United States District Court for the Northern District of Alabama

Melissa GLOBETTI and, Mark Globetti, Plaintiffs,
v.
SANDOZ PHARMACEUTICALS, CORPORATION, Defendant

No. CV-98-TMP-2649-S

Decided Sept. 6, 2000.

Counsel:

Richard R. Rosenthal, Garrison Scott Gamble & Rosenthal PC, Birmingham, AL, Denise M. Dunleavy, Ellen Relkin, Richard S. McGowan, Catherine T. Heacox, Paul J. Pennock, Jerry M. Kristal, Jill L. Mandell, Weitz & Luxenberg PC, New York City, for Plaintiffs.

Joe G. Hollingsworth, Katherine Latimer, Bruce J. Berger, William J. Cople, Serena Viswanathan, Scott S. Thomas, Spriggs & Hollingsworth, Washington, DC, Edward S. Sledge, III, Archibald T. Reeves, IV, McDowell Knight Roedder & Sledge LLC, Mobile, AL, Jeffrey A. Peck, Shanley & Fisher, Morristown, NJ, for Defendants.

ORDER DENYING SUMMARY JUDGMENT

PUTNAM, Chief United States Magistrate Judge.

Before the court is the defendant's [FN1] motion for summary judgment on medical causation, filed July 15, 1999, on which the court conducted a Daubert hearing in December 1999. [FN2] The parties have filed extensive briefs and voluminous exhibits dealing with whether the proposed opinions of plaintiffs' expert witnesses that Melissa Globetti's myocardial infarction was caused by ingestion of Parlodel are scientifically reliable under Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), and cases following it. After hearing the testimony of many imminent experts and after having struggled through much of the scientific literature offered by the parties, the court concludes that the expert opinions are scientifically reliable and, consequently, defendant's motion for summary judgment on the ground that plaintiffs cannot establish the necessary causal link between the acute myocardial infarction (AMI) and Parlodel is due to be denied.

Factual and Procedural Background

The court does not aim to write extensively about the mounds of scientific evidence presented by the parties, but a clear picture emerges from the briefs, evidence, and testimony considered by the court. In 1993, Melissa Globetti was 33 years old and pregnant with her sixth child. Her health was good. She had no known risk factors for coronary disease; she had no family history of heart disease, was not a smoker, was not overweight, was relatively young, and had very low (indeed, "protective") cholesterol levels. [FN3] Neither during the pregnancy nor the delivery did she experience any hypertension, and she had no history of high blood pressure. After giving birth, she decided not to breast feed, so, pursuant to a standing order of her obstetrician for non- breast feeding mothers, she was given 2.5 mg of Parlodel, [FN4] twice daily for fourteen days, to suppress lactation. Mrs. Globetti had taken Parlodel before in connection with some or all of her five prior deliveries.

On the fifth or sixth day after delivery, Mrs. Globetti began to experience chest pain and was rushed to the emergency room of the local hospital in Talladega. Ultimately it was found that she had suffered an acute myocardial infarction of the anterior wall of her left ventricle. Angiography failed to reveal any thrombus, dissection, or occlusion of the coronary artery that could explain the AMI, and her initial cardiologist, Dr, Watford, concluded that it had been caused by a spasm of the coronary artery. Although Dr. Watford noted the possible association between Parlodel and the AMI and advised her to avoid it and other medications known to have vasoconstrictive effects, he expressed the opinion that the spasm was simply spontaneous. Mrs. Globetti's current treating cardiologists, Drs. Finney and Cox, as well as plaintiffs' retained experts, Drs. Waller and Kulig, all now express the opinion that the Parlodel caused or contributed to the arterial spasm that caused her AMI. It is this basic causation opinion that is at the

center of the Daubert challenge underlying the motion for summary judgment.

The defendant argues in support of the motion that the plaintiffs' experts' opinion on causation is scientifically unreliable under Daubert and, therefore, must be stricken. In the absence of testimony establishing a causal link between Mrs. Globetti's AMI and the use of Parlodel, plaintiffs' cause of action would fail and defendant would be entitled to summary judgment. Sandoz contends that, absent a scientifically appropriate epidemiological study showing an increased risk of AMI associated with Parlodel use, plaintiffs' experts' opinion is nothing more than their unscientific speculation. Plaintiffs counter that, although there

is no epidemiological study dealing with the effects of Parlodel on AMIs, there is an abundance of other scientifically reliable evidence from which a well-reasoned opinion that Parlodel can cause vasoconstriction severe enough to cause an AMI can be drawn. This evidence includes animal studies, case reports, Adverse Drug Reaction reports (ADRs) to the Food and Drug Administration, and the generally accepted notion in the medical community that Parlodel is a risk factor for AMI because of its vasoconstrictive effects.

The Law of Daubert

In Daubert the United Supreme Court rejected the argument that the standard for determining the admissibility of scientific opinion testimony was the "generally accepted in the relevant scientific community" test originating in Frye v. United States, 54 App. D.C. 46, 293 F. 1013 (1923). Rather, the Court held that Federal Rule of Evidence 702, promulgated in 1976, supplanted the Frye standard with a more "flexible" approach. The Court described the old Frye test as "austere," "rigid," and "uncompromising" and signaled with Daubert (later reiterated in Kumho Tire Company, Ltd. v. Carmichael, 526 U.S. 137, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999)) a more practical and flexible approach to assessing whether a proposed expert opinion has sufficient evidentiary reliability [FN5] that the fact-finder should be allowed to consider it. While it is true that the Court listed four "factors" for measuring reliability, [FN6] it made clear, both in Daubert and Kumho Tire, that these were neither exclusive nor exhaustive and that it remains for the trial court to determine what procedures and tools are necessary

for it to analyze the "trustworthiness" of the expert's opinion. The "gatekeeping" role of the trial court requires flexibility and a practical recognition of what can be known and how it is known. If scientific methodologies can validate certain facts, scientifically reasonable inferences drawn from those facts are admissible. [FN7] Daubert did not erect insurmountable obstacles to the admissibility of expert opinion evidence; rather, it simply holds that before expert-opinion evidence should be allowed, the opinion should be based on "good grounds," that is, "supported by appropriate validation--i.e., 'good grounds,' based on what is known." Daubert, 509 U.S. at 590, 113 S.Ct. 2786. The point of the gatekeeping role is to separate opinion evidence based on "good grounds" from simple subjective speculation masquerading as scientific knowledge.

The assessment process, that is, the process of examining whether "good grounds" exist, focuses on the methodologies the witness used to reach the opinion he or she will express, not the scientific correctness of the opinion. It is not part of the trial judge's gatekeeping role to determine whether the proffered opinion is scientifically correct or certain in the way one might think of the law of gravity. The gatekeeping role is addressed to mere evidentiary admissibility; it is the fact-finder's role (usually a jury) to determine whether the opinion is correct or worthy of credence. For the trial court to overreach in the gatekeeping function and determine whether the opinion evidence is correct or worthy of credence is to usurp the jury's right to decide the facts of the case. All the trial judge is asked to decide is whether the proffered evidence is based on "good grounds" tied to the scientific method.

Application of Daubert in this Case

The court is satisfied that the proffered opinion- -that Melissa Globetti's AMI was caused by an arterial spasm arising from the vasoconstrictive effects of the Parlodel she was taking--is based on "good grounds" tied to the scientific method and that it possesses sufficient evidentiary reliability (that is, trustworthiness) that a jury should be allowed to consider it in the determination of the facts of this case. [FN8] In the words of Daubert, that opinion is an idea inferred from such facts as are scientifically known and established through appropriate scientific methodologies.

In the case of at least Drs. Finney, Cox, and Waller, the methodology used to lead them to this conclusion is the differential diagnosis, a well-recognized and widely-used technique relied upon by medical clinicians worldwide to identify and isolate the causes of disease so that they may be treated. The differential diagnosis calls for the physician to list the known possible causes of a disease or condition, usually from most likely to

least likely. Then, utilizing diagnostic tests, the physician attempts to eliminate causes from the list until he is left with the most likely cause. These diagnostic tests may include physical examination, medical history, testing of blood and other bodily fluids, X-rays, CT scans, MRIs,and any of a host of generally accepted techniques for eliminating or "falsifying" a hypothesis that the disease arose from a particular listed cause. In Mrs. Globetti's case these testing techniques included physical examination, family and medical history, coronary enzyme tests, X-ray, angiography, and an echocardiagram. All of the tests performed on Mrs. Globetti are well-recognized and scientifically accepted techniques for confirming or eliminating particular causes for her AMI. Ultimately, following the protocol of a differential diagnosis, her physicians were able to eliminate every possible cause for the AMI except for spasm. The court has no difficulty finding that that conclusion--the AMI was caused by an arterial spasm--to be well-supported and on good grounds. [FN9]

The next step in the causation opinion is that the spasm was caused by plaintiff's ingestion of Parlodel. Plaintiffs' experts offer the opinion that, because Parlodel has vasoconstrictive characteristics, it is capable of causing a coronary artery spasm and, in the absence of any other reasonable explanation, it was the most likely cause of the AMI. Defendant attacks this reasoning on two fronts: first, that the evidence that Parlodel can cause vasoconstriction is unreliable and, second, that the conclusion that there were no other causes for Mrs. Globetti's AMI is unreliable.

Without attempting to recite the extensive and voluminous scientific evidence presented on the first argument, the court is satisfied that plaintiffs' experts based their opinion that Parlodel can cause vasoconstriction sufficiently severe to cause an AMI on sound scientific evidence and methodologies. Plaintiffs' experts cite as a foundation for their opinions animal studies [FN10] that have shown ergot alkaloids similar to Parlodel to have a vasoconstrictive effect; the same studies were relied upon and acknowledged in internal Sandoz documents. Additionally, the plaintiffs' experts cite case reports and ADRs reported to the FDA indicating that Parlodel has vasoconstrictive side effects such as stroke, seizure, and myocardial infarction. While limited in number, these case reports and ADRs were further bolstered by literature reviews that identified Parlodel as a risk factor for AMI in the postpartum period. See Badui, Acute Myocardial Infarction During Pregnancy and Puerperium, ANGIOLOGY, Vol 47, No. 6 (1997); Fournie, Bramocriptine Inhibition of Lactation and Pharmacovigilance, J.GYNECOL, OBSTET. BIOL. Several medical textbooks state that bromocriptine is a risk factor for AMI in the postpartum stage. See Hurst's The Heart, Arteries and Veins 9th Edition; Heart Disease in Pregnancy, by Dr. Cecelia Oakley; and Medical Toxicology, 2nd Edition; by Matthew J. Ellenhorn.

Plaintiffs' experts point to a de-challenge/re-challenge experiment performed by Larrazet in France, published in 1993. There, a 32-year-old woman taking bromocriptine for lactation suppression following delivery of her seventh child suffered an AMI on the ninth day following delivery. An angiogram at that time confirmed a total occlusion of her right coronary artery. She was treated and bromocriptine was stopped. One month later, the woman voluntarily agreed to submit to reintroduction of bromocriptine under controlled conditions. Two hours after being given 2.5 mg of bromocriptine, angiography observed that she was suffering a 70% occlusion of her right coronary artery due to spasm, even though she was suffering no chest pain and there was no change in her electrocardiographic readings. Larrazet, Possible Bromocriptine-induced Myocardial Infarction, ANNALS OF INTERNAL MEDICINE, Vol. 118, No. 3.

Finally, Dr. Waller also testified about his own cardiopathological examination of heart and arterial tissue taken from a woman who died from an AMI while taking Parlodel. Dr. Waller is not only trained as a cardiologist, but also a cardiac pathologist, and he directs one of the largest cardiac and arterial tissue banks in the United States. He has examined thousands of heart and arterial tissue samples. He testified that he examined tissue from the Tamara Ayers [FN11] and that it was healthy heart and arterial tissue, with no signs of thrombus, plaque, or dissection. Further, upon cross-sectioning of the coronary artery, he found contraction bands in the media, evidencing that the artery had undergone spasm. While this involved only one subject, it is suggestive of a link between Parlodel use, arterial spasm, and AMI.

Additionally, Dr. Waller testified, again based on his training as a cardiac pathologist, that the blood vessels in the fingers are similar in size, histologic function, and structure to those in the heart, Given the similarities between digital arteries and cardiac arteries, it is logical to infer that if Parlodel causes digital vasoconstriction, [FN12] it could have a similar effect in coronary arteries.

Although defendant is correct that there is no epidemiological study showing an increased risk

of AMI associated with bromocriptine, there is more than adequate evidence of a scientific nature from which a reliable conclusion can be drawn about the association. While an epidemiological study may be the best evidence, Daubert requires only that reliable evidence be presented, and that evidence here consists of the animal studies, the medical literature reviews, the ADRs reported to the FDA, the "general acceptance" of the association reflected in several medical texts, the Larrazet experiment, and Dr. Waller's observations in the Ayers case. These all are recognized and accepted scientific methodologies, used for assessing the possible side-effects and hazards associated with particular drugs and the causes of disease. The fact that Mrs. Globetti's AMIwas caused by her ingestion of Parlodel can be reliably inferred from the facts known about the vasoconstrictive effect of bromocriptine.

Plaintiffs argue powerfully that an epidemiological study of the association between Parlodel and AMI is not practical because of the relative rarity of AMIs among postpartum women. To gather a population of postpartum women with a sufficient sub-population of those who have suffered an AMI to be statistically significant would require hundreds of thousands, if not millions, of women. The evidence suggests that AMI occurs in postpartum women at the rare rate of 1 to 1.5 per 100,000 live births. Thus, even in a study of one million women, the sub-population of those suffering an AMI would be only ten to fifteen women, far from enough to allow drawing any statistically significant conclusions. [FN13] In short, the best scientific evidence available as a practical matter is that presented by plaintiffs' experts.

Similarly, the opinion expressed by plaintiffs' experts is not made unreliable or inadmissible simply because it may be debatable whether there were other possible causes for Mrs. Globetti's AMI. That debate creates only a question about the weight to be accorded the plaintiffs' experts' opinions, not their admissibility. In reaching the conclusion, there is no question that Drs. Waller, Finney, and Cox utilized a recognized and valid technique called a differential diagnosis, which was explained above. Their opinion that Parlodel was the most likely explanation for Mrs. Globetti's AMI is reliably grounded on that methodology. It will be for the jury to determine which of the alternative explanations for the AMI is more likely true than not true.

Rejection of Other Parlodel Cases

Finally, the court is required to explain why it reaches a conclusion about the admissibility of this scientific testimony different from that reached in cases cited by the defendant, namely the Hollander [FN 14] and Brumbaugh [FN1 5] cases. The court believes that in those cases the Daubert standard was applied incorrectly, creating much too high a standard of admissibility. Both of these cases seem to equate Daubert 's reliability standard with scientific certainty, which is far from what the Supreme Court intended in Daubert. Science, like many other human endeavors, draws conclusions from circumstantial evidence when other, better forms of evidence is not available. As already noted above, one cannot practically conduct an epidemiological study of the association of Parlodel with postpartum AMI. Moreover, one cannot ethically experiment on human beings, exposing them to the near certainty of some number of deaths, simply to satisfy some evidentiary standard. Hollander and Brumbaugh failed to recognize that Daubert does not require, or even allow, the trial court to determine the scientific "correctness" or certainty of the evidence, but only that the facts from which the opinion is inferred are themselves scientifically reliable.

This court simply found the scientific evidence offered by plaintiffs more impressive than the Hollander and Brumbaugh courts. As mentioned, one of the factors retained by Daubert is whether the proposed opinion, methodology, or technique has gained "general acceptance" in the relevant scientific community. At least for myocardial infarctions, several authoritative medical texts identify Parlodel as a risk factor in the postpartum period. This appears to be a "general acceptance" of that conclusion. Moreover, the animal studies powerfully established a vasoconstrictive characteristic for Parlodel, particularly in postpartum women, who have lower vascular resistance. One can debate the flaws and inadequacies of any element of the scientific evidence relied upon by the experts as a foundation for their testimony, but the validity of the methodologies cannot be seriously questioned.

Also, this case involves a myocardial infarction, which at least distinguishes it from Hollander, a stroke case, and Brumbaugh, a seizure case. Other courts have rejected the defense argument in the AMI context. See Kittleson v. Sandoz Pharmaceuticals Corp., 2000 WL 562553 (D.Minn.2000); Anderson v. Sandoz Pharmaceuticals Corp. 77 F.Supp.2d 804 (S.D.Texas, 1999). This court agrees with Kittleson and, implicitly, Anderson that there is sufficient reliable scientific information from which a reasonable scientific inference can be draw that Parlodel, as an ergot alkaloid, can cause vasoconstriction under circumstances of low vascular resistance and that such vasoconstriction can cause

arterial spasm severe enough to cause a major or complete occlusion of a coronary artery, leading to a myocardial infarction of the heart muscle supplied by the occluded artery.

Conclusion

The court finds, therefore, that the expert testimony of Drs. Finney, Cox, Waller, and Kulig, to the effect that Mrs. Globetti's AMI was caused or contributed to by her use of Parlodel to be scientifically reliable under Daubert and Federal Rule of Evidence 702. Consequently, plaintiffs have shown there to be a triable issue of medical causation. The defendant's motion for summary judgment on medical causation is hereby DENIED.

Opinion Footnotes:

FN1. Although identified in the style of the case as Sandoz Pharmaceuticals Corporation, the defendant has since changed its name to Novartis Pharmaceuticals Corporation.

FN2. Although the motion challenges the ability of the plaintiffs to prove causation in all three cases assigned to the undersigned magistrate judge, Globetti, Quinn, and Brasher, the hearing held in December focused on the admissibility of expert testimony only in the Globetti case, and that will be the subject of this opinion and order. The court recognizes, however, that much of what it has to say here also will apply to the other two cases.

FN3. Several experts testified that Mrs. Globetti's cholesterol levels were so low that she had a less than average risk for heart disease.

FN4. Parlodel is the trade name for the chemical compound bromocriptine mesylate, an ergot alkaloid with an added bromine atom.

FN5. See Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 590 n. 9, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993), where that Court stated "[O]ur reference here is to evidentiary reliability--that is, trustworthiness."

FN6. These factors were testability, peer review and publication, assessing the known or potential rate of error of the proposition, and whether it has found general acceptance in the scientific community.

FN7. "The subject of an expert's testimony must be 'scientific ... knowledge.' The adjective 'scientific' implies a grounding in the methods and procedures of science. Similarly, the word 'knowledge' connotes more than subjective belief or unsupported speculation. The term 'applies to any body of known facts or to any body of ideas inferred from such facts or accepted as truths on good grounds.' " Id. at 589-90, 113 S.Ct. 2786 [italics added].

FN8. Daubert requires that expert opinion evidence be both reliable and relevant. The relevance prong of the test is concerned with whether the proffered testimony "assists the trier of fact" to determine some issue in dispute. In this case, the parties appear to agree that the question of causation is central to the plaintiffs' ability to recover from the defendant. The plaintiffs must prove by a preponderance of the evidence that Melissa Globetti suffered an injury, her AMI, because of the Parlodel manufactured by defendant. Thus, the court concludes that the expert causation opinion is relevant. The dispute is over its reliability.

FN9. The court has not overlooked the testimony of defense expert, Dr. Judelson, who opined that the AMI was caused by ruptured plaque that occluded the coronary artery. This, however, does nothing more than raise a conflict in the evidence that must be resolved by a jury. Her contrary opinion about the cause of the AMI does not undermine the scientific and evidentiary reliability of the conclusion reached by plaintiffs' experts.

FN10. The experts cite animal studies involving the hind legs of dogs, the ears of dogs, the tails of rat and mice, tongues of sheep, and a "spinal cat," all indicating that bromocriptine causes vasoconstriction sufficient to lead to necrosis. The hind leg study established that bromocriptine is both a vasoconstrictor and vasodilator, depending upon the initial vascular resistance. Low initial resistance causes bromocriptine to cause vasoconstriction, while greater vascular resistance leads to vasodilation. This is important because inthe postpartum period, vascular resistance is low due to the shifting blood volumes and hemodynamics of the female body readjusting itself to a non-pregnant state. Thus, the conclusion that postpartum women may be more susceptible to bromocriptine causing vasoconstriction is consistent with the animal study.

FN1 1. Ms. Ayers is the plaintiff in another case against Sandoz, styled Ayers v. Sandoz Pharm. Corp. Case No. 95 CV 10553, in the Superior Court, Guilford County, North Carolina.

FN 12. Internal Sandoz documents acknowledged reported incidents of digital vasoconstriction associated with Parlodel use.

FN13. While not suggested by the defendant, the court notes that it would be medically and scientifically unethical to attempt a control-group experiment. To do so would require administering Parlodel to women and exposing them to the possibility of life-threatening events like AMI and stroke. Indeed, to prove the association between Parlodel and AMI or stroke, the scientist would have to expect a certain number of deaths among the test subjects.

FN14. Hollander v. Sandoz Pharmaceuticals Corp., 95 F.Supp.2d 1230 (W.D.Okla.2000). See also, Glastetter v. Novartis Pharmaceuticals Corp. 2000 WL 1036247 (E.D.Mo.2000)

FN1 5. Brumbaugh v. Sandoz Pharmaceutical Corp., 77 F.Supp.2d 1153 (D.Mont.1999).