. **United States Court of Appeals**
FOR THE EIGHTH CIRCUIT

No. 00-3087 & No. 00-3467

Tina M. Glastetter, Steven J. Glastetter,	*	
	*	
Appellants,	*	
	*	Appeal from the United States
v.	*	District Court for the
	*	Eastern District of Missouri
Novartis Pharmaceuticals Corporation,	*	
formerly known as Sandoz	*	
Pharmaceuticals Corp.; Novartis AG,	*	
formerly known as Sandoz AG,	*	[TO BE PUBLISHED]
	*	
Appellees.	*	

Submitted: April 9, 2001

Filed: June 8, 2001 (Corrected-July 5, 2001)

Before HANSEN and BYE, Circuit Judges, and MELLOY,[1] District Judge.

PER CURIAM.

Tina Glastetter suffered a stroke two weeks after she gave birth to her third child. She blamed her stroke on medication called Parlodel, which she had taken to suppress postpartum lactation. Glastetter sued Parlodel's manufacturer, Novartis

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[1]The Honorable Michael J. Melloy, United States District Judge for the Northern District of Iowa, sitting by designation.

Pharmaceuticals Corporation, in federal court under a state-law products liability theory. The district court[2] excluded Glastetter's expert medical testimony that Parlodel caused her stroke, holding that it lacked scientific reliability. Glastetter v. Novartis Pharms. Corp., 107 F. Supp. 2d 1015 (E.D. Mo. 2000). Because the court's ruling was fatal to Glastetter's proof of causation, the court granted Novartis summary judgment and assessed costs. Glastetter now appeals, and we affirm.

I

Glastetter suffered from occasional migraines, she was overweight, and she had smoked heavily for several years. At age 36, she delivered her third child by caesarean section on August 2, 1993. Her pregnancy and delivery were uneventful. After childbirth, Glastetter chose not to breast-feed her child. Her doctor prescribed a two-week dose of Parlodel to suppress lactation. Glastetter had taken Parlodel for the same reason following a prior pregnancy. On August 16, Glastetter complained of a severe headache. The pain became intense, and she was later taken to a local hospital. At the hospital, doctors performed a CT scan, which revealed an intracerebral hemorrhage (ICH)[3] in the right frontoparietal area of Glastetter's brain. She experienced left-side paralysis and slurred speech. Doctors were unable to identify the cause of Glastetter's stroke.

Novartis introduced Parlodel in 1978. In 1980, the Food & Drug Administration approved Parlodel for use in preventing postpartum lactation. Parlodel blocks the body's production of the hormone prolactin, which acts upon the breasts to induce

[2]The Honorable E. Richard Webber, United States District Judge for the Eastern District of Missouri.

[3]An ICH is a "wet stroke," in which too much blood enters the brain. An ICH may be contrasted with an ischemic stroke, or "dry stroke," in which blood flow to the brain is restricted.

secretion of milk in postpartum women. Parlodel's active ingredient is a chemical substance called "bromocriptine mesylate" (bromocriptine).[4] About six months after Glastetter suffered her stroke, the FDA proposed to revoke its earlier approval of Parlodel for inhibiting postpartum lactation. The FDA concluded that the possible harm from using Parlodel (including the possibility of seizures and strokes in certain at-risk women) outweighed its limited benefit as a lactation suppressant. 59 Fed. Reg. 43,347 (Aug. 23, 1994). The FDA later revoked its approval of Parlodel after Novartis waived a formal hearing. 60 Fed. Reg. 3404, 3404-3405 (Jan. 17, 1995).

Glastetter brought an action against Novartis in 1997. She alleged that her ingestion of Parlodel caused her ICH. Glastetter's husband, Steven, joined a claim for loss of consortium. Following extensive discovery, Novartis moved *in limine* to exclude Glastetter's two expert witnesses on medical causation, Dr. Kenneth Kulig and Dr. Denis Petro. The district court received testimony from Drs. Kulig and Petro, and from Novartis's own medical experts, during a four-day evidentiary hearing in March 2000. On August 14, 2000, the district court excluded Glastetter's proposed expert testimony, holding that it was not scientifically valid, a prerequisite for admission under Fed. R. Evid. 702. See Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993). Because Glastetter relied upon her experts to prove causation, and because causation was an essential element of her state-law products liability theory, the district court granted Novartis summary judgment. The district court later awarded Novartis some of its costs in conducting the Daubert hearing. Glastetter then filed the instant appeal challenging both the district court's Daubert ruling as well as its award of costs to Novartis.

[4]We employ the terms "bromocriptine" and "Parlodel" interchangeably throughout this opinion.

II

A party may present expert medical testimony if the expert's opinion is scientifically valid and it will assist the jury. Daubert, 509 U.S. at 589-93. Daubert described the district court as a gatekeeper. In exercising its gatekeeping function, a district court must make "a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." Id. at 592-593. An expert opinion "must be supported by appropriate validation—i.e., 'good grounds,' based on what is known." Id. at 590. In sum, the district court's gatekeeping role separates expert opinion evidence based on "good grounds" from subjective speculation that masquerades as scientific knowledge. See Globetti v. Sandoz Pharms. Corp., 111 F. Supp. 2d 1174, 1177 (N.D. Ala. 2000). We review a district court's decision to exclude expert testimony for an abuse of discretion. General Elec. Co. v. Joiner, 522 U.S. 136, 141-43 (1997).

A

Each of Glastetter's experts conducted a "differential diagnosis," which concluded that Parlodel caused her ICH. In performing a differential diagnosis, a physician begins by "ruling in" all scientifically plausible causes of the plaintiff's injury. The physician then "rules out" the least plausible causes of injury until the most likely cause remains. The final result of a differential diagnosis is the expert's conclusion that a defendant's product caused (or did not cause) the plaintiff's injury. See generally Westberry v. Gislaved Gummi AB, 178 F.3d 257, 262-66 (4th Cir. 1999).

In Turner v. Iowa Fire Equip. Co., we held that "a medical opinion about causation, based upon a proper differential diagnosis, is sufficiently reliable to satisfy Daubert." 229 F.3d 1202, 1208 (8th Cir. 2000). Because a differential diagnosis is presumptively admissible, see id., a district court may exercise its gatekeeping function

to exclude only those diagnoses that are scientifically invalid. In the present case, the district court excluded the differential diagnoses performed by Glastetter's expert physicians because they lacked a proper basis for "ruling in" Parlodel as a potential cause of ICH in the first place. Glastetter, 107 F. Supp. 2d at 1045 & nn.28-29 ("[T]he data and methods of plaintiffs' experts are not scientifically valid bases for the conclusion that Parlodel can cause an ICH in a human."). We agree with the district court's conclusion.

B

Glastetter's experts articulated a theory to explain how Parlodel might cause an ICH. They theorized that Parlodel causes arteries to constrict (vasoconstriction), resulting in elevated blood pressure. High blood pressure is itself a recognized risk factor for ICHs. Thus the experts opined that Parlodel's vasoconstrictive properties likely caused Glastetter's ICH. Although this chain of medical reasoning appears sound, its major premise remains unproven. Glastetter's experts failed to produce scientifically convincing evidence that Parlodel causes vasoconstriction. Her experts relied on various types of scientific data—published case reports; medical treatises; human rechallenge/dechallenge data; animal studies; internal Novartis documents; and the FDA's revocation of Parlodel's indication for suppressing lactation—to establish that Parlodel acts as a vasoconstrictor. We agree with the district court's conclusion that this data does not demonstrate to an acceptable degree of medical certainty that Parlodel can cause an ICH. See Daubert, 509 U.S. at 590 n.9 ("In a case involving scientific evidence, *evidentiary reliability* will be based upon *scientific validity*.") (emphases in original).

Much of the evidence relied upon by Drs. Kulig and Petro has been culled from case reports in which doctors reported patient strokes following their ingestion of Parlodel. A case report is simply a doctor's account of a particular patient's reaction to a drug or other stimulus, accompanied by a description of the relevant surrounding

circumstances. 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, "[c]ausal attribution based on case studies must be regarded with caution." Reference Manual on Scientific Evidence 475 (Fed. Judicial Ctr. 2000); see Turner, 229 F.3d at 1209 n.5 (collecting cases). Though case reports demonstrate a temporal association between Parlodel and stroke, or stroke-precursors, that association is not scientifically valid proof of causation.

Glastetter's experts referred to several medical texts that suggest that bromocriptine acts as a vasoconstrictor. Each of these texts suffers from one or more infirmities that prevented the district court from accepting its conclusions. Some of the texts were largely grounded upon case reports and other anecdotal information. One text reported Parlodel's propensity to cause diseases *other* than ICH, such as coronary vasospasm and heart attack. Still other texts relied upon generic comparisons between bromocriptine and related chemical compounds. At least one text ventured a hesitant conclusion that Parlodel causes vasoconstriction, but the explanation made clear that more research was needed before causation could be firmly established.

Like the district court, Glastetter, 107 F. Supp. 2d at 1032-35, we find that these texts do not present persuasive scientific evidence that Parlodel causes vasoconstriction. Indeed, we regard the experts' claims with some suspicion since one leading treatise on medical toxicology concludes that bromocriptine has *no* vasoconstrictive properties. See Matthew J. Ellenhorn, Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning 1879, table 74-23 (2d ed. 1997). "[N]othing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." Joiner, 522 U.S. at 146.

The experts pointed out that bromocriptine belongs to a class of medicinal substances called ergot alkaloids. Some, perhaps many, ergot alkaloids are known to cause vasoconstriction and vasospasm. Dr. Kulig hypothesized that bromocriptine may behave like its chemical cousins—as a vasoconstrictor. But this generic assumption that bromocriptine behaves like other ergot alkaloids carries little scientific value. Even minor deviations in molecular structure can radically change a particular substance's properties and propensities. Schudel v. General Elec. Co., 120 F.3d 991, 996-97 (9th Cir. 1997).

Glastetter's experts also cite a handful of "rechallenge" and "dechallenge" events involving Parlodel. Rechallenge occurs when a doctor re-exposes a patient to a drug believed to have caused an earlier adverse reaction; dechallenge removes that exposure. See Glastetter, 107 F. Supp. 2d at 1031 n.9. Rechallenge and dechallenge data are substantially more valuable than run-of-the-mill case reports because a patient's reactions are measured against his own prior reactions. Measuring the patient's reaction bears some similarity to a controlled experiment. Of course, rechallenge and dechallenge events usually involve individual patients only (rather than study groups), and are not often subject to routine testing controls. The district court discounted Glastetter's rechallenge and dechallenge data because the paucity of examples presented statistically insignificant results. Further, a portion of the rechallenge and dechallenge data involved artery spasms and heart attacks, conditions which are quite distinct from Glastetter's ICH. Although we believe that this evidence is more potent proof of causation than the district court believed it to be, we nevertheless conclude that the court did not abuse its considerable discretion in rejecting the rechallenge and dechallenge data as proof that Parlodel acts as a vasoconstrictor.

Glastetter's experts rely upon animal studies to prove that bromocriptine causes vasoconstriction, which, in turn, could have caused an ICH. But during the Daubert hearing, Dr. Petro admitted that not a single animal study had ever concluded that ICH

was associated with bromocriptine. Glastetter, 107 F. Supp. 2d at 1041. Moreover, none of the pertinent animal studies were designed to reveal whether bromocriptine could cause ICHs. See id. Both Dr. Kulig and Dr. Petro also acknowledged the difficulty in reliably extrapolating from the results of studies on small animals to effects on much larger humans. We are convinced that the animal studies relied upon by Glastetter's expert physicians are insufficient to prove that bromocriptine causes ICHs.[5]

Glastetter argues that Novartis's internal documents admit that Parlodel causes hypertension and strokes. She points to three or four statements excerpted from company memoranda. See Glastetter, 107 F. Supp. 2d at 1036-38. 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.

Glastetter also relies upon the FDA's 1994 action which rescinded its earlier approval of Parlodel to suppress postpartum lactation. She argues that the FDA's action is strong evidence that Parlodel can cause ICHs. We disagree.

The FDA evaluates pharmaceutical drugs using a different standard than the causation standard at issue in the present case. The FDA evaluated the medical literature and concluded that Parlodel might cause seizures or strokes in women already susceptible to disease. The FDA decided that "the potential risks associated with the use of bromocriptine for the prevention of physiological lactation outweigh

[5]A cautionary note is appropriate at this juncture. 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.

its limited benefits and bromocriptine is no longer shown to be safe for use in preventing physiological lactation." 59 Fed. Reg. at 43351. In effect, the FDA balanced Parlodel's possible harm against its limited beneficial use. Such balancing is irrelevant in determining the threshold question posed in this appeal: whether Glastetter's experts properly "ruled in" Parlodel as a cause of ICHs.

The FDA's approach differs from ours in another critical aspect. The FDA will remove drugs from the marketplace upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-likely-than-not standards used to assess tort liability. "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.'" Hollander v. Sandoz Pharms. Corp., 95 F. Supp. 2d 1230, 1234 n.9 (W.D. Okla. 2000) (quoting Mitchell v. Gencorp Inc., 165 F.3d 778, 783 n.3 (10th Cir. 1999)). The FDA's 1994 decision that Parlodel can cause strokes is unreliable proof of medical causation in the present case because the FDA employs a reduced standard (vis-a-vis tort liability) for gauging causation when it decides to rescind drug approval.

Viewed in isolation, Glastetter's different pieces of scientific evidence do not substantiate her experts' conclusion that Parlodel can cause ICHs. Likewise, we do not believe that the aggregate of this evidence presents a stronger scientific basis for Glastetter's supposition that Parlodel can cause ICHs. We do not discount the possibility that stronger evidence of causation exists, or that, in the future, physicians will demonstrate to a degree of medical certainty that Parlodel can cause ICHs. Such evidence has not been presented in this case, however, and we have no basis for concluding that the district court abused its discretion in excluding Glastetter's expert evidence. See Joiner, 522 U.S. at 141-43.

C

Finally, Glastetter contends that the district court erred by ruling that epidemiological proof must be submitted to establish that a drug caused a particular medical condition. If her contention were accurate, we would likely reverse, for a plaintiff need not introduce epidemiological evidence of causation in order to satisfy Daubert's threshold for admission of expert medical testimony. But our review of the court's opinion and the voluminous record in this case convinces us that the court did not make such a ruling.

Epidemiology is the branch of science that studies the etiology, or cause, of disease. Reference Manual at 335. Understandably, epidemiological studies and reports are much desired by litigants in cases involving medical causation. In this case, Glastetter and Novartis generally agree that no reliable epidemiological evidence links Parlodel and ICHs. Conversely, no study has refuted a link between Parlodel and ICHs. Cf. Siharath v. Sandoz Pharms. Corp., 131 F. Supp. 2d 1347, 1356-59 (N.D. Ga. 2001) (criticizing the limited epidemiological evidence associated with Parlodel due to various statistical and conceptual flaws). This is hardly surprising. The statistical pool of childbearing women who suffer strokes is quite limited. And epidemiologists cannot perform controlled experiments because it would be unconscionable to induce strokes in postpartum women simply to advance the medical community's understanding of Parlodel. Globetti, 111 F. Supp. 2d at 1179 n.13.

The absence of epidemiological evidence did not doom Glastetter's case, as the district court indicated. Cf. Glastetter, 107 F. Supp. 2d. at 1044 & n.27. Of course, epidemiological evidence might have assisted Glastetter in establishing causation, and thus its absence limited the available tools with which she could prove causation. Having carefully considered the record in this case, we are convinced that the district court did not require Glastetter to present epidemiological evidence in order to prove that Parlodel caused her ICH. We find no error of the type she posits.

We affirm the district court's decision to exclude Glastetter's expert evidence, and the court's resulting grant of summary judgment in favor of Novartis.

III

After granting summary judgment in favor of Novartis, the district court awarded Novartis $15,525.26 in costs associated with the Daubert hearing. These costs included certain fees and travel reimbursements for witnesses, transcripts, deposition fees, and limited photocopying charges. The court did not award all the costs that Novartis sought, and, in several instances, the court drastically reduced Novartis's requested award. On appeal, Glastetter argues against the court's award of fees for expert witnesses and for the preparation of daily transcripts. We agree with the district court's fee award for the reasons stated in its opinion, and therefore affirm the award of costs. See 8th Cir. R. 47B.

IV

We affirm the judgment of the district court in all respects.[6]

A true copy.

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CLERK, U.S. COURT OF APPEALS, EIGHTH CIRCUIT.

[6]We grant appellants' motion to correct and supplement the record on appeal.