In re VIAGRA PRODUCTS LIABILITY LITIGATION
572 F.Supp.2d 1071 (D. Minn. 2008)
(edited)

MEMORANDUM AND ORDER

This matter is before the Court on Defendant Pfizer Inc.'s Motion to Exclude Plaintiffs' Experts under *Daubert,* and Plaintiffs' Motion to Exclude Defendant's General Causation Experts. For the reasons that follow, the Court grants Pfizer's *Daubert* Motion in part and denies it in part, and denies Plaintiffs' Motion.

BACKGROUND

This Multi-District Litigation involves claims that Viagra, manufactured by Pfizer, has caused a vision-loss disorder called non-arteritic anterior ischemic optic neuropathy ("NAION"). It is believed that NAION results from diminished blood flow to the frontal portion of the optic nerve. What causes the diminished blood flow is unclear.

Ten studies have measured Viagra's effect on eye circulation flow but none has measured blood supply to the area believed involved with the disease, apparently because existing medical technology does not permit such a study. Although the parties' experts have identified NAION as the most common optic disorder of its type among persons 50 and older, it nevertheless is a rare disorder that afflicts perhaps 2.5 to 11.8 persons per 100,000 in the general population.

Viagra use, by contrast, is anything but rare. Since 1998, when the Food and Drug Administration approved the drug to treat penile erectile dysfunction ("ED"), it has been prescribed to more than 27 million men. To date the number of Plaintiffs with actions alleging that Viagra has caused their NAION stands at 134 -- a small number when compared with how many men use Viagra.

Viagra and its active ingredient, sildenafil, work by inhibiting an enzyme called phosphodiesterase type 5 ("PDE5"), thereby causing blood vessels to expand and accordingly improving men's erections. Three epidemiologic studies have investigated whether there is a link between PDE5 inhibitor use and NAION. None has found a statistically significant increase in NAION among Viagra users.

Plaintiffs have identified four general-causation experts whose testimony they contend will assist the triers of fact with understanding the evidence and determining that Viagra can cause NAION. Pfizer has identified three experts in response. In these cross-Motions, each party asks the Court to exclude the other side's experts pursuant to Rule 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579 (1993).

DISCUSSION

A. Rule 702 and *Daubert* Standard

Expert opinion testimony from a qualified expert is admissible 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." Fed.R.Evid. 702. On a *Daubert* motion, the Court acts as a gatekeeper to "ensure that any and all scientific testimony ... is not only relevant, but reliable." *Daubert,* 509 U.S. at 589, 113 S.Ct. 2786. Factors the Court should examine when determining reliability include whether (1) a theory or technique can be and has been tested, (2) the theory or technique has been subjected to peer review and publication, (3) there is a known or potential rate of error and whether there are standards for controlling the error, (4) whether the theory or technique enjoys general acceptance within the relevant scientific community, (5) whether the expertise was developed for litigation or naturally flowed from the expert's research, (6) whether the proposed expert ruled out other alternative explanations, and (7) whether the proposed expert sufficiently connected the proposed testimony with the facts of the case. Expert testimony may be based either on professional studies or personal experience as long as the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." However, to be reliable and therefore admissible, the evidence must provide a "valid ... connection to the pertinent inquiry." "[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. A court may conclude that there is simply too great an analytical gap between the data and the opinion offered."

When a case involves expert medical testimony, the Court's function under *Daubert* is to ensure that the expert's opinion is scientifically valid and will assist the jury." The 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. An expert opinion must be supported by appropriate validation -- i.e., good grounds, based on what is known." The goal is to separate expert opinion evidence based on good grounds from subjective speculation that masquerades as scientific knowledge."

However, the general rule that the strength or weakness of the factual basis of an expert opinion goes to the credibility of the testimony, not the admissibility" applies equally to *Daubert* motions. It is common that medical experts often disagree on diagnosis and causation, and questions of conflicting evidence must be left for the jury's determination. Only if the expert's opinion is so fundamentally unsupported that it can offer no assistance to the jury must such testimony be excluded.

Expert opinions in medical-related cases typically involve results from clinical trials, epidemiologic studies, and case studies. The clinical trial is the "gold standard" of medical research. When research from a clinical trial is unavailable, epidemiologic studies often are used to assess an association between a drug and disease and in turn general causation. One approach

for expressing an association in epidemiologic research is the rate of "relative risk" ("RR"), which is reached by comparing the incidence rate of persons exposed to an agent with the incidence rate of those not exposed. *Id.* at 348. An RR greater than 1.0 suggests that "[t]here is a positive association between exposure to the agent and the disease, which could be causal." Courts sometimes conclude that an RR of 2.0 or greater provides reliable evidence of specific causation.

Another approach for expressing an association in epidemiologic research is the "odds ratio" ("OR"). "In a case-control study, the odds ratio is the ratio of the odds that a case (one with the disease) was exposed to the odds that a control (one without a disease) was exposed." Therefore, an OR greater than 1.0 means that a disease is more prevalent in persons who were exposed to a substance than those who were not. The OR is most useful in gauging an association when a disease is "relatively rare" in the general population. To determine whether an odds ratio provides reliable evidence of causation, courts frequently examine the "confidence interval" ("CI"), or the "range of values within which the true value is likely to fall." It is generally accepted that "[i]f the confidence interval is so great that it includes the number 1.0, then the study will be said to show no statistically significant association between the factor and the disease."

B. Plaintiffs' Experts

1. Gerald McGwin, Ph.D.

Plaintiffs' first general-causation expert is Gerald McGwin, Ph.D., an associate professor at the University of Alabama at Birmingham whose research interests include injury epidemiology and ophthalmic epidemiology. In his report and during a deposition, McGwin discussed three epidemiologic studies that, according to McGwin, suggest that Viagra can cause NAION. Two of the studies were published and peer-reviewed. One of those studies involved case-control research that McGwin helped perform and the other involved research of Veterans Administration data. A third study involved Pfizer-sponsored research. He examined the studies in light of the so-called "Bradford Hill criteria" that researchers use to assess causation. "The Bradford Hill factors are strength of relationship, consistency, specificity, temporality, dose response, biologic plausibility, coherence, experimental evidence, and analogy."

McGwin began his analysis by assessing the "strength of association" between Viagra and NAION. Regarding this association, McGwin stated that the McGwin *et al.* study reported an "odds ratio (OR) of 1.75 with a 95% confidence interval (CI) of 0.48 to 6.30." In other words, "the odds of Viagra use were 75% greater among men with NAION compared to age-matched controls." The study further reported an OR of 10.7 for men who reported Viagra use and had a history of myocardial infarction, and an OR of 6.9 for Viagra users who had a history of hypertension. McGwin then cited the Margo *et al.* study, which involved the related disorder nonarteritic ischemic optic neuropathy ("NION"). That study reported an RR factor of 1.10 regarding exposure to PDE5 inhibitors. In other words, "men who were dispensed PDE-5 inhibitors were 10% more likely to have a diagnosis or possible diagnosis of NION compared to those who had not been dispensed these medications." (*Id.*)

McGwin then addressed the second Bradford Hill factor regarding consistency and asserted that it was satisfied because the McGwin *et al.* and Margo *et al.* studies were consistent with each other in that they collectively demonstrate "an overall increased risk level of between 10- and 75-percent" regarding Viagra use and NAION. Regarding temporality, McGwin stated that the McGwin et al. study suggested a causal relationship between Viagra use and NAION because "the authors only evaluated Viagra use that occurred prior to [a] NAION diagnosis date," but that temporality could not be assessed in the Margo et al. study. (*Id.*) Regarding biologic plausibility, McGwin stated that Viagra's "mild systemic hypotensive" and possible "optic nerve fiber crowding" effects suggest that Viagra can cause NAION.

McGwin did not meaningfully examine the specificity or dose-response factors. As for the remaining Bradford Hill factors, McGwin stated that the findings in his report are coherent with known facts of NAION, there have been no human clinical trials or animal experiments, and that case reports regarding PDE5 inhibitor ingestion and NAION satisfy the analogy factor.

Finally, McGwin critiqued the Gorkin study, which suggests that Viagra users are at no increased risk for developing NAION than is the general population. According to McGwin, the Gorkin study is unreliable because the sample size was too small and the data ill-suited for assessing a possible temporal relationship. (*Id.* at 4-5.)

In a deposition, McGwin confirmed that the odds ratio in the McGwin et al. study and the relative risk factor in the Margo & French study were not "statistically significant," and that the data in the Gorkin study indicate that NAION incidence in sildenafil users is "consistent with the range of estimated NAION incidence in the general U.S. population." Nevertheless, McGwin again stated his conclusion as being that "to a reasonable degree of scientific certainty, it is my opinion that Viagra can cause NAION and the other ocular vascular disorders." (*Id.* at 228.)

Pfizer contends that McGwin's report is unreliable because it is not based on statistically significant data and is therefore unreliable. Statistical significance is among the factors the Court should examine when determining reliability. Because the CI in the McGwin *et al.* study "includes the number 1.0," it can be accepted that the study "show[s] no statistically significant association between the factor and the disease." In addition, because the RR in the Margo *et al.* study is 1. 10, there is authority indicating that the research fails to provide "reliable evidence of specific causation."

However, the inquiry at this stage involves *general causation.* Therefore, the authority suggesting that the RR value renders the Margo *et al.* study *per se* unreliable is distinguishable. There is persuasive authority stating that on a *Daubert* motion involving general-causation evidence, lack of statistical significance under some circumstances "does not detract from the reliability of the study. In this situation, the McGwin *et al.* and Margo *et al.* studies were peer-reviewed, published, contain known rates of error, and result from generally accepted epidemiologic research. The studies satisfy the precise standards that the Supreme Court has signaled that the Court should consider when determining reliability in *Daubert.* The Court cannot conclude at this stage that McGwin's proffered testimony "is so fundamentally unsupported that it can offer no assistance to the jury [that] such testimony must be excluded."

2. Howard D. Pomeranz, M.D.

Plaintiffs' second expert, Howard D. Pomeranz, is a medical doctor and ophthalmologist whom Plaintiffs credit with co-authoring the first case report of someone who developed NAION after taking Viagra and also analyzed other such case reports. Plaintiffs seek to have Pomeranz testify about a possible temporal relationship between sildenafil use and NAION.

The first case in Pomeranz's report was of a "healthy 50 year-old man who had ED due to prostate cancer surgery." The man experienced 30 minutes of blurred vision an hour after ingesting sildenafil and the same symptoms the next night but without improvement. A medical exam revealed "visual field defect in the left eye and a swollen left optic disk, consistent with NAION." Pomeranz described the report as "challenge-rechallenge" data. Rechallenge occurs when a doctor re-exposes a patient to a drug believed to have caused an earlier adverse reaction.

In 2002, Pomeranz co-published "a summary of 5 patients with NAION associated with sildenafil use," which included the man involved in the first case report. In 2005, Pomeranz co-published a report documenting "an additional seven patients with NAION associated with sildenafil use. Six patients experienced vision loss within 24 hours after use of sildenafil. All affected men had pre-existing vascular disease."

In his expert report, Pomeranz drew these conclusions:

> Compelling arguments for a cause-and-effect association between NAION and the ED drugs include the (1) temporal relationship between onset of ocular symptoms and drug ingestion that is well documented in the cases published in the peer-reviewed medical literature, (2) a suggestive challenge-rechallenge history also well documented in the peer-review medical literature, and (3) a biologically plausible mechanism of effect on arterial perfusion of the optic disk, described by [researcher Sohan Singh] Hayreh, a well-recognized authority on NAION.

At his deposition, Pomeranz further clarified that while he has not concluded that Viagra causes NAION, there is a temporal association between Viagra and NAION:

> QUESTION: Is it your hypothesis that Viagra can cause NAION?
> POMERANZ: No. At this time, I described in my papers that there's a temporal association between the two. And I've put forward possible hypotheses, but I don't purport to have a mechanistic answer to that. I think it's-because no one understands completely what the mechanism of NAION is, to incite something as being a specific cause without knowing all the pathophysiology that underlies a condition I think is difficult to do.

Case reports generally are less reliable than epidemiologic research. Rechallenge data, while "substantially more valuable than run-of-the-mill case reports," are properly excluded when "the paucity of examples presented statistically insignificant results." Reports of this type

are subject to the general rule that "temporal association ... is not scientifically valid proof of causation." However, "[u]nder some circumstances, a strong temporal connection is powerful evidence of causation," such as when acute symptoms are seen "immediately after ... exposure" to a substance. *See Heller v. Shaw Indus.,* 167 F.3d 146, 154 (3d Cir.1999) ("if a person were doused with chemical X and immediately thereafter developed symptom Y, the need for published literature showing a correlation between the two may be lessened").

The Court concludes that Pomeranz's report-which provides a less-than-strong temporal association between sildenafil and Viagra, a single challenge-rechallenge case fails to provide appropriate validation to Pomeranz's conclusion that there are "compelling arguments for a cause-and-effect association between NAION and the ED drugs." Pomeranz's report seems to focus on eleven men who experienced vision loss somewhere between several hours and twenty-four hours after using sildenafil. However, because a majority of them had "pre-existing vascular disease" or "identifiable vascular risk factors", any cause-and-effect relationship between Viagra and NAION would be "subjective speculation." The difficulty with case reports is distinguishing between association and causation. Simply because a patient exposed to a particular substance exhibited a set of symptoms does not mean that it was the substance that caused the symptoms."

The fact that these men out of untold millions of sildenafil users developed NAION within a 24-hour period fails to evince an "immediate" reaction to a substance as was present in *Bonner*. 259 F.3d at 930-31. The lone rechallenge case appears to stand in isolation and is fairly characterized as a "paucity." This is not a situation where the "sheer volume of case reports, case series, and spontaneous reports" bolsters the reliability of non-epidemiologic research. Accordingly, the Court grants Pfizer's *Daubert* Motion as it relates to Pomeranz's testimony in its entirety.

3. Sohan Singh Hayreh, M.D.

Plaintiffs' third expert is Sohan Singh Hayreh, a medical doctor and ophthalmologist who has studied more than 1,000 people with NAION and is credited with giving the disorder its name. His report contains an overview of factors that influence the blood flow in the optic nerve head and explains the various risk factors for NAION. Hayreh's report further suggests that there is "a cause-and-effect relationship between erectile dysfunction drugs and development of NAION." This suggestion is based on a "nocturnal hypotension" theory involving low blood pressure during sleep.

Hayreh's report begins by explaining the anatomy of the eye and optic nerve and then provides a specific but non-exhaustive list of eleven predisposing risk factors for NAION: "high blood pressure, diabetes, cardiovascular diseases, high cholesterol, atherosclerosis, arteriosclerosis, massive or recurrent bleeding, migraine, sleep apnea, defective autoregulation of the optic nerve head, narrowing of the blood vessels supplying the optic nerve head, and many more." Hayreh then identifies the "precipitating risk factors" -- specifically, "that at least 73% of patients with NAION gave a definite history of discovering the visual loss on waking up in the morning or from a nap, or early in the morning at the first opportunity to use critical vision."

His report then explains that blood pressure is lower during sleep and that drugs prescribed "for a variety of conditions, such as heart failure or other heart diseases, enlarged prostate, migraine, as well as for high blood pressure, similarly cause an abnormal drop of blood pressure during sleep." The report goes on to explain that men who take Viagra are more likely to have high blood pressure, diabetes, and other "factors that make them vulnerable to NAION."

Finally, the report suggests a "relationship between NAION and Viagra and other drugs used for erectile dysfunction." According to Hayreh, because NAION most often is reported upon awakening in the morning and Viagra is most often taken at night or before bed, "[w]hen all the evidence is put together, it becomes evident that Viagra and other erectile dysfunction drugs can result in the development of NAION-not always and in everyone but in persons with predisposing risk factors."

Pfizer asks the Court to exclude Hayreh's testimony because his nocturnal hypotension theory as it relates to Viagra has not been tested or subjected to peer review and publication and is not generally accepted. Therefore, according to Pfizer, the theory does not satisfy *Daubert's*"non-exhaustive list of factors a district court should consider when performing its gatekeeper function." Plaintiffs contend that Hayreh's theory satisfies these factors as well as "additional factors, including, whether the expertise was developed for litigation or naturally flowed from the expert's research; whether the proposed expert ruled out other alternative explanations; and whether the proposed expert sufficiently connected the proposed testimony with the facts of the case."

The Court finds Hayreh's report helpful for explaining eye and optic nerve anatomy, NAION risk factors including factors related to blood pressure, and the effect of various drugs on blood pressure. Therefore, the Court denies Pfizer's *Daubert* Motion as it relates to Hayreh's testimony on these subjects because the testimony will assist the triers of fact with "understand[ing] the evidence." Fed.R.Evid. 702.

However, the Court finds that Hayreh's hypothesis regarding a purported "relationship between NAION and Viagra and other drugs used for erectile dysfunction" fails to satisfy most of the "non-exhaustive" as well as "additional" factors referenced above. Plaintiffs do not meaningfully dispute that Hayreh's specific theory has not been tested, but they contend that this fact is not controlling because "[t]he exact mechanism by which NAION occurs is not known." The fact that NAION's cause is not known does not explain whether Hayreh's theory can or cannot be tested.

As for the publication and "general acceptance" factors, Plaintiffs state that Hayreh's theory has been published in numerous peer-reviewed journals, including the prestigious *Journal of Ophthalmology*. For support, Plaintiffs direct the Court to a footnote in an article and a "non-exhaustive list of journal articles citing to Dr. Hayreh's theory on nocturnal hypotension." These materials do not help the Court assess to what degree Hayreh's theory has been vetted in these journals or whether that theory has been generally accepted among the medical community.

Regarding the Eighth Circuit's "additional factors," the fact that Hayreh's nocturnal

hypotension theory appears not to result from this litigation weighs in favor of the theory's admissibility. However, proffered testimony about the theory fails to satisfy the other factors. Instead of ruling out alternative explanations, Hayreh essentially *rules in* eleven "predisposing risk factors" such as high-blood pressure and diabetes-risk factors that a substantial number of Viagra users, given their age, possess.

This case is not about nocturnal hypotension. It is about whether Viagra can and ultimately has caused NAION. In *Daubert,* the Supreme Court observed that although studying moon phases might help a trier of fact determine whether it was dark on a given night, evidence of a full moon does not "assist the trier of fact in determining whether an individual was unusually likely to have behaved irrationally on that night." Similarly, studying nocturnal hypotension might help a trier of fact determine what causes NAION, but Hayreh's theory does not adequately explain whether Viagra can cause NAION, and his testimony would not meaningfully assist a trier of fact with determining whether Viagra has caused NAION in the Plaintiffs. The theory is "[e]xpert testimony which does not relate to any issue in the case" and therefore "is not relevant, and, ergo, non-helpful." Rather, it would be confusing.

In conclusion, the Court grants Pfizer's *Daubert* Motion as it relates to Hayreh's proffered testimony that Viagra and other erectile dysfunction drugs can result in development of NAION. However, the Court denies the Motion as it relates to Parts I and II of his expert report that relate to eye and optic nerve anatomy, NAION risk factors including blood pressure, and the fact that several drugs affect blood pressure.