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-4113-JPG

MEMORANDUM OPINION AND ORDER

GILBERT, District Judge:

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

This is a products liability case that involves the drug Parlodel, a postpartum lactation-control drug manufactured, delivered and sold by the defendants. Ms. Caraker took Parlodel to prevent physiologic lactation ("PPL") after her delivery, and she later suffered an intracerebral hemorrhage ("ICH"). To establish the link between these two events, the plaintiffs[1] proffered the testimony of Toxicologist Kenneth Kulig and Neurologist Denis Petro. Sandoz moved to exclude the testimony of Drs. Kulig and Petro on the grounds that it is scientifically unreliable. Both sides submitted argumentative briefs and witness affidavits, and both sides had a full and fair opportunity to present their streamlined best case either for or against admissibility at a two-day

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

316

Daubert hearing this Court recently conducted.[2]

The plaintiffs had the burden of showing two things. First, they had the burden of showing that their experts' opinions were derived from the scientific method and thus 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*, 509 U.S. at 593. 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 factfinder in understanding the evidence. *See Daubert*, 509 U.S. at 590-92 & n.9. 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. In that case, the expert's principles are methodology are the conclusions they generate are not entirely distinct from one another.[3]

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.* 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 factors enumerated in newly-amended Rule 702, district courts must determine whether the expert's opinion "is genuinely scientific [or] unscientific speculation offered by a genuine

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[2]This Court will assume the parties' familiarity with the underlying facts.

[3]Newly-amended Rule 702 specifically allows a district court to consider the sufficiency of the data upon which the expert relies in reaching his opinion.

scientist." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 318 (7th Cir. 1996) (noting that "an insightful, even an inspired, hunch" is insufficient). *Daubert* gave district courts a non-exclusive checklist to use in assessing the reliability of scientific expert testimony, but district courts may determine that other factors are relevant too. *See Advisory Committee Notes to 2000 Amendments to Rule 702* (listing *Daubert* factors and other factors courts have found relevant).

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 v. Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 989 (8th Cir. 2001); *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 for the expert to reliably place the purported potential cause on the differential diagnosis in the first place as well as reliably "rule out" the other potential causes until the physician is left with the most likely one. *See Glastetter*, 252 F.3d at 989. Both of these steps must be based on sufficient and reliable data for the methodology as a whole to be reliable. *See* Fed. R. Evid. 702; *Glastetter*, 252 F.3d at 989. Thus, if the "ruling in" step is bad or if an extrapolation from the existing data is particularly questionable or involves 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 (Trans., Part 1, at 29-30); (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); *Siharath 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). They opine that Parlodel (which contains a therapeutic dose of bromocriptine for the human PPL indication) causes vasoconstriction relying on an amalgamation of bits and pieces of their puzzle: (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 "jigsaw puzzle" together.[4]

The most glaring 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

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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" (Trans, Part 1, 181).

involves a loose application of purportedly objective scientific causation standards.[5] 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. This Court will preliminarily outline some of the problems it has with the reliability of the plaintiffs' experts' methodology, as applied, and will render its final ruling on this issue after it receives the official transcript and after it receives and reviews Sandoz' proposed Findings of Fact and Conclusions of Law which should incorporate the testimony from the *Daubert* hearing as well as all the relevant exhibits of record.

This Court has observed other problems casting doubt on the reliability of the medical causation opinions of Drs. Kulig and Petro, and this Court will list them:

- *Epidemiological Studies*. Drs. Kulig and Petro generally attack the epidemiological studies as fundamentally flawed, while, at the same time, selectively pluck favorable numbers (that are not statistically significant) and herald them as crucial pieces of their bromocriptine puzzle. They come forward with no supporting epidemiological evidence.[6] Their vigorous attacks on the methodology of Sandoz' studies coupled with their reliance on these cherry-picked numbers are suspect. This Court rejects the plaintiffs' experts opinions inasmuch as they rely on selective

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[5]Dr. Petro applied the standards the FDA employs, despite the fact that the FDA employs a lesser standard scientific causation. *See Glastetter*, 252 F.3d at 991 ("The FDA evaluates pharmaceutical drugs using a different standard than the causation standard at issue in the present case."). Dr. Kulig's application of the Bradford Hill criteria was unimpressive. The plaintiffs did not expound much on it at the hearing; many of the affidavit paragraphs are curt conclusions making vast assumptions; and Dr. Kulig's application of the Bradford Hill methodology seems more like an afterthought, inasmuch as it appears that he had already came to a conclusion using a differential diagnosis and later "came to the *same* conclusion" using the Bradford Hill criteria (Trans. at 17). Justifying a conclusion after the fact by applying a methodology does not generally lead to reliable scientific knowledge.

[6]To hopefully stave off any potential appeal on this ground this Court will make itself crystal clear. 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.").

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").

- *Case Reports*. The case reports upon which Drs. Kulig and Petro rely make little attempt to isolate or exclude possible alternative causes, lack adequate controls, and lack any real analysis. Granted, an overwhelming amount of case reports of a temporal proximity between a very specific drug and a very specific adverse event might, as Dr. Buchholz admits, be enough to make a general causation conclusion sufficiently reliable. In this case, however, we have a scant number of case reports indicating that Parlodel is temporally associated with all types of adverse events (Trans, Part 1, at 255, 259). There is not the volume of or specificity within these case reports to reliably show that Parlodel causes ICH. Even the plaintiffs' experts' downplay their reliance on them as proof that Parlodel causes ICH (*See id.*, at 121-30). 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.").

- *Human Dechallenge/Rechallenge Reports*. While these reports have more control than the ordinary case reports do, there is still a lack of control in these reports and they do not contain a testable and systematic inquiry into the mechanism of causation. Here, the adverse events involve events other than ICH. Furthermore, the number of dechallenge/rechallenge reports is too scant - especially given the lack of adequate controls employed - to reliably screen out other causes or confounders to show that Parlodel causes ICH or would operate as a

vasoconstrictor under Mrs. Caraker's circumstances. This Court rejects the plaintiffs' experts opinions inasmuch as they rely on these 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").

- *Animal Studies*. 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 cord to destroy it so the animal has no intact nervous system; 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. In some cases, it appeared as though study data adverse to their hypothesis was simply ignored, suggesting that each of these experts was not "being as careful as he would be in his regular professional work outside his paid litigation consulting." *Sheehan v. Daily Racing Form, Inc.*, 104 F.3d 940, 942 (7th Cir. 1997). *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999) (expert must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field").

Moreover, to the extent that the opinions of Drs. Kulig and Petro are based on these 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." *Joiner*, 522 U.S. at 146 (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 – with all their dissimilarities – involve too many and too great of analytical gaps between the data and the opinions proffered. This Court rejects the plaintiffs' experts' opinions inasmuch as they rely on these particular 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); *Siharath*, 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.").

- *The Ergot Alkaloid Inference.* Bromocriptine is an ergot alkaloid. Some, even many, ergot alkaloids have been known to cause vasoconstriction/vasospasm. Drs. Kulig and Petro hypothesize that it would not be unlikely if bromocriptine, a member of the ergot alkaloid family, behaved 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 (Trans, Part 1, at 105); and (2) even small structural changes at the molecular level can radically change a particular substance's properties. 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 (Trans, Part 1, at 105-08). This Court agrees that the plaintiffs' experts' "generic assumption that bromocriptine behaves like other ergot alkaloids carries little scientific value." *Glastetter*, 252 F.3d at 990. 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."); *Siharath*, 131 F.Supp.2d at 1363 (finding that plaintiffs' experts' reliance on the generalized ergot alkaloid inference "raises serious questions of 'fit'").

- *Medical Texts.* A fair reading of the majority of plaintiffs' medical texts indicate 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. For

example, the plaintiffs' experts challenge Ellenhorn's insertion of the "0" in the bromocriptine-vasoconstriction-association box on the ground that Ellenhorn's observation was unsupported by the underlying study he cited. 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").

- *Sandoz Documents and Statements.* This Court does not believe that Sandoz' statements, taken in context, actually "admit" that Parlodel can cause IHC. 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.").

- *FDA actions.* This Court rejects the plaintiffs' experts' opinions inasmuch as they rely on actions taken by the FDA. The FDA's approach involves lesser showings than are required in this case. *See Glastetter*, 252 F.3d at 990-91.

- *Totality of the Circumstances and Evidence.* The decision about "*how* to test an expert's reliability" is best left to the district court's discretion. *Kumho Tire*, 526 U.S. at 152. This Court first scrutinized the individual items of proof at issues, and now considers the items of proof collectively. Individually, the plaintiffs' experts' questionable methodology was based on data insufficient to base a general causation opinion. This Court does not believe "that the aggregate of this evidence presents a stronger scientific basis for [the plaintiffs'] supposition that Parlodel can cause ICH" for the same reasons. *Glastetter*, 252 F.3d at 992.

Summary and 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, and this ruling makes no determination on that issue. The only issue here involves the scientific reliability of the testimony of Drs. Kulig and Petro. Courts are forbidden from allowing expert testimony that is scientifically unreliable, and this Court has attempted to faithfully apply that standard in this case. Unfortunately for Mrs. Caraker, this Court has found that the expert testimony of Drs. Kulig and Petro is scientifically unreliable and, thus, it must be excluded.

Accordingly, this Courts:

- **ORDERS** Sandoz to submit Proposed Findings of Fact and Conclusions of Law, which incorporate all the testimony and exhibits of record in this case, be limited to thirty (30) pages, and be filed within forty five (45) days of the date of this Order. Sandoz shall also submit one electronic copy of its Proposed Findings of Fact and Conclusions of Law adaptable to WordPerfect 8 or 9 on a 3.5 inch computer disc;

- **GRANTS** Sandoz' motion and excludes plaintiffs' experts' causation testimony. This Court will render its final ruling on this issue after it receives and reviews Sandoz' proposed Findings of Fact and Conclusions of Law; and

- **GRANTS** Sandoz leave to serve and file a summary judgment motion in this case within forty five (45) days after this Court issues its final ruling on this issue. For purposes of this summary judgment motion only, the parties are hereby relieved of the motion packet serving and filing requirements contained in Local Rule 7.1.

IT IS SO ORDERED.
DATED: September 12, 2001.

J. PHIL GILBERT
U.S. District Judge