the defendant forty-five (45) days from the date that this order is issued to file a summary judgment motion For the purposes of this summary judgment motion only, the parties are hereby relieved of the motion packet serving and filing requirements in Local Rule 7.1

IT IS SO ORDERED.

DATED: November 21, 2001.

J. PHIL GILBERT
U.S. District Judge